المستجدات الحديثة حول الضوابط والتوصيات العلمية العالمية في تشخيص ومعالجة أمراض الجهاز الهضمي والكبد لعام 2014-2015 م

الدكتور
ضياء علي أحمد المشهداني*
اختصاصي الطب الباطني
المركز التخصصي لأمراض وجراحة الجهاز الهضمي
والكبد في النجف - جمهورية العراق-نيسان 2016م

*زميل كلية الجهاز الهضمي الامريكية
*عضو الجمعية العراقية للجهاز الهضمي والكبد
*عضو مدرسة الشرق الاوسطية للكبد
*عضوالجمعية العالمية لامراض الجهاز الهضمي الوظيفية
*عمل ومنذ عام 1995م في وحدة الجهاز الهضمي والكبد في النجف
*احد مؤسسي المركز التخصصي لأمراض وجراحة الجهاز الهضمي والكبد في مدينة الصدر الطبية في النجف في عام 2008م وشغل منصب معاون مدير المركز التخصصي فيه حتى بداية عام 2016م ولازال مستمرا للعمل فيه.

Updated Guidelines and recommendations in Gastrointestinal and Liver diseases

Dr.Dheyaa Ali Ahmed*, D.M; FACG; IFFGD; MESH
AlNajaf GI&H center /IRAQ - April 2016

***Fellowship of American Colleage of Gstroenterology**
***Membership of Iraqi Society of Gastroenterolgy&Hepatology**
***Member in Middle school of Hepatology**
***Member international foundation of functional Gastrointestinal disorders.**
***worked in Alnajaf GI&H unit since 1995**
***was one of the team participating in founding Alnajaf GI&H center on 2008 and be an assistance head of it until Jan.2016**

From: **syed** Hide

To: Dheyaa

Cc: Ali Shilb > fayez sandouk > Kashif Haider

Re: Fwd: Emailing ضياء Guideline-NGIH center 2016.pdf
Today at 2:19 AM

Dear Dheyaa, salaamun alikum, thank you very much for sharing the Guidelines in Gastroenterology/Hepatology. This is a great accomplishment and very much needed to practice quality medicine. I congratulate you for your effort and hard work to collect this information and I feel confident your effort will pave the way for furthering our speciality in Iraq.
Thank you and best wishes,
Syed Saeed Bokhari, MD

Re: Emailing ضياء Guideline-NGIH center 2016.pdf
Yesterday at 9:08 PM

MABROOK AKHI DHIA FOR THIS GREAT EFFORT TO COLLECT BTHESEV DATA
THIS SHOULD BE THE BEGINING OF A NEW ERA OF MEDICAL WRITING
GOD BLESS YOU FOR YOUR EFFORTS
DO YOU REFERENCES FOR ALL THE CONTENTS
I WILL REVIEW IT AND GIVE MY COMMENTS
OIT SOUND VERY IUSEFUL AND COMPREHENSIVE AND PRACTICAL

MAKKI H FAYADH
MbChB Baghdad,MRCP UK,FRCP Ed,FRCP London
CONSULTANT PHYSICIAN & GASTROENTEROLOGIST
ADVANCED CENTER FOR DAY CARE SURGERY ACDS -ABU DHABI-UAE

From: Al-Naseri .Mohammed sa... Hide

To: Dheyaa

Re: Emailing ضياء Guideline-NGIH center 2016.pdf
Today at 1:52 AM

الأخ الفاضل د ضياء المحترم
السلام عليكم
نبارك لكم هذا الجهد الكبير وندعو لكم بالتوفيق

Mohammed Saeed Abdulzahra
Dean
Kufa college of medicine
Assistant Professor
Cardiology

From: **Kashif Harder** Hide

To: Dheyaa

Re: Emailing ضياء Guideline-NGIH center 2016.pdf
Yesterday at 6:20 PM

Salaams
Congratulations!!
This is truly wonderful.

Kashif

Sent from my iPhone

On May 4, 2016, at 1:12 AM, Dheyaa <dr_mashhadany1961@yahoo.com> wrote:

Re: Emailing ضياء Guideline-NGIH center 2016.pdf
Today at 2:33 PM

الدكتور ضياء المشهداني المحترم شكرًا جزيلا اخي العزيز
وللجهد الكبير بالرغم من مشاغلكم المهنية والاجتماعية وتعتبر
خطوة رائدة وأولى على الطريق الصحيح في مجال
الاختصاص ونتمنى من جميع الزملاء الأعزاء ومن خلال
الجمعية واللجان الاختصاصية المساهمة في إدامة وتحديث
المعلومات كلما دعت الحاجة لذلك حيث التطور السريع
والسباق مع الزمن في كافة مجالات الطب والجراحة
وفروعهما
نسال الباري عزوجل ان يحفظ الجميع ان شاء الله
مع التقدير
د صلاح الدين عبد النبي
النجف الأشرف

From: **Ali Shilb** Hide

To: Dheyaa > syed

Cc: fayez sandouk > Kashif Haider

Re: Fwd: Emailing ضياء Guideline-NGIH center 2016.pdf
Today at 7:16 AM

It's so great effort Dr. Dheyaa,for doing this guideline I think this is what we needed in Iraq, specialist doctor should be write about the disease and we should follow you.
congratulations
Sent from Yahoo Mail on Android

My regards and Thanks to my Teachesrs &colleagues :
Dr. Syed Saeed Bokhari (USA), Dr. Syed Kashif Haider(USA), Dr. Fayes Sandouk(Syria), Dr. Makki Hammadi Fayadh(UAE), Dr Mohammed Saeed Abdulzahra(Dean of Kufa college of Medicine), Dr. Salah Aldeen Abdulnabi &Dr. Ahmed Jassim (Najaf GI&H center), Dr. Ali Hussein Shilib (Babylon GI&H center), Dr. Sadiq Jaralla (Alnasiriyia GI&H unit).
My thanks also to Abdul 'ali Alghazali (Manager of Alsader Medical city in Najaf), and to Hassan Abdullah Al 'akoli (Head of Alnajaf part of Iraqi Medical Association).
For their positive feedbacks for this work and continous support to me.

Dr. Dheyaa Ali Ahmed.
May.2016

المقدمة والأهداء

بعد جهد وتواصل مستمر ولفترة تجاوزت الستة اشهر تم بعون الله انهاء هذا الكتاب الذي يتطرق لأخر المستجدات من الضوابط والتوصيات العلمية العالمية لتشخيص ومعالجة امراض الجهاز الهضمي والكبد المهمة والشائعة والتي قمت باقتباسها من المصادر العلمية الرصينة ومنها كلية الجهاز الهضمي وجمعية الجهاز الهضمي الامريكية للتنظير والجمعية الامريكية للجهاز الهضمي والجمعية الامريكية للكبد والجمعية الاوربية لدراسة الكبد والرابطة العالمية للجهاز الهضمي والجمعية الافرواسيوية للكبد وبعض الكتب والمصادر الاخرى المعتمدة عالميا و تلخيصها وتنضيدها بالشكل الذي يجعلها سهلة المراجعة والتطبيق من قبل اطباء الطب الباطني وأطباء الجهاز الهضمي والكبد في مستشفيات القطر. علما ان هذه الضوابط والتوصيات هي قابلة للتغيير حسب ماتنتجه البحوث والدراسات في داخل القطر او خارجه.

تبلغ صفحات الكتاب مائة وتسعة وتسعون صفحة توزعت على اربعة فصول يتضمن الفصل الاول أمراض الجهاز الهضمي, الفصل الثاني أمراض حركية الجهاز الهضمي, الفصل الثالث امراض الكبد بينما الفصل الرابع الحالات الطارئة لمرضى الجهاز الهضمي والكبد. في نهاية الكتاب تم تضمين العديد من الجداول والمخططات والسلايدات التوضيحية.

شكري وتقديري الى جميع الاخوة والاخوات الأعضاء في الجمعية العراقية للجهاز الهضمي والكبد والعاملين في مؤسساتنا الصحية للثقة التي منحوها لي ودعمهم لكل الجهود التي تخدم مسيرة الجهاز الهضمي والكبد وتحقيق تطوره في بلدنا العزيز.

وفي الختام احب ان اهدي هذا الكتاب الى جميع الاساتذة والزملاء العاملين في الطب الباطني وعلى الاخص العاملين في مجال طب الجهاز الهضمي والكبد متمنيا ان ينال هذا الجهد المتواضع استحسانهم ومن الله التوفيق والسداد.

الدكتور ضياء علي المشهداني

Acknowledgment and Inscription

It will be my pleaure to thank and inscribe this book (guidelines in Gastrointestinal and liver diseases) to all my colleagues, in Iraqi Society of Gastro-enterology and Hepatology and our colleagues in Ministry of Health..

This book consists of about one hundred pages, contains four parts, the first part contains updated guidelines in common Gastroenterological disorders, the second part in Gastrointestinal motility disorders, the third part in common Liver diseases while the fourth part contains GI & Liver emergencies, at the end of the book we see an interesting and informative Tables and Pictures in GI&Liver disease that might help physicians in their daily practice.These guide lines and recommondations are summarized from the updated guidelines that lastly published by American College of Gastroenterology, American Society of Gastroentistinal Endoscopy, American Association of Study of Liver, European Association of Study of Liver, Word Gastroenterology Organization, Ascian Pacific Study of the Liver (APASL), and adapted to be more practicle, with the availability of local resources.

Lastly I hope this book would be beneficial, practical and cover most of what we need to do to our patients whether in medical wards or in emergency departments and GI&Liver centers or units.

Dr. Dheyaa Ali Ahmed
Iraq/Najaf GI&H center, May. 2016

contents

Part 1
Gastroenterology

Guidelines for safety in the gastrointestinal endoscopy unit [16,17,37,61]

Recommendations for the endoscopic procedure room.

The following are issues within the endoscopic procedure room that are related to patient safety:

1. **Actual marking of the site is not required for endoscopic procedures because endoscopy does not involve lateral right-left distinction levels such as those found in spinal procedures or those done on multiple structures such as fingers or toes. Before starting an endoscopic procedure, the patient, staff, and performing physician should verify the correct patient and procedure to be performed.**
2. **A reliable and adequate source for oxygen is required. Sources may include in-wall or free-standing oxygen. In some units, carbon dioxide may be used for insufflation of the GI lumen, but this is not a requirement.**
3. **A suction source for the equipment and patient must be present either in-wall or portable. For tubing and portable suction, the manufacturer's guidelines must be followed.**
4. **An uninterruptible source of power, supplied either by a generator or battery source is required. The purpose of a secondary power source is to allow completion of the current procedure in the event that the primary power source malfunctions. Procedures should not be started when the only source of power is the secondary source.**
5. **Units must practice fire safety in adherence with the NFPA 101 Life Safety Code, which also dictates the number and type of electrical outlets tied to the generator. NFPA 101 Life Safety Code recommends that not all outlets be tied to the generator in case the the generator fails to disengage once power is restored.**
6. **The unit's defibrillator and crash cart should be checked at the beginning of each day to ensure that all components are functional, fully stocked, and readily accessible**
7. **The routine monitoring of temperature and humidity within the emdoscopic procedure area, although advocated by CMS to theoretically curtail growth of microorganisms and reduce fire hazard, has not been associated with safety outcomes in endoscopic units.**
8. **Puncture-resistant containers for biohazardous materials and sharps should be located so that sharps are not passed over the patient.**
9. **If special therapeutic procedures are planned, specific room features may be required, such as leaded walls when flat-table fluoroscopy is utilized.**

Recommendations for the endoscopic recovery area

The recovery bays should provide privacy and sufficient space for monitoring and care. The minimum space per bay has not been established. Unit facilities must be able to provide the level of recovery appropriate to the level of sedation utilized.

Recommendation for storage of supplies

1. **Sterile supply items such as intravenous (IV) solutions should be protected from splash contamination during environmental cleaning (8-10 inches off the floor), damage from compression (stacking only ridged containers), and water damage (no storage under sinks).**
2. **Units should have a process for periodically verifying that supplies marked with an expiration date have not expired. Compliance with this process should be documented.**

Infection control in endoscopy unit

Standard precautions, the minimum infection prevention practices applicable to all patient care regardless of the suspected or confirmed infection status of the patient, are the foundation of a sound infection prevention strategy. These include:

1. **Hand hygiene**
2. **PPE**
3. **Safe medication administration practices**
4. **Safe handling of potentially contaminated equipment or surfaces in the patient environment**

Recommendations for hand hygiene : Proper hand washing is considered to be the cornerstone of preventing the transmission of pathogens.

1. **Hand hygiene should be performed before patient contact (even if gloves are to be worn); after patient contact and before exiting the patient care area; after contact with blood, body fluids, or contaminated surfaces (even if gloves are worn); before performing invasive procedures (ie, placement or access of intravascular lines); and after glove removal.**
2. **The use of soap and water is required when hands are visibly soiled and after caring for patients with known or suspected infectious causes of diarrhea such as C.difficile. Otherwise, the use of alcohol-based hand agents is adequate**

Recommendations for personal protective equipment [PPE]

The unit should have written policies and procedures regarding PPE that defines activities in which PPE should be worn and the appropriate type.

For sterile environments, the use of PPE is commonly dictated by the traffic pattern and location of care, defined as unrestricted, semi-restricted, and restricted areas.

In contrast, in the non-sterile endoscopy environment, the use of PPE is dependent on the degree to which staff have the potential to come into direct contact with patients and their bodily fluids during specific activities, rather than the location of care. The risk of exposure can be categorized into low-risk exposure and high-risk exposure, which are defined as follows:

1. **Low-risk exposure: Any personnel not in direct contact with a contaminated endoscope, device or bodily fluid or with the potential for splash contamination. For example, personnel entering the procedure area for abrief period of time who are not involved in direct patient care are considered at low-risk exposure.**
2. **High-risk exposure: Any personnel working in direct contact with a contaminated endoscope, device, or bodily fluid or any personnel in direct patient care with the potential to come into contact with a contaminated endoscope , device, or bodily fluid**

Hair and shoe covers and gown classifications above Association for the Advance ment of Medical Instrumentation level 1 are often included in PPE recommendat- ions.

These items generally are mandated for the sterile operating room environment, but there is no evidence to support their requirement or benefit in the non-sterile endoscopy environment.

1. **Staff must remove and appropriately discard used PPE before leaving the procedure room. PPE should not be reused or worn to care for more than 1 patient.**
2. **Scrub attire may be worn from home, because endoscopic procedures are performed in a non-sterile environment.**
3. **Individuals may elect to wear regular clothing covered by an impervious gown. There is no requirement to change clothing once the individual arrives at work.**
4. **If clothing under the procedure room attire is contaminated with a significant amount of blood or body fluids, the items should be placed in a bag, identified as**

apotential biohazard, then sent for cleaning to leundry facility capable of properly cleaning and disinfecting clothing used in healthcare settings

Recommendations for safe medication administration practices

Units should adhere to the following:

1. **Preparing medications for multiple patients should be done in an area away from direct patient care or procedure rooms.**
2. **Units should appropriately label all medications, including those used for sedation, unless the medication is for immediate use (prepared and administered immediately without leaving the provider's hand).**
3. **Medications marked either on the container or noted in the package insert as "single patient use" should be used for a single patient only and any remaining drug should be discarded.**
4. **Units should use new fluid administration sets (eg, IV tubing) for each patient.**
5. **Units should prepare and administer injections by using aseptic technique (ie , cleansing the access diaphragms of medication vials with 70% alcohol before inserting a device in the vial). Single-dose vials, ampules, bags, or bottles of IV solution should be used for a single patient only.**
6. **Use of a single-dose vial is preferred over multiple-dose vials, particularly when medications will be administered to multiple patients.**
7. **If a multiple-dose vial will be used for more than 1 patient, they should remain in a centralized medication area and should not enter the patient procedure area. These should be dated when opened and discarded according to protocols, in compliance with nationally accepted guidelines, such as those published by the Centers for Disease Control and Prevention.**
8. **Units should not re-use a syringe to enter a medication vial or solution, even with a new needle**
9. **Units should not use the same syringe to administer medications to multiple patients regardless of whether the needle is changed or an intervening length of IV tubing is used.**
10. **Units should dispose of used syringes and needles at the point of use in a sharps container that is closable, puncture-resistant, and leak proof.**
11. **Units should develop a clearly defined policy for the management of sharps and sharps-related injuries, including the reporting of blood and body fluid exposures. This should be in compliance with federal, state, and local guidelines.**
12. **Units should mainta in a log of sedation medications wasted between patients that can be used to reconcile used and wasted vials at the end of the day.**
13. **If tubes of lubricant are used for more than one examination, the unit should observe appropriate infection control habits and discard any tube that has potentially been contaminated.**
14. **Although the multiple-society guideline recommends using sterile water in the irrigation bottle, it is acceptable to use tap water because this has been shown to be safe. The rates of bacterial cultures are no different with the use of tap water versus sterile water, and neither has been associated with clinical infections.**
15. **Units should follow federal and state requirements for the protection of healthcare personnel from exposure to blood-borne pathogens.**

Recommendations for safe handling of potentially contaminated equipment or surfaces

Environmental cleaning of surfaces with an appropriate Environmental Protection Agency–labeled disinfectant is mandatory, especially for surfaces that are most likely to become contaminated with pathogens, such as those in close proximity to the patient (eg, side rails) and other frequently touched surfaces in the unit.

Facility policies and procedures should address prompt and appropriate cleaning and decontamination of spills of blood or other potentially infectious material Units should:

1. **Maintain material safety data sheets for all chemicals used for cleaning and dis infection. These sheets Should detail the safe and proper use and emergency protocol for a chemical. Material safety data sheets should be used for training staff on each chemical's safe use.**
2. **Follow the manufacturer's directions for surface disinfection of patient care items**
   -Appropriate contact time of disinfectant to achieve germicidal kill should be followed.
   -Alcohol should not be used to clean environmental surfaces.
3. **Properly clean and disinfect surfaces that are frequently touched by personnel or dirty equipment in the endoscopic procedure area at the beginning of the day, between cases, and during terminal cleansing. Frequently-touched surfaces may include endoscopy, keyboards and video monitors and consoles**

Recommendations for terminal cleansing

Terminal cleansing involves the cleaning of surfaces to physically remove soil and biofilm, followed by proper disinfection. Typically, this requires use of 2 distinct agents because chemical disinfectants are not effective at cleansing, and cleansing agents are not effective at disinfecting surfaces.

1. **The unit should have a terminal cleansing plan that includes methods and chemical agents for cleansing and disinfecting the procedural space at the end of the day.**
2. **Agents for terminal cleansing should have efficacy in spore removal, which may differ from requirements for agents used in sterile operating rooms.**
3. **Before the first case of the day, staff should verify that all procedural and recovery areas have been properly cleansed.**
4. **A training and competency assessment program should be in place for staff members who are involved in terminal cleansing to ensure proper and safe handling and use of the chemicals**

Staffing preparation

Recommendations for preprocedure staffing

1. **Staffing models in the preprocedure area should support activities required to prepare patients for endoscopy.**
2. **The ratio of RNs to patients in preprocedure care is variable depending on the complexity of the patient mix.**

Recommendations for intraprocedure staffing based on level of sedation

1. **No sedation, one assistant (registered nurse [RN], licensed practical nurse [LPN], or unlicensed assistive personnel [UAP]) other than the physician performing the procedure should be present to assist with the technical aspects of the procedure.**
2. **Moderate sedation (also known as conscious sedation)**
   Sedation should be directed by a physician who is credentialed and privileged to do so. Moderate sedation can be administered by an RN. During the period in which the patient is sedated, the RN must monitor the patient for vital sign changes, hypoxe mia, and comfort.

The RN may assist with minor, interruptible tasks. In the event that more intense technical assistance is required, a second assistant (RN, LPN, or UAP) should be available to join the care team for the technical aspects of the procedure.

3. **Deep sedation, Most institutions require that deep sedation be administered by an anesthesia professional such as an anesthesiologist, certified registered nurse anesthe tist (CRNA), or anesthesiologist assistant who is credentialed and privileged to do so. In this situation, the anesthesia provider should be responsible for adminis-tering sedation and monitoring the patient. A second staff person (RN, LPN, or UAP) is required to assist with technical aspects of the procedure.**

Recommendations for postprocedure staffing

1. **An RN is required to monitor patients who have received sedation until the patient is stabilized and to assess for adverse events related to the endoscopic procedure.**
2. **Once the patient is stable, postprocedure activities such as providing food or drinks and assistance in changing clothes can be performed by an RN, LPN, or UAP.**
3. **The ratio of RNs to patients in the postprocedure setting is variable depending on the complexity of the patient mix**

Recommendations for training

1. **Sedation,**

   Sedation should be administered by an RN under the supervision of the endoscopist who is credentialed and privileged to do so or by anesthesia personnel (physician or CRNA) who are credentialed and privileged to do so. These individuals should be specifically trained in endoscopic sedation, including the modes of action and adverse events of the sedative agents being used. This training should be documented. The staff administering sedation must have the knowledge and skills to recognize when the sedation level becomes deeper than planned and to manage and support patients' cardiopulmonary responses to sedation accordingly. On verification of the RN's trai-ning, the unit should document the privileging of the RN to provide moderate seda tion under the direct supervision of a physician. LPNs and U APs are not qualified to administer sedation.
2. **Technical assistance,**

   Technical assistance can be provided by a variety of staff members, including UAPs, LPNs, RNs, and GI technicians. Training in the use of endoscopic equipment, access-ories, and ancillary equipment should be documented and include an objective assessment of initial competence and annual competency testing thereafter to ensure and document that skills are maintained.
3. **Basic and advanced cardiac life supportdAll staff with clinical responsibilities must have basic life support certification. At least one individual with advanced cardiac life support certification must be present in the unit when patients are present.**
4. **A written policy on staff training along with the type and frequency of core competency assessment should be documented**

Recommendations for the sedation-related environment

1. **Units should comply with applicable federal and state laws regarding licensure and/or certification of all staff involved in the administration and moni-toring of sedation and document training and competencies.**
2. **Established discharge criteria should be attained before discharge from the endo scopy unit. Patients who received IV sedation during their endoscopic procedure should be discharged in the presence of a responsible individual. A written policy on discharge requirements should be documented.**

3. An agreement should exist between the unit and a hospital facility for the transfer of patients who require escalation of care. A written transfer agreement should be documented.
4. A focused history and physical examination, including the patient's current medications and ASA classification, should be completed before the start of the procedure

Recommendations for sedation-related equipment

1. All sedation-related equipment, before initial use and then at intervals dictated by the manufacturer's guidelines, should be examined and verified to be in proper working order by a qualified biotechnician.
2. Oxygen, suction for the mouth, and electronic equipment that can monitor and display pulse, blood pressure, oxygen saturation, and continuous electrocardiographic rhythm assessment should be available in the procedure room. A written policy for equipment checks and maintenance should be in place. A log to monitor compliance should be maintained

Recommendations for patient monitoring

1. All patients undergoing endoscopy should be monitored, the frequency of which depends on procedural and patient factors (eg, type of sedation, duration and complexity of procedure, patient condition). At a minimum, monitoring should be performed before the procedure, after administration of sedatives, at regular intervals during the procedure, during initial recovery, and just before discharge.
2. Units should have procedures in place to rescue patients who are sedated deeper than intended.
3. When the target level is moderate sedation (also known as conscious sedation):
   - The individual assigned responsibility for patient monitoring may perform brief, interruptible tasks.
   - Minimal monitoring requirements include electronic assessment of blood pressure, respiratory rate , heart rate, and pulse oximetry combined with visual monitoring of the patient's level of consciousness and discomfort.
   - Currently, there are inadequate data to support the routine or required use of capnography during endoscopic procedures in adults when moderate sedation is the target.
4. When deep sedation is targeted:
   - The individual responsible for patient monitoring must be dedicated solely to that
   - task and may not perform any other function during the procedure.The use of capnography in EUS, ERCP, and colonoscopy to assess the adequacy of ventilation may reduce the incidence of hypoxemia and apnea, but its impact on the frequency of other sedation-related adverse events such as bradycardia and hypotension is unknown. As such, capnography may be considered for the perfor-mance of endoscopy under deep sedation.
   - Documentation of the clinical assessments and monitoring data during sedation and recovery is required.

Recommendations for medications

1. Written policies detailing the methods of drug storage, monitoring of drug inventory and expiration dates, and documentation of compliance with these policies are required.
2. There should be an individual qualified by training and licensure (such as a physician or pharmacist) who is directly responsible for overseeing medication usage in the unit.

3. **Medications should be securely stored under environmental conditions consistent with the manufacturer's instructions on the label. The use of single-dose vials for all sedative and analgesic medications is strongly recommended.**
4. **Controlled substances should be stored in a double locked cabinet, and a daily medication log compliant with state and federal regulations should be maintained. Disposal of unused narcotics and other controlled drugs should be witnessed by 2 individuals and documented.**
5. **Medications should be given only under the order of the supervising physician or anesthesia professionals when applicable.**
6. **Reversal agents for opioids and benzodiazepines should be readily available.**
7. **A written policy should be in place for the identification, documentation, and review of adverse drug reactions**

Recommendations for emergency management

1. **Appropriate pharmaceutical agents, oxygen, oral suction, laryngoscope, Ambu bag, and defibrillator should be readily available in the unit.**
2. **Units should train and periodically provide in-service education for staff in the use of equip ment for emergency management. Training and assessment of competency should be documented.**

Summary

The key strategies to maintain safety in the GI endoscopy unit

1- Each unit should have a designated flow for the safe physical movement of dirty endoscopes and other equipment.

2- Procedure rooms vary in size (Standard 36 inch doors, if they accommodate patient transport mechanisms, and room sizes 180 square feet are adequate and safe for endoscopy units -they do not use the same large equipment or number of staff as the operating room, with more complex procedures requiring greater space for more specialized equipment and, in some cases, additional staff.

3- Before starting an endoscopic procedure, the patient, staff, and performing physician should verify the correct patient and procedure to be performed.

4- A specific infection prevention plan must be implemented and directed by a qualified person.

Gloves and an impervious gown should be worn by staff engaged in direct patient care during the procedure. The unit should have a terminal cleansing plan that includes methods and chemical agents for cleansing and disinfecting the procedural space at the end of the day.

5- For patients undergoing routine endoscopy under moderate sedation, a single nurse is required in the room in addition to the performing physician. Complex procedures may require additional staff for efficiency but not necessarily for safety. At a minimum, patient monitoring should be performed before the procedure, after administration of sedatives, at regular intervals during the procedure, during initial recovery, and before discharge. For cases in which moderate sedation is the target, the individual responsible for patient monitoring may perform brief interruptible tasks.

Endoscope Disinfection[60]

Practice Guideline

- **Cleaning must always be performed prior to disinfection**
- **Disinfection should be carried out immediately after cleaning**
- **Alcohol must be properly stored as evaporation occurs rapidly on exposure to air - if the concentration is <70% it cannot be reliably used in the drying process.**
- **Drying should be performed after each processing cycle and not just before storage**
- **The disinfectant solution should be tested at least every day for efficacy using the manufacturer's test strip**
- **Brush reprocessing must follow the same procedures as for endoscope reprocessing**
- **Do not use tap water unless it is of drinking-water quality**
- **Cleaning is the critical step in endoscope reprocessing**
- **Any disinfection process can fail if cleaning is inadequate**
- **The value of simple soap and water should not be overlooked**
- **Careful maintenance is the key to effective and safe automatic reprocessing**
- **Accessories**

  Disposable accessories should not generally be used more than once. If they are to be used more than once due to limited resources, it is imperative that they are subjected to a complete cleaning, disinfection and sterilization cycle between each use. The steps involved are summarized as follows:

  dismantle →brush → flush→ dry
- **Consider whether legal implications allow re-use**
  - **If local regulations allow reuse, arrange for reprocessing with optimal efficacy**
    - **Consider the implications for manufacturer guarantees**

Step	General recommendations
precleaning	Preclean immediately
cleaning	Always perform leak testing and block testing before immersing the endoscope in a detergent or soap solution, as this may help prevent expensive repairs.
Later Rinsing	Always rinse between cleaning and disinfection
disinfection	• Always immerse the endoscope and valves in a disinfectant solution of proven efficacy • Always irrigate all channels with a syring until air is eliminated, to avoid dead spaces. • Always observe the manufacture's recommendations regarding the minimum contact times and correct temperature for the disinfection solution. • Always observe the manufurer's recommendationsregarding compressed air values. • Always remove the disinfection solution by flushing air before rinsing. • Always determine whether the disinfection solution is still effective by testing it with test trip provided by the manufurer.
Final Rinsing	• Always discard the rinse water after each use to avoid concentration of the disinfactant and thus damage to the mucosa. • Never use the same container for the first and final rinsing.
Drying	Always dry the endoscope properly before storage to prevent microorganism growth in the endoscope channels.
Storage	Never store in a transport container.

Table 1: Endoscope processing: general principles applying to all levels of resources Step General

Guidelines for the Management of Dyspepsia[2]

DEFINITIONS

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Discomfort is defined as a subjective negative feeling that is non painful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastro-esophageal reflux disease (GERD) until proven otherwise

Recommendation 1

Dyspeptic patients more than 55 yr old, or those with alarm features (bleeding, anemia, early satiety, unexplained weight loss (>10% body weight), progressive dysphagia, odyn ophagia, persistent vomiting, a family history of gastrointestinal cancer, previous esoph agogastric malignancy, previous documented peptic ulcer, lymphadenopathy, or an abdominal mass) should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract disease.

Recommendation2:

In patients aged 55 yr or younger with no alarm features, the clinician may consider two approximately equivalent management options:

(i) Test and treat for H. pylori using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve or

(ii) An empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk.

The test-and-treat option is preferable in populations with a moderate to high prevalence of H. pylori infection (≥10%), whereas the empirical PPI strategy is preferable in low prevalence situations. Some anxious patients may need the reassurance afforded by endoscopy. On the other hand, repeat EGD is not recommended once a firm diagnosis of functional dyspepsia has been made, unless completely new symptoms or alarm features develop. Repeat EGD is otherwise unlikely to ever be cost-effective.

The risk of malignancy increases with age and therefore empirical therapy is not currently recommended in individuals over 55 yr of age who develop new dyspeptic symptoms.

Recommendation3:

In H. pylori-negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for 4–8 wk is recommended first-line therapy, If initial acid suppression fails after 2–4 wk, it is reasonable to step up therapy, although this is based on expert opinion only; this may require changing drug class or dosing.

In patients who do respond to initial therapy, it is recommended that treatment be stopped after 4–8 wk and if symptoms recur, another course of the same treatment is justified. There are no data on long-term self-directed therapy in this condition, although this may be worth considering in some patients.

Recommendation4:

The management of endoscopy-proven functional dyspepsia is particularly challenging when initial antisecretory therapy and H. pylori eradication fails. Patients who fail to respond to simple measures need to have their diagnosis reconsidered. Dietary therapy has no established efficacy but may help some individuals. There are very limited data to support the use of herbal preparations, simethicone, and low-dose tricyclic antidepressants in functional dyspepsia. Bismuth, sucralfate, and antispasmodics are not established to be of benefit over placebo in functional dyspepsia. Hypnotherapy, psychotherapy, and cognitive-behavioral therapy are supported by limited studies but cannot be generally recommended at the present time.

In patients with resistant symptoms, it is worth reevaluating the diagnosis

Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease [1]

Gastroesophageal reflux disease (GERD) is arguably the most common disease encountered by the gastroenterologist. It is equally likely that the primary care providers will find that complaints related to reflux disease constitute a large proportion of their practice. The following guideline will provide an overview of GERD and its presentation, and recommendations for the approach to diagnosis and management of this common and important disease.

Establishing the Diagnosis of GERD :

Recommendations

1. **A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation . Empiric medical therapy with a PPI is recommended in this setting.**
2. **Patients with non-cardiac chest pain suspected due to GERD should have diagnostic evaluation before institution of therapy. A cardiac cause should be excluded in patients with chest pain before the commencement of a gastrointestinal evaluation.**
3. **Barium radiographs should not be performed to diagnose GERD.**
4. **Upper endoscopy is not required in the presence of typical GERD symptoms . Endo scopy is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications. Repeat endoscopy is not indicated in patients without Barrett's esophagus in the absence of new symptoms.**
5. **Routine biopsies from the distal esophagus are not recommended specifically to diagnose GERD.**
6. **Esophageal manometry is recommended for preoperative evaluation, but has no role in the diagnosis of GERD.**
7. **Ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy In patients with NERD, as part of the evaluation of patients refractory to PPI therapy, and in situations when the diagnosis of GERD is in question. Ambulatory reflux monitoring is the only test that can assess reflux symptom association.**
8. **Ambulatory reflux monitoring is not required in the presence of short or long - segment Barrett's esophagus to establish a diagnosis of GERD.**
9. **Screening for *Helicobacter pylori* infection is not recommended in GERD. Eradica tion of *H. pylori* infection is not routinely required as part of antireflux therapy.**

Management of GERD

Recommendations

1. **Weight loss is recommended for GERD patients who are overweight or have had recent weight gain.**
2. **Head of bed elevation and avoidance of meals 2 – 3 h before bedtime should be recommended for patients with nocturnal GERD.**
3. **Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and / or spicy foods) is not recommended in the treatment of GERD.**
4. **An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs.**
5. **Traditional delayed release PPIs should be administered 30 –60 min before meal for maximal pH control. Newer PPIs may offer dosing flexibility relative to meal timing.**
6. **PPI therapy should be initiated at once a day dosing, before the first meal of the day. For patients with partial response to once daily therapy, tailored therapy with adjust ment of dose timing and/or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance.**
7. **Non-responders to PPI should be referred for evaluation.**

8. **In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief.**
9. **Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications includ ing erosive esophagitis and Barrett's esophagus. For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy.**
10. **H 2 -receptor antagonist therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. Bedtime H2 RA thera py can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed but may be associated with the development of tachy phlaxis after several weeks of usage.**
11. **Therapy for GERD other than acid suppression, including prokinetic therapy and / or baclofen, should not be used in GERD patients without diagnostic evaluation.**
12. **There is no role for sucralfate in the non-pregnant GERD patient.**
13. **PPIs are safe in pregnant patients if clinically indicated.**

SURGICAL OPTIONS FOR GERD

Recommendations

1. **Surgical therapy is a treatment option for long-term therapy in GERD patients.**
2. **Surgical therapy is generally not recommended in patients who do not respond to PPI therapy.**
3. **Preoperative ambulatory pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus.**
4. **Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon.**
5. **Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients**
6. **The usage of current endoscopic therapy or transoral incision less fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.**

Potential Risks associated with PPI's

Recommendations

1. **Switching PPIs can be considered in the setting of side effects.**
2. **Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.**
3. **PPI therapy can be a risk factor for Clostridium difficile infection and should be used with care in patients at risk.**
4. **Short-term PPI usage may increase the risk of community acquired pneumonia. The risk does not appear elevated in long-term users.**
5. **PPI therapy does not need to be altered in concomitant clopidogrel users as clinical data does not support an increased risk for adverse cardiovascular events.**

Extraesophageal Presentations of GERD: Asthma, Chronic cough, and Laryngitis:

Recommendations

1. **GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non- GERD causes should be under-taken in all of these patients.**
2. **A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings.**

3. **A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD.**
4. **Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis.**
5. **Reflux monitoring should be considered before a PPI trial in patients with extra esophageal symptoms who do not have typical symptoms of GERD.**
6. **Non-responders to a PPI trial should be considered for further diagnostic testing, and are addressed in the refractory GERD.**
7. **Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI.**

GERD Refractory to Treatment with PPIs

Recommendations

1. **The first step in management of refractory GERD is optimization of PPI therapy.**
2. **Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies.**
3. **In patients in whom extraesophageal symptoms of GERD persist despite PPI optimization, assessment for other etiologies should be pursued through concomi-tant evaluation by ENT, pulmonary, and allergy specialists.**
4. **Patients with refractory GERD and negative evaluation by endoscopy (typical symptoms) or evaluation by ENT, pulmonary and allergy specialists (extra esophageal symptoms), should undergo ambulatory reflux monitoring.**
5. **Reflux monitoring *off* medication can be performed by any available modality (pH or impedance-pH). Testing *on* medication should be performed with impedance-pH monitoring in order to enable measurement of non-acid reflux.**
6. **Refractory patients with objective evidence of ongoing reflux as the cause of symp toms should be considered for additional anti reflux therapies that may include surgery or TLESR inhibitors.**

Patients with negative testing are unlikely to have GERD and PPI therapy should be discontinued.

WHAT ARE THE COMPLICATIONS ASSOCIATED WITH GERD?

Recommendations

1. **The Los Angeles (LA) classification system should be used when describing the endoscopic appearance of erosive esophagitis. Patients with LA Grade A esophagitis should undergo further testing to confirm the presence of GERD.**
2. **Repeat endoscopy should be performed in patients with severe ERD after a course of antisecretory therapy to exclude underlying Barrett 's esophagus.**
3. **Continuous PPI therapy is recommended following peptic stricture dilation to improve dysphagia and reduce the need for repeated dilations.**
4. **Injection of intra lesional corticosteroids can be used in refractory, complex strictures due to GERD.**
5. **Treatment with a PPI is suggested following dilation in patients with lower esophageal ring (Schatzki) rings.**
6. **Screening for Barrett 's esophagus should be considered in patients with GERD who are at high risk based on epidemiologic profile.**
7. **Symptoms in patients with Barrett's esophagus can be treated in a similar fashion to patients with GERD who do not have Barrett's esophagus.**
8. **Patients with Barrett 's esophagus found at endoscopy should undergo periodic surveillance according to guidelines.**

Diagnosis, Surveillance and Therapy of Barrett's Esophagus [3]

SIGNIFICANCE OF BARRETT'S ESOPHAGUS

Barrett's esophagus is believed to be the major risk factor for the development of esophageal adenocarcinoma. The incidence of adenocarcinoma of the esophagus continues to rise rapidly. The rate of rise is alarming and is widespread in Western countries.

DEFINITION OF BARRETT'S ESOPHAGUS

Barrett's esophagus is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus.

The grade of dysplasia determines the appropriate surveillance interval. Any grade of dysplasia by histology should be confirmed by an expert pathologist. Screening for Barrett's esophagus remains controversial because of the lack of documented impact on mortality from EAC. The large number of patients that lack reflux symptoms but have Barrett's esophagus provides a diagnosis challenge. The highest yield for Barrett's is in older (age 50 or more) Caucasian males with longstanding heartburn.

THE MANAGEMENT OF DYSPLASIA : Recommendations:

1- **Low grade dysplasia requires expert pathologist confirmation and more frequent endoscopy and biopsy. High grade dysplasia(HGD) also requires confirmation by an expert pathologist and represents a threshold for intervention. A more intensive biopsy protocol is necessary to exclude the presence of concomitant adeno carcinoma.**

2- **Any mucosal irregularity, such as nodularity or ulcer, is best assessed with endo scopic resection for a more extensive histologic evaluation and exclusion of cancer. Management of patients with high grade dysplasia is dependent on local expertise,**

3- **both endoscopic and surgical and the patient's age, comorbidity and preferences. Esophagectomy is no longer the necessary treatment response to HGD.**

4- **high-grade dysplasia the spacing of four quadrant biopsies should be every 1 cm because larger intervals (2 centimeter) lead to a 50% greater miss rates of cancer. In addition, any nodular areas within the Barrett's segment, especially if high-grade dysplasia has previously been found, should undergo endoscopic resection to obtain adequate tissue for more accurate diagnosis.**

5- **Nodularity has been demonstrated to be associated with a much higher frequency of malignancy and with spread to regional lymph nodes.**

6- **Despite careful endoscopic surveillance, occult malignancy may still be present. Lacking mucosal abnormalities, these occult lesions are likely intramucosal carcin oma without lymph node involvement. The use of large capacity forceps has been advocated, especially in the setting of high-grade dysplasia, although direct compari sons to standard biopsy forceps have not been conducted in terms of measuring changes in patient outcome. The endoscopic technique to be used to maximize tissue yield is a turn-and-suck technique, which should bring the mucosa in direct apposition to the biopsy forceps.**

7- **Endoscopic brush cytology has also been used during surveillance of Barrett's esophagus in the hope that increased ability to sample the cells might lead to better diagnoses. Studies are conflicting as to how much additional information can be obtained from cytological examination. However, the use of new genetic markers, such as fluorescent in situ hybridization may be promising in increasing the clinical utility of brush cytology.**

8- **Mucosal ablation therapy has also been advocated to decrease the risk of develo- pment of cancer within Barrett's esophagus. This is always done in conjunction with acid suppression, which appears to be a key element. The degree of acid suppr ession has not been established. However, all Photodynamic therapy has been the only therapy significantly decrease cancer risk in Barrett's esophagus Thermal**

ablation techniques were originally utilized for the treatment of Barrett's esophagus lacking dysplasia. Argon plasma coagulation at high power outputs (80watts) has been shown in case series to be able to treat high-grade dysplasia and even small cancers, although long-term followup is not available. Multipolar coagulation has been used to treat primarily low-grade dysplasia and nondysplastic Barrett's. Success rates of ablating the entire Barrett's mucosa usually are in the 80–90% range with multiple applications of the devices. Most of the thermal devices have been utilized in relatively small cohorts of patients followed over short periods of time.

9- **Surgical resection (esophagectomy) has been a standard of therapy for Barrett's esophagus with high grade dysplasia based upon concerns that endoscopic surveillance protocols**

10- **For patients with Barrett's esophagus, the goal of pharmacologic acid suppression with agents such as the proton pump inhibitors is to control reflux symptoms.**

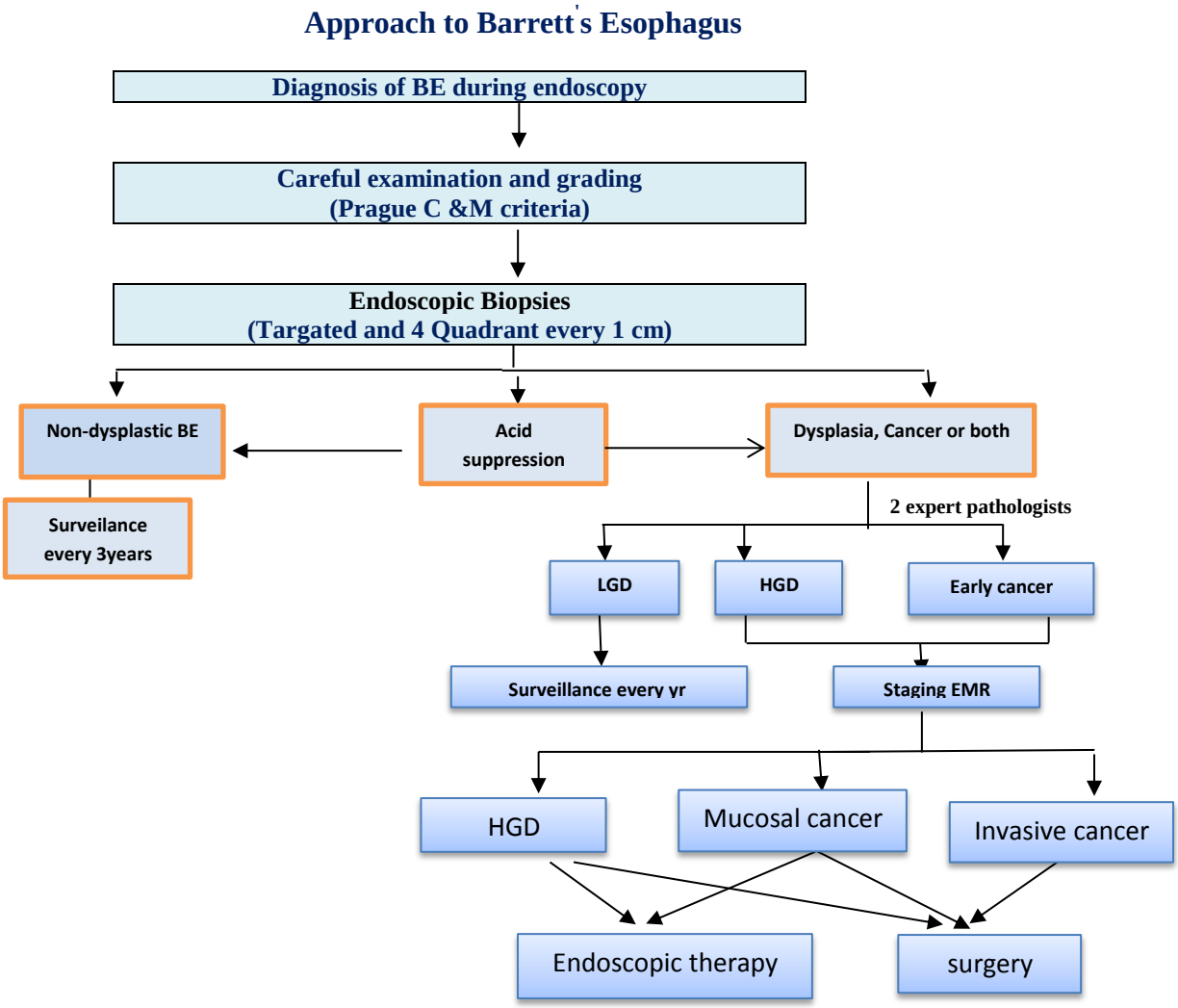


Figure 1: Modified Sharma P. NEJM For Barrett's Esophagus

Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE) [32]

AGA Institute Definition of EOE:
A primary disorder of esophagus characterized by UGI symptoms,esophageal biopsy ≥ 15 eos/hpf, and the absence of pathologic GERD

Clinical guideline

Recommendations for the diagnosis:

1. **esophageal eosinophilia, the finding of eosinophils in the squamous epithelium of the esophagus, is abnormal and the underlying cause should be identified.**
2. **EOE is clinical pathologic disorder diagnosed by clinicians(Esophageal biopsy are required to diagnose EoE. 2-4 biopsies should be obtained from both proximal and distal esophagus). taking in to consideration both clinical and pathologic information with out of either of these parameters interpreted in isolation, and defined by the following criteria:**

- **Symptoms related to esophageal dysfunction**
- **Eosinophil predominant inflammation on eosinophil body, characteristically consisting of a peak value of ≥ 15 eosinophils per high power field (eos/ hpf)**
- **Mucosal eosinophilia is isolated to the esophagus and persists after a PPI trial.**
- **Secondary causes of esophageal eosinophilia excluded(Eosinophilic gastrointestinal diseases, PPI responsive esophageal eosinophilia, Celiac disease, Crohn's disease, infection, Hyper-eosinophilic syndrome, Achalasia, Drug hypersensitivity, Vasculitis, Pemphigus, Connective tissue diseases, Graft vs. host disease)**
- **A response to treatment (dietary elimination: topical corticosteroids) support but it is not required for diagnosis.**

Recommendations for treatment of EoE:

1- **The endpoints therapy of EoE include improvements in clinical symptoms and esophageal eosinophilic inflammation.**
2- **Topical steroids(i.e., fluticasone or budenoside, swallowed rather than inhaled, for an initial duration of 8 weeks) are the first-line pharmacologic therapy for treatment of EoE.**
3- **Prednisone may be useful to treat EoE if topical steroids are not effective or in patients who require rapid improvement in symptoms.**
4- **Dietary elimination can be considered as an initial therapy in the treatment of EoE both children and adults.**
5- **Gastroenterlogists should consider consultation with an allergist to identify and treat extraesophageal atopic conditions, assist with treatment of EoE, and to help guide elemental and elimination diets.**
6- **Esophageal dilation, approached conservatively may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy.**

A Guideline on the Management of *Helicobacter pylori* Infection [14]

Helicobacter pylori (H. pylori) remains a prevalent, worldwide, chronic infection. Though the prevalence of this infection appears to be decreasing in many parts of the world, H. pylori remains an important factor linked to the development of peptic ulcer disease, gastric malignancy and dyspeptic symptoms.

Diagnosis of H. Pylori Infection

Recommendations

1- **Testing for H. pylori infection is indicated in patients with active peptic ulcer disease, a past history of documented peptic ulcer, or gastric MALT lymphoma.**
2- **The test-and-treat strategy for H. pylori infection is a proven management strategy for patients with uninvestigated dyspepsia who are under the age of 55 yr and have no "alarm features" (bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer, previous esophagogastric malignancy).**
3- **There is evidence to suggest that a small but significant subgroup of patients with functional dyspepsia will experience clinical benefit following H. pylori eradication.**
4- **There is no clear evidence to support that eradicating H. pylori consistently worsens or improves GERD symptoms. Treatment of H. pylori should not be withheld related to concerns of creating or worsening GERD.**
5- **H. pylori and NSAIDs are independent risk factors for the development of PUD. Therefore, regardless of whether or not a patient is taking an NSAID, all patients with a peptic ulcer should be tested and when infected, treated for H. pylori.**
6- **The available data support an association between H. pylori infection and iron deficiency but do not prove cause and effect.**
7- **Though there is some evidence to suggest that curing H. pylori may prevent progression of intestinal metaplasia to gastric adenocarcinoma, there is no defini tive population based data to suggest that H. pylori eradication reduces the incid ence of gastric adenocarcinoma. Pursuing H. pylori in patients at increased risk for gastric cancer should be individualized taking into consideration comorbid illness, which might have bearing on the benefits offered by treatment, and patient prefer ences.**
8- **Testing for H. pylori should only be performed if the clinician plans to offer treatment for positive results.**
9- **Deciding which test to use in which situation relies heavily upon whether a patient requires evaluation with upper endoscopy and an understanding of the strengths, weaknesses, and costs of the individual tests.**
10- **In patients who have not been on a PPI within 1–2 wk or an antibiotic or bismuth within 4 wk of endoscopy, the rapid urease test (RUT) provides an accurate, inex pensive means of identifying H. pylori.**
11- **For patients who have been taking a PPI, antibiotics, or bismuth, endoscopic testing for H. pylori should include biopsies from the gastric body and antrum for histol ogy with or without rapid urease testing.**
12- **Though culture or polymerase chain reaction (PCR) are the primary means by which antibiotic sensitivities can be determined, neither is widely available for clini cal use in the United States and therefore, cannot be routinely recommended.**
13- **Antibody testing is inexpensive and widely available but poor PPV in populations with a low prevalence of H. pylori infection limits its usefulness in clinical practice.**
14- **The UBTs and fecal antigen tests provide reliable means of identifying active H. pylori infection before antibiotic therapy.**
15- **The UBT is the most reliable non-endoscopic test to document eradication of H. pylori infection.**

16- **The monclonal fecal antigen test provides another non-endoscopic means of establishing H.pylori cure after antibiotic treatment.**

17- **Testing to prove H. pylori eradication appears to be most accurate if performed at least 4 wk after the completion of antibiotic therapy.**

18- **Testing to Prove Eradication After Antibiotic Therapy:**

- **Any patient with an H. pylori-associated ulcer.**
- **Individuals with persistent dyspeptic symptoms despite the test-and-treat strategy,**
- **those with H. pylori-associated MALT lymphoma and Individuals who have under gone resection of early gastric Cancer.**

Treatment of H. Pylori Infection

Primary Treatment of H. pylori Infection:The recommended primary therapies for H. pylori infection include: a PPI, clarithromycin, and amoxicillin, or metron idazole (clarithromycin-based triple therapy) for 14 days or a PPI or H2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days.

.Sequential therapy consisting of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days may provide an alternative to clarithromycin-based triple or bismuth quadruple therapy.

•Salvage Therapy for Persistent H. pylori Infection

1. **In patients with persistent H. pylori infection, every effort should be made to avoid antibiotics that have been previously taken by the patient.**
2. **Bismuth-based quadruple therapy for 7–14 days is an accepted salvage therapy.**
3. **Levofloxacin-based triple therapy for 10 days is another option in patients with persistent infection, which requires validation.**

What Is New ?

- **A subset of patients with functional dyspepsia derives benefit from H. pylori eradication.**
- **Emerging evidence suggests an association between H. pylori and unexplained iron deficiency anemia.**
- **In populations with a low pretest probability of H. pylori infection, nonendoscopic tests such as the urea breath test and fecal antigen test offer superior positive predictive value compared with antibody tests.**
- **Eradication rates with a PPI, clarithromycin, and amoxicillin are decreasing worldwide. Fourteen-day courses of therapy are more effective than seven-days treatment regimens.**
- **Newer treatments such as sequential therapy require validation in the United States before they can be recommended as a standard first-line therapy.**
- **A PPI, levofloxacin, and amoxicillin for 10 days appear to be more effective and better tolerated than a PPI. bismuth, tetracycline, and metronidazole in patients with persistent H. pylori infection but require validation.**

Management of Diarrhea[44]

- **Can be acute or chronic diarrhea**
- **Acute diarrhea is less than four weeks duration, usually infectious etiology (<1week more likely viral or bacterial, 1-4weeks more likely protozoa), some-times the start of chronic diarrheal disorder.**
- **Traveler's Diarrhea: might cause IBS with diarrhea, causative organisms commo nly E.coli, Shigella, Salmonella, and Compylobacter—effectively treated with quino lones, Rifaxamin.**
- **Chronic diarrhea: may be defined as the abnormal passage of three or more loose or liquid stools per day for more than four weeks and/or a daily stool weight greater than 200 g/day. It might be watery(osmotic or secretory types),or inflammatory or fatty diarrhea**
- **Characteristics of watery diarrhea are: fluid stools, typically pourable, no blood, pus or fat evident, little or no fever. Can be characterized as osmotic or secretory by fecal electrolyte analysis and calculation of fecal osmotic gab (Electrolyte content =2x ([Na]+[K]), Luminal osmolality = 290 mosm/kg)**
- **Causes of Osmotic Diarrhea either carbohydrate / sugar alcohol Malabsorption (Lactose in lactase deficient, Sorbitol in mannitol ingestion, Generalized Malabso rption) or poorly absorbed ions (Magnesium, Phosphate, Sulfate).**
- **Causes of secretory diarrhea (Congenital syndromes, Bacterial toxins, Ileal bile acid Malabsorption, Inflammatory bowel disease, Vasculitis, Drugs and poisons, Stimu lant laxatives, Disordered regulation, Endocrine diarrhea, ther tumors, Idio pathic secretory diarrhea)**
- **Characteristics of inflammatory diarrhea: Blood and pus usually present, Fecal occult blood test and fecal leukocytes are positive, stool weight is moderate, patient may complain of tenesmus, Fever may be present. And causes of it might Inflammatory bowel disease, or Invasive infections, or Ischemia, or Radiation enteritis, or Neoplasia.**
- **Characteristics of Fatty diarrhea: Gross steatorrhea may be present, Sudan stain or quantitative analysis positive, Oil may be seen in commode, the patient may complain of weight loss & gaseousness. its causes is either Malabsorption (muco-sal disease, short bowel syndrome, post resection diarrhea, small bowel bacterial overgrowth, or mesenteric ischemia), or Maldigestion (pancreatic exocrine insu-fficiency or inadequate luminal bile acid concentration).**
- **Management strategies:**

- **Test and treat: when you have a good idea of likely diagnosis and a definitive test is available.**
- **Empiric treatment: when you think you are dealing with functional or self-limited problems with no good test and no alarm findings are present.**
- **Categorize, test and treat: when you are unsure of the diagnosis.**

- **Categorize, test and treat:**

- **When the pretest probability of a specific diagnosis is low, appropriately classifying diarrhea by duration and stool characteristics can lead to more expeditious evaluation and targeted management.**
- **Algorithm approach feasible.**

- **Difficult diagnoses: like in Fecal incontinence, Drug-induced diarrhea, surrep-titious laxative ingestion, microscopic colitis syndrome, small bowel bacterial**

overgrowth, carbohydrate Malabsorption, pancreatic exocrine insufficiency, Bile acid diarrhea, Endocrine tumor, neuropathy, idiopathic secretory diarrhea.

Recommendation for endoscopy in the management of patients with diarrhea:

1- **Stool and laboratory tests should be the initial step for the evaluation of clinical scenarios suggestive of infectious diarrhea.**
2- **In patients with chronic unexplained diarrhea, we suggest colonoscopy with random biopsies of the right and left side of the colon, sigmoidoscopy is an alterna tive option, although this may miss right sided organic disease.**
3- **We recommend intubation of the terminal ileum during colonoscopy for patient undergoing evaluation of chronic diarrhea. There are insufficient data to determine whether the biopsy of endoscopically normal-appearing terminal ileum should be routinely performed, but the yield of this is likely low.**
4- **We recommend EGD with small-bowel biopsy in patients with chronic diarrhea or suspected Malabsorption and inconclusive evaluation after colonoscopy with biopsy and in patient with positive celiac serology.**
5- **We recommend obtaining a minimum 4 duodenal biopsy specimens for evalua-tion of suspected celiac disease.**
6- **Enteroscopy is not recommended for the routine evaluation of chronic diarrhea but may be useful for evaluation of small-bowel disease when other inves-tigations are not diagnostic.**
7- **VCE is not recommended for routine evaluation of chronic diarrhea.**
8- **In patients with HIV and diarrhea, we suggest either flexible sigmoidoscopy or colonoscopy if laboratory evaluation is nondiagnostic.**
9- **In the absence of a diagnostic on flexible sigmoidoscopy, we recommend a full colonoscopy with biopsy and/or EGD with biopsy for HIV patients with persistent diarrhea.**
10- **In patient with suspected Graft –versus- host disease (GVHD) and diarrhea we suggest flexible sigmoido-scopy with distal colon biopsies as the initial endo-scopic evaluation. In the event of negative colonic histology findings or when upper GI symptoms predominate, we recommend an EGD with biopsies.**

Malabsorption

Maldigestion: impaired breakdown of nutrients(carbohydrates, protein, fat) to absorbable split-products (mono-, di-, or oligodisaccharides; aminoacids; oligopeptides; fatty acids; monoglycerides)

Malabsorption: defective mucosal uptake and transport of adequately digested nutrients including vitamines and trace elements.even this term is widely used as the global term for all aspects of impairment of digestion and absorption.

Diagnostic approach:

1. **Consider family history**
2. **Note any evidence of malabsorption on physical examination**
3. **Look at stool for volume, appearance, admixtures of mucus, blood, parasites**
4. **Draw blood for screening laboratory tests**
   Tests for endomysial &tissue transglutaminase antibodies (celiac disease), Giardia Lamblia enteropatho-genic bacteria, parasites and ova, H2-breath tests for carbohydrate malabsorption .
5. **Abdominal ultrasound (gallbladder; liver; pancrease; intestinal wall; adenopathy; etc.)**

6. **Oesophago-gastro-duodenoscopy including biopsies from stomach (autoimmune gastritis? H. pylori?) and duodenum (celiac disease? inflammatory bowel disease?)Especially duodeno-jejunal involvement is associated with malabsorption.**
7. **Ileocolonoscopy including biopsies of colon and ileum (ileal disease? bile salts low? it B12 low?)**
8. **If pancreatic disease with secretory insufficiency is suspected, consider:**

- **tests for secretory function e.g. elastase or chymo-trypsin in stool**
- **Sectretin-pancreozymin-test**
- **Computed tomography; magnetic resonance imaging of pancreatic duct –system or ERCP, When in doubt a therapeutic trial with pancreatic enzyme supplementation therapy may be considered.**

9. **If small bowel disease is still suspected, consider:**

Schilling test (vit. B12), Glucose H2 test (bacterial overgrowth),a1- antitrypsin Clearance (intestinal protein loss), small bowel x-ray (fistula , diverticula , blind loops , Short bowel, etc.) , Angiography of celiac and mesenteric arteries (ischemic bowel damage)

Important Practical investigatory points for with chronic diarrhea:

Stool collection

-Random fat stain

-Quantitative collection-24 hours: for weight, Fat, Electrolyte, Laxative screen

24-Hour Stool Fat

- **Eating 100gms of fat for 3days prior**
- **Lab won't test electolyte on formed or soft stools.**
- **Normal weight,200-300grams(higher end with high CHO diet)**
- **Normal fat, 5-7grams/24 hours**
- **Qualitative fat: 0-19%**
- **Large-volume scretory diarrhea can drag fat-can see 14 grams/24 hours.**

Elevated Fecal Fat causes:

- **Mucosal as in celiac disease and croh'ns disease**
- **Luminal as in pancreatic insuffiency and Bile acid deficiency like in ileal resection, and also can occur in Rapid transit and in short bowel, where there are uncommon small intestinal disease diagnosed by biopsy like in collagenous sprue, Eosinophilic , whipple's, etc**

Bile acid diarrhea: bile acids cause colonic salt and water secretion and increased colonic motility,

- **secondary bile acid malabsorption can occur in ileal resection or disease like in croh'ns if the segment <100cm it leads to watery, if >100cm it will lead to malab sorption**
- **primary bile acid malabsorption(BAM) now called bile acid diarrhea (BAD) where hepatic bile acids impaired, accounted for 20-25% of IBS-D cases in recent study prospective study-most moderate to sever (Aziz et al. CGH 2015:13:1650).**

Secretory diarrhea: Stool Osmotic Gap: normally 290-2 (Na + K) , <50 in secretory, >125 in osmotic while >375 in contamination.

So if 24 hour stoo Na 119 and K 17, so osmotic gap, 290-2(119+ 17)= 3 thus it is secretory diarrhea (better calculated than measured osms)

We have to rule out infection by culture, mucosal lesion by celiac antibodies and biopsy (EGD&Colon Bx, abdominal CT scan), rule out Factitious, then rule out hormonal causes such as VIP, ZE (gastrin off PPI level, octerotide scan), Carcinoid (5HIAA level), Medullar Ca thyroid (calcitonin level

Diagnosis and Management of Celiac Disease[46]

Conditions in which CD might be suspected:

- **Symptomatic malabsorption Pulmonary hemosiderosis**
- **Diarrhea with weight loss**
- **Unexplained male or female infertility**
- **Chronic diarrhea with or without abdominal pain**
- **Dyspepsia**
- **Chronic iron deficiency and anemia**
- **Amenorrhea**
- **Metabolic bone disease and premature osteoporosis**
- **Chronic fatigue**
- **Postprandial bloating and gaseousness**
- **Apparent malabsorption of thyroid replacement medication**
- **Unexplained weight loss**
- **Epilepsy or ataxia**
- **Abnormal elevated liver enzymes**
- **Constipation**
- **Incidental discovery of villous atrophy endoscopically or histologically**
- **Recurrent abdominal pain**
- **Dermatitis herpetiformis**
- **Peripheral neuropathy**
- **Oral aphthous ulcers**
- **Growth failure**
- **Discolored teeth**

RECOMMENDATIONS

(1) Patients with symptoms, signs, or laboratory evidence suggestive of malabsor-ption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdo-minal pain, and bloating, should be tested for CD.

(2) Patients with symptoms, signs, or laboratory evidence for which CD is a treatable cause should be considered for testing for CD.

(3) Patients with a first-degree family member who has a confirmed diagnosis of CD should be tested if they show possible signs or symptoms or laboratory evidence of CD.

(4) Consider testing of asymptomatic relatives with a first degree family member who has a confirmed diagnosis of CD.

(5) CD should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found.

(6) Patients with Type I DM should be tested for CD if there are any digestive symptoms, or signs, or laboratoryevidence suggestive of CD.

(7) IgA anti-TTG antibody is the preferred single test for detection of CD in individuals over the age of 2 years.

(8) When there exists a high probability of CD where in the possibility of IgA deficiency is considered, total IgA should be measured. An alternative approach is to include both IgA and IgG-based testing, such as IgG DGPs, in these high-probability patients.

(9) In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed.

(10) If the suspicion of CD is high, intestinal biopsy should be pursued even if serolo-gies are negative.

(11) All diagnostic serologic testing should be done with patients on a gluten-containing diet.

(12) Antibodies directed against native gliadin are not recommended for the primary detection of CD.

(13) Combining several tests for CD in lieu of TTG IgA alone may marginally increase the sensitivity for CD but reduces specificity and therefore are not recommended in low-risk populations.

(14) When screening children younger than 2 years of age for CD, the IgA TTG test should be combinedwith DGPs (IgA and IgG).

(15) The confirmation of a diagnosis of CD should be based on a combination of findings from the medical history, physical examination, serology, and upper endoscopy with his tological analysis of multiple biopsies of the duodenum.

(16) Upper endoscopy with small-bowel biopsy is a critical component of the diagnostic evaluation for persons with suspected CD and is recommended to confirm the diagnosis.

(17) Multiple biopsies of the duodenum (one or two biopsies of the bulb and at least four biopsies of the distal duodenum) are recommended to confirm the diagnosis of CD.

(18) Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for CD and other causes should also be considered.

(19) HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD.

(20) HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations. Examples of such clinical situations include but are not limited to:

- **a. Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients**
- **b. Evaluation of patients on a GFD in whom no testing for CD was done before GFD**
- **c. Patients with discrepant celiac-specific serology and histology**
- **d. Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question.**
- **e. Patients with Down's syndrome.**

(21) Capsule endoscopy should not be used for initial diagnosis except for patients with Positive celiac-specific serology who are unwilling or unable to undergo upper endosc opy with biopsy.

(22) Capsule endoscopy should be considered for the evaluation of small-bowel mucosa in patients with complicated CD.

(23) Intestinal permeability tests, D-xylose, and small-bowel follow-through are neither specific nor sensitive and are not recommended for CD diagnosis.

(24) Stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD.

(25) Symptoms or symptom response to a GFD alone should not be used to diagnose CD, as these do not differentiate CD from non-celiac gluten sensitivity.

(26) A diagnosis of non-celiac gluten sensitivity should be considered only after CD has been excluded with appropriate testing.

(27) While standard diagnostic tests (specific serology and intestinal biopsy) have a high PPV for CD, they should not be relied upon to exclude CD in patients already adhering to a GFD.

(28) HLA-DQ2 / DQ8 genotyping should be used to try to exclude CD prior to embar-king on a formal gluten Challenge.

(29) CD should be differentiated from non-celiac gluten sensitivity in order to identify the risk for nutritional deficiency states, complications of CD, risk for CD and associated disorders in family members, and to influence the degree and duration of adherence to the GFD.

(30) Formal gluten challenge should be considered, where necessary, to diagnose or exclude CD in patients already adhering to a GFD.

(31) Despite the disadvantages of neither confirming nor excluding a diagnosis of CD, some patients will opt to continue on a strict GFD without undergoing formal gluten challenge;such patients should be managed in a similar fashion to those with known CD.

(32) People with CD should adhere to a GFD for life. A GFD entails strict avoidance of all products Containing the proteins from wheat, barley, and rye.

(33) While pure oats appear to be safely tolerated by the majority of people with CD, oats should be introduced into the diet with caution and patients should be monitored closely for evidence of adverse reaction.

(34) People with CD should be referred to a registered dietitian who is knowledgeable about CD in order to receive a thorough nutritional assessment and education on the GFD.

(35) People with newly diagnosed CD should undergo testing and treatment for micro nutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12.

(36) People with CD should be monitored regularly for residual or new symptoms, adherence to GFD, And assessment for complications. In children, special attent-ion to assure normal growth and development is recommended.

(37) Periodic medical follow-up should be performed by a health-care practitioner with knowledge of CD. Consultation with a dietitian should be offered if gluten contam-ination is suspected.

(38) Monitoring of adherence to GFD should be based on a combination of history and serology [IgA TTG or IgA (or IgG) DGP antibodies].

(39) Upper endoscopy with intestinal biopsies is recommended for monitoring in cases with lack of clinical response or relapse of symptoms despite a GFD.

(40) Monitoring of people with CD should include verification of normalization of laboratory abnormalities detected during initial laboratory investigation.

(41) Patients with non responsive celiac disease (NRCD) should be evaluated carefully to identify and treat the specific etiology in each patient.

(42) Early steps in the evaluation should include measurement of celiac serologies and a thorough review of the patient's diet by a dietitian who is experienced in CD management.

(43) Differentiation should be made between Type I and Type II refractory CD as this is important for management and prognosis.

(44) Treatment with medication, as an adjunct to the GFD, should be considered in refra ctory CD.

(45) Patients with RCD should be monitored closely and receive aggressive nutritional support, including parenteral nutrition whenever indicated.

Ulcerative Colitis Practice Guidelines in Adults [5,18]

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by diffuse mucosal inflammation limited to the colon. It involves the rectum in about 95 % of cases and may extend proximally in a symmetrical, circumferential, and uninterrupted pattern to involve parts or all of the large intestine. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus. The clinical course is marked by exacerbations and remissions, which may occur spontaneously or in response to treatment changes or intercurrent illnesses. UC affects approximately 8 – 12 per 100,000 population per year .

Etiology of severe and acute colitis must identified: infectious gastroenteritis(C. Difficile, CMVin patients on striods), Narcotics, Antibiotics, Cessation of smooking, Non-adherence with maintenance therapy, antidiarrheal agents, Pregnancy.

APPROACH TO MANAGEMENT

Goals of treatment are induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk. After the diagnosis of UC is confirmed, the anatomic extent is assessed endoscopically. The key question to be addressed at this point is whether the inflammation is "distal" (i.e., limited to below the descending colon and hence within reach of topical therapy) or extends proximal to the descending colon, requiring systemic medication

RECOMMENDATIONS FOR DIAGNOSIS AND ASSESSMENT

In a patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus, stool examinations and sigmoidoscopy or colonoscopy and biopsy should be performed to confirm the presence of colitis and to exclude the presence of infectious and non infectious etiologies. Characteristic endoscopic and histologic findings with negative evaluation for infectious causes will suggest the diagnosis of UC.

RECOMMENDATIONS FOR MANAGEMENT OF MILD – MODERATE DISTAL COLITIS

Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids. Topical mesalamine agents are superior to topical steroids or oral aminosalicylates. The combination of oral and topical aminosalicylates is more effective than either alone. In patients refractory to oral aminosalicylates or topical corticosteroids, mesalamine enemas or suppositories may still be effective. The unusual patient who is refractory to all of the above agents in maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40– 60 mg per day, or infliximab with an induction regimen of 5 mg / kg at weeks 0, 2, and 6, although the latter two agents have not been studied specifically in patients with distal disease.

RECOMMENDATIONS FOR MAINTENANCE OF REMISSION IN DISTAL DISEASE

Mesalamine suppositories are effective in the maintenance of remission in patients with proctitis, whereas mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night. Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission; the combination of oral and topical mesalamine is more effective than either one alone. Topical corticosteroids including budesonide.

- **Mesalamine suppositories in doses of 500 mg daily or twice daily are effective in maintaining remission with an apparent dose –response relationship; only 10 % of patients**

treated with 500 mg twice daily relapsed at 1 year, compared with a relapse rate of 36 % with once daily dosing.

- **Mesalamine enemas in doses of 2–4 g maintained remission when administered daily (78% effective), every other day (72 % effective), or even as infrequently as every third day (65 % effective).**
- **Sulfasalazine in a dose of 2 g per day, olsalazine 1 g per day, Eudragit-S-coated mesal amine 3.2g per day, balsalazide 3–6 g per day, and granulated extended release mesalamine capsules 1.5 g per day. were all above regime effective in maintaining remission in distal disease.**
- **The combination of oral mesalamine 1.6 g per day and mesalamine enema 4 g twice weekly was more effective than the oral mesalamine alone.**
- **Topical corticosteroids, whether hydrocortisone or budesonide, have not proven effective for maintaining remission in distal colitis.**
- **The indications for the use of thiopurines (6-mercaptopurine (6-MP) or azathioprine) and infliximab When all of these measures fail to maintain remission in distal disease, thiopurines. but not corticosteroids, may prove effective. are identical to those described in the section on maintenance in extensive colitis although they have not been studied in trials limited to patients with distal disease.**

RECOMMENDATIONS FOR MANAGEMENT OF MILD –MODERATE EXTEN SIVE COLITIS: ACTIVE DISEASE[2-iii]

Patients with mild to moderate extensive colitis should begin therapy with

- **oral sulfasalazine in daily doses titrated up to 4 – 6 g per day,**
- **or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicy late acid (5-ASA) moiety.**
- **Oral steroids are generally reserved for patients who are:**

refractory to oral aminosalicylates in combination with topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement.

- **6-MP and azathioprine are effective for patients who do not respond to oral steroids, and continue to have moderate disease, and are not so acutely ill as to require intravenous therap.**
- **Infliximab is an effective treatment for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant of these medications. The infliximab induction dose is 5 mg / kg intravenously at weeks 0, 2, and 6 weeks . Infliximab is contraindicated in patients with active infection, untreated latent TB, preexisting demyelinating disorder or optic neuritis, moderate to severe congestive heart failure, or current or recent malignancies.**

RECOMMENDATIONS FOR MILD–MODERATE EXTENSIVE COLITIS: MAIN TENANCE OF REMISSION

Once the acute attack is controlled, a maintenance regimen is usually required, especially in patients with extensive or relapsing disease.

- **Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses . Patients should not be treated chronically with steroids.**
- **Azathioprine or 6-MP may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid dependent but not acutely ill.**
- **Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen.**

Sulfasalazine reduces relapse rates in UC in a dose-related manner, with benefits showed at 2–4 g per day. Although the 4 g per day regimen is the most effective in

preventing relapse, up to one quarter of patients cannot tolerate the side effects at this dose, which limits its overall utility.

The newer aminosalicylate preparations are including olsalazine, mesalamine, balsal-azide, granulated extended release mesalamine capsules , and multimatrixmesalamine

RECOMMENDATIONS FOR MANAGEMENT OF SEVERE COLITIS

- **The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5 mg / kg if urgent hospitalization is not necessary.**
- **The patient who presents with toxicity should be admitted to hospital for a course of intravenous steroids.**
- **Failure to show significant improvement within 3 – 5 days is an indication for either colectomy or treatment with intravenous cyclosporine in the patient with severe colitis.**
- **Long-term remission in these patients is significantly enhanced with the addition of maintenance 6-MP. Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting.**

RECOMMENDATIONS FOR SURGERY

<u>Absolute indications</u> for surgery are:

- **exsanguinating hemorrhage,**
- **perforation,**
- **and documented or strongly suspected carcinoma.**

<u>Other indications</u> for surgery are severe colitis with or without toxic megacolon un responsive to conventional maximal medical therapy, and less severe but medically intractable symptoms or intolerable medication side effects.

RECOMMENDATIONS FOR THE MANAGEMENT OF POUCHITIS

Patients who develop typical symptoms and signs of pouchitis after the IPAA should be treated with a short course of antibiotics . Controlled trial studies show efficacy for metronidazole in a dose of 400 mg three times daily, or 20 mg / kg daily, or cipro-floxacin 500 mg twice daily.

Management of Crohn's Disease in Adults[6]

Guidelines are intended to apply to the clinical situation for all physicians and to be flexible.

INTRODUCTION

Crohn's disease (CD) encompasses a multisystem group of disorders with specific clinical and pathological features characterized by focal, asymmetric, transmural, and, occasionally, granulomatous inflammation primarily affecting the gastrointestinal (GI) tract. This multisystem disorder with potential for systemic and extra-intestinal compli cations can affect any age group, but the onset (diagnosis) is most common in the second and third decades (teenagers and young adults).The incidence and prevalence of CD in the United States are similar to other " Westernized " countries, and estimated to be 5/ 100,000 and 50/100,000, respectively. It is important to differentiate CD from other inflammatory bowel diseases that can simulate or complicate its clinical course.

CLINICAL FEATURES

heterogeneity of manifestations, a potentially insidious onset, the presence of over lapping features with other inflammatory bowel diseases, and / or the presentation without GI symptoms (i.e., extraintestinal symptoms), can make the diagnosis of CD dificult .

