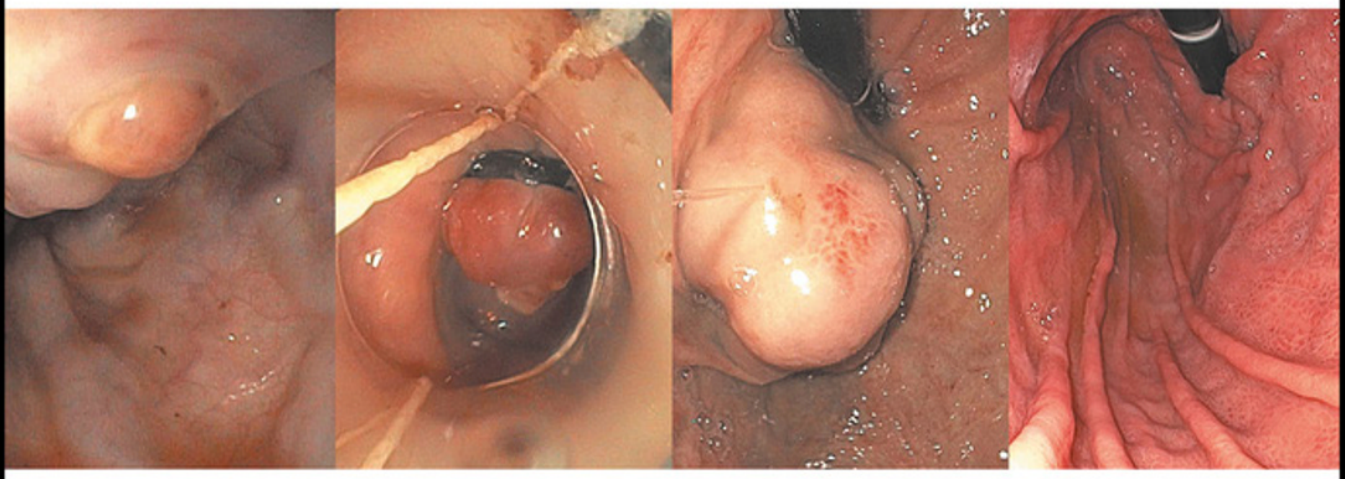
ENDOSCOPY
IN LIVER DISEASE



EDITED BY JOHN N. PLEVRIS, PETER C. HAYES,
PATRICK S. KAMATH, LOUIS M. WONG KEE SONG

with website

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Endoscopy in Liver Disease

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Edited by

John N. Plevris
Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
University of Edinburgh
Edinburgh, Scotland, UK

Peter C. Hayes
Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
University of Edinburgh
Edinburgh, Scotland, UK

Patrick S. Kamath
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, USA

Louis M. Wong Kee Song
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, USA

WILEY Blackwell

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List of Contributors

Ignacio Alfaro, MD
Specialist Member
Institute of Digestive Diseases and Metabolism
Hospital Clinic
Barcelona, Spain

Stuart K. Amateau, MD, PhD
Assistant Professor of Medicine
Director of Endoscopy
Division of Gastroenterology and Hepatology
University of Minnesota
Medical Center
Minneapolis, Minnesota, USA

Todd H. Baron, MD, FASGE
Professor of Medicine
Director of Advanced Therapeutic Endoscopy
Division of Gastroenterology and Hepatology
University of North Carolina
Chapel Hill, North Carolina, USA

Annalisa Berzigotti, MD, PhD
Associate Professor of Medicine (Hepatology)
University Clinic for Visceral Surgery and Medicine
Inselspital, University of Bern
Bern, Switzerland

Alan Bonder, MD
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts, USA

Jaime Bosch, MD, PhD, FRCP
Professor of Medicine and Senior Consultant Hepatologist
Hepatic Hemodynamic Laboratory and Liver Unit
Hospital Clinic
University of Barcelona
Barcelona, Spain;
Guest Professor of Hepatology
Inselspital, University of Bern
Bern, Switzerland

Stephen Caldwell, MD, FAASLD
Professor of Medicine
GI/Hepatology
Digestive Health Center
University of Virginia
Charlottesville, Virginia, USA

Andres Cardenas, MD, MMSc, PhD, AGAF, FAASLD
Faculty Member/Consultant
Institute of Digestive Diseases and Metabolism
Hospital Clinic
Barcelona, Spain

Khadija Chaudrey, MD
Gastroenterologist
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, USA

Roberto de Franchis, MD
Professor of Gastroenterology
Department of Biomedical and Clinical Sciences
University of Milan
Milan, Italy

Larissa Fujii-Lau, MD
Assistant Professor of Medicine
Department of Gastroenterology
Queens Medical Center
University of Hawaii
Honolulu, Hawaii, USA

Tom K. Gallagher, MCh, FRCSI
Consultant Hepatobiliary and Transplant Surgeon
St. Vincent's University Hospital
Dublin, Ireland

Juan Carlos García-Pagán, MD, PhD
Barcelona Hepatic Hemodynamic Laboratory
Liver Unit, Hospital Clinic Barcelona
Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)
University of Barcelona
CIBERehd (Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas)
Barcelona, Spain

O. James Garden, CBE, MD, FRCSEd
Regius Professor of Clinical Surgery and Honorary Consultant Surgeon
Hepatobiliary and Pancreatic Surgical Services
Department of Clinical Surgery
Royal Infirmary of Edinburgh
Edinburgh, Scotland, UK

Martin Goetz, MD
Professor of Endoscopy
Innere Medizin 1
Universitätsklinikum Tübingen
Tübingen, Germany

Gregory J. Gores, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, USA

Ewen M. Harrison, PhD, FRCSEd
Clinical Senior Lecturer and Honorary Consultant Surgeon
Hepatobiliary and Pancreatic Surgical Services
Department of Clinical Surgery
Royal Infirmary of Edinburgh
Edinburgh, Scotland, UK

Robert H. Hawes, MD
Professor of Medicine
University of Central Florida College of Medicine
Medical Director
Florida Hospital Institute for Minimally Invasive Therapy
Florida Hospital Orlando
Orlando, Florida, USA

Peter C. Hayes, MD, PhD
Professor of Hepatology
Liver Unit and Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
University of Edinburgh
Edinburgh, Scotland, UK

Julie K. Heimbach, MD
Professor of Medicine
Department of Surgery
Mayo Clinic
Rochester, Minnesota, USA

Virginia Hernández-Gea, MD, PhD
Barcelona Hepatic Hemodynamic Laboratory
Liver Unit, Hospital Clinic Barcelona
Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)
University of Barcelona
CIBERehd (Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas)
Barcelona, Spain

Michael S. Hoetker, MD
Innere Medizin 1
Universitätsklinikum Tübingen
Tübingen, Germany

Scott Inglis, BSc, MSc, PhD, MIPEM, CSci
Senior Clinical Scientist and Honorary Lecturer
Medical Physics, NHS Lothian/
University of Edinburgh
Royal Infirmary of Edinburgh
Edinburgh, Scotland, UK

Ivan Jovanovic, MD, PhD
Professor of Medicine
University of Belgrade
Belgrade, Serbia

Mouen A. Khashab, MD
Associate Professor of Medicine
Department of Medicine and Division of Gastroenterology and Hepatology
The Johns Hopkins Hospital
Baltimore, Maryland, USA

Anastasios Koulaouzidis, MD, FEBG, FACG, FASGE
Associate Specialist
Endoscopy Unit, Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
Edinburgh, Scotland, UK

Selina Lamont, MBChB, FRCPSGlasg
Consultant Gastroenterologist
Royal Alexandra Hospital
Paisley, Scotland, UK

Ryan Law, DO
Clinical Lecturer of Medicine
Division of Gastroenterology
University of Michigan
Ann Arbor, Michigan, USA

Michael J. Levy, MD
Professor of Medicine
Division of Gastroenterology and Hepatology, Mayo Clinic
Rochester, Minnesota, USA

Alvaro Martinez-Alcala, MD
Visiting Fellow
Therapeutic Endoscopy
Basil I. Hirschowitz Endoscopic Center of Excellence
University of Alabama
Birmingham, Alabama, USA

Klaus Mönkemüller, MD, PhD, FASGE
Professor of Medicine
Helios Klinikum Jerichower Land
Teaching Hospital of the
Otto-von-Guericke University
Burg, Germany

John N. Plevris, MD, PhD, FRCPE, FEBGH
Professor and Consultant in Gastroenterology
Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
University of Edinburgh
Edinburgh, Scotland, UK

Cristina Ripoll, MD
Assistant Professor
First Department of Internal Medicine
Martin-Luther-Universität
Halle-Wittenberg
Halle (Saale), Germany

Marcus C. Robertson, MBBS (Hons), BSci (Biotechnology)
Liver Transplant and Hepatology Fellow
Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
Edinburgh, Scotland, UK

Emanuele Rondonotti, MD, PhD
Gastroenterology Unit
Valduce Hospital
Como, Italy

Giovani E. Schwingel, MD
Attending Physician, Consultant
Cirurgia do Aparelho Digestivo
Gastroenterologia
São Bento do Sul
Santa Catarina, Brazil

Raj J. Shah, MD, AGAF
Professor of Medicine
Division of Gastroenterology and Hepatology
Director, Pancreaticobiliary Endoscopy
University of Colorado Anschutz Medical Campus
Aurora, Colorado, USA

Rohit Sinha, MBBS, MRCP(UK), PgDip(Lon)
Clinical Research Fellow in Hepatology
Centre for Liver and Digestive Disorders
Royal Infirmary of Edinburgh
University of Edinburgh
Edinburgh, Scotland, UK

