David J. Hass
Editor

Capsule Endoscopy

A Guide to Becoming an Efficient and Effective Reader

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To Lauren, Samantha, Ethan, and Jordan – thank you for always inspiring me every day and for allowing me the opportunity to complete this project. I am grateful beyond words for your patience, understanding, and love and for always reminding me of what is important.

Preface

The concept of this text was born out of a desire to teach. I have always thoroughly enjoyed teaching and feel it to be my responsibility to be an educator for tomorrow's physicians. Importantly, in order to ensure that physicians learn in an efficient manner, it requires a standardization of method and an understandable approach. The goal of this text is to provide that understanding for those who desire the skillset to understand capsule endoscopy technology.

This text is meant to provide the baseline knowledge and framework necessary to develop the comfort level to begin to read capsule endoscopy studies independently. The chapter authors have provided easy-to-understand text so that the reader can easily develop an algorithm for capsule reading. Our hope is that the readers will take this framework and then hone their skillset to become more proficient capsule readers. Further, readers of the text should know that the capsule network is robust and that the learning never stops. Remember it is the sign of an astute and diligent clinician to ask for another set of eyes to look at potential pathology so as to ensure that the patient is taken care of in the best manner possible.

We hope you enjoy the text and enjoy visualizing and studying the small bowel as much as we do. Thank you for taking the first step to become an effective and efficient capsule endoscopist.

Hamden, CT, USA — David J. Hass

Acknowledgments

I am so fortunate to have had impactful mentors and teachers throughout my entire medical career, and to all of the incredible physicians who I have been privileged to call mentors and friends, thank you. Specifically, I would like to recognize Dr. Larry Brandt and Dr. David Greenwald for their enthusiasm and guidance throughout my training and beyond which have afforded me the drive to strive to become a better clinician, educator, and mentor myself. I appreciate all of the time and sacrifice that you both provided to educate me. This book is one example of a humble attempt to continue to pay it forward for future colleagues. I share this endeavor with both of you.

Thank you to all of the chapter authors who contributed to this book. I truly appreciate your dedication and committment to this project and I am privileged to be able to call each of you friend and colleague. I also want to recognize my current colleagues at Gastroenterology Center of Connecticut and Physicians Alliance of Connecticut (PACT) for continually supporting me in my endeavors and projects. Your support is truly appreciated and noted.

My parents and sister have certainly provided me with the foundation of understanding what it means to have a strong work ethic and to give any effort 110 %. I am truly grateful for their dedication and love and for their support and encouragement throughout my entire life.

A special thank you to the team previously and currently at Medtronic (Deborah Mutter, Sherry Fox, Lisa Willkie, Robin Price, Scott Kraun and Elizabeth Levy Karen) for providing many of the images in this book and for continually supporting educational initiatives to help train tomorrow's clinical gastroenterologists. Your prioritization of medical education is unparalleled and truly appreciated.

Finally, it is equally important to recognize all of the patients that afford us the opportunity every day of caring for them and for trusting the care we provide. We are truly privileged to call ourselves physicians and always must remember not to take this unique privilege for granted.

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Chapter 1
The History and Development of the Small Bowel Capsule/Comparison of Current Available Capsule Platforms

Jonathan A. Erber

The History and Development of the Small Bowel Capsule

Introduction

It has been 16 years since the introduction of small bowel VCE to the world of gastroenterology and gastrointestinal endoscopy, a story now 35 years in the making from design conception to reality and further innovation. The development of VCE is a classic story of necessity being the mother of invention (Republic, Plato).

Development

Despite the advances that took place in the field of endoscopy throughout the 1970s that allowed gastroenterologists to peer into the upper and lower GI tract with flexible fiber-optic endoscopes, examination of the small bowel remained somewhat illusive. In 1981, Dr. Gavrial Iddan (the inventor of the CE), an Israeli electro-optical engineer working at Rafael Ltd. (a government defense lab in Israel), was developing imaging devices for defense missiles. While on sabbatical in Boston, he met and became friends with Professor (Prof.) Eitan Scapa, an Israeli gastroenterologist who was also on sabbatical in Boston [1–3]. The two discussed the advantages and the shortcomings of fiber-optic endoscopy (video endoscopy was not introduced to the USA for another 6 years). In particular, fiber-optic endoscopic evaluation did not evaluate the small bowel in its entirety. Shortly thereafter, small charge-coupled device (CCD) imagers were developed and introduced into both commercial and medical imaging cameras, and within a few short years, video

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endoscopy was introduced to the world and largely replaced fiber optics in GI endoscopy. Despite the major advance of video endoscopy, the small bowel still remained largely inaccessible because of its length (~20 meters) and loose mesentery, making advancement of flexible endoscopes very challenging and time-consuming. Push enteroscopy, sonde enteroscopy, and intraoperative enteroscopy were the mainstays for small bowel endoscopy however often with disappointing diagnostic and therapeutic yields.