Characteristic symptoms of chronic or nocturnal diarrhea and abdominal pain, weight loss, fever, or rectal bleeding reflect the underlying inflammatory process (the absence of rectal bleeding may suggest CD over ulcerative colitis) .

Clinical signs include pallor, cachexia, an abdominal mass or tenderness, or perianal fssures, fistula, or abscess.

<u>Associated extraintestinal features</u> can include inflammation of:

Skin: cutanous manifestations (erythema nodosum and pyoderma gangrnosum)

Joints:

1- **Spondyloarthrosis (ankylosing spondylitis and sacroiliitis)**
2- **Peripheral arthritis**

eyes: ocular inflammation (uveitis, episcleritis, or sclero-conjuctivitis),

primary sclerosing collangitis, and coagulability.

in children: anemia, fever, the failure of growth, or delayed development of secondary sex characteristics can be observed, gastric biopsies demonstrating focal gastritis in the absence of Helobacter pylori has been helpful in the diagnosis of CD in children with intermediate colitis. Although the onset is typically insidious, occasionally, CD can present in a fulminant manner at its onset or with the presence of toxic megacolon. Despite its potential heterogeneity, individual manifestations, and complications, there are definable patterns according to disease location and type (inflammatory, fibro stenotic, and fistulizing) that are important in determining clinical outcomes. However, even the most recent classification system that considers age at diagnosis, disease location, and disease behavior is not stable throughout the disease course, particularly regarding the phenotypic disease behavior that tends to progress to fibrostenosis or fistulization .

the ileum and colon are the most frequently affected sites, commonly complicated by intestinal obstruction, inflammatory mass , or abscess.

<u>Luminal CD</u>. CD typically has a chronic, relapsing course with approximately half of all patients being in clinical remission at any particular time. If an individual patient is in remission for 1 year, there is an 80 % chance that this individual will remain in remission over the course of the subsequent year. For a patient who has active disease in the past year, there is a 70 % chance that this patient will be active in the forthcoming year; with a 50 % chance of being in remission within the ensuing 3 years. Overall, 13

% of patients will have a relapse-free course, 20 % have relapses of disease every year, and 67 % have had a combination of years in relapse and years in remission within the first 8 years after initial diagnosis. Less than 5 % of patients will have a continuous course of active disease. .

Fistulizing CD . The life time risk of fistula development in patients with CD has been reported to range from 20 to 40 % . In a population-based series from Olmsted County, Minnesota, the cumulative risk for the development of fistula was 33 % at 10 years and 50 % are over 20 years, and in up to 45 % of patients fistula development preceded the diagnosis of CD. The clinical course of fistulae is variable and depends on their location and complexity. Internal fistulas, such as enterovesical (bowel to bladder), or entero-enteric (bowel to bowel), are more difcult in general to close with medical therapy. External fisstulas may be enterocutaneous (bowel to skin); this subtype of fistula represents the majority of cases.

DIAGNOSIS

The diagnosis of CD is based on a composite of endoscopic, radiographic, and pathological findings documenting focal, asymmetric, transmural, or granulomatous features. The sequence of diagnostic maneuvers is based on presenting symptoms, physical findings, and basic laboratory abnormalities.

Currently, the measurement of genetic mutations in patients with CD remains a research tool that is not yet proven to be of clinical benefit for the general assessment of diagnosis, guidance of patient care, or prediction of response to specific medical therapies. The use of genetic testing is currently not recommended in the caring of patients with CD. Additionally, serological studies evaluating

antibodies against *Saccharomyces cerevisiae* , antineutrophil cytoplasmic antibodies, antibodies directed against CBir1, OmpC are evolving to provide adjunctive support for the diagnosis of CD but are not su: ciently sensitive or specific to be recommended for use as a screening tools.

1. **In endemic areas and when there is limited access to diagnosis, give a course of anti-ameba therapy.**
2. **In endemic areas for TB, consider a trial of anti-TB therapy for 1 month to determine the response.**
3. **Sulfasalazine (least expensive) for all mild to moderate colitis and for maintenance of remission.**
4. **Steroid enemas* for distal colon disease.**
5. **Trial of metronidazole for ileocolonic or colonic disease.**
6. **Oral prednisone for moderate to severe disease.**
7. **If there is a short segment of small-bowel disease, consider surgery.**
8. **Azathioprine or methotrexate.**
9. **Metronidazole for postoperative maintenance.**

   *** Steroid enemas can sometimes be made with locally available resources, sometimes at lower cost. Budesonide can be used for mild ileal or ileocolonic disease (right colon).**
10. **If patients fail to maintain remission after a course of steroids, then consider azathioprine (or 6-MP/AZA); in case of azathioprine failure, consider methotrexate. Infliximab or adalimumab or certolizumab can be considered for moderate to severe steroid-dependent or steroid-resistant disease. Immunosupressive drugs, such as 6-MP and AZA, can also be very helpful in the treatment of fistulas in CD.Tacrolimus can be considered when anti-TNF fails.**

    *** Some traditional Chinese medicines are deemed to be useful as alternative medicines for anemia in China. These are not typically used in the West. Some Chinese agents suggested include powder of natural indigo, powder for treating throat disease (*xilei***

powder), Yunnan white drug, or oral prescriptions such as *Pulsatilla* decoctions; and some single components in Chinese medicine, such as *Pulsatilla* root, *Coptis* root, Amur corktree bark, Baikal skullcap root, and curcumin.

CONTROVERSIAL ISSUES

Many unresolved questions remain regarding practice guidelines for CD because of insufficient data and inadequate experience to make formal recommendations.

(i) **Novel end points for successful medical therapy, including the potential to modify long-term disease behavior and long-term disease outcome, and prognostic factors to predict evolution of the natural history of disease are needed.**

(ii) **Additional trials to compare "top – down" vs. " step-up " therapy with appropriate patient selection are needed.**

(iii) **The optimal dose and formulation of mesalamine therapy (including potential benefits of rectal mesalamine) for acute and maintenance therapy of CD remain to be established.**

(iv) **Additional studies of antibiotics as active and maintenance (including postoperative maintenance) therapies are needed.**

(v) **Long-term studies to evaluate the safety and efficacy of budesonide at maintaining remissions at doses above 6 mg are needed.**

(vi) **Studies to optimize thiopurine antimetabolite dosing are needed.**

(vii) **Dose-ranging and maintenance studies of methotrexate are needed.**

(viii) **Studies to define optimal approaches to minimize immunogenicity to evolving biologic therapies are needed.**

(ix) **Natalizumab has been efficacious in clinical trials, but safety concerns need to be clarified.**

(x) **Despite expanding evidence of the carcinogenic potential of long standing CD, surveillance guidelines have yet to be defined.**

(xi) **Additional studies of probiotic therapies and alternative therapies are needed.**

(xii) **Additional clinical data are required regarding novel biological agents targeting alternative cytokines and their receptors.**

Outcome studies comparing medical vs. surgical approaches should be perfomed.

Perianal fistulas are common manifestations of Crohn's disease that can result in tremendous morbidity, including scarring, persiostent drainage, and fecal incontinence. The typical course for patients with perianal Crohn's disease includes long time periods of actively draining fistulas nd frequent relapses

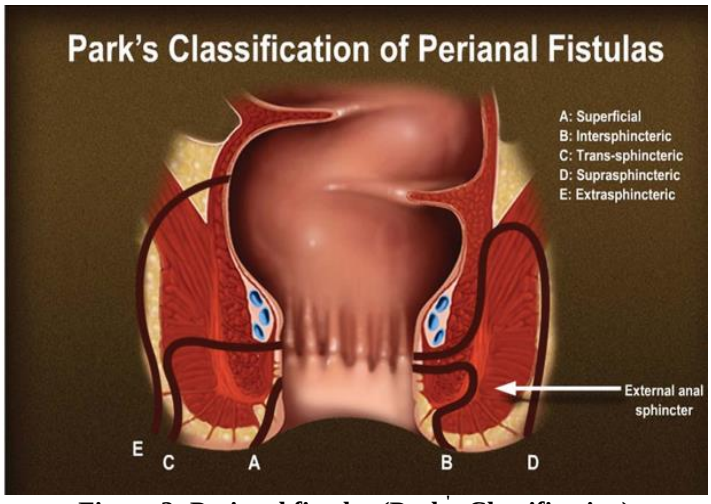


Figure 2: Perianal fistulas (Park's Classification)

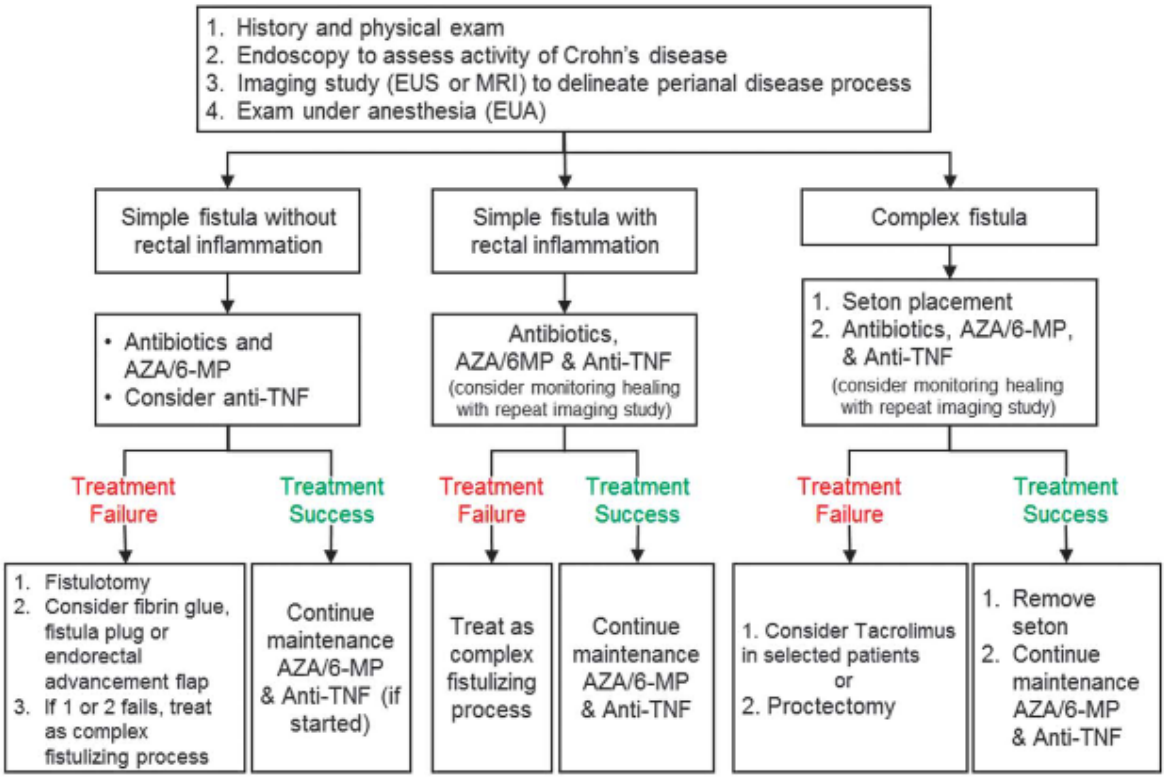


Figure 3: proposed treatment algorithm for patients with Crohn's perianal fistulas.

Microscopic Colitis [48]

A new American Gastroenterological Association Institute guideline on the medical management of microscopic colitis supports the first-line use of budesonide for induction and, when appropriate, maintenance therapy. The guideline appears in the January 2016 issue of *Gastroenterology*.

Microscopic colitis affects predominantly those older than 60 years, , Although it is not associated with increased mortality, symptoms can reduce quality of life.

"Unlike other inflammatory colitides, there is no evidence that the persistence of histological inflammation portends long-term unfavorable outcomes such as colorectal cancer or need for surgery". "Accordingly, the goal of medical therapy reflected in these recommendations is to relieve symptoms and improve quality of life while minim izing drug-related adverse effects.

Microscopic colitis is characterized by chronic watery diarrhea caused by inflammation in the colon and diagnosed by colonic biopsy. With a predilection for those 60 years of age or older, it comprises 2 subtypes, lymphocytic colitis and collagenous colitis; there is a female predominance in the latter. The reported prevalence of microscopic colitis ranges from 48 to 219 per 100,000. Microscopic colitis is not associated with increased mortality, although symptoms can lead to impaired quality of life. Unlike other inflammatory colitides, there is no evidence that the persistence of histological inflammation portends long-term unfavorable outcomes such as colorectal cancer or need for surgery. Accordingly, the goal of medical therapy reflected in these recommendations is to relieve symptoms and improve quality of life while minimizing drug-related adverse effects.

recommendations

1. **In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over no treatment for the induction of clinical remission.**
2. **In patients with symptomatic microscopic colitis, the AGA recommends treatment with budesonide over mesalamine for the induction of clinical remission.**
3. **In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with mesalamine over no treatment for the induction of clinical remission..**
4. **In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with bismuth salicylate over no treatment for the induction of clinical remission.**
5. **In patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests treatment with prednisolone (or prednisone) over no treatment for the induction of clinical remission.**
6. **In patients with symptomatic microscopic colitis, the AGA suggests against combination therapy with cholestyramine and mesalamine over mesalamine alone for the induction of clinical remission.**
7. **In patients with symptomatic microscopic colitis, the AGA suggests against treatment with Boswellia serrata over no treatment for the induction of clinical remission.**
8. **In patients with symptomatic microscopic colitis, the AGA suggests against treatment with probiotics over no treatment for the induction of clinical remission.**

For patients with recurrence of symptoms following discontinuation of induction therapy for microscopic colitis, the AGA recommends budesonide for maintenance of clinical remission.

Guidelines in the management of C.difficili [50]

INTRODUCTION

Antibiotic-associated diarhea and colitis are imporrant and increasingly frequent complications of antibiotic therapy. While these occur most often in hospitals and nursing homes, they also occur in the community. Antibiotic-associated dianhea is even more common; it is caused bv Clostridium dfficile in only l5-20% of cases, and is of unknown cause in most of the remaining cases. The type of antibiotic – associated diarrhea that is not caused by C. Dfficile is relatively mild, self-limited, unassociated with intestinal lesions, is treatable with nonspecific supportive measures and by discontinuation of antibiotics, and is also referred to by a variety of terms such as simple, benign, or enigmatic antibiotic-associated diarrhea. In contrast, C . difficile associated diarrhea is usually associated with colitis caused by the combined effects of toxins A and B produced by C. dfficile within the intestinal lumen and is a serious and potentially life-threatening disease. C. dfficile, a sporeforming obligate anaerobic bacillus, is a component of the normal fecal flora of many infants, and about 5% of healthy adults; it may be found in the stools of l0% or more of hospitalized adults without diarrhea who have received antibiotics or cancer chemo therapeutic agents. C. Dfficile causes a spectrum of diarrheal syndromes that vary widely in severity and merge with one another; they are also commonly referred to by a variety of names, including C. dfficile diarrhea, C. dfficile colitis, antibiotic- associated C. difficile colitis, and pseudomembranous colitis. The diarrheal illness caused by C. dfficile may and often does closely resemble the more frequent benign or simple antibiotic diarrhea. Patients with antibiotic-associated diarrhea in which C. Difficile cannot be incriminated, which is true about 80% of the time, are assumed to have the simple or benign diarrhea of unknown cause. C. dfficile diarrhea, colitis without pseudomembranes, and pseudomembranoucso litis are toxin-mediatedm ucosal inflammatory processes that are usually characterized by the presence of grossly or microscopically visible pseudomembranes consisting of nodules or large plaques containing leukocytes, fibrin, mucus, and epithelial cells loosely adherent to the surface of the underlying inflamed and necrotic mucosa. A lmost all cases of antibiotic-associated colitis or pseudomembranous colitis are causedb y both toxin A and B producing strains of C. Dfficile.

Practice Guide lines for diagnosis of Clostridium difficite Diarrheal syndromes:

1. **The diagnosiss hould be suspected in any one with diarrhea who has received antibiotics within the previous 2 months and/or whose diarrhea began 72 h or more after hospital i zation.**
2. **When the diagnosis of C. dfficile diarrhea is suspected, a single stool specimen should be sent to the laboratory for testing for the presence of C. difficile and/or its toxins.**
3. **If the results of those tests are negative but diarrhea persists, one or two additional stools can be sent for test in with the same or different tests.**
4. **Endoscopy is reserved for special situations, such as when a rapid diagnosis is needed and test results are delayed or the test is not highly sensitive, or the patient has ileus and a stool is not available, or when other colonic diseases are in the differential.**

Practice Guidelines for Treatment of Clostridium dfficile Diarrhea or Colitis

1. **Antibiotics should be discontinued if possible.**
2. **Nonspecific supportive therapy should be given, and is often all that is needed in treatment. Specific antibiotics should not be given routinely.**
3. **When the diagnosis of C. dfficile diarrhea is confirmed and specific therapy is indicated, metronidazole given orally is preferred.**
4. **If the diagnosis of C. dfficile diarrhea is highly likely and the patient is seriously ill, metronidazole may be given empirically before the diagnosis is definitely established.**
5. **Vancomycin given orally is reserved for therapy of C. dfficile' associated diarrhea until one or more of the following conditions are present:**

(a) The patient has failed to respond to metronidazole.
(b) The patient's organism is resistant to metronidazole.
(c) The patient is unable to tolerate metronidazole, or is allergic to it, or is being treated with ethanol containing solutions.
(d) The patient is either pregnant or a child under the age of l0 years of age.
(e) The patient is critically ill because of C. dfficile-associated diarrhea or colitis.
(i) There is evidence suggesting the diarrhea is caused by staphyloccus aurius.

Practice Guidelines for Management of Relapses

1. **Reconfirm the diagnosis.**
2. **Discontinue medications that may be contributing to the diarrhea, and treat the patient with nonspecific supportive therapy.**
3. **If specific therapy is needed, treat the patient with a standard course of metronidazole given orally for 7 to l0 days, or with vancomycin, as in the Treatment Guidelines.**
4. **When possible, avoid treating (minor) infections with antibiotics for the next 2 months after treatment of a relapse.**
5. **No treatment available in the United States has been proven to prevent recurrences. If the patient has suffered from multiple recurrences considering one of the following antimicrobial regimens with or without one of the other therapeutic measures as an adjunct. These are not presented in an order of preference.**

(a)Oral metronidazole (or vancomycin).

(b)Specific therapy with vancomycin or metronidazole given orally for I to 2 months, either intermittently (sucb as every other day or week) or with gradual tapering, with or without adiunctive
therapy with an oral anion-binding regimen such as cholestyramine or colestipol begun near the end of antimicrobial therapy and gradually tapered.

(c)Oral vancomycin plus rifampin.

(d)Oral yogurt, Lactobacillus preparations, or Lactobacillus GG.

(e)Saccharomycesb oulardii (500 mg orally twice daily), if available, may be given for I month, if the patient is not immunocompromised, beginning 4 days before a lO-day course of specific antibiotic therapy has been completed.

(f)Human immune globulin by intravenous infusion, for patients with documented defficiencies.

Practice Guidelines .for Prevention of Clostridium dfficile Dirtrrhea

1. **Limit the use of antimicrobial drugs.**
2. **Wash hands between contact with all patients.**
3. **Use enteric (stool) isolation precautions for patients with C. Dfficile diarrhea.**
4. **Wear gloves when contacting patients with C. dfficile dianhea/colitis or their enviro nment.**
5. **Disinfect objects contaminated with C. dfficile with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide**
6. **Educate the medical, nursing, and other appropriate staff members about the disease and its epidemiology.**

Colonic diverticulosis and diverticular disease [7]

Introduction

Colonic diverticulosis has been recognized as an increasingly common clinical condition in industrialised countries, the highest rates occurring in the United States and Europe. This condition now adays ranks as fifth most important gastrointestinal disease in terms of direct and indirect costs. Diverticular disease (DD) is a term generally used to include diverticulosis and diverticulitis.

Definition and epidemiology

1. **'Diverticulosis' is merely the presence of colonic diverticula; these may become symptomatic or complicated.**
2. **Symptomatic uncomplicated diverticular disease (SUDD) is a syndrome characteri zed by recurrent abdominal symptoms (i.e.abdominal pain and bloating resembling or overlapping irritable bowel syndrome (IBS) symptoms) attributed to diverticula in the absence of macroscopically evident alterations other than the presence of diverticula.**
3. **Acute diverticulitis is an acute episode of severe, prolonged, lower abdominal pain (usually on the left side), change in bowel movements, low-grade fever and leucocytosis. The clinical presentation has a broad spectrum ranging from mild self-limiting episodes to abscess, perforation and peritonitis.**
4. **A small subset of patients with diverticulosis may develop segmental colitis associa-ted with diverticulosis (SCAD).**
5. **The prevalence of diverticulosis and diverticular disease (DD) is increasing in Western countries in parallel with increased life-expectancy.**
6. **DD is a relevant cause of hospitalization and not devoid of mortality, particularly in elderly patients.**
7. **Mortality in perforated disease remains elevated, due to the high rate of relevant comorbidity.**
8. **In general, DD has a favourable long-term outcome with a very low incidence of complications. Symptomatic disease, acute diverticulitis and complicated DD represent distinct clinical entities among groups.**
9. **DD does not increase the risk of colon cancer.**

Diagnosis

1. **SCAD is a defined pathological entity characterized by a chronic inflammatory response involving the interdiverticular mucosa of a colonic segment involved. The rectum and the right colon are spared from inflammation. Hence, SCAD can be considered a separate pathological entity.**
2. **Limitation of mucosal lesion to the diverticular segment is the most important diagnostic criterion for SCAD (rectal sparing). Rectal and descending colon biopsies are required to distinguish SCAD from inflammatory bowel disease (IBD).**
3. **For bleeding per rectum a prompt colonoscopy (i.e. within 12–24 h) is mandatory for diagnosis and to direct therapy. Massive bleeding should be managed with selective angiography.**
4. **US can be used as a sensitive and specific diagnostic technique to detect acute diverticulitis and its septic abdominal complications, provided that the procedure is carried out by an expert investigator.**
5. **Colonoscopy and CT colonography (CTC) must be considered the first-line test to diagnose or rule out colonic diverticula. The choice for CTC or colonoscopy depends on the patient's age, risk factors, clinical status and preference.**
6. **Diagnostic accuracy of double contrast barium enema (DCBE) for DD is similar to that of CTC. Use of DCBE should be considered only if CTC is unavailable.**
7. **Contrast-enhanced computerized tomography (CE-CT) should be considered as the first-line colonic examination since it offers a more comprehensive evaluation of**

uncomplicated and complicated forms; CE-CT can also be used to guide therapeutic interventions.

8. **The use of magnetic resonance colonography (MRC) in diagnosing diverticulitis is not sustained by robust data. Feasibility seems to be limited by the difficult access to magnetic resonance (MR) scanners in emergency departments.**
9. **Endoscopic follow-up should be reserved only to patients with persistently severe symptoms to exclude either cancer or IBD.**

Medical and surgical treatment

1. **There is no rationale for drug treatment of asymptomatic diverticulosis, but there are limited indications to suggest an increase in dietary fibre.**
2. **There is a possible relationship between low dietary fibre intake, particularly insoluble fibre, and the development of DD. A high daily fibre intake is recommended to reduce the risk of DD.**
3. **There is no rationale to avoid in the diet the consumption of nut, corn and popcorn to prevent diverticular complications.**
4. **Regular treatment with aspirin or Nonsteroidal anti-inflammatory drugs (NSAIDs) carries the potential risks of diverticular complications.**
5. **Fibre supplementation alone provides controversial results in terms of symptoms relief.**
6. **Fibre plus rifaximin provide a greater prevalence of symptom-free patients compared to fibre alone.**
7. **Rifaximin plus fibre is more effective than fibre alone in preventing acute diverticulitis with a low therapeutic advantage.**
8. **There is no clear evidence that mesalazine alone is effective in reducing symptoms.**
9. **There is no clear evidence that mesalazine reduces acute episodes of diverticulitis.**
10. **There is insufficient evidence that probiotics are effective in reducing symptoms.**
11. **Management and treatment approaches depend on severity (uncomplicated and complicated) and complexity (i.e. abscess, fistula, etc.) of the condition.**
12. **Antibiotics may not improve outcome in acute uncomplicated diverticulitis (AUD) and are used on a case-bycase basis.**
13. **In severe/complicated acute diverticulitis (AD), hospitalization, bowel rest and broad-spectrum antibiotics are needed.**
14. **The decision to perform elective resection after one or more episodes of AD should be undertaken on a 'caseby- case' basis.**
15. **Elective surgery should be recommended in patients with symptomatic complicated diverticular disease (e.g. fistula, stenosis). Specific clinical situations should be carefully evaluated (persisting symptoms and signs, age, degree of diverticulitis, immunocompromised patients).**
16. **Elective resection in a patient with an episode of AD is safer when performed in an inflammation-free interval.**
17. **Laparoscopic resection is safe and provides faster recovery in uncomplicated cases; it has to be performed by well trained surgeons.**
18. **Several surgical options may be appropriate, but the choice mostly depends on the severity of peritonitis. Laparoscopic peritoneal lavage should be considered as an alternative to primary resection and anastomosis in purulent peritonitis.**
19. **The best treatment option for a diverticular abscess >4 cm in diameter is percutaneous guided drainage. Diverticular abscesses not responding, or not amenable, to non-operative management should be treated surgically.**
20. **Though technically feasible, laparoscopic resection for perforated diverticulitis has to be restricted to selected cases and to experienced laparoscopic surgeons.**

21. **Current evidence is inadequate to support an urgent laparoscopic colorectal resection for perforated diverticulitis. This approach should be reserved to centres and surgeons with appropriate laparoscopic expertise.**

[*] The statements produced by the Consensus Conference on Diverticular Disease promoted by GRIMAD (Gruppo Italiano malattia Diverticolare, Italian Group on Diverticular Diseases) are reported..

Colonoscopy Surveillance After Screening and Polypectomy[8,47]

A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer:

Screening for colorectal cancer (CRC) in asymptomatic patients can reduce the incidence and mortality of CRC. Adenomatous polyps are the most common neoplasm found during CRC screening. There is evidence that detection and removal of these cancer precursor lesions may prevent many cancers and reduce mortality. However, patients who have adenomas are at increased risk for developing metachronous adenomas or cancer compared with patients without adenomas. There is new evidence that some patients may develop cancer within 3–5 years of colonoscopy and polypectomy—so-called interval cancers. Ideally, screening and surveillance intervals should be based on evidence showing that interval examinations prevent interval cancers and cancer-related mortality. A key principle of the 2006 guideline was risk stratification of patients based on the findings at the baseline colonoscopy. The surveillance schema identified 2 major risk groups based on the likelihood of developing advanced neoplasia during surveillance:

Low-risk adenoma (LRA) refers to patients with 1–2 tubular adenomas <10 mm in diameter.

High-risk adenoma (HRA) refers to patients with tubular adenoma ≥10 mm, 3 or more adenomas, adenoma with villous histology, or HGD.

The British Society of Gastroenterology surveillance guideline in 2010.Their risk stratification differs from the US guideline, dividing patients into 3 groups:

- **Low risk (1–2 adenomas <10 mm),**
- **Intermediate risk (3–4 small adenomas or one ≥10 mm),**
- **High risk (5 small adenomas or 3 with at least one ≥10 mm).**

They recommend that the high-risk group undergo surveillance at 1 year because of concerns about missed lesions at baseline..

NOTE. The recommendations assume that the baseline colonoscopy was complete and adequate and that all visible polyps were completely removed.

serrated polyposis syndrome

***A* Based on the World Health Organization definition of serrated polyposis syndrome, with one of the following criteria:**

(1) at least 5 serrated polyps proximal to sigmoid, with 2 or more ≥10 mm;

(2) Any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome;

(3) ≥20 serrated polyps of any size through out the colon.

Recommendation.

- **patients with one or more adenomas ≥10 mm have an increased risk of advanced neoplasia during surveillance compared with those with no neoplasia or small (<10 mm) adenomas.**
- **There is no basis for changing the recommended 3-year surveillance interval. This recommendation assumes that the examination was of high quality and complete removal of neoplastic tissue occurred at baseline.**
- **If there is question about complete removal (i.e., piecemeal resection), early follow-up colonoscopy is warranted.**

Recommendation. For 3 year surveillance interval to adenomatous polyp:

- **patients with one or more adenomas with villous histology have an increased risk of advanced neoplasia during surveillance.**
- **The presence of an adenoma with HGD is an important risk factor for development of advanced neoplasia and CRC during surveillance.**

Recommendations for 3year surveillance interval to serrated polyp:

- **size (≥10 mm), histology a sessile serrated polyp is a more significant lesion than an HP;**
- **a sessile serrated polyp with cytological dysplasia is more advanced than a sessile serrated polyp without dysplasia,**
- **location proximal to the sigmoid colon**

These are risk factors that might be associated with higher risk of CRC and should be managed like HRA. Serrated polyps that are <10 mm and do not have cytological dysplasia may have lower risk and can be managed like LRA.

Recommendation. LRA at baseline and negative findings at first surveillance can have their next surveillance examination at 10 years. Patients who have HRA at any exam ination appear to remain at high risk and should have shorter follow-up intervals for surveillance.

EFFECT OF INADEQUATE PREPARATION ON POLYP/ADENOMA DETECTION AND RECOMMENDED FOLLOW-UP INTERVALS

Recommendations

1. **Preliminary assessment of preparation quality should be made in the rectosigmoid colon, and if the indication is screening or surveillance and the preparation clearly is inadequate to allow polyp detection greater than 5 mm, the procedure should be either terminated and rescheduled or an attempt should be made at additional bowel clea- nsing strategies that can be delivered without cancelling the procedure that day.**
2. **If the colonoscopy is complete to cecum, and the preparation ultimately is deemed inadequate, then the examination should be repeated, generally with a more aggressive preparation regimen, within 1 year; intervals shorter than 1 year are indicated when advanced neoplasia is detected and there is inadequate preparation.**
3. **If the preparation is deemed adequate and the colonoscopy is completed then the guideline recommendations for screening or surveillance should be followed.**

Recommendations for adequate preparation:

1. **Use of a split-dose bowel cleansing regimen is strongly recommended for elective colonoscopy .**
2. **A same-day regimen is an acceptable alternative to split dosing, especially for patients undergoing an afternoon examination.**
3. **The second dose of split preparation ideally should begin 4–6 h before the time of colonoscopy with completion of the last dose at least 2 h before the procedure time.**
4. **By using a split-dose bowel cleansing regimen, diet recommendations can include either low-residue or full liquids until the evening on the day before colonoscopy.**
5. **Health care professionals should provide both oral and written patient education instructions for all components of the colonoscopy preparation and emphasize the importance of compliance.**
6. **The physician performing the colonoscopy should ensure that appropriate support and process measures are in place for patients to achieve adequate colonoscopy preparation quality.**
7. **Adequacy of bowel preparation should be assessed after all appropriate efforts to clear residual debris have been completed.**
8. **Measurement of the rate of adequate colon cleansing should be conducted routinely.**

9. **Adequate preparation, defined as cleansing that allows a recommendation of a screen ing or surveillance interval appropriate to the findings of the examination, should be achieved in 85% or more of all examination a peron-physician base**

FDA-APPROVED PREPARATIONS

Recommendations

1. **Selection of a bowel- cleansing regimen should take into consideration the patient's medical history, medications, and, when available, the adequacy of bowel preparation reported from prior colonoscopies.**
2. **A split-dose regimen of 4 L PEG-ELS provides high-quality bowel cleansing.**
3. **in healthy non constipated individuals, a 4-L PEG-ELS formulation produces a bowel-cleansing quality that is not superior to a lower-volume PEG formulation.**

Recommendations

1. **The OTC bowel cleansing agents have variable efficacy that ranges from adequate to superior, depending on the agent, dose, timing of administration, and whether it is used alone or in combination; regardless of the agent, the efficacy and tolerability are enhanced with a split-dose regimen.**
2. **Although the OTC purgatives generally are safe, caution is required when using these agents in certain populations; for example, magnesium-based preparations (both OTC and FDA-approved formulations) should be avoided in patients with chronic kidney disease.**
3. **The routine use of adjunctive agents for bowel cleansing before colonoscopy is not recommended.**

DIFFERENCES IN PATIENT PREFERENCE/ WILLINGNESS TO REPEAT COMPARISONS

Recommendations

1. **Split-dose bowel cleansing is associated with greater willingness to repeat regimen compared with the day before regimen.**
2. **The use of low-volume bowel cleansing agents is associated with greater willingness to undergo a repeat colonoscopy.**

SELECTION OF BOWEL PREPARATION IN SPECIFIC POPULATIONS

Recommendations

1. **There is insufficient evidence to recommend specific bowel preparation regimens for elderly persons; however, we recommend that Na P preparations be avoided in this population.**
2. **There is insufficient evidence to recommend specific bowel preparation regimens for children and adolescents undergoing colonoscopy; however, we recommend that Na P preparations should not be used in children younger than age 12 or in those with risk factors for complications from this medication.**
3. **Na P should be avoided in patients with known or suspected inflammatory bowel disease.**
4. **Additional bowel purgatives should be considered in patients with risk factors for inadequate preparation (e.g., patients with a prior inadequate preparation, history of constipation, use of opioids or other constipating Medications, prior colon resection, diabetes mellitus, or spinal cord injury)**
5. **Low-volume preparations or extended time delivery for high volume preparations are recommended for patients after bariatric surgery.**
6. **Tap water enemas should be used to prepare the colon for sigmoidoscopy in pregnant women.**
7. **There is insufficient evidence to recommend specific regimens for persons with a history of spinal cord injury; additional bowel purgatives should be considered.**

There is insufficient evidence to recommend a single salvage strategy for those patients encountered with a poor preparation that precludes effective completion of the colonoscopy. The following options can be considered in such cases:

Recommendations

1. **Large-volume enemas can be attempted for patients who, presenting on the day of colonoscopy, report brown effluent despite compliance with the prescribed colon-cleansing regimen.**
2. **Through-the-scope enema with completion colonoscopy on the same day can be considered, especially for those patients who receive propofol sedation.**
3. **Waking the patient entirely from sedation and continuing with further oral ingestion of cathartic with same day or next-day colonoscopy has been associated with better outcomes than delayed colonoscopy.**

Guidelines in screening for Colorectal Cancer(CRC)[53]

colorectal cancer (CRC) is the third most common cancer diagnosed among men and women and the second leading cause of death from cancer after lung cancer. The cause of CRC is multifactorial, with environment and inheritance playing varying roles in different patients. Approximately 70 – 80 % of patients with CRC seem to have sporadic disease with no evidence of an inherited disorder. In the remaining 20 – 30 %, a potentially definable inherited component might be causative.

1- **CRC largely can be prevented by the detection and removal of adenomatous polyps, and survival is significantly better when CRC is diagnosed while still localized. In the guidelines, screening tests are grouped into those that primarily detect cancer early and those that can detect cancer early and also can detect adenomatous polyps, thus providing a greater potential for prevention through polypectomy.**

2- **Average- risk individuals over age 50 years to detect and prevent CRC. This can reduce CRC mortality by detecting cancer at an early, curable stage and by detecting and removing clinically significant adenomas. No CRC screening test is perfect, either for cancer detection or adenoma detection. Each test has unique advantages, each has been shown to be cost-effective, and each has associated limitations and risks.**

Updated guidelines for CRC screening or surveillance for individuals at increased and high risk.

Individuals at increased risk due to a history of adenomatous polyps;

3- **A personal history of curative-intent resection of CRC.**

4- **A family history of either CRC or colorectal adenomas diagnosed in a first- degree relative before age 60 years.**

5- **High risk due to a history of inflammatory bowel disease of significant duration or the presence of one of 2 hereditary syndromes.**

Lynch syndrome (LS)[45]

an autosomal dominant condition, is the most common cause of inherited CRC, accounting for about 3 % of newly diagnosed cases of colorectal malignancy. The eponym "Lynch syndrome " recognizes Dr Henry T. Lynch, the first author on the original 1966 publication that comprehensively described this condition In the early 1990s, mutation of genes in the DNA mismatch repair (MMR) pathway were implicated as the cause of LS, and the presence of the mutations now defines the syndrome. genetic testing for LS can confirm the diagnosis at the molecular level, justify surveillance of at risk persons, decrease the cost of surveillance by risk stratif ication, aid in surgical and chemoprevention management, and help in decisions concerning family and career planning.

Amsterdam I and II criteria for diagnosis of hereditary nonpolyposis colorectal cancer

<u>Amsterdam I criteria</u> : 40% of families that meet this criteria do not have LS

1. **Three or more relatives with histologically verified colorectal cancer, 1 of which is a first-degree relative of the other two. Familial adenomatous polyposis should be excluded.**
2. **Two or more generations with colorectal cancer.**
3. **One or more colorectal cancer cases diagnosed before the age of 50 years.**

<u>Amsterdam II criteria</u>: utilizing it involves the clinical evaluation of the patient and patients' pedigree for colorectal and other LS cancers. These guidelines (low sensitive, highly specific) are:

1. **Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of which is a first-degree relative of the other**
2. **Familial adenomatous polyposis should be excluded.**
3. **Cancer involving at least 2 generations.**
4. **One or more cancer cases diagnosed before the age of 50 years.**

<u>Revised Bethesda Guidelines</u> (these guidelines specify circumstances in which a patients' CRC should be tested for MSI), these guidelines (sensitive 82%, specific 77%) are:

1. **CRC diagnosed at younger than 50years.**
2. **Presence of synchronous or metachronous CRC or other LS-associted tumors(include tumor of the colorectum, endometrium, stomach,ovary, pancrease, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and keratoacathomas).**
3. **CRC with MSI-high pathologic-associated features (crohn- like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.**
4. **Patient with CRC and CRC or LS-associated tumor diagnosed in at 1 first-degree relative younger than 50 years old.**
5. **Patient with CRC and CRC or LS-associated tumor at any age in 2 first-degree or second- degree relatives.**

N.B :Growing but not conclusive evidence exists that use of aspirin is beneficial in preventing cancer in LS patients.

<u>Guidelines for screening and management at-risk or affected persons with Lynch syndrome:</u>

- **Screening for CRC by colonoscopy is recommended in persons at risk (first-degree relatives of those affected) or affected with LS every 1 to 2 years, beginning between ages 20–25 years or 2–5 years before the youngest age of diagnosis of CRC in the family if diagnosed before age 25 years. In surveillance of MMR germ line mutation-positive patients, consideration should be given to annual colonoscopy.**

In carriers of deleterious *MSH6* and *PMS2* mutations, the risk of CRC is lower and age at diagnosis later than in patients with *MLH1 and MSH2* mutations. In these affe cted individuals, consideration could be given to starting screening at age 30 years in *MSH6* and 35 years in *PMS2* carriers, unless an early-onset cancer exists in a given family.

- **Screening for endometrial cancer (EC) should be offered to women at risk for or affected with LS by pelvic examination and endometrial sampling annually starting at age 30 – 35 years.**
- **Screening for ovarian cancer should be offered to women at risk for or affected with LS by transvaginal ultrasound annually starting at age 30 – 35 years.**
- **Hysterectomy and bilateral salpingo-oophorectomy should be recommended to women with LS who have finished childbearing or at age 40 years. Patient considerations in this decision could include differences in uterine cancer risk, depending on MMR gene mutation; morbidity of surgery; and the risk of menopausal symptoms, osteoporosis, and cardiac disease if hormone replacement therapy is not given.**
- **Screening for gastric cancer should be considered in persons at risk for or affected with LS by esophagogastro duodenoscopy (EGD) with gastric biopsy of the antrum at age 30 – 35 years with treatment of *H pylori* infection when found. Subsequent, surveillance every 2 – 3 years can be considered based on individual patient risk factors.**
- **Routine screening of the small intestine is not recommended, but attention to investigation of the distal duodenum and ileum during endoscopic studies. (The NCCN suggests capsule endoscopy screening can be considered at 2 – 3 year intervals beginning at age 30– 35 years).**
- **Screening for cancer of the urinary tract should be considered for persons at risk for or affected with LS, with urinalysis annually starting at age 30 – 35 years.**
- **Routine screening of the pancreas is not recommended. The benefit of screening for pancreatic cancer with this magnitude of risk is not established. However, an international pancreas consensus panel recommends that MMR gene mutation carriers with 1 affected first degree relative with pancreatic cancer should be consid-ered for screening**
- **Routine screening of the prostate and breast cancer is not recommended beyond what is advised for the general population.**
- **Colectomy with ileorectal anastomosis is the primary treatment of patients affected with LS with colon cancer or colon neoplasia not removable by endoscopy. Consideration for less extensive surgery should be given in patients older than 60 – 65 years of age and those with underlying sphincter dysfunction.**

Guidelines for endoscopy in pregnant and lactating women[21]

INTRODUCTION

The safety and the efficacy of GI endoscopy in pregnant patients is not well studied. Studies involving humans tend to be small and retrospective. Much of the drug safety data is based on animal studies. Invasive procedures are justified when it is clear that by not doing so could expose the fetus and/or the mother to harm. Informed consent should include risks to the fetus as well as the mother. The fetus is particularly sensitive to maternal hypoxia and hypotension, either of which may cause fetal hypoxia that can lead to fetal death. Maternal over sedation, with resulting hypoven tilation or hypotension, or maternal positioning that might lead to inferior vena caval compression by the gravid uterus can lead to decreased uterine blood flow and fetal hypoxia. Other potential risks to the fetus include teratogenesis (both from medication given to the mother and radiation exposure from fluoroscopy) and prema-ture birth.In situations where therapeutic intervention is necessary,endoscopy offers a relatively safe alternative to radiologic or surgical inter-vention.

FDA classification of drugs in pregnancy

The FDA has a categorization of drug risk to the fetus that runs from "Category A" (safest) to "X" (known danger--don't use!): Controlled studies in women fail to demo-nstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote consultation with an obstetrician regarding medication should be considered. For most procedures, the level of sedation should be anxiolysis or moderate sedation. If deep sedation is necessary, it should be administered by an anesthesiologist.

Meperidine (category B)

Meperidine does not appear to be teratogenic are ported in two large studies. It is preferred over morphine (category C), which crosses the fetal blood–brain barrier more rapidly, and

Fentanyl (category C)

This narcotic has a rapid onset of action and a shorter patient recovery time than meperidine. Fentanyl is not teratogenic but was embryocidal in rats.7 It appears safe in humans when given in low doses typical for endoscopy.

Naloxone (category B)

This rapidly acting opiate antagonist crosses the placenta within 2 minutes of intravenous administration.

It does not appear to be teratogenic. Its use is contraindicated in mothers dependent on opiates, because it can precipitate opiate-withdrawal symptoms. It should only be used in respiratory depression, hypotension, or unresponsiveness in a closely monit-ored setting.

Benzodiazepines(categoryD)

Sustained use of diazepam during early pregnancy(firsttrimester) has been associated with cleft palate and, when used later in the pregnancy, neurobehavioral disorders,8-10 although this association is challenged by some investigators.

Diazepam should not be used for sedation in pregnant women.

Midazolam, although also category D, has not been reported to be associated with congenital abnormalities.Midazolam is the preferred benzodiazepine when sedation with meperidine is inadequate. Avoid the use of midazolamin the first trimester if possible.

Flumazenil (category C) Little is known of the safety profile of this benzodiazepine antagonist. Although it is not teratogenic in rats and mice, it does produce subtle neurobehavioral changes in male offspring of rats exposed to the drug in utero.

Propofol (category B) **In the pregnant patient, it is recommended that propofol be administrated by an anesthesiologist, because of its narrow therapeutic index and the importance of close monitoring. Safety in the first trimester has not been well studied.**

Simethicone (category C)This is a category C drug because of a lack of studies,but, it commonly is given to pregnant women and probably is safe.

Glucagon (category B)Glucagon is an antispasmodic, commonly used during ERCP, that is not contraindicated during pregnancy.

Topical anesthetics, e.g., lidocaine (category B), often are used to decrease the gag reflex and to make intubation

Indications for endoscopy in pregnancy

1. **Significant or continued GI bleeding**
2. **Severe or refractory nausea and vomiting or abdominal pain**
3. **Dysphagia or odynophagia**
4. **Strong suspicion of colon mass**
5. **Severe diarrhea with negative evaluation**
6. **Biliary pancreatitis, choledocholithiasis, or cholangitis**
7. **Biliary or pancreatic ductal injury**

General principles guiding endoscopy in pregnancy

1. **Always have a strong indication, particularly in high-risk pregnancies**
2. **Defer endoscopy to second trimester whenever possible**
3. **Use lowest effective dose of sedative medications**
4. **Wherever possible, use category A or B drugs**
5. **Minimize procedure time**
6. **Position pregnant patients in left pelvic tilt or left lateral position to avoid vena caval or aortic compression**
7. **Presence of fetal heart sounds should be confirmed before sedation is begun and after the endoscopic procedure**
8. **Obstetric support should be available in the event of a pregnancy-related complication**
9. **Endoscopy is contraindicated in obstetric complications such as placental abruption, imminent delivery, ruptured membranes, or eclampsia**

Antibiotics

Most antibiotics can be safely used in pregnancy, and the indications for their prophylactic use are similar to those in non pregnant patient.

However,some antibiotics are contraindicated because of adverse fetal effects, and others are safe in only certain trimesters.

Colon-cleansing agents

The safety of polyethylene glycol (PEG) electrolyte isotonic cathartic solutions has not been studied in pregnancy. PEG solutions are category C. Sodium phosphate preparations(category C) may cause fluid and electrolyte abnormalities and should be used with caution.15

Tap water enemas may be sufficient for flexible sigmoidoscopy.

PROCEDURES

For all endoscopy procedures, it is suggested that

1. **the patient who is in the second or third trimester not lie on her back while waiting for the procedure or afterward in recovery. This is because the pregnant uterus can compress the aorta and/or the inferior vena cava (IVC),causing maternal hypotension and decreased placental perfusion. By placing a wedge or pillow under the right hip, a ‘‘pelvic tilt’’ is created to prevent this. The patient also may sit up if she so prefers, because this will prevent IVC compression. Most procedures are done in the left**

lateral position where this is not an issue. Pregnant patients also are more likely to aspirate gastric contents or secretions than non pregnant ones.

2. **In addition to the usual patient monitoring, maternal–fetal monitoring should be performed.**
3. **Consultation with an obstetrician should be considered before endoscopy. Procedural considerations in pregnancy.**
4. **Upper endoscopy is performed as in non pregnant patients. Case series and case-control studies suggest it is safe and effective. In a case-control study of 83 upper endoscopies (EGD) performed during pregnancy, the diagnostic yield for upper-GI bleeding was 95%. In this study, EGD did not induce premature labor and no congenital malformations were reported. Studies assessing the safety of colonoscopy in pregnancy involve extremely small numbers, limiting the ability to detect uncommon adverse outcomes. In late pregnancy, patients should not be placed supine or prone during colonoscopy. If external abdominal pressure is required, great care should be taken to apply mild force and to direct It away from the uterus.**

ERCP

1. **ERCP generally is safe, provided care is taken to minimize radiation exposure to the fetus (B) and risks to the mother.(C)**
2. **Bipolar electrocautery is preferred over monopolar.**
3. **ERCP should only be used when therapeutic intervention is intended.**
4. **Biliary pancreatitis, choledocholithiasis, or cholangitis are the usual indications, and can lead to fetal loss if not treated properly. Several studies have confirmed the safety of ERCP in pregnancy.**
5. **The fetus should be shielded from the ionizing radiation. Leadshields are placed under the pelvis and lower abdomen, remembering that the x ray beam originates from beneath the patient. Measuring radiation exposure to the area of the uterus also should be considered. Radiation exposure is reduced by collimating the beam to the area of interest. Use brief ‘‘snapshots’’ of fluoroscopy to confirm cannula position and common bile-duct stones.**
6. **Avoid taking hard copy x-ray films, because these involve additional radiation. Consultation with a radiologist or a hospital radiation safety officer may be useful in minimizing the radiation exposure to the fetus.With thoughtful precaution, the fetal exposure is well below the 5 to10 rad level considered to be of concern for radiation induced teratogenesis.**
7. **Only experienced endoscopists should attempt the procedure.**

<u>Electrocautery and hemostasis</u>

1. **Amniotic fluid can conduct electrical current to the fetus.**
2. **The grounding pad should be placed in such a position that the uterus is not between the electrical catheter and the grounding pad.**
3. **Bipolar electro cautery should be used to minimize this risk of ‘‘stray’’ currents going through the fetus**
4. **Although electrocautery is relatively safe when used for sphincterotomy and hemo stasis, polyp removal should be post poned until after pregnancy .**

<u>Epinephrine is pregnancy category C</u> and causes a decrease in uterine blood flow. Its safety, when used as an endoscopic injectant, has not been studied, although, when given in low-dose combinations for analgesia,it is safe.Its use for hemostasis should balance the benefits with the potential risks.

Antibiotic safety in pregnancy

Safe inpregnancy- Penicillins Quinolones Metronidazole Sulfonamides

Avoid in pregnancy

Avoid in first trimester- Cephalosporins Streptomycin Nitrofurantoin, Erythromycin (except estolate)

Avoid in third trimester-Tetracyclines Clindamycin

BREAST-FEEDING

Diagnostic and therapeutic endoscopy in lactating women do not vary in terms of indication, preprocedural preparation, procedural monitoring, radiation exposure, and endoscopic equipment. Caution needs to be exercised in the use of certain medications, because these drugs may be transferred to the infant through breast milk. In these instances, where there is a concern regarding the transfer to the infant, the woman should be advised to pump her breast milk and discard it, with the timing dependent upon the agent of concern.Sedation and analgesia The sensitivity to and risks of sedation in a lactating woman is similar to any adult.

Midazolam is excreted in breast milk. However, a study of 12 women receiving 15 mg midazolam orally found no measurable concentrations (<10 nmol/L) in milk samples obtained 7 hours after ingestion.Additional investigations on two women showed that midazolam and its metabolite, hydroxymidazolam, were undetectable after 4 hours The American Academy of Pediatrics considers the effects of midazolam unknown on the nursing infant, but the drug may be of concern. Based on these data, it would be advisable to recommend withholding nursing of the infant for at least 4 hours after administration of midazolam .

Fentanyl: is excreted in breast milk, but the concentrations are too low to be pharmacologically significant and fall to undetectable levels by 10 hours after adminis tration. The American Academy of Pediatrics considers fentanyl to be compatible with breast-feeding.

Meperidine: is concentrated in breastmilk and may be detectable up to 24 hours afteradministration. Studies have suggested that meperidine can be transferred to the breast-fed infant and may have neurobehavioral effects. Whereas, the American Academyof Pediatrics classified meperidine as compatible with breast-feeding in their 1983 statement, it may be reasonable to use an alternative, e.g.,fentanyl, where possible.

Propofol: is excreted in breast milk, with maximum concentrations at 4 to 5 hours after administration. The effects of small oral doses of propofol on the infant is unknown. Continued breast-feeding after propofol exposure is not recommended, although the period of prohibition has yet to be determined.

Naloxone and flumazenil.

The safety of naloxone and flumazenil in this setting is unknown

Antibiotics

Penicillins and cephalosporins. Penicillins and cephalosporinsare excreted in breast milk in trace amounts and are considered compatible with breast-feeding.Ofloxacin and ciprofloxacin.

Ofloxacin and ciprofloxacinare excreted in breast milk, and their toxicity has not been well studied .

Quinolones. As there is a potential for arthropathy inthe infant, quinolones should be avoided.

Sulfonamides. Sulfonamides are contraindicatedwhen nursing infants younger than 2 months because of the risk of kernicterus. It is recommended that sulfonamides be avoided in infants that are ill, premature, and glucose-6-phosphate dehydrogenase deficient.

Part 2
Gastrointestinal motility disorders

Achalasia [9]

Is a primary esophageal motor disorder of unknown etiology characterized manometrically by insufficient lower esophageal sphincter relaxation causing dysphagia to solids and liquids, regurgitation, and occasional chest pain with or without weight loss. Endoscopic finding of retained saliva with puckered gastroesophageal junction or barium swallow showing dilated esophagus with birds beaking in a symptomatic patient should prompt appropriate diagnostic and therapeutic strategies.

The gold standered test to diagnose achalasia is esophageal manometry, by which the new modalities of systems with catheter having large number of pressure sensors that measuring peristalsis pressures of the esophagus (the high resolution type) we can further classification the achalasia in to three types:

Type I associated with complete failure of peristalsis of the body of esophagus,

Type II with panesophageal pressurization of the body

Type III is called spastic achalasia which is associated with premature contractions of the body of esophagus, some studies had shown another achalasia phenotype which is called esophageal gastric outflow obstruction which associated with some instances of normal esophageal peristalsis in spite of increase of lower esophageal sphinecter relaxation pressure and can be classified as Type 1V achalasia.

Recommendations for the management of achalasia:

Achalasia must be suspected in those with dysphagia to solids and liquids and in those with regurgitation unresponsive to an adequate trial of proton pump inhibitor (PPI) therapy.

Recommendations for diagnosis of achalasia

1. **All patients with suspected achalasia who do not have evidence of a mechanical obstruction on endoscopy or esophagram should undergo esophageal motility testing before a diagnosis of achalasia can beconfirmed.**
2. **The diagnosis of achalasia is supported by esophagram findings including dilation of the esophagus, a narrow esophagogastric junction with "bird-beak" appearance, aperista lsis, and poor emptying of barium.**
3. **Barium esophagram is recommended to assess esophageal emptying and esophago gastric junction morphology in those with equivocal motility testing.**
4. **Endoscopic assessment of the gastroesophageal junction and gastric cardia is recommen ded in all patients with achalasia to rule out pseudoachalasia.**

Recommendations for treatment of achalasia

1. **Either graded pneumatic dilation (PD) or laparoscopic surgical myotomy with a partial fundoplication are recommended as initial therapy for the treatment of achalasia in those fit and willing to undergo surgery.**
2. **PD and surgical myotomy should be performed in high-volume centers of excellence.**
3. **the choice of initial therapy should be guided by patients' age, gender, preference, and local institutional expertise.**
4. **Botulinum toxin therapy is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy.**
5. **Pharmacologic therapy for achalasia is recommended for patients who are unwilling or cannot undergo definitive treatment with either PD or surgical myotomy and have failed botulinum toxin therapy. Patient follow- up after therapy may include assessment of both symptom relief and esophageal emptying by barium esophagram.**
6. **Surveillance endoscopy for esophageal cancer is not recommended.**

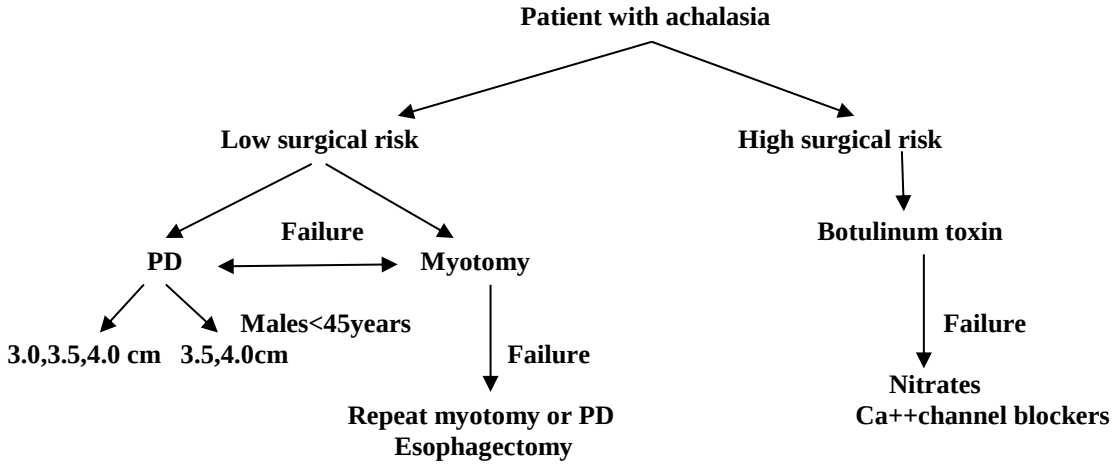


Figure 4: Recommended treatment algorithm for patients with achalasia. PD, pneumatic dilation

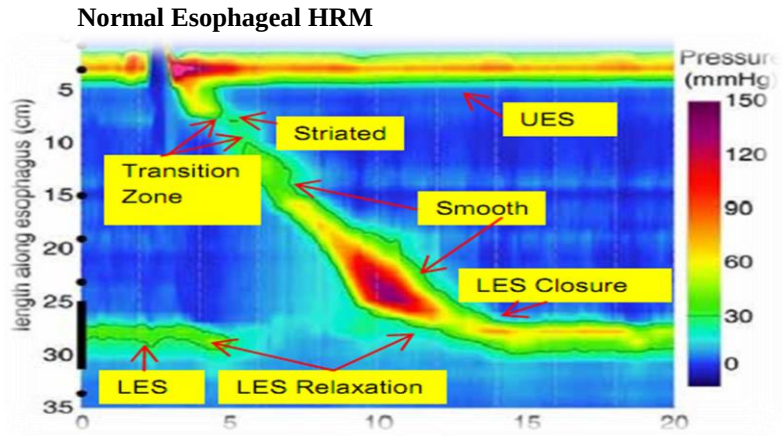


Figure 5: High Resolution Esophageal Manometry showing esophageal peristalsis during swallowing with different land marks.

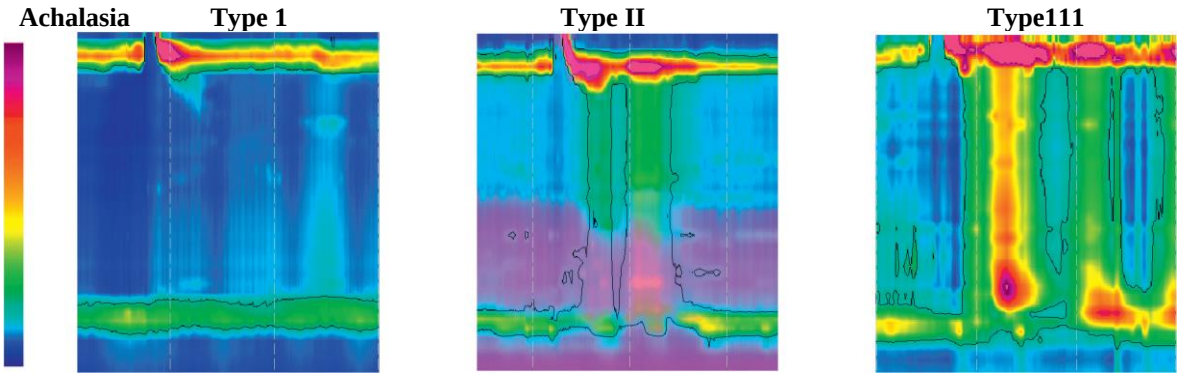


Figure 6: High Resolution Esophageal Manometry findings in different Achalsia types.

Management of Gastroparesis : Clinical Guideline [4]

Gastroparesis is defined as a syndrome of objectively delayed gastric emptying in the absence of mechanical obstruction and cardinal symptoms including early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain.

Recommendations

1. **The diagnosis of gastroparesis is based on the combination of symptoms of gastro pare sis, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying.**
2. **Accelerated gastric emptying and functional dyspepsia can present with symptoms similar to those of gastroparesis; therefore, documentation of delayed gastric emptying is recommended before selecting therapy with prokinetics agents or GES.**
3. **Patients with gastroparesis should be screened for the presence of diabetes mellitus, thyroid dysfunction, neurological disease, prior gastric or bariatric surgery, and autoimmune disorders. Patients should undergo biochemical screen for diabetes and hypothyroidism; other tests are as indicated clinically.**
4. **A prodrome suggesting a viral illness may lead to gastroparesis (postviral gastroparesis). This condition may improve over time in some patients. Clinicians should inquire about the presence of a prior acute illness suggestive of a viral infection.**
5. **Markedly uncontrolled (> 200 mg/dl) glucose levels may aggravate symptoms of gastroparesis and delay gastric emptying. Optimization of glycemic control should be a target for therapy; this may improve symptoms and the delayed gastric emptying.**
6. **Medication-induced delay in gastric emptying, particularly from narcotic and anticholinergic agents and GLP-1 and amylin analogs among diabetics, should be consi dered in patients before assigning an etiological diagnosis. Narcotics and other medica tions that can delay gastric emptying should be stopped to establish the diagnosis with a gastric emptying test.**
7. **Gastroparesis can be associated with and may aggravate GERD. Evaluation for the presence of gastroparesis should be considered in patients with GERD that is refractory to acid-suppressive treatment.**
8. **Documented delay in gastric emptying is required for the diagnosis of gastroparesis. Scintigraphic gastric emptying of solids is the standard for the evaluation of gastric emptying and the diagnosis of gastroparesis. The most reliable method and parameter for diagnosis of gastroparesis is gastric retention of solids at 4 h measured by scinti gra phy. Studies of shorter duration or based on a liquid challenge result in decreased sensitivity in the diagnosis of gastroparesis.**
9. **Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and ^{13}C breath testing using octanoate or spirulina incorporated into a solid meal; they require further validation before they can be considered as alternates to scintigraphy for diagnosis of gastroparesis.**
10. **Medications that affect gastric emptying should be stopped at least 48 h before diagno stic testing; depending on the pharmacokinetics of the medication, the drug may need to be stopped > 48 h before testing.**
11. **Patients with diabetes should have blood glucose measured before starting the gastric emptying test, and hyperglycemia treated with test started after blood glucose is < 275 mg/dl.**
12. **The presence of rumination syndrome and/or eating disorders (including anorexia nervosa and bulimia) should be considered when evaluating a patient for gastroparesis.**

These disorders may be associated with delayed gastric emptying, and identification of these disorders may alter management.

13. **CVS defined as recurrent episodic episodes of nausea and vomiting should also be considered during the patient history. These patients may require alternative therapy.**
14. **Chronic usage of cannabinoid agents may cause a syndrome similar to CVS. Patients presenting with symptoms of gastroparesis should be advised to stop usage of these agents.**
15. **The first line of management for gastroparesis patients should include restoration of fluids and electrolytes, nutritional support and in diabetics, optimization of glycemic control.**
16. **Oral intake is preferable for nutrition and hydration. Patients should receive counseling from a dietician regarding consumption of frequent small volume nutrient meals that are low in fat and soluble fiber. If unable to tolerate solid food, then use of homogenized or liquid nutrient meals is recommended.**
17. **Oral intake is the preferable route for nutrition and hydration. If oral intake is insufficient, then enteral alimentation by jejunostomy tube feeding should be pursued (after a trial of nasoenteric tube feeding). Indications for enteral nutrition include unintentional loss of 10% or more of the usual body weight during a period of 3–6 months, and/or repeated hospitalizations for refractory symptoms.**
18. **For enteral alimentation, postpyloric feeding is preferable to gastric feeding because gastric delivery can be associated with erratic nutritional support.**
19. **Enteral feeding is preferable to parenteral nutrition.**
20. **Good glycemic control should be the goal. Since acute hyperglycemia inhibits gastric emptying, it is assumed that improved glycemic control may improve gastric emptying and reduce symptoms.**
21. **Pramlintide and GLP-1 analogs may delay gastric emptying in diabetics. Cessation of these treatments and use of alternative approaches should be considered before initiation of therapy for gastroparesis.**
22. **In addition to dietary therapy, prokinetic therapy should be considered to improve gastric emptying and gastroparesis symptoms, taking into account benefits and risks of treatment.**
23. **Metoclopramide is the first line of prokinetic therapy and should be administered at the lowest effective dose. The risk of tardive dyskinesia has been estimated to be < 1%. Patients should be instructed to discontinue therapy if they develop side effects includ ing involuntary movements.**
24. **For patients unable to use metoclopramide, domperidone can be prescribed with investi gational new drug clearance from the FDA and has been shown to be as effective as metoclopramide in reducing symptoms without the propensity for causing central nervous system side effects; given propensity of domperidone to prolong corrected QT interval on electrocardiogram, a baseline electrocardiogram is recommended and treat ment withheld if the corrected QT is > 470 ms in male and 450 ms in female patients. Follow-up electrocardiogram on treatment with domperidone is also advised.**
25. **Erythromycin improves gastric emptying and symptoms from delayed gastric emptying. Administration of IV erythromycin should be considered when IV prokinetic therapy is needed in hospitalized patients. Oral treatment with erythromycin improves gastric**

emptying also. However, the long-term effectiveness of oral therapy is limited by tachy phylaxis.

26. **Treatment with antiemetic agents should occur for improvement of associated nausea and vomiting but will not result in improved gastric emptying.**
27. **TCA can be considered for refractory nausea and vomiting in gastroparesis but will not result in improved gastric emptying and may potentially retard gastric emptying.**
28. **Intrapyloric injection of botulinum toxin is not recommended for patients with gastro paresis based on randomized controlled trials.**
29. **GES may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Symptom severity and gastric emptying have been shown to improve in patients with DG, but not in patients with IG or PSG.**
30. **Gastrostomy for venting and/or jejunostomy for feeding may be performed for symptom relief.**
31. **Completion gastrectomy could be considered in patients with PSG who remain markedly symptomatic and fail medical therapy.**
32. **Surgical pyloroplasty or gastrojejunosotomy has been performed for treatment for refractory gastroparesis. However, further studies are needed before advocating this treatment. Partial gastrectomy and pyloroplasty should be used rarely, only in carefully selected patients.**
33. **Acupuncture can be considered as an alternative therapy. This has been associated with improved rates of gastric emptying and reduction of symptoms.**

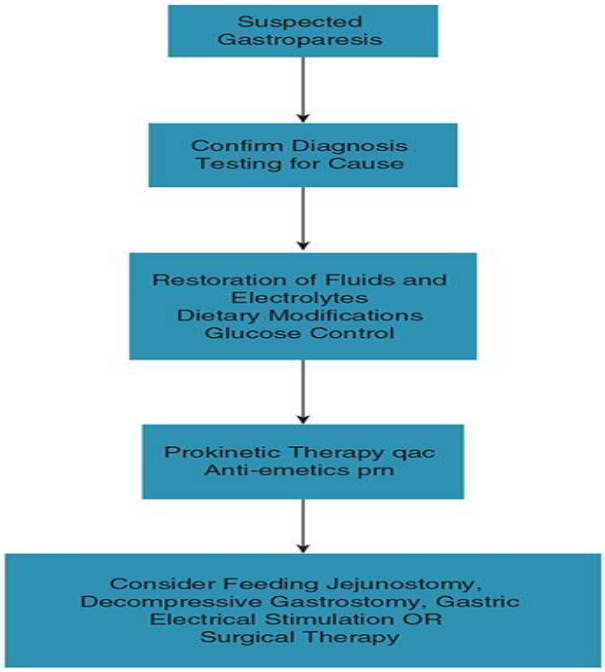


Figure 7: Step wise algorithm for gastroparesis diagnosis and management

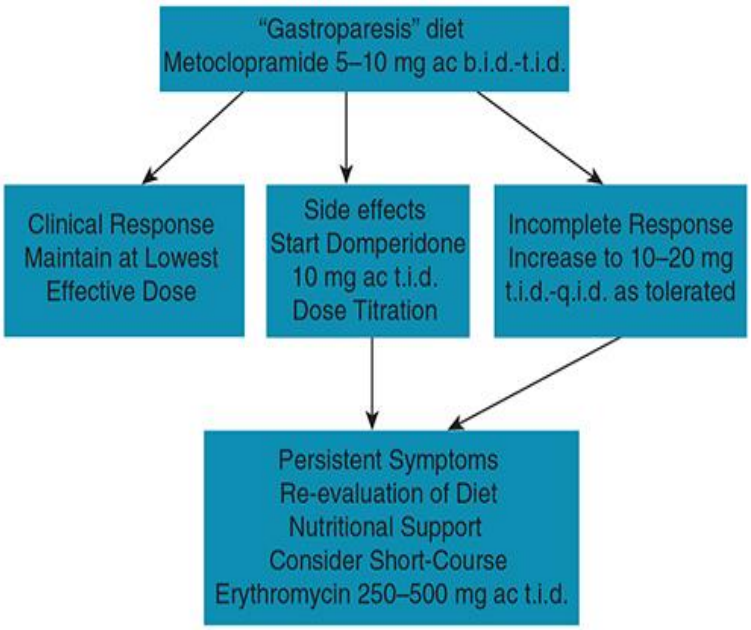


Figure 8: Treatment algorithm for gastroparesis.

Constipation [31]

Chronic constipation is a common condition with multiple mechanisms.

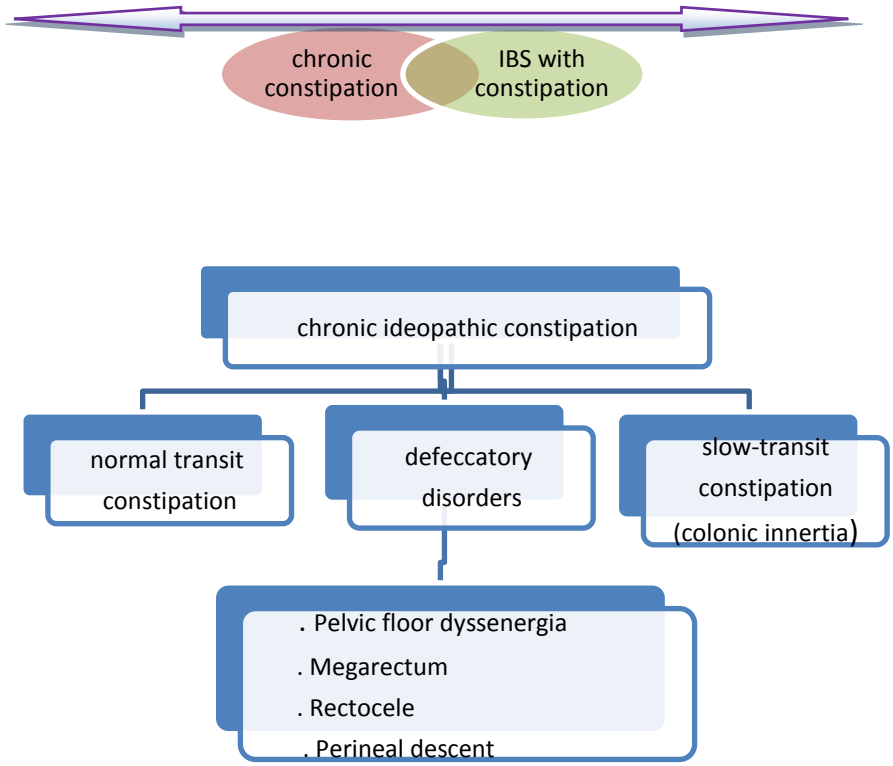


Figure 9: Pathophysiology of constipation

Distinguishing between constipation subtypes:

1. **Suggestive of slow transit**
- **Lack of urge**
- **Decreased stool frequency**

2. **Suggestive of defecatory disorder**
- **Hard stools**
- **Impaction**
- **Need for digital maneuvers**
- **Feelings of anal blockage**
- **Sever straining**
- **High anal sphincter tone at rest**
- **Minimal <1.0cm or excessive >3.5cm perineal descent**
- **Puborectalis muscle is tender on palpation**
- **Defect in anterior wall of the rectum suggestive of a rectocele**

<u>If no red flags present</u> (hematochezia, family history of colon cancer, family history of IBD, anemia, positive fecal occult blood test, unexplained weight loss≥ 10 pounds, sever persistent constipation that is unresponsive to treatment, new- onset constipation in an elderly patient) can limit diagnostic testing and start empiric treatment

PEG, lactulose, and lubiprostone have been shown to be efficacious in treating chronic idiopathic constipation.

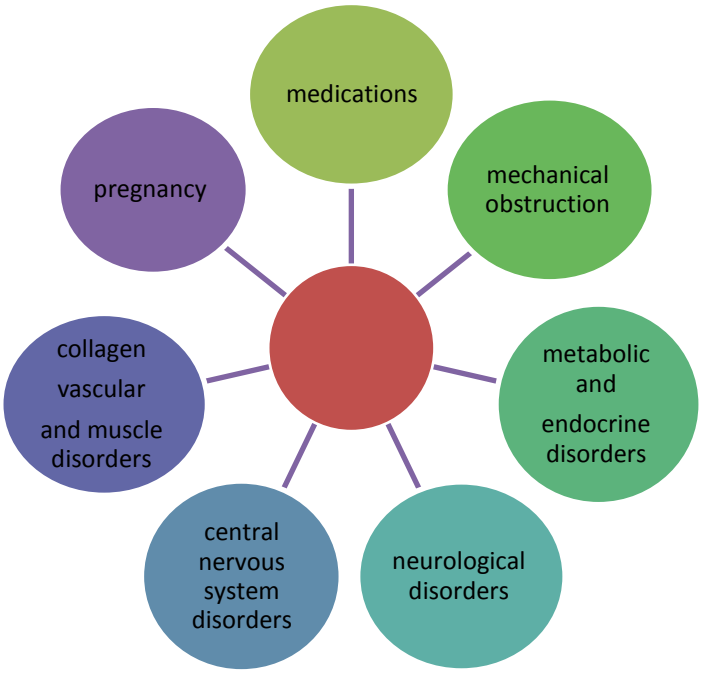


Figure 10: Potential underlying causes of constipation:

- **Basic clinical laboratory tests: complete blood count, thyroid function tests (TSH, free T4), measurement of calcium, and electrolytes.**
- **Routine colon cancer screening is recommended for all patients ≥50years.**
- **<u>Advanced Diagnostic tests:</u>**

- **Anorectal manometry (firstly-to assess the internal and external anal sphincters, pelvic floor, and associated nerves, secondly-as a screening test of choice for outlet obstruction.**
- **Balloon expulsion as simple, office-based screening test to detect defecatory disorders.**
- **Defecography (not widely available, poor reliability) to detect structural abnormalities of the rectum.**
- **Colonic transit time to measure the rate at which fecal mass moves through colon. (The 5-day marker retention study is a simple method for mesure colonic transit, Markers are ingested on one occasion and remaining markers are counted on a plain abdominal radiograph 120 hours later. If more than 20% of the markers remain in the colon, transit is delayed. Distal accumulation of markers may indicate an evacuation disorder, and in typical cases of slow-transit constipation almost all markers remain and markers are seen in both right and left colon. Several companies produce markers, but can be made from safe radiopaque tube by cutting it in small pieces (2-3mm in length), a suitable number of markers(20-24) can be placed in gelatin capsules to facilitate ingestion)**

First –line approaches to treat constipation:

- **<u>Life style measures</u>**

1. **Increase fluid(up to 1.5-2.0 L/day) and dietary fiber intake which might improve stool frquency and decrease the need for laxative.**
2. **Exercise**
3. **Dedicated time to have a BM**

- **<u>Fiber supplementation</u>(Bran fiber, Psyllium, Methyl cellulose, Calcium polycarbophil, Guar gum)**

1. **Begin with 4-6 grams per day**
2. **Increase gradually as tolerated**
3. **Recommended intake is 20 to 25 grams per day.**

- **<u>Pharmacological Treatments for Chronic Constipation</u>:**

Recommendations:

1- **Bulking agents (Psyllium/Isphagula)**
2- **Stool softeners (Ocusate sodium)**

3- **Prokinetic Agents(Prucalopride)**
4- **Osmotic Laxatives (PEG 3350, Magnesium salts)**
5- **Stimulants Laxatives (Picosulfate, Bisacodyl Senna)**
6- **prosecretaryAgents (Lubiprostone, Linaclotide, Piocanatide, Elobiobat)**

(If a dietary approach fails, polyethylene glycol(17g PEG laxative for 14days) or lubiprostone- stimulation ileal secretion and thus increasing fecal water, 24mg twice per day, can be used to promote bowel function in chronic constipation., Prokinetic agents, e.g., the 5-HT_4 receptor agonist prucalopride) can be used in costipation-predominant IBS)

Scheme for general management of constipation:

1- patient history & physical examination

2- classify the patient's type of constipation

- **normal-transit constipation,constipation-predominant IBS**
- **Slow-transit constipation(with normal pelvic floor function)**
- **Evacuation disorder**
- **Idiopathic/organic/secodary constipation.**

3- medical approach in uncomplicated normal - transit constipation without alarm symptoms:

- **Fiber, milk of magnesia**
- **Add lactulose/PEG**
- **Add bisacodyl/sodium picosulfate**
- **Adjust medication as needed**

4- In treatment-resistant constipation, specialsed investigations can often identify a cause and guide treatment:

- **Standard blood test and colonic anatomic evaluation to rule out organic causes; manage the underlying constipation causing the pathology**
- **The majority of patients will have normal/negative clinical evaluation and may meet the criteria for constipation-predominant IBS. These patients will probably benefit from treatment with fiber and/or osmotic laxatives.**

5- If treatment fails, continue with specialized testing:

- **Identify STC with a radiopaque marker study**
- **Exclude evacuation disorder with anorectal manometry and balloon expulsion test**
- **Evaluate anatomic defects with defecography.**

6- Treatment of STC with aggressive laxative programs.