Adrian Stanley, MBChB, MD, FRCPEd, FRCPSGlasg
Consultant Gastroenterologist and Honorary Clinical Associate Professor
Glasgow Royal Infirmary
Glasgow, Scotland, UK

Bezawit Tekola, MD
Senior Fellow
GI/Hepatology
Digestive Health Center
University of Virginia
Charlottesville, Virginia, USA

William M. Tierney, MD, FASGE, AGAF
Professor of Medicine
Digestive Diseases and Nutrition Section
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma, USA

Fanny Turon, MD
Barcelona Hepatic Hemodynamic Laboratory
Liver Unit, Hospital Clinic Barcelona, CIBERehd (Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas), Barcelona, Spain

Shyam Varadarajulu, MD
Professor of Medicine
University of Central Florida College of Medicine
Medical Director
Center for Interventional Endoscopy
Florida Hospital Orlando
Orlando, Florida, USA

Louis M. Wong Kee Song, MD, FASGE
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota, USA

Preface

Endoscopy is an integral part of the diagnosis and therapy of several conditions related to liver disease. Over the past decade, there has been a dramatic improvement in the technology and the number of endoscopic techniques available to the hepatologist or gastroenterologist with an interest in liver disease. This book fulfills the need for a comprehensive cover of all aspects of endoscopic procedures in the patient with liver disease including post-liver transplantation. These range from well established procedures, such as endoscopic band ligation of varices, to novel approaches, such as EUS guided coil or glue injection of gastric varices and radiofrequency ablation of gastric antral vascular ectasia. The apparatus we use has improved continuously with the development of endoscopes for enhanced imaging, confocal probes, and dedicated stents for variceal tamponade, to mention but a few.

We, at the Mayo Clinic and at Royal Infirmary of Edinburgh, envisioned the utility of putting together a collection of articles about the role of endoscopy in liver disease, which would be of interest to those working or training in this area. We have been fortunate to enlist clinicians and scientists with international recognition in the field to contribute highly informative and practically useful chapters to the book. We acknowledge the support of Wiley for bringing this endeavor to fruition.

John N. Plevris
Peter C. Hayes
Patrick S. Kamath
Louis M. Wong Kee Song

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/plevris/endoscopyinliverdisease

The website includes 11 high quality videos illustrating optimum endoscopy practice, all clearly referenced in the text.

Video 4.1 Primary prophylaxis of esophageal varices with endoscopic band ligation.
Video 5.1 Endoscopic injection sclerotherapy as salvage modality for failed band ligation of bleeding esophageal varices.
Video 5.2 Endoscopic band ligation of esophageal varices with stigmata of recent bleeding.
Video 5.3 Endoscopic band ligation of an actively bleeding esophageal varix.
Video 5.4 Endoscopic band ligation of actively bleeding gastroesophageal varices type I (GOV1).
Video 5.5 Endoscopic cyanoacrylate injection of fundal varices with stigmata of recent bleeding.
Video 8.1 Argon plasma coagulation of watermelon stomach.
Video 8.2 Management of polypoid lesions secondary to thermal therapy of gastric vascular ectasia.
Video 8.3 Radiofrequency ablation of gastric vascular ectasia.
Video 8.4 Cryotherapy of diffuse and extensive gastric vascular ectasia.
Video 8.5 Endoscopic band ligation of gastric vascular ectasia.

1

Equipment, Patient Safety, and Training

John N. Plevris[1] and Scott Inglis[2]

[1] *Professor and Consultant in Gastroenterology, Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, University of Edinburgh, Edinburgh, Scotland, UK*
[2] *Senior Clinical Scientist and Honorary Lecturer, Medical Physics, NHS Lothian/University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK*

Introduction

Liver disease and cirrhosis remain common causes of morbidity and mortality worldwide [1–3]. The significant advances in our understanding and treatment of liver disease, including liver transplantation over the last 25 years, have resulted in hepatology increasingly becoming a separate specialty. Although in many countries hepatologists have received background training in gastroenterology and endoscopy, subspecialization often means that they are no longer practicing endoscopists.

On the other hand, there are healthcare systems where hepatologists come from an internal medicine background with no prior training in endoscopy. It is therefore important for the modern hepatologist to have a full appreciation and up to date knowledge of the potential of endoscopy in liver disease and to ensure that there is a close collaboration between hepatology and endoscopic departments. In parallel to this, endoscopy has undergone a period of rapid expansion with numerous novel and specialized endoscopic modalities that are of increasing value in the investigation and management of the patient with liver disease.

The role of endoscopy in liver disease is both diagnostic and interventional. Endoscopy is commonly offered to patients with relevant symptoms (unsuspected liver disease may be diagnosed in this manner) and has a role in the management of inpatients with pre-existing liver disease, mainly for variceal screening and therapy. Furthermore, such patients can be challenging to sedate and the complexity and number of endoscopies in liver disease continue to increase with rising numbers of end-stage liver disease patients, patients who are considered for liver transplantation, and in post-liver transplant patients.

It is therefore not surprising that advanced endoscopic modalities, such as endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy (e.g., SpyGlass™), confocal endomicroscopy, and double balloon enteroscopy, have all become integral in the detailed investigation and treatment of liver-related gastrointestinal and biliary pathology (Figure 1.1).

It is now clear that the role of endoscopy in liver disease is well beyond that of just treating varices. As endoscopic technology advances, so do the indications and role of the endoscopist in the management of liver disease.

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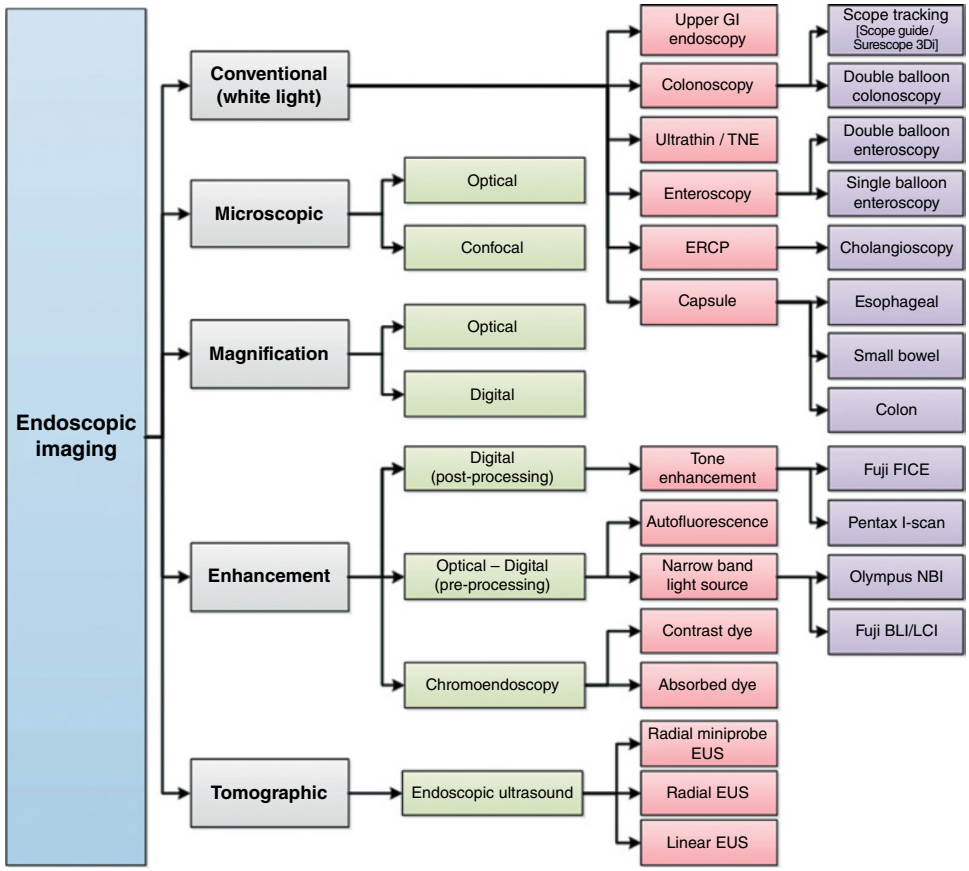


Figure 1.1 Endoscopic modalities used in the investigation and treatment of hepatobiliary disease and related disorders. BLI/LCI, blue color imaging/linked color imaging; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FICE, flexible spectral imaging color enhancement; GI, gastrointestinal; NBI, narrow band imaging; TNE, transnasal endoscopy.

Equipment

Endoscopy Room Setup

Optimum design and layout of the endoscopy room are important to ensure maximum functionality and safety while accommodating all the state of the art technology likely to be needed in the context of investigating complex patients with liver disease. The endoscopy room needs to be spacious with similar design principles to an operating theatre. Gas installations and pipes should descend from the ceiling and the endoscopy stack unit and monitors should be easy to move around and adjust according to the desired procedure, or mounted on pendants to maximize floor space.

A multifunctional endoscopy room able to accommodate different endoscopic procedures, such as esophagogastroduodenoscopy (EGD), enteroscopy, ERCP, and EUS, is advantageous. As such, the room design should be able to contain the following equipment:

1) An endoscopic stack system containing a light source and video processor unit that has advanced features (e.g., high definition (HD), alternate imaging modalities, image processing), HD capable monitor, and HD video and image capture device.