On a subsequent sabbatical to the USA in 1991 at Eastman Kodak in Rochester, Dr. Iddan and Prof. Scapa again met and discussed the challenges and potential solutions to the problem of viewing the small bowel. By this time CCD chips were ubiquitous in endoscopes (located in the tip of the endoscope). The concept of cutting the camera tip off of the so called cord (endoscope) was proposed to allow a camera like "missile" to move naturally through the GI tract and use a mini transmitter to send video images back to a recording device. In 1992, Dr. Iddan began spending more time on the new idea of a transmitter-equipped camera. Consultations with CCD experts were discouraging, and in 1993, power consumption was the main issue, as current solid-state CCD chips of the day (that would be small enough to swallow) would only be able to operate for a few minutes until the battery would be depleted (Iddan, personal communication). Additional power concerns included the necessary power that would be required for a light source (white LEDs were not invented yet) and power requirements of the transmitter. Other challenges included optics, visualization, and viewing times. (How would the lens be kept clean? Would the physician need to be present to view the video during the long small bowel transit time?) Three major problems were outlined and solved over the following decade: (1) optics, (2) long viewing times, and (3) power consumption of video chips and radiofrequency transmitters.

Optics

To avoid window contamination and obscuring of view, an axicon optic window (ogive-shaped) was designed to allow for contact with tissue and to facilitate contact imaging and self-wiping of the transparent window. In 1993, a prototype was designed using a miniature CCD (1/4 inch), these optics, and a miniature incandescent light source, and experiments demonstrated that reasonably good images could be acquired (Fig. 1.1; Iddan image, personal communication).

Viewing Times

The problem of long viewing hours was solved conceptually by designing a system that had three separate components: (1) the capsule containing the imager, light source, transmitter, and battery, (2) a recording device with an antenna and receiver, and (3) a workstation that would incorporate the video processing software and

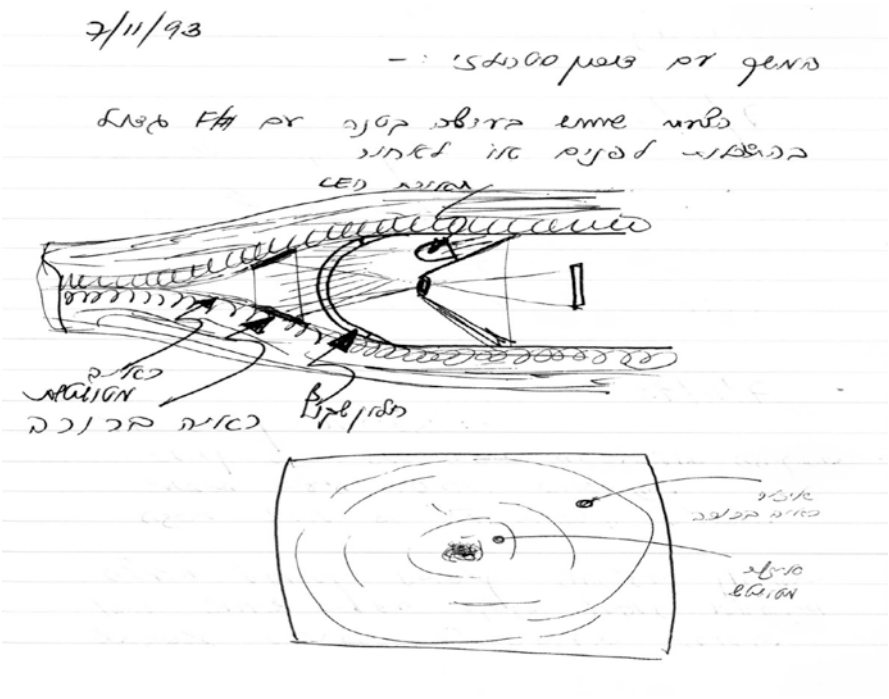


Fig. 1.1 Early drawings of the small bowel capsule endoscope; Personal communication, Prof. Iddan

reader. In order to separate these components, however, effective video transmission through biologic tissue had to be demonstrated (effective and safe). Dr. Iddan performed simple experiments with store-bought frozen chickens that helped determine proper frequency and power (microwatt) required to transmit clear video images through tissue.