- **Fiber, milk of magnesia, bisacodyl/sodium picosulfate**
- **Prucalopride, lubiprostone**
- **Add lactulose/PEG if no improvement**
- **In refractory constipation, a few highly selected patient may benefit from surgery(either total colectomy with ileorectal anastomosis or reversible colostomy)**

Irritable Bowel Syndrome[59]

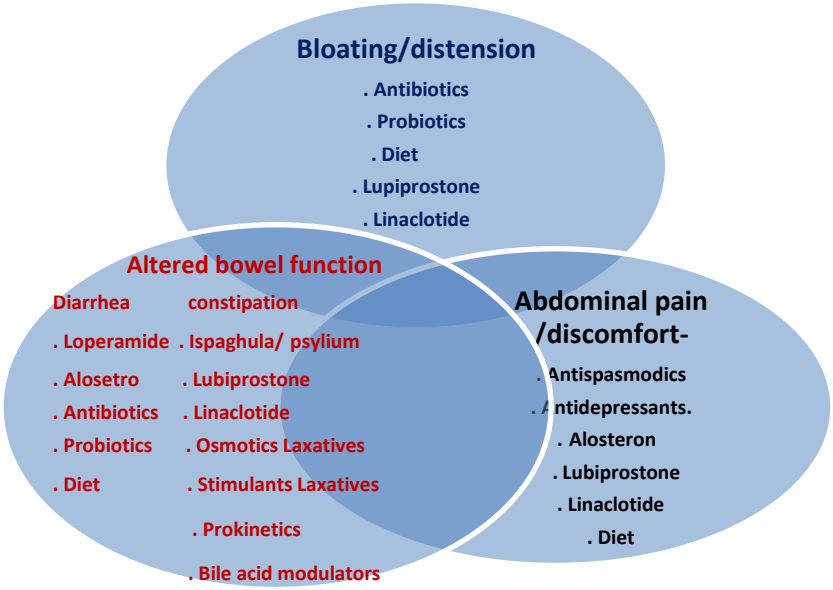
Diagnostic criteria used to define IBS:

Rome III Criteria*

Recurrent abdominal pain or discomfort at least 3 days/months associated with two or more of the following:

- **Improvement with defecation**
- **Onset associated with a change in the frequency of stool**
- **Onset associated with a change in the form of stool**

*** Criteria fulfilled for the last 3months with symptom onset at least 6months prior to diagnosis**



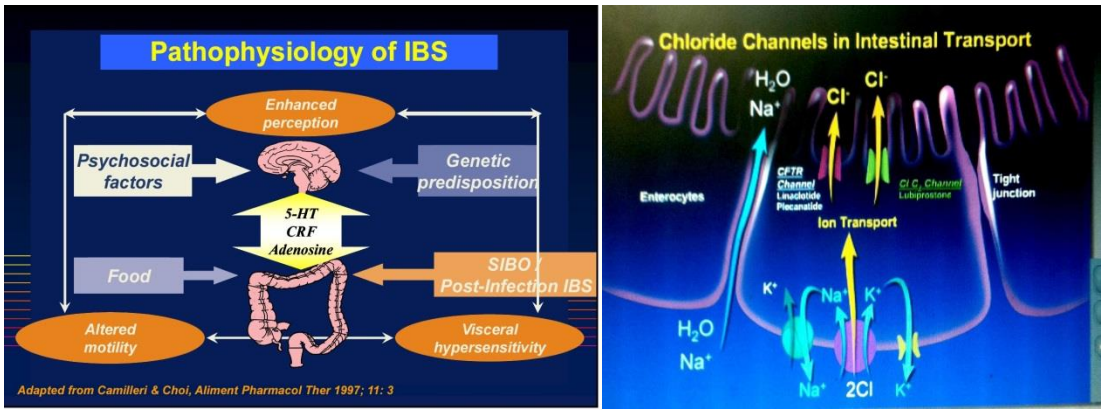


Figure 11: patho phsiology of IBS&Pharmacologic treatments for it.

Rational for use of probiotics in IBS:

- **Modification of gut mucosal barrier function**
- **Effects on the luminal microbiome**
- **Immunomodulatory effects**
- **Effect on visceral hypersensitivity.**

Linaclotide for IBS-C:

- **Minimaly absorbed, 14-aminoacid investigational peptide**
- **It is Guanylate cyclase-C(GC-C) agonist, results in generation of cyclic guanosine monophosphate(cGMP)**
- **cGMP is proposed to have two activities:**

Intracellular: activation of CFTR leads to increased luminal fluid secretion and intestinal transit.

Extracellular: inhibition of pain fiber activity, which is thought to result in reduced visceral pain.

Elobixibat(A3309): Increasing Delivery of Bile Acids to colon, induces secretion and motility through:

- **partially blocks the ileal bile acid transporter(IBAT) from the luminal side, increasing the delivery of bile acids to colon, inducing secretion and motility.**
- **It has no effect on the uptake of fat soluble nutrients.**
- **As synthesis of bile acids from cholestrol requires increased uptake of cholestrol, IBAT inhibition by A3309 leads to decrease in plasma LDL cholestrol.**
- **It is useful in IBS-C and slow transit constipation.**

Other emerging drugs that act on chloride channels intestinal transport can be used in IBS-C and Chronic constipation like:

- **Lubiprostone that acts on C1 C_2 channel**
- **Linaclotide and Plecanatide that act on CFTR channel.**

Management of Benign Anorectal Disorders[42]

These guidelines summarize the definitions, diagnostic criteria, differential diagnoses, and treatments of a group of benign disorders of anorectal function and / or structure.

Disorders of function include defecation disorders, fecal incontinence, and proctalgia syndromes, whereas disorders of structure include anal fissure and hemorrhoids.

Defecation disorders:

Recommendations for diagnostic assessment of defecation disorders:

1. **Defecation disorders (DDs) are defined as difficulty in evacuating stool from the rectum in a patient with chronic or recurring symptoms of constipation.**
2. **Gastroenterologists and other providers should not make the diagnosis of DD on the basis of a single abnormal test because none is sufficiently specific. However, confidence in the diagnosis is increased if there is a combination of a clinical history of chronic constipation and two abnormal tests, i.e., impaired ability to evacuate a 50-ml water-filled balloon or abnormal defecography and evidence from pelvic floor EMG or ARM That the patient is unable to relax pelvic floor muscles or increase rectal pressure during simulated defecation.**
3. **Digital rectal examination is a useful first test to screen for DD, as it has good negative predictive value.**
4. **Barium or MR defecography can identify structural causes of outlet obstruction if one is expected. They may also confirm or exclude the diagnosis of DD when the clinical features suggest DD but the results of ARM and BET are equivocal.**

Recommendations for treatment of disordered defecation

Biofeedback is the preferred treatment for DD in adults. And the treatment protocols include the following steps:

1) **Patient education- explains to patients that they unconsciously squeeze their anus when they are trying to defecate and this holds the stool in the rectum.**
2) **Simulated defecation training for patients who do not increase intraabdominal pressure during simulated defecation, the use of feedback on rectal balloon pressure teaches them to tighten their abdominal wall muscles and lower their diaphragm to push stool out.**
3) **Training to relax pelvic floor muscles while simulating defecation for patients who paradoxically contract their pelvic floor muscles during simulated defecation, provide visual feedback on anal canal pressure or averaged EMG activity from the anal canal to teach this skill.**
4) **Practicing simulated defecation , patients practice defecation of a lubricated, inflated balloon while the therapist gently pulls on the catheter to assist them. Remind the patient to relax the pelvic floor muscles, increase abdominal pressure using abdominal wall muscles, and concentrate on the sensations produced by balloon passage.**

Chronic proctalgia

Recommendations for diagnostic assessment

1. **Diagnosis of chronic proctalgia based on a history of recurring episodes of rectal pain, each lasting at least 20 minutes, a digital rectal examination showing tenderness to palpation of the levator ani muscles, and exclusion of other causes for rectal pain by history and diagnostic testing.**
2. **An imaging study or endoscopy is recommended to rule out structural causes of rectal pain.**
3. **A BET and ARM is needed to identify patients with chronic proctalgia and levator muscle tenderness who are likely to respond to biofeedback.**

Recommendations for treatment

1. **Biofeedback to teach relaxation of pelvic floor muscles during simulated defecation is the preferred treatment.**
2. **Electrical stimulation is superior to digital massage but inferior to biofeedback.**

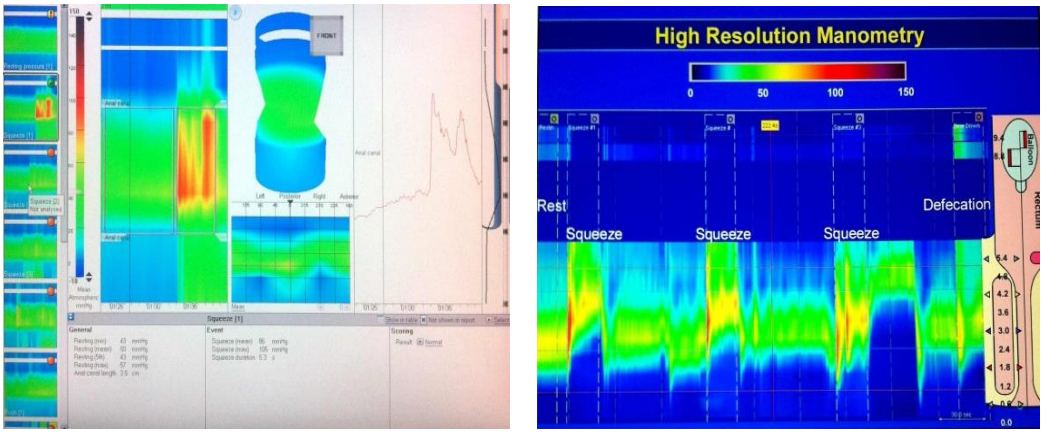


Figure 12: High resolution anorectal manometry to patient with defeculatory disorder.

Proctalgia fugax

Recommendations for diagnostic assessment

1. **We should make a diagnosis of proctalgia fugax on the basis of a history of intermittent bouts of severe pain in the anal canal or lower rectum lasting less than 20 minutes.**
2. **We should exclude structural causes of anorectal pain (e.g., anal fissure, hemorrhoids, cryptitis, and malignancy) by imaging, endoscopy, or other appropriate tests.**

Recommendations for treatment

Should assure patients that the disorder is benign. The evidence for specific treatments is no better than anecdotal.

Fecal incontinence

Continence of stool is a complex process requiring a functional sphincter muscle, the ability to squeeze the anus shut, a compliant rectum that expands to hold stool, adequate sensation in the rectum to provide warning of the need to defecate, and physical mobility to reach the bathroom. Loose stool is more difficult to control than formed stool. If a large volume of stool arrives rapidly in the rectum, there may not be enough warning to reach a bathroom.

Depending on their cause, the volume and consistency of stool and the transit time through the intestine can be treated or altered to improve continence.

Diarrhea

Diarrhea or loose stool that enters the rectum rapidly can overwhelm marginally funct ioning sphincter muscles. Dietary changes may help improve the consistency and

frequency of bowel movements. People with lactose intolerance (intolerance to lactose [milk sugar]) can cause symptoms such as gas or diarrhea may improve if they avoid dairy products or add lactose enzyme to their diet.

Constipation

While diarrhea is a contributing factor for some incontinent people, constipation or incomplete evacuation is an issue for others. If the rectum does not empty completely with defecation, the remaining stool may later leak. At times, the rectum is so full of stool (fecal impaction) that loose stool from above leaks around the solid stool in the rectum (overflow incontinence). In some of these instances the loose stool leads to an incorrect diagnosis and treatment for diarrhea, which only worsens the underlying problem.

Recommendations for diagnostic assessment for fecal incontinence

1. **We should ask patients about the presence of FI directly rather than relying on spontaneous reporting.**
2. **We should identify conditions (in the list below) that may predispose to FI.**
3. **Should determine symptom severity by quantifying stool type using the Bristol stool scale, as well as characterizing the frequency, amount of leakage, and the presence of urgency.**
4. **Should obtain bowel diaries because they are superior to self- reports for characterizing bowel habits and FI.**

Common causes of fecal incontinence

Anal sphincter weakness

- **Traumatic: obstetric, surgical (e.g., fistulotomy, internal sphincterotomy)**
- **Nontraumatic: scleroderma, internal sphincter degeneration of unknown etiology**
- **Neuropathy: peripheral (e.g., pudendal) or generalized (e.g., diabetes mellitus)**

Disturbances of pelvic floor: rectal prolapse, descending perineum syndrome

Inflammatory conditions: radiation proctitis, Crohn's disease, ulcerative colitis

Central nervous system disorders: dementia, stroke, brain tumors, multiple sclerosis, spinal cord lesions

Diarrhea: irritable bowel syndrome, post-cholecystectomy diarrhea

Other: fecal retention with over flow, behavioral disorders Reproduced and modified with permission from Bharucha.

Recommendation for physical examination

1. **Should perform a physical examination to eliminate diseases to which FI is secondary.**
2. **Should perform a digital anorectal examination to identify rectal masses, gauge anal sphincter tone at rest, during voluntary contraction of the anal sphincter and pelvic floor muscles, and during simulated defecation.**
3. **Should perform a digital rectal examination before making a referral for anorectal manometry.**

Recommendations for diagnostic testing

1. **ARM, BET, and rectal sensation should be evaluated in patients who fail to respond to conservative measures.**
2. **Pelvic floor and anal canal imaging, as well as anal EMG, should be considered for patients with reduced anal pressures who have failed conservative therapy, particularly if surgery is being considered.**

Medical treatments of diarrhea causing FI (Recommendations):

1. **Diarrhea can also be treated with medications to slow transit time through the intestine. Fiber supplements and various medications can be used to increase the consistency of the stool and slow its transit. Although individual responses vary, for many people fiber supplements absorb the excess water in loose stool resulting in fewer and more formed bowel movements.**
2. **Loperamide (Imodium) affects absorption and motility of the intestine. It is available over the counter in 2-mg tablets or liquid. It is generally effective in reducing stool**

frequency and improving stool consistency. It can be taken long-term and physical dependency has not been reported. Loperamide has also been shown, in one study, to tighten the sphincter muscle, an increase in resting tone was noted. The exact mech anism of this action is unclear.

3. **Diphenoxylate hydrochloride (Lomotil, Lonox), another anti-diarrhea agent, is a derivative of a narcotic and requires a prescription. It works directly upon internal smooth muscle and decreases stool frequency. Diphenoxylate hydrochloride works the same way as Loperamide except that it also contains atropine, which reduces diarrhea by another mechanism. However, the atropine component may also cause side effects of dry mouth and sometimes blurred vision.**
4. **Codeine, another narcotic, is also used to control diarrhea. It decreases motility in the small intestine allowing more time for absorption. Unfortunately, side effects of nausea, cramping and physical depend ency are encountered frequently.**
5. **People with abnormal or surgically removed ileum (the last portion of the small intestine) may not absorb the bile acids secreted by the liver. After gallbladder removal, some people will also have trouble absorbing all the bile acids produced. Those bile acids are irritating to the colon and may produce diarrhea. Cholestyramine (Questran) is a prescription drug that binds with bile acids in the intestines and prevents their reabsorption so they do not reach the colon. It can be helpful in controlling diarrhea after the removal of the ileum or gallbladder.**

Recommendations to manage patients with constipation and FI:

1. **The first step is to increase their fiber intake to about 25 grams of fiber per day either through their diet or fiber supplements. Fiber works by holding water in the stool so it is important to have an adequate fluid intake (the usual recommendation is to drink eight 8–ounce glasses per day).**
2. **Planned daily evacuation through bowel training programs may also help people with overflow incontinence and regulate bowel habits. People are started on high fiber diets with high adequate fluid intake, and sometimes stool softeners. They are instructed to attempt defecation at a specified time, often after a meal. If they are unable to defecate, a suppository, enema or laxative is used.**
3. **Laxatives which pull water into the bowel (osmotic laxatives) are safer long term than stimulant laxatives. Examples of safe laxatives are polyethylene glycol and lactulose.**
4. **For some people with both constipation and incontinence, retention of an enema is difficult. A possible alternative is a procedure called antegrade continent enema. A small opening in the intestine is constructed and connects to the skin. Fluid can then be administered through the opening functioning as an "enema from above" to help empty the lower colon. This procedure has been employed successfully in both children and adults.**

An individual must have some rectal sensation and sphincter muscle function and be able to comprehend the instructions.

In summary the recommendations for nonsurgical treatments

1. **Should manage patients with FI using education, dietary modifi cations, skin care, and pharmacologic agents to modify stool delivery and liquidity before diagnostic testing, particularly when symptoms are mild and not bothersome.**
2. **Should prescribe antidiarrheal agents for FI in patients with diarrhea. Pelvic floor rehabilitative techniques are effective and superior to pelvic floor exercises alone in patients with FI who do not respond to conservative measures.**
3. **Minimally invasive procedures such as injectable anal bulking agents may have a role in patients with FI who do not respond to conservative therapy.**

Recommendations for minimally invasive procedures

There is insufficient evidence to recommend radiofrequency ablation treatment to the anal sphincter (SECCA) at this time.

Recommendations for surgical treatment

1. **Sacral nerve stimulation should be considered in patients with FI who do not respond to conservative therapy.**
2. **Anal sphincteroplasty should be considered in patients with FI who do not respond to conservative therapy and who have an anatomic sphincter defect.**
3. **Dynamic graciloplasty and artificial anal sphincter, where available, may possibly allow the occasional patient with FI to avoid colostomy.**
4. **Colostomy is a last resort procedure that can markedly improve the quality of life in a patient with severe or intractable FI.**

Biofeedback

One approach to medical management of incontinence is to address stool volume and consistency. Another approach is to focus on the function of the sphincter muscle. Biofeedback is a training process in which people are provided information about a specific function as they attempt to change or improve that function. Biofeedback techni ques are used successfully to treat incontinence. It can also be used to treat constipation and pain associated with spasms of the pelvic floor muscles.

In brief, a probe or balloon is inserted into the rectum and connected to a device that displays sphincter squeeze pressures or pelvic floor muscle tension on a computer screen. The device provides feedback information to the patient as he or she undergoes training to improve their rectal sensation and sphincter function. Done in an outpatient setting, the training is inexpensive and without complications. Improvement has been reported in 50–90% of people. To be a candidate for biofeedback,

ANAL FISSURE

Definitions and epidemiology

Anal fissure is an ulcer-like, longitudinal tear in the midline of the anal canal, distal to the dentate line. In almost 90 % of cases, an idiopathic fissure is located in the posterior midline, but it can also occur in the anterior midline. Fissures in lateral positions should raise suspicion for disease processes such as Crohn's disease, tuberculosis, syphilis, HIV / AIDS, dermatologic conditions (e.g., psoriasis), and anal carcinoma. An acute fissure looks like a simple tear in the anoderm, whereas a chronic fissure, defined as lasting more than 8 to 12 weeks, is further characterized by edema and fibrosis.

Recommendations for treatment of acute anal fissure

1. **Gastroenterologists and other providers should use non operative treatments such as sitz baths, psyllium fi ber, and bulking agents as the first step in therapy of acute fissure.**

Recommendations for treatment of chronic anal fissure

2. **Gastroenterologists and other providers should treat chronic anal fissure with topical pharmacologic agents such as a calcium channel blockers or nitrates.**
3. **Gastroenterologists and other providers should refer patients who do not respond to conservative or pharmacologic treatment for local injections of botulinum toxin or surgical internal anal sphincterotomy.**

HEMORRHOIDS

Definitions and epidemiology

Hemorrhoids are among the most common problems encountered in the industrialized world. The normal proximal anal canal structures, called the anal cushions, are renamed internal hemorrhoids when they bleed and / or protrude. Hemorrhoids are not well understood, and a large number of diverse symptoms may be attributed to them by patients and referring physicians. The cardinal signs of internal hemorrhoids are hemorrhoid pattern bleeding-defined as painless bleeding with bowel movements and intermittent, reducible protrusion.

Recommendations for diagnostic assessment

Should diagnose hemorrhoids by history and physical examination. If there is bleeding, the source often requires confirmation by endoscopic studies.

<u>Recommendations for treatment of thrombosed external hemorrhoid</u>

- **Most patients who present urgently (within <3 days of onset) with a thrombosed external hemorrhoid benefit from excision.**

<u>Recommendation for treatment of internal hemorrhoids</u>

1. **Should treat patients with symptomatic hemorrhoids first with increased fiber intake and adequate fluids.**
2. **Should consider patients with first-to third-degree hemorrhoids that remain sympto matic after dietary modifications for office procedures such as banding, sclerotherapy, and infrared coagulation. Ligation is probably the most effective option.**
3. **Should refer for surgical operations (hemorrhoidectomy, stapled hemorrhoidopexy , and Doppler-assisted hemorrhoidal artery ligation) those patients :**

- **Who are refractory to or cannot tolerate office procedures,**
- **Who have large, symptomatic external tags along with their hemorrhoids,**
- **Who have large third-degree hemorrhoids,**
- **or who have fourth-degree hemorrhoids.**

Part 3
Hepatology

Diagnosis, Management, and Treatment of Hepatitis C: An Update [22,23,30]

Hepatitis C virus (HCV) is an RNA containing virus of the Flavivridae type, the inocubation period varies between 14-160 days with a mean of 7 weeks, most acute and chronic infections are asymptomatic if symptoms occur they usually last 2-12 weeks. The lack of a strong T-lymphocyte response is responsible for the high rate of chronic infection. Anti HCV is not protective(neutralizing) antibodies.

Recommendations (Prevention of HCV infection):

1. **as part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection.**
2. **Persons who are at risk should be tested for the presence of HCV infection.**
3. **All countries must introduce universal screening of blood donors for anti-HCV antibodies, with third-or fourth- generation EIA or CIA**
4. **Persons infected with HCV should be counseled on how to avoid HCV transmission to others.**
5. **Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV.**
6. **Acute hepatitis C is a well-recognized entity. In the stage of acute hepatitis, patients should be monitored for spontaneous viral clearance. Patient with symptomatic acute hepatitis and female patients are more likely to clear the virus. A spontaneous clearance is also more likely in symptomatic patients, women, and those infected with HCV genotype 3.**
7. **In chronic HCV infection, elevated serum ALT level suggests progressive liver damage. However, normal ALT level does not exclude significant liver disease. The liver fibrosis progression rate is 0.10–0.13 U/year in untreated patients.**
8. **In chronic HCV infection, it is well recognized that excessive alcohol and insulin resistance are associated with disease progression. It is recommended that patients consume less than the WHO guidelines for alcohol intake, and that obesity and insulin resistance be controlled through exercise and dietary, (Persons with chronic HCV infection should be advised to abstain from alcohol consumption an in obse patients intervention to achieve ideal BMI).**
9. **In patients with HCV-related liver cirrhosis, the risk of hepatic decompensation is approximately 3–4% per year and 1.4–6.9% per year for HCC. In chronic HCV infection, a surveillance program for the early detection of HCC should be offered. Invasive or noninvasive procedures may predict progression toward liver fibrosis and cirrhosis. Staging of fibrosis with transient elastography with or without liver biopsy may enable early prediction of HCC occurrence.**
10. **All persons with chronic HCV infection who lack antibodies to hepatitis A and B should be offered vaccination against these two viral infections.**
11. **No recommendation can be made for the use of herbal products. There is no current Evidence that herbal products have a role in the treatment of patients with acute or chronic HCV infection.**
12. **HCV RNA testing should be performed in:**

a) **Patients with a positive anti-HCV test**
b) **Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay**
c) **Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection.**

HCV infection and laboratory testing: Recommendations:

1. **Anti-HCV antibody testing should be conducted with approved anti-HCV third or fourth generation EIA or CIA.**
2. **Samples that test negative with an approved EIA/CIA can be reported as anti-HCV negative. However, it should be noted that individuals on hemodialysis or those coinfected with HIV might be HCV RNA positive, but anti-HCV negative.**
3. **Samples reactive in an approved single EIA can be reported as an anti-HCV positive, provided signal to-cut off ratio is sufficiently high to be predictive of a true positive.**
4. **For samples that do not reach this threshold or have reactivity close to cutoff, a sensitive HCV RNA test should be considered and/or a further follow-up sample be obtained for both anti-HCV and HCV RNA NAT.**
5. **HCV RNA testing requires appropriate contamination controls.**
6. **A dedicated sample/aliquot not derived from other test samples is preferred for HCV testing.**
7. **HCV RNA quantitation should be reported in IU/mL (optional to include copies/mL).**
8. **Monitoring of HCV loads during treatment is important for response-guided therapy to determine treatment protocol and duration.**
9. **HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response.**
10. **partipation in an external quality assurance program for all testing is ideal.**
11. **Internal quality assurance testing is required for all testing.**
12. **Testing DBSs that are sampled with a disposable lancet and are stable at room tempera ture could enhance the public health surveillance of HCV among IDUs.**
13. **A liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prog nostic purposes or to make a decision regarding treatment.**
14. **Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitisC infection, but should not replace the liver biopsy in routine clinical practice.**

Treatment of HCV infection: Recommendations

1. **Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, the presence of comorbid conditions and the patient's readiness for treatment.**
2. **The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels.**
3. **<u>Prior to starting interferon and ribavirin treatment,</u> the following should be completed:**
   - **Full medical history and clinical examination.**
   - **Baseline laboratory tests including Hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosph atase levels), calculated glomerular filtration rate (GFR)., complete blood count (CBC); international normalized ratio (INR), Thyroid-stimulating hormone (TSH) if IFN is used, and auto-antibody studies.**
   - **Serum HCV RNA (quantitative) and HCV genotyping/ sero-typing.**
   - **Liver biopsy, if appropriate.**
   - **Cardiac and pulmonary evaluation, if indicated.**
   - **Psychiatric evaluation, if indicated.**

- **Pregnancy test.**

(Assessment of potential drug-drug interactions with concomitant medications is recommended).

4. **<u>Recommended monitoring during antiviral therapy:</u>**
   - **clinic visit telephone contact, , Full medical history and clinical examination at every visit. Psychiatric evaluation, Chest X-ray, Cardiac assessment ophthalmic or audiogram examination, if are indicated.Reinforcement of advice regarding need for contraception. Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) are frequent Special caution against skin disorders such as rash, drug eruption, and erythema should be taken at every hospital visit.When skin disorders of grade 2–4 occur, clinicians should consult adermatologist for the reduction or discontinuation of protease inhibitors.**
   - **Complete blood count at 2, 4, and 6 weeks and every 4 weeks thereafter, Liver biochemistry and renal function (calculated GFR or creatinine level)every 4 weeks.**
   - **TSH is recommended every 12weeks for patient receiving IFN.**
   - **More frequent assessment for drug-related toxic effects (e.g. CBC for patients receiving RBV) is recommended as clinically indicated.**
   - **Any 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy. Any increase in ALT activity of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or increased bilirubin, alkaline phosphatase or INR, should also prompt discontinuation of therapy.**
   - **Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.**
   - **Quantitative HCV viral load testing is recommended after 4 weeks and 12 weeks of therapy. Antiviral drug therapy should not be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.**
   - **Quantitative HCV viral load testing can be considered at the end of treatment and 24weeks or longer following the completion of therapy.**
5. **For patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis provided they do not have contraindications to therapy, while Patients with no (F0) or minimal (F1) hepatic fibrosis do not necessarily need antiviral therapy. However, they should receive advice concerning the following:**
   - **Natural history of their disease, especially the likelihood and projected timing of any possible liver-related complications.**
   - **Efficacy of available treatments.**
   - **Cost of available treatments.**
   - **Adverse effects of available treatments, and need for ongoing contraception after administration of ribavirin.**
6. **Special care for interferon and ribavirin treatment includes the following.**
   - **Persons who take ribavirin should practice strict contraception during treatment and for 6 months after the termination of treatment.**
   - **Adverse events are usually more severe in the initial weeks of treatment and can often be managed with analgesics and antidepressants.**
   - **Adverse events due to ribavirin and interferon can be controlled by erythropoietin and granulocyte colony stimulating factor (GCSF).**
7. **Conditions requiring special caution for interferon administration(neutropenia-neutro phil count <1.500 cells/IL, thrombocytopenia-platelet count<85,000/IL, organ transplan**

tation,history of auto-immune disease, presence of thyroid autoantibodies, age >70years of life, whether acute or chronic infection, IL28B (interferon lambda 3)- associated SNPs, favorable genotype, virological factors (HCV RNA, low viral load-<400000 IU/mL, HCV genotype,non-1, HCV genotype 1 core substitutions, 70 wild, HCV genotype1 NS5A 2209-2248, ISDR mutations, mutant type, HCV genotype 1 NS5A 2334-2379, IRRDR), Therapeutic factors (adherence to therapy-dose and duration, reapid virological response), Treatment-nai'ye(ISDR interferone sensitivity-determining region, IRRDR interferon/ ribavirin resistance-determining region.

Treatment of Acute HCV infection: Recommendations:

1. **Treatment of acute hepatitis C should be delayed for 8–16 weeks to allow for spontaneous resolution, especially in symptomatic patients. However, patients with an unfavorable IL28B genotype can be offered treatment earlier than 12 weeks, as the chances of spontaneous resolution of infection are low.**
2. **Both standard interferon (high dose) and peginterferon can be used for treating subjects with acute hepatitis C**
3. **Treatment of acute HCV infection should be continued for 24 weeks in the case of genotype 1 and for 12 weeks in the case of genotypes 2 or 3.**
4. **The addition of ribavirin does not appear to increase SVR in patients with acute hepatitis C treated with either interferon or peginterferon.**
5. **Although excellent results were achieved using standard interferon monotherapy, it is appropriate to consider the use of peg interferon because of its greater ease of administration.**
6. **Patients with active drug use and HCV/HIV coinfection can be usefully treated with peginterferon for 24 weeks. Chronic HCV infection (treatment with SOC).**
7. **SVR should be the goal of antiviral therapy for HCV infection. Biochemical (ALT levels) and histological response should be used only as secondary descriptors, although normalization of ALT levels histological improvement might also modify the natural history and clinical outcomes.**

Treatment for Chronic HCV infection:

The optimal therapy for chronic HCV infection is the combination of peginterferon and ribavirin . HCV RNA should be tested by a highly sensitive quantitative assay at the initiation of or short before treatment and at week 12 of therapy,

Genotypes 1 and 4 HCV Infection: Recommendations:

1. **Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peginterferon alfa-2a is 180 μg subcutaneously per week together with ribavirin using doses of 1,000 mg for those < 75 kg in weight and 1,200 mg for those >75 kg; the dose for peginterferon alfa-2b is 1.5 μg/ kg subcutaneously per week together with ribavirin using doses of 800 mg for those weighing <65 ; 1,000 mg for those weighing 65 kg to 85 kg, 1,200 mg for >85 kg to 105 kg, and 1,400 mg for >105 kg.**
2. **Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment).**
3. **Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re- tested at week 24, and if HCV RNA remains positive, treatment should discontinued.**
4. **For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks.**
5. **Patients with genotype 1 infection whose treatment continues through 48 to 72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a**

sustained virological response(SVR; HC RNA negative 24 weeks after cessation of treatment).

(APASL consensus statement)In chronic HCV genotype 1 infection, the following apply, and could be considered for therapy, especially when liver biopsy shows moderate to advanced fibrosis, their ALT level is close to the upper limit, and the expected SVR rate is high.

A- Treatment with peginterferon and ribavirin for 48 weeks is recommended.

B- In patients who achieve an RVR at week 4, treatment can be discontinued after24 weeks if the HCV RNA at baseline is >400,000 IU/mL. • In patients who achieve a complete EVR at week 12, treatment should be continued up to 48 weeks.

C- In patients who do not achieve an EVR at week 12, but show a significant reduction in HCV RNA levels (partial EVR) and negativity of HCV RNA at week late virological response, (LVR), treatment may be continued up to 72 weeks

Genotype 2 or Genotype 3 HCV Infection: Recommendations:

1. **Patients with HCV genotype 2 and 3 can be treated regardless of the stage of the disease.**
2. **Treatment with peginterferon plus ribavirin should be administered for 24weeks, using a ribavirin dose of 800 mg.**
3. **Patients whose treatment continues through 24 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative should be retested for HCV RNA 24 weeks later to evaluate for an SVR.**

(APASL consensus statement) ,In chronic HCV genotype 2 or 3 infection, the following apply).

- **Treatment with either conventional interferon alfa plus ribavirin or peginterferon alfa with or With out ribavirin for 24 weeks is recommended (although peginterferon plus ribavirin might be more effective in patients with cirrhosis or a high viral load.**
- **There is some evidence that shortening duration of therapy to 16weeks in patients with HCV genotype 2 infection provides equal SVR to 24 weeks of treatment.**

Retreatment for patients with HCV infection: Recommendations:

1. **Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after A prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered.**
2. **Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or with out ribavirin, or with peg- interferon monotherapy, particularly if they have bridging fibrosis or cirrhosis .**
3. **Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin.**

After treatment: Recommendations:

1. **If end-of-treatment virological response (ETVR) is achieved, the patient should be followed up and serum HCV RNA levels should be reassessed 24 weeks later to document SVR.**
2. **Effective birth control should be continued for at least 6 months after the end of treatment with ribavirin.**
3. **In those who have undergone previous treatment with conventional interferon or pegin-terferon monotherapy and experienced non-response or relapse, retreatment with peginterferon plus ribavirin can be considered, particularly in those with significant fibrosis or cirrhosis.**
4. **Peginterferon maintenance therapy is not universally recommended to CHC patients who do not respond to standard therapy.**

Recommendations for discontinuation of treatment because of lack of efficacy.

If quantitative HCV viral load is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment 6weeks). If quantitative HCV viral load has increased by greater than 10folds (>1 $\log_{10}$ IU/Ml) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.

Recommended monitoring for pregnancy-related issues prior to and during antiviral therapy that includes RBV.

1. **Women of childbearing age should be cautioned not to become pregnant while receiving RBV- containing antiviral regimens, and for 6months after stopping.**
2. **Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes RBV.**
3. **Assessment of contraceptive use and possible pregnancy is recommended at appropriate intervals during (and for 6months after) RBV treatment for women of childbearing potential, and for female partners of men who receive RBV treatment.**

Recommended monitoring for patients in whom treatment failed to achieve a sustained virological response.

1. **Disease progression assessment every 6months to 12months with a hepatic function panel, complete blood count (CBC), and international normalized ration (INR) is recommended.**
2. **Surveillance for hepatocellular carcinoma with ultrasound testing every 6months is recommended for patients with advanced fibrosis (Metavir stage F3 or F4).**
3. **Endoscopic surveillance for esophageal varices is recommended if cirrhosis is present.**
4. **Evaluation for retreatment is recommended as effective alternative treatments become available. While routine monitoring for HCV drug resistance-associated variants during therapy is not recommended.**

Recommended follow-up for patients who achieve a sustained virological response (SVR):

1. **For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0-F2), recommended follow -up is the same as if they were never infected with HCV.**
2. **Assessment for HCV recurrence or re-infection is recommended only if the patient has going risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than anti-HCV serology test is recommended to test for HCV recurrence or re-infection.**
3. **Surveillance for hepatocellular carcinoma with twice-yearly ultrasound testing is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4) who achieve an SVR.**
4. **A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated.**
5. **Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR.**

HCV and HBV coinfection: Recommendations:

1. **Routine screening for HBs Ag is recommended in patients with chronic HCV infection, especially IDUs or other high-risk populations.**
2. **Routine testing for serum HBV DNA is not recommended in HBs Ag-negative patients with chronic HCV infection**
3. **HCC screening tests, including liver ultrasonography and tests for alpha-fetoprotein levels, are required for coinfected patients.**
4. **HBV and HCV coinfected patients may be selected for antiviral treatment by the same criteria as those used for patients with mono-infection.**

5. **It is helpful to determine which virus is dominant in patients with dual infection before commencing treatment.**
6. **In patients who are anti-HCV, HBs Ag, and HCV PCR positive, peginterferon alfa combined with ribavirin, 48 weeks for HCV genotype 1 and 24 weeks for HCV genotype 2 or 3, is recommended**
7. **For patients who test positive for both anti-HCV and HBs Ag, but have significant levels of serum HBV DNA and undetectable serum HCV RNA, peg-IFN alfa or nucleos (t)ide analogs or both can be used.**
8. **In HCV/HBV coinfected patients who achieve an SVR with peginterferon alfa and ribavirin treatment, long term follow-up and monitoring for relapse of HBV infection are recommended.**
9. **HBV vaccination should be offered for hepatitis C patients who are HBsAg negative.**

For children with HCV infection: recommendations:

1. **The diagnosis and testing of children suspected of being infected with HCV should proceed as for adults.**
2. **Routine testing for anti-HCV at birth of children born to HCV-infected mothers is not recommended because of the high rate of positive antibody due to passive transfer from the mother. Testing for anti-HCV may be performed at 18 months of age or older.**
3. **Testing for HCV RNA may be considered at 1-2 months of age in infants born to HCV-infected mothers if early diagnosis is desired.**
4. **Children aged 2-17 years who are infected with HCV should be considered**
5. **Children should be treated with pegylated interferon alfa-2b, 60 μg/m2 weekly (modify the dose according to body surface area) in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks**

HCV infection in thalassemia and hemophilia: Recommendations:

1. **Patients with thalassemia or hemophilia who have chronic HCV infection should be considered For anti-viral treatment.**
2. **In patients with thalassemia or hemophilia, peginterferon monotherapy or combination therapy with ribavirin is recommended, but careful monitoring is needed to detect anemia and other hematologic side effects.**
3. **Following bone marrow transplantation in thalassemia patients, treatment of HCV infection should Be considered after immune suppression therapy has been stopped.**

For patient with HIV infection: Recommendations:

1. **Anti-HCV testing should be performed in all HIV-infected persons.**
2. **HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease.**
3. **Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy.**
4. **Initial treatment of hepatitis C in most HIV infected patients should be peginterferon alfa Plus ribavirin for 48 weeks at doses recommended for HCVmono-infected patients.**
5. **When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin.**
6. **HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peg interferon Alfa and ribavirin and may be candidates for liver transplantation.**

While APASL consensus statements for HCV and HIV coinfection were:

- **Routine screening for HIV is recommended in patients with hepatitis C following exposure risk assessment and pretest counseling.**
- **HIV/HCV coinfected patients with advanced HIV disease (CD4 count<100/lL) should receive highly active anti-retroviral therapy (HAART) with HCV treatment delayed until immune function is improved, preferably until a CD4 count>200/lL is achieved.**
- **Antiretroviral therapy-naı̈ve HIV/HCV coinfected patients with a CD4 count of 100–350/lL should commence HAART prior to HCV treatment.**
- **HIV/HCV coinfected patients with a CD4 count >350/lL should be considered for HCV treatment and do not require HAART.**
- **Peginterferon and ribavirin combination therapy for 48 weeks is the recommended HCV treatment; weight-based ribavirin dosing should be considered for HCV genotype 1 patients**
- **Undetectable HCV RNA at week 4 of treatment is the best predictor of SVR in HCV/HIV coinfected patients. Extending peginterferon and ribavirin treatment beyond 48 weeks may not improve the overall treatment outcomes.**
- **Deferral of HCV treatment should be considered in HIV/HCV coinfected patients with HCV genotype 1 and high viral load (>800,000 IU/mL) if early liver disease (F0/1) is detected on liver biopsy.**
- **There is insufficient evidence to support administration of HCV treatment to patients with persistently normal ALT levels, but treatment could be considered in those with moderate or severe fibrosis.**
- **SVR to peginterferon alfa and ribavirin reduces liver related complications and mortality in HCV/HIV coinfected patients.**
- **Didanosine, zidovudine, and stavudin should be avoided if the HCV treatment regimen includes ribavirin.**
- **As observed in HCV mono-infection, IL28B gene variations may independently predict SVR in HCV/ HIV coinfected patients with genotype 1 or non-genotype 1 HCV infection.**

for patients with chronic kidney disease: Recommendations

1. **HCV-infected patients should be screened for proteinuria and hematuria at least annually so as to detect HCV-associated kidney disease.**
2. **Regular serological screening of dialysis staff is indicated.**
3. **Maintenance hemodialysis (CKD stage 5D) confers a significant risk of nosocomial infection. Therefore, standard precautions for prevention of nosocomial infections must be rigorously observed.**
4. **All persons with chronic kidney disease awaiting renal replacement therapy, namely Hemodialysis or kidney transplantation, should be screened for hepatitis C in order to plan for management and treatment.**
5. **Patients on hemodialysis should be screened with serological tests and RT-PCR at first hemodialysis or when transferring from another hemodialysis unit. Maintenance hemodialysis patients and kidney transplant candidates should be tested for Anti-HCV antibodies every 6–12 months, and RT-PCR should be performed for patients with unexplained elevated amino-transferases (s).**
6. **The decision to perform a liver biopsy in patients with kidney disease should be individualized, based upon the clinical assessment for the need for therapy and the need to establish the severity of the liver disease. In dialysis patients with chronic HCV infection, liver biopsy is not mandatory, but is recommended especially when the results**

would influence treatment decisions and when progression of the liver disease needs to be assessed.

7. **Persons with chronic HCV infection and mild kidney disease (GFR >60 mL/minute) can be treated with the same combination antiviral therapy as that used in persons without kidney disease.**
8. **Persons with chronic HCV infection and severe kidney disease not undergoing hemodialysis can be treated with reduced doses of both peg interferon(alpha- 2a, 135 μg/week;alpha-2b,1μg/kg/week)and ribavirin (200-800 mg/ day) with careful monitoring for adverse effects.**
9. **Treatment of HCV in patients on dialysis may be considered with either standard interferon (2a or 2b) in a dose of 3 mU t.i.w. or reduced dose pegylated interferon 2a, 135 ug/week or 2b 1ug/kg/week. Ribavirin can be used in combination with interferon in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects.**
10. **Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis or unless the benefits of the treatment outweigh the risks.**
11. **Patients with cryoglobulinemia and mild to moderate proteinuria and slowly progressive Kidney disease can be treated with either standard interferon or reduced doses of pegylated interferon alfa and ribavirin.**
12. **Patients with cryoglobulinemia and marked proteinuria with evidence of progressive kidney disease or an acute flare of cryoglobulinemia can be treated with Rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange followed by interfero n-based treatment once the acute process has subsided.**

cirrhotic patients: Recommendations

1. **Patients with HCV-related compensated cirrhosis (CTP class A) but not decompensated Cirrhosis can be considered for treatment, can be treated with the standard regime of pegylated interferon and ribavirin but will require close monitoring for adverse events.**
2. **Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC.**
3. **Patients with HCV-related decompensated cirrhosis should be referred for considera tion of liver transplantation.(Patients with decompensated hepatitis C can be considered for antiviral treatment, provided they have a Child–Pugh score B7 and a MELD score B18 with a platelet count>60,000. Patients should be monitored closely by an experienced liver unit. A low ascending dose regimen should be adopted, and supportive therapies to prevent variceal bleeding and infections, and correct cytopenias are recommended)**
4. **Interferon-based therapy may be initiated at a lower dose in patients with decompen sa ted cirrhosis (CTP class B and C), as long as treatment is administered by experienced clinicians with vigilant monitoring for adverse events preferably in patients who have already been accepted as candidates for liver transplan tation.**
5. **Growth factors can be used for treatment-associated anemia and leukopenia to improve quality of life and may limit the need for antiviral dose reductions in patients with decompensated cirrhosis.**

For patients with liver transplantation: Recommendations:

1. **Treatment of HCV-related disease following liver transplantation should be initiate in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation.(In hepatitis C patients being considered for liver transplantation, the minimal listing criteria should be identical to those for other primary liver diseases).**

2. **Treatment of established recurrence (6 months after transplant) should be considered in those with sever disease. The preferred regimen is at least 48weeks peg interferon plus ribavirin.**
3. **Peg interferon alpha either with or without ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation.**
4. **Over-immunosuppression should be avoided in the early post-transplant period.**
5. **Interferon-based therapy should not be used in recipients of heart, lung, and kidney grafts, except for patients who develop fibrosing cholestatic hepatitis.**
6. **Rapid steroid withdrawal should also be avoided in the later post-transplant period.**

Illicit drug users and psychiatric patients: Recommendations:

1. **Treatment of HCV infection can be considered for persons even if they currently use illicit drugs or who are on a methadone maintenance program, provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception.**
2. **Persons who use illicit drugs should receive continued support from drug abuse and psychiatric counseling services as an important adjunct to treatment of HCV infection.**
3. **Patients with HCV infection and concomitant mental and psychiatric disorders can be considered for treatment using the currently approved regimens.**
4. **Treatment of hepatitis C infection in patients with psychiatric disorders should be undertaken only with the support of a multi-displinary team that should include psychiatric counseling services.**

HCV infection and extrahepatic manifestations: Recommendations:

1. **Patients with symptomatic mixed cryoglobulinemia, glomerulonephritis, neuropathy, or vasculitis should be screened for HCV infection and considered for standard antiviral treatment if positive.**
2. **Patients with glomerulonephritis and impaired renal function (GFR 50 mL/min) should be treated with interferon monotherapy.**
3. **Patients with low-grade B-cell non-Hodgkin's lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and splenic lymphoma should be screened for HCV infection as antiviral therapy might induce remission.**
4. **Patients with life-threatening vasculitis and organ failure can be considered for anti-B-cell therapy**

Recommendations for updated initial treatment of HCV infection:

Genotype 1

Genotype 1a- Three options:

1. **Daily fixed dose combination of ledipasvir (90mg)/ sofosbuvir (400mg) for 12 weeks is recommended for treatment-naïve patients with HCV genotype 1a infection.**
2. **Daily fixed-dose combination of paritaprevir(150mg)/ritonavir (100mg) /ombitasvir (25mg) plus twice-daily dosed dasabuvir (250mg) and weight-based RBV (1000mg if wt.>75kg) to (1200 mg if > 75kg) for 12weeks(no cirrhosis) or 24 weeks (cirrhosis)**
3. **Daily sofosbuvir (400mg) plus simeprevir (150mg) with or without weight-based RBV for 12 weeks (no cirrhosis), or 24 weeks (cirrhosis)**

Genotype 1b- also three options:

1. **Is the same as in Genotype 1a first option.**
2. **is the same as in genotype 1a second option**
3. **Is the same as in genotype 1a third option without RBV.**

Genotype 2

Daily sofosbuvir (400mg) and weight-based RBV is recommended. Extending treatment to 16 weeks is recommended in patients with cirrhosis

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Genotype 3

1. **Daily sofosbuvir (400mg) and weight -based RBV for 24 weeks.**
2. **Alternative regimen for treatment-naïve patients with HCV Genotype 3 infection: Daily sofosbuvir (400mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks.**

Genotype 4

Three options

1. **Daily fixed-dose combination of ledipavir (90mg)/sofosbuvir (400mg) for 12weeks**
2. **Daily fixed-dose combination of partiprevir (150mg)/ritonavir(100mg)/ombitasvir (25mg) and weight-based RBV for 12weeks .**
3. **Daily sofosbuvir (400mg) and weight-based RBV for 24 weeks.**

Alternative regimen for treatment-naïve patients with HCV genotype 4.

1. **Daily sofosbuvir(400mg) and weight-based RBV plus weekly PEG-IFN for 12weeks is an acceptable regimen .**
2. **Daily sofosbuvir (400mg) plus simeprevir (150mg) with or without weight-based RBV for 12weeks is also an acceptable regimen.**

Genotype 5 and 6

Recommended regimen for treatment-naïve patients with HCV genotype 5:

1. **Daily sofosbuvir (400mg) and weight-based RBV plus weekly PEG-IFN for 12weeks alternative regimen (IFN-eligible) weekly PEG-INF plus weight-based RBV for 48weeks.**
2. **Recommended regimen for treatment-naïve patients with HCV genotype 6: Daily fixed-dose compensation of ledipasvir (90mg)/sofosbuvir (400mg) for 12 weeks. Alternative regimen (IFN-eligible patients) Daily sofosbuvir (400mg) and weight based-RBV plus weekly PEG-INF for 12weeks.**

N.B: -Daclatasvir 60mg with Sofosbuvir 400mg is effective in type 1 and 3 HCV genotype, not need adjusment if creatinine clearance is more than 30ml/hour.

-a new FDA approval useful in genotype 1 and 4 called Zepatier(Grazoprevir 50mg/Elbasvir 100mg)

Recommendations for chronic HBV management [28,30]

Hepatitis B virus(HBV) is a DNA containing virus of Hepadnaviridae type. The virus is present in most of body fluids of individuals with acute or chronic hepatitis and in inactive carriers.
HBV incubation time is 60days and can vary from 28-160 days
Approximately 30% of infections among adults present as iteric hepatitis and 0.1-0.5% develope fulminant hepatitis(when fulminant hepatitis occurs the immune response to infected hepatocytes is overwhelming and there is often no evidence of viral replication, testing for HbsAg may be negative; hence the need for further anti HBc(IgM) testing.

GUIDELINES FOR THE PREVENTION, CARE AND TREATMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION MARCH 2015

Acute HBV infection	**New-onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs (antibodies to hepatitis B surface antigen), usually within 3 months.**
Chronic HBV infection	**Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV. Throughout the guidelines, the term chronic hepatitis B (CHB) has been used to indicate chronic HBV infection.**
Immune-tolerant phase	**High replicative phase of infection seen in the early stage of CHB among people infected at birth or in early childhood**
Immune-active phase	**Phase of hepatitis B e antigen (HBeAg)-positive disease characterized by fluctuating aminotransferases and high HBV DNA concentrations. May result in seroconversion from HBeAg to anti-HBe (antibody to hepatitis B e antigen)**
Inactive phase (or Immune - control phase)	**Low replicative phase of chronic hepatitis B characterized by HBeAg negativity, anti-HBe positivity, normal alanine aminotransferase (ALT) and HBV DNA concentration below 2000 IU/mL**
HBeAg seroconversion	**Loss of HBeAg and seroconversion to anti-HBe**
HBeAg-negative chronic hepatitis B (immune-escape phase)	**HBeAg-negative but anti-HBe-positive disease with variable levels of HBV replication and liver injury**
HBsAg seroconversion	**Loss of HBsAg and development of anti-HBs**
HBeAg reversion	**Reappearance of HBeAg in a person who was previously HBeAg negative and usually associated with increased HBV replication**
Cirrhosis	**An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation**
Decompensated cirrhosis	**Clinical complications of cirrhosis become manifest, including jaundice, ascites, spontaneous bacterial peritonitis, oesophageal varices and bleeding, hepatic encephalopathy, sepsis and renal failure**
Hepatocellular carcinoma (HCC)	**Primary cancer of the liver arising in hepatocytes**

Table 2: NATURAL HISTORY OF HBV INFECTION

Hepatitis B surface antigen (HBsAg)	**HBV envelope protein and excess coat particles detectable in the blood in acute and chronic hepatitis B infection**
Hepatitis B core antigen (HBcAg)	**HBV core protein. The core protein is coated with HBsAg and therefore not found free in serum**
Hepatitis B e antigen (HBeAg)	**Viral protein found in the high replicative phase of hepatitis B. HBeAg is usually a marker of high levels of replication with wild-type virus but is not essential for viral replication**
Hepatitis B surface antibody (anti-HBs)	**Antibody to HBsAg. Develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity**
Anti-HBe	**Antibody to HBeAg. Detected in persons with lower levels of HBV replication but also in HBeAg-negative disease (i.e. HBV that does not express HBeAg)**
Hepatitis B core antibody (anti-HBc)	**Antibody to hepatitis Bcore(capsid) protein. Anti-HBc antibodies are not neutralizing antibodies and are detected in both acute and chronic infection**
IgM anti-HBc	**Subclass of anti-HBc. Detected in acute hepatitis B but can be detected by sensitive assays in active chronic HBV**
IgG anti-HBc	**Subclass of anti-HBc detected in past or current infection**
Occult HBV infection	**Persons who have cleared hepatitis B surface antigen, i.e. they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL); most are also anti-HBc positive**
Treatment failure	**May be primary or secondary.** **In settings where HBV DNA testing is available: Primary antiviral treatment failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by ≥1 x $\log_{10}$ IU/mL within 3 months of initiating therapy. Secondary antiviral treatment failure may be defined as a rebound of HBV DNA levels of ≥1 x $\log_{10}$ IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x $\log_{10}$ IU/mL decrease in serum HBV DNA).** **In settings where HBV DNA testing is not available: Treatment failure and drug resistance may be suspected based on the following features: receiving antiviral drugs with a low barrier to resistance together with documented or suspected poor adherence, laboratory measures such as an increase in serum aminotransferases, and/or evidence of progressive liver disease. Note: Elevation in ALT level tends to occur late and is a relatively poor predictive marker of resistance.** **Confirmation of antiviral drug failure can be established by sequencing the HBV DNA polymerase and identifying specific genetic markers of antiviral drug resistance.**

Table 3: SEROLOGICAL MARKERS OF HBV

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	**Intracellular enzymes which, as they are released after cell injury or death, reflect liver cell injury**
HBV DNA	**HBV viral genomes that can be detected and quantified in serum. HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL.** **1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5. (i.e. 10 000 copies/mL = 2000 IU/mL;100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). All HBV DNA values in the recommendations in these guidelines are reported in IU/mL.** **An undetectable viral load is an HBV DNA level below the level of sensitivity of the laboratory assay. For sensitive polymerase chain reaction assays, this is generally a concentration below 15 IU/ml.**
AFP (alpha-fetoprotein)	**A host cellular protein. High levels can occur in persons with hepatocellular carcinoma.**
Persistently abnormal or normal ALT level	**ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, although local laboratory normal ranges should be applied. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.**

Table 4: TESTS FOR ASSESSMENT AND MONITORING OF HEPATITIS B INFECTION

APRI	**Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations.** **A formula for calculating the APRI is given: APRI = (AST/ULN) x 100) / platelet count (10^9/L). Cutoff value is 0.7 if more= advanced fibrosis An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri**
FIB-4	**A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. Formula for calculating FIB-4:** **FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)$^{1/2}$]). If>3.25=advanced fibrosis, An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4**
FibroTest (FibroSure)	**Commercial biomarker test that uses the results of six blood markers to estimate hepatic fibrosis**
Transient elastography (FibroScan)	**A technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver**

Table 5: ASSESSMENT OF LIVER FIBROSIS BY NON-INVASIVE TESTS

Phase	HBe Ag Serological status	pattern	Indications for treatment
1.Immune tolerant	HbeAg positive	-Stage seen in many HbeAg –positive children and young adults, particularly among those infected at birth -High levels of HBV replication(HBV DNA levels>200000 IU/mL) -Persistently normal ALT -Minimal histological disease	Treatment not Generally indicated,but monitoring required
2".Immune active' (HbeAg-positive[a] chronic hepaitis)	HbeAg positive; may develope anti-HBe	-Abnormal or intermittently abnormal ALT -High fluctuating levels of HBV replication(HBVDNA levels>2000 IU/mL) -Histological necroinflammatory activity present -HbeAg to anti-HBe seroconversion possible, with normalisation of ALT leading to immune-control phase.	Treatment may be indicated
3.inactive chronic hepatitis (immune control) previously called inactive carrier	HbeAg negative, anti-HBe positive	-Persistently normal ALT -Low or undtectableHBV DNA(HBV DNA levels <2000 IU/mL) -Risk of cirrhosis and HCC reduced -May develop HbeAg-negative disease	Treatment not generally indicated,but Monitoring required for Reactivation, and HCC
4.Immune escape (HbeAg-ve chronic hepatitis)	HbeAg negative, with or with out being anti-HBe positive	-HBeAg negative and antiHBe positive -Abnormal ALT(persistently or intermittently abnormal) -Moderate to high levels of HBV replication(HBV DNA>20000 IU/mL) -Older persons especially at risk for progressive disease (fibrosis/cirrhosis)	Treatment may be indicated
5.Reactivation or acute-on-chronic hepatitis	HbeAg positive or negative	-Can occur spontaneously or be precipitated by immune suppression from chemo-or immune suppressive therapy,HIV infection or transplantation, development of antiviral resistance, or withdrawal of antiviral therapy -Abnormal ALT -Moderate to high levels of HBV replication -Seroconversion to HbeAg positivity can occiur if HbeAg negative -High risk of decompensation in presence of cirrhosis	Treatment indicated

Table 6: Phases of chronic hepatitis B

Not all persons after HbeAg seroconversion enter the inactive phase. Up to 20% may progress directly from HbeAg immune active to anti-HBe immune escape phase.

Recommendations

<u>WHO TO TREAT AND WHO NOT TO TREAT IN PERSONS WITH CHRONIC HEPATITIS B</u>

1. **a priority, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels.**
2. **Treatment is recommended for adults with CHB who do not have clinical evidence of Cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular) and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status. (Where HBV DNA testing is not available: Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status).**

<u>Existing recommendation for HBV/HIV-coinfected persons</u>

- **In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all those with a CD4 count ≤500 cells/mm3, regardless of stage of liver disease.**

<u>Who not to treat but continue to monitor</u>

- **Antiviral therapy is not recommended and can be deferred in persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), and with persistently normal ALT levels and low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age.**
  (Where HBV DNA testing is not available: Treatment can be deferred in HBeAg-positive persons aged 30 years or less and persistently normal ALT levels).
- **Continued monitoring is necessary in all persons with CHB, but in particular those who do not currently meet the above-recommended criteria for who to treat or not treat, to determine if antiviral therapy**

may be indicated in the future to prevent progressive liver disease. These include:

-- persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/mL but persistently normal ALT levels;

-- HBeAg-negative persons without cirrhosis aged 30 years or less, with HBV DNA levels that fluctuate between 2000 and 20 000 IU/mL, or who have intermittently abnormal ALT levels;

Where HBV DNA testing is not available: Persons without cirrhosis aged 30 years or less, with persistently normal ALT levels, regardless of HBeAg status.

FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years.

NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended.

Existing recommendation for HBV/HIV-coinfected persons

In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART.

SECOND-LINE ANTIVIRAL THERAPIES FOR THE MANAGEMENT OF TREATMENT FAILURE

In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended.

WHEN TO STOP TREATMENT

Lifelong NA therapy • All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analogues (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute- on-chronic liver injury.

Discontinuation of NA therapy may be considered exceptionally in:

1- **persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults); and who can Be followed carefully long term for reactivation**
2- **and if there is evidence of HBeAg loss and seroconversion to anti-Hbe)in persons initially HBeAgpositive) and after completion of at least one additional year of treatment**
3- **and in association with persistently normal ALT levels and persistently undetectable HBV DNA levels where HBV DNA testing is available .(Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HbsAg loss after completion of at least one additional year of treatment regardless of prior HBeAg status.**

Retreatment • Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HbeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) where HBV DNA testing is available.

Monitoring for disease progression and treatment response in persons with CHB prior to, during and `post treatment

It is recommended that the following be monitored at least annually:

1- **ALT level (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels(where HBV DNA testing is availabl).**
2- **Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those with out cirrhosis at baseline;**
3- **If on treatment, adherence should be monitored regularly and at each visit.**

More frequent monitoring

- **In persons who do not yet meet the criteria for antiviral therapy: More frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20 000 IU/mL (where HBV DNA testing is available) and in HIV-coinfected persons.**
- **In persons on treatment or following treatment discontinuation: More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected persons; and in persons after discontinuation of treatment.**

Monitoring for tenofovir and entecavir toxicity

- **Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy.**
- **Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children.**

Monitoring for hepatocellular carcinoma

Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:

--persons with cirrhosis, regardless of age or other risk factors

--persons with a family history of HCC

--persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available).

PREVENTION

Infant and neonatal hepatitis B vaccination-Existing recommendations in infants and neonates

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses.

Prevention of mother-to-child HBV transmission using antiviral therapy

In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.

Existing recommendations in HIV-infected pregnant and breastfeeding women:

In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine +efavirenz) is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped.

Recommendations

1. **Thorough evaluation and counseling are mandatory before considering drug therapy**
2. **Patients with viral replication but persistently normal or minimally elevated ALT levels should not be treated, except for those with advanced fibrosis or cirrhosis. They need adequate follow-up and HCC surveillance every 3–6 months.**
3. **Assessment of liver fibrosis is recommended in viremic patients with high normal or minimally raised ALT levels and patients older than 40 years, except for patients with clinical evidence of cirrhosis.**
4. **Chronic HBV-infected patients with ALT ≥2 times ULN, and HBV DNA ≥$2.0x10^4$ IU/mL if HBeAg positive and >$2.0x\ 10^3$ IU/mL if HBeAg-negative as well as patients with advanced fibrosis or cirrhosis with any ALT level should be considered for treatment. Treatment should be started as early as possible in case of impending or overt hepatic decompensation. Otherwise, 3–6 months' observation is recommended to ensure the need of therapy. Indications are similar for retreatment.**
5. **Treatment-naı̈ve patients can be treated with conventional IFN 5–10 MU 3 times per week or Peg-IFN-α2a 180 µg weekly or Peg-IFN-α2b 1–1.5 µg/kg weekly, ETV 0.5 mg daily, TDF 300 mg daily, ADV 10 mg daily, LdT 600 mg daily, or LAM 100 mg daily. Thymosin α 1.6 mg 2 times per week can also be used. ETV or TDF is the preferred nuc.**
6. **During therapy, ALT, HBeAg, and/or HBV-DNA should be monitored at least every 3 months. Renal function should be monitored if TDF or ADV is used. Muscle weakness should be monitored, especially if LdT is used. During IFN-based therapy, monitoring of blood cell counts and other adverse effects are mandatory.**
7. **After the end of therapy, levels of ALT and HBV DNA should be monitored monthly for the first 3 months to detect early relapse, and then every 3 months in the first year after therapy. If uneventful, monitor every 3 months (for cirrhotic patients) to 6 months (for responders) thereafter. For non-responders, further monitoring of HBV markers is required to both recognize a delayed response or to plan retreatment when indicated.**
8. **When to stop therapy?**

- **For conventional IFN: inHbeAg (+) the recommended duration of therapy is 4-6months, for HbeAg (-) duration of therapy is at least 12months**
- **For peg-INF, the recommended duration for therapy is 12months**

- **For thymosin α, the recommended duration of therapy is 6months for both**
- **For nuc: in HBeAg(+), treatment can be stopped when HBeAg seroconversion with undetectable HBV DNA has been maintained for at least 12months, in HBeAg(-), no limit time if HBsAg remains(+) but stop treatment can be considered if the patient had been treated for at least 2years with undetectable HBV DNA documented on three separate occasions 6 months apart.**
- **In compliant patients with primary treatment failure at month 3 or suboptimal viral response at month 6, switch to a more potent drug or add a drug without cross resistance if LAM, LdT, or ADV was used.**

9. **For female patients of childbearing age,**

- **IFN-based therapy is preferred for non pregnant women. Pregnancy is discouraged during IFN therapy.**
- **Pregnant women who need treatment can be treated with category B nucs .For the prevention of mother-to child transmission,**
- **Pregnant women with high HBV DNA (>2x10^6 IU/mL) can be treated with LdT in the third trimester. TDF is an alternative.**

10. **For patients with HIV-HBV coinfected individuals, ART containing TDF + FTC/LAM is the treatment of choice for the majority of these coinfected individuals. If the CD4 count is greater than 500 and ART is not warranted, ADV or PEG-IFN can Be considered.**
11. **In patients with concurrent HCV or HDV infection, determine which virus is dominant and treat the patients accordingly. IFN is usually contraindicated in patients with decompensated liver disease. Nucs with potent and prompt HBV suppressive action should be used immediately.**
12. **ETV or TDF is the agent of choice for patients with obvious or impending hepatic decompensation. LdT, LAM, or ADV can also be used in nuc-naı̈ve patients. Renal function and lactic acidosis should be monitored in this group of patients; especially those with MELD score greater than 20.**
13. **Anti viral prophylaxis:**

- **Before receiving immunosuppression or chemotherapy, patients should be Screened for HBs Ag. If they are HBs Ag positive, start nuc. Treatment if clinically indicated. Otherwise, prophylactic therapy with LAM before the start and up to at least 6 months after the end of immunosuppression or chemotherapy is recommended. ETV and TDF can also be used for prophylaxis.**
- **Patients who are going to receive biologic agent such as anti-CD 20 rituximab or anti-tumor necrosis factor-a etanercept should be screened for anti-HBc. If they are anti-HBc positive, HBVDNA should be closely monitored and treated with nuc when needed.**

14. **Patient in the setting of organ transplantation:**

- **Nuc(s) treatment should be commenced in all HBV patients who are listed for organ transplantation and have detectable HBV DNA.**
- **Late (at least 12-month post transplant) HBIg substitution by ADV provides safe and Cost-effective prophylaxis. Late conversion to LAM mono-therapy may be considered in 'low-risk' patients.**
- **HBV-naı̈ve patients receiving a liver from an anti-HBc (+) donor should receive long-term prophylaxis with either LAM or HBIg.**

15. **Nuc. Treatment should be commenced in all HCC patients with HBV DNA> 2,000 IU/mL before and/or after curative therapy of HCC as in their counterparts without HCC. Preemptive nuc therapy should be initiated in all HCC patients who are undergo transarterial embolization.**

In summary:

The of Goals of therapy

HBeAg- positive

- **Best response if ALT>2 times upper limit of normal (80 U/L)**
- **HBeAg loss and seroconversion to anti-HBe**
- **Durable suppression of HBV DNA to low or undetected levels**
- **Normalization of ALT**

HBeAg – Negative

- **Treat persons with at least moderate hepatitis or fibrosis (Ishak, Metavir stage 2/4)**
- **Durable suppression of HBV DNA to low or undetectable levels**
- **Normalization of ALT**
- **Long-term therapy the rule with oral agents**

New Goals for evaluation of treatment of patients with chronic HBV infection

- **Elevated ALT or AST and HBV DNA>2000 IU/L**
- **HBV DNA >20, 000 and ALT >20 women or 30 men in persons age 40 years or over.**
- **Persons with persistently elevated ALT or AST levels but HBV DNA<2000 on all follow-up draws, need for evaluation for other liver diseases, and follow ALT and HBV DNA to detect flare.**

Drugs for treating chronic HBV patients

- **First line drugs(Peg-Interferon, Entecavir, Tenofovir)**
- **Second line drugs (Lamavudine-high resistance rate-, Telbuvidine Emtricitabine, Adenofovir)**

Recommendations to follow patients on nucleoside Analogues

- **ALT, AST, HBV DNA every 3-6months.**
- **If HBV DNA level increases 1 log or above 2000 units, test for resistance**

Hepatitis B Vaccination [29]

We have two types: (without significant differences in safety, immunogenicity or efficacy between the two)

- **Recombinant or gentically engineered vaccines are made using HBsAg synthesized in yeast (Saccharomyces cerevisiae) or in mammalian cells into which the HBsAg gene has been inserted. Both consist of a HB surface antigen.**
- **Human plasma-derived vaccine(PDV) are prepared from purifief HBsAg from plasma of persons with chronic HBV infection. There are more than 15 different PVDs licensed worldwide.**

HBV vaccine will generate protective levels(>10 IU/ml)of antibodies to HbsAg in 95% of children and 90% of persons who donot respond to primary vaccination. Revaccination of non-responders is not recommended after two series of vaccination(6 doses). Adistinction can be made between pre-exposure and post-exposure vaccination.

Preexposure Vaccination:

This is especially relevant in high risk group, the two available recombinant vaccines are similar in efficacy but dosing differs:

Age	Recombiax-HB(10µg of HBsAg)	Engerix-B(20µg of HBsAg)
Child	If<11yr HBsAg negative mother 2.5µg If <11yr HBsAg positive mother 5 µg If child 11-19 yr of age 5 µg	Child <10yr 10 µg Child>10yr 20 µg
Immunocompetent adult	10 µg	20µg
Immunosuppressed person	40 µg	40µg
Dialysis person	40µg	40µg

Table 7: HB vaccination in different groups

Post- exposure vaccination

A compenation of hepatitis B immunoglobulin(HBIg) and HBV vaccine is recom mended, this is of special relevance in neonates where an immidiate start of post exposure immunisation will prevent neonatal infection in infants of HBV infected mothers. It is important to vaccinate within 24 hours, there is no evidence of a protective effect if the vaccine is given >7 days later.

Direct exposure(percutaneous inoculation or transmucosal exposure) to HbsAg positive body fluid (eg needlestick injury):

- **HBIg single intramuscular dose of 0.06 ml/kg (as soon as possible)**
- **Followed by complete course of HBV vaccination (within 7days)**

Direct exposure following sexual contact with a patient with HBV:

- **HBIg single intramuscular dose of 0.06ml/kg (with in 14 days)**
- **Followed by complete course of HBV vaccination.**

Needle stick injury and accidental exposure to blood [29]

Needlestick injury: the accidental puncture of the skin by a needle during a medical intervention.

Accidental exposure to blood: the unintended contact with blood and or with boody fluids mixed with blood during a medical intervention.

Risks: HBV= 5-40%, HCV= 3-10%, HIV= 0.2-0.5%

Immediate action after injury:

- **Taking care of the woung immediately after the accident: let the wound bleed for a moment and then cleanse thoroughly with a water or a saline solution, Disinfect the wound using ample amount of soap and water followed by 70% alcohol. In case of contact with mucous membranes it is important to rinse immediately and thoroughly, using water or saline solution only, not alcohol.**
- **Reporting the accident: report the case to the department dealing with occupational accidents for beter management of the case.**
- **Immediate action (injured person):**

1- **As discussed before; rinse wound with water, disinfect with 70% alcohol , rinse mucous memebrane with**
2- **Report to resonsible department**
3- **Take sample of blood from the source for HBV, HCV, &HIV if the result negative, no action,**

<u>If Hepatitis B positive (in sample of source)</u> , the following action is recommended:

HBV immunity	Action
Earlier HBV?	No action
If person is fully vaccinated	If the primary response ≥100 IU/L No action If the primary response 10-100 IU/L , HBIG+booster vaccination hepatitis B.
If person is without or partial immunity	HBIG+vaccination for HB.

Table 8: accidental exposure to infected blood with HBV.

<u>If Hepatitis C virus positive (in sample of the source)</u>, follow up the person up to one year, if during this time became postive by PCR, then treat the person with alpha-interferone therapy for three months.

<u>If HIV (in sample of the source) postive</u> follow up the person for one year (1,3,6,12 months) and immediate post exposure prophylaxis(PEP) if indicated such as percuta neous or mucous memberan(with broken skin) and if the result is positive then treat HIV by HIV expert.

Liver fibrosis[30]

1. **Liver fibrosis can be considered as an end point parameter in the treatment of chronic hepatitis, provided it is adequately quantitated before and after the therapy.**
2. **More evidence is needed to prove that treatment of chronic hepatitis significantly reduces the rate of progression of liver fibrosis. Hepatic fibrosis as assessed by tissue pathology can regress especially after specific treatment.**
3. **There is not enough evidence to suggest that cirrhosis is reversible; however, remodeling can occur.**

Assessment of liver fibrosis

Assessment of liver fibrosis is important clinically for decision making. Although liver biopsy remains the ''gold standard'' to assess liver fibrosis, alternative noninvasive approaches to liver fibrosis have assumed great importance.

Consensus statements -Liver biopsy

1. **Percutaneous liver biopsy is an invasive procedure, but major complications are very rare**
2. **Indication and contraindications of liver biopsy should be clearly established.**
3. **Patient should be properly prepared. Premedication and informed consent are must.**
4. **Image-guided liver biopsy is strongly recommended.**
5. **If there is coagulopathy or thrombocytopenia >100,000/cumm or ascites, a transjugular liver biopsy (TJLB) is advised.**
6. **However, further study is needed to standardize the methodology of TJLB and validate its relevance in routine clinical practice.**

Preprocedure requirements for percutaneous liver biopsy

1. **Indications and contraindications of percutaneous liver biopsy should be reconfirmed in the patient.**
2. **Informed consent should be obtained.**
3. **Non-steroidal anti-inflammatory drugs and salicylates should be withheld 1 week prior to and after liver biopsy.**
4. **For patients on anticoagulants, stop oral anticoagulants at least 72 h before the biopsy and start heparin and oral anticoagulants 24 h and 48–72 h, respectively, after biopsy. Patients with a prothrombin time prolonged to more than 4 s should be given 2–3 units of FFP, and for those with a platelet count of less than 60,000 cells/cumm should be given platelet-rich plasma infusions**
5. **In patients with chronic renal failure, biopsy should be done after dialysis and with minimum use of heparin on the day of biopsy.**
6. **Patient's blood group should be known and facilities for blood and FFP transfusion must always be available.**
7. **Patient should be fasting for 12 h before the biopsy.**
8. **An intravenous catheter should be fixed.**
9. **Patient should be trained to hold breath for a few seconds in expiration.**
10. **Patient should be given intravenous meperidine and midazolam to allay anxiety and pain before theprocedure.**
11. **Biopsy needle should be at least 16 G.**
12. **Preferable core length should be longer than 15 mm or contain at least ten portal tracts. A repeat pass should be done, if biopsy length is<1 cm.**
13. **Liver biopsy should be performed only by experts with minimum training of 50 biopsies under supervision.**

Non invasive tests for detection of liver fibrosis

These include:

- **Noninvasive imaging (e.g., transient elastography).**
- **Noninvasive blood marker panels (e.g., aspartate aminotransferase– platelet ratio index (APRI), FibroTest, FIBROSpect II, Hepascore, FibroMeter, and FibroFast).**

AST/platelet ratio index (APRI): higher value of the APRI increase the liklihood of cirrhosis, and the low values decrease the likelihood of cirrhosis.

APRI =(AST/upper limit of normal AST) X (100/platelet count[x10^3/mm^3])

Banacini cirrhosis discriminant score(CDS): has a range of possible values from 0 to 11; higher scores identify patients with a higher likelihood of cirrhosis, and lower scores identify patients with low likelihood of cirrhosis.