2) A physiological stats monitor to monitor vital signs such as blood pressure, heart rate, blood oxygenation levels, and electrocardiographic (ECG) readings.
3) An ultrasound (US) scanner/processor compatible with EUS endoscopes. Such a scanner usually includes modalities such as tissue harmonics, Doppler, color and power flow, contrast, and elastography.
4) A reporting system that allows for the speedy capture of images and the generation of reports connected to the central patient record system. This should be compatible with the hospital Picture Archiving and Communication System (PACS) for high resolution image transfer or videos.
5) A C-arm installation connected to a central PACS system for image archiving can be used in a well-equipped endoscopy room shielded for radiation. Alternatively, in many hospitals, ERCP or other interventional procedures requiring fluoroscopic guidance are carried out in the radiology department in order to benefit from regular updates of high quality radiology equipment and the presence of a radiographer.
6) Basic equipment required for patient treatment and safety, such as suction, water jet units, argon plasma coagulation (APC), electrosurgery, and emergency trolleys for acute cardiorespiratory arrest, as well as equipment for elective and emergency intubation and for delivery of general anesthesia.
7) Onsite pathology facilities (e.g., for real-time assessment of samples from EUS guided fine needle aspiration) may be found in many endoscopy units.

Endoscopic Stack

Modern endoscopic stacks have many common components – the light source to provide illumination and the video processor, which takes the endoscopic image from the charge coupled device (CCD) chip within the tip of the endoscope, processes the image and then displays it on the monitor in real time.

At present there are two methods employed for the transmission of light and display of the received image (Figure 1.2). One method is to transmit separate red (R), green (G), and blue (B) color spectrum wavelength components generated by RGB rotating filter lenses via an optical fiber bundle into the gastrointestinal tract. The reflected light intensity changes obtained from each RGB light are detected via a monochrome CCD where the video processor combines these with the appropriate R, G, or B color to generate a "white light" or color image, where each element of the CCD is one pixel of each frame of the video. The second option is to transmit white light, without alteration, and then detect the image using a color or RGB CCD, where multiple elements of the CCD are used to create one pixel in the video frame. A newer method, not widely used currently, that removes the need for the fiber transmission bundles, is the introduction of light emitting diodes (LEDs) built into the tip or bending section of the endoscope. The anatomy is imaged using a RGB CCD. Each transmission method has advantages and disadvantages, but in general visible resolution and detail definition of the image, due to advances in CCD manufacture and technology, have greatly improved irrespective of the technique used.

Furthermore, as camera chip or CCD technology has increased in resolution and decreased in size, manufacturers have been able to take advantage of improvements in display technology to visualize the gastrointestinal tract in high resolution, thus giving the endoscopist a new dimension in detecting pathology.

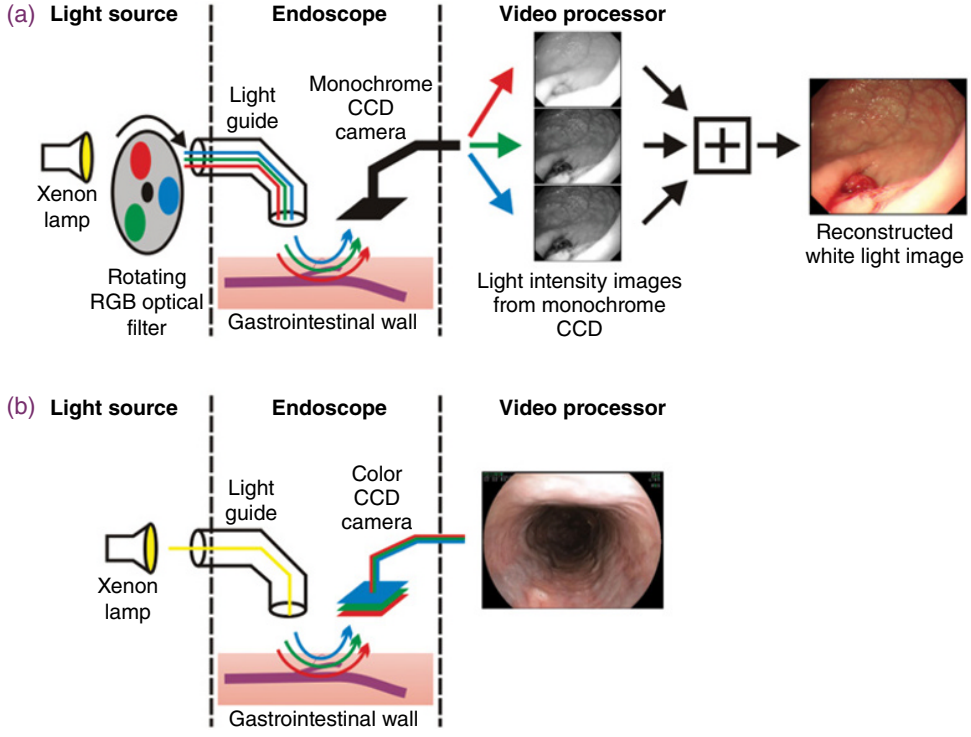


Figure 1.2 (a) Transmission of RGB (red, green, blue) light wavelengths that are detected using a monochrome charge coupled device (CCD). (b) Transmission of white light that is visualized using a color CCD.

Image Enhancing Modalities

Manufacturers have introduced various image enhancement techniques (Figure 1.3) to aid in the detection and delineation of pathology for more accurate diagnosis and targeted treatment [4]. Examples of these include narrow band imaging (NBI; Olympus Corp., Tokyo, Japan), flexible spectral imaging color enhancement (FICE; Fujinon Corp., Saitama, Japan), and i-Scan (Pentax Corp., Tokyo, Japan). NBI operates on a different principle to the other systems, as it limits the transmitted light to specific narrow band wavelengths centered in the green (540 nm) and blue (415 nm) spectra. This allows for detailed mucosal and microvascular visualization, thus facilitating early detection of dysplastic changes. Alternatively, FICE and i-Scan use post-image capture processing techniques that work on the principle of splitting the images into "spectral" components. Specific spectral components are then combined, with the "white light" image, in a number of permutations, thus creating different settings that aim to enhance the original endoscopic image and delineate the gastrointestinal mucosa or vascular structures.

New Advances in Image Enhancement

An alternate image enhancement technique to NBI, i-Scan, and FICE has been introduced by Fujifilm with the release of the ELUXEO™ endoscopy system, consisting of a new video processor and light source. Within the light source, Fujifilm have replaced the standard xenon lamp and have instead incorporated four LEDs with wavelengths in the red, green, blue,

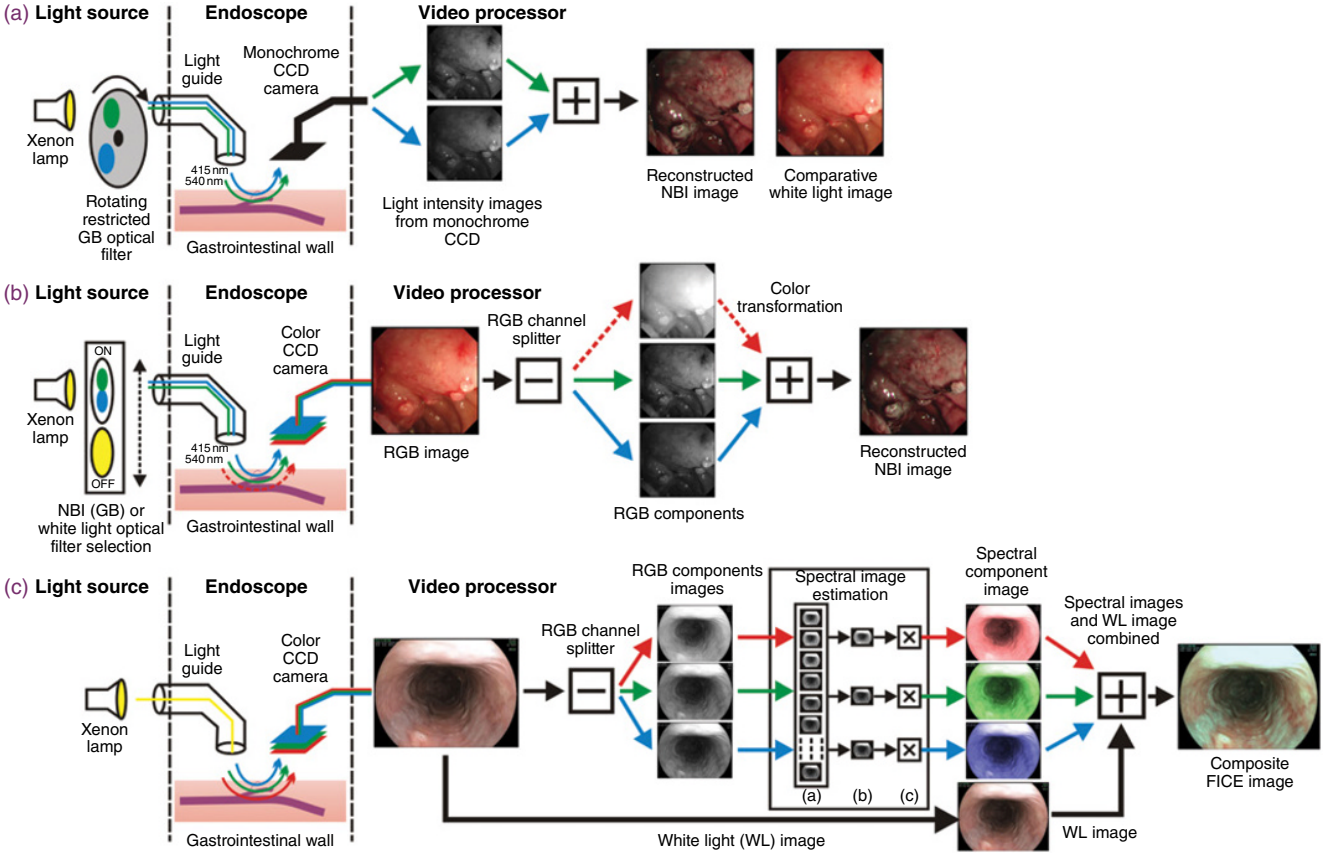


Figure 1.3 (a) Narrow band imaging (NBI) using a monochrome charge coupled device (CCD) camera (mainly used in UK and Japan). (b) Altered version of NBI for use with the color CCD camera (Europe and USA/rest of world). (c) Flexible spectral imaging color enhancement (FICE). B, blue; G, green; R, red; WL, white light.

and blue-violet spectra. They have replaced FICE with two dedicated image enhancement techniques: (i) blue light imaging (BLI); and (ii) linked color imaging (LCI). The incorporation of a dedicated blue-violet LED takes advantage of the short wavelength absorption of hemoglobin (410 nm), which can enhance the underlying superficial vascularity and mucosal patterns (Figure 1.4). LCI is an image processing technique that separates the four color channels to allow for the enhancement of the difference in the red color spectrum and improve the detection and delineation of mucosal inflammation (Figure 1.5).