Power Consumption

Power consumption was still a major challenge to overcome. The design of the VCE was ultimately possible because of progress made in imaging sensors, circuit design, and white light emitting diodes (LED). In 1993, Dr. Iddan came across a major advance in imaging that made the development of VCE more feasible. In a paper published by Eric Fossum, a scientist at the Jet Propulsion Laboratory in Pasadena, California [4], a new video imager, the active-pixel sensor (APS) was described, which could be integrated on to a single chip (complementary metal oxide semiconductor—CMOS) with all the necessary camera circuits. This new chip consumed only 1 % of the power required by existing CCD chips. Dr. Iddan realized that advances in CMOS design were crucial to the development of the capsule and to it

becoming a reality. Advances in chip design with application-specific integrated circuit (ASIC) devices allowed the integration of very small video transmitters of sufficient power output, efficiency, and bandwidth. Dr. Iddan initially thought of using mini lamps for illumination; however, the final exciting development came with the innovation of white LEDs. Red and green LEDs had been around for decades, but developments in highly energy-efficient blue LEDs did not progress until the early 1990s, and this allowed for the emergence of the white LED that are now so ubiquitous in our homes for lighting and most of our consumer electronics. So significant was this advance that the three inventors of this technology were awarded the Nobel Prize in Physics in 2014 (Isamu Akasaki, Hiroshi Amano, and Shuji Nakamura). In January 1994, Dr. Iddan and his team submitted their initial patent application [US Patent No 5,604,531, later published in 1997; Fig. 1.2].

While progress was made in Israel, Prof. C. Paul Swain and his colleagues in London were also independently experimenting with radiotelemetry capsules in the esophagus and stomach to measure pH and with mini transmitters and video chips for experimental endoscopy [1–3]. In September 1994, Prof. Swain presented a talk at the World Congress of Gastroenterology in Los Angeles discussing the possibility of using microwaves for transmitting video images from a robotic capsular camera, the first abstract on this topic being published in *Gut* [5] and *Gastrointestinal Endoscopy (GIE)* [6]. At the time with commercially available CCD chips, transmitters, a halogen light source, and best available small batteries, their calculations suggested that an orally ingested endoscope was feasible and could transmit 15 min of color video. Prof. Swain's team developed several large prototype wireless endoscopic devices using commercially available components. Several experiments were performed with ex vivo and in vivo models using pig stomachs, and the work was then published in abstract form in 1996 and 1997 [7, 8]. Swain's group acquired the first live images from the stomach of a pig in 1996 with a prototype wireless endoscope comprised of a camera with CCD technology, light source, microwave transmitter, and battery in a transparent container. They also performed the first feasibility studies on "airless" endoscopy [9] studying a variety of lenses, wire cage, and transparent balloon fronted endoscopes and water immersion techniques and determined that the best views could be obtained of the small bowel using curve-shaped short focal length lenses.

Co-development (Drs. Iddan, Swain, and Meron)

In 1995, Dr. Iddan and his group met with Gavriel Meron, PhD, who at the time was the CEO of a company specializing in small endoscopic cameras for fiberscopes, which are flexible fiber-optic bundles with an eyepiece on one end and a lens on the other that can be used to examine the GI tract. The fiberscope consists of numerous fiber-optic cables which are made of pure glass and are as thin as a human hair. Dr. Meron was excited about the possibility of a new video pill endoscopic device. At that time, Dr. Meron tried but failed to raise money from his board to support further research. By 1997, tremendous advances had been made in the field of