CDS= Platelet score + ALT/ AST ratio score + INR score.

score	Platelet ($\times 10^3/mm^3$)	ALT/AST ratio	INR
0	>340	>1.7	<1.1
1	280-340	1.2-1.7	1.1-1.4
2	220-279	0.6-1.19	>1.4
3	160-219	<0.6	-
4	100-159	-	-
5	40-99	-	-
6	<40	-	-

Table 9: Banacini cirrhosis discriminant score CDS) score to assess the degree of fibrosis in liver

Consensus statements

1. **Noninvasive tests are useful for identifying only those patients with no fibrosis or with extreme levels of fibrosis.**
2. **Staging of liver fibrosis in the intermediate range cannot be satisfactorily predicted by any of the Available tests.**
3. **A stepwise algorithm incorporating noninvasive markers of fibrosis may reduce the number of liver biopsies by about 30%.**
4. **Although ultrasonographic data proved reliable in differentiating cirrhosis from milder stages of fibrosis, diagnostic value has not been definitely clarified, as documented by the wide range of sensitivity and specificity rates.**
5. **The FI calculated from Doppler parameters is promising and needs to be validated.**
6. **Contrast-enhanced US with microbubble contrast agent may be promising as an indirect assessment tool for hepatic fibrosis.**
7. **Noncontrast-enhanced US is expected to be a direct assessment tool for hepatic fibrosis.**
8. **Clinical utility of FibroScan techniques would be proven by further studies in large number of patients.**
9. **Hepatic venous portal pressure gradient (HVPG):**

. HVPG measurement is a relatively simple procedure.
. HVPG is a safe procedure with a very low complication rate in experienced hands.
. HVPG measures both the irreversible and reversible components of portal hypertension. It is a dynamic marker of disease progression, especially pre-cirrhotic stage.
. HVPG closely correlates with the degree of advanced fibrosis and can be recommended as a marker of fibrosis.
. The etiology of cirrhosis does not significantly influence HVPG levels.

Non-cirrhotic portal fibrosis/idiopathic portal hypertension:

Consensus statements

- **NCPF/IPH is an important cause of portal hypertension.**
- **While NCPF and IPH represent the same disease entity, there are some differences.**
- **The patients of NCPF are generally young adults in the third and fourth decade of life (the mean age of presentation is about 30 years); IPH generally presents in the fourth and fifth decade of life.**
- **In NCPF, there is no sex predilection. IPH is more common in females.**
- **NCPF/IPH is linked to low socioeconomic status.**
- **NCPF/IPH is a heterogeneous group of diseases, which could be a result of the varied degree of portal venous injury.**
- **Injury predominantly manifests in the presinusoidal region.**
- **The factors/agents that have been reported to be associated with NCPF/IPH include umbilical/portal pyemia, diarrheal diseases, or bacterial infections in infancy; autoimmune disorders; prothrombotic states; chronic exposure to arsenic, vinyl chloride monomers, or copper sulfate (vineyard sprayers); prolonged treatment with methotrexate; hypervitaminosis A; and renal allograft recipients under treatment of 6-mercaptopurine, azathioprine, and corticosteroids. However, the exact etiology in the majority of cases remains unknown.**
- **Most cases of NCPF/IPH present with enlarged spleen and GI bleeding (hematemesis) and some have features of anemia.**
- **Autoimmune features are common in IPH while rare in NCPF.**
- **Irregular parenchymal nodules and bile duct proliferation are more common in NCPF than IPH.**
- **Wedged hepatic venous pressure is almost normal in NCPF, while it is moderately raised in IPH.**
- **Signs of chronic liver disease like palmar erythema, spider angioma, testicular atrophy in abdominal wall veins, and gynecomastia are rare.**
- **Jaundice, ascites/edema, and signs of liver failure are uncommon.**

- **Ascites is transient and usually seen soon after a variceal bleed.**
- **Bleeding rate from gastroesophageal varices is high in patients with NCPF/IPH (32–95%).**
- **Mortality from variceal rupture is generally lower in NCPF/IPH, because of better liver functions compared with cirrhosis.**
- **Management of gastroesophageal varices to prevent the rupture should be a priority in the care of patients with NCPF/IPH.**
- **The incidence of PV thrombosis is more frequent in patients with IPH than in patients with liver cirrhosis. The same should also be studied in NCPF.**
- **Development of portal vein thrombosis in patients with IPH may be a significant factor for poor prognosis.**
- **Ascites is not rare in patients with IPH in spite of preserved liver functions. It occurs in association with PVT. While clinical ascites is rare in patients with NCPF and it is transient after a bleed.**
- **Ascites is considered to be a sign for deterioration of the condition in patients with IPH.**
- **In NCPF/IPH, the liver probably undergoes atrophy, owing to reduced blood supply to the periphery. It is not necessarily progressive, and the liver functional reserve is well maintained.**
- **The survival rate for patients with NCPF/IPH is much better than that for patients with cirrhosis.**
- **PV thrombosis and ascites may indicate the deterioration of the condition in certain cases of IPH, and thrombosis and ascites may be mutually related in this disease.**

Histopathology of NCPF/IPH

Diagnostic criteria of NCPF/IPH on needle liver biopsy are as follows:

- **Absence of regenerative nodules with features of possible or definite cirrhosis in an adequate-sized Liver biopsy.**
- **Features usually seen (however, these may not be seen in all):**
  1. **Small portal vein obliteration;**
  2. **Aberrant vasculature; portal tract fibrosis, rounded or streaky;**
  3. **Absence of significant hepatocellular injury.**

Laboratory studies in NCPF/IPH

- **Results of liver function tests are normal or near normal in patients of NCPF/IPH.**
- **Hypersplenism is common but usually asymptomatic.**
- **The frequency and characteristics of the coagulation abnormalities in these patients need to be investigated further.**

Features at endoscopy in NCPF/IPH

- **Esophageal varices are seen in 85–90% of patients.**
- **These varices are generally large at the time of diagnosis.**
- **If esophageal varices are small, investigations for the presence of gastric varices and spontaneous Shunts are required.**
- **Gastric varices are seen in about 25% of patients with NCPF/IPH.**
- **Portal hypertensive gastropathy is uncommon in these patients.**
- **Anorectal varices are common in NCPF. While the prevalence of anorectal varices in IPH is not known.**

Hemodynamics in NCPF/IPH

- **Hepatic venous pressure gradient (HVPG) is normal or near normal in NCPF/IPH.**
- **Hemodynamic studies indicate site of resistance as predominantly presinusoidal.**
- **Whether HVPG increases on long-term follow up needs to be studied.**
- **Portal venous blood flow is significantly increased.**

Diagnosis of NCPF/IPH

Diagnostic features of NCPF/IPH:

- **Presence of moderate to massive splenomegaly**
- **Evidence of portal hypertension, varices, and/or collaterals**
- **Patent spleno-portal axis and hepatic veins on ultrasound Doppler,**
- **Test results indicating normal or near-normal liver functions,**
- **Normal or near-normal hepatic venous pressure gradient,**
- **Liver histology—no evidence of cirrhosis or parenchymal injury.**

Other features:

- **Absence of signs of chronic liver disease,**
- **No decompensation after variceal bleed except occasional transient ascites,**
- **Absence of serum markers of hepatitis B or C virus infection,**
- **No known etiology of liver disease, and Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hyperechoic areas.**

Management of acute bleeding in NCPF/IPH

- General measures for the control of acute bleeding are same as for cirrhosis.
- Endoscopic therapy is effective for the control of acute variceal bleed in NCPF/IPH.
- If a diagnosis of NCPF/IPH is unlikely, the condition should be treated as cirrhosis.
- In case of failure of medical management (as in Baveno IV), decompressive surgery or TIPS is useful and should be used on the basis of available expertise.
- Patients with transient ascites should undergo devascularization procedure.
- Screening all patients of moderate to massive splenomegaly with suspected NCPF should have screening endoscopy.

Primary prophylaxis

- EVL is recommended for large varices. There is no consensus on the use of beta blockers in such patients.
- Balloon-occluded retrograde transvenous obliteration (BRTO) may be an option in patients with large gastric varices.
- Decompressive shunt surgery is not recommended for primary prophylaxis.

Secondary prophylaxis

Endoscopic therapy and elective decompressive surgery are effective and safe.
There should be head-to-head comparison between these two modalities.
There is insufficient data on the role of TIPS in secondary prophylaxis.

- BRTO is effective in patients with NCPF/IPH with gastric variceal bleed if gastrorenal shunt is present.

Gastroesophageal Variceal Bleeding[26]

Variceal bleeding is a consequence of portal hypertension, which, in turn, is the major complication of liver cirrhosis. Upper gastrointestinal endoscopy (UGIE) should be performed once the diagnosis of cirrhosis is established and is the gold standard for the diagnosis of varices.

Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis:

The primary prophylaxis of variceal bleed has been mainly the VBL and nonselective b-blockers

Recommendations

1. Because rupture of gastroesophageal varices is associated with high morbidity and mortality, all newly diagnosed cirrhotic patients should be screened for varices.
2. Mortality due to bleeding is high in patients with high-risk varices (>5 mm in size with red signs). particularly in the presence of severe liver disease (up to 20%).
3. Endoscopic screening is currently the best practice for variceal detection in clinically diagnosed cirrhotic patients and should be carried out on all cirrhotic patients at diagnosis.
4. On EGD, esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted.
5. For defining variceal risk:
   ‘‘High-risk’’varices: Large (>5 mm) varices with at least one of the following red signs: cherry-red spots, hematocystic spots, or red wale markings.

   ‘‘Low-risk’’ varices: Small (≤5 mm) varices without red signs. Varices with these features require further studies to define their risk potential: Large (>5 mm) varices without red signs and small (≤5 mm) varices with red signs.
6. Varices may progress in size from small to large in 5–12% of cirrhotic patients per year. However, the rate of progression is highly dependent on the severity of liver disease.
7. Nonendoscopic screening: This has currently not shown to be a consistently effective modality of investigation in screening for varices and to preselect patients for high

yield at endoscopy. Modalities such as platelet count, platelet count/spleen diameter ratio, and fibroscan could have a good predictive value, but need confirmation by further studies.

8. **b-Blocker prophylaxis to prevent variceal enlargement or bleeding may be started in compensated cirrhosis with small varices.**
9. **In patients who have compensated cirrhosis and no varices on the initial EGD, it should be repeated in 3 years. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually.**
10. **In patients with cirrhosis and small varices that have not bled but have criteria for increased risk of hemorrhage (Child B/C or presence of red wale marks on varices), nonselective β-blockers should be used for the prevention of first variceal hemorrhage.**
11. **In patients with cirrhosis and small varices that have not bled and have no criteria for increased risk of bleeding, β-blockers can be used, although their long-term benefit has not been established, (It might prevent variceal enlargement or bleeding).**
12. **In patients with small varices that have not bled and who are not receiving β-blockers,**

. EGD should be repeated in 2 years.

. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually.

. In patients with small varices who receive β-blockers, a follow-up EGD is not necessary

13. **In patients with medium/large varices that have not bled but have a high risk of hemorrhage (Child B/C or variceal red wale markings on endoscopy), nonselective β-blockers (propranolol or nadolol) or EVL may be recommended for the prevention of first variceal hemorrhage.**
14. **VBL and nonselective b-blockers are effective primary prophylactic therapies.**
15. **b-Blockers reduces the risk of primary variceal hemorrhage and bleeding-related mortality compared with no treatment.**
16. **VBL reduces the risk of primary variceal bleeding, bleeding-related mortality, and overall mortality compared with no treatment.**
17. **VBL reduces the risk of initial bleeding episodes compared with b-blockers, but there is no survival advantage.**
18. **The addition of b-blockers to VBL does not further reduce the risk of primary bleeding, but it does reduce variceal recurrence rates.**
19. **In patients with medium/large varices that have not bled and are not at the highest risk of hemorrhage (Child A patients and no red signs), nonselective β-blockers (propranolol, nadolol) are preferred and EVL should be considered in patients with contraindications or intolerance or non-compliance to β-blockers.**
20. **Patients with large varices should be treated with nonselective b-blockers, preferably with monitoring of HVPG or VBL to prevent initial variceal bleeding.**
21. **<u>Recommendations for HVPG measurement:</u>**

- **HVPG is a good predictor of the risk of first variceal bleed.**
- **Reduction of HVPG to 12 mm Hg or less or 20% reduction from baseline reduces the risk of first bleed.**
- **HVPG can reliably distinguish responders from nonresponders to pharmacotherapy.**
- **HVPG is recommended in identifying patients with high risk of variceal bleeding and non responders to pharmacotherapy.**

22. **However, HVPG has limitations of being invasive and not being widely available, and hence its routine use in clinical practice cannot be recommended.**
23. **If a patient is placed on a nonselective β-blocker, it should be adjusted to the maximal tolerated dose; follow-up surveillance EGD is unnecessary. If a patient is treated with EVL, it should be repeated every 1–2 weeks until obliteration with the first survei**

llance EGD performed, 1–3 months after obliteration and then every 6–12 months, to check for variceal recurrence.

24. **Nitrates (ISMN) can lower portal pressure when added to b-blockers, but evidence that a combination of the two drugs reduces the risk of bleeding compared with b-blockers alone is lacking**
25. **Nitrates (either alone or in combination with βblockers), shunt therapy, or sclero therapy should not be used in the primary prophylaxis of variceal hemorrhage.**
26. **Acute GI hemorrhage in a patient with cirrhosis is an emergency that requires prompt attention with intravascular volume support and blood transfusions, being careful to maintain a hemoglobin of >8 g/d.**
27. **Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage. Oral norfloxacin (400 mg BID) or intra venous ciprofloxacin (in patients in whom oral administration is not possible) is the recommended antibiotic. In patients with advanced cirrhosis intravenous ceftriaxone (1 g/day) may be preferable particularly in centers with a high prevalence of quinolone -resistant organisms.**
28. **Pharmacological therapy (somatostatin or its analogues octreotide and vapreotide; terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 3–5 days after diagnosis is confirmed.**
29. **EGD, performed within 12 hours, should be used to make the diagnosis and to treat variceal hemorrhage, either with EVL or sclerotherapy.**
30. **TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endos copic therapy.**
31. **Balloon tamponade should be used as a temporizing measure (maximum 24 hours) in patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS or endoscopic therapy) is planned.**
32. **Because probability of bleeding and associated mortality is high, primary prophylaxis for high-risk gastric varices is justified provided procedure is safe and effective.**
33. **In patients who bleed from gastric fundal varices, endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available. Otherwise, EVL is an option.**
34. **A TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy.**
35. **Patients with cirrhosis who survive an episode of active variceal hemorrhage should receive therapy to prevent recurrence of variceal hemorrhage(secondary prophy laxis)**
36. **Combination of nonselective β-blockers plus EVL is the best option for secondary prophylaxis of variceal hemorrhage.**
37. **TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy. In centers where the expertise is available, surgical shunt can be considered in Child A patients.**
38. **Patients who are otherwise transplant candidates should be referred to a transplant center for evaluation.**
39. **The formation of varices is predicted by HVPG and severity of liver disease.**
40. **Risk of variceal bleeding increases with increase of variceal pressure.**
41. **Changes of HVPG predicts the risk of variceal bleeding.**

Primary prophylaxis for gastric varices

Gastric varices can occur alone or in combination with esophageal varices. The incidence of first time bleeding from gastric varices (especially GOV2 and IGV1) in patients who have never received treatment is about 10–25%. Patients with gastric variceal hemorrhage bleed more profusely and have higher mortality than those who bleed from esophageal varices

Recommendations

1. **Gastric varices (GOV2 and IGV1) at high risk of bleeding are:**
   a. varices 5 mm or more in diameter. b. varices with red spots. c. varices in Child-Turcotte-Pugh class B or C liver cirrhosis.
2. **In the absence of randomized controlled trials, it is acceptable to use nonselective b-blockers for primary prophylaxis for gastric varices because a reduction of HVPG would have beneficial effects.**
3. **Data are insufficient regarding the use of cyanoacrylate for primary prophylaxis of gastric variceal bleed.**
4. **Endoscopic procedures, EIS and VBL, used alone are not suitable for primary prophy laxis in gastric variceal bleeding.**
5. **Balloon-occluded procedures, BO-EIS and B-RTO, are effective and safe.**
6. **B-RTO may be considered for high-risk gastric varices in centers where expertise exists.**
7. **B-RTO is effective for duodenal varices with lienorenal shunt.**
8. **Size of esophageal varices may increase after B-RTO.**
9. **Treatment with haptoglobin reduces the risk of hemoglobinuria after B-RTO.**
10. **Concomitant hepatocellular carcinoma is the most important prognostic factor after B-RTO.**

BRTO Balloon-occluded retrograde transvenous obliteration
BO-EIS Balloon-occluded endoscopic injection sclerotherapy

General measures

1. **Patients with esophageal varices should avoid activities that cause increase in variceal pressure, such as lifting heavy objects, straining at defecation, stretching, and coughing, to avoid variceal bleeding.**
2. **Total volume paracentesis may decrease variceal pressure and improve portal hemody namics, which restores within 24 h of total volume paracentesis.**
3. **Further trials are needed before routine total volume paracentesis can be recommended to prevent variceal bleeding in patients with esophageal varices.**
4. **Moderate exercise may increase HVPG and decrease hepatic blood flow.**
5. **Propranolol therapy may protect from the deleterious effects of a moderate physical exercise on portal hemodynamics at the expense of reduction of liver perfusion in patients with cirrhosis.**
6. **Cirrhotic patients with portal hypertension should be advised of potential risk of bleeding during moderate exercise.**
7. **Postprandial hyperemia increases HVPG.and may increase the risk of variceal bleeding.**
8. **Postprandial hyperemia might be blunted by octreotide and ISMN. Propranolol decreases only the baseline HVPG.**
9. **Effect of acute ethanol consumption on portal hemodynamics is not conclusive, but it is wise to abstain from alcohol.**
10. **Acute ethanol consumption may cause variceal bleeding.**

Management of Adult Patients with Ascites Due to Cirrhosis: An Update [25]

Cirrhosis was the twelfth leading cause of death. Ascites is the most common of the three major complications of cirrhosis; the other complications are hepatic encephalopathy and variceal hemorrhage. Approximately 50% of patients with "compensated" cirrhosis, i.e., without having developed one of these complications, develop ascites during 10 years of observation. Ascites is the most common complication of cirrhosis that leads to hospital admission.

Differential Diagnosis of Ascites

Cirrhosis
Alcoholic hepatitis, Heart failure, Cancer (peritoneal carcinomatosis, massive liver metastases, etc)
"Mixed" ascites, i. e., cirrhosis plus Pancreatitis
another cause for ascites: Nephrotic syndrome, Tuberculous peritonitis, Acute liver failure, Budd-Chiari syndrome, Sinusoidal obstruction syndrome, Postoperative lymphatic leak, Myxedema

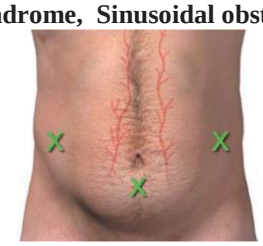

Diagram of the abdomen showing the three usual sites for abdominal paracentesis. the left lower quadrant is the preferable site

Recommendations:

1. **Abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites.**
2. **Because bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended.**
3. **The initial laboratory investigation of ascetic fluid should include an ascitic fluid cell count and differential, ascitic fluid total protein, and SAAG.**
4. **If ascitic fluid infection is suspected, ascitic fluid should be cultured at the bedside in blood culture bottles prior to initiation of antibiotics.**
5. **Other studies of ascitic fluid can be ordered based on pretest probability of disease**
6. **Testing serum for CA125 is not helpful in the differential diagnosis of ascites. Its use is not recommended in patients with ascites of any type.**
7. **Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption.**
8. **First-line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol/ day [2000 mg/day]) and diuretics (oral spironolactone with or without oral furosemide).**
9. **Fluid restriction is not necessary unless serum sodium is less than 120-125 mmol/L.**
10. **An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated.**
11. **Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.**
12. **Liver transplantation should be considered in patients with cirrhosis and ascites.**
13. **Serial therapeutic paracenteses are a treatment option for patients with refractory ascites.**
14. **Post paracentesis albumin infusion may not be necessary for a single paracentesis of less than 4-5 L.**
15. **<u>For large-volume paracenteses</u>, an albumin infusion of 6-8 g/L of fluid removed can be considered. (The International Ascites Club recommends using albumin at a dose of 8 g/L ascites removed for those in whom greater than 5 L ascites is removed) , (AASLD**

practice guidelines: "For large-volume paracenteses, an albumin infusion of 6-8 g per liter of fluid removed appears to improve survival and is recommended")

16. **Referral for liver transplantation should be expedited in patients with refractory ascites.**
17. **Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome.**
18. **Patients with cirrhosis, ascites, and type I hepatorenal syndrome should have an expedited referral for liver transplantation.**
19. **Patients with ascites admitted to the hospital should undergo abdominal paracentesis. Paracentesis should be repeated in patients (whether in the hospital or not) who develop signs or symptoms or laboratory abnormalities suggestive of infection (e.g., abdominal pain or tenderness, fever, encephalopathy, renal failure, acidosis, or peripheral leuko cytosis).**
20. **Patients with ascitic fluid PMN counts ≥250 cells/mm3 (0.25 X 10^9/L) should receive empiric antibiotic therapy, e.g., an intravenous third-generation cephalosporin, prefer ably cefotaxime 2 g every 8 hours.**
21. **Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine >3 mg/dL.**
22. **Patients with ascitic fluid PMN counts <250 cells/mm3 (0.25 X 10^9/L) and signs or symptoms of infection (temperature >100°F or abdominal pain or tenderness) should also receive empiric antibiotic therapy, e.g., intravenous cefotaxime 2 g every 8 hours, while awaiting results of cultures.**
23. **When the ascitic fluid of a patient with cirrhosis is found to have a PMN count ≥250 cells/mm3 (0.25 X 10^9/L) and is high suspicion of secondary peritonitis, it should also be tested for total protein, LDH, glucose, Gram stain, carcinoembryonic antigen, and alkaline phosphatase to assist with the distinction of SBP from secondary peritonitis.**
24. **Patients with ascitic fluid PMN counts ≥250 cells/mm3 (0.25 X10^9/L) and clinical suspicion of SBP, who also have a serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL should receive 1.5 g albumin/kg body weight within 6 hours of detection and 1.0 g/kg on day 3.**
25. **Intravenous ceftriaxone for 7 days or twice daily norfloxacin for 7 days should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage.**
26. **Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/sulfamethoxazole) because this is the most data-supported indication for long term outpatient prophylaxis.**
27. **In patients with cirrhosis and ascites but no gastrointestinal bleeding, long-term use of norfloxacin(or trimethoprim/sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL and at least one of the following is present: serum creatinine >1.2 mg/dL, blood urea nitrogen >25 mg/dL, serum sodium <130 mEq/L or Child-Pugh >9 points with bilirubin >3 mg/dL.**
28. **Intermittent dosing of antibiotics to prevent bacterial infections may be inferior to daily dosing (due to the development Of bacterial resistance) and thus daily dosing should preferentially be used.**

Once ascites becomes refractory:

1. **Discontinue beta blockers, ACE inhibitors, angiotensin receptor blocker**
2. **Consider adding midodrine specially in hypotension**
3. **Serial therapeutic paracentesis**
4. **TIPS (Patient selection affects outcome):**
   - **<60 y/o**
   - **Ejection fraction > 50%**
   - **Target HVPG <8 mm Hg**
   - **Child-Pugh <10, bilirubin <5**
   - **No severe spontaneous encephalopathy**
   - **Use Diuretics post TIPS**
   - **MELD <18 (3-mo survival)**
   - **No alcoholic hepatitis (80% mortality)**
5. **Peritoneovenous shunt, performed by a surgeon experienced with this technique, should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.**

Alcoholic Liver Disease (ALD) [10]

Alcohol remains a major cause of liver disease worldwide. It is common for patients with ALD to share the risk factors For simultaneous injury from other liver insults (e.g., co-existing non- alcoholic fatty liver disease, or chronic viral hepatitis). Many of the natural history studies of ALD and even treatment trials were performed before these other liver diseases were recognized, or specific testing was possible. Alcoholic liver disease (ALD) encompasses a spectrum of injury, ranging from simple steatosis to frank cirrhosis.

Recommendations for management of ALD:

1. **Clinicians should discuss alcohol use with patients, and any suspicion of possible abuse or excess should prompt use of a structured questionnaire and further evaluation.**
2. **For patients with a history of alcohol abuse or excess and evidence of liver disease, further laboratory tests should be done to exclude other etiologies and to confirm the diagnosis.**
3. **Patients with ALD and suggestive symptoms should be screened for evidence of other end-organ damage, as appropriate.**
4. **For patients with a clinical diagnosis of severe AH for whom medical treatment is contemplated, or for those in whom reasonable uncertainty exists regarding the underly ing diagnosis, a liver biopsy should be considered. This decision will depend on local expertise and ability in performing a liver biopsy in patients with coagulopathy, the patient's severity of illness, and the type of therapy under consideration.**
5. **Should have their risk for poor outcome stratified using the Maddrey discriminant function, as well as other available clinical data. Evaluating a patient's condition over time with serial calculation of the MELD score is also justified.**
6. **In patients with evidence of alcohol-induced liver disease, strict abstinence must be recommended, because continued alcohol use is associated with disease progression.**
7. **Naltrexone or acamprosate may be considered in combination with counseling to decrease the likelihood of relapse in patients with alcohol abuse / dependence in those who achieve abstinence.**
8. **All patients with AH should be counseled to completely abstain from alcohol.**
9. **All patients with AH or advanced ALD should be assessed for nutritional deficiencies (protein-calorie malnutrition), as well as vitamin and mineral deficiencies. Those with severe disease should be treated aggressively with enteral nutritional therapy.**
10. **Patients with mild-to-moderate AH :defined as a Maddrey score of < 32, without hepatic encephalopathy, and with improvement in serum bilirubin or decline in the MDF during the first week of hospitalization should be monitored closely, but will likely not require nor benefit from specific medical interventions other than nutritional support and abstinence.**
11. **Patients with severe disease (MDF score of ≥ 32, with or without hepatic encephalo pathy) and lacking contraindications to steroid use should be considered for a 4-week course of prednisolone (40 mg / day for 28 days, typically followed by discontin uation or a 2-week taper).**
12. **Patients with severe disease (i.e., a MDF ≥ 32) could be considered for pentoxifylline therapy (400 mg orally 3 times daily for 4 weeks), especially if there are contra-indications to steroid therapy.**
13. **Patients with alcoholic cirrhosis should receive frequent interval feedings, emphasizing a nighttime snack and morning feeding, to improve the nitrogen balance.**
14. **PTU and colchicine should not be used in the treatment of patients with ALD; *S* -adenosyl L -methionine should be used only in clinical trials.**
15. **The use of complementary or alternative medicines in the treatment of either acute or chronic alcohol-related liver disease has shown no convincing benefit and should not be used out of the context of a clinical trial.**

16. **The appropriate patients with end-stage liver disease secondary to alcoholic cirrhosis should be considered for LT just as other patients with decompensated liver disease, after a careful evaluation of their medical and psychosocial candidacy. In addition, this evaluation should include a formal assessment of the likelihood of long-term abstinence.**

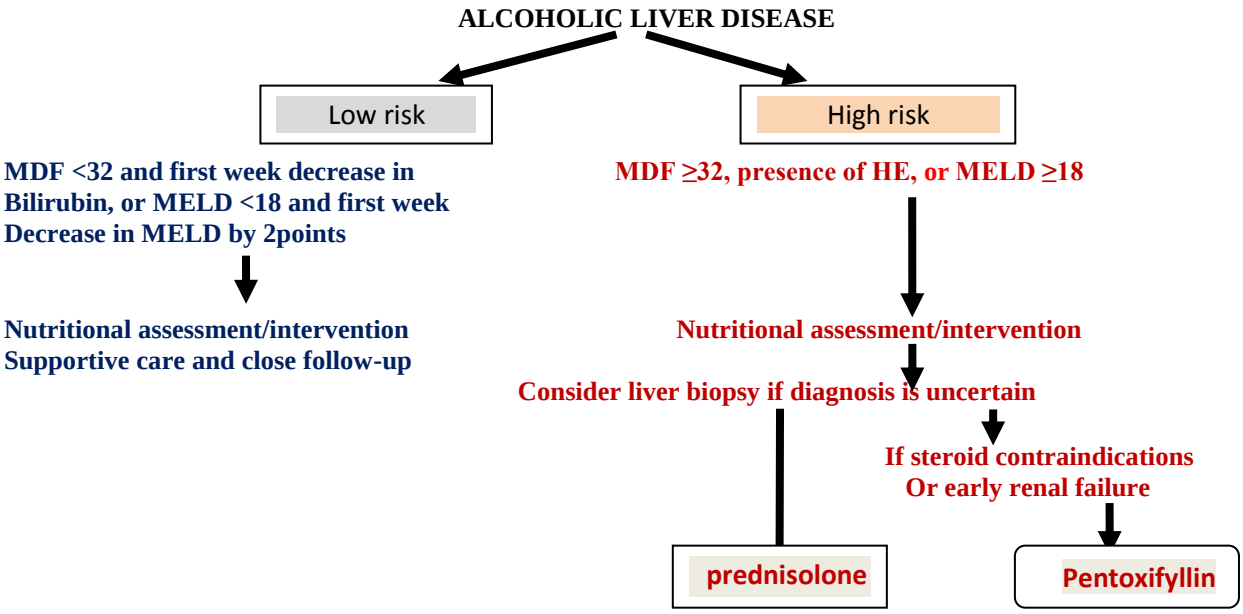

Figure 13: Proposed algorithm for alcoholic hepatitis.
MDF, Maddrey discriminant function (Maddrey discriminant function,(MDF) = 4.6 (patient's PT − control PT) + total bilirubin (mg / dl); MELD, model for end-stage liver disease.

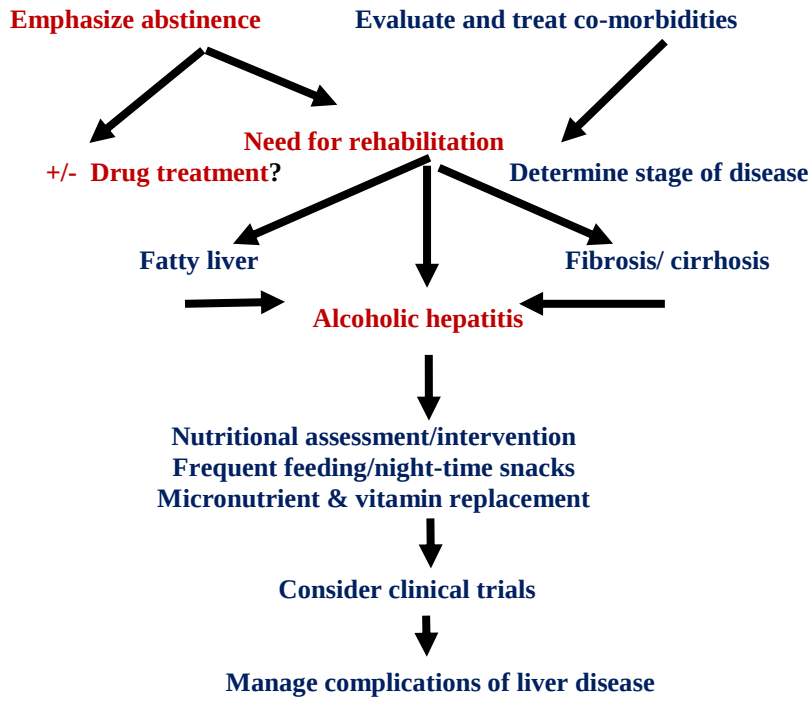

Figure 14: Proposed therapeutic algorithm for the long-term management of alcoholic liver disease

Recommendations on hepatocellular carcinoma(HCC) [27]

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer. Approximately three-fourth of cases occur in Asian countries because of a high prevalence of chronic infection with HBV. HCC is undoubtedly a great health threat in Asian region.

Prevention:

1- **Patients with cirrhosis due to HBV or HCV are at the highest risk for HCC. The incidence of HCC was significantly higher in those who were HBeAg positive or have HBV DNA with high loads (104 copies/mL) and older than 40 years. Coinfection with HBV and HCV may have synergistic effect on the development of HCC. Male sex, aging, and familial history are independent risk factors for HCC. Chronic and heavy alcohol intake, high body mass index (BM>25) and diabetes mellitus leading to liver disease increases the risk for HCC.**

2- **Universal hepatitis B vaccination should be implemented in the countries where HBV infection is endemic or hyperendemic. Interferon (IFN) therapy in adult with active hepatitis may be effective in reducing the incidence of HBV-related HCC. Maintained HBV suppression by oral antiviral agent(s) can reduce the risk of HCC**

3- **The control of transfusion-related, iatrogenic, and illicit drug use related viral transmission is of paramount importance.**

4- **Efficient screening for HCV infection would find patients who require treatment.**

5- **Interferon therapy is indicated in acute hepatitis C to prevent chronicity.**

6- **Sustained virologic response to an IFN-based therapy reduces the risk of HCV-related HCC in patients with compensated chronic hepatitis C.**

7- **Prevention of HCC by elimination of aflatoxin contamination is advised.**

8- **Prevention of HCC in patients with nonalcoholic steatohepatitis (NASH) is primarily through lifestyle modification with diet and exercise.**

Surveillance for HCC

1 **In high-risk populations is recommended .**

2 **should be performed by ultrasonography (US) and a-fetoprotein (AFP) every 6 months**

3 **a-Fetoprotein alone is not recommended for the diagnosis of HCC.**

4 **Cutoff value of AFP should be set at 200 ng/mL for diagnosis.**

5 **Simultaneous measurement of AFP and DCP provides higher sensitivity without Decreasing specificity.**

6 **Ultrasonography is a screening test and not a diagnostic test for confirmation**

7 **Contrast-enhanced US (CEUS) is as sensitive as dynamic CT or dynamic MRI in the diagnosis of HCC .**

Diagnosis of HCC

1. **Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test result is abnormal.**
2. **Hallmark of HCC during CT scan or MRI is the presence of arterial enhancement, followed By washout of the tumor in the portal-venous and/ or delayed phases.**
3. **Typical HCC can be diagnosed by imaging regardless of the size if a typical vascular pattern, i.e., arterial enhancement with portalvenous washout, is obtained on dynamic CT, dynamic MRI, or CEUS.**
4. **Nodular lesions show an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal-venous wash out, should undergo further examinations.**

Treatment of HCC

1 **Liver resection is a first-line curative treatment of solitary or multifocal HCC confined to the liver, anatomically respectable, and with satisfactory liver function reserve.**

2 **Liver transplantation for HCC provides the best curative treatment of solitary HCC 5 or less cm or 3 or less tumor nodules, each 3 <1 cm (Milan criteria) associated with Child-Pugh (C-P) class C cirrhosis.**

3 **Bridge therapy using local ablation or chemoembolization may reduce dropout rate with long waiting time of more than 6 months, but there is no proven benefit in longterm survival or down staging to allow expanded indication.**

4 **Ablation**

- **Local ablation is an acceptable alternative to resection for small HCC (<3 cm) in C-P class A cirrhosis .**
- **Local ablation is a first-line treatment of unresectable, small HCC with 3 or fewer nodules in C-P class A or B cirrhosis.**

5 **TACE is recommended as a first-line treatment for patients with unresectable, large / multifocal HCCs who do not have vascular invasion or extrahepatic spread .**
Selective TACE can be performed in early-stage patients in whom RFA is difficult to be performed because of tumor location or medical comorbidities.

6 **Systemic therapy, Sorafenib**

a. **is recommended for the treatment of advanced stage patients (portal vein invasion or extrahepatic spread) who are not suitable for locoregional therapy and who have C-P class A liver function .**
b. **Sorafenib may be used with caution in patients with C-P class B liver function .**
Cytotoxic drugs are not routinely recommended but may be considered in highly selected patients whose general and hepatic conditions are adequate.

Tertiary prevention

1. **Interferon may be effective in reducing the recurrent HBV-related HCC after curative ablation of the lesion.**
2. **Lamivudine may be effective in reducing the recurrent HBV-related HCC after curative ablation of HCC.**
3. **Interferon-based antiviral treatments after complete removal or ablation of HCV-related HCC may reduce HCC recurrence and improve survival.**

LIVER DISEASES IN PREGNANY GUIDE LINES: [15]

Introduction

The cause of liver disease in pregnancy can be difficult to diagnose. Making the correct diagnosis is of paramount importance as failure to do so can result in morbidity or mortality for not only the mother, but also for her fetus. Pregnancy causes very few alterations in the results of standard liver tests. Thus, elevations in aminotransferases or GGTP signify pathology, and should prompt a search for disease. Use the gestational age of the pregnancy as the best guide to the differential diagnosis of liver disease in the pregnant woman.

Disorders Unique to Pregnancy

1 **Hyperemesis gravidarum should be considered in the differential diagnosis of abnormal liver tests presenting in the first trimester. As a rule, hyperemesis gravidarum resolves by wk 20 of gestation, but in some patients it may persist for the entire gestation. In the modern era, the outcome is good, with no ill effects for the mother or fetus and with no increase in prematurity or birth defects.**

The aminotransferases are abnormal in 50% of patients, usually <1000 U. Jaundice may occur rarely in severe cases. Management is empiric, aimed at alleviating the vomiting, and includes gut rest and i.v. fluids. No comparative trials exist, but antiemetics such as promethazine, odansetron, or droperidol have been reported to be useful. Rare patients

will require enteral or parenteral feeding. Corticosteroids have been reported to be effective.

2 **Cholestasis of pregnancy is common, and should be considered in the differential diagnosis of abnormal liver tests presenting initially in the second trimester. Affected pregnancies are at increased risk for prematurity and stillbirth, and early delivery should be considered when possible. Itching is the cardinal symptom. The clinical spectrum is broad, ranging from modest pruritus to intractable itching associated with jaundice. and it resolves within days after delivery. The pathogenesis is unclear, but Progesterone may be involved in the pathogenesis. Ethnicity and inheritance play a role. Laboratory tests may suggest hepatitis rather than cholestasis, as the GGTP is normal and the aminotransferases may be quite elevated (<1000 U). The most useful laboratory test is the serum bile acid level, which may be measured as cholylglycine. Initial therapy is aimed at symptomatic improvement of the pruritus with sedatives and antipuritics. Ursodeoxycholic acid in a dose of 13–15 mg/kg/day, divided twice a day, has shown in small controlled trials to be partially effective.. Cholestyramine has been used, but aggravates the fat malabsorption associated with this condition. Care should be taken in patients treated with cholestyramine to give supplementary vitamin K, which may be further depleted by the resin. S-adenosyl-methionine has been advocated as treatment, but with inconstant results. No data exist in the literature to support the benefit of using rifampin or grapefruit juice. The only completely effective therapy is delivery. Consideration should be given to early delivery, at 38 wk in most cases, and at 36 wk in severe cases if fetal lung maturity has been reached. The only long term sequela for the mother is a modest increase in risk for gallstones.**

3 **HELLP (hemolysis, elevated liver tests, low platelets) syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis of abnormal liver tests in the second half of pregnancy, usually in the third trimester.**

- **In HELLP syndrome, patients have signs of pre-eclampsia as well as thrombocytopenia. Pre-eclampsia affects 3–10% of pregnancies, and HELLP syndrome occurs in 20% of patients with severe pre-eclampsia. The most common symptom is abdominal pain, but it occurs in only 65% of affected patients. Many patients have no specific symptoms, and the condition is diagnosed when laboratory tests are done on patients with pre-eclampsia. Renal failure or seizures (eclampsia) may complicate the pre-eclampsia. As many as 30% of patients with HELLP present, or are diagnosed, after delivery. As with pre-eclampsia, the pathogenesis of this condition is unknown. Aminotransferase elevations are the hallmark of this syndrome, with AST elevations ranging from 70 to 6,000, with a mean of 250 in a large series. This is not a true hepatic failure, and the prothrombin time is normal except in the most severe cases complicated by dissem inated intravascular coagulation. The thrombocytopenia may be modest to very severe. Most patients are not jaundiced, and the hemolysis is manifested as schistocytes and burr cells on peripheral smear. The differential diagnosis includes viral hepatitis or, rarely, ITP. Viral serologies are useful. Management is obstetrical, with careful fetal monitoring and prompt delivery.**
- **HELLP syndrome is presumed to be the initial pathology that leads, in rare cases, to subcapsular hemorrhage with hepatic rupture, often resulting in death of both the mother and fetus. Such patients present with shock and hemoperitoneum, and are best managed surgically by a trauma team experienced in liver lacerations .**
- **HELLP syndrome may also underlie hepatic infarction, associated with fever, very high levels of aminotransferase (>5000), and anemia. The infarctions are best seen on CT or MRI scanning, and resolve spontaneously. HELLP syndrome and hepatic hematoma may recur in subsequent pregnancies. Once delivered, the infants have no liver**

involvement or thrombocytopenia and have an outcome appropriate for gestational age. There are no long term hepatic sequelae for the mother.

4 **Patients with acute fatty liver of pregnancy have true hepatic dysfunction, and may, or may not, have signs of pre-eclampsia and HELLP syndrome. Acute fatty liver of pregnancy (AFLP) is rare, reported to occur in 1/13,000–16,000 deliveries. Like the HELLP syndrome, it may present postpartum. This may be an underestimate, as the spectrum of clinical involvement is broad, ranging from asymptomatic elevations in aminotransferases to fulminant hepatic failure with jaundice, profound coagulopathy, hepatic coma, and hypoglycemia, requiring maximum supportive care. Nephrogenic diabetes insipidus may complicate the course. The pathogenesis remains unclear. Preeclampsia is present in 50% of cases. However, the hepatic histology is distinct from that of HELLP syndrome, and involves a microvesicular fatty infiltrative disorder similar to that in Reye's syndrome.**

- **Recent studies document that infants born of affected pregnancies can be deficient in one of the enzymes of mitochondrial beta oxidation of fatty acids, long chain 3-hydroxyl -acyl CoA dehydrogenase (LCHAD). Affected infants are at risk for developing nonketotic hypoglycemic coma, often with death, when stressed and fasted. Some women affected with AFLP have been shown to be heterozygous deficient for LCHAD, and it appears that many cases of AFLP are due to an inherited partial deficiency in beta oxidation of fatty acids, brought out in susceptible women by a fetus that is fully deficient, or by the stress of preeclampsia. Not all workers have been able to demonstrate such abnormalities. DNA testing in now available for several known defects in LCHAD.**
- **Laboratory tests in AFLP demonstrate a long prothrombin time and low fibrinogen. The aminotransferases are usually elevated but <1000 U. Hypoglycemia and hyper-amonemia may complicate the course.**
- **The differential diagnosis includes fulminant hepatic failure of other etiologies, especially viral, such as hepatitis E in endemic areas, or herpes simplex. HELLP syndrome may be in the differential diagnosis, if the platelet count is low because of attendant severe liver disease with disseminated intravascular coagulation. Given the clinical setting, liver biopsy usually is not indicated.**
- **Management consists of prompt delivery with maximal support as the liver recovers. Liver transplantation has been done for AFLP, but should not be necessary with early diagnosis and delivery. Because of the association with LCHAD deficiency, consideration should be given to testing both the mother and child for this disorder.**

Swansea Criteria for diagnosis of Acute Fatty liver of pregnancy[34]: Six or more criteria required in the absence of another cause:

1- **Vomiting**
2- **Abdominal pain**
3- **Polydipsia/polyuria**
4- **Encephalopathy**
5- **Elevated bilirubin >14µmmol/l**
6- **Hypoglycemia < 4µmol/l**
7- **Elevated urea > 340µmol/l**
8- **Leukcytosis >11x 10□ /l**
9- **Ascites or bright liver on ultrasound scan**
10- **Elevated transaminases (AST or ALT) > 42 IU/L** 11- **Elevated amonia > 47 µmol/l**
11- **Renal impairment; creatinine >150µmol/l**
12- **Coagulopathy; prothrombine time >14 seconds or APPT>34 seconds.**
13- **Microvascular steatosis on liver Biopsy.**

Recommendations:

1. **Consider viral or drug-induced hepatitis, gallstone disease, or malignancy in the differential diagnosis of abnormal liver tests in any of the trimesters of pregnancy.**
2. **Pregnant women may be affected by intercurrent diseases during pregnancy, and some of these are exacerbated by the underlying pregnant state. Viral hepatitis is the most common liver disease, and acute viral hepatitis can present problems in the pregnant woman.**
3. **The natural course of acute hepatitis A or B is not altered in the pregnant woman, and interruption of the pregnancy or early delivery is not indicated.**
4. **Acute hepatitis B in the second or third trimester may pose a risk for transmission to the baby, and immunoprophylaxis with hepatitis B hyperimmune globulin as well as the standard vaccination program is indicated for the neonate.**
5. **For unclear reasons, both herpes simplex and hepatitis E, can cause fulminant hepatic failure with a high maternal mortality when affecting the pregnant woman, particularly during the third trimester. Hepatitis serologies are useful in the differential diagnosis of possible viral hepatitis in pregnancy. A history of potential exposure should be sought.**
6. **Typically, patients with herpes simplex have marked elevations of aminotransferases (3000–6000 U) but are not jaundiced. Such patients usually have a rash and can be effectively treated with intravenous acyclovir, thus not requiring early delivery.**
7. **Pregnancy predisposes to gallstone disease, and the biliary sludge and gallstones that form during pregnancy may resolve after delivery with the return to non-pregnant physiology. If possible, acute cholecystitis is best managed medically in the first and third trimesters, when the risk of premature delivery prompted by surgery is greater than in the second trimester. Choledocholithiasis can be managed with endoscopic retrograde cholangiography, which may be necessary in the management of sympto matic common bile duct stones leading to cholecystitis or pancreatitis.**
8. **Pregnancy is associated with a heightened procoagulant state, and patients who have an underlying procoagulant state, such as an inherited deficiency in protein C or protein S, or the presence of an anticardiolipin or antiphospholipid antibody, may be at an increased risk for thromboses during pregnancy. This may take the form of Budd-Chiari syndrome, thrombosis of the major hepatic outflow tract, leading to painful hepatomegaly, often with liver failure, and portal hypertension with ascites. Liver transplantation may be necessary in this setting. Life-long anticoagulation is indicated in patients who survive.**
9. **Malignancy with metastases to the liver may occur in pregnancy, and there may be some permissive effect of pregnancy promoting tumor growth. The presence of a palpable liver during pregnancy, when the liver is usually forced up under the rib cage, is ominous, and should prompt investigation with laboratory tests and imaging.**
10. **<u>Chronic hepatitis B or C requires no therapy in pregnancy</u>, but poses a risk of transmission to the offspring. Pre-existing liver disease, when severe, usually is not compatible with pregnancy, and such patients are anovulatory and infertile.**
    - **However, most patients who are chronically infected with hepatitis B or hepatitis C are well, and can conceive and carry the gestation with no increased risk to themselves.**
    - **There is, however, a risk to their offspring. For women with hepatitis B who are hepati tis Be antigen– positive, the risk of transmission of the virus to the baby is 90%. Because of this risk, all pregnant women are now screened for the presence of hepatitis Bs antigen. If positive, the infant is passively immunized at birth with hepatitis B hyper**

immune globulin along with the hepatitis B vaccine that is now given as a standard to all newborns.

- **The risk of transmission of hepatitis C is substantially lower (6–10%) and depends on the mother's level of viremia. For example, the risk of hepatitis C transmission is higher for mothers with HIV, who have high levels of hepatitis C viremia. Unfortunately, no effective immunoprophylaxis is available for lowering this risk, and gamma globulin does not prevent transmission.**
- **Breast feeding is safe for the offspring of mothers with hepatitis B, once appropriately immunized, and with hepatitis C.**

11 **Patients with autoimmune hepatitis or with Wilson's disease improve on therapy, regain their fertility, and can conceive. Such patients should continue their therapy during the pregnancy. Like all patients with chronic liver disease, they are at increased risk for preeclampsia and premature delivery.**

12 **Many survivors of liver transplantation are young women, who return to normal fertility after the transplant. Like the patients with chronic liver disease, they are at increased risk for pregnancy complications such as hypertension or prematurity, but their infants do not have an increased risk for birth defects.**

The Diagnosis and Management of Non-alcoholic Fatty Liver Disease[40]

Nonalcoholic fatty liver disease and related definitions

Nonalcoholic fatty liver disease (NAFLD): Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis

Nonalcoholic fatty liver (NAFL): Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fi brosis. The risk of progression to cirrhosis and liver failure is minimal

Nonalcoholic steatohepatitis (NASH): Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer

NASH cirrhosis : Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis

Cryptogenic cirrhosis Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome

NAFLD activity score (NAS): An unweighted composite of steatosis, infl ammation, and ballooning scores. It is a useful tool to measure changes in Liver histology in patients with NAFLD in clinical trials

Common causes of secondary hepatic steatosis

1 **Macrovesicular steatosis: Excessive alcohol consumption, Hepatitis C (genotype 3), Wilson's disease, Lipodystrophy, Starvation, Parenteral nutrition, Abetalipoproteinemia, Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids).**

2 **Microvesicular steatosis: Reye's syndrome, Medications (valproate, antiretroviral medicines), Acute fatty liver of pregnancy, HELLP syndrome, Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)**

Recommendations:

1 **Ongoing or recent alcohol consumption > 21 drinks on average per week in men and > 14 drinks on average per week in women is a reasonable definition for significant alcohol consumption when evaluating patients with suspected NAFLD in clinical practice.**

2 **When patients with unsuspected hepatic steatosis detected on imaging have symptoms or signs attributable to liver disease or have abnormal liver biochemistries, they should be evaluated as though they have suspected NAFLD and worked-up accordingly.**

3 **In patients with unsuspected hepatic steatosis detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries, it is reasonable to assess for metabolic risk factors (e.g., obesity, glucose intolerance, dyslipidemia) and alternate causes for hepatic steatosis such as significant alcohol consumption or medications.**

4 **In patients with unsuspected hepatic steatosis detected on imaging who are asympto matic and have normal liver biochemistries, a liver biopsy cannot be recommended.**

5 **Screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost effectiveness of screening.**

6 **Systematic screening of family members for NAFLD is currently not recommended.**

7 **When evaluating a patient with suspected NAFLD, it is essential to exclude competing etiologies for steatosis and coexisting common chronic liver disease.**

8 **Persistently high serum ferritin and increased iron saturation, especially in the context of homozygote or heterozygote C282Y HFE mutations may warrant a liver biopsy.**

9 **High serum titers of autoantibodies in association with other features suggestive of autoimmune liver disease (very high aminotransferases, high globulin) should prompt a more complete work-up for autoimmune liver disease.**

10 **As the metabolic syndrome predicts the presence of steatohepatitis in patients with NAFLD, its presence can be used to target patients for a liver biopsy.**

11 **NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/ or cirrhosis.**

12 **Although serum/ plasma CK18 is a promising biomarker for identifying steatohepatitis, it is premature to recommend in routine clinical practice.**

13 **Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis.**

14 **The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis.**

15 **Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and coexisting chronic liver diseases cannot be excluded without a liver biopsy.**

16 **Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.**

17 **Loss of at least 3 – 5 % of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10 %) may be needed to improve necroinflammation.**

18 **Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown.**

19 **Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH.**

20 **Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that the majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long-term safety and efficacy of pioglitazone in patients with NASH is not established.**

21 **Vitamin E (α-tocopherol) administered at daily dose of 800 I U / day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.**

22 **Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.**

23 **UDCA is not recommended for the treatment of NAFLD or NASH.**

24 **It is premature to recommend omega-3 fatty acids for the specific treatment of NAFLD or NASH but they may be considered as the first-line agents to treat hypertrigly ceridemia in patients with NAFLD.**

25 **Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (but without established cirrhosis).**

26 **The type, safety, and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis due to NAFLD are not established.**

27 **It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.**

28 **Patients with NAFLD should not consume heavy amounts of alcohol.**

29 **Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH.**

30 **Until RCTs with histological end points prove their efficacy, Statins should not be used to specifically treat NASH.**

31 **When steatosis and steatohepatitis are evident in patients with other types of chronic liver disease, it is important to assess for metabolic risk factors and alternate etiologies for hepatic steatosis.**

32 **In patients with other types of chronic liver diseases who have coexisting NAFLD and NASH, there are no data to support the use of vitamin E or pioglitazone to improve the liver disease**

33 **Patients with NASH cirrhosis should be screened for gastroesophageal varices and should also be considered for HCC screening**

34 **Current evidence does not support routinely repeating a liver biopsy in patients with NAFL or NASH.**

35 **Children with fatty liver who are very young or not overweight should be tested for monogenic causes of chronic liver disease such as fatty acid oxidation defects, lysosomal storage diseases, and peroxisomal disorders, in addition to those causes considered for adults.**

36 **Low serum titers of autoantibodies are oft en present in children with NAFLD, but higher titers, particularly in association with higher serum aminotransferases and high globulin should prompt a liver biopsy to evaluate for possible autoimmune hepatitis.**

37 **Due to a paucity of evidence, a formal recommendation cannot be made with regards to screening for NAFLD in overweight and obese children despite a recent expert committee recommendation for biannual screening for liver disease with liver enzyme measurements in this population.**

38 **Liver biopsy in children with suspected NAFLD should be performed in those where the diagnosis is unclear, where there is possibility of multiple diagnoses, or before starting therapy with potentially hepatotoxic medications.**

39 **A liver biopsy to establish a diagnosis of NASH should be obtained before starting children on pharmacologic therapy for NASH.**

40 **Pathologists interpreting pediatric NAFLD biopsies should recognize the unique pattern frequently found in children to not misidentify pediatric NAFLD.**

41 **Intensive lifestyle modification improves aminotransferases and liver histology in children with NAFLD and thus should be the first line of treatment.**

42 **Metformin at 500 mg twice daily offers no benefit to children with NAFLD and thus should not be prescribed. The effect of metformin administered at a higher dose is not known.**

43 **Vitamin E 800 I U/ d ay (RRRα-tocopherol) offers histological benefits to children with biopsy-proven NASH or borderline NASH but confirmatory studies are needed before its use can be recommended in clinical practice.**

The diagnosis and management of Idiosyncratic Drug-Induced Liver Injury (DILI)[41]

Idiosyncratic drug-induced liver injury (DILI) is a rare adverse drug reaction and it can lead to jaundice, liver failure, or even death. Antimicrobials and herbal and dietary supplements are among the most common therapeutic classes to cause DILI.

Terminology and definitions:

- **Intrinsic DILI: hepatotoxicity with potential to affect all individuals to varying degrees. Reaction typically stereotypic and dose dependent(e.g., acetaminophen)**
- **Idiosyncratic DILI: Hepatotoxicity affecting only rare susceptible individuals. Reaction less dose dependent and more varied in latency, presentation, and course.**
- **Chronic DILI: Failure of return of liver enzymes or bilirubin to pre-DILI baseline, and /or other signs or symptoms of ongoing liver disease (e.g., ascites, encephalopathy, portal hypertension, coagulopathy) 6months after DILI onset.**
- **Latency: Time from medication (or Herbal and dietary supplement-HDS*) start to onset of DILI.**
- **Wash-out, resolution, or de-challenge : Time from DILI onset to return of enzymes and /or bilirubin to pre-DILI bases line levels.**
- **Rechallenge: Re-adminstration of medication or HDS to a patient who already had a DILI to the same agent.**
- **Hy's law : observation made by late Hyman Zimmerman suggesting a 1 in 10 mortality risk of DILI if the following three criteria are met:**

1. **Serum ALT or AST >3XULN**
2. **Serum total bilirubin elevated to >2Xuln, without initial findings of cholestasis(elevated serum alkaline phosphatase)**
3. **No other reason can be found to explain the combination of increased aminotra nsferases and bilirubin, such as viral hepatitis A,B,C, or other preexisting or acute liver disease.**

- **Temple's corollary: An imbalance in the frequency of ALT >3XULN between active treatment and control arms ina randomized controlled trial. This is used to assess for hepatotoxic potential of a drug from premarketing clinical trials.**
- **R-value: ALT/ULN÷AP/ULN. Used to defined hepatotoxicity injury patterns: hepatocellular (R >5), mixed (R= 2-5), and cholestatic (R<2)..**
- **RUKAM: Diagnostic algorithm that uses a scoring system based on clinical data, pre-existing hepatotoxicity literature on the suspected agent and rechallenge.(RUKAM, Roussel uclaf Causality Assessment Method)**

Recommendations:

<u>In individuals with suspected hepatocellular or mixed DILI:</u>

a. **Acute viral hepatitis (A, B, and C) and autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing.**
b. **Routine anti-hepatitis E virus IgM testing cannot be recommended owing to unclear performance characteristics of the currently available commercial tests. However, it should be considered in the setting of heightened clinical suspicion (e.g., recent travel in an endemic area).**
c. **Testing for acute cytomegalovirus, acute Epstein-Barr virus, or acute herpes simplex virus infection should be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis and lymphadenopathy suggest such causes.**
d. **Wilson's disease and Budd-Chiari syndrome should be considered when clinically appropriate.**

In individuals with suspected cholestatic DILI:

e. **Abdominal imaging (ultrasound or computerized tomography scan) should be performed in all instances to exclude biliary tract pathology and infiltrative processes.**

f. **Serological testing for primary biliary cirrhosis should be limited to those with no evidence of obvious biliary tract pathology on abdominal imaging**

g. **Endoscopic retrograde cholangiography should be limited to instances where routine imaging is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreatico-biliary malignancy**

When to consider a liver biopsy?

h. **A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated .**

i. **A liver biopsy may be considered in the following situations:**

- **If there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent,**
- **If the peak alanine aminotransferase level has not decreased by > 50 % at 30 – 60 days after the onset in cases of hepatocellular DILI, or if the peak alkaline phosphatase has not fallen by > 50 % at 180 days in cases of cholestatic DILI despite stopping the suspected off ending agent ,**
- **In cases of DILI where continued use or re-exposure to the implicated agent is expected,**
- **If liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver Diseases (CLDs) and chronic DILI.**

Out come and prognosis:

In general, outcomes of idiosyncratic DILI are good, with only ~10% reaching the threshold of ALF (coagulopathy and encephalopathy).

- **DILI that does evolve to ALF carries a poor prognosis, with 40% requiring liver transplantation and 42% dying of the episode. Advanced coma grade and high MELD scores are associated with bad outcomes.**
- **Prognostic scores to predict outcome for DILI reaching the threshold of ALF are poor or rudimentary.**

Re-exposure to a drug that is thought likely to have caused hepatotoxicity is strongly discouraged, especially if the initial liver injury was associated with significant aminotransferase elevation (for example, > 5xULN, Hy's law, or jaundice). An excep tion to this recommendation is in cases of life-threatening situations where there is no suitable alternative.

In individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction, the suspected agent(s) should be promptly stopped

No definitive therapies are available either for idiosyncratic DILI with or without ALF: however, NAC may be considered in adults with early-stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients NAC is not recommended for children with severe DILI leading to ALF

Chronic DILI occurs in about 15–20% of cases of acute DILI.

Patients experiencing DILI because of prescription medications or dietary supplements or herbal products should be followed up clinically and biochemically to complete resolution.

DILI patients with severe acute cholestatic liver injury appear to be at an increased risk of developing chronic liver injury and require careful long-term follow-up

HDS account for an increasing proportion of DILI events in the United States, with body building and weight loss supplements being the most commonly implicated.

The current regulation for HDS differs substantially from conventional prescription medication most importantly, there is no requirement for premarketing safety analyses of HDS.

Patients and providers must be aware that regulation is not rigorous enough to assure complete safety of marketed products. Patients should be made aware of this fact, and of the potential for HDS to cause liver injury.

Current causality assessment approaches are not well suited for HDS hepatotoxicity, given the possibility of product variability and contamination; however, expert opinion is probably the best suited for HDS hepatotoxicity, as all information is taken into consideration in assigning a likelihood of injury. Voluntary reporting of suspected HDS hepatotoxicity cases through the FDA MEDWATCH system is essential. Patients should be encouraged to report the use of HDS to their health-care providers, and be reminded that supplements are not subjected to the same rigorous testing for safety and efficacy as are prescription medications .

The same diagnostic approach for DILI is applicable to suspected HDS hepatotoxicity. That is, other form of liver injury must be excluded through a careful history and appropriate laboratory testing and hepato- biliary imaging. Excluding other causes, the diagnosis of HDS hepatotoxicity can be made with confidence in the setting of recent use of HDS.

<u>Patients with suspected HDS hepatotoxicity should stop all HDS hepatotoxicity and be monitored for resolution of Their liver injury</u>

- **There are no data to show that underlying CLD is a major risk factor for all-cause DILI, but it may increase the risk for DILI due to selected medications. Patients with chronic HBV and HCV may be more prone to develop liver injury due to specific agents such as isoniazid and antiretrovirals, and may experience more severe outcomes.**
- **Individuals with underlying fatty liver disease are not at an increased risk for hepatotoxicity from statins.**

<u>Treatment of DILI:</u>

- **Stop and avoid re-exposure**
- **Symptomatic**
- **Jaundice: low fat diet, anti-pruritic agents(doxepin, hydroxyizine, etc.)**
- **DILI specific:**
  - **Mucomyst(PO or IV) for acetaminophen or ALF**
  - **L-carnitine(IV) for valproate**
  - **Cholestyramine for Leflunomide**
  - **Cholestyramine and ursodiol for cholestatic**
  - **Steroid only for drug induced autoimmune hepatitis.**

The Diagnosis and Management of Focal Liver Lesions (FLL) Clinical Guideline[43]

Focal liver lesions (FLL) have been a common reason for consultation faced by gastroenterologists and hepatologists. The increasing and widespread use of imaging studies has led to an increase in detection of incidental FLL. It is important to consider not only malignant liver lesions, but also benign solid and cystic liver lesions such as hemangioma, focal nodular hyperplasia, hepatocellular adenoma, and hepatic cysts, in the differential diagnosis.

Recommendations for diagnosis and management of FLL.

1. **An MRI or triple-phase CT should be obtained in patients with cirrhosis with an ultrasound showing a lesion of > 1 cm.**
2. **Patients with chronic liver disease, especially with cirrhosis, who present with a solid FLL are at a very high risk for having HCC and must be considered to have HCC until otherwise proven.**
3. **A diagnosis of HCC can be made with CT or MRI if the typical characteristics are present: a solid FLL with enhancement in the arterial phase with washout in the delayed venous phase should be considered to have HCC until otherwise proven.**
4. **If an FLL in a patient with cirrhosis does not have typical characteristics of HCC, then a biopsy should be performed in order to make the diagnosis.**
5. **MRI or CT should be obtained if CCA is suspected clinically or by ultrasound**
6. **A liver biopsy should be obtained to establish the diagnosis of CCA if the patient is non operable**
7. **Oral contraceptives,ormone-containing intrauterine devices, and anabolic steroids are to be avoided in patients with hepatocellular adenoma**
8. **Obtaining a biopsy should be reserved for cases in which imaging is inconclusive and biopsy is deemed necessary to make treatment decisions.**
9. **Pregnancy is not generally contraindicated in cases of hepatocellular adenoma < 5 cm and an individualized approach is advocated for these patients.**
10. **In hepatocellular adenomas ≥5 cm, intervention through surgical or nonsurgical modalities is recommended, as there is a risk of rupture and malignancy.**
11. **If no therapeutic intervention is pursued, lesions suspected of being hepatocellular adenoma require follow-up CT or MRI at 6- to 12-month intervals. The duration of monitoring is based on the growth patterns and stability of the lesion over time.**
12. **<u>For cases with liver hemangioma</u>:**
    - **An MRI or CT scan should be obtained to confirm a diagnosis of hemangioma.**
    - **Liver biopsy should be avoided if the radiologic features of a hemangioma are present .**
    - **Pregnancy and the use of oral contraceptives or anabolic steroids are not contra indicated in patients with a hemangioma.**
    - **Regardless of the size, no intervention is required for asymptomatic hepatic heman giomas.**
    - **Symptomatic patients with impaired quality of life can be referred for surgical or nonsurgical therapeutic modalities by an experienced team.**
13. **<u>For focal nodular hyperplasia</u>:**
    - **An MRI or CT scan should be obtained to confirm a diagnosis of FNH. A liver biopsy is not routinely indicated to confirm the diagnosis.**
    - **Pregnancy and the use of oral contraceptives or anabolic steroids are not contra indicated in patients with FNH.**
    - **Asymptomatic FNH does not require intervention.**
    - **Annual US for 2 –3 years is prudent in women diagnosed with FNH who wish to continue OCP use. Individuals with a firm diagnosis of FNH who are not using OCP do not require follow- up imaging.**

14. **Recommendation For NRH**

- **Liver biopsy is required to confirm the diagnosis of NRH**
- **Pregnancy and the use of oral contraceptives or anabolic steroids are not contraindica ted in patients with an NRH.**
- **Asymptomatic NRH does not require intervention.**
- **Management of NRH is based on diagnosing and managing any underlying predis posing disease processes.**

15. **A hepatic cyst identified on US with septations, fenestrations, calcifications, irregular walls, or daughter cysts :**

- **should prompt further evaluation with CT or MRI.**
  Asymptomatic simple hepatic cysts should be observed with expectant management.
- **Aspiration of asymptomatic, simple hepatic cysts is not recommended.**
- **Symptomatic simple hepatic cysts may be managed with laparoscopic deroofing rather than aspiration and sclerotherapy, dictated based on availability of local expertise.**

16. **when BCA is suspected because of limited**

- **Routine fluid aspiration is not recommended sensitivity and the risk of malignant dissemination.**
- **Imaging characteristics suggestive of BC or BCA, such as internal septations, fenestrations, calcifications, or irregular walls, should lead to referral for surgical excision.**
- **Complete surgical excision, by an experienced team, is recommended if BC or BCA is suspected.**

17. **Routine medical therapy with mammalian target of rapamycin inhibitors or somato statin analogs is not recommended.**
18. **Aspiration, deroofing, resection of a dominant cyst can be performed based on the patient's clinical presentation and underlying hepatic reserve.**
19. **Liver transplantation with or without kidney transplantation can be considered in patients with refractory symptoms and significant cyst burden.**
20. **MRI is preferred over CT for concomitant evaluation of the biliary tree and cystic contents.**
21. **Monotherapy with antihelminthic drugs is not recommended in symptomatic patients who are surgical or percutaneous treatment candidates.**
22. **Adjunctive therapy with antihelminthic therapy is recommended in patients undergoing PAIR or surgery, and in those with peritoneal rupture or biliary rupture.**
23. **Percutaneous treatment with PAIR is recommended for patients with active, hydatid cysts who are not surgical candidates, who decline surgery, or who relapse after surgery.**
24. **Surgery, either laparoscopic or open, based on available expertise, is recommended in complicated hydatid cysts with multiple vesicles, daughter cysts, fistulas, rupture, hemo rrhage or secondary infection.**

Chronic nonviral hepatitis

Autoimmune hepatitis (AIH)[24]:

Is a heterogeneous group of chronic necroinflammatory hepatic disorders of suspected autoimmune origin that can lesd to end-stage liver disease and hepatic failure. it is not uncommon disease, more common in Women than in men.

Recommendations for diagnosis and treatment:

1- **Serologic findings (abnormal liver biochemical tests, autoantibodies, elevated IgG).**
2- **Liver biopsy**
3- **Ruling out other chronic liver diseases (drug-induced liver injury, viral hepatitis, inherited and metabolic liver disorders).**
4- **Overlap syndromes include features of other chronic liver disorders (e.g., primary biliary cirrhosis, primary sclerosing cholangitis).**
5- **The clinical outcome is usually favorable with early diagnosis and appropriate immuno-suppressive therapy.**
6- **Acute hepatitis may present as fulminant liver failure and may have poor outcome, particularly if therapy is delayed.**
7- **Worsening hyperbilirubinemia and MELD score higher than 12 at presentation predict treatment failure.**
8- **Liver transplantation is concerning in following circumstances:**

- **High MELD score i.e. >12 (in particular, high INR)**
- **Any suggestion of encephalopathy (even mild) in setting of hyperbilirubinemia and elevated INR.**
- **Deterioration after commencing immunosuppressive therapy or no improvement**

Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis

The median ALT values at reintroduction of medication were 273 U/L (range 42–1072). No patient suffered hepatic decompensation. Treatment was usually reinstituted with a short course of dual immunosuppressive therapy, going back to azathioprine mono therapy (dosage: 1.5 mg/kg/body weight) after about 3 months. This approach led to the rapid reinduction of remission.

So proper patient selection including a sustained complete biochemical remission on immunosuppressive monotherapy for a minimum of 2years can markedly improve the sucess rates.

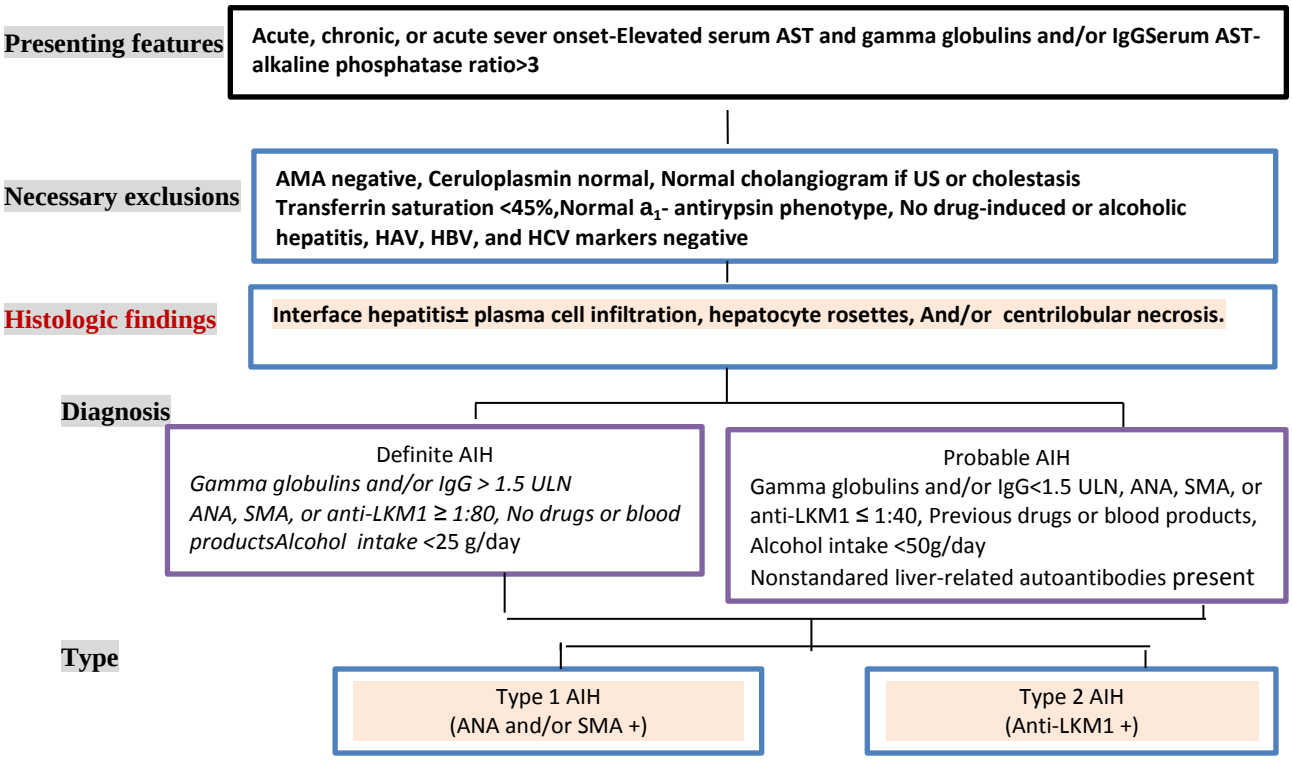

Figure 15: Diagnostic algorithm for autoimmune hepatitis (AIH)

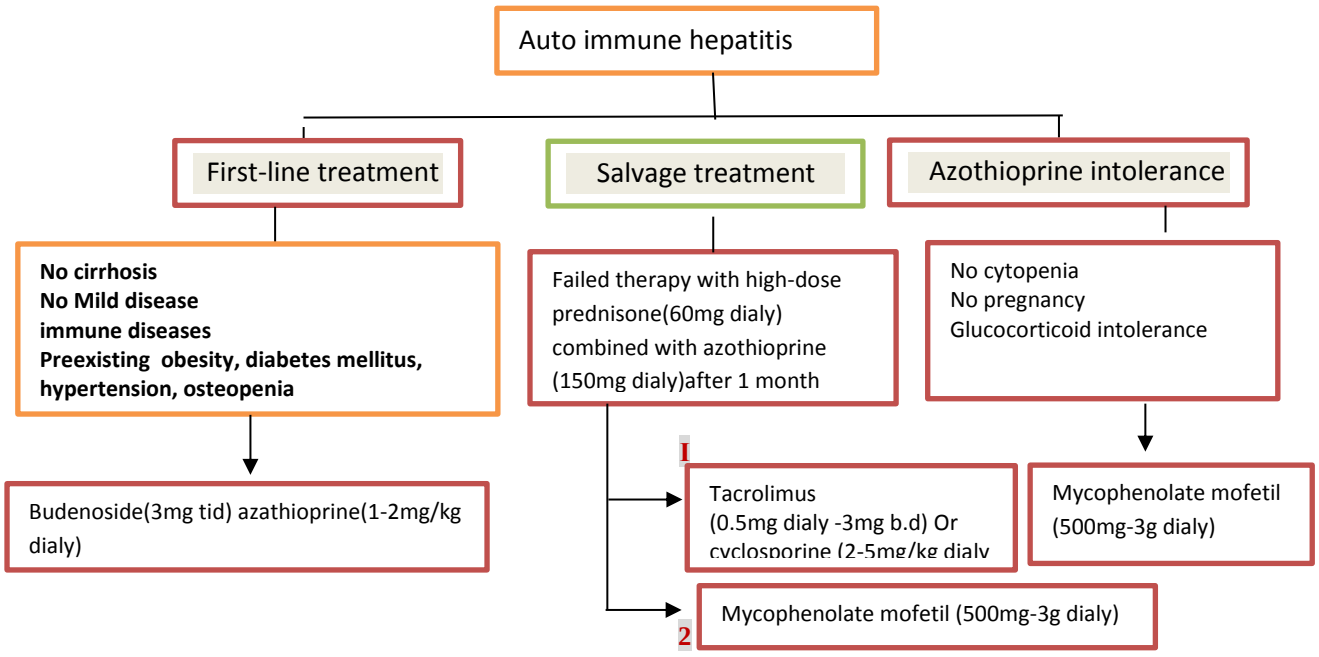

Figure 16: Treatment algorithm for AIH

Primary Sclerosing Cholangitis(PSC) [13]

Is a chronic idiopathic cholestasis liver and biliary tract disease,defined as the presence of beading and stricture formation of the intra and/or extrahepatic bile ducts that cannot be ascribed by another cause, thus differentiating PSC from secondary Sclerosing cholangitis. Many if not most, cases of PSC are associated with inflammatory bowel disease(IBD),

-Most common symptoms and at the time of dagnosis of PSC ordered in frequency from most common to less (Fatigue, Abdominal pain, Pruritus, Fever/Night sweats, None, Weight loss)

-Most common signs at the time of diagnosis of PSC ordered in frequency from most common to less: (Jaundice, Hepatomegaly, Spleenomegaly, Hyperpigmentation, Ascites)

Recommendations:

MRCP is preferred over endoscopic retrograde cholangiopancreatography(ERCP) to establish a diagnosis of PSC.