Endoscopes

The quality of modern endoscopes has greatly improved; they are far more ergonomic in design and lighter, with superior picture resolution and definition. Endoscopes have also become slimmer and this has significantly impacted on patient safety and comfort. The incorporation of high resolution (up to 1 million pixels) and high definition (>1 million pixels) camera technologies into modern endoscopes and the introduction of new image enhancement techniques have significantly enhanced the endoscopist's arsenal in the detection and treatment of gastrointestinal pathologies. With such advanced optics, fine mucosal details can be visualized which may reveal subtle pathology, such as angioectactic lesions, watermelon stomach, portal hypertensive gastropathy, enteropathy, and ectopic varices at a far earlier stage than with older generation endoscopes.

Modern endoscopes are far more advanced than previous generation ones, resulting in more space being available in the insertion tube, and therefore larger working channels can be included, allowing for more powerful air suction and insufflation, as well as water irrigation to clean the lenses. Powerful air insufflation can often flatten even large varices. This has to be taken into account when grading varices using a commonly used classification system by Westaby et al. [5], which depends on the percentage of circumference of the esophageal lumen occupied by a varix and whether the varix can be flattened by air insufflation.

In general, the types of upper gastrointestinal endoscopes used in the context of liver disease are the standard endoscopes that possess a working channel of 2.8 mm, the therapeutic endoscopes with a working channel of 3.2 or 3.6 mm (often used in the context of upper gastrointestinal bleeding), and more recently the high resolution ultrathin endoscopes (5.9 mm). The latter have become more popular in the last few years, not only in diagnostics, but also in the assessment of varices, particularly for patients who have been finding frequent surveillance endoscopies to monitor variceal progression stressful. Such endoscopes can be used transnasally, which has been shown in some studies and select patient populations to be more comfortable than standard endoscopy [6]. Ultrathin endoscopes improve patient tolerance while maintaining an adequate or even near standard size working channel (2.4 mm) for endoscopic biopsies. Such endoscopes, however, are not suitable for endoscopic variceal banding (Figure 1.6).

Endoscopic Ultrasound

Side and front optical viewing endoscopes with appropriate technology have been used to perform EUS, and these are commonly used for diagnosis and therapy in the patient with liver disease. This technique can be of value in the diagnosis of varices, particular ectopic varices (Figure 1.7), in assessing eradication of varices, and in delivering EUS guided therapies, such as thrombin or cyanoacrylate injection for variceal obliteration [7]. EUS guided measurement of the hepatic venous pressure gradient (HVPG) is possible, as are biopsies of the hepatic parenchyma

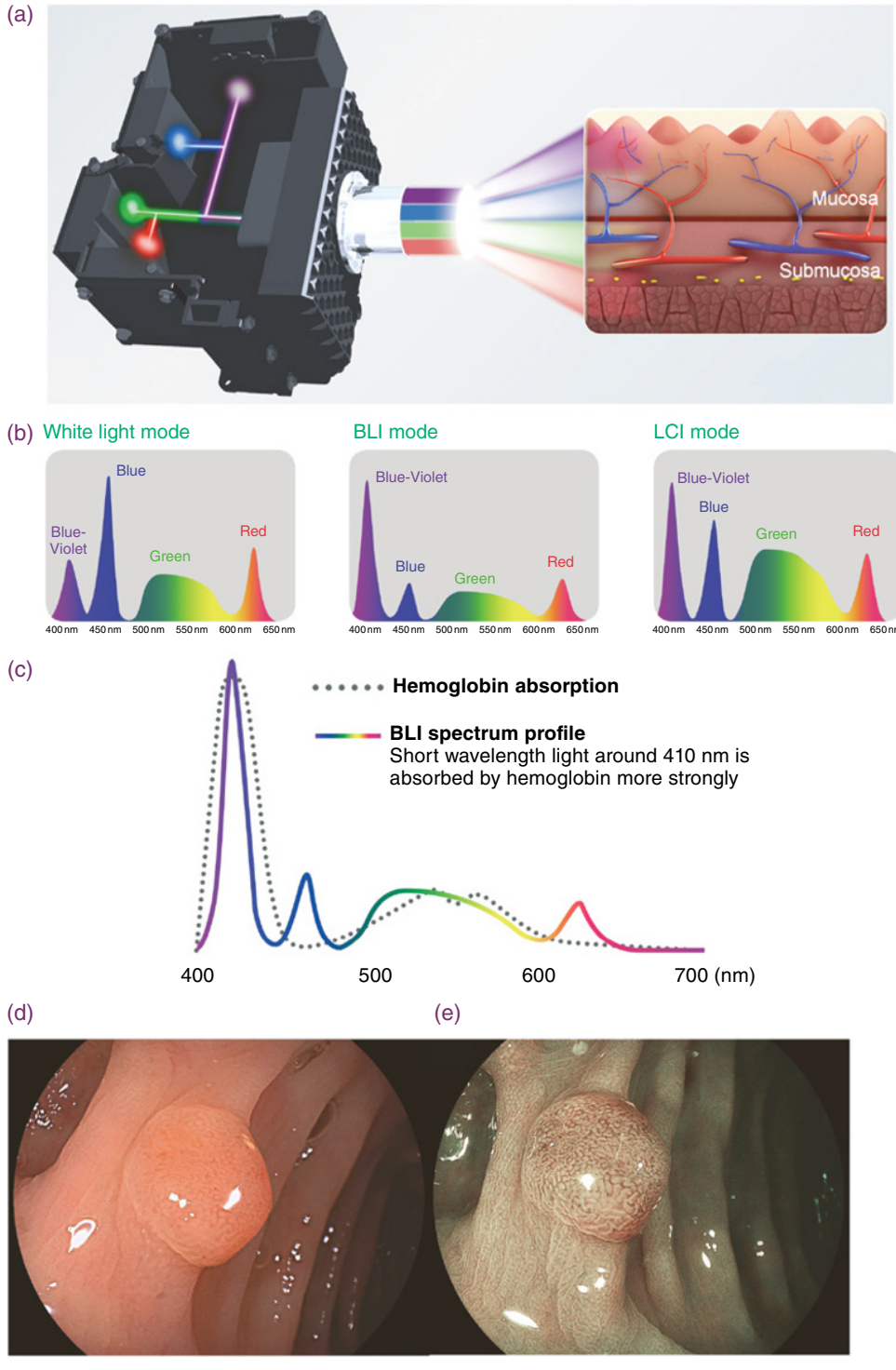


Figure 1.4 (a) The function of the four light emitting diodes (LEDs) in relation to the depth of penetration of the light spectra from the new ELUXEO™ light source. (b) The difference in the transmitted spectra when in white light, blue light imaging (BLI) and linked color imaging (LCI) modes. (c) The short wavelength absorption characteristics of hemoglobin in comparison to the transmitted light spectra of BLI. (d, e) Images of a polyp captured using (d) white light, and (e) BLI.
Source: Reproduced with permission of Aquilant/Fujifilm.

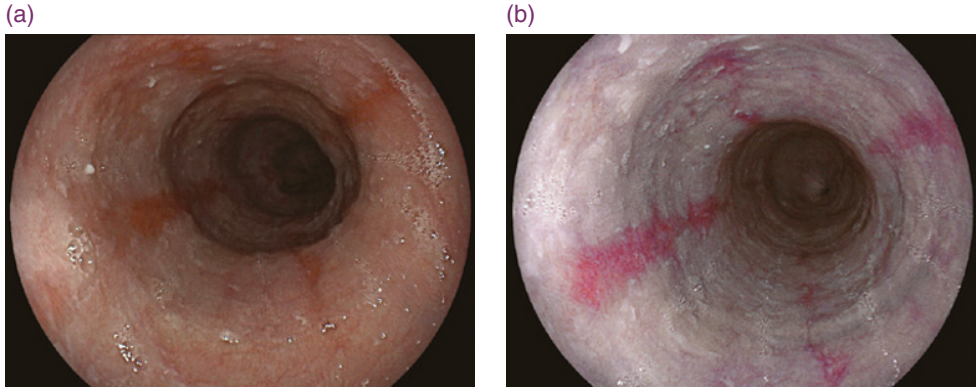


Figure 1.5 Views of the esophagus in (a) white light mode and (b) linked color imaging mode. Source: Reproduced with permission of Aquilant/Fujifilm.