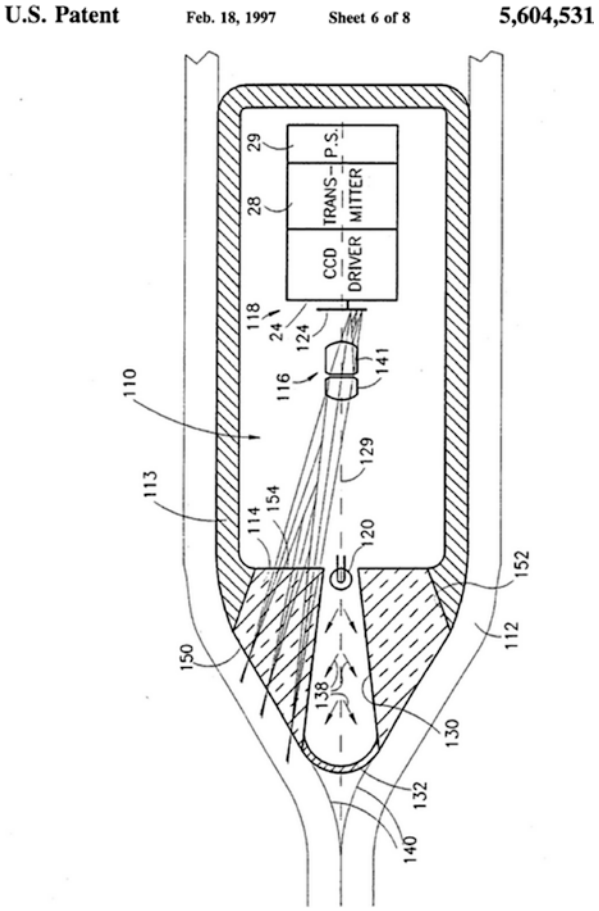


Fig. 1.2 US patent; http://www.google.com/patents/US5604531

imaging that would make the small bowel capsule endoscope a reality. Dr. Iddan's initial patent was published and titled "in vivo video camera system" [10]. Dr. Meron joined the Rafael Development Corporation (RDC) Ltd. and helped incorporate a new start-up company to develop and bring the capsule endoscope to market. That same year, Dr. Meron met Prof. Swain at a European gastroenterology conference, both surprised that they were independently working on wireless imaging technology. In January 1998, Given Imaging Ltd. (Yoqneam, Israel, now a subsidiary of Medtronic) was founded. After a second meeting between Dr. Meron and Prof. Swain in 1998, the two agreed to collaborate.

Work progressed rapidly from 1998 to 2000 under the direction of Dr. Arkady Glukhovsky who led the research and development team at Given Imaging. It was agreed to develop the circuit for Given Imaging, and CMOS chip prototypes were completed in early 1999, with several studies subsequently performed in canine models (Figs. 1.3, 1.4, 1.5, and 1.6). The sentinel landmark event took place in October 1999 when Prof. Swain himself ingested the first two capsules, first at the