Liver biopsy inPSC:

1. **is not necessary to make a diagnosis in patients with suspected PSC based on diagnosed cholangiographic findings.**
2. **is recommended in patient with suspected small duct PSC or to exclude other conditions such as suspected overlap with autoimmune hepatitis.**
3. **Liver biopsy is needed for the diagnosis in small-duct PSC with normal cholangiogram**
4. **Antimitochondrial autoantibodies testing can help exclude primary biliary cirrhosis. Patients with PSC should be tested at least once for elevated serum immunoglobulin G4 (IgG4) levels.**

ERCP in PSC:

1. **with balloon dilatation is recommended for PSC patients with dominant stricture and pruritus, and/or cholangitis, to relieve symptoms.**
2. **PSC with a dominant stricture seen on imaging should have an ERCP with cytology, biopsy and FISH to exclude diagnosis of cholangiocarcinoma.**
3. **PSC patients undergoing ERCP should have antibiotic prophylaxis to prevent post-ERCP cholangitis.**
4. **Routine testing after dilation of a dominant stricture is not required, whereas short-term stenting may be required in patients with severe stricture.**

Colonoscopy in PSC:

1. **Annual colon surveillance preferably with chromoendoscopy is recommended in PSC patients with colitis beginning at the time of PSC diagnosis.**
2. **A full colonoscopy with biopsies recommended in patients with PSC regardless of the presence of symptoms to assess for associated colitis at the time of PSC diagnosis.**
3. **Some advocate repeating the exam every 3-5years in those without prior evidence of colitis.**

IBD and its relation with PSC:

1. **is prevalent in the majority of patients with PSC; however, PSC is present in the less than 10% of patients with IBD.**
2. **IBD can occur de novo after liver transplantation for PSC.**
3. **PSC can occur de novo after proctocolectomy for ulcerative colitis (UC).**
4. **Patients with UC and PSC are at increased risk for colorectal neoplasia compared with patients with UC but not PSC. Furthermore, when colorectal neoplasia is found, it's in the right colon about 75% of the time. This stresses the importance of a full colonoscopy with a good bowel preparation regimen.**
5. **PSC without IBD, think of IgG4-associated cholangitis (and sometimes associated with Sclerosing of the pancreatic ducts and autoimmune pancreatitis) which can respond to a course of steroids unlike PSC without IgG4 cholangitis , So IgG4 level should be checked.**

Ursodeoxycholic acid therapy is not effective to halt the progression of PSC and has increased side effects at the higher doses(UDCA in doses>28mg/kg/day should not be used for management of patients with PSC).Thus it is not recommended routinely for PSC. However, it may be considered in select patients with PSC who have a particular increased risk for colorectal neoplasia (due to family history, etc), as some retrospective studies have shown a decreased risk for colorectal neoplasia in patients with PSC taking Ursodeoxycholic acid.

Cholangiocacinoma

1. **occurs in about 10% of patients with PSC. However, as opposed to colorectal malignancy in UC, which tends to present well after the initial diagnosis of UC, Cholangiocacinoma is present within 1 year of the time of diagnosis of PSC in about half of the patients who develop it.**
2. **Consider screening for cholangiocarcinoma with regular cross-sectional imaging with ultrasound or MR and serial CA 19-9every 6-8months.**

Gall bladder polyps in PSC are frequently malignant. Thus, cholecystectomy needs to be considered in PSC patients with significant gallbladder polyps..

Liver transplantation, when possible, is recommended over medical therapy or surgical drainage in PSC patients with decompensated cirrhosis, to prolong survival.Patients should be referred for liver transplantation when their MELD score exceeds 14.

Independant Predictors of Survival and Prognostic index Formula

Reviced Mayo Model* is using Age, Bilirubin, Albumin, AST, and Variceal bleedings parameters in the quotion as below:

R(Risk score) = 0.03× age+ 0.54× $\log_e$(bilirubin)+ 0.54× $\log_e$(AST)+ 1.24× Variceal bleeding- 0.84× albumin

King's College Model is using Age, Hepatomegaly, Histologic stage, Spleenomegaly, and Alkaline phosphatase in the quotion as below:

R(Risk score)= 1.81× hepatomegaly+0.88×splenomegaly+2.66×log(alk phos) + 0.58 × histologic stage+ 0.04× age

(Age expressed in years; albumin in g/dL; alkaline phosphatase in U/L; bilirubin in md/dL; values for hepatomegaly, splenomegaly, and variceal bleeding are 1 if present, 0 if absent).

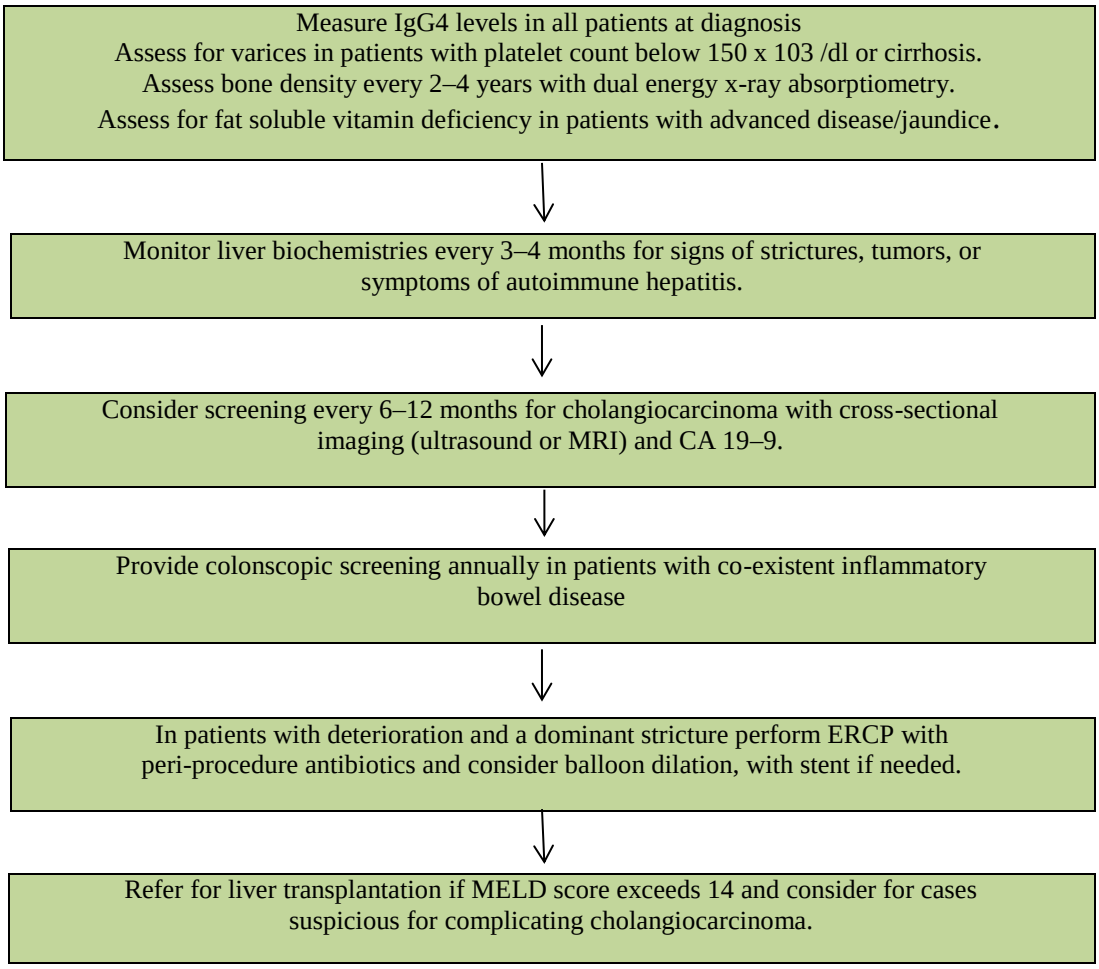

Figure 17: Management of primary sclerosing cholangitis

Wilson disease (WD) or hepatolenticular degeneration[49]

Was described by Kinnear Wilson about 100years ago. It is an autosomal recessive condition marked by impaired biliary secretion of copper as a result of a mutation in the ATP7B WD gene on chromosome 13; this leads to accumulation of copper in the liver, brain, cornea, and kidneys causing injury to these organs.In its earlier form, the liver biopsy reveals periportal inflammation, interface hepatitis, and bridging fibrosis. Mallory bodies are found in 25% to 50%.

Test	Normal Adults	Wilson Disease*
Serum ceruloplasmin(mg/L)	200-350	0-200
Serum copper(µg/L) (µmol/L)	700-1500 11-24	190-640 3-10
Basal 24-hr urinary copper (µg/day) (µmol/day)	 <40 ≤ 0.6	 40-10,000 >0.6
Liver copper (µg/g dry weight)	20-50	>250(possibly>70)

Table 10: Biochemical Parameters in Normal Adults and in Patients with Wilson Disease:
***For all the assays, results in homozygotes and heterozygotes may develop.**

Clinically useful 10 fact lets to know about WD.:

1) **The acute hepatitis and acute liver failure phases of WD are often marked by an abrupt hemolytic anemia.**
2) **Low ALP levels (not high ones) and low serum uric acid levels may occur in symptomatic liver or neurological disease due to Fanconi syndrome of the proximal renal tubules.**
3) **WD happens in young people (A serum ceruloplasmin level should be part of the investigations for all patients <40 years of age of age with abnormal liver enzymes of unknown etiology, even its normal level of serum ceruloplasmin does not rule out WD).**
4) **The presence of neurological findings is almost synonymous with cirrhosis- it's very unusual to have neurological findings in the absence of cirrhosis.**
5) **Kayser-Fleischer rings occur from deposition of copper in the Descemet's membrane of the inner cornea, whereas the characteristic "sunflower cataract" is from copper deposi tion in the lens capsule.**
6) **In the setting of classical neurological symptoms from deposition of copper in the basal ganglia (eg. Dystonia, chorea, dysartheria, parkinsonian features), the presence of KF rings on slit-lamp examination is pathognomonic for WD, but the absence of KF rings with neurologic symptoms nearly excludes WD(ie, high negative predictive value of absence KF rings when there are neurologic symptoms).**
7) **Although 95% of patients with WD have depressed serum ceruloplasmin levels (<20 mg/dL) and 85% have elevated urine copper excretion(>100mcg/24hrs), low cerulo plasmin and high urine copper are sensitive but not entirely specific for WD, because both are seen in some asymptomatic heterozygotes, among other conditions. (cholestasis of any etiology may cause low ceruloplasmin levels and increased urinary copper levels)**
8) **The gold standerd for diagnosis remains quantification of hepatic copper, where a concentration above 250mcg copper/g dry tissue is diagnostic of WD-yet copper distribution may be heterogeneous, so a negative study does not entirely rule out WD, but a positive study is diagnostic in the right clinical setting.**
9) **It's vital to screen first –degree family members of affected individuals with slit-lamp examination and measurement of serum ceruloplasmin levels.**
10) **Both neurologic symptoms and liver tests may initially worsen after starting therapy (such as the chelating agents which more so with D-penicillamine than trientine), but subsequent improvement typically occurs after 6months of starting therapy (i.e., it takes a while for the medicine to work, so don't discontinue it if the symptoms initially worsen unless there is a serious side effects). Gradually increasing the dose of these agents may help in decreasing this problem, in addition to that D-penicillamine inactivates pyrido xine so small doses of pyridoxine (25mg/day) should be given with D-penicillamine.**

Recommendations for asymptomatic WD:

1. **Asymptomatic individuals should be encouraged to continue zinc treatment lifelong.**
2. **Those who become asymptomatic on treatment should not stop treatment, but can be switched to zinc alone. Zinc may be considered in patients who cannot tolerate first line agents or who have worsening of neuropsychiatric disease with the chelating agents.**

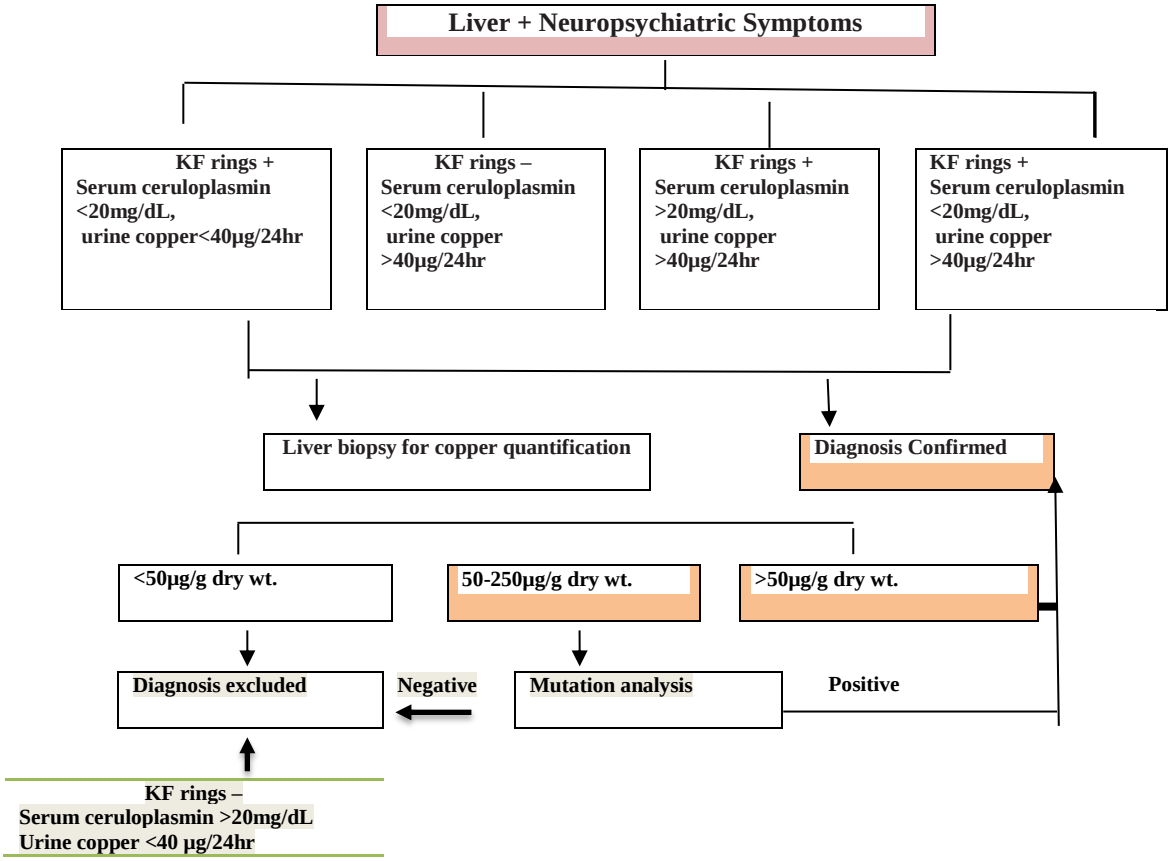

Figure 18: Diagnostic algorithm for Wilson disease

Associated conditions with WD:

Coombs negative hemolytic anemia.
Renal abnormalities including aminoaciduria and nephrolithiasis.
Skeletal abnormalities including premature osteoporosis and arthritis.
Cardiomyopathy.
Pancreatitis.
Hypoparathyroidism.
Infertility or repeated miscarriages.

Copper –Rich Foods to Avoid in Wilson Disease (in no particular order):

Chocolate
Sesame seeds (بذور السمسم)
Raw cashews
Sunflower seeds
Poppy seeds (بذور الخشخاش)
Liver
. Navy beans
. Garbanzo beans
. Soybeans
. Cooked barley
. Oysters (المحار)

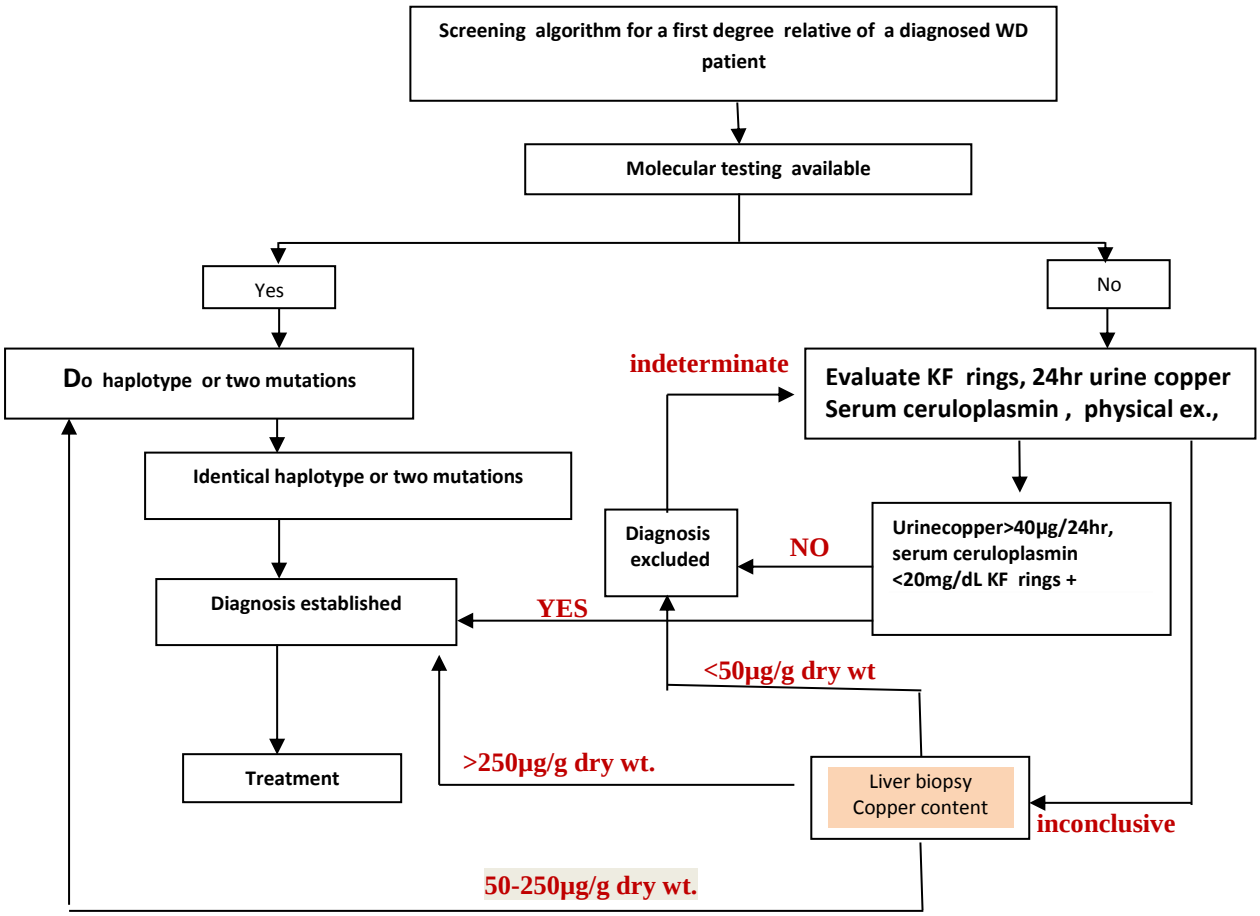

Figure 19: Screening algorithm for WD

EASL Clinical Practice Guidelines for HFE Hemochromatosis[39]

European Association for the Study of the Liver 2010

Iron overload in humans is associated with a variety of genetic and acquired conditions. Of these, HFE hemochromatosis. (HFE-HC) is by far the most frequent and most well-defined inherited cause when considering epidemiological aspects and risks for iron-related morbidity and mortality. The majority of patients with HFE-HC are homozygotes for the C282Y polymorphism. Without therapeutic intervention, there is a risk that iron overload will occur, with the potential for tissue damage and disease.

Recommendations for genetic testing:

General population:

• Genetic screening for HFE-HC is not recommended, because disease penetrance is low and only in few C282Y homozygotes will iron overload progress Patient populations:

• HFE testing should be considered in patients with unexplained chronic liver disease pre-selected for increased transferrin saturation.

• HFE testing could be considered in patients with:

– porphyria cutanea tarda.

– well-defined chondrocalcinosis.

– hepatocellular carcinoma.

– type 1 diabetes.

• HFE testing is not recommended in patients with

– unexplained arthritis or arthralgia.

– Type 2 diabetes.

<u>Recommendations for the diagnosis of HFE-HC:</u>

1. **Patients with suspected iron overload should first receive measurement of fasting transferrin saturation and serum ferritin, and HFE testing should be performed only in those with increased transferrin saturation.**
2. **Patients from liver clinics should be screened for fasting transferrin saturation and serum ferritin and offered genetic HFE testing if transferrin saturation is increased.**
3. **HFE testing for the C282Y and H63D polymorphism should be carried out in all patients with otherwise unexplained increased serum ferritin and increased transferrin saturation.**
4. **Diagnosis of HFE hemochromatosis should not be based on C282Y homozygosity alone, but requires evidence of increased iron stores.**
5. **C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin (>200 mg/L in females, >300 mg/L in males), increased trans ferrin saturation (>45% in females, >50% in males) or increased liver iron should first be investigated for other causes of hyperferritinemia.**
6. **In C282Y homozygote patients with increased iron stores, liver biopsy is no longer necessary to diagnose hemochromatosis. Liver biopsy could be offered to C282Y homozygous patients with serum ferritin above 1000 mg/L, elevated AST, hepato megaly, or age over 40 years.**
7. **Genetic testing of 'other hemochromatosis genes' (TFR2, SLC40A1, HAMP, HJV) could be considered in patients with increased iron stores after exclusion of C282Y homozygosity if (i) iron excess has been proven by direct assessment, i.e. by MRI or liver biopsy, and (ii) other hepatic and haematological disorders have been ruled out.**
8. **According to the autosomal recessive transmission of HFE-HC, genetic testing of siblings of individuals with HFE-HC should be carried out. Genetic testing of other 1st degree relatives should be considered.. (Practical and cost effective strategies for family screening have been published.**

Recommendations for the management of HFE-HC:

1. **Patients with HFE-HC and evidence of excess iron should be treated with phlebotomy.**
2. **C282Y homozygotes without evidence for iron overload could be monitored annually and treatment instituted when the ferritin rises above normal.**
3. **Phlebotomy should be carried out by removing 400–500ml of blood (200–250mg iron) weekly or every two weeks. Adequate hydration before and after treatment, and avoidance of vigorous physical activity for 24 h after phlebotomy is recommended.**
4. **Phlebotomy can be carried out also in patients with advanced fibrosis or cirrhosis.**
5. **Before the initiation of phlebotomy, patients with HFE-HC should be assessed for complications including diabetes mellitus, joint disease, endocrine deficiency (hypoth yroidism), cardiac disease, porphyria cutanea tarda, and osteoporosis.**
6. **Complications of HFE-HC (liver cirrhosis, diabetes, arthropathy, hypogonadism, PCT) should be managed regardless of whether or not HC is the underlying cause and whether there is symptomatic relief or improvement during phlebotomy.**
7. **To minimize the risk of additional complications, patients with HFE-HC could be immunized against hepatitis A and B while iron overloaded..**

Alpha-1 Antitripsin Dificiency

Alpha-1 antitrypsin (AAT) deficiency is a rare autosomal codominant inherited disease primarily affecting the lungs (most common manifestation is early onset emphysema- in the 3rd to 4th decade of life-) and liver(which is a less common and affect both children and adults), which is most often due to a defect in the release of AAT from hepatocytes into the circulation.

In children, liver disease associated with AAT deficiency presents with cholestatic jaundice, anormal liver enzymes, hepatitis or even cirrhosis.

AAT dificiency should be suspected in any person who presents with unexplained liver or respiratory symptoms

Diagnosis involves measurement of serum levels of AAT along with determination of the phenotype or genotype (e.g. MM,ZZ) by serum protein isoelectric focusing.

Family members should be questioned about lung or liver disease. In addition smoking and smoke exposure history are important as well as invirnmental and occupational exposures.

Recommendations:

Smoking cessation: it is regarded as the most effective strategy in preventing progression of lung disease and slows liver disease progression.

Avoiding environmental and occupational pollutant exposure.

Vaccination for influenza and pneumococcal has been recommended in all patients with AAT difficiency. Those with overt liver disease are advised to receive hepatitis A and B vaccination.

Apart from liver transplantation, specific liver-related treatment is not available is not available but enzyme replacement therapy is available for those with lung disease.

Pediatric Hepatology[51,54]

Metabolic Liver Disease:

Jaundice in Neonate

- **Unconjugated Jaundice**
- **Crigler Najjar Syndrome**
- **Galactosemia, hypothyroidism initially**
- **HLH**

Infantile Cholestasis

- **Galactosemia**
- **Tyrosinemia**
- **Hypo/hyperthyroidism**
- **Hypopituitarism(SOD)**
- **Bile acid defects**
- **Gaucher's disease**
- **Fructosemia**
- **NN hemochromatosis**
- **Alpha-1 antitrypsin def**
- **PFIC**
- **Cystic fibrosis**
- **HLH**
- **Peroxisomal disorders**
- **NiemannPick Band C**
- **Wolman's Disease**
- **Organic acidemia**

Presentation

- **Infantile Cholestasis**
- **Acute liver failure**
- **Neonatal Ascites**
- **Hepatomegaly/splenomegaly**
- **Hyperammonemia/Acidosis**

Common Features

- **Positive family history**
- **Unexplained neonatal deaths/multiple miscarriages**
- **Consanguinity**
- **Recurrent episodes of unexplained vomiting, encephalopathy**
- **Developmental delay/regression**
- **Dysmorphism**

Cholestatic jaundice:

Progressive familial intrahepatic cholestasis (PFIC), types 1, 2 and 3, are due to defects in genes involved in bile secretion (FIC1, BSEP, MDR3). PFIC and inborn errors of bile acid synthesis (IEBAS) often present in infancy with cholestasis. The distinctive feature of PFIC 1 and 2 and IEBAS is a normal level of GGT, while IEBAS are suspected in patients with low plasma bile acids concentration. Molecular testing, urinary bile acid analysis (IEBAS), liver biopsy and immuno-staining are used for the diagnosis. Some patients with PFIC can be successfully treated with ursodeoxycholic acid or partial external biliary diversion. IEBAS is treated with cholic acid. Liver transplantation is required for cirrhosis with liver failure. Hepatocarcinoma has been reported in PFIC2.

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Liver cirrhosis in children: the causes can be classified according to their pathologic mechanism.

1- **Cholestatic causes: Biliary atresia, Cystic fibrosis, progressive intrahepatic familial cholestasis(formerly called Byler's disease, Histeocytosis X.**
2- **Liver inflammatory diseases: Chronic hepatitis B, Chronic hepatitis C, Autoimmune hepatitis.**
3- **Metabolic disorders: Alpha-1-antitrypsin dificiency, Wilson's disease, Glycogenosis typesIII and IX, Glycogenosis typeIV(also called amylopectinosis), Tyrosinemia, Niemann-Pick type C.**
4- **Toxic disorders(nutrotional): Total parenteral nutrition (TPN)**

Recommendations for diagnosis and management of liver disease in pediatrics:

1. **Diagnosis of Metabolic Liver diseases, is made by**
   a. Measuring missing protein.
   b. Measuring accumulated toxins
   c. Measuring enzyme levels
   d. Clinical syndrome
   e. Mutational analysis
2. **Metabolic liver disease, the management options:**

   <u>Non-Transplant</u>:

   Dietary restriction (galactosemia,fructosemia), Enzyme inhibition (tyrosinemia type I (NTBC)), Enzyme induction(Crigler-Najjar type II (phenobarbitone), Replacement of the deficient metabolite(inborn errors of bile acids (cholic acid), Removal of the toxin Wilson disease (penicillamine, trientine, zinc).

   <u>Transplant</u>:

   Cirrhotic liver disease: Orthotopic whole liver replacement

   Non-cirrhotic single enzyme metabolic disease: Auxiliary liver transplantation (Rela et al. Arch Surg1999), Hepatocyte transplantation (Fox et al. N Engl J)

   <u>Combined Transplantations</u>:

   Liver + kidney: Primary hyperoxaluria (Watts et al, QJM 1985), Methyl Malonic Acidemia

   Liver + /islet cells/Pancreas: Cystic Fibrosis

   What would be an ideal treatment for Metabolic defects? Dietary/Medical therapy Small molecules ,enzyme replacement, Cells , Gene therapy
3. **Early diagnosis of the etiology of the cholestasis is essential for effective treatment, most importantly in cases of EHBA, metabolic, or infectious liver diseases, and for manag ement of complications of chronic liver disease.**
4. **Patients with early diagnosis of biliary atresia(<60days of life) have a better prognosis following a portoenterostomy. A missed diagnosis of biliary atresia leads to progressive liver disease and the need for liver transplantation.**
5. **Although patients with biliary atresia classically have acholic stool, the presence of pigmented stools does not rule out biliary atresia.**
6. **Inborn errors of bile acid synthesis:Deficiencies of:Hydroxy-delta5-C27-dehydrogenase-isomerase, Delta4-3oxosteroid-5beta-reductase, others.**

   Severe progressive intrahepatic cholestasis, low GGT, no pruritus, low and abnormal plasma bile salts.

   Respond well to exogenous bile acid therapy
7. **Alpha1-Antitrypsin Deficiency: Management is symptomatic,Treat complication, HCC Surveillance, Protein replacement, AAT infusion (in lung disease), Organ Transplan**

tation: Curative, Chemical 'Chaperonin': 4 phenyl-butyric acid (Burroughs JA et al, PNAS, 2000,97:1796-1801)

Hepatocellular Jaundice:

Autoimmune Hepatitis

- **AIH in children can present with acute hepatitis illness, AIH is a diagnosis of exclusion.**
- **Growth in children is of utmost importance as part of the clinical examination**
- **Celiac disease may be associated with AIH**
- **IgA deficiency is associated with AIH in 10-20%.**
- **Mainstay of management is immunosuppression**
- **Only 10-20 % can stop immunosuppressive therapy**

Wilson's Disease (Hepatolenticular Degeneration)

Slit lamp examination (Kayser-Fleischer ring)
Coeruloplasmin in serum < 20 mg/dl
Copper in urine > 3-fold urine copper excretion
Penicillamine challenge test > 15-fold urine copper excretion
Copper content of the liver > 250 µg/g dry weight

Hereditary Hemochromatosis ("Bronze Diabetes")

Genetics -Autosomal recessive
Total iron content in the body 20 – 60 g
Diagnosis usually confirmed 5 – 10 years after first symptoms
Male : female = 10 : 1
HCC in 10 – 30 %

Cirrhosis and Portal hypertension:

1. **The spectrum of portal hypertension is different both in adults and in children.**
2. **The spectrum also varies from country to country. In the West, intrahepatic causes of portal hypertension are common in children, whereas in the East, portal hypertension in children is mainly due to extrahepatic portal venous obstruction.**
3. **Should be suspected in any child with significant GIB or unexplained spleenomegaly.**
4. **All children with cirrhosis should have a screening endoscopy for varices at diagnosis.**
5. **No well-established approaches exist to preprimary and early primary prophylaxis in children.**
6. **b-Blockers without prior assessment of the presence of esophageal varices are not recommended.**
7. **VBL is safe in preventing first variceal bleeding in children with large varices.**
8. **Data are insufficient to recommend the use of nonselective b-blockers as standard clinical practice in children.**

Acute liver failure:

1. **Diagnosis of ALF in children is more complex than in adults, as encephalopathy may be subtle, appear late and even remain unrecognized.**
2. **Children with ALF should be referred to a pediatric liver transplant center**
3. **Children with encephalopathy or an INR> 4(with out encephalopathy) should be admitted to an ICU for continuous monitoring.**
4. **In neonatal liver failure, IV acyclovir should be started at the earliest opportunity, while awaiting definitive diagnosis, specific therapies are available for HSV, acetamino phen overdose, sever metabolic diseases, neonatal hemochromatosis, hemoph agocytic syndrome, Wilson disease and AIH.**
5. **Liver transplantation remains the definitive treatment with reduced (split) and living donor grafts to increase donor pool.**

Part 4
Guide lines &Recommendations in Gastrointestinal & Liver emergencies

Management of Patients with Ulcer Bleeding[38]

This guideline presents recommendations for the step-wise management of patients with overt upper gastrointestinal bleeding.

Recommendations

Initial assessment and risk stratification

1. **Hemodynamic status should be assessed immediately upon presentation and resusci tative measures begun as needed.**
2. **Blood transfusions should target hemoglobin ≥7 g / dl, with higher hemoglobins targeted in patients with clinical evidence comorbidities, such as coronary artery disease and in those with intravascular volume depletion (i.e., hypotension and tachycardia) in whom the hemoglobin is " artificially " elevated before repletion with intravascular fluid. Intubation may be considered to protect the airway and prevent aspiration in patients with severe ongoing hematemesis and / or altered mental status; it may also be necessary in some patients (e.g., those with comorbidities) to safely and effectively provide sedation for endoscopy.**
3. **Risk assessment should be performed to stratify patients into higher and lower risk categories and may assist in initial decisions such as timing of endoscopy, time of discharge, and level of care.**
4. **Discharge from the emergency department without inpatient endoscopy may be considered in patients with urea nitrogen < 18.2 mg / dl; hemoglobin ≥13.0 g / dl for men (12.0 g / dl for women), systolic blood pressure ≥110 mm Hg; pulse < 100 beats / min; and absence of melena, syncope, cardiac failure, and liver disease, as they have < 1 % chance of requiring intervention.**
5. **Intravenous infusion of erythromycin (250 mg ~ 30 min before endoscopy) should be considered to improve diagnostic yield and decrease the need for repeat endoscopy. However, erythromycin has not consistently been shown to improve clinical outcomes.**
6. **Pre-endoscopic intravenous PPI (e.g., 80 mg bolus followed by 8 mg / h infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. However, PPIs do not improve clinical outcomes such as further bleeding, surgery, or death.**
7. **If endoscopy will be delayed or cannot be performed, intravenous PPI is recommended to reduce further bleeding .**
8. **Nasogastric or orogastric lavage is not required in patients with UGIB for diagnosis, prognosis, visualization, or therapeutic effect.**
9. **Patients with UGIB should generally undergo endoscopy within 24 h of admission, following resuscitative effortsto optimize hemodynamic parameters and other medical problems.**
10. **In patients who are hemody-namically stable and without serious comorbidities endos copy should be performed as soon as possible in a non-emergent setting to identify the substantial proportion of patients with low-risk endoscopic findings who can be safely discharged.**
11. **In patients with higher risk clinical features (e.g., tachycardia, hypotension, bloody emesis or nasogastric aspirate in hospital) endoscopy within 12 h may be considered to potentially improve clinical outcomes.**
12. **Stigmata of recent hemorrhage (SRH) should be recorded as they predict risk of further bleeding and guide management decisions. The stigmata, in descending risk of further bleeding, are active spurting, non-bleeding visible vessel, active oozing, adherent clot, flat pigmented spot, and clean base. serious bleeding does not occur from an erosion due to the absence of veins and arteries in the mucosa. Rather serious bleeding**

occurs when an ulcer erodes into vessels in the submucosa or deeper. Ulcers larger than 1 – 2 cm are associated with increased rates of further bleeding with conservative therapy and SRH are terms that describe the appearance of an ulcer base at endoscopy in patients with ulcer bleeding. SRH provide prognostic information regarding the risk of rebleeding, need for therapeutic intervention, and death. SRH are therefore used to stratify patients with ulcer bleeding and guide management decisions including endoscopic and medical therapy, admission vs. discharge, and level of care in hospital. In the absence of clinical evidence of bleeding, however, the presence of SRH does not appear to be associated with a risk of sub sequent bleeding after endoscopic therapy.

13. TREATMENT AND FOLLW UP:

Endoscopic therapy

a) Endoscopic therapy should be provided to patients with active spurting or oozing bleeding or a non-bleeding visible vessel.

b) Endoscopic therapy may be considered for patients with an adherent clot resistant to vigorous irrigation. Benefit may be greater in patients with clinical features potentially associated with a higher risk of rebleeding (e.g., older age, concurrent illness, inpatient at time bleeding began).

c) Endoscopic therapy should not be provided to patients who have an ulcer with a clean base or a flat pigmented spot.

d) Epinephrine therapy should not be used alone. If used, it should be combined with a second modality.

e) Thermal therapy with bipolar electrocoagulation or heater probe and injection of sclerosant (e.g., absolute alcohol) are recommended because they reduce further bleeding, need for surgery, and mortality.

f) Clips are recommended because they appear to decrease further bleeding and need for surgery. However, comparisons of clips vs. other therapies yield variable results and currently used clips have not been well studied .

g) for the subset of patients with actively bleeding ulcers, thermal therapy or epinephrine plus a second modality may be preferred over clips or sclerosant alone to achieve initial hemostasis.

Medical therapy after endoscopy

a) After successful endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/h continuous infusion for 72 h should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot.

b) Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (e.g., oral PPI once daily).

Repeat endoscopy

a) Routine second-look endoscopy, in which repeat endoscopy is performed 24 h after initial endoscopic hemostatic therapy, is not recommended.

b) Repeat endoscopy should be performed in patients with clinical evidence of recurrent bleeding and hemostatic therapy should be applied in those with higher risk stigmata of hemorrhage. If further bleeding occurs after a second endoscopic therapeutic session, surgery or interventional radiology with transcathether arterial embolization is generally employed.

Hospitalization

a) Patients with high-risk stigmata (active bleeding, visible vessels, and clots) should generally be hospitalized for 3 days assuming no rebleeding and no other reason for hospitalization. They may be fed clear liquids soon after endoscopy.

b) Patients with clean-based ulcers may receive a regular diet and be discharged after endoscopy assuming they are hemodynamically stable, their hemoglobin is stable, they

have no other medical problems, and they have a residence where they can be observed by a responsible adult.

Long-term prevention of recurrent bleeding ulcers

a) **Patients with *H. pylori* -associated bleeding ulcers should receive *H. pylori* therapy. After documentation of eradication, maintenance antisecretory therapy is not needed unless the patient also requires NSAIDs or antithrombotics.**
b) **In patients with NSAID-associated bleeding ulcers, the need for NSAIDs should be carefully assessed and NSAIDs should not be resumed if possible. In patients who must resume NSAIDs, a COX-2 selective NSAID at the lowest effective dose plus daily PPI is recommended.**
c) **In patients with low-dose aspirin-associated bleeding ulcers, the need for aspirin should be assessed. If given for secondary prevention (i.e., established cardiovascular disease) then aspirin should be resumed as soon as possible after bleeding ceases ideally within 1 – 3 days and certainly within 7 days). Long-term daily PPI therapy should also be provided. If given for primary prevention (i.e., no established cardiovascular disease), anti-platelet therapy likely should not be resumed in most patients.**
d) **In patients with idiopathic (non- *H. pylori* , non-NSAID) ulcers, long-term antiulcer therapy (e.g., daily PPI) is recommended.**

Endoscopic hemostatic modalities & their technique

Endoscopic hemostatic modalities are generally applied to the bleeding site to halt bleeding and in the immediate area of the SRH in the ulcer base with the intent to close or obliterate the underlying vessel and prevent rebleeding.

The technique used to treat adherent clots reporting benefit of endoscopic therapy was:

1. **epinephrine injection into all four quadrants of the ulcer followed by mechanical clot removal (e.g., snare; manipulation with forceps, probe, or tip of endoscope) and application of thermal therapy. Dilute (1:10,000 or 1:20,000 in saline) epinephrine is generally injected in 0.5 – 2 ml aliquots in and around the stigmata of hemorrhage in the ulcer base. Although large volumes of epinephrine (e.g., 30 – 45 ml) are reported to be more effective as monotherapy, no studies have documented the optimal volume when used in combination with other modalities. We recommend injection until active bleeding slows or stops or, for non-bleeding stigmata, in all four quadrants next to the SRH in the ulcer base.**
2. **Absolute alcohol is generally administered in 0.1 – 0.2 ml aliquots with a limitation of 1 – 2 ml due to the concern for tissue injury with higher volumes.**
3. **Five percent ethanolamine is administered in 0.5 – 1.0 ml aliquots; widely variable total volumes of 0.5 – 14 ml have been reported in randomized trials for ulcer bleeding.**
4. **Bipolar electrocoagulation should be performed with the endoscope tip as close as possible to the bleeding ulcer; the large (3.2 mm) probe should be applied en face or at the least possible angulation with firm / maximal pressure. A setting of ~ 15 W and 8 – 10 s applications are recommended. Multiple applications should be applied in the ulcer base on and around the SRH, until bleeding has stopped, the vessel is flattened, and the base is whitened.**
5. **Recommendations for the heater probe are identical with a setting of 30 J being used.**
6. **Clips should be placed over the bleeding site and on either side of the SRH in an attempt to seal the underlying artery.**

Management of the Adult Patient with Acute Lower Gastrointestinal Bleeding[20]

DEFINITIONS

acute lower gastrointestinal bleeding refers to:

1. blood loss from the gastrointestinal tract of recent Onset

2. emanating from a location distal to the ligament of Treitz

3. resulting in instability of vital signs, anemia, and/or need for blood transfusion

This definition is not useful for the purpose of a practice guideline. The source of acute gastrointestinal bleeding is not always apparent from initial history and physical examination.

The acute onset of hematochezia is the most common clinical presentation of acute lower gastrointestinal bleeding necessitating hospitalization and immediate evaluation and management. This guideline will focus on the evaluation of hematochezia associated with instability of vital signs, anemia, and/or need for blood transfusion. The limitations in this definition are recognized, as the source of bleeding in a subset of patients with hematochezia will be from the upper gastrointestinal tract, and melena in some patients will be due to a source distal to the ligament of Treitz. This guideline is *not* intended for patients presenting with stool that is positive for occult blood, chronic bleeding of obscure origin, or obvious self-limited bleeding where the likelihood of a change in vital signs or anemia is low (*e.g.*, anal outlet bleeding). An algorithm outlining the approach to the adult patient with acute lower gastrointestinal bleeding is presented.

Lesions Frequently Encountered in Evaluation of Hematochezia :

Diverticular disease its frequency is 17–40% c Stops spontaneously in 80% of patient, surgery was unlikely if, 4 U red cell transfusion given in 24 h, but required in 60% of patients receiving .4 U in 24 h .

Colonic vascular ectasia its frequency is 2–30% c Frequency of these lesions vary widely , Acute bleeding appears to be more frequently due to lesion proximal colon.

Colitis (ischemia, infectious, inflammatory) its frequency is 9–21% Ischemic colitis often presents with abdominal pain and hematochezia, Colitis is most often affecting splenic flexure in radiation proctopathy. Bloody diarrhea is most frequent symptom of infectious colitis and inflammatory bowel disease of the colon.

Colonic neoplasia/post-polypectomy bleeding its frequency is 11–14% c , Post polypectomy bleeding is frequency self-limited, and may occur with in 14 days after polypectomy (12)

Others Anorectal causes (including hemorrhoids, rectal varices) 4–10% c Anoscopy/proctoscopy should be included in the initial evaluation of these patients

Upper gastrointestinal sites (including duodenal/ gastric ulcer, varices) 0–11% c A negative nasogastric aspirate does not exclude this possibility Small bowel sites, including Crohn's ileitis,

vascular ectasia, Meckel's diverticula, tumors 2–9% c Frequency diagnosed by radiologic studies or enteroscopy after the acute bleeding episode has resolved

INITIAL EVALUATION

A focused history and physical examination is essential in the initial evaluation of the patient with acute lower gastrointestinal bleeding. Initial laboratory testing should include measurement of complete blood count, electrolytes, type and *cross match, and coagulation profile*. Historical points to be recorded include: the nature and duration of bleeding, including stool color and frequency c associated symptoms, including abdominal pain, recent change in bowel habits, fever, urgency/tenesmus, weight loss , relevant past history, including previous bleeding episodes, trauma, past abdominal surgeries, previous peptic ulcer disease, history of inflammatory bowel disease, history of radiation therapy to the abdomen and pelvis, and prior history of major organ dysfunction (including cardiopulmonary, renal, and liver disease) , current/recent medications (including NSAIDs, aspirin, and anticoagulants), and allergies, presence or absence of chest pain/palpitations, dyspnea at rest or on exertion, lightheadedness, or postural symptoms. Physical examination should include (at a minimum):

- **immediate recording of vital signs with postural changes. A drop of >10 mm Hg or an increase of 10 beats/min in pulse is indicative of acute blood loss of .800 ml (15% of total circulatory blood volume).**
- **Marked tachycardia and tachypnea, associated with hypotension and depressed mental status is indicative of a blood loss of .1500 ml (30% circulatory blood volume).**
- **cardiopulmonary, abdominal and digital rectal examination.**
- **Initial laboratory studies should include measurement of complete blood count; it should be remembered that initial hemoglobin/ hematocrit value may not reflect the degree of blood loss due to volume contraction, and may fall significantly after hydration.**
- **serum electrolytes, blood urea nitrogen, and creatinine. In upper gastrointestinal bleeding, the serum blood urea nitrogen may rise without a commensurate rise in se rum creatinine. This appears to be due to absorption of proteins from blood in the gastrointestinal tract, and from dehydration. However, the absence of a rise in blood urea nitrogen does not rule out an upper gastrointestinal source.**

- **Coagulation profile (PT/PTT), particularly if there is any history of liver disease or if the patient has been taking anticoagulant medication.**
- **Type and cross match, and prepare blood for transfusion.**
- **electrocardiogram for patients >50 yr of age, younger patients with risk factors for coronary artery disease or history of dysrhythmia, or patients with chest pain/ palpitations associated with the bleeding episode.**

DETERMINATION OF THE SOURCE OF BLEEDING Recommendations

1. **For the patient in the third or fourth decade of life presenting with maroon colored stool, evaluation for a Meckel's diverticulum might be performed very early in the structural evaluation.**
2. **A patient with hematochezia who had undergone colonoscopy and removal of a sigmoid colon polyp 3 days previously may require no structural evaluation if bleeding stops spontaneously.**
3. **In the patient with hematochezia, an upper gastrointestinal bleeding source must be considered. A nasogastric aspirate showing copious amounts of bile and negative for blood makes an upper gastrointestinal source unlikely.Upper gastrointestinal endoscopy should be performed if the results of nasogastric aspiration shows evidence of upper gastro intes tinal bleeding, or is negative for blood and bile ,patients with hematochezia most frequently bleed from a colonic source. However, when bleeding is brisk, an upper gastrointestinal source of bleeding may present as hematochezia.**
4. **Endoscopy (colonoscopy or sigmoidoscopy) is the test of choice for the structural evalua tion of lower gastrointestinal bleeding.**
5. **Arteriography should be reserved for those patients with massive, ongoing bleeding when endoscopy is not feasible, or with persistent/ recurrent hematochezia when colonoscopy has not revealed a source.**
6. **There is no role for barium enema in the evaluation of acute, severe hematochezia.**
7. **Colonoscopy is generally safe in the setting of acute lower gastrointestinal bleeding, as long as the patient has been sufficiently resuscitated before the procedure, Endoscopic therapy includes the use of thermal coagulation (including heater probe, bipolar /multipolar coagulation, and laser therapy), and injection of vasoconstrictors and/or sclerosants. All of these methods appear effective in controlling bleeding**
8. **Patients with persistent or recurrent lower gastrointestinal bleeding may require surgery. Accurate presurgical localization of the bleeding site improves postoperative morbidity and mortality.**
9. **In cases of lower gastrointestinal bleeding where no plausible colonic source is identified , evaluation of the small bowel may be necessary.Evaluation for a Meckel's diverticulum should be performed in younger patients with acute lower gastrointestinal bleeding. Enteroscopy and small bowel radiography video capsule endoscopy may also be performed in the patient in whom active bleeding has ceased. In circumstances where hematochezia has ceased and vital signs have clearly stabilized, other structural studies of the small intestine may be undertaken. Endoscopic evaluation of the small intestine is frequently accomplished with "push" enteroscopy, where a long colonoscope or dedicated endoscope (insertion tube length 160–300 cm) is advanced per os into the small intestine. Push enteroscopy confers the advantage of biopsy of mass lesions or therapy for bleeding.**

   The reported sensitivity and specificity rates for nuclear medicine scanning for Meckel's diverticulum are 85% and 95% respectively. These lesions, as well as some other structural lesions of the small intestine including mass lesions, ulcers, and Crohn's disease, may be detected by barium contrast studies of the small intestine. The literature suggests that small bowel enema techniques (enteroclysis) may have an increased diagnostic yield over standard small bowel follow-through series.

ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding[52]

Bleeding from the small intestine remains a relatively uncommon event, accounting for 5–10% of all patients presenting with gastrointestinal (GI) bleeding. Given advances in small bowel imaging with video capsule endoscopy (VCE), deep enteroscopy, and radiographic imaging, the cause of bleeding in the small bowel can now be identified in most patients. The term small bowel bleeding is therefore proposed as a replacement for the previous classification of obscure GI bleeding (OGIB). We recommend that the term OGIB should be reserved for patients in whom a source of bleeding cannot be identifi ed anywhere in the GI tract. A source of small bowel bleeding should be considered in patients with GI bleeding after performance of a normal upper and lower endoscopic examination. Second-look examinations using upper endoscopy, push enteroscopy, and/or colonoscopy can be performed if indicated before small bowel evaluation.

<u>Diagnosis of small bowel bleeding</u>:

Recommendations

1. **Second-look upper endoscopy should be considered in cases of recurrent hematemesis, melena, or a previously incomplete exam (strong recommendation, low level of evidence).**
2. **Second-look colonoscopy should be considered in the setting of recurrent hematochezia or if a lower source is suspected (conditional recommendation, very low level of evidence).**
3. **If the second-look examinations are normal, the next step should be a small bowel evaluation (strong recommendation, moderate level of evidence).**
4. **Push enteroscopy can be performed as a second-look examination in the evaluation of suspected small bowel bleeding (conditional recommendation, moderate level of evidence).**
5. **VCE should be considered a fi rst-line procedure for small bowel (SB) evaluation after upper and lower GI sources have been excluded, including second-look endoscopy when indicated (strong recommendation, moderate level of evidence).**
6. **Owing to the lower detection rate of lesions in the duodenum and proximal jejunum with VCE, push enteroscopy should be performed if proximal lesions are suspected (strong recommendation, very low level of evidence).**
7. **Total deep enteroscopy should be attempted if there is a strong suspicion of a small bowel lesion based on clinical presentation or abnormal VCE study (strong recommendation, moderate level of evidence).**
8. **Any method of deep enteroscopy can be used when endoscopic evaluation and therapy is required based on similar diagnostic yields (strong recommendation, high level of evidence).**
9. **Intraoperative enteroscopy (IOE) is a highly sensitive but invasive diagnostic and eff ective therapeutic procedure. Its usage should be limited to scenarios where enteroscopy cannot be performed, such as patients with prior surgeries and intestinal adhesions (strong recommendation, low level of evidence).**
10. **VCE should be performed before deep enteroscopy to increase diagnostic yield. Initial deep enteroscopy can be considered in cases of massive hemorrhage or when VCE is contraindicated (strong recommendation, high level of evidence).**

<u>Diagnosis using radiographic techniques</u>

Recommendations

1. **Barium studies should not be performed in the evaluation of small bowel bleeding (strong recommendation, high level evidence).**
2. **CTE should be performed in patients with suspected small bowel bleeding and negative capsule endoscopy because of higher sensitivity for the detection of mural-based small**

bowel masses, superior capability to locate small bowel masses, and ability to guide subsequent deep enteroscopy. (strong recommendation, low level of evidence).

3 **CT is preferred over MR imaging for the evaluation of suspected small bowel bleeding. MR can be considered in patients with contraindications for CT or to avoid radiation exposure in younger patients (conditional recommendation, very low level of evidence).**

4 **CTE could be considered before VCE in the setting of established infl ammatory bowel disease, prior radiation therapy, previous small bowel surgery, and/or suspected small bowel stenosis (strong recommendation, very low level of evidence).**

5 **In patients with suspected small bowel bleeding and negative VCE examination, CTE should be performed if there is high clinical suspicion for a small bowel source despite the performance of a prior standard CT of the abdomen (conditional recommendation, very low level of evidence).**

<u>Overt acute GI bleeding</u>

Recommendations

1 **In acute overt massive GI bleeding, conventional angiography should be performed emergently for hemodynamically unstable patients (strong recommendation, low level of evidence). In hemodynamically stable patients with evidence of active bleeding, multiphasic CT (CTA) can be performed to identify the site of bleeding and guide further management (strong recommendation, low level of evidence).**

2 **In patients with acute overt GI bleeding and slower rates of bleeding (0.1‑0.2 ml/min), or uncertainty if actively bleeding, tagged red blood cell (RBC) scintigraphy should be performed if deep enteroscopy or VCE are not performed to guide timing of angiography (strong recommendation, moderate level of evidence).**

3 **In brisk active overt bleeding,CTA is preferred over CTE (conditional recommendation, very low level of evidence).**

4 **Conventional angiography should not be performed as a diagnostic test in patients without overt bleeding (conditional recommendation, very low level of evidence).**

5 **Provocative angiography can be considered in the setting of ongoing overt bleeding and negative VCE, deep enteroscopy, and/or CT examination (conditional recommendation, very low level of evidence).**

6 **In younger patients with ongoing overt bleeding and normal testing with VCE and enterography examinations, a Meckel's scan should be performed (conditional recommendation, very low level of evidence).**

<u>Treatment and outcomes</u>

Recommendations

1 **If a source of bleeding is found by VCE and/or deep enteroscopy in the small intestine that is associated with signifi cant ongoing anemia or active bleeding, then the patient should be managed with endoscopic therapy (strong recommendation, low level of evidence).**

2 **If aft er appropriate small bowel investigation no source of bleeding is found, the patient should be managed conservatively with oral iron or by intravenous infusion as is dictated by the severity and persistence of the associated irondeficiency anemia. In this context, a small vascular lesion found on capsule endoscopy does not always need treatment (strong recommendation, very low level evidence).**

3 **If bleeding persists in either of the above situations with worsening anemia, a further diagnostic workup should include a repeated upper and lower endoscopy, VCE, deep enteroscopy, CT, or MRI enterography as is appropriate for the clinical situation and availability of investigative devices (strong recommendation, low level evidence).**

4 **If bleeding persists or recurs or a lesion cannot be localized consideration may be given to medical treatment with iron, somostatin analogs, or antiangiogenic therapy (strong recommendation, moderate level evidence).**

5 **Anticoagulation and/or antiplatelet therapy should be discontinued if possible in patients with small bowel hemorrhage (conditional recommendation, very low level evidence).**

6 **Surgical intervention in massive small bowel bleeding may be useful, but is greatly aided with presurgical localization of the bleeding site by marking the lesion with a tattoo (strong recommendation, low level evidence).**

7 **IOE should be available at the time of the surgical procedure to provide assistance to localize the source of bleeding and to perform endoscopic therapy (conditional recommendation, low level of evidence).**

8 **Patients with Heyde's syndrome (aortic stenosis and angioectasia) and ongoing bleeding should undergo aortic valve replacement (conditional recommendation, moderate level of evidence).**

9 **For patients with recurrence of small bowel bleeding, endoscopic management can be considered depending on the patient's clinical course and response to prior therapy (conditional recommendation, moderate level of evidence).**

Practice Guidelines in Acute Pancreatitis [11]

diagnosis of acute pancreatitis requires two of the following three features:

1) abdominal pain characteristic of acute pancreatitis,

2) serum amylase and/or lipase ≥3 times the upper limit of normal,

3) characteristic findings of acute pancreatitis on CT scan.

This definition allows for the possibility that an amylase and/or lipase might be <3 times the upper limit of normal in acute pancreatitis.

The height of the serum amylase and/or lipase does not correlate with the severity of acute pancreatitis.

Systemic Inflammatory Response Syndrome (SIRS):

Defined by Two or More of the Following Criteria:

- **Pulse >90 beats/min**
- **Respiratory rate >20/min or PCO2 <32 mmHg**
- **Rectal temperature <36◦C or >38◦C**
- **White blood count <4,000 or >12,000/mm3**

The differential diagnosis of acute pancreatitis is broad and includes mesenteric ischemia or infarction, perforated gastric or duodenal ulcer, biliary colic, dissecting aortic aneurysm, intestinal obstruction, and possibly inferior wall myocardial infarction.

- **In severe pancreatitis, the patients appear toxic and quite ill.(The two most important markers of severity in acute pancreatitis are organ failure -particularly multisystem organ failure- and pancreatic necrosis).**
- **In mild pancreatitis, the patients generally appear uncomfortable but not as ill during the initial hospitalization for acute pancreatitis,**

Recommendation:

Reasonable attempts to determine etiology are appropriate, and in particular those causes that may affect acute management. Relevant historical clues include any previous diagnosis of biliary tract disease or gallstones, cholecystectomy, other biliary or pancreatic surgery, acute or chronic pancreatitis or their complications, use of ethanol, medications and the timing of their initiation, recent abdominal trauma, weight loss or other symptoms suggesting a malignancy, or a family history of pancreatitis

Blood tests within the first 24 h should include liver chemistries, calcium, and triglycerides.

Recommendation:

Abdominal ultrasound is usually performed at the time of admission to assess for gallstones as the etiology rather than to establish the diagnosis of acute pancreatitis(the ultrasound findings might reveal features that are consistent with the diagnosis of acute pancreatitis including diffuse glandular enlargement, hypoechoic texture of the pancreas reflective of edema, and ascites).

Recommendation:

Contrast-enhanced CT scan (and in particular a contrast-enhanced thin-section multi detector-row CT scan) is the best imaging technique to exclude conditions that masquerade as acute pancreatitis, to diagnose the severity of acute pancreatitis, Contrast-enhanced CT scan also it is the best available test to distinguish interstitial from necrotizing pancreatitis, particularly after 2–3 days of illness. (Mortality of sustained multisystem organ failure in association with necrotizing pancreatitis is generally >36%). and to identify complications of pancreatitis . Findings on CT scan that confirm the diagnosis of acute pancreatitis include enlargement of the pancreas with diffuse edema, heterogeneity of pancreatic parenchyma, peripancreatic stranding, and peripancreatic fluid collections. With the use of IV contrast, and CRP >150 mg/L within the first 72 h- strongly correlates with the presence of pancreatic necrosis- a diagnosis of pancreatic necrosis can be established. In addition, contrast-enhanced CT scan may give clues as to the etiology of acute pancreatitis: for example, a common bile duct stone may occasionally be directly visualized, pancreatic calcifications may indicate underlying chronic pancreatitis due to alcohol or other causes, a pancreatic mass may suggest malignancy, and diffuse dilation of the pancreatic duct or a cystic lesion may suggest intraductal papillary mucinous neoplasia or cystic neoplasm.

Severe Acute Pancreatitis as Defined by Atlanta Symposium

Early Prognostic Signs

Ranson signs ≥3

APACHE-II score ≥8

Organ Failure

and/or Local Complications(necrosis, abscess, and pseudocyst)

Organ Failure as Defined by Atlanta Symposium

Shock–systolic pressure <90 mmHg, PaO2 ≤60 mmHg, Creatinine >2.0 mg/L after rehydration, Gastrointestinal bleeding >500 cc/24 h

DIAGNOSTIC GUIDELINE I: Look for risk factors of severity at admission.

Older age (>55), obesity (BMI >30), organ failure at admission, and pleural effusion and/or i nfiltrates a. Patients with these characteristics may require treatment in a highly supervised area, such as a step-down unit or an intensive care unit.

DIAGNOSTIC GUIDELINE II: Determination of Severity by laboratory at admission or ≤48 H

The two tests that are most helpful at admission in distinguishing mild from severe acute pancreatitis are APACHE-II score and serum hematocrit. It is recommended that APACHE-II scores be generated during the first 3 days of hospitalization and thereafter as needed to help in this distinction. It is also recommended that serum hematocrit be obtained at admission, 12 h after admission, and 24 h after admission to help gauge adequacy of fluid resuscitation.(APACHE-II score ≥8 and serum hematocrit a value <44 strongly suggests mild acute pancreatitis).

Complications in acute pancreatitis

- **That can be recognized on abdominal CT scan include pancreatic fluid collections, gastrointestinal and biliary complications (such as obstruction of duodenum or stomach, inflammation of the transverse colon, and biliary obstruction), solid organ involvement (such as splenic infarct), vascular complications (such as pseudoaneurysms, splenic vein thrombosis with varices, portal vein thrombosis), and pancreatic ascites.**

It is recommended that a standardized organ failure score that stratifies for severity (including need for pressor agents for shock, assisted ventilation for refractory hypox emia, and dialysis for renal failure) be used to grade the severity of organ failure and results of therapy among institutions.

TREATMENT GUIDELINE

I: Supportive Care:

- **measures that prevent hypoxemia and insure adequacy of fluid resuscitationis a critical component in the care of patients with acute pancreatitis.**
- **It is important to obtain vital signs at frequent intervals (such as every 4 h) and to obtain measurement of bedside oxygen saturation whenever vital signs are recorded. These measurements are of utmost importance during the first 24 h of admission**
- **It is recommended that supplemental oxygen be administered during the first 24–48 h, especially if narcotic agents are used to control pain. Supplemental oxygen should be continued until the clinician is fully satisfied that there is no further threat of hypo xemia. Blood gas analysis should be performed when oxygen saturation is ≤95% or when other clinical manifestations suggest the possibility of hypoxemia (including labored respiration or hypotension refractory to a bolus of IV fluids) .There is no specific value of bedside oxygen saturation that correlates accurately with a PO2 ≤60 mmHg**
- **Aggressive IV fluid replacement is of critical importance to counteract hypovolemia caused by third space losses, vomiting, diaphoresis, and greater vascular permeability caused by inflammatory mediators. Hypovolemia compromises the microcirculation of the pancreas and is a major contributor to the development of necrotizing pancreatitis.**

Clinically, the adequacy of fluid resuscitation should be monitored by vital signs, urinary output, and decrease of hematocrit at 12 and 24 h after admission (particularly for patients with hemo concentration at admission). Monitoring of central venous press ure is generally not required. Prompt transfer to an intensive care unit should take place for sustained organ failure.

II: Transfer to an intensive care unit: Transfer to an intensive care unit (or possibly a step-down care unit) should be considered if there are signs that suggest that the pancreatitis is severe or is likely to be severe.

III: Nutritional Support:

- **Whenever possible, enteral feeding rather than total parenteral nutrition (TPN) is suggested for patients who require nutritional support.**
- **Low fat diet,**
- **pancreatic enzymes supplement in severe necrotizing pancreatitis (especially when most or all of the pancreas is necrotic but also when the body of the pancreas is totally necrotic such that enzymes from a remnant viable tail of the pancreas cannot gain access to the duodenum).**
- **proton pump inhibitor on a daily basis because of the likelihood that bicarbonate secretion by the pancreas is severely diminished rendering the patient susceptible to a duodenal ulcer.**

There is reason to believe that enteral feeding is preferable to TPN,

- **First, there is compelling evidence that in severe acute pancreatitis gut barrier function is compromised resulting in greater intestinal permeability to bacteria (which may lead to infected necrosis) and endotoxins (which stimulate nitric oxide and cytokine produc tion that contribute to organ failure).**
- **There is also evidence that there is a higher incidence of gastric colonization with potentially pathogenic enteric bacteria in severe disease that may also contribute to septic complications Because enteral feeding stabilizes gut barrier function,**
- **There has been considerable interest in the ability of enteral feeding not only to provide appropriate nutritional support, but also to prevent systemic complications and improve morbidity and mortality.**

- **Finally, there are numerous complications associated with the use of TPN (including line sepsis) that can be avoided by use of enteral feeding.**

IV: <u>Use of Prophylactic Antibiotic in Necrotizing Pancreatitis:</u>

The use of prophylactic antibiotics to prevent pancreatic infection is not recommended at this time among patients with necrotizing pancreatitis

V: <u>Treatment of Infected Necrosis:</u>

CT-guided percutaneous aspiration with Gram's stain and culture is recommended when infected necrosis is suspected. Treatment of choice in infected necrosis is surgical debridement. Alternative minimally invasive approaches may be used in selected circumstances. If CT-guided percutaneous aspiration reveals the presence of Gram-negative organisms, choices for antibiotic treatment include a carbipenem, a fluoro quinolone plus metronidazole, or a third generation cephalosporin plus metronidazole pending results of culture and sensitivity if Gram's stain reveals the presence of Gram positive bacteria, a reasonable choice is vancomycin until results of culture and sensitivity are determined. The standard of care for infected pancreatic necrosis is surgical debridement unless patients are too ill to undergo surgical intervention , the types of surgery that have generally been recommended have included

- **necrosectomy with closed continuous irrigation via indwelling catheters,**
- **necrosectomy and open packing,**
- **Or necrosectomy with closed drainage without irrigation.**

All are generally considered to provide equal benefit in skilled surgical centers.

- **More recently, The first technique is minimally invasive retroperitoneal necrosectomy which uses a percutaneous technique to gain access to the necrotic area, dilatation of the tract to a 30-French size, an operating nephroscope for piecemeal retrieval of solid material, irrigation with high volume lavage, and placement of catheters for long-term continuous irrigation This technique requires general anesthesia and has not been compared in a prospective fashion to more traditional surgical debridement,**
- **Another technique is laparoscopic necrosectomy with placement of large caliber drains under direct surgical inspection.**
- **A third technique is percutaneous catheter drainage of infected necrosis,**

Apancreatic abscess (whether in the form of an infected peripancreatic pseudocyst or late liquefaction of an area of pancreatic necrosis) generally takes place after 5 wk in a patient who is in the recovery phase of acute pancreatitis. Mortality of a properly treated pancreatic abscess is very low. Appropriate treatments include surgical drai nage, percutaneous catheter drainage, or possibly endoscopic drainage

VI: <u>Treatment of Sterile Necrosis:</u>

Sterile necrosis is best managed medically during the first 2–3 wk. After this interval, if abdominal pain persists and prevents oral intake, debridement should be considered. This is usually accomplished surgically, but percutaneous or endoscopic debridement is a reasonable choice in selected circumstances with the appropriate expertise. Pancreatic duct leaks and fistulas are common and may require endoscopic or surgical therapy.

Organ failure occurs in at least 48% of patients with sterile necrosis

VII: <u>Role of ERCP and Biliary Sphincterectomy in Gall stone Pancreatitis:</u>

ERCP is indicated for clearance of bile duct stones in patients with severe pancreatitis, in those with cholangitis, in those who are poor candidates for cholecystectomy, in those who are postcholecystectomy, and in those with strong evidence of persistent biliary obstruction. Gallstones are suspected as a cause of acute pancreatitis when there are elevations of liver chemistries (particularly ALT ≥3 times the upper limit of normal), when gallstones are visualized, and to a lesser extent when the common bile duct is found to be dilated on the basis of ultrasound or computerized axial tomography,

- **Overall, these studies suggest that ERCP and biliary sphincterotomy is indicated (preferably within 24 h of admission) for patients with severe biliary pancreatitis with retained common bile duct stones and for those with cholangitis.**

SUMMARY

Suggested Indications for ERCP, EUS, and MRCP in Patients with Acute Biliary Pancreatitis

Urgent ERCP (Preferably Within 24 h of Admission):

Severe pancreatitis (organ failure)

Suspicion of cholangitis

Elective ERCP with Sphincterotomy:

Imaging study demonstrating persistent common bile duct stone

Evolving evidence of biliary obstruction (such as rising liver chemistries)

Poor surgical candidate for laparoscopic cholecystectomy

Strong suspicion of bile duct stones postcholecystectomy

Endoscopic Ultrasound or MRCP to Determine Need for ERCP:

Clinical course not improving sufficiently to allow timely laparoscopic cholecystec tomy and intraoperative cholangiogram

Pregnant patient

High-risk or difficult ERCP (*e.g.*, coagulopathy, altered surgical anatomy)

Uncertainty regarding biliary etiology of pancreatitis.

Early Management (0-72 hours) for patients with Acute Pancreatitis:

Diagnosis acute pancreatitis ≥2 of the following:

1- Typical abdominal pain

2- Amylase/lipase ≥3x ULN

3- Confirmatory findings on US/CT imaging

After diagnosing the case start the following :

(1) <u>Assess severity</u> (Bedside evaluation, APACHE>8, BISAP>2, BUN>22, SIRS, CRP>150 at 48 hrs) :

- **If predicted sever/complicated consider transfer to ICU or specialized referral center.**
- **If predicted mild/uncomplicated continue supportive management.**

(2) <u>Initial resuscitation</u> (-volume challenge 20cc/kg, monitor response in urine output, orthostasis -maintain urine output >0.5 cc/kg/hr-supplemental oxygen- Analgeasia with parenteral narcotics.) evaluate response to initial resuscitation if good continue supportive management, while if persistent pain, SIRS or organ dysfunction ≥72hrs → obtain contrast-enhanced CT scan, search for possible sources of infection, initial enteral nutrition ,no role for prophylactic antibiotics also consider transfer to ICU.

(3) <u>Determine etiology</u> (History, Medications, Liver function tests, serum Triglycerides, Serum calcium, Abdominal US) if Gall stone think of cholangitis, persistent obstruction or organ dysfunction?

If they are not present conservative management with cholecystectomy if present Urgent ERCP for stone extraction+ sphinecterotomy 24-48hrs.

BISAP, bedside index of severity in acute pancreatitis; CRP, c-reactive protein; ERCP, endoscopic retrograde cholangiopancreaticography; ULN, upper limit normal; US, ultrasound.

Acute-on-chronic liver failure(ACLF)[55,56]

acute-on chronic liver failure (ACLF) is an acute deterioration of known or unknown chronic liver disease, or a chronic decompensation of an end-stage liver disease

So we have 3 types:

Type A ACLF occurs in patients with chronic liver disease but no underlying cirrhosis (e.g., hepatitis B reactivation)

Type B ACF occurs in patients with well-compensated cirrhosis who rapidlydeteriorate following a major hepatic insult.

Type C ACLF occurs in patients with decompensated cirrhosis.

(Liver failure can develop as acute liver failure (ALF) in the absence of any pre-existing liver disease).

Recommendations

1 Major pathophysiologic events of ACLF:

- **There is a central role of inflammation and neutrophil dysfunction in organ failure.**
- **Systemic inflammatory response syndrome as a marker of prognosis in predicting mortality in patients with ACLF needs further validation.**
- **High ADMA and SDMA concentrations are markers of poor prognosis in patients with ACLF.**
- **Dimethyl arginine score of >1.23 indicates higher mortality.**

2 Role of sepsis and cytokines in ACLF:

- **It is likely that cytokines influence the development and course of ACLF.**
- **Inhibition of the inflammatory cytokine responses might offer a novel approach for reducing the morbidity and mortality in patients with ACLF.**
- **Circulating toxins in the setting of ACLF cause secondary liver damage, and liver regeneration is impaired despite circulating growth factors.**
- **TNF-a and IL-6 probably have dual action, induce hepatocyte death on one hand and promote hepatocyte proliferation on the other through differential interactions with Kupffer cells and hepatocytes.**

3 Hemodynamics in ACLF:

- **HVPG of patients with ACLF ranges between those with compensated and decompen sated chronic liver diseases.**
- **Large varices in patients with ACLF reflect high HVPG resulting in poor prognosis.**
- **Higher liver blood flow levels in patients with ACLF correlate with higher mortality.**

4 Liver histology in ACLF:

- **Liver histology is quite helpful in assessing the presence and degree of hepatic fibrosis and/or cirrhosis.**
- **Two distinct histologic patterns are seen:**

  Pattern I: Hepatocyte ballooning, rosette formation, cellular cholestasis, variable interface activity, and fibrosis

  Pattern II: Marked ductular proliferation, coarse, inspissated bile plugs, foci of confluent necrosis / bridging necrosis, eosinophilic degeneration of hepatocytes, higher stage of fibrosis, and variable activity
- **The need of liver biopsy in ACLF should be individualized.**

5 Following etiologies were included as acute events leading to the development of ACLF.

<u>Infectious etiology:</u>

Hepatotropic and nonhepatotropic viruses.

Reactivation of hepatitis B (overt or occult) or hepatitis C.

Other infectious agents afflicting the liver.

<u>Noninfectious etiology</u>:

- **Alcohol: active drinking within the last 4 weeks.**
- **Use of hepatotoxic drugs, herbs.**
- **Flare of autoimmune hepatitis or Wilson's disease.**

- **Surgical intervention.**
- **Variceal bleed.**
- **Unknown hepatotoxic etiology.**

6 Defining the underlying CLD: diseases Included :

- ❖ **Compensated cirrhosis of any etiology.**
- ❖ **Chronic hepatitis.**
- ❖ **Nonalcoholic steatohepatitis.**
- ❖ **Cholestatic liver disease.**
- ❖ **Metabolic liver disease.**

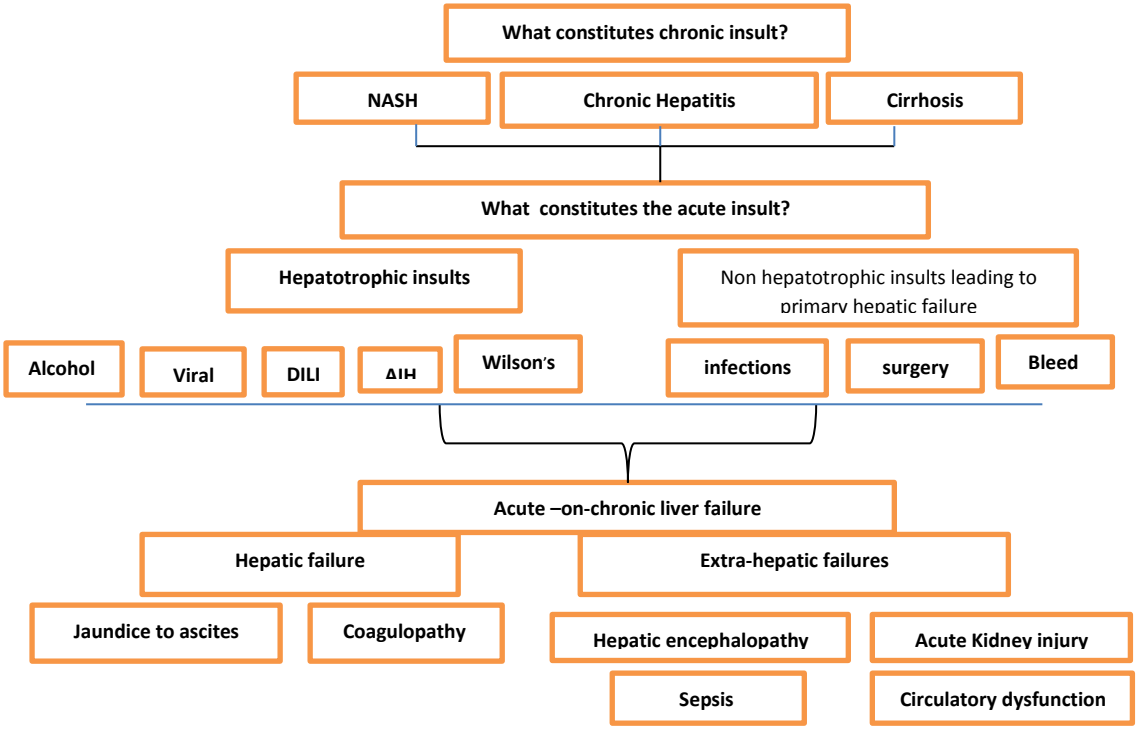

Figure20: Acute and chronic insults in ACLF and outcome

Etiology		Diagnostic Test(s)
Screen in all cases	HAV HBV HEV Acetaminophen Autoimmune hepatitis	IgM anti-HAV HbsAg, IgM anti-HBc,HBV DNA IgM anti-HEV Drugs levels in blood Autoantibodies (Antinuclear antibodies, smooth muscle antibodies; possibly antibodies to liver-kidney microsome type 1), serum Ig levels.
Test if etiology suspected	Idiosyncratic drug reaction Acute fatty liver of pregnancy HELLP Preeclampsia or eclampsia Wilson disease Budd-Chiari syndrome Hepatic malignancy Ischemic hepatitis	Eosinophil count, liver histology US, serum uric acid level, liver histology Platelet count Serum aminotransferase levels Urinary copper, serum ceruloplasmin level, Serum alkaline phosphatase/bilirubin ratio, serum AST/ALT ratio, slit-lamp examination for Kayser-Fleisher rings. Imaging of hepatic veins Imaging of liver, liver histology

Table 11: Diagnostic Testing for the Etiology of Acute Liver Failure

7 Defining the liver failure in ACLF: Jaundice (serum bilirubin >5 mg/dl [85 µmol/l]) and coagulopathy (INR >1.5 or prothrombin activity 40%) are mandatory.