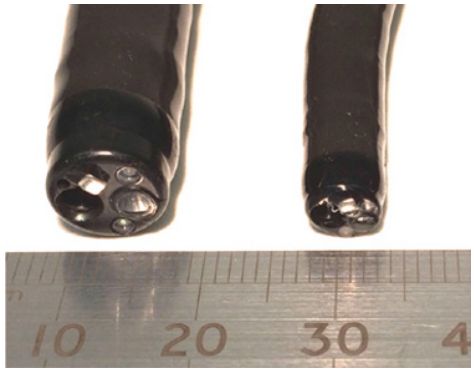


Figure 1.6 Tip of a standard endoscope (9.2 mm, left) versus the tip of an ultrathin endoscope (5.9 mm, right).

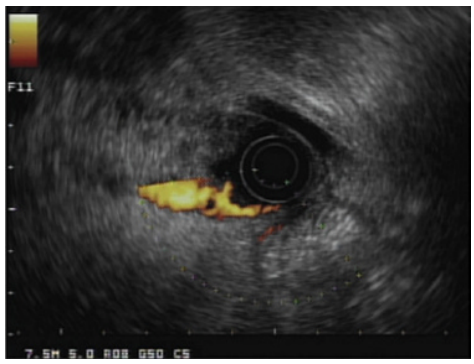


Figure 1.7 Appearance of an ectopic varix under endoscopic ultrasound in the second part of the duodenum.

and masses in the left lobe of the liver. Both linear and radial echoendoscopes (Figure 1.8) should be available with appropriate clinical expertise in a center dealing with complex patients with liver disease. Additional modalities, such as tissue harmonics, Doppler color and power flow, contrast, and elastography (for assessing tissue stiffness), are also of value in the context of liver disease. The use of high frequency (12 or 15 MHz) ultrasound miniprobes through the working channel of a standard or double channel therapeutic endoscope can also be used for a quick assessment of variceal obliteration (Figure 1.9).

Endoscopic Retrograde Cholangiopancreatography

The latest ERCP scopes, together with the SpyGlass™ technology [8], have enabled direct visualization of the biliary tree and this has significantly improved our ability to diagnose malignant biliary disease. In 2007, the first generation SpyGlass™ Direct Visualization System (Boston Scientific Corp., Natick, MA, USA) was introduced (Figure 1.10). This relied on a small fiberoptic bundle with an external CCD, introduced into a dedicated catheter, to visualize the biliary tree. The SpyGlass™ DS system introduced in 2015 has evolved

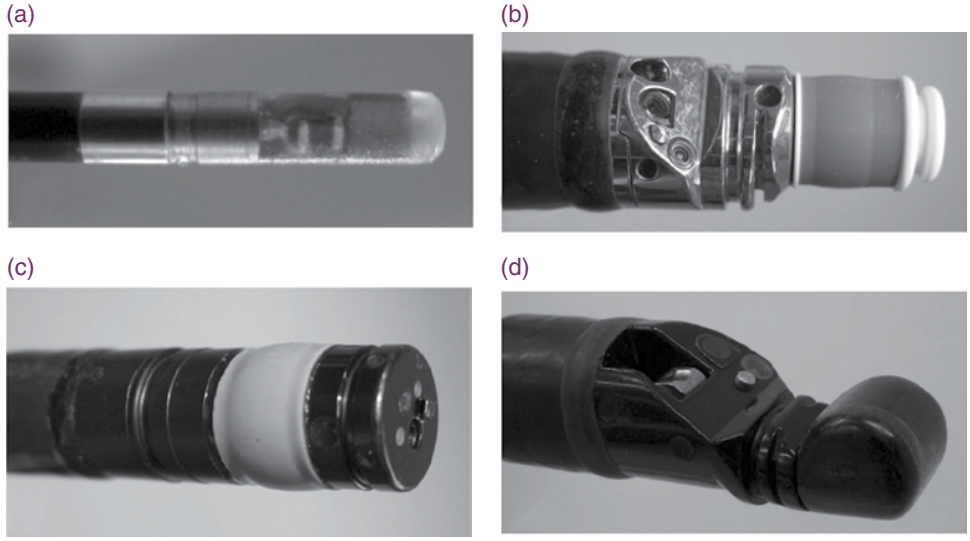


Figure 1.8 Endoscopic ultrasound (EUS) equipment with (a) a miniprobe 2.6 mm in diameter; (b) and (c) are 360° radial views, one with side viewing optics and the other with front viewing optics, respectively; and (d) the linear or fine needle aspiration EUS instrument.

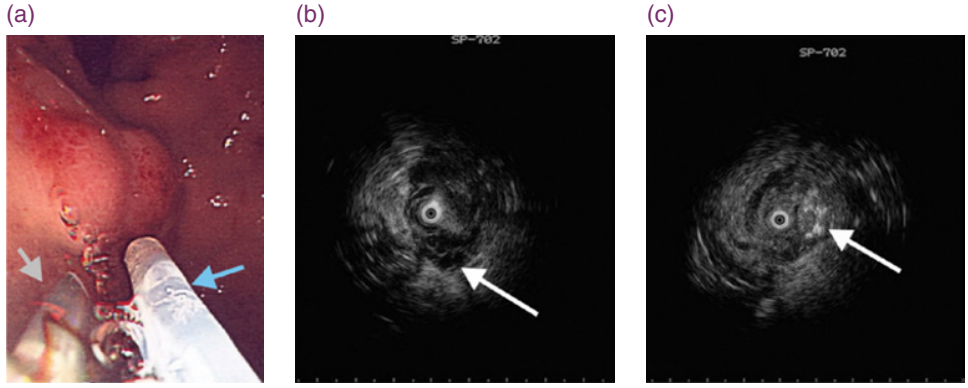


Figure 1.9 (a) Injection of thrombin for variceal obliteration using an endoscopic ultrasound miniprobe (grey arrow) and an injection needle (blue arrow). (b) Appearance of varices under a 12 MHz miniprobe (white arrow). (c) "Snow storm" appearance of an obliterated area of a varix (white arrow) following thrombin injection.

to be a small digital endoscope, with improved optical resolution (approximately × 4), a wider field of view (60%), and dedicated LED illumination.

Recently there have been safety concerns about the design of the ERCP endoscopes and their ability to be sterilized adequately as bacterial transmission of resistant bacteria from patient to patient has been reported [9–12]. As can be appreciated by the complex design of the tip of the ERCP endoscope (Figure 1.11), meticulous cleaning is required to ensure high level decontamination of such endoscopes. This has led to the revision of decontamination protocols [13] and calls for the revision of the design of the latest ERCP endoscopes [14].

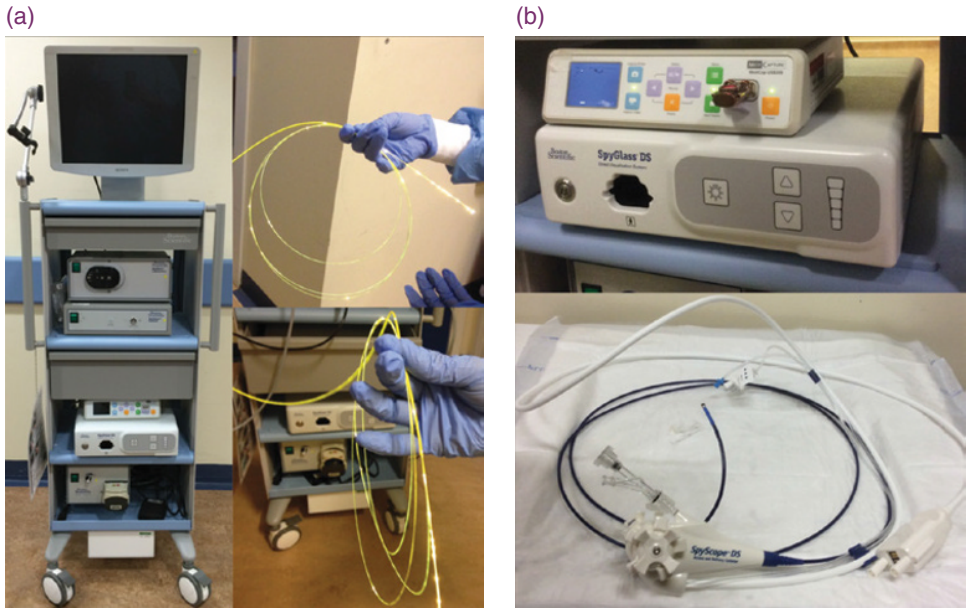


Figure 1.10 (a) SpyGlass™ system and first generation catheter for the direct visualization of the biliary tree. (b) Second generation SpyGlass™ DS processor and single use endoscope.

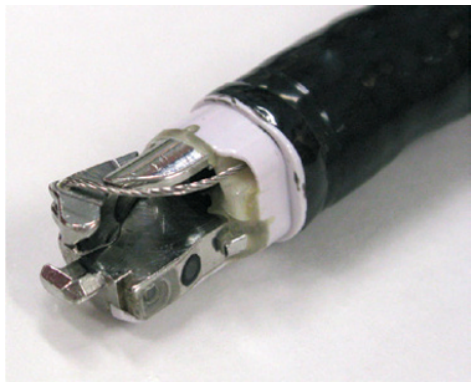


Figure 1.11 Tip of an ERCP endoscope. The complex design to ensure effective movement of the bridge is associated with increased risk of infection transmission despite appropriate decontamination.