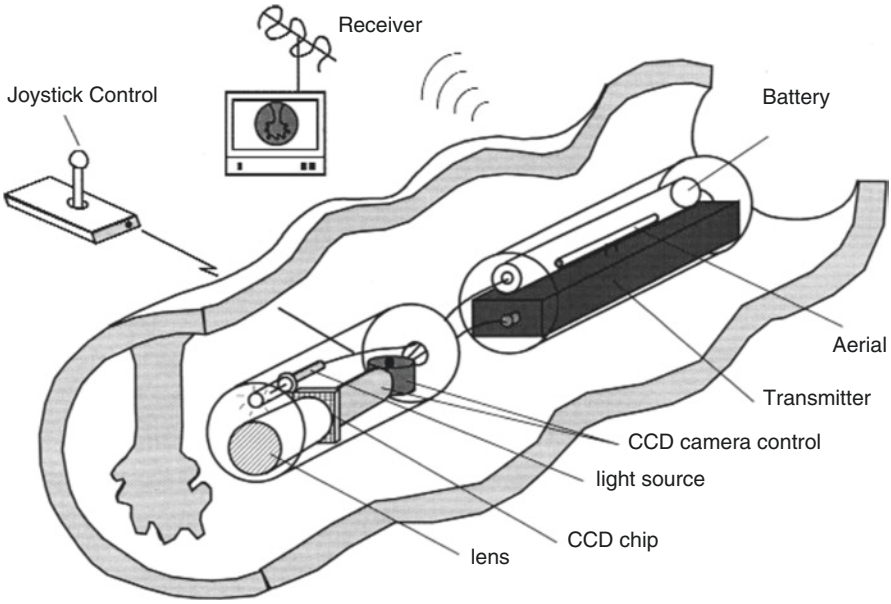


Fig. 1.3 Early conceptions of capsule endoscope

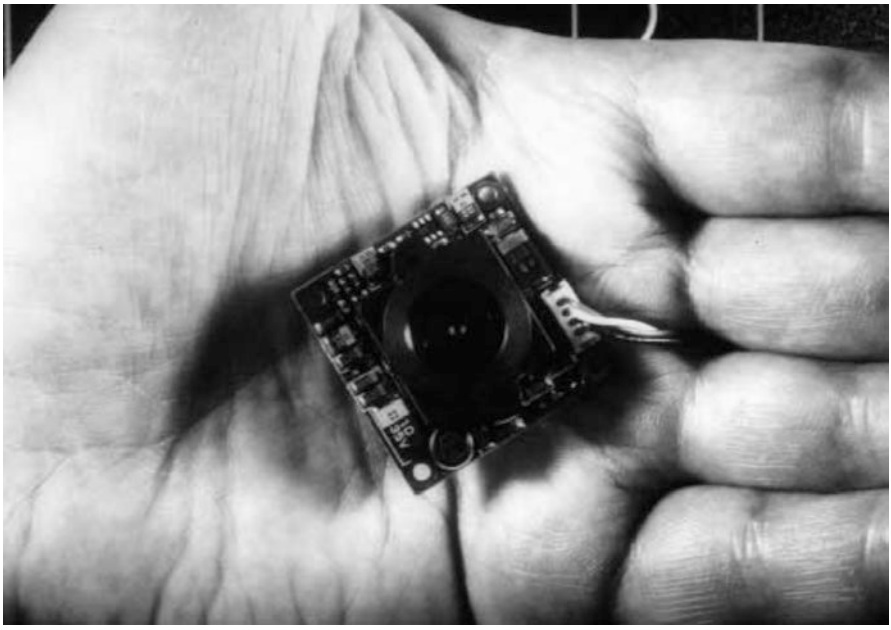


Fig. 1.4 A miniature CCD camera and video processor

Fig. 1.5 In this photograph a miniature CCD color camera on the dark square in the foreground transmits an image of the photographer and assistant by means of a microwave transmitter wrapped in a postmortem stomach on the pale square to the left of the foreground to a cube-shaped distant receiver and television monitor

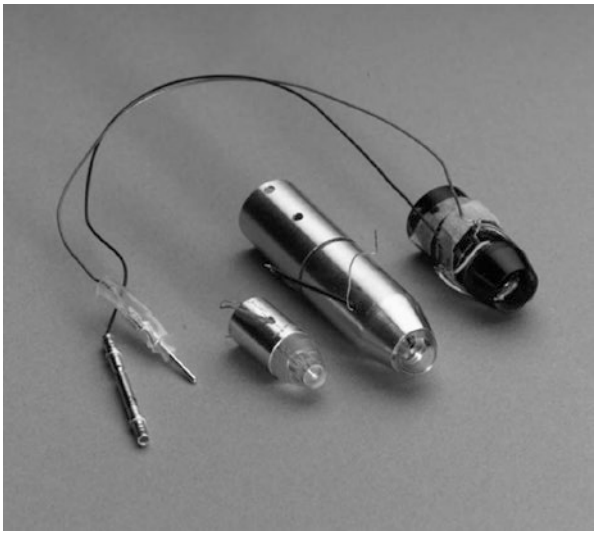


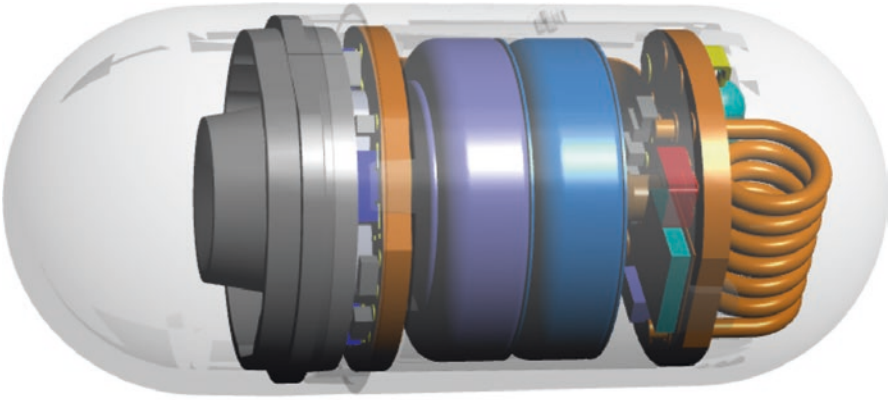
Fig. 1.6 Early capsule prototypes

private clinic of Prof. Scapa in Israel and the second, some days later in a hotel room in Tel Aviv, Israel [1–3]. Prof. Swain introduced the capsule to the gastroenterology community at the plenary session of the ASGE on May 24, 2000, when he showed a videotape of transmitted endoscopic images of his own small intestine. Subsequently, the first human studies were conducted on ten normal human volunteers. The capsule (11 × 30 mm) was easily swallowed, caused no discomfort, and successfully transmitted images from the stomach, small bowel, and colon with video transmission lasting up to 6 h. This work and development of earlier capsule prototypes was published in *Nature* and *Gastrointestinal Endoscopy* and presented in San Diego at DDW in 2000 [11, 12]. In 2001, the *New England Journal of Medicine* published Prof. Swain's group's experience with their first four patients with obscure recurrent gastrointestinal bleeding [13]. In August 2001, the first small bowel capsule called the M2A (Mouth2Anus) received FDA approval (Given Imaging Ltd).