8 Care plan for patient with ACLF:

1-	**Establish the diagnosis and assess the prognosis.**
2-	**Consider liver transplantation; place the patient on the wait-list if the prognosis is poor**
3-	**Institute appropriate monitoring, especially hemodynamic and neurologic.**
4-	**Monitor coagulation regularly, prophylactic replacement of clotting factors is not adviced unless an invasive procedure is planned. Treat bleeding with coagulation factors and platelet when appropriate.**
5-	**Mechanically ventilate the patient when grade 3 encephalopathy develops.**
6-	**Maintain a cerebral perfusion pressure >55 mmHg and intracranial pressure <25mmHg. First-line therapy for cerebral edema is mannitol or hypertonic saline; second-line options include barbiturates, hypertonic saline, indomethacin, hyperventilation, and hypothermia.**
7-	**Treat hemodynamic instability with fluid replacement and inotropic agents (norepinephrine, epinephrine) to maintain a mean arterial pressure>90mmHg.**
8-	**After mechanical ventilation for grade 3 encephalopathy, aim for a physiologic oxygen concentration and mild hypocapenia.**
9-	**For renal dysfunction, institute early continuous renal replacement therapy; correct electrolyte abnormalities (e.g., hypokalemia, hypophosphatemia)**
10-	**Perform dialy culture surveillance; start broad -spectrum antibiotics if infection is suspected; begin a systemic antifungal agent in high-risk patients.**
11-	**Monitor for hypoglycemia hourly; consider the possibility of fuctional adrenal insufficiency.**
12-	**Protect the gastric mucosa with a PPI or H2RA,; institute eneral feeding within 24 hours; otherwise start parenteral nutrition; consider the possibility of pancreatitis (especially in acetaminophen-related acute liver failure).**

Table 12: 12-point Care Plan for Patients with Acute Liver Failure:

- **Prognostic scores for ACLF: CPT, MELD, SOFA, and APACHE scores are generally not different In patients with different etiologies of ACLF.**

<u>Use of antivirals in ACLF.</u>

- **Antiviral therapy should be initiated in patients with ACLF due to hepatitis B.**

Lamivudine may be used for a short-term period, but other potent drugs such as Entecavir or tenofovir may be preferred in view of the long-term need for viral suppre ssion with low frequency of drug resistance.

- **Prophylactic therapy is recommended for HBsAg-positive patients undergoing chemo therapy.**

There is insufficient data to recommend antiviral therapy for HBs Ag-negative and anti-HBc-positive patients.

<u>Use of liver support devices in ACLF:</u>

- **Molecular adsorbent recirculating system does not offer any survival benefit to patients with ACLF.**
- **Role of MARS as a bridge to transplantation in patients with ACLF is still to be defined.**
- **Molecular adsorbent re-circulating system may improve hepatic encephalopathy in patients with ACLF.**

- **Plasma exchange needs further validation for the treatment of ACLF.**

Liver transplant in patients with ACLF:

Criteria when to transplant:

1. **Liver transplantation should be performed according to prognosis scores suggesting death within the next 3months.**
2. **King's College Hospital criteria need further validation for patients with ACLF.**
3. **Earlier intervention if HRS develops.**
4. **However, liver transplantation should not be performed when there is HRS with anuria.**
5. **Results of liver transplantation are better when HRS has been partially controlled by terlipressin.**

Criteria when not to transplant:

a. **Hemodynamic instability and high dose inotrope requirement (sepsis, bleeding).**
b. **Severe bacterial infection.**
c. **Fungal infection.**
d. **Cerebral edema or intracranial bleeding.**

Living donor liver transplantation for patients with ACLF:

The use of liver graft of sufficient graft weight for the recipient and with uniform venous outflow is preferred.

Management of acute liver failure[58]:

Acute liver injury versus failure, the impotance of time to failure.

Acute Liver Failure: Features of injury(elevated AST, ALT, Hyperbilirubinemia, increase INR.) with Mental status changes (confusion, agitation, seizures, coma).

Classification based on time to Failure: Hyperacute(>7days), Acute(1-4weeks), Subacute(5-12weeks), Late(>12weeks). The longer it takes to develope mental status changes the poorer the outcome.

Recommendations

- **Common etiologies**
  1. **Hyperacute and acute: Acetaminophen, Ischemia, Viral, Toxins, Drugs**
  2. **Subacute: Drugs, Viral**
  3. **Chronic: Drugs, Viral (HBV)**
- **Prognosis depends on:**
  1. **Severity of liver dysfunction(INR, Factor VI, V, Bilirubenemia, Hypoglycemia).**
  2. **Finding suggestive of dead liver: Acidosis, Hyperkalemia.**
  3. **Complications: severity of mental status, Cerebral edema, Multiorgan failure and sepsis,**
- **Patients with acute liver failure (ALF) should be hospitalized and monitored frequently, preferably in an ICU.**
- **Initial evaluation: test for etiology, Test severity of dysfunction(Hepatic panel, INR, Factor IV,V), ABG, comprehensive met panel, Panculture, chest X ray, Lipase, Neurocheck, Glucose measurement.**
- **Contact with a transplant center if available**
- **The precise etiology of ALF should be sought to guide further management decisions.**
- **For patients with known or suspected acetaminophen overdose within 4hours of presentation , give activated charcoal just prior to starting N-acetylcystein dosing**
- **Begin N-acetylcystein promptly(150 mg/kg IV load and then 12.5 mg/kg q4 hr.) in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impeding or evolving liver injury.**
- **N-acetylcystein may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning.**

- **In ALF patients with known or suspected mushroom poisoning, consider administration of Silybinin, Pencillin G and N-acetylcysteine, And should be listed for transplantation, as this procedure is often the only lifesaving option.**
- **Determine ingredients of non-prescription medications whenever possible.**
- **Viral A-(and E-) related acute liver failure must be treated with supportive care as no virus-specific treatment has proven to be effective.**
- **Nucleos(t)ide analogues should be considered for patient B-associated acute liver failure and for prevention of post-transplant recurrence.**
- **Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (5-10mg/kg IV every 8 hours)and may be considered for transplantation.**
- **To exclude <u>Wilson disease</u> one should obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser- Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio. And when Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation.**
- **If you suspect <u>Auto immune hepatitis</u> as a cause of ALF**

1. **Liver biopsy is recommended when autoantibodies are negative.**
2. **coagulopathy and mild hepatic encephalopathy in autoimmune hepatitis , cortico stero id treatment is recommended (prednisone, 40-60mg/day)**
3. **Patients with autoimmune hepatitis should be considered for transplantation even while corticosteroids are being administered.**

- **For <u>Acute fatty liver of pregnancy or the HELLP syndrome</u>, expeditious delivery of the infant is Recommended. Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery.**
- **In ALF patients with evidence of <u>ischemic injury</u>, cardiovascular support is the treatment of choice(pressors).**
- **<u>Hepatic vein thrombosis</u> with acute hepatic failure is an indication for liver transplant, provided the underlying malignancy is excluded.(Budd Chiari might benifit from revascularization).**
- **In patients with acute liver failure who have a previous cancer history or massive hepatomegaly, consider <u>underlying malignancy</u> and obtain imaging and liver biopsy to confirm or exclude the diagnosis.**
- **If the etiological diagnosis remains elusive after extensive initial evaluation, liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy.**
- **<u>Regarding encephalopathy</u> :**

- **In early stages of encephalopathy, lactulose may be used either orally or rectally to effect a bowel purge, but should not be administered to the point of diarrhea, and may interfere with the surgical field by increasing bowel distension during liver trans plantation.**
- **Patients who progress to high-hepatic encephalopathy (grade III or IV) should under endotracheal intubation.**

- **Seizure activity should be treated with phenytoin and benzodiazepines with short half-lives. Prophylactic phenytoin is not recommended.**
- **<u>Intracranial pressure in ALF</u>:**

- **Intracranial pressure (ICP) monitoring is recommended in ALF patients with high grade hepatic encephalopathy, in centers with expertise in ICP monitoring, in patients awaiting and undergoing liver transplantation.**
- **In the absence of intracranial pressure monitoring, frequent (hourly) neurological evaluation is recommended to identify early evidence of intracranial hypertension.**
- **In the event of intracranial hypertension, a mannitol bolus (0.5-1.0 gm/kg body weight) is recommended as first-line therapy; however, the prophylactic administration of mannitol is not recommended.**
- **Corticosteroids should not be used to control elevated intracranial pressure in patients with ALF.**

- **In ALF patients at highest risk for cerebral edema (serum ammonia>150 µM, grade 3/4 hepatic encephalopathy, acute renal failure requiring vasopressors to maintain mean arterial pressure) the prophylactic induction of hypernatremia with hypertonic saline to a sodium level of 145-155 mEq/L is recommended.**
- **Short-acting barbiturates and the induction of hypothermia to a core body temperature of 34-35ºC may be considered for patients refractory to osmotic agent as a bridge to liver transplantation.**
- **Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotics treatment should be initiated promptly according to surveillance culture results at the earliest sign of infection or deterioration (progression to high grade hepatic encephalopathy or elements of the systemic inflammatory response syndrome).**
- **Prophylactic antibiotics and antifungals have not been shown to improve overall out comes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy.**
- **Replacement therapy for thrombocytopenia and/or prothrombin time is recommended only in the setting of hemorrhage or prior to invasive procedures.**
- **Patients with ALF in the ICU should receive prophylaxis with histamine-2(H_2) blocking agents or proton pump inhibitors (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress.**
- **Fluid resuscitation and maintenance of adequate intravascular volume are recom mended on presentation in patients with ALF. The initial treatment of hypotension should be with intravenous saline.**
- **If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used.**
- **Pulmonary artery catheterization is rarely necessary in patients with ALF and is associated with significant morbidity.**
- **Instead, appropriate volume status should be ensured with a volume challenge.**
- **Systemic vasopressors support with agents as norepinephrine should be administered in volume-refractory hypotension or to ensure adequate cerebral perfusion pressure (CPP). Vasopressin or terlipressin can be added to norepinephrine in norepinephrine-**

refractory cases, but should cautiously in severely encephalopathic patients with intracranial hypertension.

- **Goals of circulatory support in patients with ALF are a mean arterial pressure (MAP) ≥ 75mmHg and a cerebral perfusion pressure (CPP) 60-80 mmHg.**
- **Metabolic homeostasis must carefully maintained in ALF patients. Over all nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently, with expeditious correction of derangements. Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death.**
- **Strategies to reduce cerebral edema and rise in intracrenial pressure:[58]**

1. **Elevation of head**
2. **Sedate with propofol when agitated develops- protect air way.**
3. **Quadruple-H intervention: Hyperventilate(pCO2 35mmHg), Hypothermia(core temp 33-35 ^{o}C), Hypernatremia (Na 140-145 meq), Hemofiltration (Blood NH3<60mM).**

HEPATIC ENCEPHALOPATHY [12]

Hepatic encephalopathy (HE) may be defined as a disturbance in central nervous system function because of Hepatic insufficiency. This broad definition reflects the existence of a spectrum of neuro-psychiatric manifestations related to a range of pathophysiological mechanisms Present in both acute and chronic liver failure, these neuro-psychiatric manifestations are potentially reversible.

Pathophysiology: **The main tenet of all theories of the pathogenesis of HE is firmly accepted: nitrogenous substances derived from the gut adversely affect brain function. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. Once in brain tissue, they produce alterations of neurotransmission that affect consciousness and behavior. Abnormalities in glutamatergic, serotoninergic, g-aminobutyric acid– ergic (GABA- ergic), and catecholamine pathways, among other , have been described in experimental HE. The research challenge lies in The dissection of each of these systems and their Possible pharmacological manipulation to improve treatment.**

TREATMENT OPTIONS :

Treatment of HE is based on several, non–mutually exclusive options.

<u>Nutritional Management</u>: Patients with HE should avoid prolonged periods of dietary protein restriction and receive the maximum tolerable protein intake, aiming at 1.2 g of protein/kg/day (range 1–1.5) Vegetable and dairy sources are preferable to animal protein, as they provide a higher calorie to nitrogen ratio and, in the case of vegetable protein, provide non-absorbable fiber, a substrate for colonic bacteria and subsequent colonic acidification. Zinc, a cofactor of urea cycle enzymes , may be deficient in cirrhotic patients, especially if associated with malnutrition. Zinc supplementation improves the activity of the urea cycle in experimental models of cirrhosis.

<u>Reduction in the Nitrogenous Load Arising From the Gut</u>:

A. **Bowel Cleansing: Bowel cleansing is a standard therapeutic measure in HE . Irrigation with a 5-L isotonic solution of mannitol, 1 g/kg, has been shown in a controlled trial to prevent encephalopathy after a GI hemorrhage**
B. **Non absorbable Disaccharides: Lactulose is a first-line pharmacological treatment of HE. Lactitol, more palatable is available in Europe but not the United States**
C. **Antibiotics: Antibiotics are a therapeutic alternative to nonabsorbable disacch arides for treatment in acute and chronic encephalopathy and cirrhosis. For acute encephalopathy, neomycin (3–6 g/day p.*o.*) should be given for a period of 1–2 wk. For chronic encephalopathy, neomycin (1–2 g/day p.*o.*) should be given, with periodic**

renal and annual auditory monitoring. Neomycin can be combined with oral lactulose in problematic cases. Metronidazole should be started at a dose of 250 mg b.i.d.

D. Other Therapies: Ornithine aspartate drug is not available in the United States. It provides substrates for the Urea cycle (ornithine) as well as for the synthesis of glutamine (aspartate, via transamination to glutamate). It is available in oral and *i.v.* formulations. Preliminary experience in both acute and chronic encephalopathy has been encouraging.

Drugs That Affect Neurotransmission Flumazenil (1 mg bolus *i.v.*) is indicated for patients with HE and suspected benzodiazepine intake. *and* bromocriptine(30 mg p.o. b.i.d.) is indicated for the treatment of chronic encephalopathy in patients unresponsive to other therapy administration may have a therapeutic role in selected patients.

Manipulation of the Splanchnic Circulation

- **The presence of large spontaneous portal-systemic shunts should be sought in selected patients with recurrent episodes of encephalopathy despite medical therapy, where a precipitating factor is not found.**
- **Occlusion of portal-systemic collaterals should be undertaken only in centers with experienced interventional radiologists and after all other medical measures have failed.**

1. Acute Encephalopathy in Cirrhosis

A. General Measures: Tracheal intubation in patients with deep encephalopathy should be considered. A nasogastric tube is placed for patients in deep encephalopathy. Avoid sedatives whenever possible. Correction of the precipitating factor is the most important measure.

B. Specific Measures:

i. Nutrition. In case of deep encephalopathy, oral intake is withheld for 24–48 h and i.v. glucose is provided until improvement. Enteral nutrition can be started if the patient appears unable to eat after this period. Protein intake begins at a dose of 0.5 g/kg/day, with progressive increase to 1–1.5 g/kg/ day.

ii. Lactulose is administered via enema or nasogastric tube in deep encephalopathy. The oral route is optimized by dosing every hour until stool evacuation appears. Lactulose can be replaced by oral neomycin.

iii. Flumazenil may be used in selected cases of suspected benzodiazepine use.

2. Chronic Encephalopathy in Cirrhosis

i. Avoidance and prevention of precipitating factors, including the institution of prophylactic measures.

ii. Nutrition. Improve protein intake by feeding dairy products and vegetable-based diets. Oral branchedchain amino acids can be considered for individuals intolerant of all protein.

iii. Lactulose. Dosing aims at two to three soft bowel movements per day. Antibiotics are reserved for patients who respond poorly to disaccharides or who do not exhibit diarrhea or acidification of the stool.

Chronic antibiotic use (neomycin, metronidazole) requires careful renal, neurological, and/or ontological monitoring.

iv. Refer for liver transplantation in appropriate candidates. For problematic encephalo pathy (non-responsive to therapy),

consider imaging of splanchnic vessels to identify large spontaneous portal-systemic shunts potentially amenable to radiological occlusion. In addition, consider the combination of lactulose and neomycin, addition of oral zinc, and invasive approaches, such as occlusion of TIPS or surgical shunts, if present.

Minimal or Subclinical Encephalopathy

Treatment can be instituted in selected cases. The most characteristic neuro psy chological deficits in patients with cirrhosis are in motor and attentional skills. Although these may impact the ability to perform daily activities, many subjects can compensate for these defects. Recent studies suggest a small but significant impact of these abnormalities on patients' quality of life, including difficulties with sleep. In patients with significant deficits or complaints, a therapeutic program based on dietary manipulations and/or nonabsorbable disaccharides may be tried. Benzodiazepines should not be used for patients with sleep difficulties.

Assessment of the need for liver transplantation.

The development of overt HE carries a poor prognosis with a 1-yr survival of 40%. Appropriate candidates should be referred to transplant centers after the first episode of overt encephalopathy of any type.

If you suspect variceal hemorrhage the following scheme is recommended:

1- **General resuscitation measures**
   A=airway B=breathing C=circulation with two iv lines access
2- **Start pharmacotherapy, e.g. Octereotide 50µg i.v bolous followed by 50µg/h iv for 3-5days (or terlipressin)**
3- **Blood & fluid replacement if indicated with restrictions**
4- **Administer antibiotics, e.g. ciprofloxacin or ceftriaxone vial**
5- **Emergency endoscopy with in 24h(if the patient hemodynamically stable),to verify diagnosis and to perform band ligation or sclerotherapy.**
6- **In case of early rebleeding (with in 5 days of index-bleed) : repeat endoscopic therapy once, if possible.**
7- **Recurrent or uncontrolled bleeding or endoscopic treatment failure(early re-bleeding after two endoscopic attempts): place balloon tamponade, consider TIPS or surgery.**

The candidate for endoscopic examination and therapeutic intervention must be hemodynamically stable i.e. pulse rate < 100p/min., systolic B.P >100mm/Hg, No postural hypotension, normal SPO_2,no ECG with changes suggestive of ischemic changes, N.B. the mortality risk increase if the case associated with other co morbid diseases and the patient was old. chart for follow up of the patient is mandatory.CBP, RBS, b. urea, s. creatinine, s.electrolyte, LFT and ECG to be done initially. (The patient and their relatives must sign on the consent if there was any plan for endoscopic examination).

If the patient was presented with upper GI bleeding (Melena with or without hematemesis), the management suggested is:

1- **General resuscitation measures**
   A=airway B=breathing c=circulaion- with two acess i.v lines
2- **Blood loss replacement**
3- **PPI(Esomeprazole-Nexium) vial 80mg starting dose followed by 8mg/h infusion for 72h.**
4- **Endoscopic examination is undertaken with in 24h of initial presentation to verify the lesion and stop the bleeding if the patient haemodynamically stable with anesthetist assistant for airway and endotracheal intubation**

The candidate for endoscopic examination and therapeutic intervention must be hemodynamically stable i.e. pulse rate< 100p/min., systolic B.P >100mm/Hg,

No postural hypotension, normal SPO_2,no ECG with changes suggestive of ischemic changes, the mortality risk increase with other co morbid diseases and the patient is too

old. Chart for follow up patient is mandatory. CBP, RBS, blood urea, s. creatinine, s. electrolyte, liver enzymes and ECG to be done initially.

(The patient and their relatives must sign on the census if there was any plan for endoscopic examination).

<u>Hepatic encephalopathy is a diagnosis of exclusion.</u>

In patients with cirrhosis and overt encephalopathy, two staging classifications have been used for patients with HE.

1. **The West Haven criteria of altered mental state in HE(numerous studies have employed variations of these criteria).**

   Stage 0. Lack of detectable changes in personality or behavior. Asterixis absent.

   Stage 1. Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria or depression. Asterixis can be detected.

   Stage 2. Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis.

   Stage 3.Gross disorientation. Bizarre behavior. Semistupor to stupor. Asterixis generally absent.

   Stage 4. Coma.

2. **Evaluation of the level of consciousness with the Glasgow Scale: although the Glasgow coma scale has not been rigorously evaluated in patients with HE, its widespread use in structural and metabolic disorders of brain function justifies its application in acute and chronic liver disease. The best score is 15 and the worst 3**

   Severe encephalopathy is defined as a score of 12

Acute Cholangitis[57]

It can be defined as bacterial infection of the bile ducts, 80-90%due to stones, it potentially life threatening(Intraductal pressure leading to bacteremia and endotoxemia , but can or self-limited,e.g, when stone passes) other causes stones(not just like stones), Ampullary mass, PSC, Asian"Oriental"Cholangiohepatitis, Pararasites (1-Flukes-Clonorchis, Opisthorcis, Metorchis, 2-Ascaris- 25% of the world is infected), Iatrogenic (stents, Post organ liver transplantation, Post-biliary surgery).

Pathophysiology: Obstruction, Pus under pressure, Bacterial translocation and Bacterimia, Endotoxemia, Sepsis syndrome.

Recommendations for Diagnosis of Cholangitis:

- **Cracot's triad: Fever, RUQ pain, Jaundice only 60-70%**
- **Reynold's Pentad: Above plus hypotension and altered mental status.**
- **Labs: elevated bilirubin, alkaline phosphatase,and GGT.**
- **ALT>1000 rare unless severe with hepatocyte necrosis.**
- **Elevated amylase lipase suggests gallstone pancreatitis.**
- **Imaging: dilted ducts(stricture,stones, mass).**
- **Might the patient had Criteria for Sepsis Syndrome:**

<u>Systemic Inflammatory Response Syndrome(SIRS)</u>

<u>Infection with at least 2</u>:

1. **Fever(>38), or Hypothermia(<36)**
2. **Tachycardia(>90BPM)**
3. **Tachypnea(>20 BrPM) or Hypocapnia(pCO2<32 mmHg), or mechanical ventilation**
4. **Leukocytosis(>12000) or Leukopenia (<4000)**

<u>Septic shock</u>, above plus Hypotension: SBP<90, MAP<70, After 30ml/kg crystalloids.

Practical points for management:

1- **Resuscitation and physiological support(IV Fluids, possible Intubation, Pressors if needed- increase vascular resistance).**
2- **Labs (CBC, LFT's, INR)**
3- **Broad spectrum antibiotics (Pip-Tazo, Cipro, Carbapenem)**
4- **Imaging: US usually adequate (dilated duct, stones)**
5- **Monitored bed (ICU versus step-down).**
6- **Almost all respond to fluids and antibiotics**
7- **ERCP is preferred modality(success rate, morbidity and mortality superior than surgery, and PTC).**
8- **In altered anatomy like Gastric Bypass or Roux Y and Failed ERCP PTC is indicated (at least initially), EUS may have a role.**
9- **Emergent ERCP and Non-emergent ERCP(within 24-48hours)**

High probability cholangitis, persistent shock(need pressors, organ systemic failure)

Resuscitated, intubated, monitored

At initial ERCP, relieve obstruction(plastic CBD stent)

Try to use fluoroscopy(avoid bedside)

No sphincterotomy

NB Tubes out of favor.

Bile culture is not needed

10- **Coagulopathy may be acquired(sepsis) or due to anticoagulants**

- **Correct if possible to INR<2, Platelet>50 but if life threatening don't delay**
- **INR>5, Platelet<20 is associated with spontaneous bleed, contraidicated to any intervention until corrected!!.**

Foreign body management[19]

Most common in pediatric age group (80%), edentulous adults, inebriat group, prisoners then psychiatric patients.

Complication

Perforation <1%, mediastinitis, lung abscess, fistula, and aspiration.
Consider the possibility of more than one foreign in one patient
Commonly ingested objects:
Children: Coins, Toys, Crayons, Batteries, bottle caps
Adults: food impaction (meat, bones), Dentures, headed pins
Patient presentation:
Dysphagia (92%), Neck tenderness (60%), odynophagia, hypersalivation, regurgitation, abdominal pain.
In children: sudden refused to eat.
History of object swallowed, Timing of object swallowed
Physical examination (mental status, respiratory status, Drooling=complete esophageal obstruction
Subcutaneous emphysema = esophageal perforation
Peritoneal signs = GI perforation
Evaluation:
Radiological imaging (location of object, subcutaneous air, peumomediastinum, pleural effusion, free air under diaphragm)
Most ingested foreign bodies are radiopaque (exceptions chicken &fish bones, wood, plastic, and glass)
Avoid barium
Gastrograffin is contraindicated in obstructed esophagus (extremely hypertonic, can cause pulmonary edema if aspirated)
Biplanar plain radiographs films
Chest X- ray and/or CT scan for suspected perforation

Indications for Endoscopic Removal of Foreign Bodies:

1. **Esophageal Foreign bodies should be removed with in 12-24 hours to prevent complications (air way compromise, perforation, aortic or pulmonary fistula) .**
2. **Foreign bodies leading with sharp/pointed end**
3. **Objects >5cm and wider than >2cm do not (usually) pass through pylorus or IC valve.**

Indications for Urgent Endoscopy:

1. **Respiratory distress/compromise**
2. **Pain**
3. **Complete esophageal obstruction(unable to handle secretions)**
4. **Sharp objects below the UES (if above UES= ENT)**
5. **Lateral image (Determine location in esophagus versus trachea)**
6. **Bottom battries with in reach of gastroscope**

Endoscopy is contraindicated in:

1. **Asymptomatic and no foreign body remaining**
2. **Drug packets**

Tools of Trade:

- **Grasping forceps**
- **Polypectomy snare**
- **Roth retrieval net: for round objects like coins, bottom batteries**
- **Stone retrieval basket**
- **Hood: for sharp objects (toothpicks, nails, needles, razor blades, pens, safety pins, dental appliances.**
- **Overtubes**

Management of Esophageal Food Bolus Impaction:

- **Push bolus into stomach if possible**
- **Bypass obstruction with endoscope if possible**
- **Assess cause of obstruction angle at GE junction**

- **Reposition endoscope- push food bolus from the right**
- **Gentle advance**
- **Beware bone spicule with in bolus(perforation risk)**
- **Extract food through mouth**
- **Overtube to protect airway**
- **Grasping forceps**
- **Avoid papain (Meat tenderizer) like enzymatic digestion of meat= enzymatic digestion of esophagus**
- **Glucagon (1-3mg)even low success rate(30%-50%)it will decrease LES pressure, but has no effect on rings or strictures**
- **Follow-up EGD to assess/ treat stricture.**

SUGESTED GUIDELINES GI FOREIGN BODY REMOVAL:

- **Recognize indications for urgent endoscopy**
  - **Complete esophageal obstruction (drooling is one of sign)**
  - **Sharp objects in esophagus**
  - **Button batteries**
  - **Patient distress.(for for children sudden refusal to eat)**
- **Recognize contraindication for endoscopic retrieval**

1. **Asymptomatic and no foreign body remaining**
2. **Drug packets**

- **Be familial with available equipment**
- **Protect the airway**
- **Plan your strategy before endoscopy**
- **Avoid papain(Meat tenderizer)**
- **Biplanar plain films may important**
- **Chest x-ray and/or chest CT for suspected perforation**
- **Avoid barium**
- **Gastrograffin contraindicated in obstructed esophagus**

Caustic ingestion[35]

In adults are often in the setting of suiside attempt. It is common emergency seen in clinical practice, The majority will have mild injury and will recover.

- **Large volume imgestion of a corressive agent are associated significant morbidity and mortality**
- **Bleeding, perforation, and fistula formation often occur with in 3 weeks of the ingestion.**
- **Long-term complication are mainly stricture formation in the pharynx, esophagus, or stomach**

Management:

- **Uppon presentation patients should be admitted to the ICU for initial assessement and resuscitation**
- **Adetailed history from the patient or the family/friends is critical to determine the type of ingestion. The most common ingestions are alkali pH >12 or acidic pH <2.**
- **Attempts to induce vomiting, place NGT, neutralize the agent often not recommended, since it can make things worse.**
- **It is important to recognize and understand when emergent endoscopic intervention is needed, which is not in all situation.**
- **It is often requires both endoscopic and CT imaging depending on clinical presentation.**
- **Treatment algorithm is often based on the endoscopy findings using the Zarger Classification.**

Grade	Endoscopic findings
1	Edema and mucosal hyperemia
11a	Superficial localized ulcerations, friability, and blisters
11b	Circumferential and deep ulcers
111a	Multiple deep ulcers and small scattered areas of necrosis.
111b	Extensive necrosis
1V	Perforation

Table 13.Zarger Classification

Patients with esophagus Grde 0-1 or gastric 0 to 11a can advance a regular diet and discharge home within 24hours.

Patients with grade 11a (esophagus) and grade 11b gastric are placed on parenteral nutrition with repeat endoscopy in 1 week. If there is mucosal healing then oral nutrition should be started, but if no improvement a feeding jejunostomy is placed with repeat endoscopy in 3 weeks.

If the patient shows signs of decompensation (abdominal pain, shock, systemic organ failure, leukocytosis/ acidosis) then a CT scan should be done to determine the need for surgery.

Acid reducing medication (PPI) may help prevent reflux related stenosis long-term, but no proven benefit immediately after ingestion.

If stricture formation occurs in the esophagus first-line therapy is dilation, but should wait 6 weeks post ingestion.

Surgery for stricture formation is considered, if there no improvement after 5 sessions of dilation.

Temporary esophageal stenting has been tried with success ranging from 0-99%.

If a patient has grade 111a injury with transmural necrosis on CT imaging, the emergent surgery is recommended.

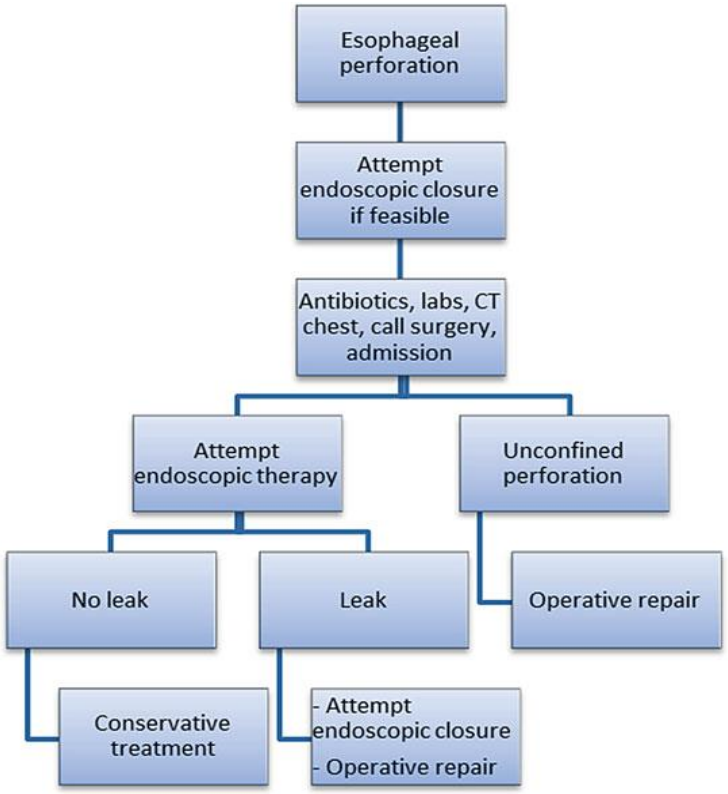

Figure 21: Suggested management algorithm for esophageal perforation

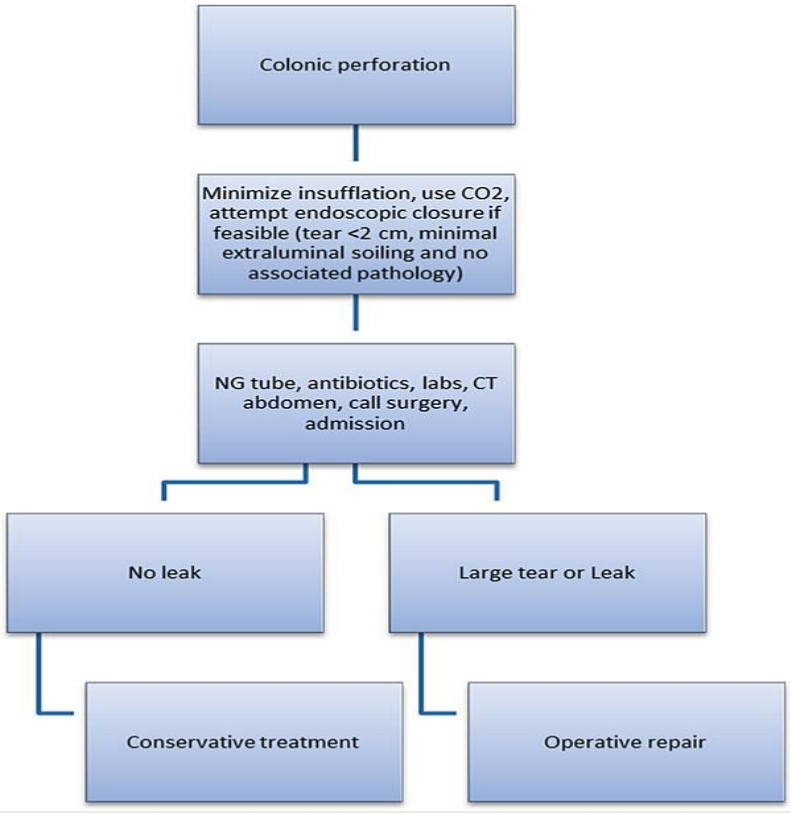

Figure 22: Suggested management algorithm for colonic perforation

Non-endoscopic management of acute colonic pseudo-obstruction (ACPO) and mechanical colonic obstruction (MCO). [36.]

Ogilvie's syndrome or acute **colonic pseudo obstruction was first described by Sir William Ogilvie in 1948 when he reported two patients with sudden onset of abdominal pain, constipation, and dilation of the large bowel. Both patients had retroperitoneal tumor invasion of the celiac plexus and prevertebral sympathetic ganglia. From this eponym, the definition has evolved to the clinical signs and symptoms of large bowel obstruction and colonic dilation on radiographic imaging, but without an identifiable source of mechanical obstruction**

In contrast, mechanical colonic obstruction is due to anatomic obstruction of the colon causing distension proximal to the blockage. Subsequent intestinal transit is impaired leading to clinical symptoms. Partial obstruction allows some gas and liquid stool to pass, while complete obstruction does not.

<u>The clinical presentation of both conditions is similar.</u>

- **ACPO typically presents with abdominal pain and distension. Distension is progressive and the timing ranges from 24 h to 7 days before treatment is sought. Abdominal pain is typically non-colicky and may be only mild to moderate in severity despite significant distension. Nausea and vomiting are often present. Although patients generally complain of constipation, up to 40 % of patients may continue to pass stool or flatus.**
- **MCO In complete mechanical obstruction, the passage of fecal material is rare and these patients are often constipated. In contrast to ACPO, abdominal pain is cramping or colicky in nature and more frequently localized in the hypo gastric or periumbilical regions. Symptom course varies widely based on the etiology of obstruction. MCO due to malignancy or stricture can display a gradual progression with predominance of constipation and/or distension, while volvulus tends to be more sudden in onset and acutely painful. Sigmoid volvulus can present with intermittent pain reflecting spont aneous resolution and recurrence of volvulus. Cecal volvulus can cause pain ranging from hours to days. Distension, nausea, and vomiting are also typical. When the obstruction is distal, nausea tends to occur later. in the clinical course earlier onset nausea and emesis are more consistent with small bowel obstruction.**

On physical examination,

- **bowel sounds may be present, absent, or abnormal with either pathology and are not particularly useful diagnostically.**
- **A palpable mass on rectal exam is concerning for rectal neoplasm causing obstruction, but this is rare.**
- **The presence of fever, abdominal rigidity, guarding, shock, or signs of sepsis is concerning for ischemia, peritonitis, and/or colonic perforation.**
- **Severe abdominal distension is seen more commonly in ACPO.**

Etiology and Predisposing Factors

- **It is important to rule out toxic megacolon due to *Clostridium difficile* infection, which can present similarly. Patients with toxic megacolon typically have numerous watery bowel movements, marked leukocytosis, and a history of recent antibiotic exposure or healthcare contact. Infection can be excluded by stool toxin or *C. difficile* PCR testing. ACPO and MCO can be difficult to distinguish on clinical grounds and mechanical obstruction should be excluded before rendering a diagnosis of ACPO. ACPO is responsible for about 20 % of all large bowel obstructions.**

Pseudo-obstruction is more common in males older than age 60 and the risk increases with longer hospital stays.

- **Numerous surgical, conditions have been identified as predisposing factors, The most common associated surgical factors include orthopedic and gynecologic surgery, trauma (surgical and nonsurgical), and burns. Cesarean section and hip procedures are the most frequently implicated gynecologic and orthopedic surgeries, respectively as well as certain medications and metabolic derangements.**
- **Predisposing medical conditions include systemic or intra-abdominal infection, myocardial infarction and congestive heart failure, alcohol abuse, liver or renal failure with related metabolic disturbances, diabetes, respiratory pathology (including pneum onia and mechanical ventilation), leukemia, retroperitoneal tumors or history of pelvic radiation, and herpes zoster infection. Less commonly associated factors include chronic neurologic conditions, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, and cerebrovascular accidents.**
- **Medications that impair intestinal motility are often implicated in ACPO, including opiates, antihistamines, antipsychotics, tricyclic antidepressants, corticosteroids, and epidural anesthesia. In addition to Parkinson's disease being a risk factor for ACPO, drugs used to treat the condition, such as dopamine agonists and anti cholinergics, have been linked to ACPO.**
- **Metabolic derangements are commonly present in ACPO patients and may be inciting or aggravating factors. Hypothyroidism, hyponatremia, hypocalcaemia, hypokalemia, hypomagnesaemia, and elevated urea nitrogen have all been described in association with ACPO**

Mechanical Colonic Obstruction

The specific etiology of MCO is usually more definitive.

- **The most common cause is colorectal cancer, accounting for 33-60 % of mechanical obstructions, with three quarters of these cancers being adenocarcinomas. Overall, 10-30 % of colorectal cancer patients will develop obstruction.**
- **Volvulus causes about 10-15 % of obstructions**
- **chronic diverticular disease (abscess and stricture) accounts for 10 %.**
- **metastatic tumors to the abdomen, including ovarian and uterine cancers, can lead to extrinsic compression of the colonic lumen.**
- **benign strictures due to ischemia, diverticular disease, diverticulitis and inflammatory bowel disease (secondary to acute inflammation or chronic strictures), nonsteroidal anti-inflammatory agents (NSAIDs), and high dose pancreatic enzymes can cause MCO**
- **Intussusception, adhesions, hernia, fecal impaction, and endometriosis are less frequent causes .**
- **Very rarely, infectious sources, including Actinomyces , Taenia saginata , botulism, and Salmonella , have been reported to cause mechanical colonic obstruction**

Diagnosis and Evaluation

Radiographic imaging is critical in the diagnosis and management of either type of colonic obstruction.

- **In ACPO, plain abdominal X-ray typically reveals massive gas-filled dilation of colon without air-fluid levels and little or no small bowel dilation. Stool and gas can be seen distal to the dilated segment since a mechanical obstruction is not present. Careful attention should be paid to the amount of stool in the rectal vault to exclude distal stool impaction, which would be managed differently than ACPO. The cecum and right colon are usually the sites showing dilation of the largest diameter, averaging 10-16 cm on radiographs and conferring the highest risk of perforation due to Laplace's law.**

- **In MCO, plain abdominal films reveal dilation proximal to the obstruction with air-fluid levels in the colon and small bowel. Distal to the obstruction, the colon is decompressed and devoid of stool and air. Cecal volvulus typically displays a markedly distended loop of large bowel extending from the right lower quadrant to the epigastrium or left upper abdomen. Sigmoid volvulus can present with an inverted-U or a coffee bean shape on X-ray due to massive dilation. Upright abdominal and chest films are more useful than supine films in determining if free air due to perforation is present. If bowel ischemia is present, plain films may reveal thumb printing due to mucosal edema and sub mucosal hemorrhage. But unfortunately, plain radiographs have poor sensitivity in diagnosing colonic obstruction. Plain abdominal imaging may also not be reliable in differentiating between ACPO and MCO. In another series, 30 % of patients diagnosed with MCO on plain X-ray actually had ACPO, whereas 20 % of those diagnosed with ACPO had mechanical obstruction. CT with oral or rectal contrast is advised in all suspected cases to differentiate ACPO from mechanical obstruction and to assess for evidence of complications. Contrast CT studies have the added ability to characterize bowel mucosa for signs of ischemia or perforation. Water-soluble contrast enema is preferred over barium enema due to the risk of barium impaction at the site of obstruction and barium peritonitis if perforation is present. CT findings that are characteristic of ACPO include preserved haustral markings and luminal dilation in the absence of an obstructive lesion. If mechanical colonic obstruction is present, the source is very likely to be seen on these studies. Volvulus can be diagnosed by the presence of a bird's beak pattern on contrast studies. Also On CT imaging, sigmoid volvulus is characterized by limbs of the twisted loop converging toward a fulcrum point, which appears as a "whirl sign" when the view plane is orthogonal to the rotation axis of the loop. In most cases, the whirl sign is found in the left lower abdomen with a craniocaudal axis. The rectum and the upstream colon are usually flat, whereas the twisted loop is highly distended and located in the anterior part of the abdomen. Cecal volvulus is the torsion of a mobile cecum around its own mesentery, which often results in a closed loop obstruction; twisted terminal ileum, distended cecum, and twisted ascending colon are seen.(Cecal volvulus may occur by three mechanisms: type 1 develops from clockwise axial torsion or twisting of the cecum around its mesentery; type 2 loop volvulus develops from counterclockwise axial torsion of the cecum around its mesentery; and type 3 or Cecal bascule involves upward folding of the cecum as opposed to axial twisting), In most cases of Cecal volvulus, the whirl sign is found in the right part of the abdomen with a lateral or an antero-posterior axis. Pneumatosis or gas in mesenteric veins in concert with bowel wall thickening strongly suggests that bowel infarction has occurred. Management**

1. **Initial management of ACPO and MCO is conservative unless there is significant concern for present or impending complications.**
2. **Endoscopic interventions are central to the management of both MCO and ACPO.**
3. **ACPO Cases unresponsive to conservative measures after 24‑48 h, symptom duration more than 3‑4 days, and colonic diameter more than 10‑12 cm warrant further treatment.**
4. **MCO can also be managed conservatively for a short time interval while preparing for more definitive endoscopic or surgical therapy.**
5. **Close monitoring with serial abdominal examination and plain abdominal radiographs obtained every 12‑24 h should be performed to monitor for peritoneal signs suggestive of ischemia or impending perforation while conservative measures are being instituted.**
6. **Initial conservative management of ACPO consists of :**
   - **noting by mouth, intravenous fluids**

- **placement of a nasogastric tube to intermittent suction for proximal decompression, and rectal tube placement to gravity drainage.**
- **Metabolic and/or electrolyte imbalances should be corrected and any underlying associated condition(s) treated.**
- **All medications that can worsen GI motility should be discontinued whenever possible. Positional maneuvers are also advised, when feasible, including knee-to-chest position, prone position with hips elevated on a pillow, and hourly rotation to right and left lateral decubitus positions.**
- **Laxatives should not be given to relieve constipation, specifically lactulose, as this sugar provides substrate for enteric bacterial fermentation and can worsen gas. Water-soluble (e.g., Gastrografin) enema can be performed if there is concern for distal obstruction or fecal impaction; this will also act as a laxative agent to relieve fecal impaction, if present.**

7. **Conservative management of mechanical colonic obstruction is similar except that rectal tubes are not indicated as the colon distal to the obstruction is typically decompressed**
8. **Pharmacologic Therapy: The most effective pharmacologic treatment for pseudo-obstruction is neostigmine, an acetyl cholinesterase inhibitor, with success rates ranging from 50 to 94 %.The mechanism of action is thought to be indirect stimulation of muscarinic parasympathetic receptors in the gut. Neostigmine has a rapid onset of action and the effect is short-lived. Intravenous (IV) dosing is advised due to variable oral absorption; doses range from 2 to 2.5 mg IV. In the setting of a partial response or relapse after an initial response, a second dose may be administered. The most common adverse effect is mild to moderate abdominal cramping and most common significant side effect is bradycardia. Neostigmine is contraindicated in the presence of mechanical bowel obstruction, perforation, pregnancy, arrhythmia, renal failure, and broncho spasm. Cardiac monitoring and atropine present at the bedside are recommended due to the possibility of bradycardia.**
9. **Erythromycin is a motilin receptor agonist that stimulates GI motility. It can relieve ACPO at doses of 250‑500 mg administered either IV or orally, though success with this agent is limited to anecdotal case reports and, thus, cannot be routinely recommended.**
10. **Methylnaltrexone, a recently approved enteric specific opiate antagonist, has been reported to relieve ACPO in a patient who did not respond to 2 doses of neostigmine.**
11. **In the presence of colonic obstruction, opiates and anticholinergics can be used for pain relief, but may worsen motility. Antiemetics may be used, but metoclopramide is not advised due to its prokinetic properties. Corticosteroids have been shown to relieve nausea and inflammation but do not improve mortality. Small studies have also reported clinical improvement with administration of octreotide**
12. **Surgical Therapy**

- **Surgical management of ACPO is reserved for patients who fail medical and endoscopic management and for those who develop signs or symptoms concerning for peritonitis or perforation. Risk factors for perforation include the absolute size of colonic distension (>12‑14 cm) and longer duration of illness (>2 days), but the most important factor may be the rate of Cecal distension. Surgical options depend on whether perforation has occurred. If the bowel has not perforated, cecostomy or right hemi colectomy with primary anastomosis may be performed. If perforation has occurred, total colectomy with ileostomy and Hartmann's procedure may be required. Fortunately, surgery is rarely required and it carries greater morbidity and mortality than either medical or endoscopic treatment. MCO is ultimately treated by surgical**

treatment of the anatomic abnormality. Right- and left-sided colonic tumors are treated with right and left hemi colectomy, respectively. Diverticular strictures may be treated with either sigmoidectomy or left hemi colectomy depending on the extent and severity of disease. Sigmoid volvulus is best managed in clinically stable patients with initial endoscopic detorsion followed by surgical resection. Recurrence rates for sigmoid volvulus are 50‑60 %. If the patient is a good surgical candidate, elective resection can be undertaken with mesosigmoidopexy and primary anastomosis after successful endoscopic decompression. If gangrene and/or perforation has occurred,then a Hartma's procedure may be required; bowel reanastomosis may be performed at a later date. The initial treatment of Cecal volvulus is surgical detorsion with resection by right hemi colectomy or ileocolic resection. Cecopexy or colopexy may also be performed. Endoscopic detorsion of cecal volvulus is technically challenging with very high failure rates and is not routinely recommended. As with ACPO, surgical intervention is also indicated for any cause of MCO whenever there is significant concern for ischemia, peritonitis, or perforation and after failed pharma cologic/ endoscopic interventions. Finally, small case series have shown success ful decompression with simple surgical loop colostomy for palliation in frail patients

Complications

- **The most significant complications for both MCO and ACPO are ischemia and perforation. Perforation or ischemia occurs in 3‑15 % of ACPO cases. ACPO has an overall mortality of 25‑31 % .However, if complications develop, mortality increases to 40‑50 %. Mortality as a result of MCO varies widely based on etiology, presence of complications, and patient comorbidities.**
- **MCO due to colon cancer carries a perforation rate of 1‑11 % and mortality rates ranging from <1 % to 50 %, depending on comorbidities.**
- **In sigmoid volvulus, gangrenous colon is present in 10‑20 % of patients, with reported mortality rates of 12‑45 %.**
- **In a case series of cecal volvulus, perforation and gangrenous colon were present in about 20 % of cases with an overall mortality of 17 %**

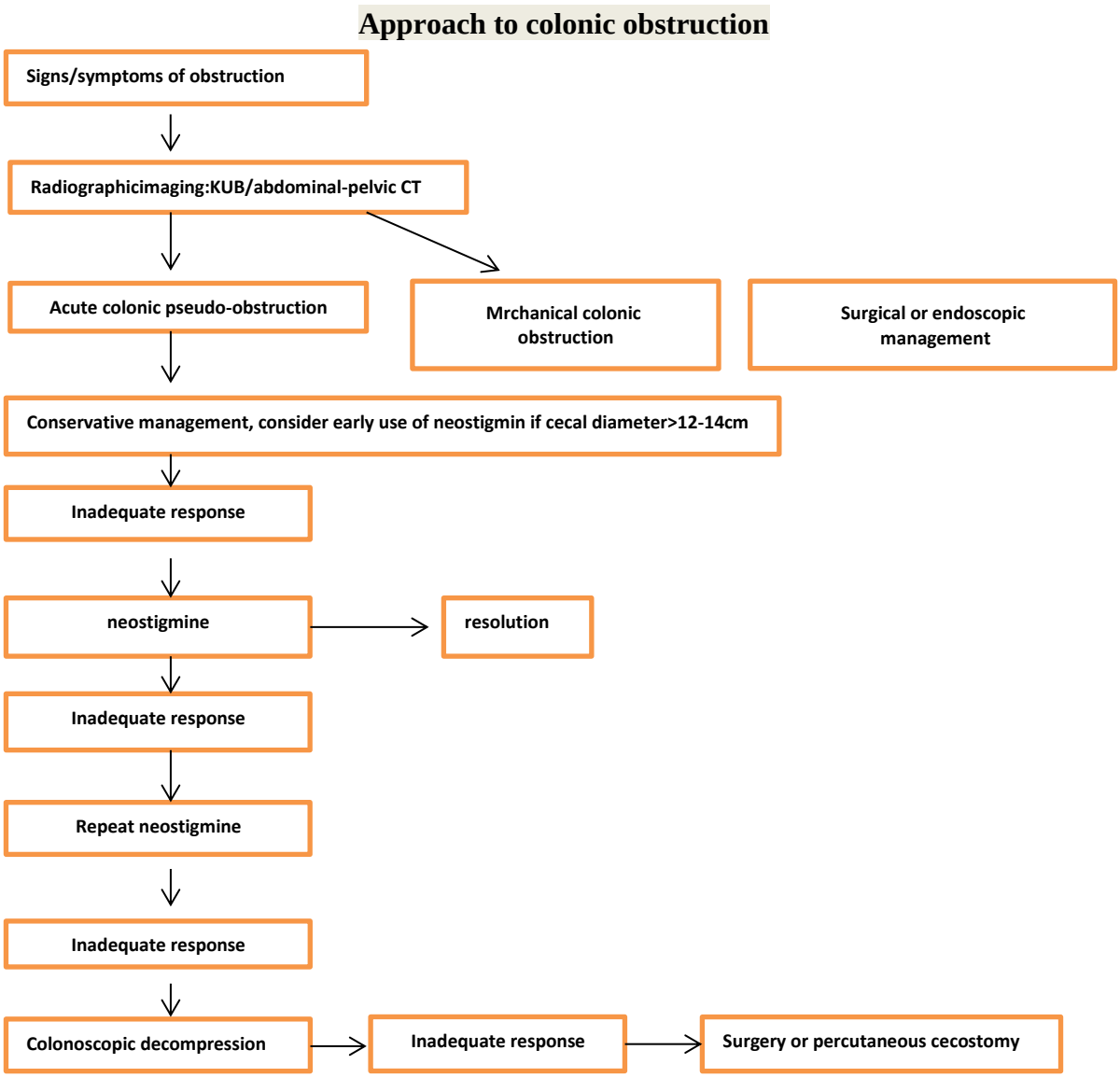

Figure 23: Algorithmic approach to the management of acute colonic obstruction

Common Tables, and Figures[33]
In GI & Liver disorders

Test	Change in pregnancy
AST/ALT	↔
Bilirubin	↔
Prothrombin/INR	↔
Albumin	↓
Alkaline phosphatase	↑
Hemoglobin	↓
Alpha fetoprotein	↑
S'nucleotidase	↔
Gamma glutamyl transpeptidase	↔

Table 14: Normal physiolgic changes in lab tests during pregnancy

Liver disease	ALT/AST ratio	cause	Type of disease
Chronic, Mild Elevations	ALT>AST (<150U/L or 5x normal)	Hepatic	A_1-Antitrypsin deficiency Autoimmune hepatitis Chronic viral hepatitis(B,C,D) Hemochromatosis Medications and toxins Steatosis & steatohepatitis Wilson disease
		Nonhepatic	Celiac disease Hyperthyroidism
Sever, Acute Elevations	ALT>AST (>1000 U/L or >20-25x normal	Hepatic	Acute bile duct obstruction Acute Budd-Chiari syndrome Acute viral hepatitis Autoimmune hepatitis Drugs and toxins Hepatic artery ligation Ischemic hepatitis Wilson disease
Sever, Acute Elevations	AST>ALT (>1000 U/L or >20-25 x normal	Hepatic	Medications or toxins in a patient with underlying alcoholic liver disease
		Nonhepatic	Acute rhabdomyolysis
Chronic, Mild Elevations	AST>ALT (<150 U/L, <5x normal	Hepatic	-Alcohol-related liver injury(AST/ALT > 2:1, AST nearly always <300 U/L -Cirrhosis
		Nonhepatic	Hypothyroidism Macro-AST Myopathy Strenuous exersize

Virtually any liver disease can cause moderate aminotransverase elevations (5-15 x normal)

Table 15: Causes of Elevated Serum Aminotransferase Levels

Variable		Result	Points
Autoantibodies	ANA or SMA	≥1:40	+1
	ANA or SMA	≥1:80	+2
	Anti-LKM1	≥1:40	+2
	Anti-SLA	Positive	+2
Immunoglobulin level	Immunoglobulin G	>ULN >1.1 ULN	+1 +2
Histologic findings	Interface hepatitis, with lymphoplasmacytic infiltrate in the portal area , no granuloma	Compatible Typical	+1 +2
Viral disease markers	No viral hepatitis	No viral markers	+2
Pretreatment aggregate score:	Definitive diagnosis		≥7
	probable diagnosis		6

Table 16: Simplified international scoring system for the diagnosis of autoimmune hepatitis (IAIHG)

ANA, antinuclear antibodies; anti-LKM1, antibodies to liver kidney microsome type 1; anti-SLA, antibodies to soluble liver antigen; SMA, smooth muscle antibodies; ULN, upper limit normal.

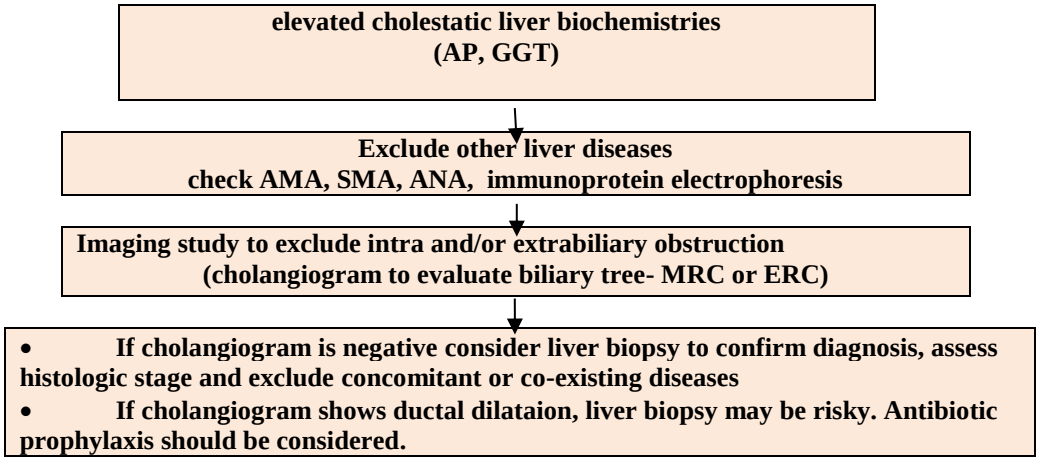

Figure 24: Algorithm for Diagnosis of primary biliary cirrhosis & primary sclerosing cholangitis

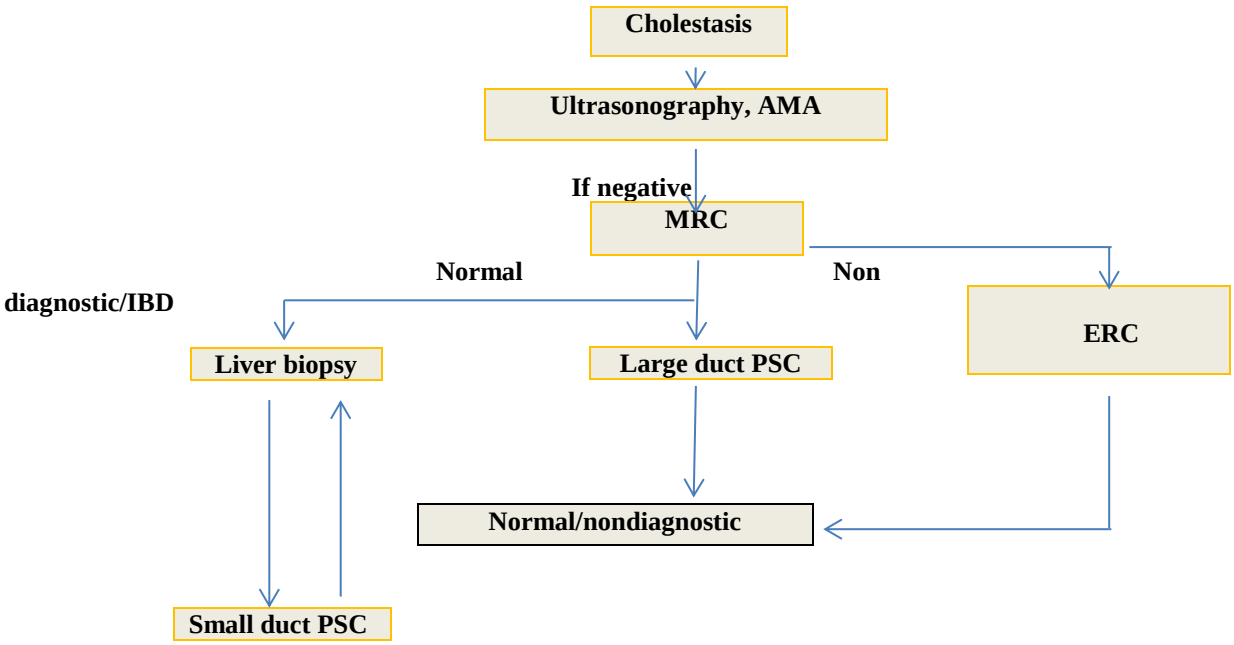

Figure 25: Algorithm for the evaluation of patients with cholestatic liver biochemistry test results, non diagnostic ultrasound, and negative antimitrochondrial antibodies (AMA), If magnetic resonance cholangiography (MRC) is of good quality, the specificity is greater than 95%. Although the sensitivity of MRC is high (approximately 85%), if the quality is poor or the index of suspicion is high, as in patients with inflammatory bowel disease, endoscopic retrograde cholangiography(ERC) should be pursued.

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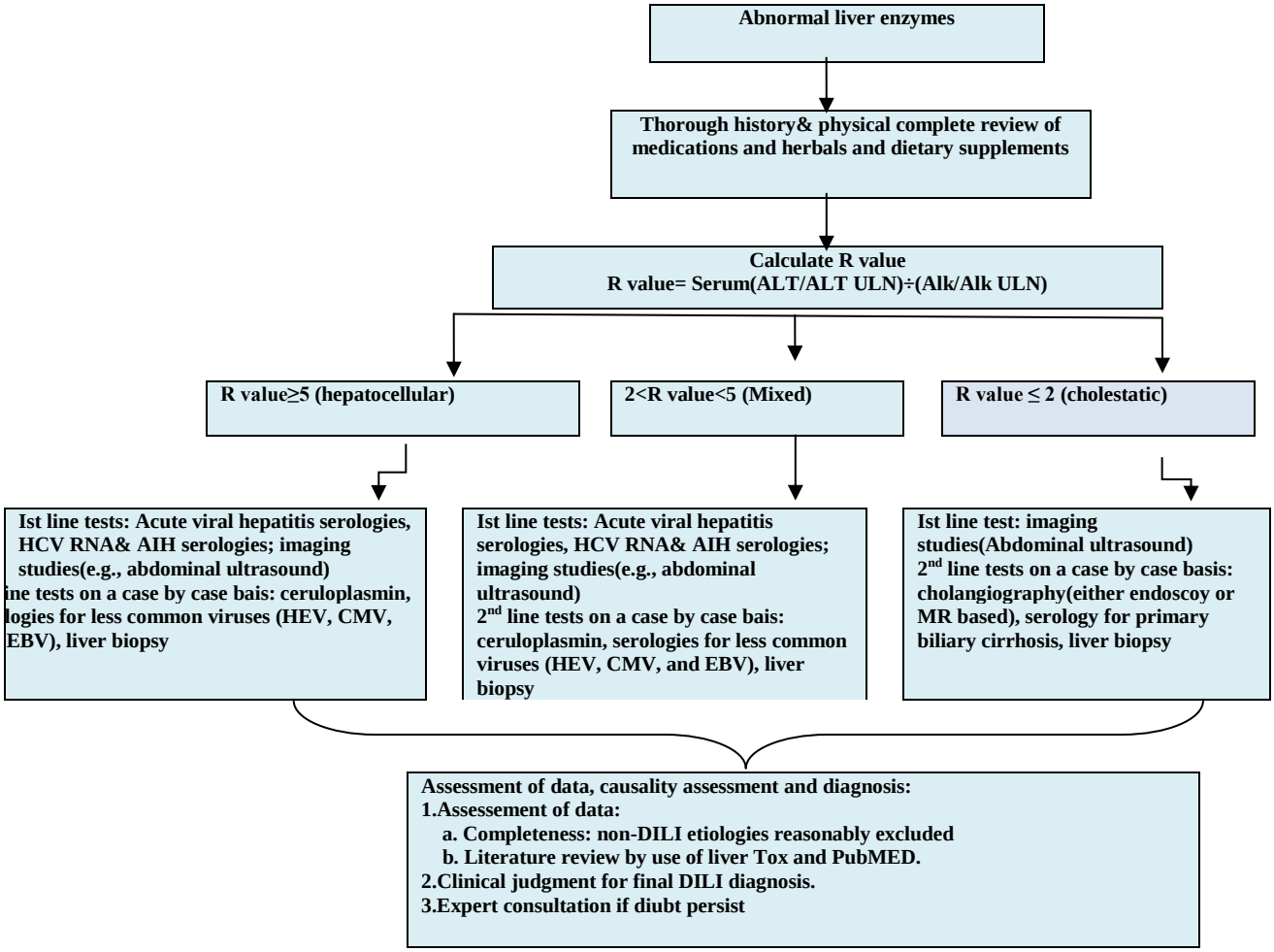

Figure 26: Algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI)

steatosis	**Fat droplets(triglyceride) with in hepatocytes**
Inflammation	**Mixed neutrophilic and mononuclear cell infiltrates are present within the lobule, portal chronic inflammation, ballooning of hepatocytes.**
Mallory-Denk bodies	**Eosinophilic cytoplasmic aggregates of keratins smaller than those in alcoholic hepatitis and are usually found in ballooned hepatocytes.**
Glycogen nuclei	**Clear intranuclear vacuoles fill the nucleus.**
Fibrosis	**Similar to alcoholic liver disease, with periventricular deposition around the central vein and a "chicken wire" pattern of sinusoidal fibrosis.**

Table 17: Histologcal findings of nonalcoholic hepatosteatohepatitis (NASH)

Stage	**Histological findings**
Stage 1	**Perisinusoidal or periportal fibrosis only**
Stage 2	**Perisinusoidal and periportal fibrosis**
Stage 3	**Bridging**
Stage 4	**Cirrhosis**

Table 18: Sinusoidal fibrosis stages

METAVIR Score:

The fibrosis is graded on a 5-point scale from 0 to 4, The activity, which is the amount of inflammation specifically, the intensity of necro-inflammatory lesions), is graded on a 4-point scale from A0-A3.

Fibrosis score:	**Activity score:**
F0 = no fibrosis	**A0 = no activity**
F1 = portal fibrosis without septa	**A1 = mild activity**
F2 = portal fibrosis with few septa	**A2 = moderate activity**
F3 = numerous septa without cirrhosis	**A3 = severe activity**
F4 = cirrhosis	

Scores for to identify more severe cases of acute alcoholic liver disease in order to determine if treatment with corticosteroids is indicated:

- **Maddrey Discriminant Function score (DF)**
  DF= [4.6(prothrombin time-control) $_{sec}$] + bilirubin $_{mg/Ml}$
- **MELD score:**
  MELD = 3.8 X log (e)(bilirubin mg/dL) + 11.2x log(e)(INR)+ 9.6log(e) (creatinine mg/dL)
  A MELD of 21 portends a similar prognosis as A Maddrey Discriminant Function score of 32.
  If Maddrey score ≥ 32 or MELD score ≥18-21→ prednisolon 32mg/dayx4weeks, then 4 week taper, but those with creatinine > 2.3m/dL or GI bleed do not benefit.

For NASH we can use a formula ALD/NAFLD index (ANI index) may be useful to differentiate it from ALD.

ANI score= - 58.5+O.637 (MCV) + 3.91 (AST/ALT)- 0.406(BMI)+ 6.35 for male gender

- **ANI>0 favors ALD**
- **ANI<0 favors NAFLD**

- **Homeostasis model index (HOMA) can be used to estimate the presence of insulin resistance**

$$\frac{\text{Fasting insulin (mIU/mL)} \times \text{fasting glucose (mmol/L)}}{22.5}$$

if HOMA >2.5 indicates insulin resistance

(convert glucose from mg/dL to mmol/L multiplying by 0.0555)

NAS:The NAS score was developed as a histologic scoring system for use in clinical trials to assess for improvement in histologic features of NASH of paired biopsy specimens before and after treatment intervention.

<u>NAS score</u> = unweighted sum of:

Steatosis (0-3: <5%, 5-33%, 33-66%, >66%)

Lobular inflammation (0-3: none, mild, moderate, severe)

Ballooning (0-2: none, few, many)

Metabolisyndrome definition (National Cholestrol Education Program Adult Treatment Panel III Guidelines). Three or more of the following criteria:

Abdominal obesity (waist circumference:men >102cm, women >88cm)

1- **Triglycerides ≥ 150mg/dL**
2- **Low HDL (men<40mg/dL, women<50mg/dL)**
3- **Hypertension (BP ≥ 130/85mmHg)**
4- **Fasting glucose ≥100mg/dL**

Note: lower waist circumference threshold for Asians: men >90cm, women >80cm

Disease severity of NASH

Grades	**Grade1:steatosis<33%**	**Occasional ballooning, mild lobular inflammation, non or mild portal inflammation.**
	Grade II: steatosis33-66%	**Zone 3 ballooning, mild lobular inflammation, mild to moderate portal inflammation.**
	Grade III: steatosis>66%	**Marked ballooning(predominantly zone 3), acute and chronic lobular inflammation, mild to moderate portal inflammation**
Stages	**Stage I**	**Zone 3 perivenular perisinosoidal/pericellular fibrosis.**
	Stage II	**Periportal fibrosis**
	Stage III	**Bridging fibrosis**
	Stage 1V	**Cirrhosis**

Table 19: Histological grading &staging of NASH is based on the Brunt classification criteria

ALF secondary to acetaminophen over dose	**ALF not associated with acetominophen**
pH<7.30 (irrespective of the grade of encephalopathy)	**INR>6.5 (PT>100SEC) (irrespective of the grade of encephalopathy)**
or	**or**
INR>6.5 (PT>100sec) and serum creatinine >3.4mg/dL (300µmol/L) in patients with grade 3or 4 encephalopathy	**any 3 of the following: 1-Age <10 and>40yr 2-Cause non-A, non-B hepatitis or idiosyncratic drug reaction. 3-Duration of jaundice before encephalopathy >7days 4-INR>3.5(PT>50sec) 5-Serum bilirubin>17.6mg/dL(>300µmol/L)**

Table 20: Assessment of prognosis in acute liver failure (King's College criteria) for Liver transplantation

1.	**One lesion ≤ 5cm**
2.	**Up to 3 lesions, all ≤ 3cm**
3.	**No vascular invasion**
4.	**No distant metastases**

Table 21: Milan Criteria for Liver Transplantation

Numerical score			
parameter	**1**	**2**	**3**
Bilirubin (mg/dL)	**<2.0**	**2.0-3.0**	**>3.0**
Albumin (mg/L)	**>3.5**	**2.8-3.5**	**<2.8**
Prothromin time(sec. increased)	**1-3**	**4-6**	**>6.0**
Ascites	**None**	**Mild**	**Moderated-sever**
Encephalopathy	**None**	**Slight/moderate**	**Moderate/sever**

Score: 5-6=child class A; 7-9=Child class B; >10-15= Child class C

Table 22: Modified Child-Turcotte-Pugh scoring system for cirrhosis

Grades	**Manifestations**
Subclinical (0)	**Abnormal psychometric tests but no obvious abnormalities in consciousness, personality, or behavior**
1	**Trivial lack of awareness, short attention span, reversed day-night sleep cycle**
2	**Lethargy, disorientation, personality change, inappropriate behavior**
3	**Somnolence to semi stupor, confusion, response to noxious stimuli preserved**
4	**Coma; no response to noxious stimuli**

Table 23: Grades of hepatic encephalopathy

category	Name of the drug	dose	Potency	Genetic barrier	Rate of resistance	Side effects
Nucleoside analogue	Lamivudine (LAM)	10mg/d	Potent	low	high	Safe
	Telbivudine(LdT)	600m/d	Potent	low	high	Can cause myopathy and peripheral neuropathy
	Entecavir (ETV)	0.5-1mg/d	Potent	High	Low	Safe
Nucleotide analogue	Adenofovir dipivoxil (ADV)	10mg/d	Less potent	High	low	Potentially nephrotoxic.
	Tenofovir (TDF)	300mg/d	Potent	High	low	Less nephrotoxic than Adenofovir. (rarely cause Fanconi syndrome and decrease in bone density).

Table 24: Nucleos(t)ide analogues

Despite their high antiviral potency (greater than that of interferon), these drugs are not able to eradicate HBV, but they can maintain the sustained suppression of replication. Advantages: potent; negligible adverse effects; oral administration; safe; and effective at all ages; suitable for cirrhotic and HIV-coinfected patients.