There has been an increase in the use of deep enteroscopy (both single and double balloon) in the management of patients with chronic liver disease [15]. These endoscopes are used for deep intubation and access to the common bile duct (double balloon assisted– ERCP) in the context of altered anatomy (e.g., Roux-en-Y in cases of hepaticojejunostomy) or for the investigation and treatment of small bowel pathology in the patient with liver disease (e.g., treatment of ectopic varices or biopsies of the small bowel in the post-liver transplant patient to exclude sinister pathology such as lymphoma). Such procedures require special expertise, are time consuming, and preferably should be performed under general anesthesia.

Colonoscopy

Colonoscopy in the patient with liver disease is not dissimilar to other patients. HD colonoscopes should be used to ensure diagnosis and therapy are optimized. Appropriate enhanced imaging modalities, such as NBI and FICE, are available although their value in the colon has been debated compared with that in the upper gastrointestinal tract.

High quality colonoscopy is particularly important in the workup of patients prior to liver transplantation to ensure that colon cancer is not missed. This is particularly important in the context of primary

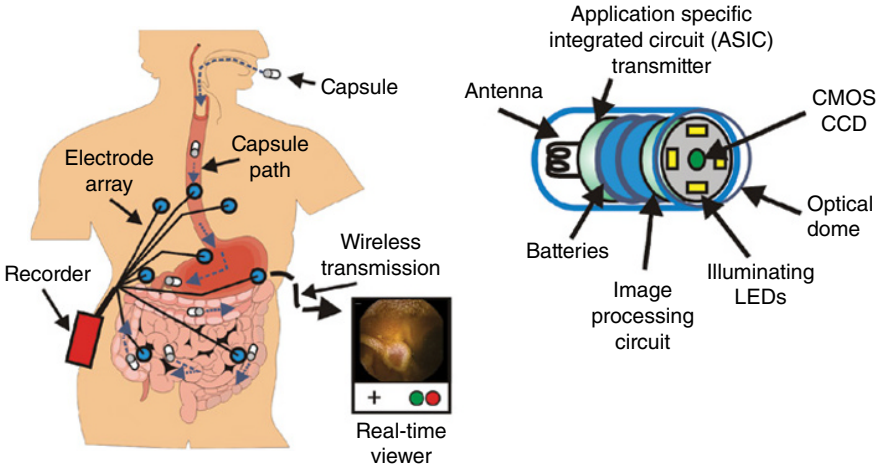


Figure 1.12 Wireless capsule measurement setup and basic capsule schematic. CCD, charge coupled device; CMOS, complementary metal oxide semiconductor; LED, light emitting diode.

sclerosing cholangitis. Colonoscopy may also be required in the evaluation of gastrointestinal bleeding and the treatment of colonic (mainly rectal) varices.

Wireless Endoscopy

Wireless capsule endoscopy is valuable in the assessment of esophageal varices in a selected group of patients with liver disease who for a number of reasons may not be keen to undertake routine endoscopic surveillance [16] and in patients with suspected small bowel sources of bleeding [17]. The basic schematic of the capsule and the procedure setup are detailed in Figure 1.12. They mainly consist of a power source (batteries), a CMOS (complementary metal oxide semiconductor) or CCD chip, lens and associated imaging board, illuminating LEDs, and a transmitter to wirelessly transmit or stream the video to an external recorder. Several companies now compete and produce high quality wireless systems with slightly different capsule characteristics (Figure 1.13).

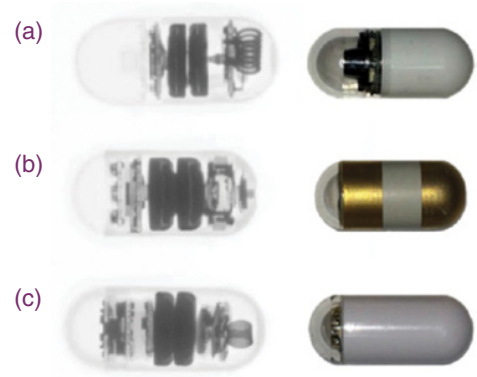


Figure 1.13 Examples of the internal and external structure and components of the main capsule systems. Both (a) and (c) use radiofrequency (RF) transmission and dedicated RF receiver arrays for wireless video recording, whereas (b) uses the body to transmit the video to the recorder. Standard electrodes in an array are used to pick up the video signals.

Accessories and Consumables

A number of accessories are routinely used in the context of endoscopy in liver disease. These include variceal band ligators, endoloops, injection needles for delivering sclerosants (rarely used nowadays), thrombin or cyanoacrylate (superglue), and fine needle devices for the deployment of coils. All these techniques have been shown to be relatively minimally invasive but effective in controlling variceal bleeding [18–20]. Other modalities include APC for the

delivery of coagulation for bleeding from gastric vascular ectasia, as well as recently introduced radiofrequency ablation (RFA) probes for the therapy of obstructing cholangiocarcinoma. It is now widely accepted that single use accessories and consumables should be used to ensure maximum infection control.

In conclusion, a well-designed and well-equipped endoscopy unit is important for the delivery of state of the art endoscopic therapy for patients with liver disease, whose diseases for the most part are high risk and of high complexity.

Patient Safety and Training

Patient safety is best achieved by high standards of equipment disinfection and maintenance, appropriate patient selection, and endoscopy of high risk patients in a safe environment (e.g., critical care unit) with adequate support from anesthesiologists and an appropriately trained team of endoscopists and nurses.

Cleaning and Disinfection of Endoscopes

Endoscopes need to go through a complex disinfection/sterilization procedure to eliminate the transmission of bacteria, viruses, parasites, fungi, and spores, as well as prions that can transmit spongiform encephalopathy. As such, strict operating protocols should be in place and followed in a very rigorous manner based on published guidelines and standards relating to disinfection/sterilization processes. This improves the safety and minimizes the risk of infection in patients undergoing endoscopy. Publications such as the *Guidelines and Tools for the Sterile Processing Team* [21] and sterile processing accreditation surveys [22] published by the Association of periOperative Registered Nurses' (AORN) journal, and important communications and updates from regulatory bodies such as the Food and Drug Administration and Centers for Disease Control, raise awareness among healthcare professionals and ensure that a high level of safety is maintained [23,24].

Accreditation surveys performed by specialist agencies and professional organizations are peer reviewed and focus on safety and quality of patient care, thus encouraging the development and adherence to robust processes for endoscopy units in order to achieve accreditation.

In most endoscopy units, automated cleaning/washing machines are available for cleaning and reprocessing the endoscopes. Depending on the number of endoscopy rooms and the volume of endoscopic procedures per week, specific guidelines exist regarding the design of decontamination facilities to ensure effective risk control. The *Choice Framework for Local Policy and Procedures 01-06* by the UK Department of Health [25] details the best evidence based policies and gives comprehensive guidance on the management and decontamination of reusable medical devices.

It is particularly important to ensure that the workflow within the endoscopy unit is from dirty to clean. Such workflow avoids recontamination of reprocessed endoscopes from unprocessed, and thus contaminated, devices. An example of a high throughput reprocessing unit is illustrated in Figure 1.14.

Employment of appropriately trained staff accountable to a management structure is important to ensure adherence to decontamination protocols and best utilization of resources. The purchase of suitable automated endoscope reprocessors is important. Optimal reprocessing also depends on the local quality of water used, the decontamination agents used, and the endoscope manufacturer to ensure compatibility and minimization of the damaging effect of disinfection on endoscopes.

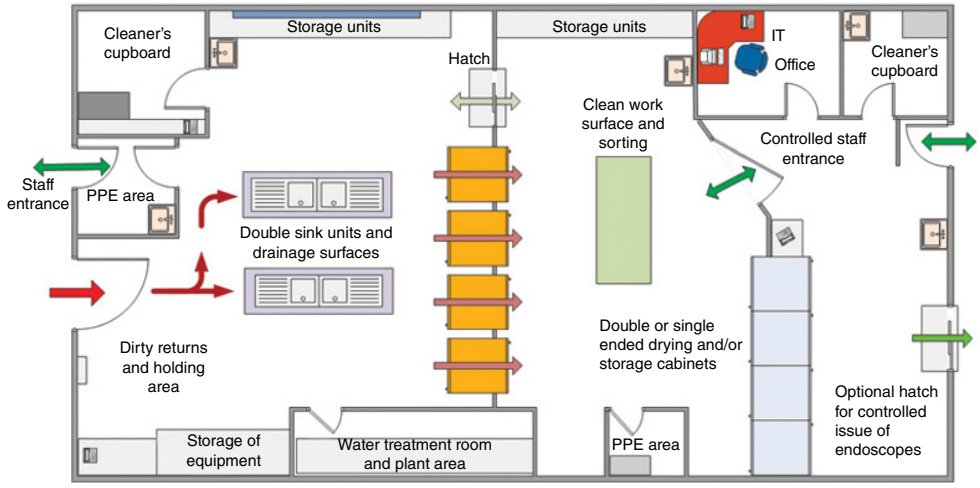


Figure 1.14 Optimum layout of a disinfection/decontamination unit as recommended by the UK Department of Health. PPE, personal protective equipment. Source: Adapted from © British Crown Copyright 2016, licensed under http://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/.

The previously used aldehyde based detergent (glutaraldehyde) should be avoided as this may result in fixing prions inside the endoscopes, thus increasing the risk of transmission of prions, leading to spongiform encephalopathy. In general, neutral pH or neutral enzymatic agents are recommended because of their effective decontamination while having the least damaging effect on endoscopes.