Comparison of Current Available Capsule Platforms

Capsule Systems

Since the introduction of VCE in 2001, there have been many refinements to the original small bowel capsule (M2A, now called the PillCam® SB), and several additional capsule endoscopes have been developed. Currently there are five manufacturers of VCE systems in the world. The capsules house either a CMOS or CCD imager, LED light source, battery, and, in most cases, a wireless transmitter (Figs. 1.7 and 1.8). Most of capsules measure from 24 to 31 mm in length by 11–13 mm in diameter and weigh about 3 g. Aside from dimensions and weight, the capsules differ somewhat in terms of the imaging sensors used (CCD vs CMOS), number of LEDs, frame rate capture, field of view, battery life, and image transmission. The capsules can acquire up to 72,000 frames over a recording period of up to 15 h. The capsules are ingested orally and propelled through the small bowel via peristalsis and visualize the entire small bowel in 70–90 % of cases [14]. Most VCE systems are comprised of a data recorder and computer workstation with proprietary software. The patient wears a belt that contains the data recorder attached to a sensor array and the radiofrequency (RF) receiver. The data recorder connected to the RF sensor array receives and stores the video images acquired from the capsule. The stored imaging data is then downloaded to a computer workstation and processed for review and reporting with proprietary software. The software platforms include a variety of features used for patient registration, case storage, data download and analysis, and report generation. In addition, there are a variety of algorithms that each platform employs to aid in diagnosis, localization, efficient review time, and reporting.



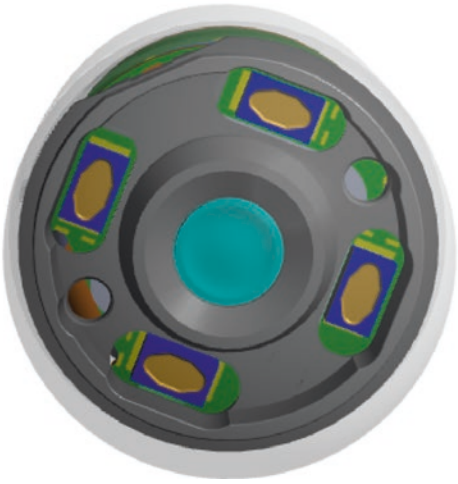


Fig. 1.7 Components of the Capsule Endoscope

The following paragraphs will summarize the various systems used today and highlight some of the differences and unique technological strategies used in both the capsules and software platforms available today (Table 1.1).

PillCam® SB (Given Imaging, Covidien, Medtronic, Yoqneam, Israel)

Since the introduction of the M2A Capsule in 2001, the Given Capsule, now called the PillCam® SB (Given Imaging, Covidien, Medtronic, Yoqneam, Israel), has undergone many refinements. The PillCam is the most commonly used capsule

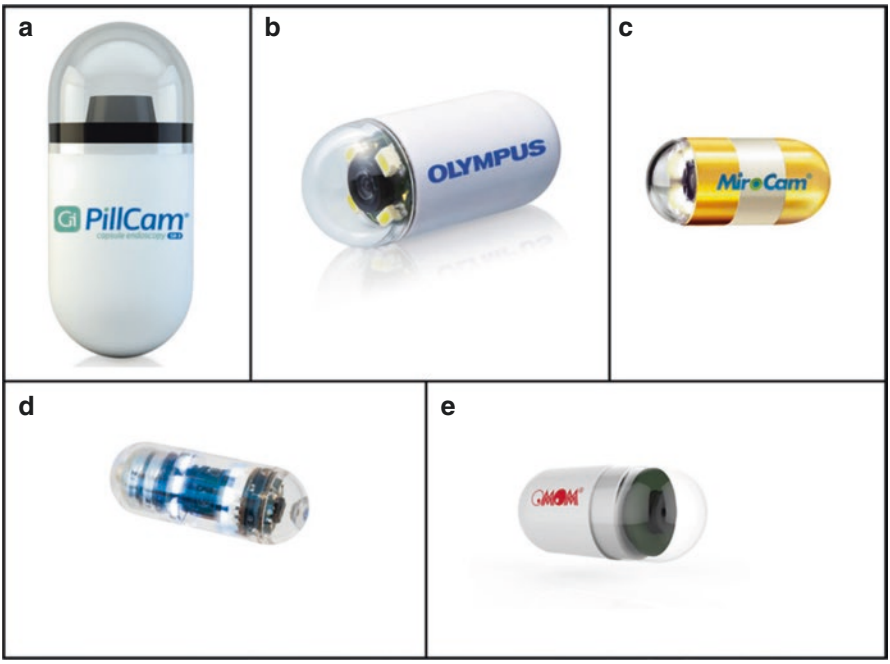
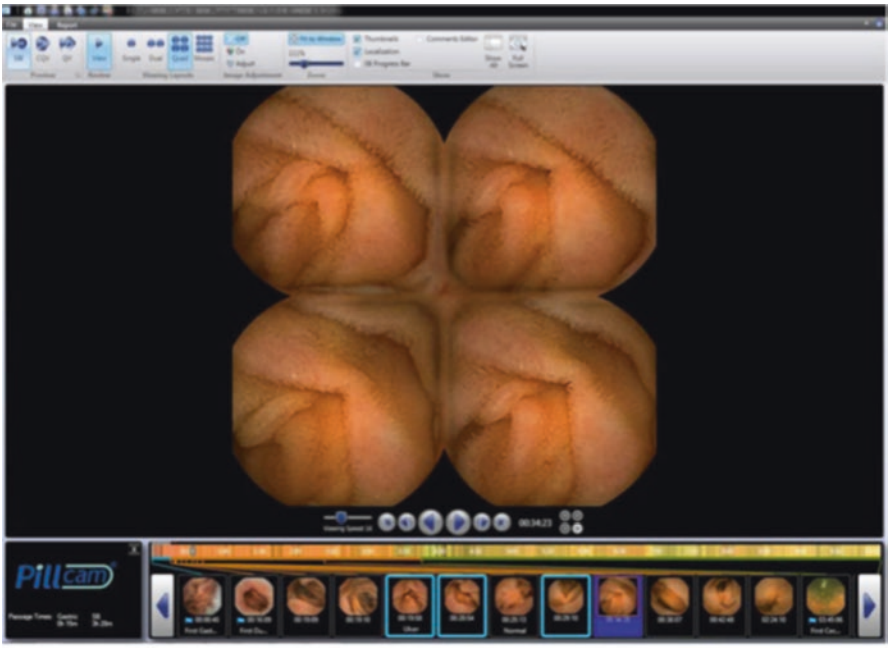