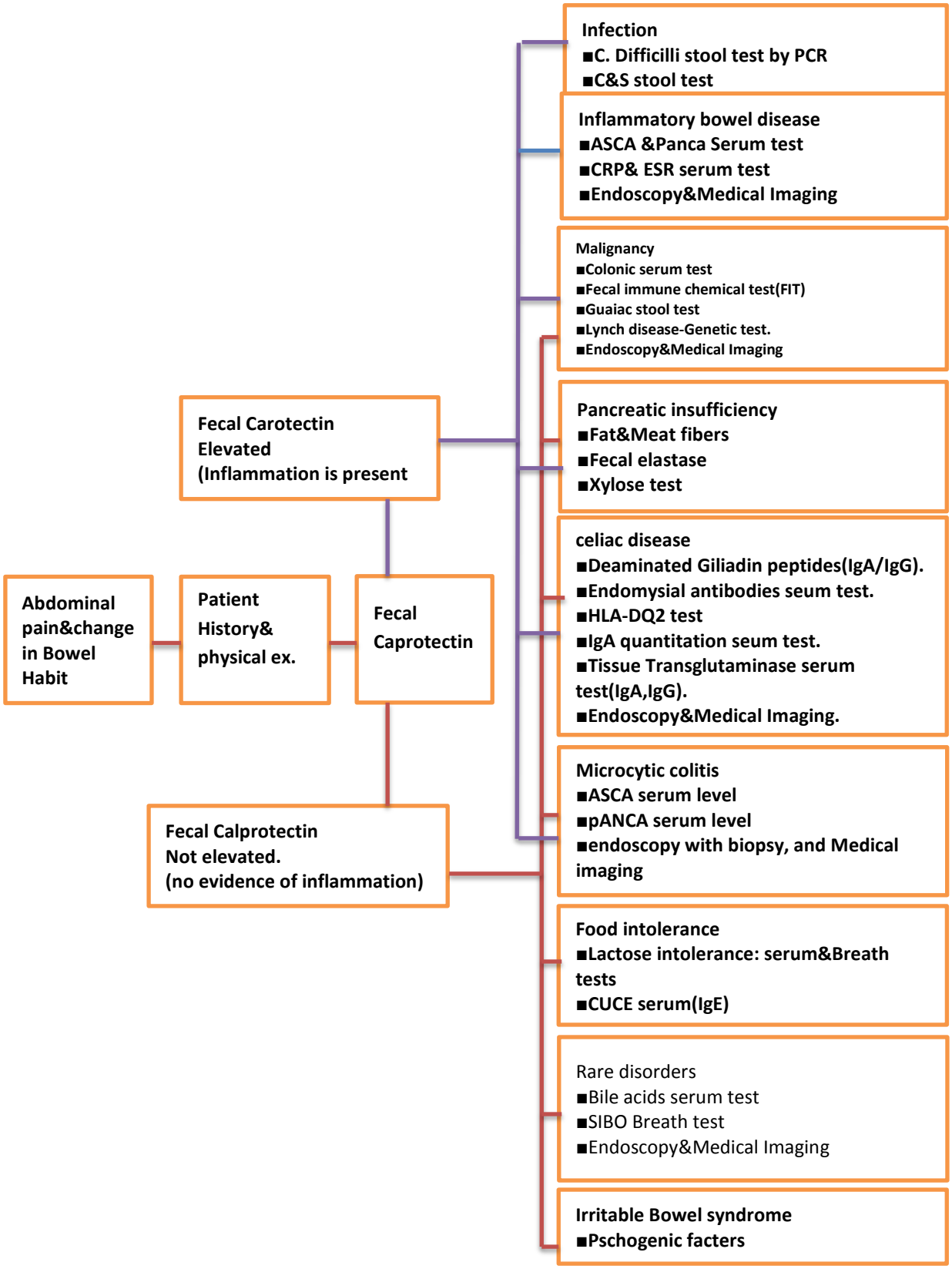

Figure 27: Diagnostic Aid for Gastrointestinal Disease

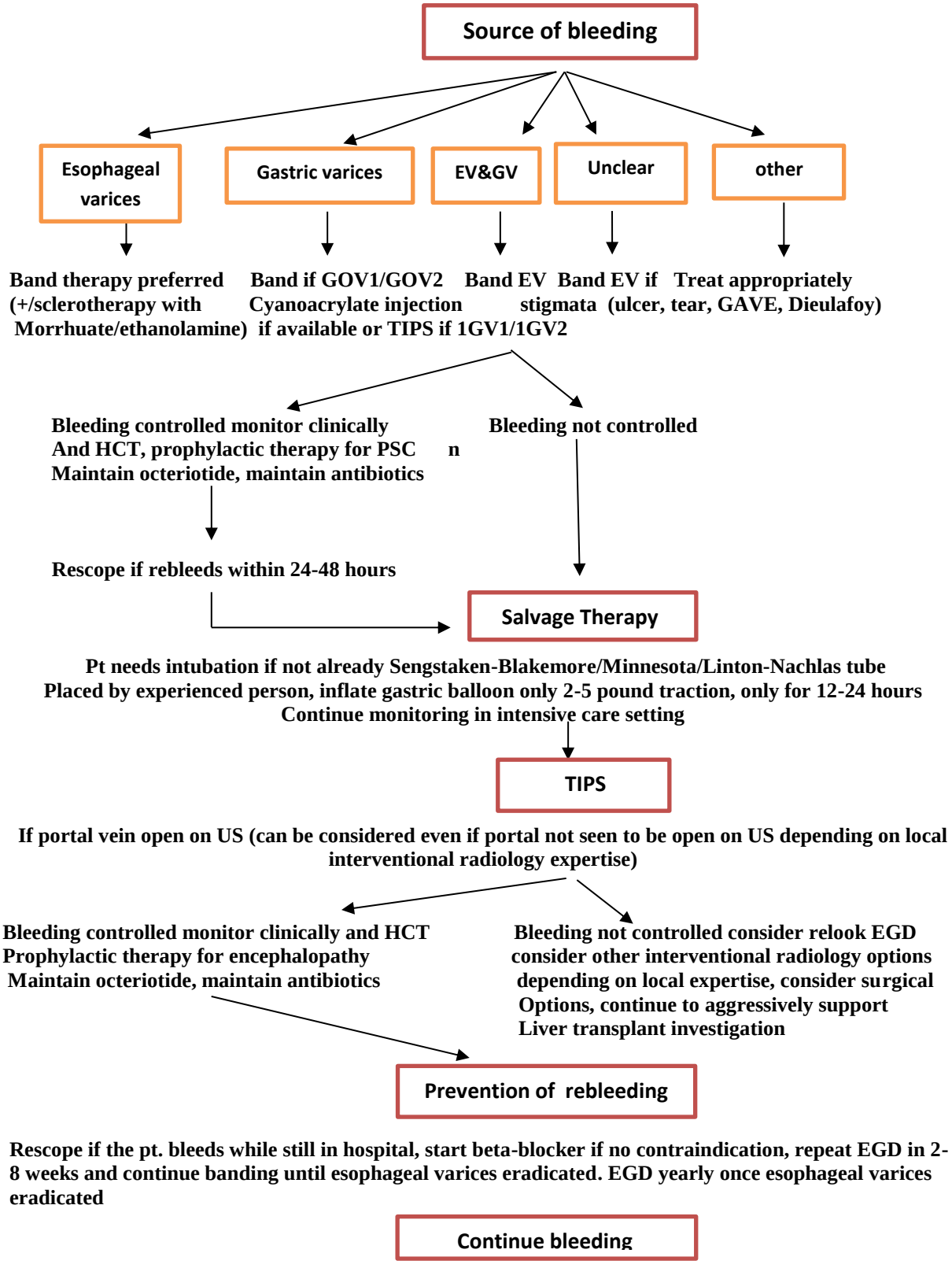

Figure 28: Source of GI bleeding

1.	**Coat the endoscope tip with silicone oil and flush oil through the instrument channel to minimize the risk of glue adherence**
2.	**Prime the injection needle catheter with either sterile water for enbucrilate injection or saline for ocrylate injection.**
3.	**Confirm that the initial injection with water or saline is free flowing into the varix and not forming a submucosal bleb.**
4.	**Inject the cyanoacrylate into the varix in aliquots 0.5-1 ml. If used undiluted, enducrilate must be rapidly injected over a few seconds to avoid premature glue solidification. Due to its longer polymerization rate, ocrylate must be used undiluted and slowly injected over 30-45 s.**
5.	**After the glue has been injected, flush out the dead space of the cathter with sterile water or saline**
6.	**Retract the needle from the varix while continuously flushing to keep the needle patent for possible repeat glue injection**
7.	**If there is no bleeding at the puncture site, palpate the varix with a plant tip cathter or closed forceps. If the varix still soft, additional glue injections are performed.**

Table 25 :Technical steps for cyanoacrylate injection (Hemostasis of acute gastric variceal bleeding)

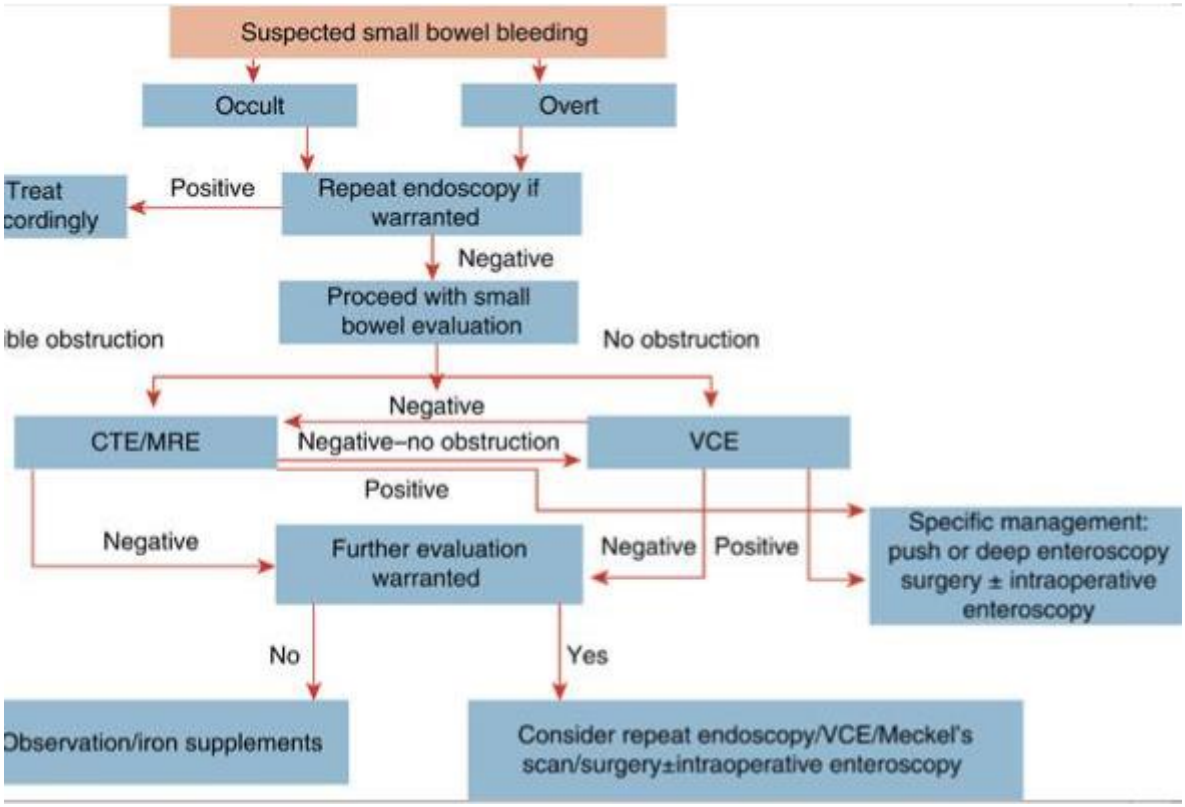

Figure 29: New ACG guidelines, Diagnosis and management of small bowel bleeding.

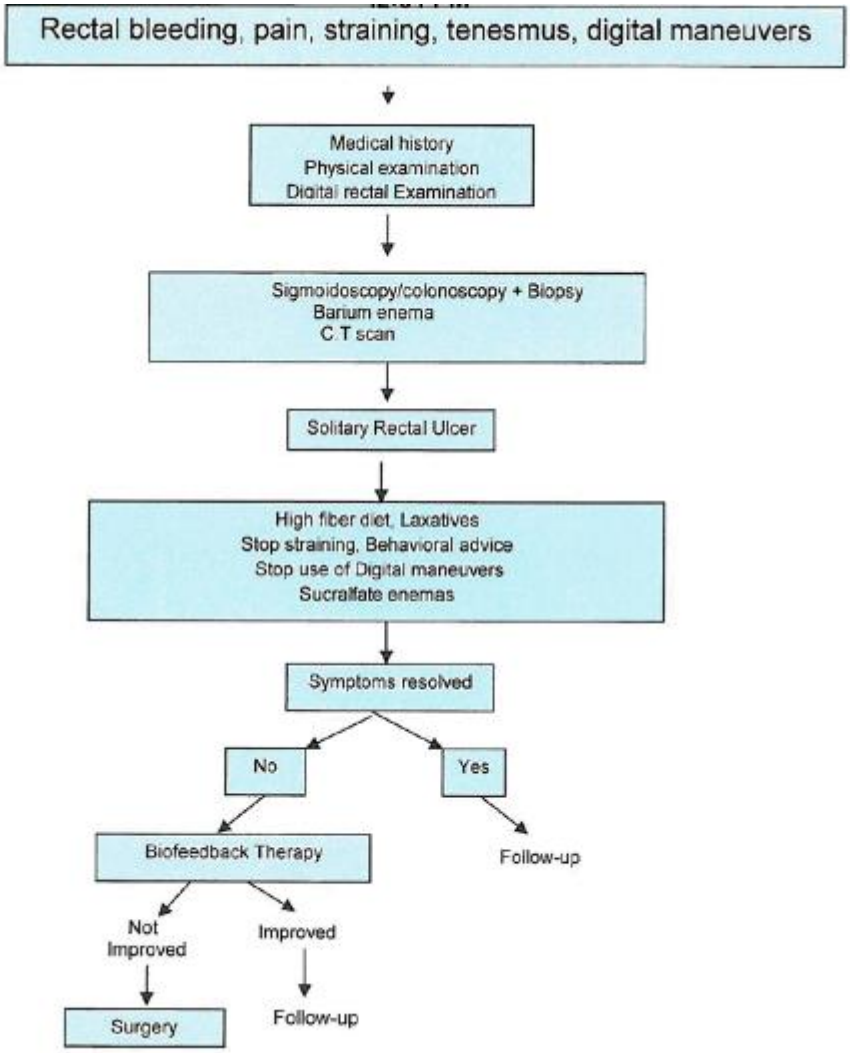

Figure 30: Solitary rectal ulcer management

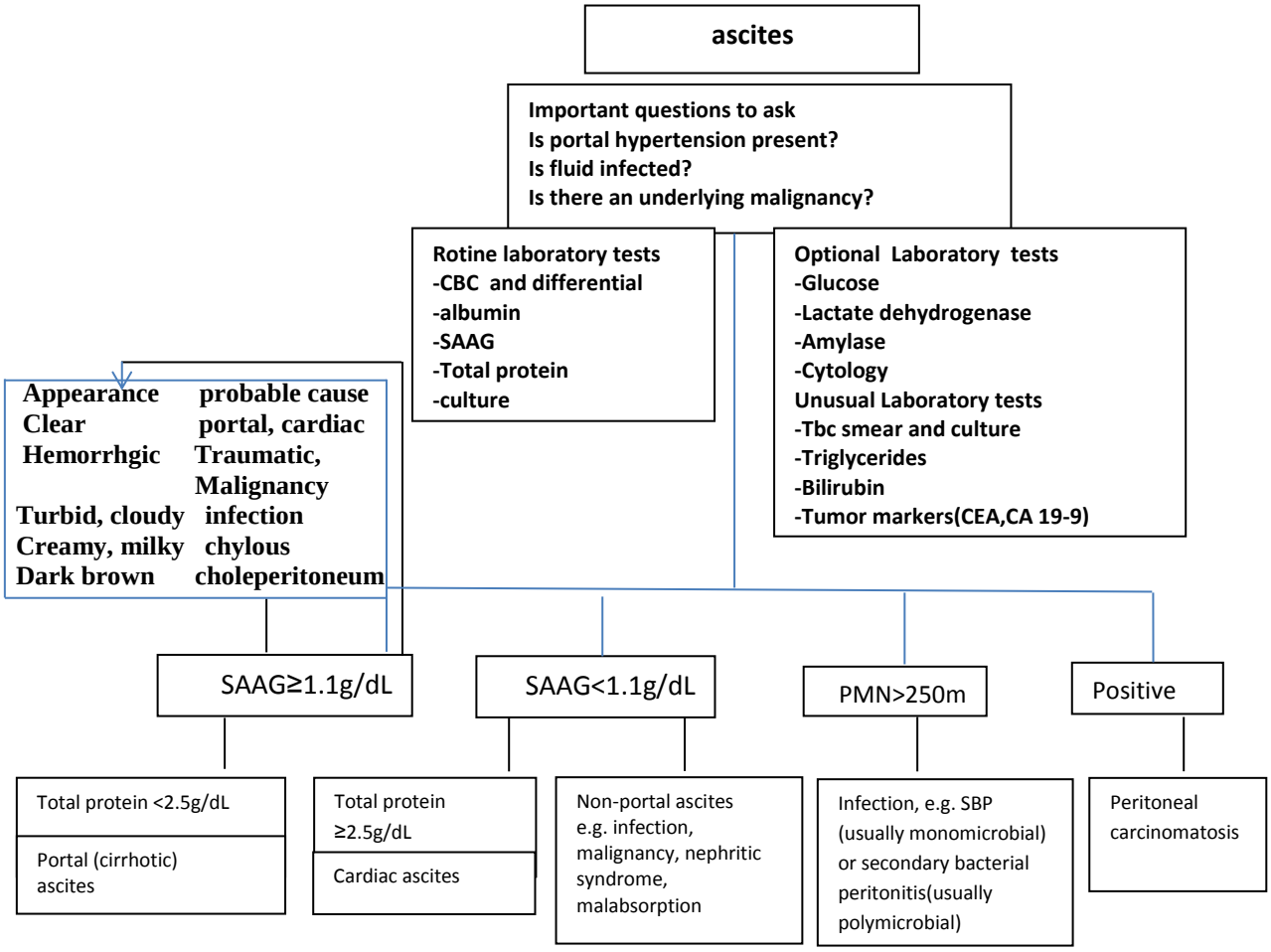

Figure 31: Algorithm for diagnostic approach to ascites

Note. Some patient with portal ascites have an SAAG <1.1g/dL , think it might be due to the infection 3.

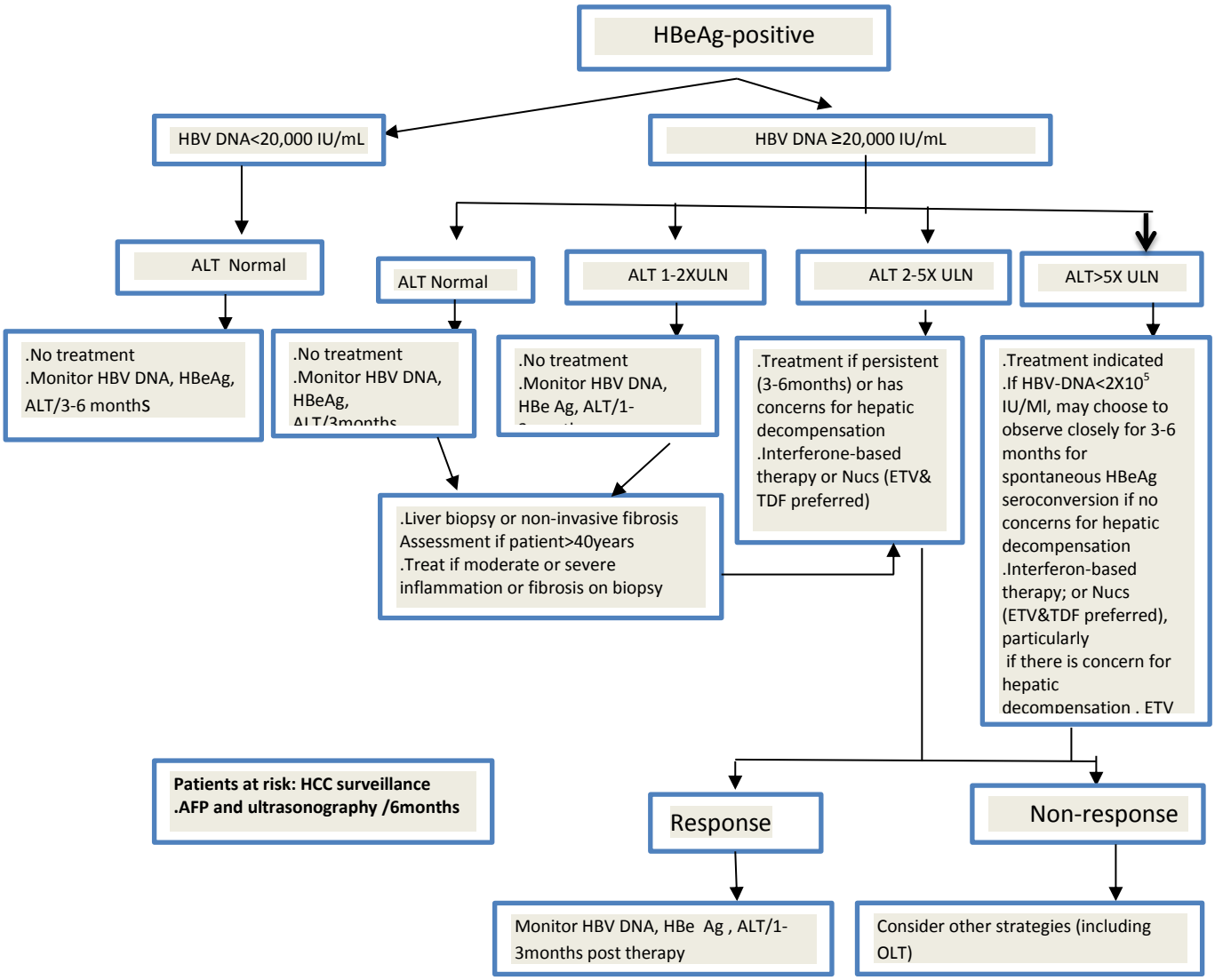

Figure 32: Algorithm for the management of HBeAg (positive) patients with chronic hepatitis B

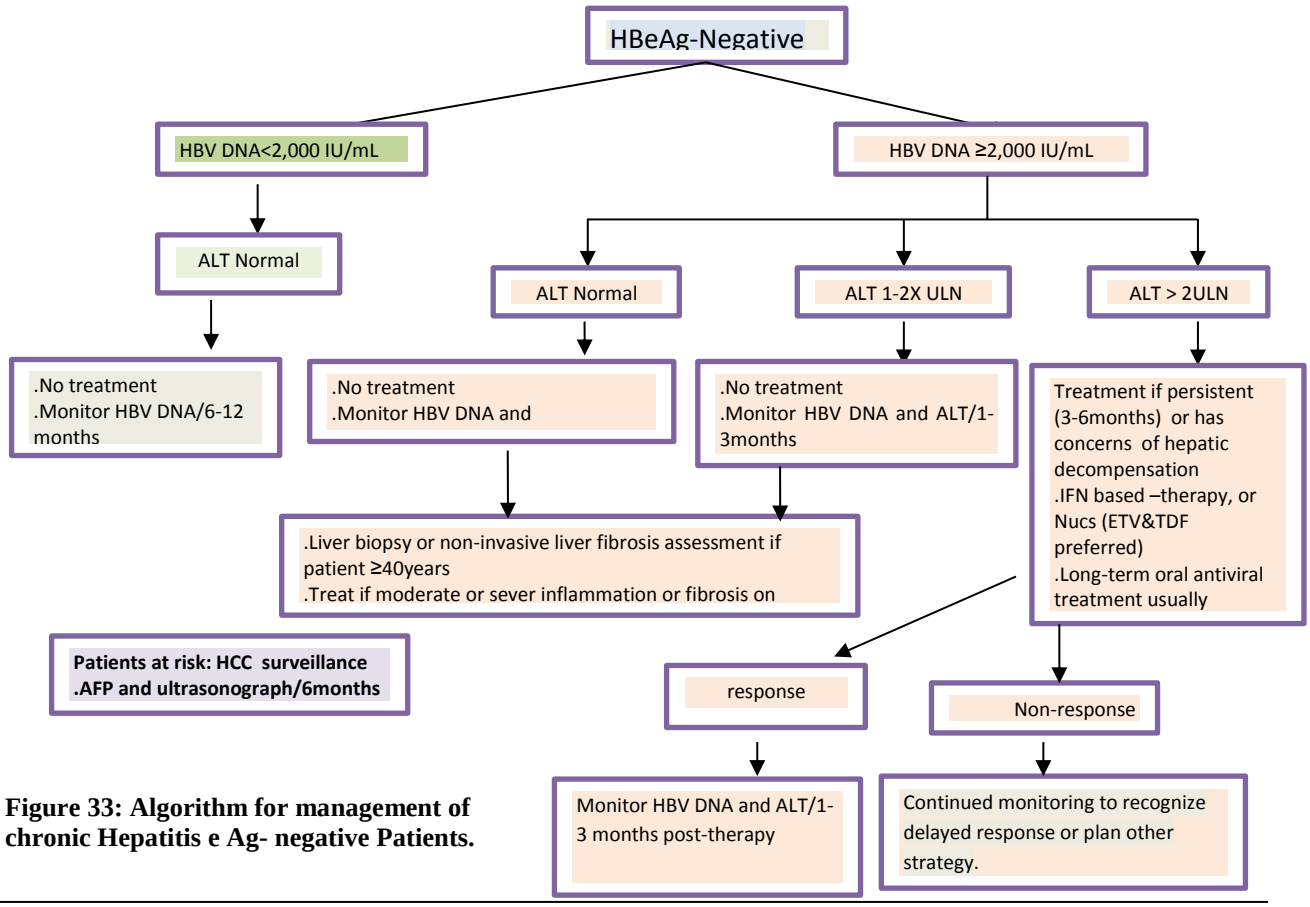

Figure 33: Algorithm for management of chronic Hepatitis e Ag- negative Patients.

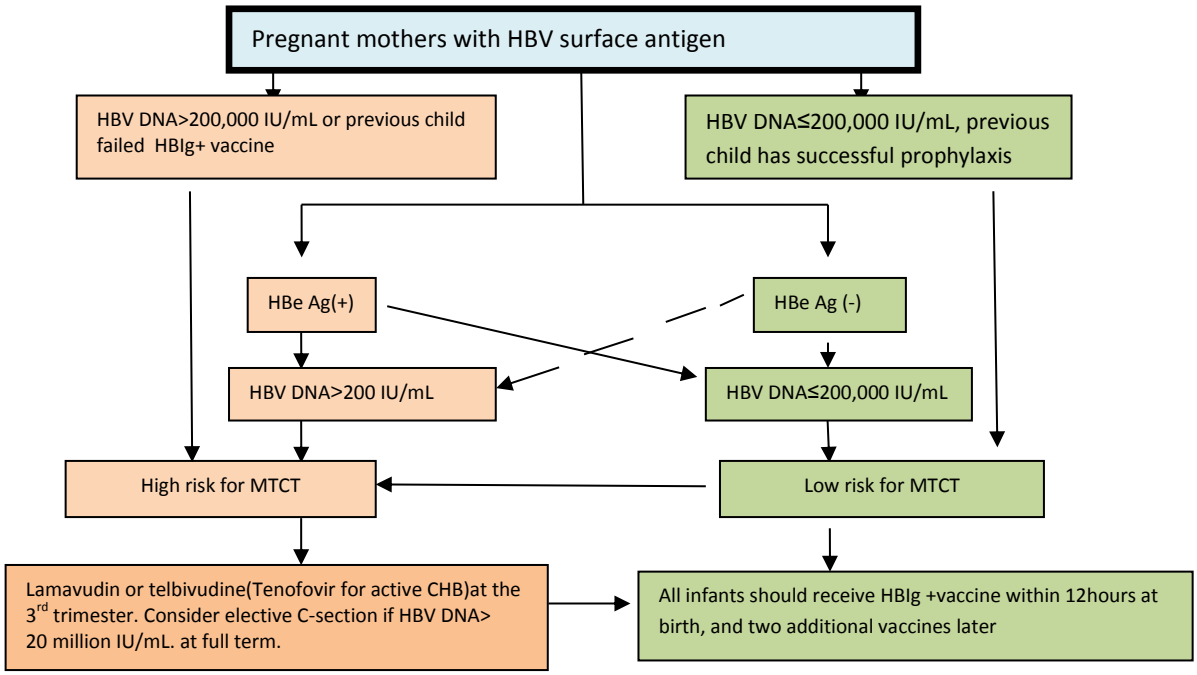

Figure 34: Algorithm for risk assessment and prevention of MTCT of HBV. Tenofovir is a category B medication for pregnancy and might be an option in preventing MTCT if the mother has chronic active hepatitis B and long-term treatment is indicated

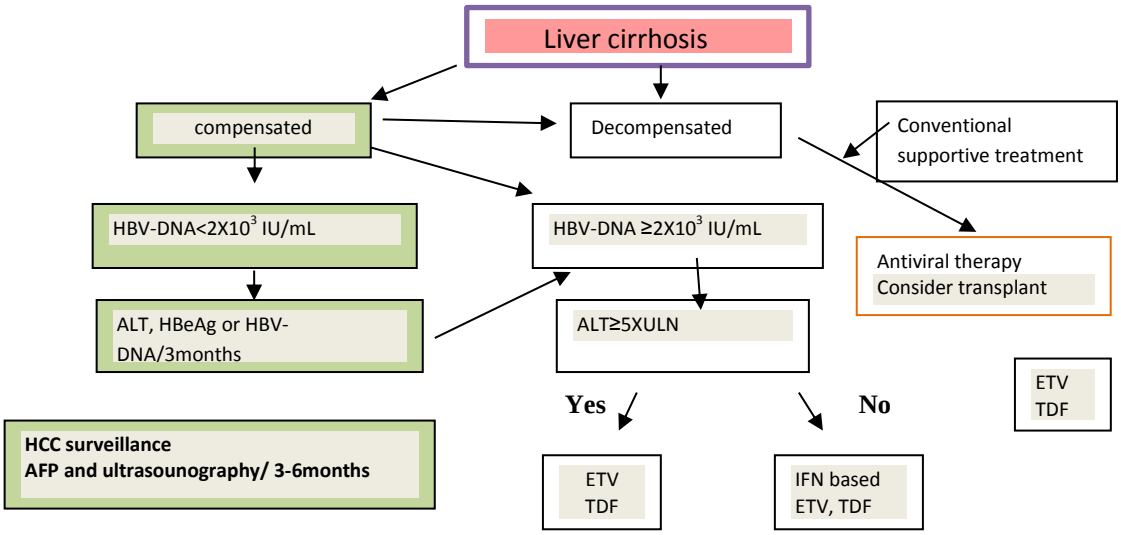

Figure 35: Algorithm for the management of chronic hepatitis B patients with liver cirrhosis

Recommendations

APRI (aspartate aminotransferase [AST]-to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g. FibroScan) or FibroTest be the preferred NITs in settings where they are available and cost is not a major constraint.

APRI = (AST/ULN) x 100) / platelet count (10^9/L)

FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)$^{1/2}$])

For APRI, ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken. For example, in a patient with an AST of 82 IU/L (where laboratory ULN for AST is 40 IU/L) a a platelet count of 90x10^9/L, the APRI would be: (82/40)x100/90 = 2 . 28 . This value is >2 and is consistent with the presence of cirrhosis.

HVPG measurement is done after overnight fasting, under conscious sedation, and vital sign monitoring (including heart rate, arterial blood pressure, digital oxygen saturation, and electrocardiogram) under local anesthesia and a septic condition, the time required in this procedure ranges from 10 to 20 minutes the rate of successful hepatic catheterization is 95%. Although HVPG is easy and simple technique, accurate measurements require specific training.

HVPG reflects the interaction between the hepatic vascular resistance and blood flow, and as such , is thought to closely indicate disease severity, it is a dynamic marker of disease progression, especially pre-cirrhotic stage

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Table 26: Clinical threshold values in common liver disease[9].

Value	Most likely
1.0	**If the ratio of urine sodium to potasium in a spot urine sample is greater than this value in cirrhotic pt.(i.e more urinary Na than K)then the pt. has a sufficient response to diuretic therapy and is likely to have >78mEq Na per day during afull 24-hour urine collection.**
1.1	**If the seum –ascites albumin gradient (SAAG) equals or exceeds this value, then portal hypertensive ascites is 97% likely.**
1.5	**If ALT:LDH ratio exceeds this value in the setting of sever transaminemia (eg, ALT and AST in the 1000+ range), then acute viral hepatitis is likely. If the ratio is lower than this, consider drug- induced, toxin-induced , or hypoximic induced liver injury.**
2	**If the AST : ALT ratio exceeds this value in the setting of biochemical hepatitis, and assuming the ALT is below 500 U/L, then alcoholic liver injury is likely. Of note, cirrhosis due to any cause can also have this ratio, but typically with lower transaminase levels than in alcoholic hepatitis.**
2X ULN	**If the ALP exceeds this upper limit of normal (ULN) threshold in the setting of a culprit medication (eg, erythromycin, estrogen, rifampin, amoxicillin, chrorpromazine) then drug-induced cholestasis is likely. Similarly, if the ALP : AST ratio exceeds 2 then this is a supportive criterion for canalicular (" bland")type cholestasis.**
2.5 mg/dL	**If the ascitic fluid total protein exceeds this level with a SAAG ≥ 1.1, then cardiac ascites,Budd-chiari syndrome,or myxedema, from hypothyroidism is in the differential diagnosis.**
3 cm	**Maximum allowable size for multifocal hepatocellular carcinoma (HCC) lesions in order to remain eligible for liver transplantation, assuming there are no more than 3 total lesions and no metastatic disease and no vascular invesion(Milan criterion see"5cm"threshold for an additional Milan criterion).**
3XULN	**If ALT is above this thresholdin the setting of acute pancreatitis, then the positive predictive value for a gall stone etiology is 95%.**
3.4mg/dL	**If the serum creatinine exceeds this level in the setting of acetaminophen-induced acute liver injury, then it portends a poor prognosis if INR >6.5 and there is grade 3 or 4 encephalopathy (per King's College criteria)**
3.9 mcg/L	**An AFP of 3.9 mcg/L on day 1 after peak ALT can be used to predict survival in acetaminophen-induced liver failure with a sensitivity of 100%, a specificity of 74%, a positive predictive value of 45%, and a negative predictive value of 100%.**
4 weeks	**Undetectable hepatitis C virus(HCV) RNA at this treatment milestone indicates a rapid virological response (RVR). The likelihood of treatment success with sustained virological response (SVR) is 90% when an RVR is acheived.**
5	**If the ratio of AST : ALP exceeds this threshold in the setting of a culprit medication, then it suggests a hepatocellular form of drug-induced liver injury.**

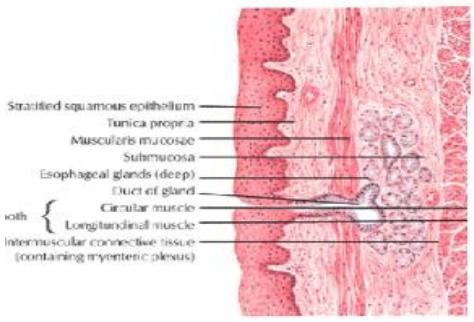
5 cm	**Maximum allowable size for a solitary HCC lesion in order to remain eligible for liver transplantation, provided that there is no vascular invasion and no metastatic disease (Milan criterion)**
5%	**Brain uptake of technetium macroaggregated albumin(TcMAA) exceeding this amount indicates intrapulmonary shunting and supports a diagnosis of hepato-pulmonary diaiagnosis of hepatopulmonary syndrome (HPS) assuming hypoximia (PaO_2 <70 mmHg) and an A-a gradient >20 mmHg.**
5xULN	**If the AST exceeds this threshold in autoimmune hepatitis(AIH), and the gamma glbulin concurrently exceeds >2x the ULN, then consider starting medical therapy. Of course, there are other indications to begin treatment to AIH- see other thresholds later in this list.**
6	**Minimum possible Model for End-Stage Liver Disease (MELD) score.**
6 months	**If a patient with resetable HCC is unlikely to receive an orthotopicliver transplantation (OLT) for at least this amount of time, then initiation of locoregional bridge therapy with radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) is a reasonable while awaiting OLT.**
6.5	**If INR exceeds this level in the setting of acetoaminophen-induced acute liver failure in conjunction with creatinine >3.4 and grade 3 or 4 encephalopathy, then it portends a poor prognosis (per King' Cllege criteria).**
6 to 12 cm	**Normal liver span by percussion.**
7.3	**If arterial pH falls below this value after fluid resuscitation in the setting of acetaminophen- induced acute liver failure, then it portends a poor prognosis (per King's Colleg Criteria).**
7.5 g	**If more than this amount of acetaminophen is consumed at once, then acetaminophen can be hepatotoxic even to a patient with out pre-existing liver disease.**
10 mmol/L	**The goal of diuretic therapy is to induce natriuresis, defined by a spot urine sodium exceeding this threshold.**
10 cm	**If an echinococcal liver cyst exceeds this size, then it likely requires surgery for difinitive therapy due to high risk of rapture.**
10x ULN	**If the AST exceeds this threshold in AIH, then consider starting medical therapy regardless of the gammaglobulin level.**
12 g	**Quantity of alcohol in a standard alcohol drink in the united states.**
12 mmHg	**If the hepatic venous pressure gradient (HVPG) exceeds this value, then variceal formation is enhanced. Goal of beta-blocker therapy is to reduce pressure to beneath this threshold .**
12 weeks	**A 2-log drop or more in HCV RNA at this treatment milestone indicates an early virologica response or EVR. When an EVR is achieved, the likelihood of achieving an EVR is 66% in genotype 1 HCV.**
13 to15mg/ kg/day	**Target range for therapeutic dosing of usodeoxycholic accid for management of primary bilaiary cirrhosis (PBC) and intrahepatic cholestasis of pregnancy(ICP).**
15	**Usual minimal MELD listing score for liver transplantation.**
15mmHg	**Pulmonary capillary wedge pressure must be below this threshold in order to diagnose portopulmonary hypertension, assuming the meam pulmonary artery pressure (MPAP) is above 25mmHg and pulmonary vascular resistance(PVR) is above 240 dynes/s/cm^{-5}.**

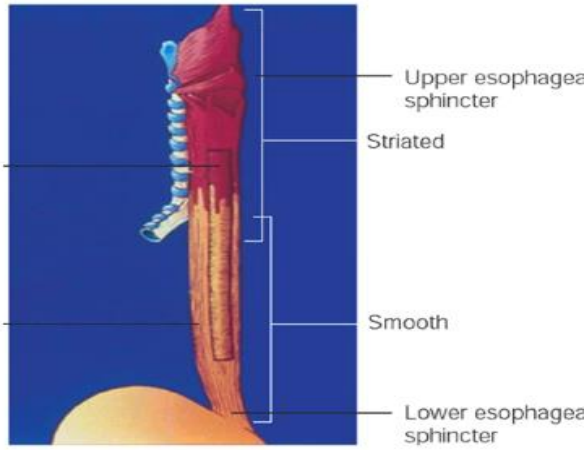
20 mg/dL	**Ceruloplasmin levels below this value are sensitive (but not specific) for wilson disease.**
20mmHg	**A-a gradient must exceed this threshold in order to diagnose HPS assuming there is hypoximia with PaO_2 >70 mmHg.**
20mmHg	**Goal of treatment in acute liver failure complicated by elevated intracrenial pressure is to drop intracrenial pressure to below this threshold.**
22	**Automated MELD score initially assigned by the United Network of Organ Sharing (UNOS) for a patient with HCC that fits Milan criteria, regardless of other MELD parameters.**
25	**Body mass index (BMI) at or above this threshold defines "over weight"**
25mmHg	**MPAP must be above this threshold in order to diagnose portopulmonary hypertension, assuming the PVP is above 240dynes/s/cm^{-5} and pulmonary capillary wedge pressure is less than 15 mmHg.**
30	**BMI at or above this threshold defines "obesity".**
32	**If the Maddrey discriminant function score (4.6 x Δ prothrombin time + total bilirubin) is above this value in acute alcoholic hepatitis, then consider starting steriod or pentoxiphylline.**
34 weeks	**Weeks of gestation at which an HbeAg-positive mother with elevated hepatitis B virus (HBV) DNA level should begin oral anti HBV therapy to minimize vertical transmission of HBV to the new born.**
35mmHg	**Maximum MPAP often considered acceptable for liver transplantation in the setting of portopulmonary hypertension.**
40	**BMI at or above this threshold defines "morbid obesity".**
40	**Maimum possible MELD score.**
40µmol/L	**When the seum concentration of bile acids exceed this value in pregnancy, the risk of developing complications from ICP increases significantly.**
40%	**Brain uptake of TcMAA exceeding this amount is a poor prognostic indicator in HPS indicating a high level of shunting and ia a contra indication to liver transplantation.**
50	**Goal in hereditary hemochromatosis is to drive ferittin below this level.**
50mmHg	**PaO_2 below this threshold is a poor prognotic indicator in HPS and a contraindication to liver transplantation.**
50 to 60 mmHg	**Goal in acute liver failure is to keep cerebral perfusion pressure (CPP) above this threshold (CPP= mean arterial pressure- intracrenial pressure)**
70 mmHg	**PaO_2 must fall below this threshold in order to diagnose HPS, assuming the A-a gradient is above 20 mmHg.**
78 mEq/l	**Goal of diuretic therapy in cirrhotic ascites to achieve at least this amount of sodium excretion over a 24-hour urine collection. Because 24-hour collection is difficult to obtain, most use a spot urine to estimate what a 24-hour collection might have yielded. A urine sodium : potasium ratio > 1.0 predicts ≥78 mEq/L of sodium excretion in 24-hour collection.**
88	**If pletelet is below this value in cirrhosis, then the risk of underlying varices increases substantially.**
100 mcg / 24 hours	**Urinary copper excretion above this level is found in almost all symptomatic patients with wilson disease.**
240 dynes / s/cm^{-5}	**PVP must exceed this threshold in order to diagnose portopulmonary hypertension, assuming the pulmonary capillary wedge pressure is below 15 mmHg and the MPAP is >25mmHg.**

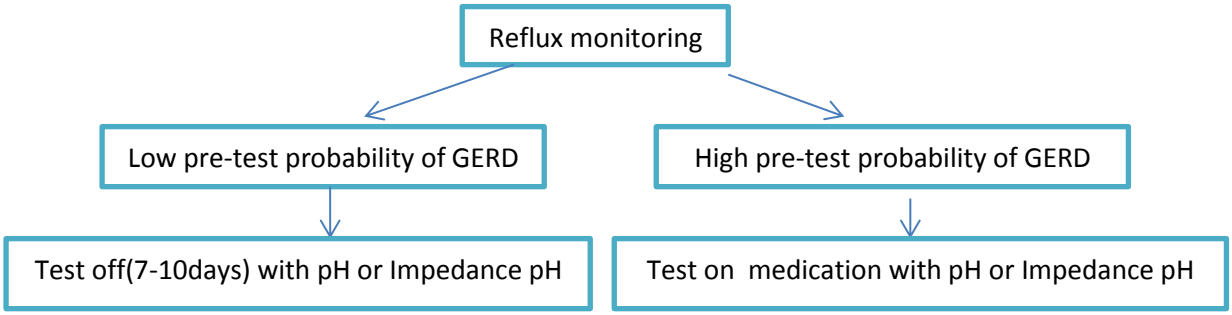
250	**If the PMN count in ascites exceeds this value in cirrhosis, then the patient likely has spontaneous bacterial peritonitis.**
250 mcg/g	**Hepatic copper concentration above this level occurs in Wilson disease.**
500mL	**Physiologically, this is the maximum amount of ascites that can be absorbed from peritoneum in 1 day.**
1000ng/mL	**A patient under 40 years old with hemochromatosis who has a ferritin value less than 1000 ng/mL is unlikely to have underlying cirrhosis, and liver biopsy can be often be avoided.**
5700	**6-methylmercaptopurine levels above 5700 are associated with increase risk of hepatotoxicity when using azothioprine or 6-mercaptopurine.**

Endoscope unit design

Figure 36: Design of GI endoscopy unit: GI Endoscopy is a specialty that requires unique working environment. This includes developing infrastructure and space planning with special attention to fresh water needs, ventilation, forced air capability, vacuum capabilities, power source, waste disposal and infection control procedure room with large door access, size of the room 220 square feet or 20m for regular, 300 square feet or 28m for complex procedures, Flouroscopy based procedure will need up to 400 square feet of space to accomodate need for anesthesia storage and other rolling equipment.preparation and recovery room usually 60-80 square feet(generally 2 recovery pays are needed per endoscopy room contain monitored beds, oxygen, suction,in addition to nurse station.







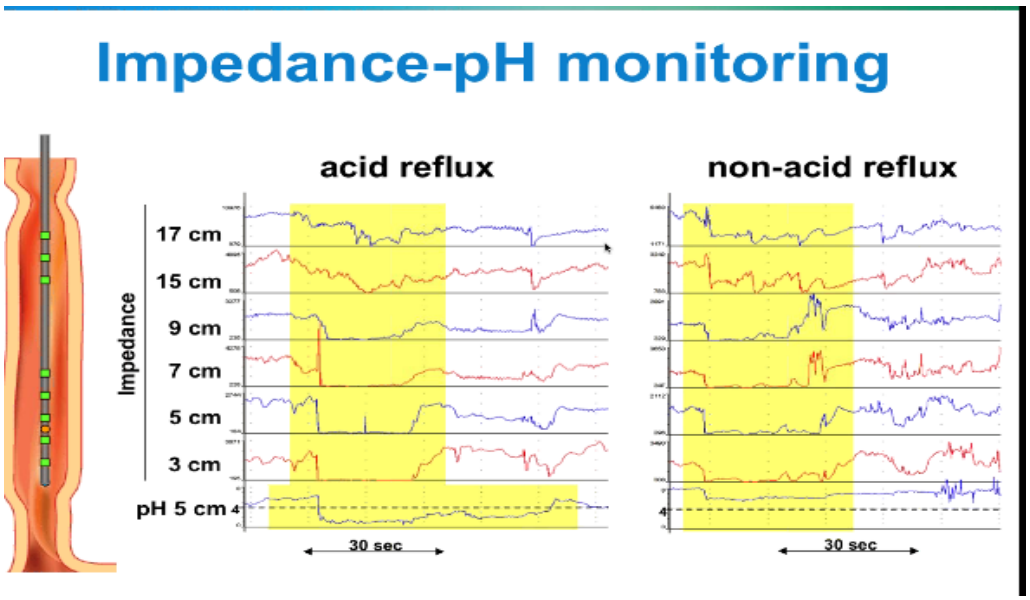
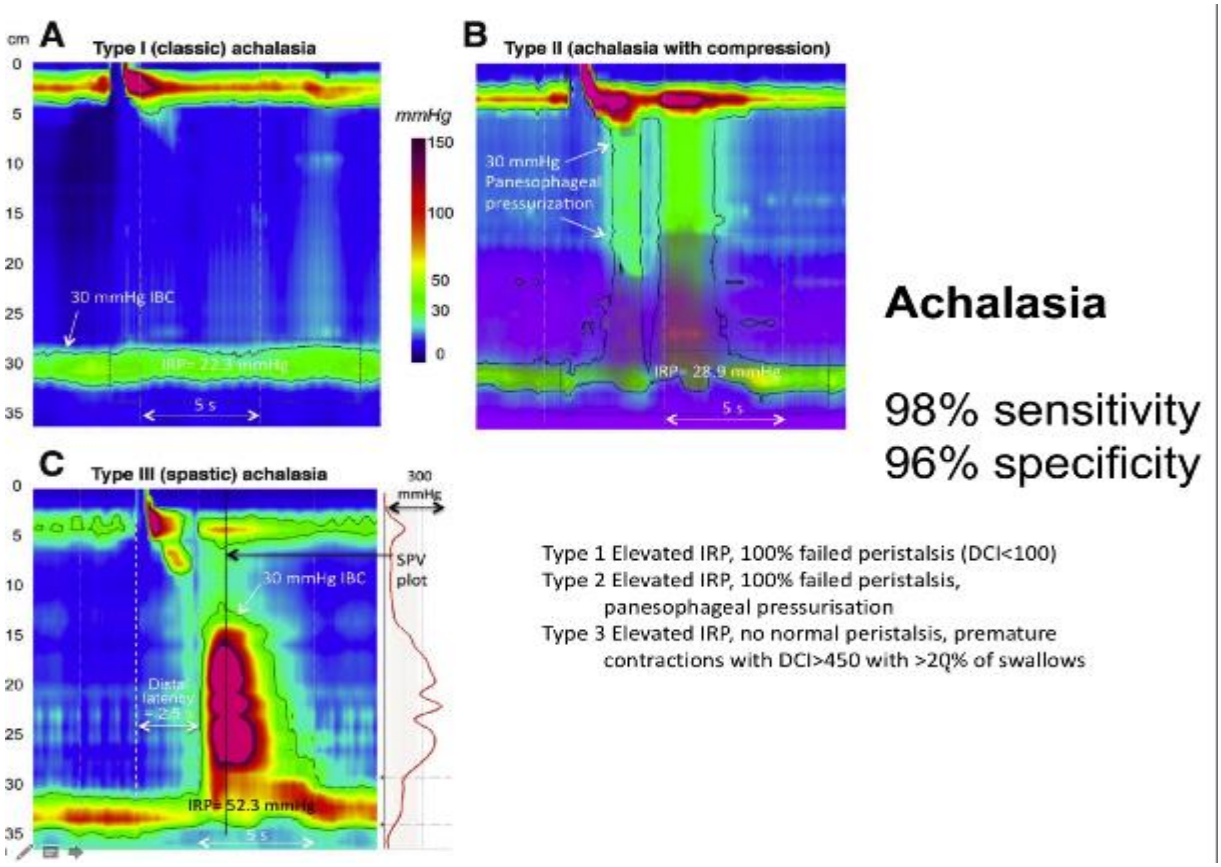


Figure 37: Impedance pH-Impedance monitoring



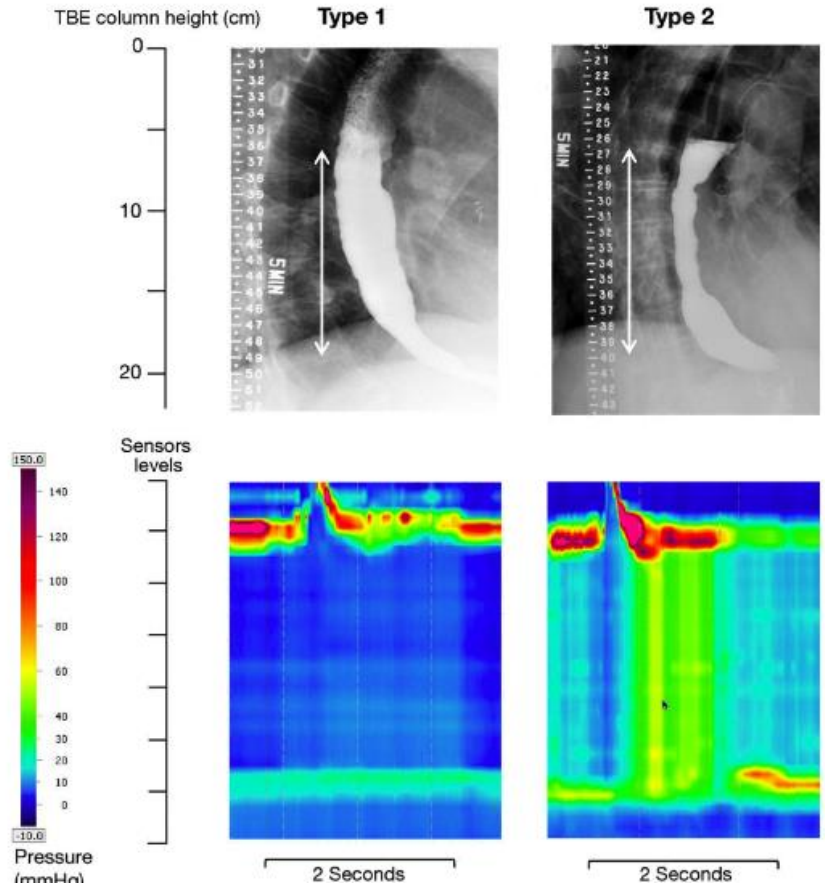


Figure 38: Esophageal High Resolution Manometry

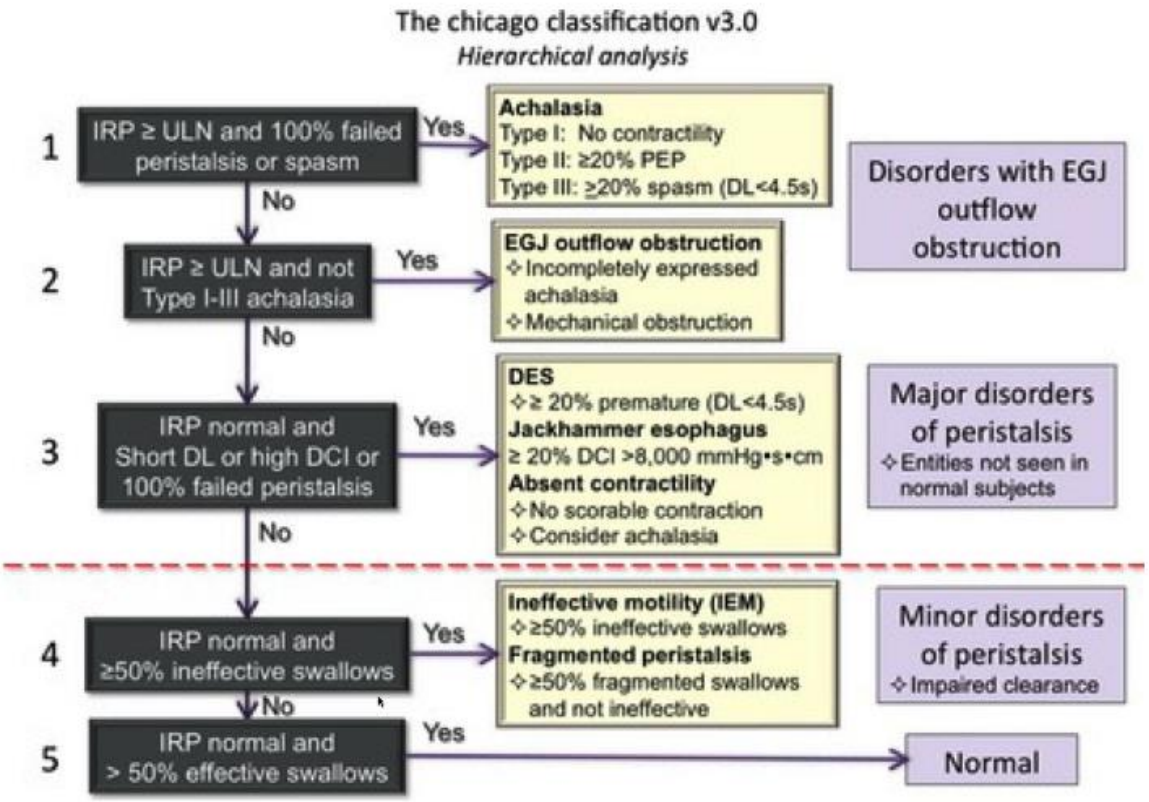
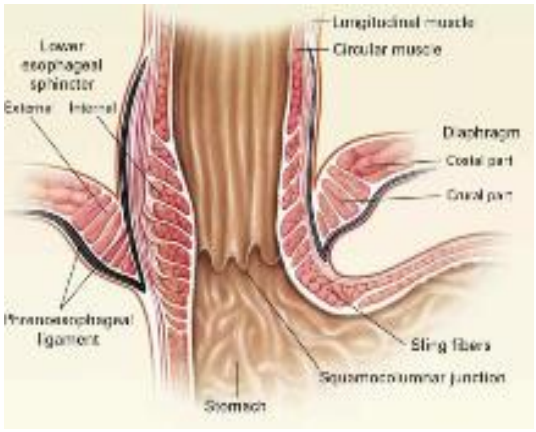


Figure 39: The chicago classification v3.0 based on Esophageal HRM



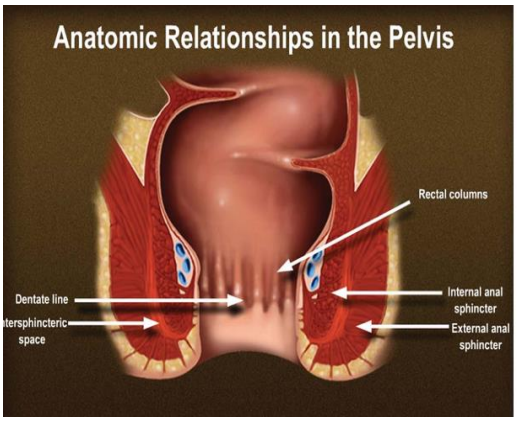


Figure 40: Anal sphincter anatomy. The IAS is formed from the continuation of the circular smooth muscle layer of the muscularis propria of the rectum. The EAS is formed from downward extension of the skeletal muscle from puborectalis muscle.

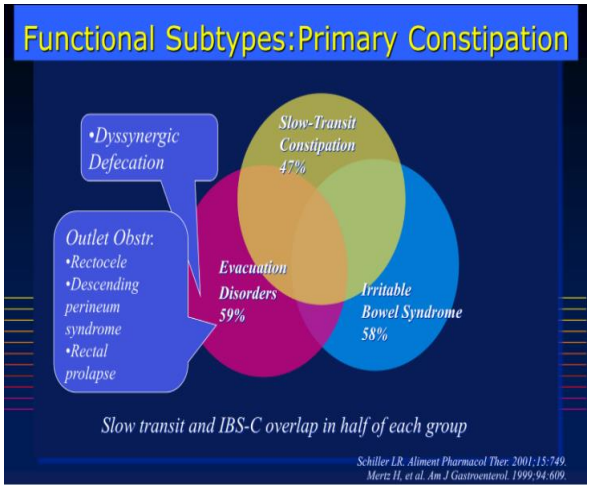


Figure 41: Functional Subtypes

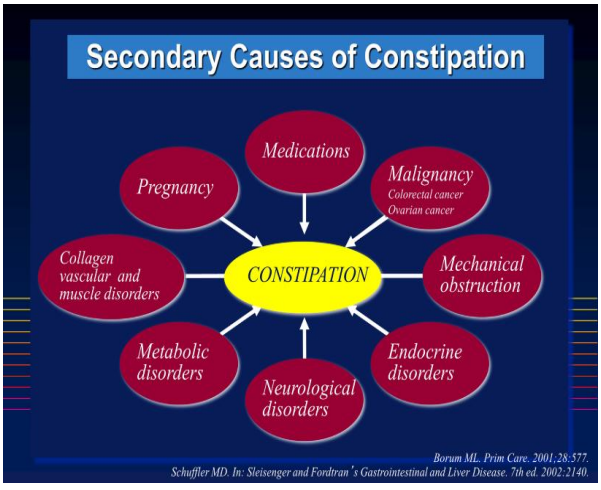


Figure 42: secodary causes of constipation

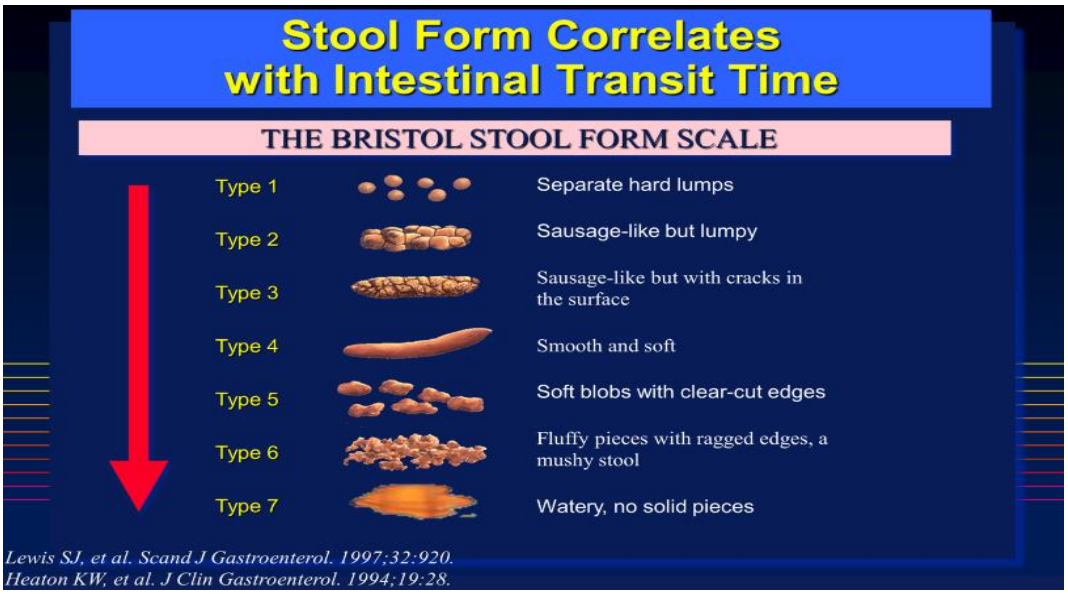


Figure 43: The Bristol Stool Form Scale

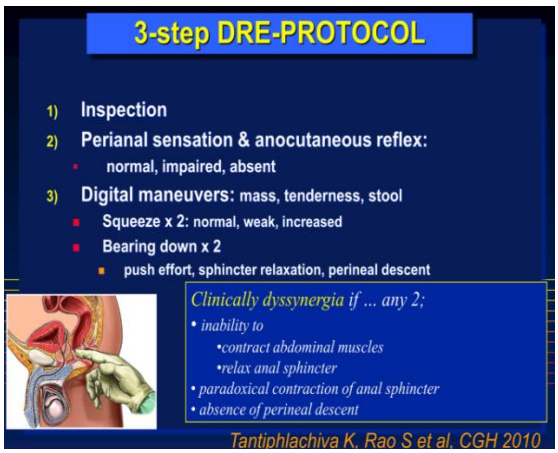


Figure 44: 3-DRE-protocol

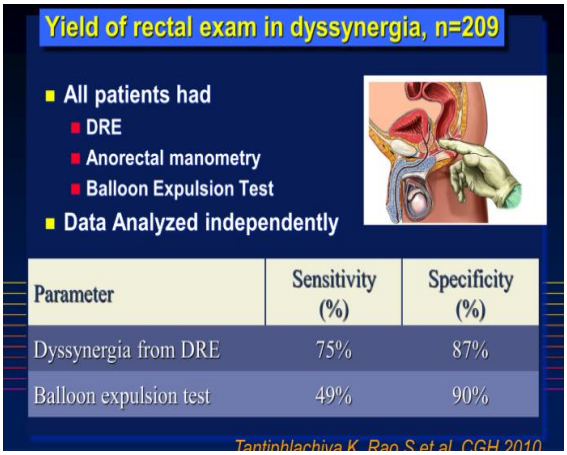


Figure 45: Yield of rectal examination

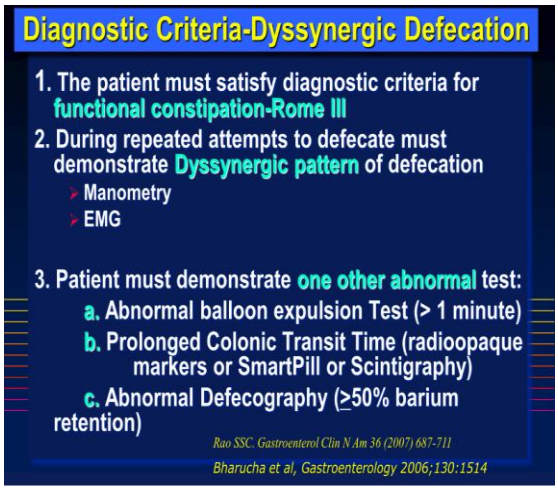


Figure 46: Diagnostic Criteria-Dyssynergic Defecation.

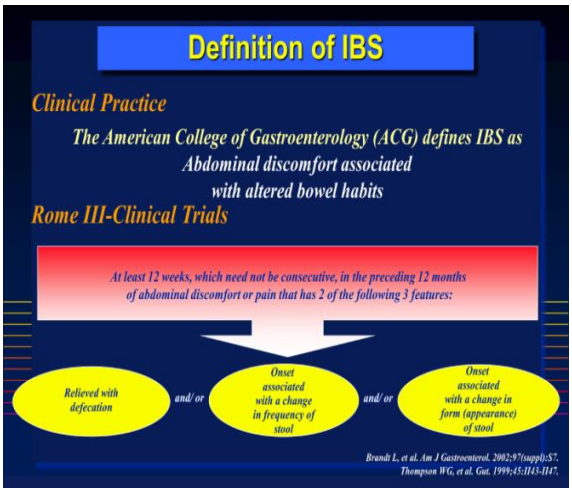


Figure 47: Definition of IBS

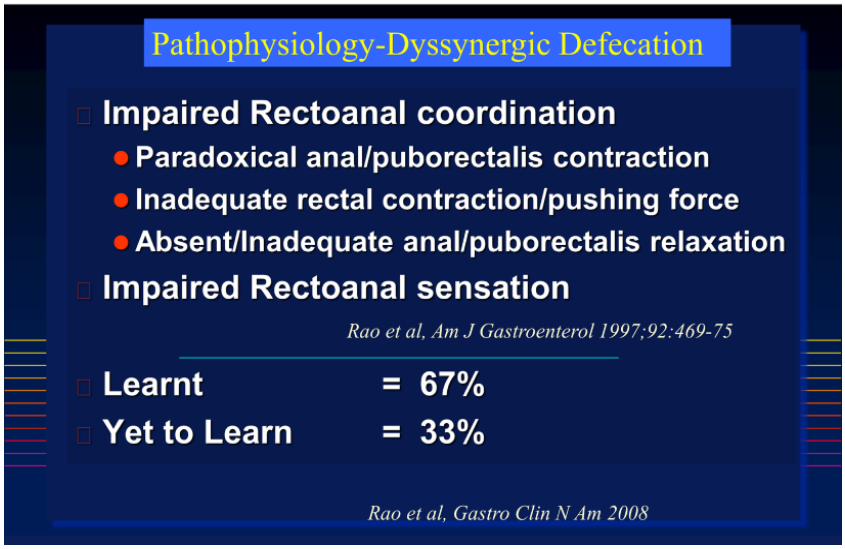
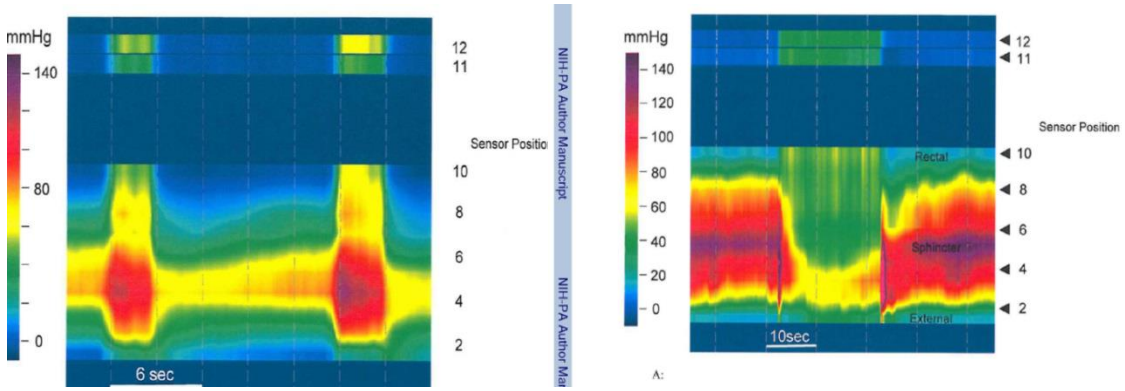


Figure 48: Pathophysiology-Dyssynergia Defecation



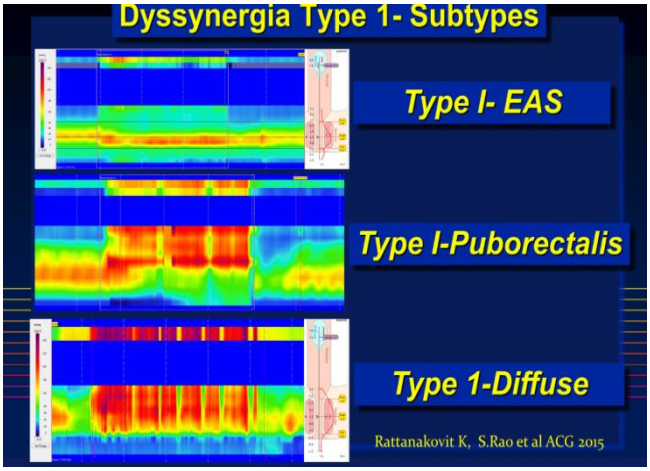


Figure 49: HRAM in Dyssynergia types

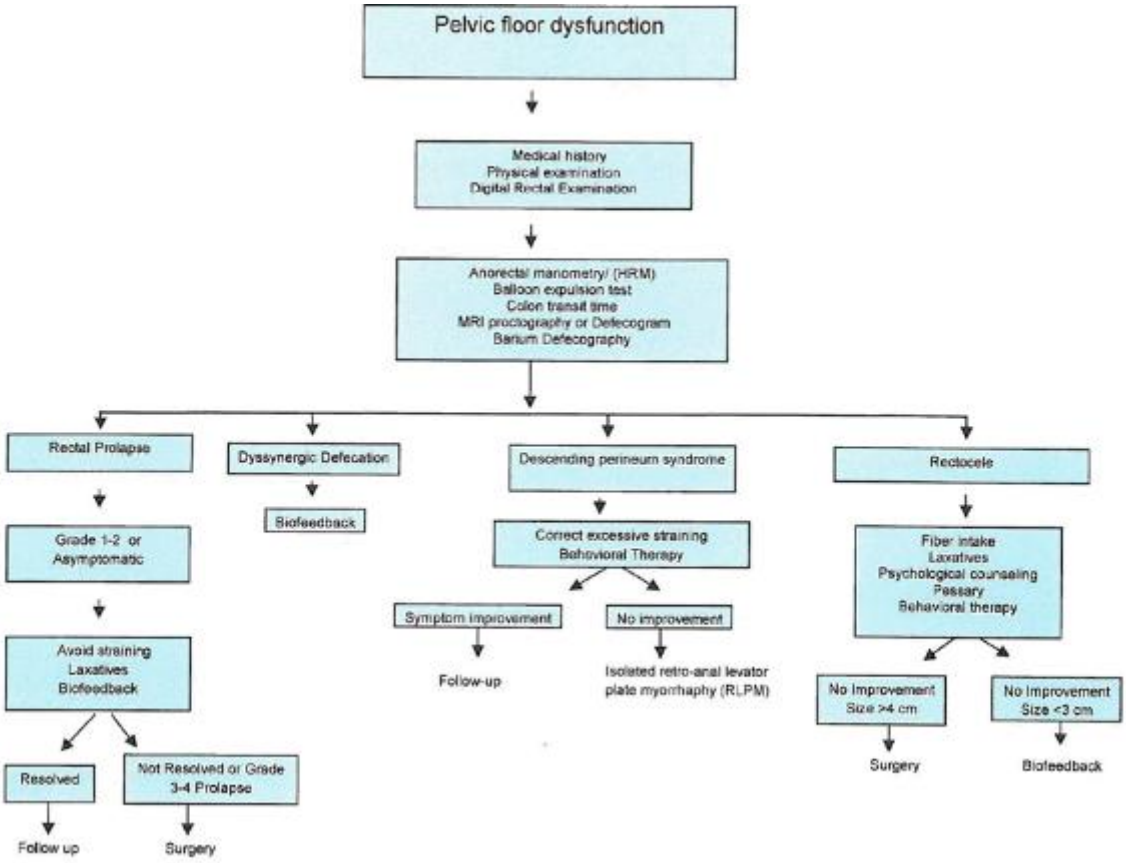


Figure 50: Algorithm for management of pelvic muscle dysfunction

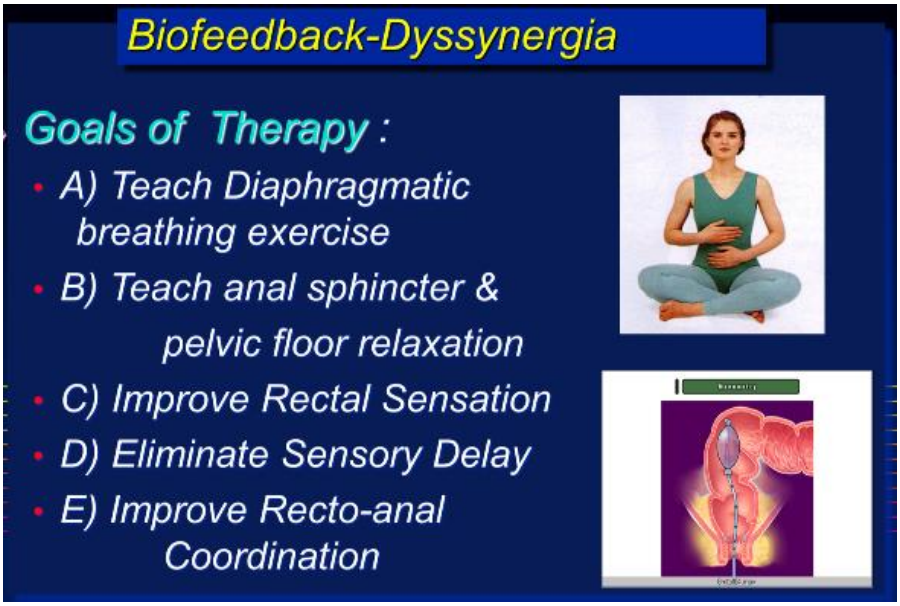


Figure 51: Biofeedback-Dyssynergia

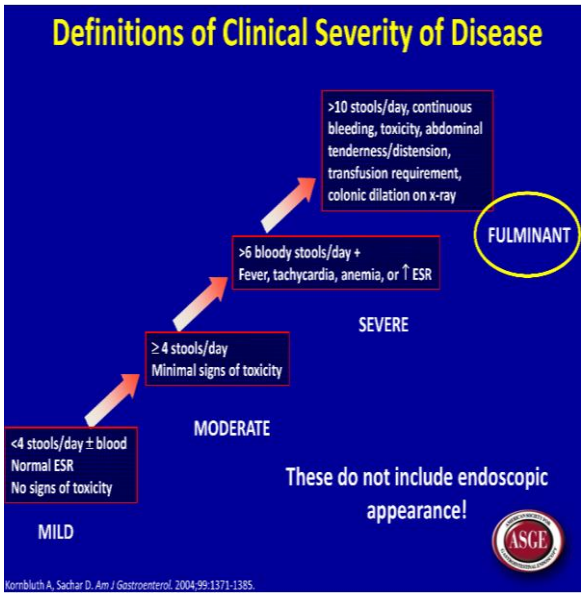


Figure 52: clinical severity of UC

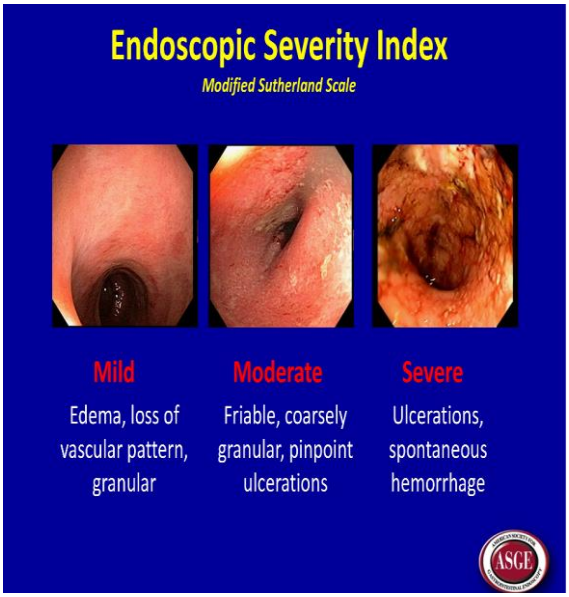


Figure 53: Endoscopic Severity Index in UC

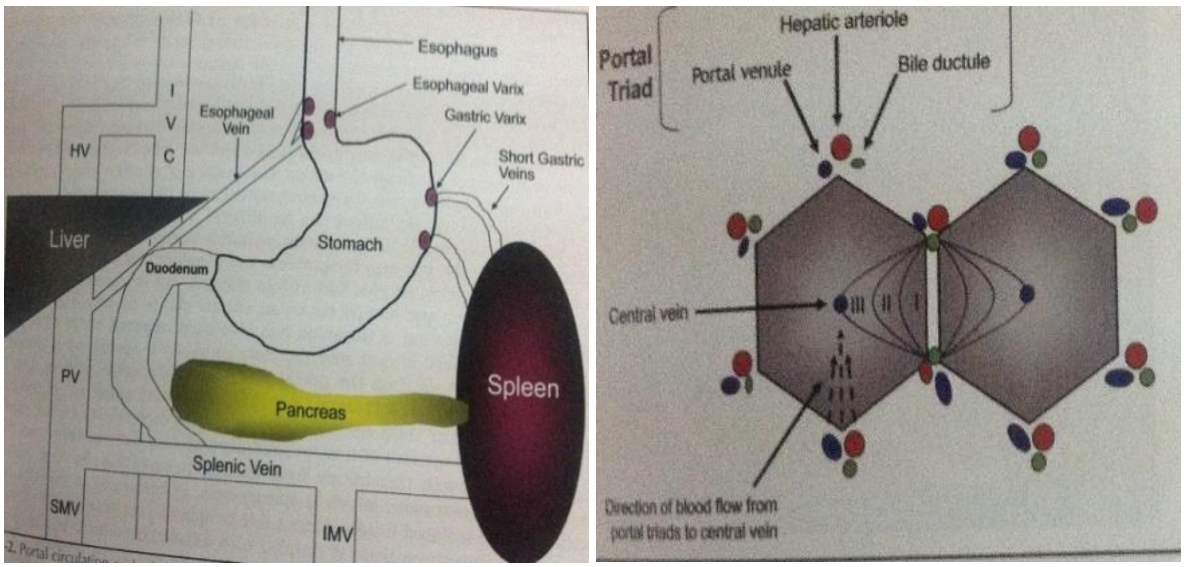


Figure 54: Portal circulation and related anatomy

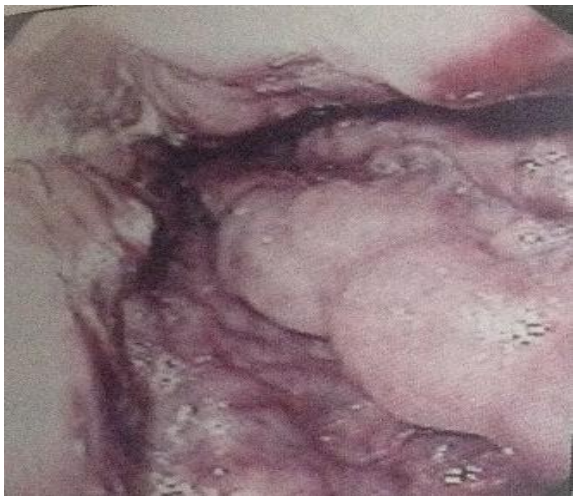


Figure 55: Esophageal varices found on upper endoscopy

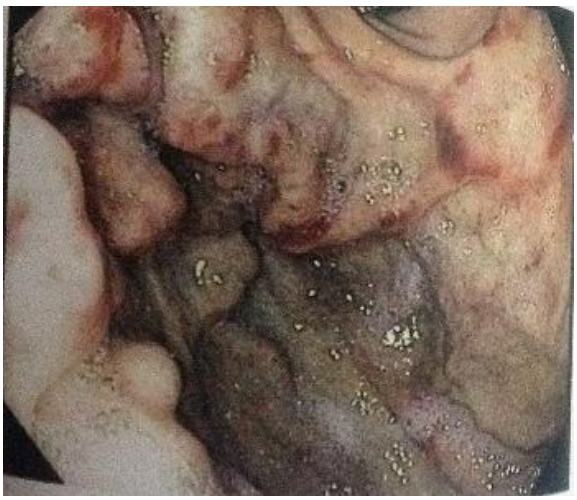


Figure 56: fundic varices

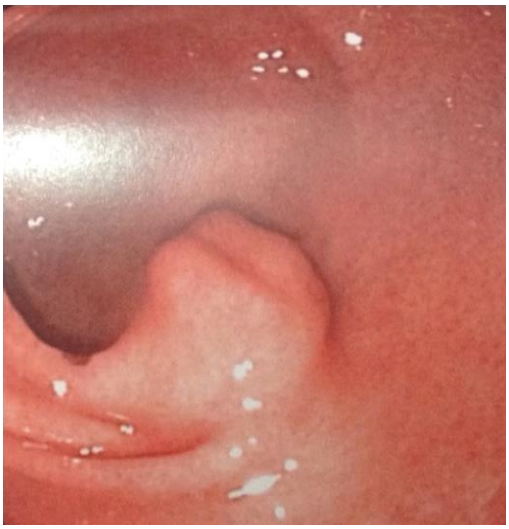


Figure 57: Pancreatic rest

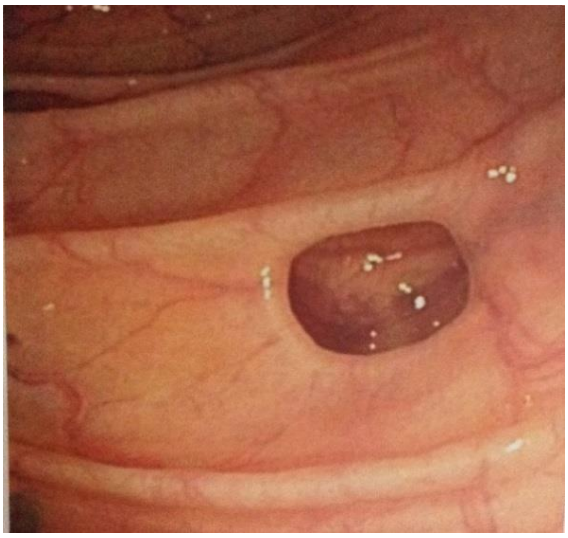


Figure 58: Divericulum

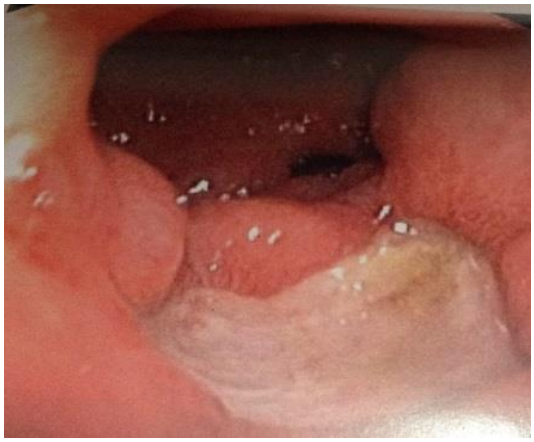


Figure 59: Clean based prepyloric ulcer

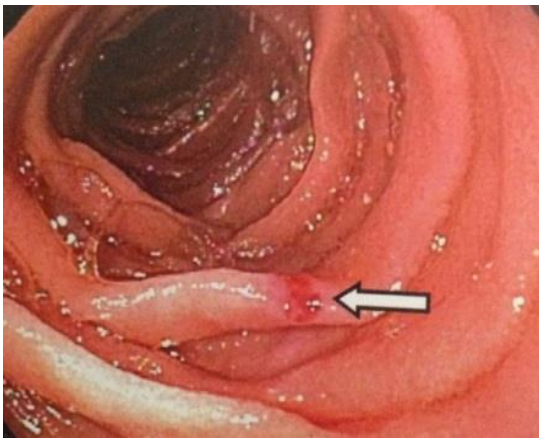


Figure 60: Vascular malformation in the dudenum

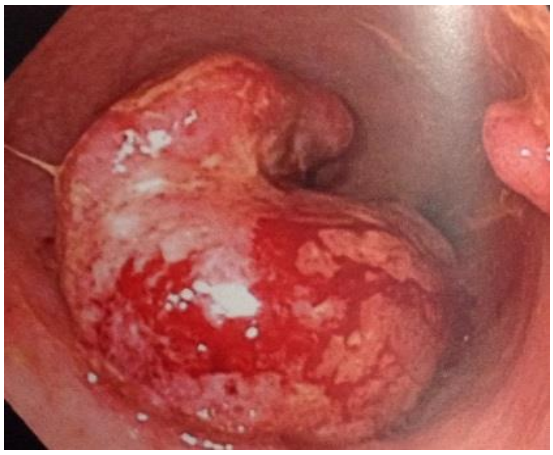


Figure 61: Colon cancer

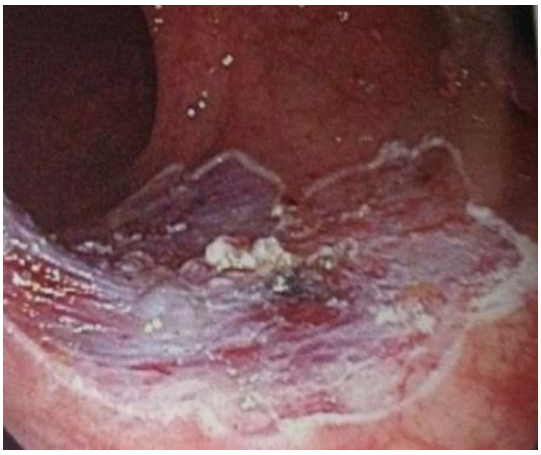


Figure 62: Apperance after snare removal

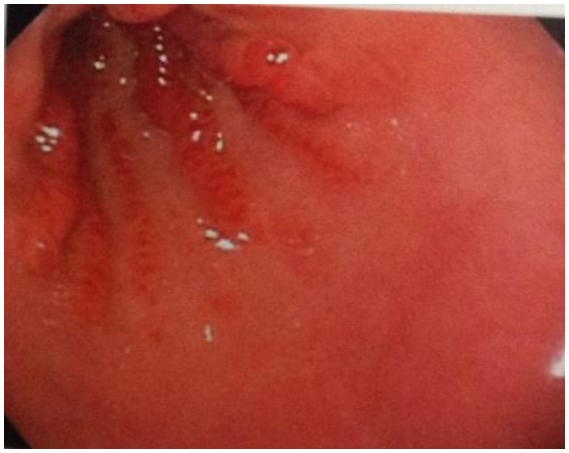


Figure 63: Watermelon stomach

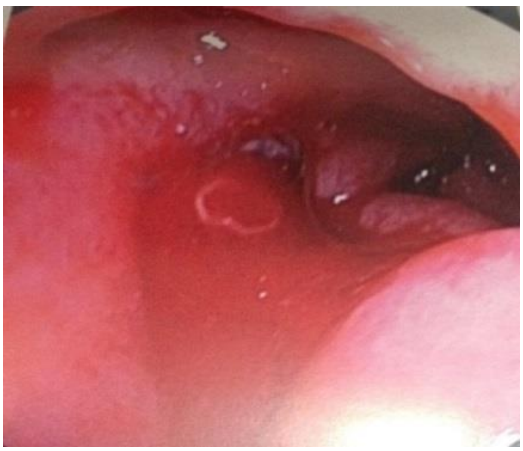


Figure 64: Duodenal ulcer with active bleeding.