Rigorous and regular microbiological tests reflecting the best evidence based practice are necessary to ensure that the decontamination process remains of high standard. The decontamination room staff should constantly be in communication with the infection prevention and control teams, which typically include medical and nursing personnel and a microbiologist trained in infection control.

Transmission of hepatitis viruses is very rare if all standard operating procedures are followed. It is, however, particularly important in the context of liver disease to ensure that there are robust systems in place for tracking all endoscopes used through a unique endoscope identifier, as well as being able to trace the journey of a particular endoscope through its decontamination and clinical usage. Such information is critical in the unfortunate event of a safety breach, which may expose several patients to risks of infection, so as to be able to recall all patients who underwent procedures with inadequately sterilized endoscopes and provide prophylactic therapy as appropriate.

Specifically in the context of prion transmission, it is of paramount importance that early action be taken in the event that the guidelines have not been followed during a procedure with a high risk for transmission of variant Creutzfeldt–Jakob disease (vCJD), thus potentially contaminating the endoscope. Such endoscopes need to be quarantined immediately, as once they have been contaminated there is no safe method of disinfection. These endoscopes should be reserved exclusively for an individual patient at high risk of vCJD if future endoscopic procedures are required. Specific guidelines regarding prion transmission are in place through the British and American Societies of Gastroenterology. A summary of these guidelines is presented in Figure 1.15 [26,27].

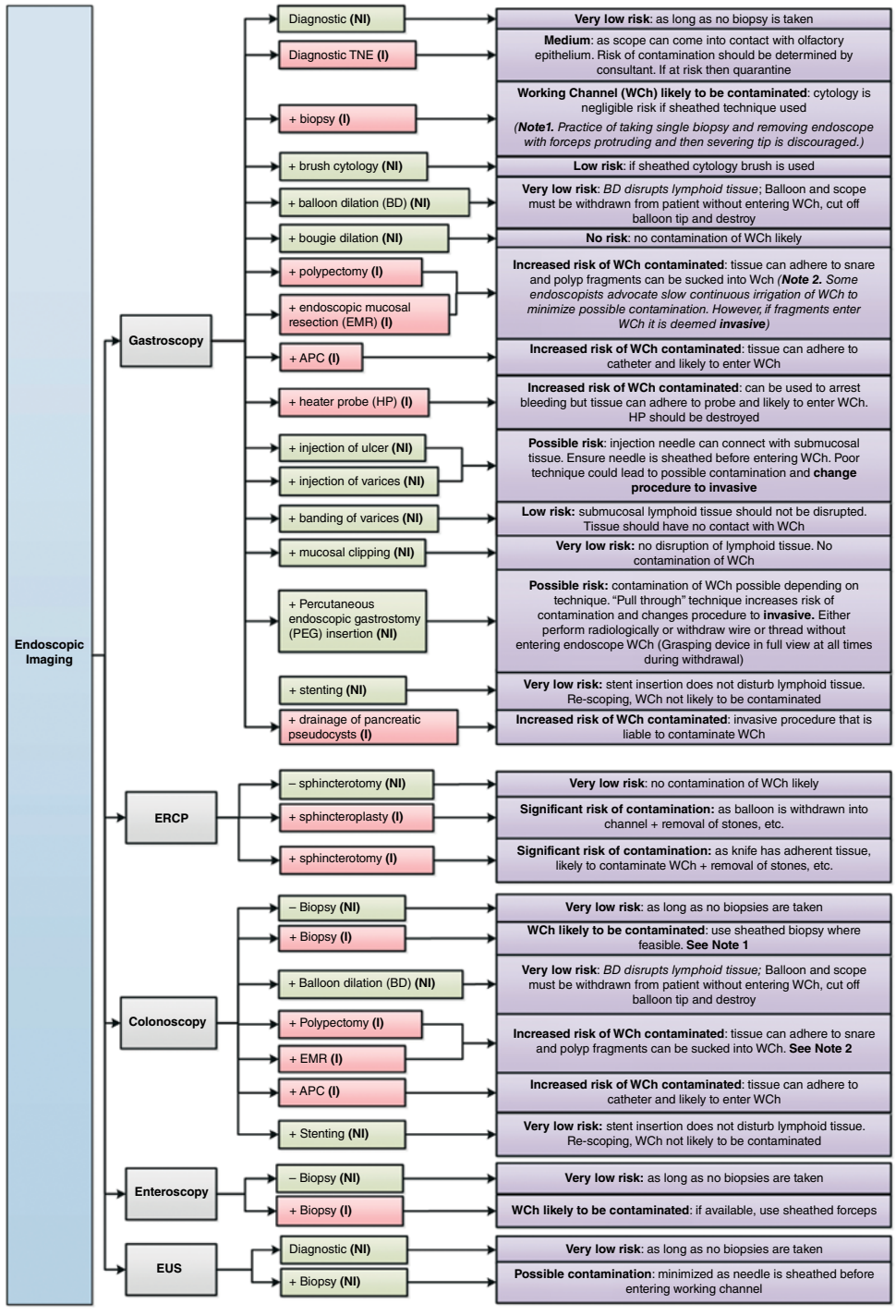


Figure 1.15 Endoscopic procedures considered high risk for prion transmission in pink and low risk in green. APC, argon plasma coagulation; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; I, invasive; NI, non-invasive; TNE, transnasal endoscopy. Summarized from *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection: Annex F*: Endoscopy, 2015.

It is now recommended to routinely use single use endoscopic accessories, which minimize the risk of transmission of infection. Storage of disinfected endoscopes should be in designated clean and dry areas, preferably in dedicated storage cabinets with HEPA (high efficiency particulate air) filtered air, which allows the endoscopes to be stored and dry for 72 hours without the need for reprocessing. This is particularly useful in busy units with regular off hours endoscopy.

Patients

A detailed history of previous infection should be taken to ensure that high risk patients for viral hepatitis, as well as vCJD and other infectious diseases, are identified. In that respect, important information, such as travel to endemic areas for infections and previous blood transfusions or administration of blood products or surgery in the past, needs to be carefully recorded.

Patients with liver disease at risk of cardiorespiratory compromise should receive the endoscopy under anesthetic support. This is particularly important for patients with encephalopathy and those with alcohol withdrawal symptoms who are far more sensitive and run a high risk of permanent brain injury even after short periods of hypoxia following aspiration or cardiac arrest.

Endoscopy in patients at risk of multiorgan failure should be performed in a critical care environment. The decision and timing of endoscopy should always be balanced against the risks for the individual patient with liver disease. Optimization of the patient's clinical condition by correction of coagulopathy, prophylactic antibiotics, and judicious use of blood transfusion is the cornerstone of safe endoscopy in such patients.

Health Personnel and Training Issues

Since each patient or health staff member is a potential source of infection, precautions are necessary from the personnel point of view to avoid being infected or to pass infection to patients. Personnel should be vaccinated in case of hepatitis A or B or other infection, such as typhoid, depending on the prevalence of such infections in their environment. Meticulous hand washing before and after treating each patient should be practiced. It is also desirable that operators wear protective gowns during endoscopic procedures, as well as gloves, designated shoes, and, whenever appropriate, masks and protective eyewear. Training and operating protocols should be available in each endoscopy room, reviewed at regular intervals, and evaluated to ensure that they are followed. Any incident should be immediately notified to the hospital safety team to ensure that the incident is investigated. Such incidents should be reviewed at regular endoscopy quality improvement meetings to ensure that policies and procedures can be modified to avoid similar incidents in the future.

All practitioners performing endoscopy in patients with liver disease should have adequate training to recognize and treat esophagogastric varices in the elective and acute setting. Familiarization with appropriate equipment and accessories on models and simulators in "hands-on" workshop sessions can greatly enhance training prior to participating in real life cases.

Medical teams should be particularly aware that the patient with liver disease is often likely to have hepatic decompensation in the context of significant bleeding or a complication. Therefore, further management is often required in a critical care environment. This is particularly important for the cirrhotic patient with bleeding varices who has become encephalopathic and runs the risk of aspiration. Appropriate training to recognize such patients for transfer to a critical care unit and assisted ventilation is important. Close collaboration between the endoscopist and hepatologist is necessary, so that the endoscopist is fully aware of

hepatic complication risks and, likewise, the hepatologist is fully aware of the latest endoscopic developments available that can be used to maximize the quality of care of the patient with liver disease.

Acknowledgment

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2

Sedation and Analgesia in Endoscopy of the Patient with Liver Disease

Rohit Sinha[1], Anastasios Koulaouzidis[2], and John N. Plevris[3]

[1] *Clinical Research Fellow in Hepatology, Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, University of Edinburgh, Edinburgh, Scotland, UK*
[2] *Associate Specialist, Endoscopy Unit, Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK*
[3] *Professor and Consultant in Gastroenterology, Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, University of Edinburgh, Edinburgh, Scotland, UK*

Introduction

Sedation for endoscopy in patients with liver disease can be a challenging issue. Endoscopists often face the dilemma over providing sufficient sedation to allow for maximum patient comfort whilst maintaining safety. Although performing endoscopy under sedation is not always necessary in the context of liver disease it ensures patient comfort, improved tolerance, and procedure success. This translates to compliance with future procedures, as repeat endoscopies are often necessary for screening or treatment of portal hypertension complications. Sedation is associated with increased patient satisfaction and greater willingness to have a repeat procedure [1].