Fig. 1.8 PillCam, EndoCapsule, Mirocam, CapsoCam, OMOM

Table 1.1 Different capsules and capsule systems

Capsule system	PillCam® SB3 Given/ Medtronic	Endocapsule® Olympus America	MiroCam® Intromedic Company	OMOM® 2 Jianshan Science & Technology	CapsoCam® Plus CapsoVision
Length (mm)	26.2	26	24.5	25.4	31
Diameter (mm)	11.4	11	10.8	11	11
Weight (g)	3	3.3	3.25–4.7	<4.5	4
Battery life (h)	≥8	≥8	≥10	≥10	≥15
Field of view	156°	145°	170°	157°	360°
Depth of view (mm)	N/A	0–20	7–20	0–35	0–20
Frame rate per second	2–6	2	3	2–4	3–5 (per camera)
Resolution (pixel)	340 × 340	512 × 512	320 × 320	256 × 256	221,884 pixels
EMA certified/ FDA approved	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/No

PillCam Capsule Endoscopy System (Workstation, PillCam Recorder, Sensor Belt)



Rapid 8 View screen

Fig. 1.9 SB3

endoscope in the world, and in 2013, the FDA approved the use of its most recent capsule, the PillCam® SB3 (Fig. 1.9). The capsule measures 26 × 11 mm and weighs 3 g. It contains a CMOS imaging sensor, a short focal length lens, four white LEDs, and an ultrahigh-frequency radiotelemetry transmitter to communicate with a portable data recorder that is worn in a belt around the patient's waist. The capsule still has a field of view of 156°, and the minimal detection size is estimated to be 0.07 mm. Instead of a static frame rate, capturing 2 frames per second (FPS) as in the PillCam® SB2, the PillCam® SB3 has a unique feature called "adaptive frame rate," with video acquisition ranging from two to six FPS, depending on how fast the capsule is traveling through the small bowel (two FPS if traveling slowly, six FPS if traveling fast). There are also two choices of the battery for the capsule, one with an 8-h battery life or one with a 12-h battery life. The new data recorder, DR3, can be used with either the traditional eight-sensor array that allows for estimation of capsule location in the bowel or the sensor belt that contains a three-sensor array conveniently designed as an insert in the belt worn around the patient. The DR3 has a recording capacity of up to 15 h and allows for real-time viewing with a color LCD.

The most current version of the reviewing RAPID software can be installed on a PC workstation. The software has undergone a variety of refinements since its initial launch in 2001, the most significant being the Quad View that allows for the visualization of four consecutive images at once in a clockwise fashion at a playback of up to 40 FPS and an automated view mode (A-mode) that through a proprietary algorithm can cut down on reading times by eliminating redundant images. There are several additional review modes, the most practical being the Quick View mode that allows for a fast preview of the video (not meant to be used as a substitute for reviewing the entire video) by only displaying images that may be of interest in the video stream. Complementary Quick View mode displays only images that are not included in the Quick View mode. The Suspected Blood Indicator (SBI) mode shows images suspected of containing blood for fast review in sequence. Fujinon's Intelligent Chromoendoscopy (FICE) mode and Blue mode can also be utilized to aid in observing surface characteristics and vascularity by visually enhancing suspected potential abnormal pathology. In addition, there is a progress indicator that is based on time elapsed, linear distance traveled, and capsule motion information to assist in localizing lesions.