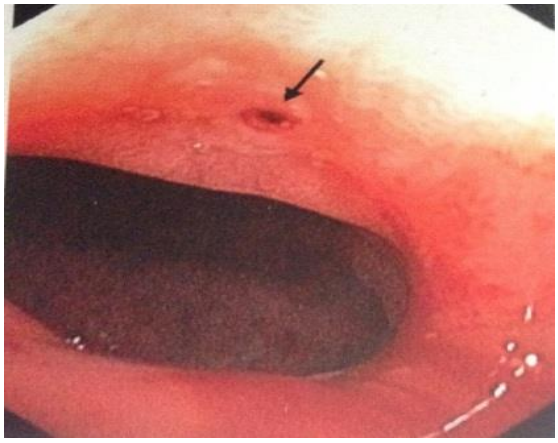


Figure 65: A pyloric channel ulcer with a pigmented, nonbleeding visible vessel(arrow)

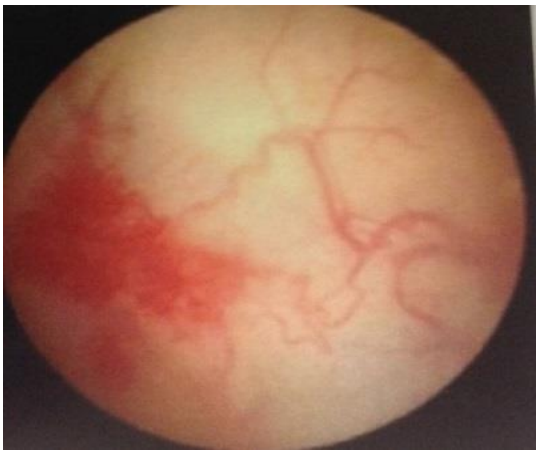


Figure66: Small bowel angioectasia, VCE

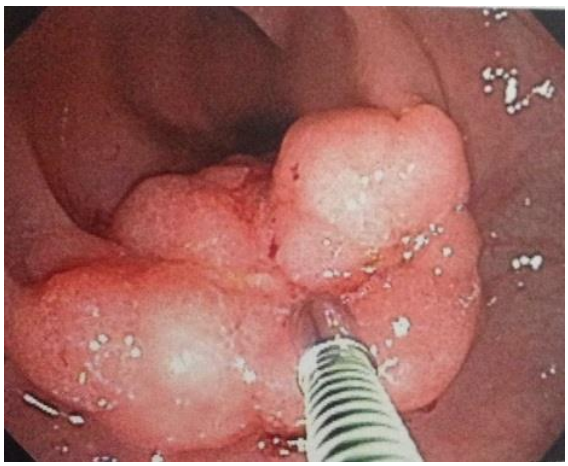


Figure 67: Endoscopic mucosal resection: needle injection method

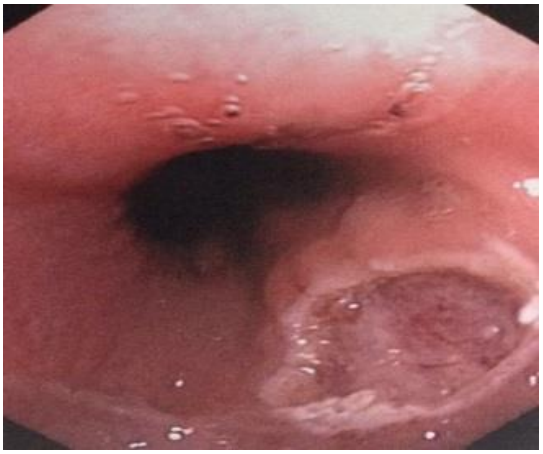


Figure 68: Barrett nodule after snare resection

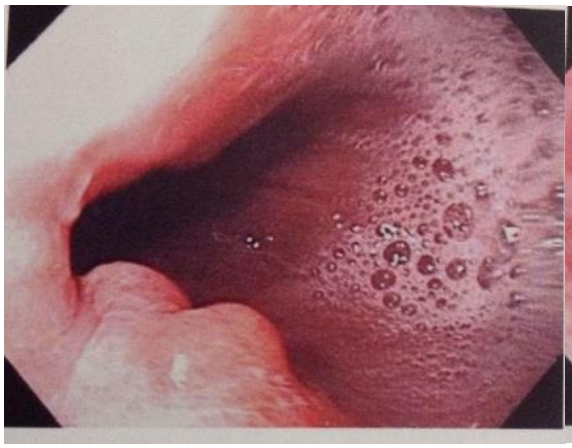


Figure 69:Nodule of high grade dysplasia in Barrett esophagus

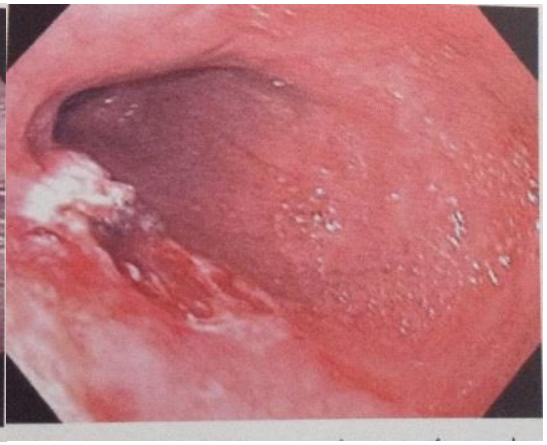


Figure 70:Same patient after endoscopic resection.

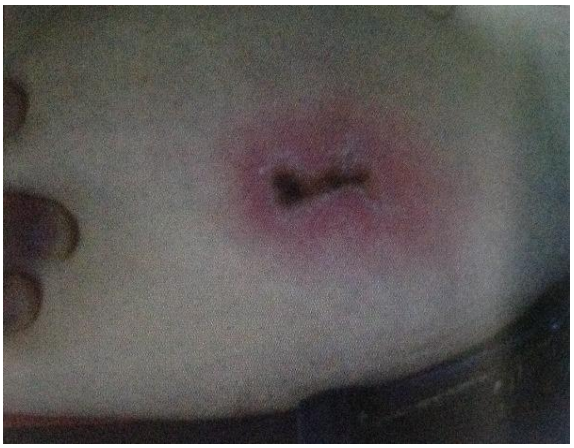


Figure 71: cutaneous reaction to interferon (IFN) injections.

Figure 72: EOE endoscopic findings

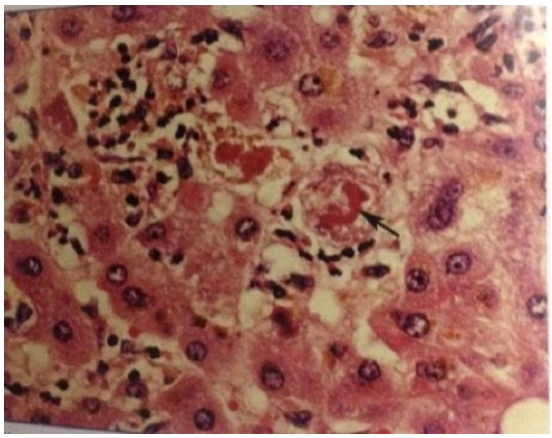


Figure 73: Classic Mallory body inclusion with in a hepatocyte (arrow) NASH .

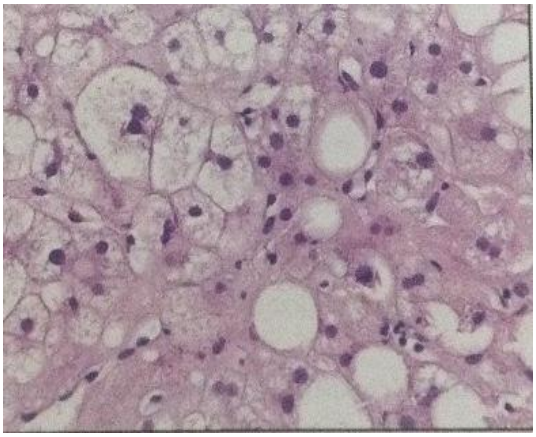


Figure 74: Ballooning degeneration with fatty infiltration in The Mallory body has a characteristic twisted-rope appearance, This image reveals the inclusion within a ballooning hepatocyte, which is a chacteristic of both alcoholic and nonalcoholic fatty liver disease.

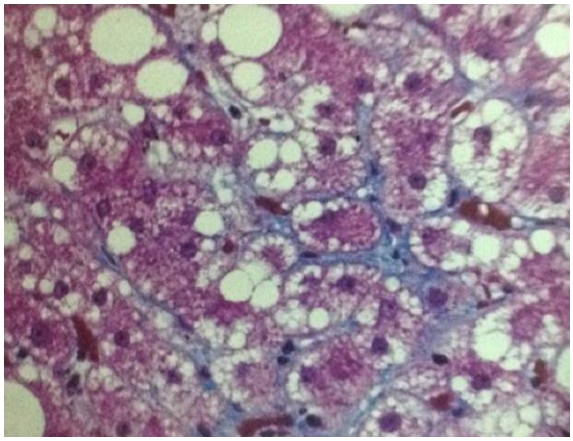


Figure 75: Nonalcoholic steatohepatitis with evidence of" chicken-wire" fibrosis investing the liver parenchyma on trichrome staining. The blue fibrous strands course between the ballooning hepatocyte in this advanced stage of disease

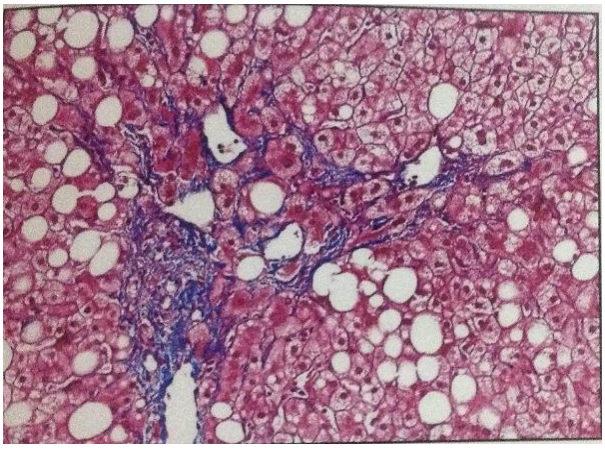


Figure 76: Nonalcoholic steatohepatitis(NASH), Liver biopsy with trichrome stain, reveals steatosis, lobular inflammation, ballooning hepatocytes (steatohepatitis) with in a mesh of " chicken wire fibrosis" cirrhosis may be right around the corner if this continues. (NASH Histopathology Board Buzzwords: Lobular inflammation, Ballooning hepatocytes, Portal inflammation, Mallory bodies).

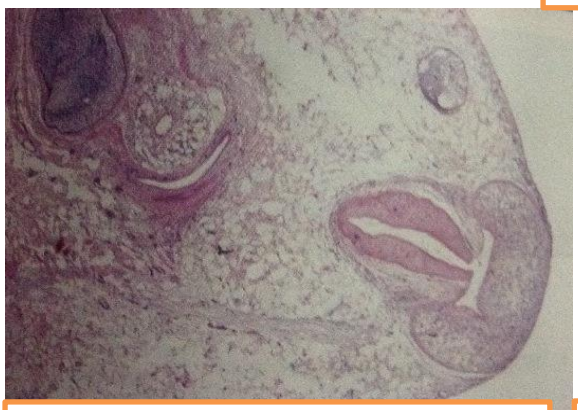


Figure 77: Histologic section of Fasciola parasite showing the mouth-like area. This parasite eats its way through intestinal wall, into the peritoneum, through the liver capsule, and through the liver parenchyma before finally taking residence in the biliary tree.

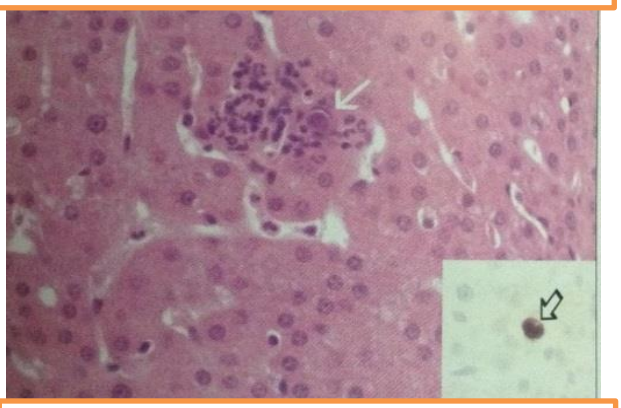


Figure 78: CMV hepatitis.Aggregate of neutrophils surrounds an infected hepatocyte (white arrow), containing an intranuclear inclusion with a surrounding hallo also known as an : owl's eye inclusion. In the inset, CMV immunohistochemistry stains an infected hepatocyte (black open arrow), confirming the presence of CMV

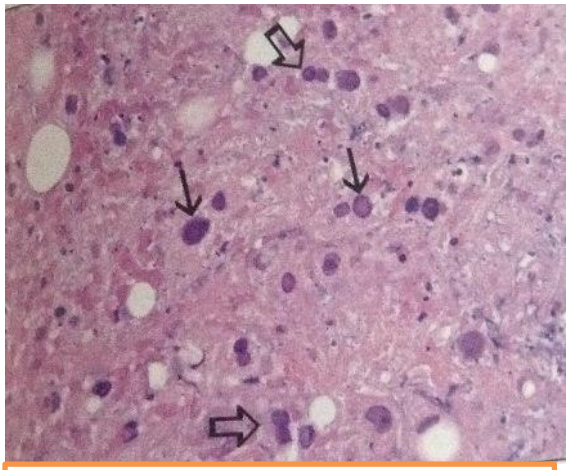


Figure 79: HSV, The hepatic parenchyma shows extensive necrosis with scattered hepatocytes with glassy nuclear inclusions (arrows) and occasional multinucleated cells (open arrows) amidst necrosis

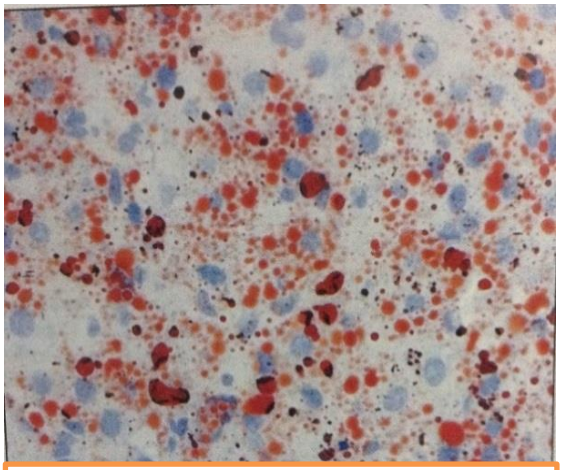


Figure 80: Acute fatty liver of pregnancy with oil red O stain showing the microvesicular Fatty infiltration in the hepatocytes

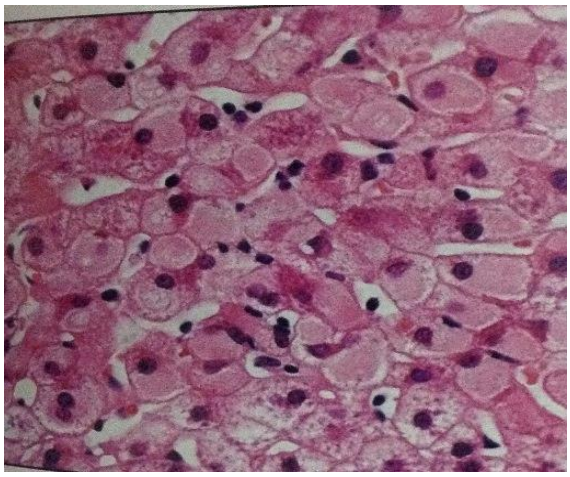


Figure 81: Hepatitis B virus with ground-glass hepatocytes

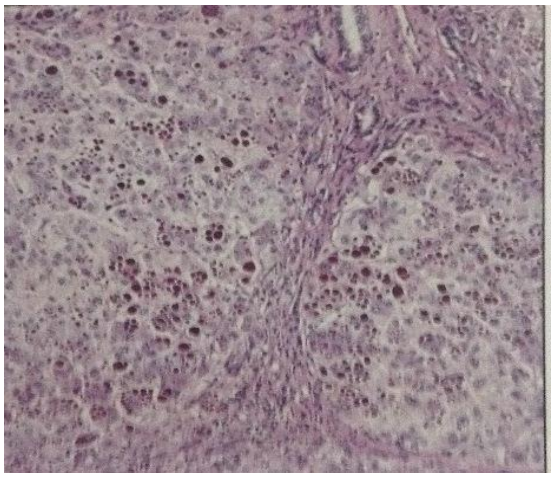


Figure 82: A1AT deficiency with PAS stain demonstrating "diastase - resistent" intrahepatic globules.

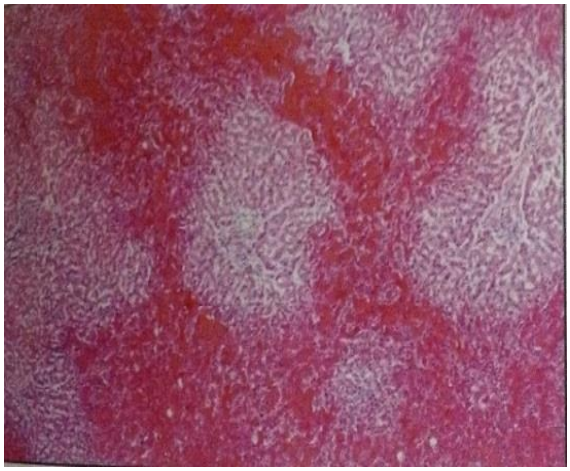


Figure 83: Congestive hepatopathy, dark areas from dilated hepatic interface venules that are full of blood and light Areas that are unaffected surrounding parenchyma. (Nutmeg liver) most commonly results from right-sided heart failure or Budd-Chiari syndrome.

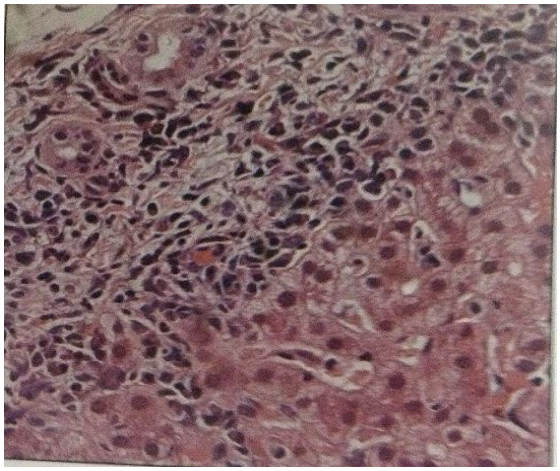


Figure 84: Autoimmune hepatitis with plasma cell infiltrate and hepatitis.

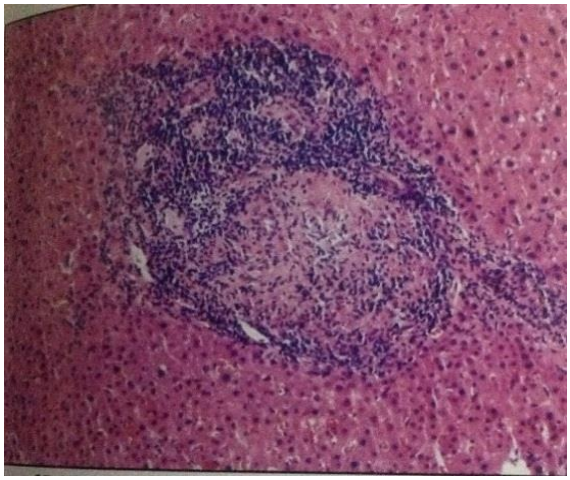


Figure 85: Micrograph of primary biliary cirrhosis with obliterative granulomatous infiltration of the bile ducts and a florid duct Lesion

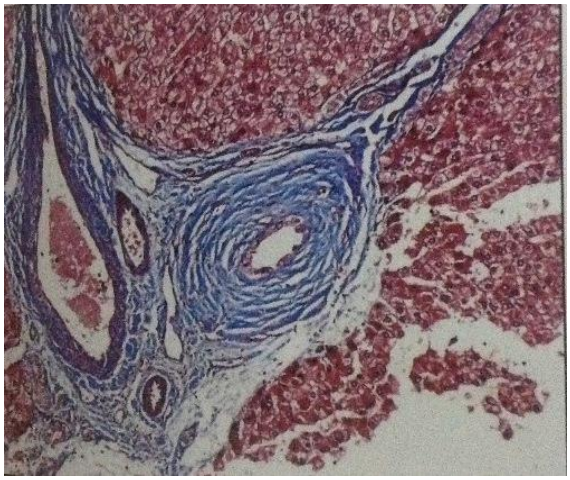


Figure 86: Primary sclerosing cholangitis with "onion-skinning" fibrosis on trichrome staining

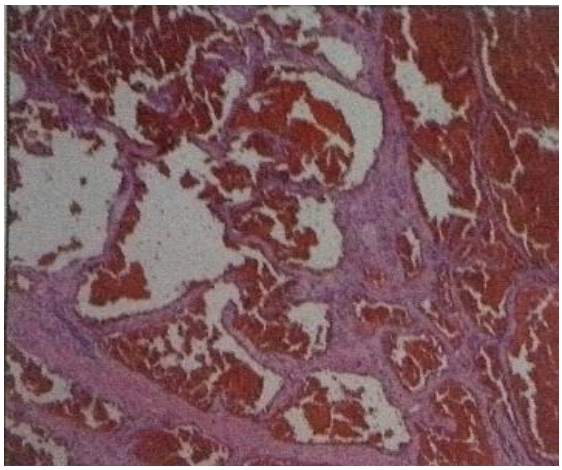


Figure 87: micrograph of hepatic hemangioma demonstrating networks of blod-filled vascular spaces separated by fibrous Stroma

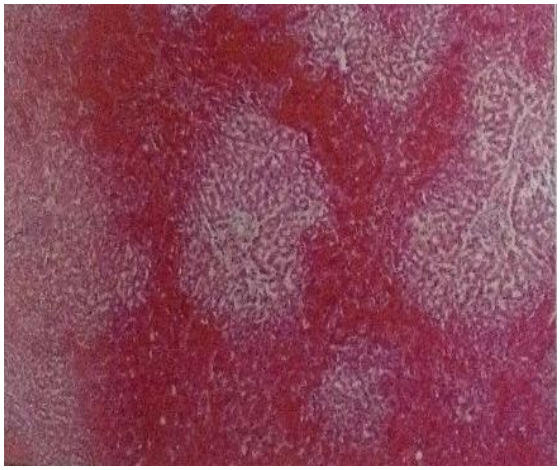


Figure 88: Budd-Chiari syndrome with passive congestion in zone 3.

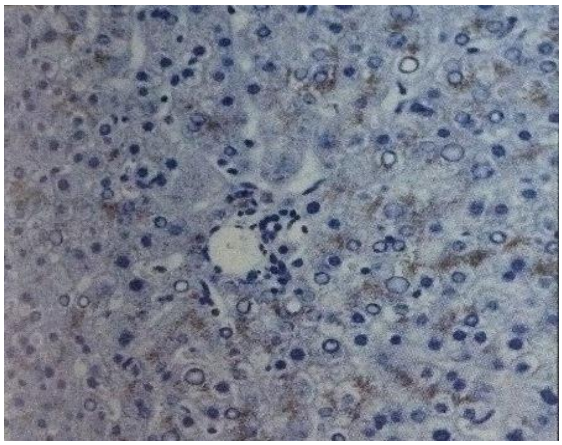


Figure 89: Rhodanine stain of the liver in wilson disease. large, granules of copper are seen in the hepatocytes.

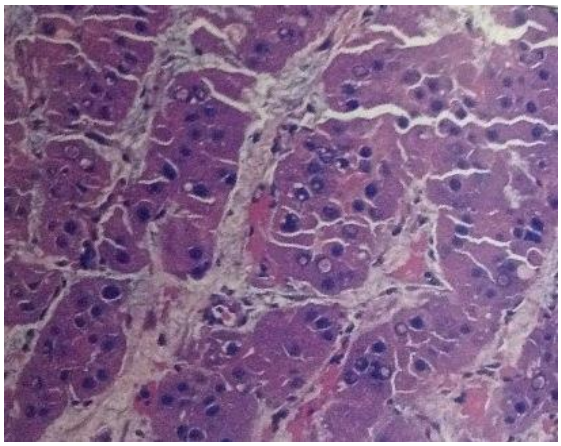


Figure 90: Microscopy of FLHCC lesion demonstrating Red granular cells with intervening fibrous bands

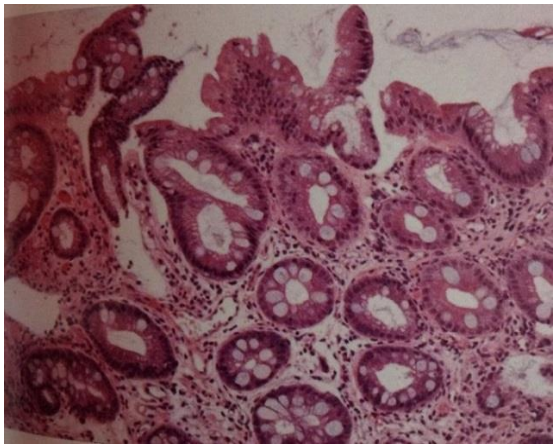


Figure 91: nondysplastic BE. Glandular epithelium containing goblet cells displays nuclear stratification, limited to the lower

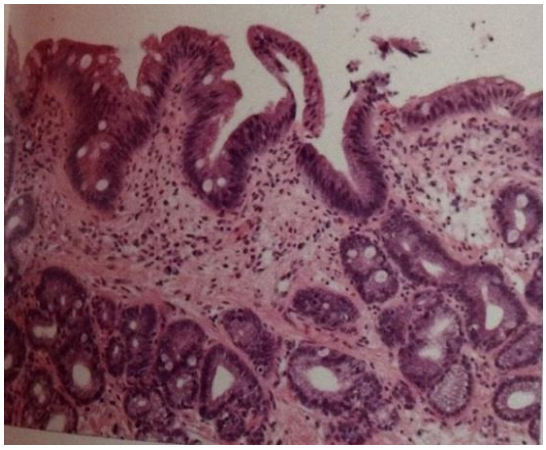


Figure 92: low-grade dysplasia in BE., the surface epithelium half of the cytoplasm

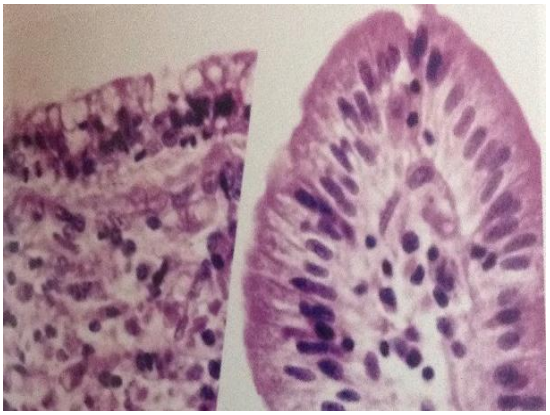


Figure 93: Surface absorptive cells are decreased in hight and vacuolated, , A large bile duct and the nuclei have lost their polarity, lymphoctes(IEL) can be seen adjacent epithelial cells, the underlying Lamina propria is heavily infiltrated with lymphocytes and plasma cells.

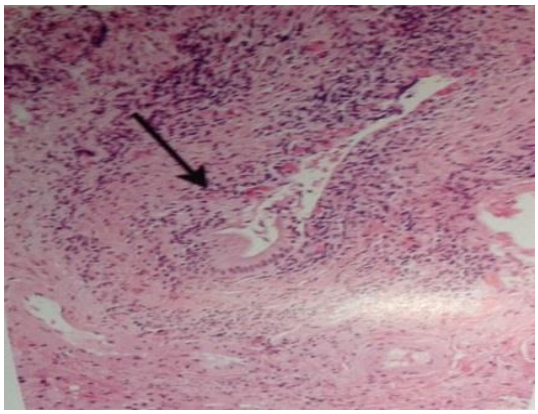


Figure 94: non suppurative destructive chollangitis numerous intrepithelial (arrow) shows lymphocytic infiltration and periductal (" onion-skin") fibrosis.

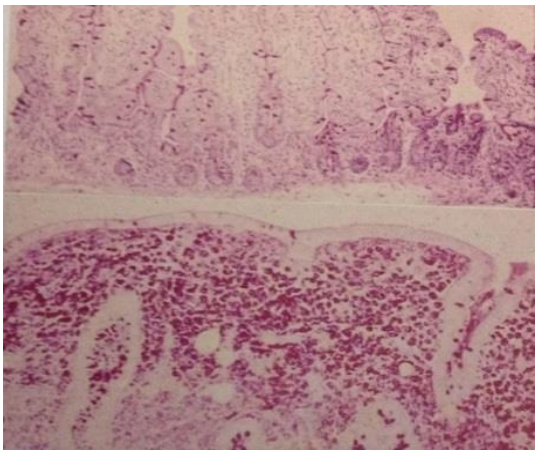


Figure 95: upper panel normal, The glycoprotein-rich epithelial cell brush border and the goblet cell mucous are PAS-positive.
Lower panal biopsy from a patient with untreated whipple disease
The villus architecture is markedly distorted and the lamina propria is packed with large PAS-postive macrophage that virtually replace the lymphoctes and plasma cells that would normally be seen, additionally, profiles of dilated lymphatics are evident in the lamina propria.

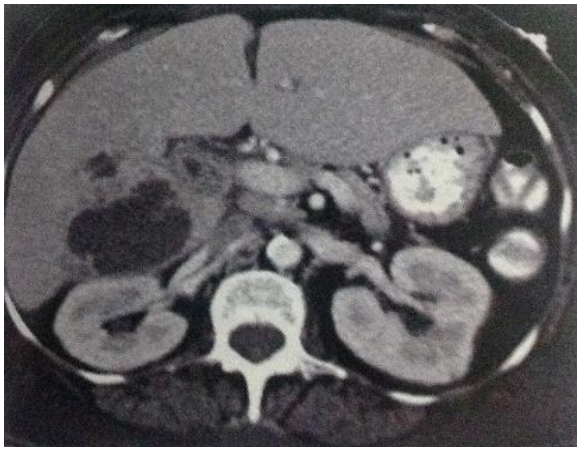


Figure 96: Amebic liver abscess, the CT scan reveals a large, round measuring 6cm.

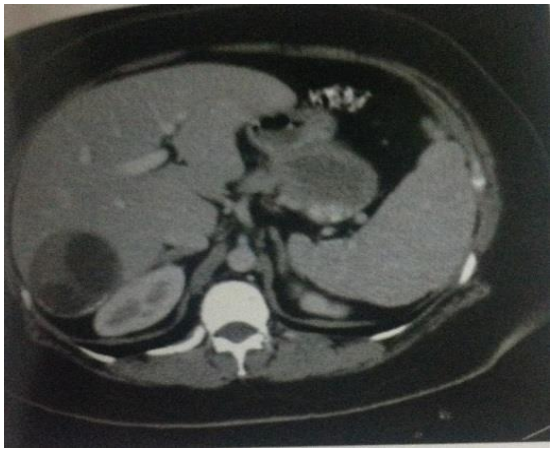


Figure 97: Typical echinoccocal liver cyst in the right lobe , Right hepatic lobe, attenuation lesion with an enhancing in the low- liver rim.

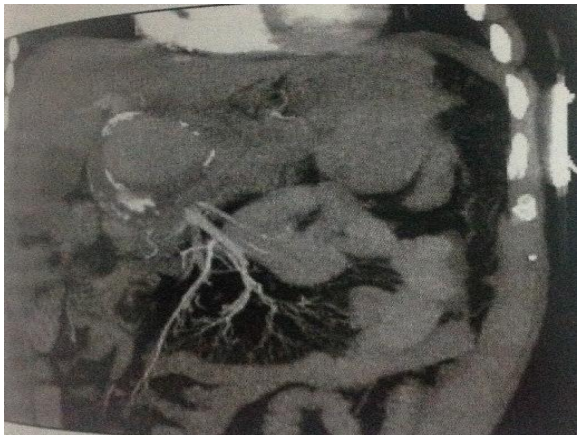


Figure 98: CT with vascular contrast enhacement extrahepatic Hepatic artery aneurysm with calcifications appearing acyst-Like near the structure porta hepatis

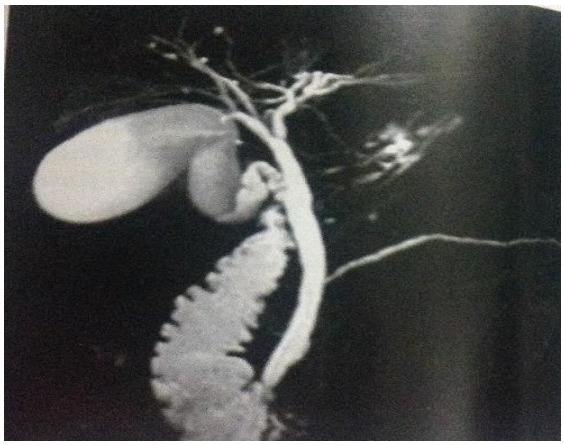


Figure 99: MRCP, a small –duct primary sclerosing cholangitis (PSC) But it can be considered normal. Liver biopsy is diagnostric for smll-duct PSC

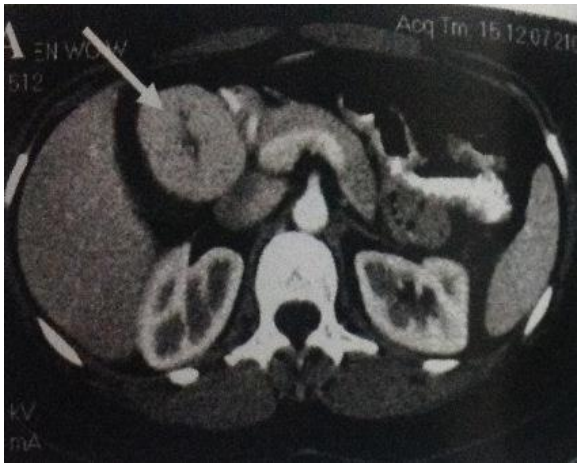


Figure 100: Arterial phase from triphasic CT scan of a focal Hyperplasia lesion with a characteristic center scar. This is a very different lesion from FLHCC.

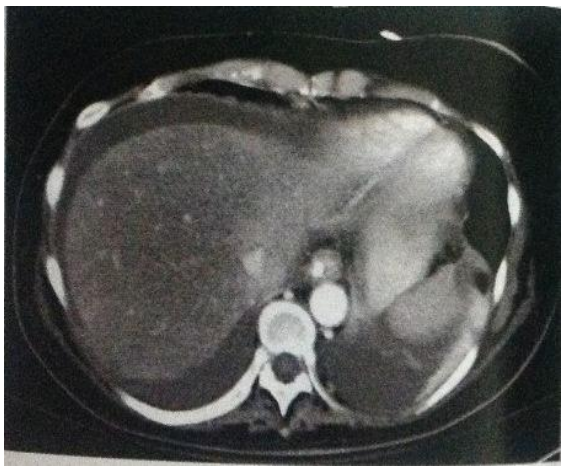


Figure 101: Budd-Chiari syndrome with characteristic caudate lobe hypertrophy.

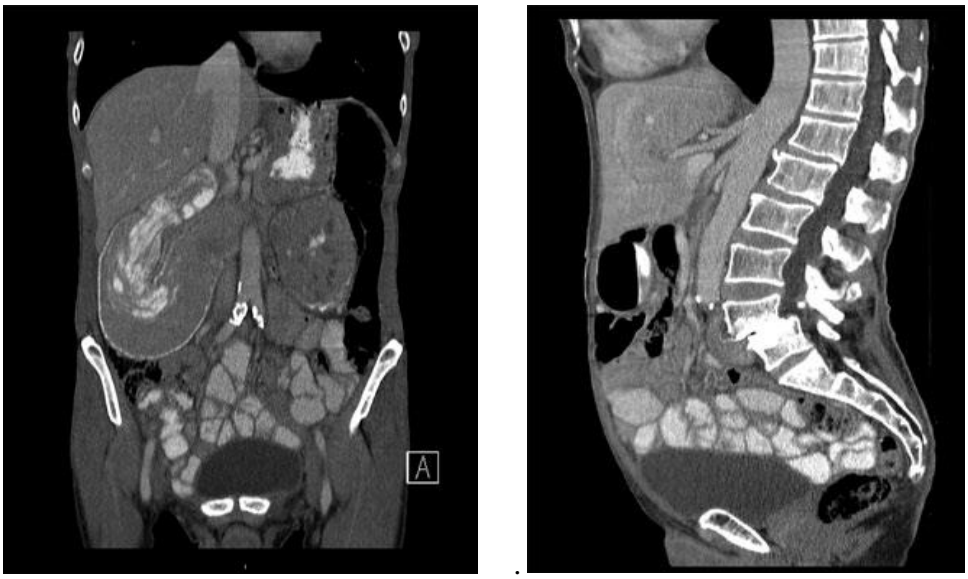


Figure 102: Superior mesenteric artery syndrome,A 55-year-old man presented with persistent nausea, chronic diarrhea, and a 20-pound weight loss over one year. Upper endoscopy was significant for 500 cm_2 of bilious fluid aspirated from the stomach and a severely dilated descending duodenum. Computed tomography with intravenous contrast revealed findings consistent with superior mesenteric artery syndrome. The coronal view (left) shows a dilated stomach along with first and second portions of the duodenum, with a transition point at the level of the superior mesenteric artery. The sagittal view (right) demonstrates narrowing of the angle between the superior mesenteric artery and aorta to 22°, resulting in external compression of the duodenum. The patient was initially treated conservatively with endoscopic decompression and antiemetic pharmacotherapy. He was subsequently placed on a weight-gain regimen, which led to improvement of his symptoms. (Submitted by Jarred Marshak, Anik M. Patel, and David M. Friedel, Winthrop University Hospital, Mineola, New York, and Prakriti Merchant, Norwalk Hospital, Norwalk, Connecticut.)

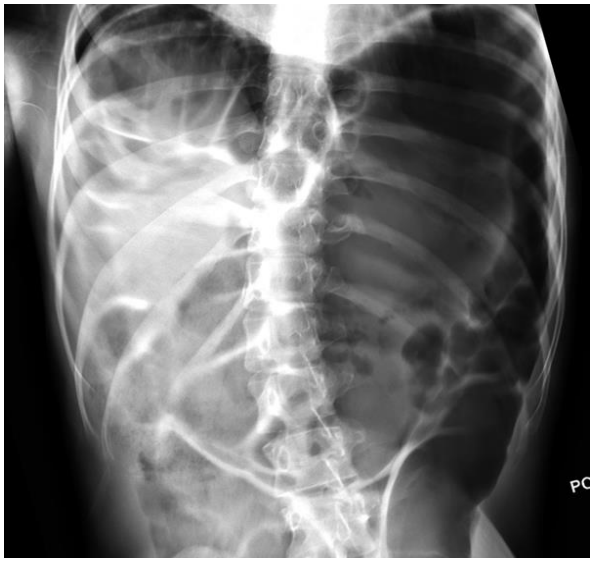


Figure 103: Acute colonic pseudo- obstruction . Abdominal X-ray reveals diffusely dilated loops of small and large bowel

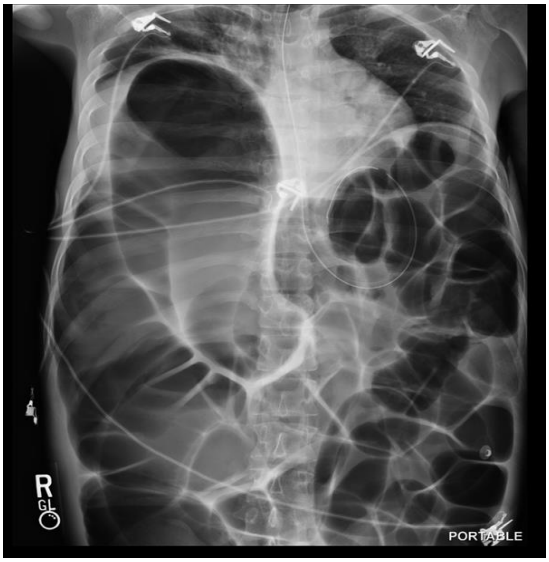


Figure 104: Acute colonic pseudo-obstruction Abdominal X-ray reveals diffuse gaseous distension of small bowel loops and colon causing diaphragm elevation bilaterally.

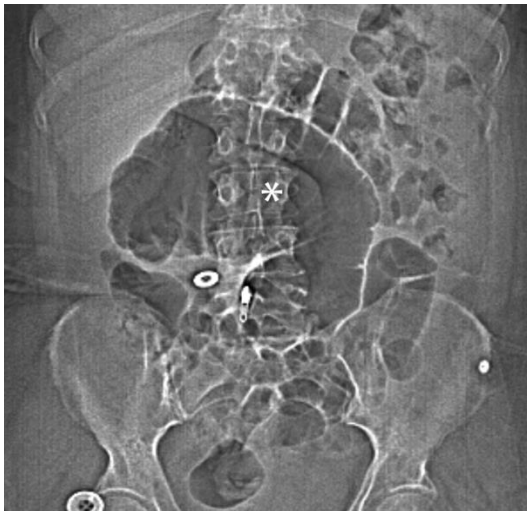


Figure 105: Cecal volvulus
CT topogram with *indicating marked dilation of the Cecum.

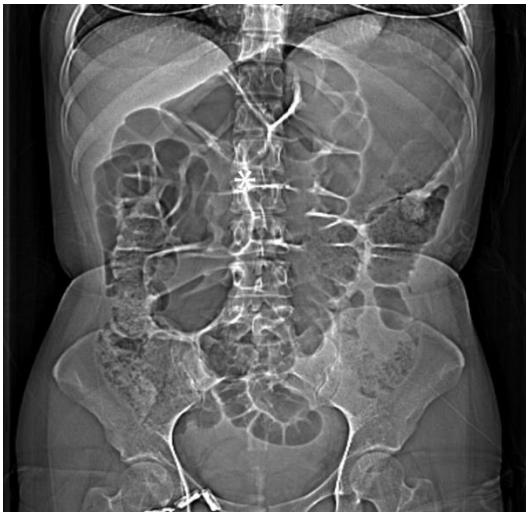


Figure 106: Sigmoid volvulus, Abdominal X-ray with * indicates classic coffee bean appearance .

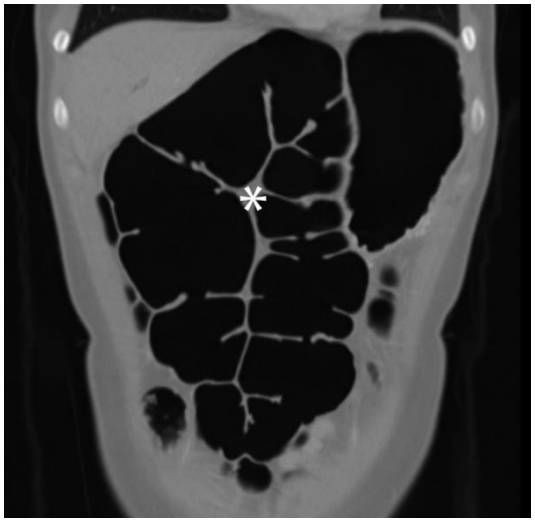


Figure 107:Sigmoid volvulus . CT topogram with * indicates Classic coffee bean appearance

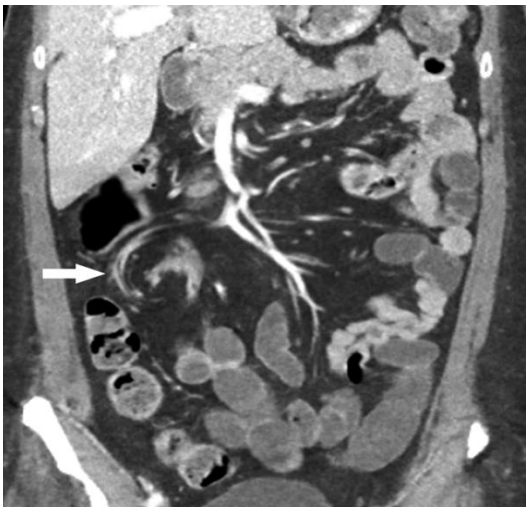


Figure 108: Cecal volvulus .CT with arrow indicating swirling of the mesentery or "whirl sign" within the right lower quadrant of the abdomen

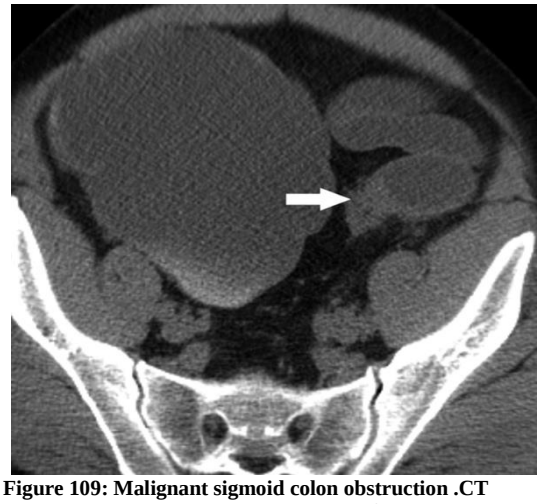


Figure 109: Malignant sigmoid colon obstruction .CT with arrow Indicating abrupt transition from dilated to decompressed sigmoid colon in the setting of cancer involving the proximal sigmoid colon.

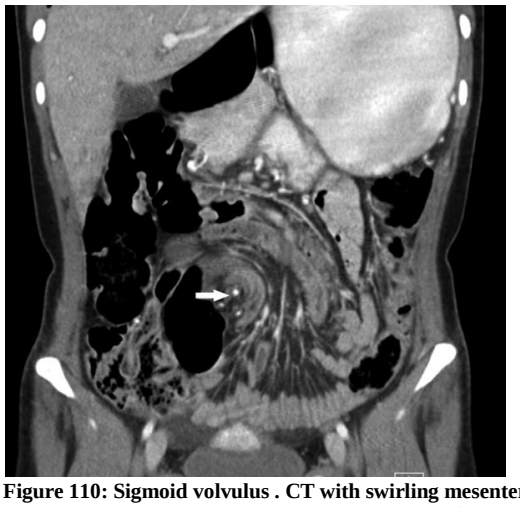


Figure 110: Sigmoid volvulus . CT with swirling mesentery or "whirl sign" in the lower abdomen in the setting of a sigmoid volvulus

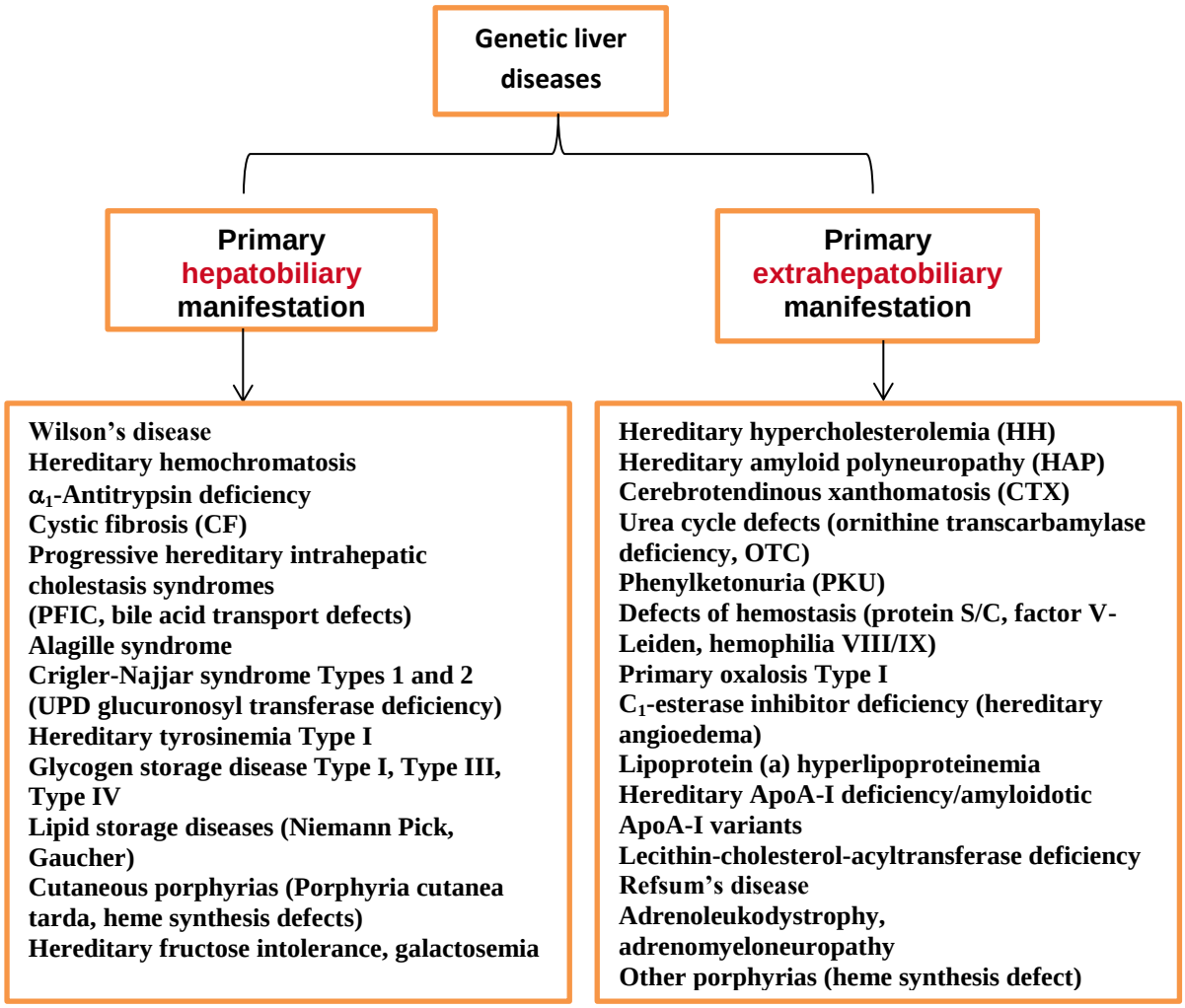
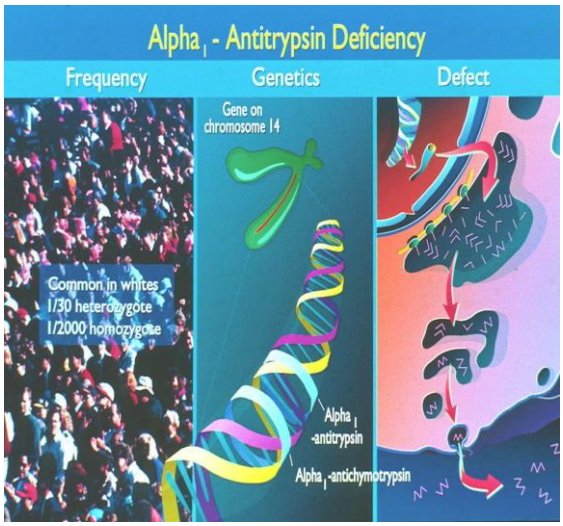
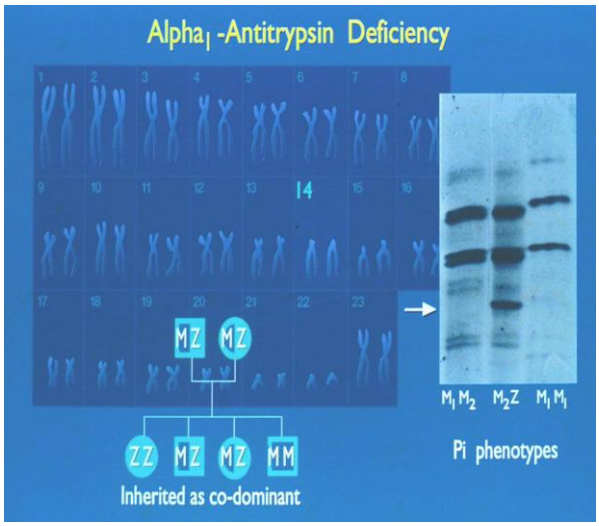


Figure 111: Genitic liver diseases

Clinical Clues	Metabolic liver diseases
□ Coarse facies	Gangliosidosis, MPS, Sialidosis
□ Macroglossia	GM1 Gangliosidosis
□ Diarrhea	Wolman's Disease, Cystic fibrosis
□ Mild Lymphadenopathy	Wolman's Disease, Gaucher's Disease
□ Upward gaze palsy,opisthotonous	Gaucher's Disease
□ Cherry red spot	Niemann-Pick,GM1Gangliosidosis
□ Abnormal odor Sweat feet Rancid, fishy, or cabbage like	 Glutaric acidemia, Isovaleric acidemia Tyrosinemia
□ Significant hepatosplenomegaly □ Cirrhosis (splenomegaly, portal hypertension) □ Small liver (coagulopathy)	Wolman's, Gaucher's, MPS VII, Gangliosidosis, Sialidosis II, HLH (with coagulopathy) Alpha-1-antitrypsisn deficiency Neonatal hemachromatosis
□ lactic acidosis During feeding During fasting Perminant	 Resp chain dis, Pyruvate carbo def, Glycogen synth def(II), Glyconeogenesis def(I), Fatty ac ox def(SCAD, MCAD,LCAD, LCHAD), Organic aciduria(Methyl malonic, proprionic, glutaric isovaleric), Urea cycle defect
Radiologic Clues	
□ Adrenal Calcification	Wolman's Disease
□ Stippled Epiphysis	Zellweger's Syndrome, GM1 Gangliosidosis
□ Rickets	Tyrosinemia.
Histologic Clues Liver	
□ PAS +/diastase resistant granules	Alpha-1-antitrypsin def, GSD 4, Afibrinoginemia
□ Iron	Zellweger's Syndrome, Neonatal hemochromatosis
□ Fatty change	Non specific but important indicator
□ Glycogen and plant like cells	Glycogen Storage Disease
□Copper	Wilson's Disease, other copper disorders but could indicate chronic cholestasis
Histologic Clues	
□ Skin Biopsy	Laffora body disease, GM1 Gangliosidosis
□ Bone Marrow	Wolman's Disease, Gaucher's Disease, Niemann-Pick type C, Hemophagocytic Lymphohistiocytosis
Glycogen Storage Disease	□ Doll like face, Big belly □ Sweating, irritability,sweet craving □ Hepatomegaly □ No Jaundice □ Usually no splenomegaly (type IV) □ Elevated Cholestrol/TG, Uric acid,Lactate □ Liver enzymes not very elevated

Table 27: Liver Metabolic diseases on clinical point of view.





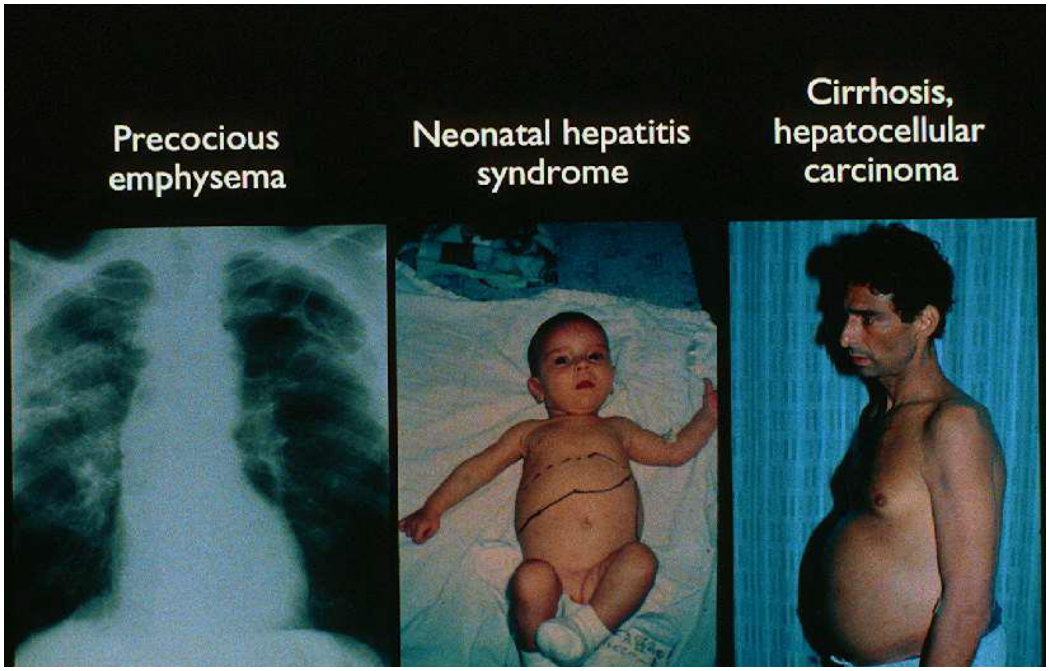


Figure 112: Alpha$_1$ antitrypsin difficiency

Abreviation List

99TcMAA	**Technetium labeled macro-aggregated albumin**
AAP	**American Academy of Pediatrics**
AASLD	**American Association of the Study of Liver Diseases**
AAT	**alpha-1 antitripsin**
ABG	**Arterial blood gas**
ABW	**Adjusted body weight**
ACR	**Acute cellular rejection**
ADH	**Alcohol dehydrogenase**
ADV	**Adenofovir**
AFLP	**Acute fatty liver of pregnancy**
AFP	**Alpha-fetoprotein**
AH	**Alcoholic hepatitis**
AIDS	**Acquired immunodefficiency syndrome**
AIH	**Autoimmune hepatitis**
ALF	**Acute liver failure**
ALT	**Alanine aminotransferase**
AMA	**Antimitochondrial antibodies**
ANA	**Antinuclear antibody**
Anti-HAV	**Antibodies to the hepatitis A virus**
Anti-HBc	**Antibodies to the hepatitis B core antigen**
Anti-HBs	**Antibodies to the hepatitis B surface antigen**
Anti-LKM	**anti-liver lidney microsomal(antibody)**
AP	**Alkaline phosphatase**
ASA,	**American Society of Anesthesiologists**
ASGE,	**American Society for Gastrointestinal Endoscopy**
ASMA	**Anti-smooth muscle antibody**
AST	**Aspartate aminotransferase**
BCS	**Budd-Chiari syndrome**
BISAP,	**bedside index of severity in acute pancreatitis**
BMI	**Body Mass Index**
BOC	**Boceprevir**
BO-EIS	**BO-EIS Balloon-occluded endoscopic injection sclerotherapy.**
Breaks	**Peristaltic Breaks (cm), > 5cm is significant Break.**
BRTO	**Balloon retrograde transvenous obliteration.**
CBC	**Complete blood count.**
CDC	**Center for Disease Control and Prevention**
CDP	**Contractile Deceleration Point**
Cevr	**Complete early virological response**
CFV	**Contractile Front Velocity, normal <9cm/s**
CHB	**Chronic hepatitis B**
CIA	**Chemiluminescent immunoassay;**
CK	**Creatine Kinase**
CKD	**Chronic Kidney disease**
CMS,	**Centers for Medicare and Medicaid Services**
CMV	**Cytomegalovirus**
COPD	**Chronic obstructive pulmonary disease**
CRNA,	**Certified registered nurse anesthetist**
CRP	**C-reactive protein**
CTP	**Child-Pugh-Turcotti Score**
CVP	**Central venous pressure**
CVVH	**Continuous veno-venous hemofiltration**
CVVHD	**Continuous veno-venous hemodialysis**
DAA	**Direct acting antiviral agent**
DCI	**Distal Contractile Integral (mmHg.s.cm)**
DF	**Maddrey Discriminant Function score**
DGF	**Delayed graft function**

DIC	**Disseminated intravascular coagulation**
DILI	**Drug-induced liver injury**
DL	**Distal Latency (seconds): interval between UES relaxation and CDP normal ≥4.5 seconds**
DVR	**Delayed virological response**
EBV	**Epstein-Barr virus**
Eevr	**Extended early virological response**
EGD	**Esophagogastroduodenoscopy**
EHBA	**Extrahepatic biliary atresia**
ELISA	**Enzyme-linked immunosorbent assay**
EOT	**End of treatment**
ERCP,	**Endoscopic retrograde cholangiopancreaticography;**
Ervr	**Extended rapid virological response**
ESLD	**End-stage liver disease**
ESPEN	**European Society for Parenteral and Enteral Nutrition**
ESR	**Erythrocyte sedimentation rate**
ESRD	**End-stage renal disease**
ETV	**Entecavir**
EUS	**Endoscopic ultrasound**
EV	**Esophageal varices**
EVR	**Early virological response**
FDA	**U.S. Food and Drug Administration**
FHF	**Fulminant Hepatic Failure**
FNA	**Fine needle Aspirate**
FNH	**Focal nodular Hyperplasia**
GABA	**Gamma-aminobutyric acid**
GGT	**Gamma glutamyl transpeptidase**
GI,	**Gastrointestinal**
GIB	**Gastrointestinal bleeding**
HAART	**Highly active antiretroviral therapy**
HAIC	**Hepatic arterial infusional chemotherapy**
HAT	**Hepatic aretery thrombosis**
HbcAb IgG	**Hepatitis B core antibody immunoglobulin G**
HbcAb IgM	**Hepatitis B core antibody immunoglobulin M**
HBIg	**Hepatitis B immunoglobulin**
HbsAb	**Hepatitis surface antibody**
HBsAg	**Hepatitis B surface antigen**
HBV	**Hepatitis B virus**
HCC	**Hepatocellular carcinoma**
HCT	**Hmatocrit**
HCV	**Hepatitis C virus**
HDL	**High density lipoprotein**
HE	**Hepatic Encephalopathy**
HELLP	**Hemolytic anemia, elevated liver enzymes and low platelet count**
HEV	**Hepatitis E virus**
HFE	**Hemochromatosis**
HG	**Hyperemesis gravidarum**
HH	**Hereditary hemochromatosis**
HHT	**Hereditary hemorrhgic telengiectasia**
HIC	**Hepatic iron concentration**
HIDA	**Hepatobiliary immunodiacetic acid (scan)**
HII	**Hepaic iron index**
HIV	**Human immunodeficiency virus**
HLA	**Human leukocyte antigen**
HLH	**Hemophagocytic Lymphohistiocytosis)**
HOMA	**Homeostasis model assessment(index)**
HPS	**Hepatopulmonary syndrome**
HRM	**High Reolution Manometry**

HRS	**Hepatorenal syndrome**
HSV	**Herpes simplex virus**
HVPG	**Hepatic venous pressure gradient**
IBD	**Inflammatory bowel disease**
IBW	**Ideal body weight**
ICH	**Intracrenial hypertension**
ICP	**Intrahepatic cholestasis of pregnancy**
ICU	**Intensive care unit**
IDU	**injection drug user, injecting drug users, or intravenous drug user.**
IDUS	**Intravenous drug users**
IFN	**Interferon**
INR	**International normalized ratio**
IRI	**Ischemic reperfusion injury**
IRP	**Integrated Relaxation Pressure (mmHg)**
ISC	**Incomplete septal cirrhosis**
IV,	**intravenous**
IVC	**Inferior vena cava**
IVIG	**Intravenous immunoglobulin**
KF	**Kayser-Fleischer (rings)**
LCHAD	**Long chain 3-hydroxyacylcoenzyme A dehydrogenase**
LCT	**Long-chain triglycerides**
LDH	**Lactate dehydrogenase**
LDLT	**Liver donor liver transplantation**
LKM-1	**Liver kidney microsomal type 1**
LKM-3	**Liver kidney microsomal type 3**
LLOD	**Lower limit of detection**
LLOQ	**Lower limit of quantification**
LPN,	**licensed practical nurse**
LPS	**Lipopolysaccharide**
LR	**Likelihood ratio**
LT	**Liver transplantation**
LVP	**Large volume paracentesis**
MCV	**Mean cell volume**
MDR	**Multi-drug resistant**
MELD	**Model for end stage liver disease (score)**
MHE	**Minimal hepatic encephalopathy**
MRA	**Magnetic resonance angiogram**
MRCP	**Magnetic resonance cholangiopancreaticography**
MRI	**Magnetic resonanance imaging**
MTCT	**Mother-to-child transmission**
NAC	**N-acetylcysteine**
NAFLD	**Non-alcoholic fatty liver disease**
NASH	**Non-alcoholic steatohepatitis**
NCPH	**Non-cirrhotic portal hypertension**
NFPA,	**National Fire Protection Association**
NNASPGHAN	**The north American Society for pediatric Gastroenterology, Hepatology**
	and nutrition
NR	**Null response**
NRH	**Nodular regenerative hyperplasia**
NRTIs	**Nucleoside reverse transcriptase inhibitors**
NSAID,	**non-steroidal anti-infl ammatory drug**
NSAIDS	**Non-steriodal anti-inflammatory drugs**
OCP	**Oral contraceptive pill**
OLT	**Orthotopic liver transplant**
OPV	**Obliterative portal venopathy**
P-ANCA	**Perinuclear-staining antineutrophil cytoplasmic antibody**
PAS	**Periodic acid schiff**
PASP	**Pulmonary artery systolic pressure**

PBC	**Primary biliary cirrhosis**
PBS	**Primary biliary sclerosis**
PCP	**Primary care provider**
PCR	**Polymerase chain reaction**
PEG-INF	**Pegylated interferon**
PFIC	**Progressive familial intrahepatic cholestasis**
PHT	**Portal hypertension**
PHTN	**Pulmonary hypertension**
PI	**Protease inhibitor**
PMN	**Polymorphonuclear leukocytes**
PPE,	**personal protective equipment**
PPE,	**personal protective equipment**
PPHTN	**Portopulmpnary hypertension**
PPI	**Proton-pump inhibitor**
PR	**Partial non-response**
PSC	**Primary sclerosing cholangitis**
PSE	**Portal systemic encephalopathy**
PT	**Prothrombin time**
PTC	**Percutaneous transhepatic cholangiography**
PTT	**Partial throboplastin time**
PVT	**Portal vein thrombosis**
RBV	**Ribavirin**
RFA	**Radiofrequency ablation**
RN,	**registered nurse**
RVR	**Rapid virological response**
SAAG	**Serum-ascites albumin gradient**
SBP	**Spontaneous bacterial peritonitis**
SIRS	**Systemic inflammatory response syndrome**
SLA/LP	**Soluble liver antigen/ liver pancreas**
SLE	**Systemic lupus erythematosis**
STC	**Slow transit constipation**
SMA	**Smooth muscle antibody**
SRH	**Stigmata of recent hemorrhage**
SVR	**Sustained virological response**
TACE	**Transarterial chemoembolization**
TDF	**Tenofovir disoproxil fumerate**
TIBC	**Total iron binding capacity**
TIPS	**Transjugular intrahepatic portosystemic shunting**
TNF	**Tumour necrosis factor**
TPN	**Total parenteral nutrition**
TSB	**Total serum bilirubin**
TSH	**Thyroid stimulating hormone**
TTG	**Transglutaminase antibody**
TVR	**Telaprevir**
UAP,	**unlicensed assistive personnel.**
UDCA	**Ursodeoxycholic acid**
UGIB,	**Upper gastrointestinal bleeding.**
ULN	**Upper limit of normal**
ULN,	**Upper limit normal;**
US,	**Ultrasound**
WD	**Wilson disease**
WHO	**World Heath Organisation**

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