Pharmacokinetics is altered in liver disease due to impaired metabolism and often coexisting renal impairment. An altered unbound drug fraction due to decreased albumin synthesis and portal–systemic shunting will affect drug distribution. This complex interplay alters first pass clearance and drug elimination. Furthermore, drug to drug interactions, coexisting alcohol consumption, cerebral sensitivity [2], and minimal hepatic encephalopathy (HE) also affect pharmacodynamics. The majority of patients with cirrhosis and portal hypertension may have covert or minimal HE [3,4]; these patients are more sensitive to benzodiazepines, which may then precipitate overt HE.

Deep sedation has substantial variability regarding its effect on portal pressure and hepatic blood flow [5]. Despite most drugs being metabolized in the liver, there are no widely agreed guidelines on sedation and analgesia for diagnostic or therapeutic endoscopic procedures in patients with liver disease.

Conscious sedation in gastrointestinal endoscopy is commonly practiced in the UK, North America, and most European centers. Endoscopists often choose to administer opioid analgesics in addition to a sedative medication, particularly for therapeutic endoscopy.

The need for sedation and/or analgesia is dictated by the complexity of the procedure,

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Table 2.1 Summary of sedatives and analgesics commonly used in gastrointestinal endoscopy.

Drug	Dose	Reversal agent	Advantages	Disadvantages
Topical agent (lidocaine pharyngeal anesthesia)	100–200 mg topical spray	None	45–90 seconds Rapid action	Anaphylaxis, aspiration
Midazolam	30–80 µg/kg	Flumazenil	3–5 minutes Quick action	Slower recovery* Higher risk of precipitating HE*
Propofol	2–2.5 mg/kg (<55 years) 1–1.5 mg/kg (>55 years)	None	30–45 seconds Rapid action	Narrow therapeutic window Expert administration needed Advanced monitoring needed
Fentanyl	50–100 µg	Naloxone	3–5 minutes Quick onset	May precipitate HE
Pethidine (meperidine)	25–50 mg	Naloxone	5–8 minutes Quick onset	Higher risk of precipitating HE†

* Relative to propofol.
† Relative to fentanyl.
HE, hepatic encephalopathy.

the presence of comorbidities, and the severity of the liver disease as determined by the Child–Pugh or Model for End-stage Liver Disease (MELD) score. In general, complex and prolonged therapeutic procedures require deeper sedation and the co-administration of analgesia. In such instances, it is important to receive input from an anesthesiologist to assess the need for general anesthesia or deeper sedation with a combination of propofol and opiates in a controlled and closely monitored environment.

In this chapter we discuss the commonly used medications for sedation and analgesia (Table 2.1) and the indications for deeper sedation, including a general anesthetic.

Midazolam

General

Midazolam is a benzodiazepine that acts as a depressant of the central nervous system, with a sedation potency 1.5–3.5 times greater than that of diazepam [6]. Benzodiazepines have anxiolytic, amnesic, and sedative properties; and at higher doses act as anticonvulsants and muscle relaxants. Midazolam is preferred in most centers due to its pharmacokinetic profile as well as its potent amnesic properties [3]. It has a dose dependent action mediated through gamma aminobutyric acid (GABA) receptors and is reversed by the specific antagonist flumazenil.

Midazolam reaches its maximum effect after 3–4 minutes, although the duration of the effect is between 15 and 80 minutes, depending on cofactors including obesity, advanced age, and comorbidities such as liver or kidney disease [7].

Administration

Midazolam is usually given as an initial bolus of 30–50 µg/kg body weight for upper and lower gastrointestinal endoscopy [6]. This translates to an initial dose of 2–3 mg in a 70 kg male. Subsequent 0.5–1 mg bolus doses can be given until the desired sedation depth is reached.

Lower starting doses are recommended for patients who are frail, elderly, and with more advanced liver disease [6]. Midazolam administration by non-anesthesiologist is commonly practiced as there is an antagonist available (flumazenil) that can rapidly reverse sedation [1]. McQuaid and Laine [8], in their systematic review and meta-analysis, suggest that moderate sedation provides a high level of physician and patient satisfaction as well as a low risk of serious adverse events.

Midazolam is rapidly metabolized in the liver by the cytochrome P450 via hydroxylation and conjugation with glucuronic acid [9]; therefore, the elimination half-life and clearance of its metabolites can be significantly altered in liver disease [10]. MacGilchrist et al. [9] observed a twofold prolongation of the elimination half-life of midazolam (3.9 versus 1.6 hours) as a result of decreased clearance in patients with end-stage liver disease. In comparison with propofol, midazolam is more likely to precipitate overt HE in chronic liver disease [6,11,12], and even more so in advanced liver disease [13]. Therefore, caution is advised during administration, with adherence to dosages as recommended above. Midazolam in patients with decompensated cirrhosis can result in prolongation of the sedative effect for up to 6 hours following administration [2].

Chalasani et al. [14] showed that the bioavailability of midazolam in patients with cirrhosis and a transjugular intrahepatic portosystemic shunt was increased almost threefold compared with cirrhotic controls or healthy volunteers.

Propofol

General

Propofol is a sedative with minimal analgesic and amnesic effects. It is very lipophilic, which explains its rapid mode of action. It readily crosses the blood–brain barrier and acts on GABA receptors to induce its sedative effect. It has an onset of action of approximately 30–45 seconds, peaking at 2 minutes, with an overall duration of 4–8 minutes. The depth of propofol sedation depends on the dose; even a single dose can result in various levels of sedation, therefore administration of propofol requires significant clinical expertise in assessing the level of sedation so the dose can be adjusted appropriately [7].

A meta-analysis found evidence that propofol is superior to midazolam for rapid sedation and recovery, with minimal risk of sedation-related side effects [15]. Due to concerns of potential progression to general anesthesia from deep sedation, the American Society of Anesthesiologists (ASA) recommend propofol administration by trained healthcare professionals who are independent from the endoscopist carrying out the procedure. Their consensus statement prohibits non-anesthetists from using propofol [16]. The concept of non-physician assisted propofol sedation has been much debated; in established practices it has been deemed safe, although not completely free of risk even in healthy individuals [17].

Due to higher risk of apnea, prolongation of the QT interval, and hypotension, continuous cardiac and respiratory monitoring with capnography is recommended during propofol administration. Furthermore, propofol does not offer analgesia, and physiological response to pain can still be seen. Combining opiates may have additive benefit but the risk of deeper sedation and prolongation of recovery may be an undesirable effect. Propofol sedation during colonoscopy appears to have lower odds of cardiopulmonary complications compared with traditional agents, but for other procedures the risk of complications is similar [18].

Administration

The dose of propofol for anesthesia induction in those <55 years of age is 2–2.5 mg/kg administered as 40 mg IV boluses every 10 seconds until the onset of deep sedation. For patients >55 years age or debilitated or with stage ASA III/IV disease, the dose is 1–1.5 mg/kg administered as 20 mg IV boluses every 10 seconds until onset of deep sedation. As there is no reversal agent for propofol, personnel fully trained in performing cardiopulmonary resuscitation with the necessary equipment should be readily available throughout the procedure.

New drugs and drug delivery systems for endoscopic sedation, including fospropofol disodium, patient controlled sedation, target controlled infusion (TCI), and computer assisted personalized sedation, are currently being evaluated for effectiveness and safety [19]. TCI uses a mathematical model to calculate the initial dosage needed to achieve a desired concentration of drug and then makes appropriate adjustments in the rate of infusion to maintain that level. A computer assisted personalized sedation device (Sedasys, Ethicon Inc., Somerville, New Jersey, USA) has recently received US Food and Drug Administration (FDA) approval. This innovative device combines target controlled infusion of propofol, a unique feedback system based on patient response to audible and tactile stimuli, and a physiological monitoring unit. This system is programmed with a drug specific, population based pharmacokinetic model that calculates the infusion rate necessary to achieve the target or desired drug concentration in the blood, thus minimizing the risk of oversedation. However, this device has not gained clinical traction and has been pulled off the market.

Propofol provides more rapid sedation and recovery than midazolam and the risk of sedation related side effects does not differ significantly from that of midazolam [15]. Pharmacokinetics and protein binding of propofol are not significantly affected by moderate or compensated cirrhosis and, therefore, propofol is deemed safe in Child–Pugh A and B cirrhosis, although data in advanced liver disease are lacking. Nevertheless, experienced anesthetists usually administer lower doses in liver disease patients. Propofol is preferred for sedation in patients with liver disease due to its short half-life, reflected in rapid recovery and time to discharge [20]; additionally it has a lower risk of inducing HE compared with midazolam [1,6,11,15,21,22].

Opiate Analgesics

Opiates bind to receptors in the central nervous system and act by increasing the pain threshold and altering pain perception. The liver is the major site of biotransformation for most opiates. The oxidation of pethidine (meperidine) is reduced in patients with cirrhosis and its clearance is diminished, resulting in increased bioavailability. Thus, pethidine should be avoided in patients with liver disease. The onset of action for pethidine is 5 minutes, with the peak effect at 10 minutes, and duration of action lasting 2–4 hours.

Fentanyl, in contrast, is a lipophilic synthetic morphine analog that is chemically related to pethidine but is about 600 times more potent [7]. The maximum effect is expected after 6 minutes and the duration of effect is 20–30 minutes. The initial dose is usually 50–100 µg. Conversely, fentanyl has a shorter duration of effect due to redistribution into lipid storage sites. Fentanyl is transformed into an inactive metabolite that is excreted by the kidneys. However, in repeated or higher doses, it tends to accumulate.