Endocapsule EC-S10 (Olympus America, Center Valley, PA, USA)

The Endocapsule EC-S10 (Olympus America, Center Valley, PA, USA) is the newest version of the small bowel capsule manufactured by Olympus and approved for use by the FDA in March 2013. The original Olympus Endocapsule was approved by the FDA in September 2007. The EC-10 is similar in size and weight to the SB3, weighing 3.3 g. The capsule has a high-resolution CCD image sensor and automatic

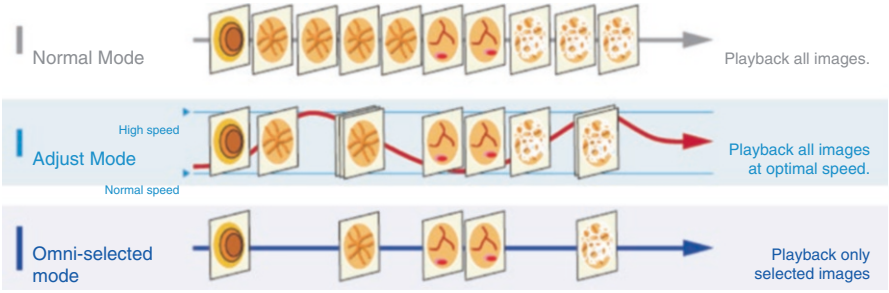
brightness adjustment and captures images at 2 FPS with a wider field of view of 160° (prior endocapsule had a 145° field of view). The capsule has a battery life of 12 h. Similar to the PillCam® SB platform, there is a sensor belt, with an eight-sensor array conveniently inserted into a belt worn around the waist of the patient. The data recorder has a battery life of 12 h and is built in real-time viewing capabilities with a color LCD that also allows for capture of images and playback in real time.

The accompanying software, Endocapsule Software 10, has similar viewing and reporting capabilities compared to the RAPID reader with a Quad View as well as a proprietary algorithm that also allows for shorter viewing times by reducing redundant images viewed. The new Adjust mode changes playback speed depending on differences in images. Images showing no change are superimposed on each other, and the review speed is optimized to move quickly past images indicating no characteristic differences compared to preceding images. In Omni-selected Mode, images that overlap with previous ones are skipped, and new images are selected when only minute changes are present. This algorithm can recognize that an image is similar even when the capsule is displaying the same section of the small bowel from a different angle. There is also a SBI for red color detection of suspected bleeding. In addition to the standard time bar, there is a three-dimensional tracking function that helps localize capsule findings (Fig. 1.10) (Capsule, DR, Sensor Belt, Software Display; Sample Images).

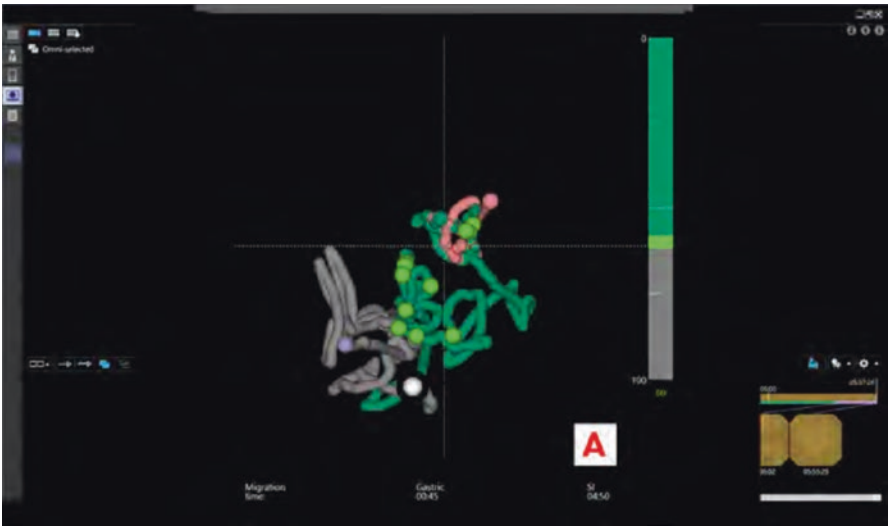
MiroCam® MC1000-W (Intromedic, Seoul, Korea)

The MiroCam® MC1000-W (Intromedic, Seoul, Korea) was approved for use by the FDA in May 2012. It is similar to both the PillCam® SB and EC-S10 in size and weight; however, it has several notable differences. It is slightly smaller in size at 24.55 × 10.88 mm and weighs 3.25 g compared to other capsule endoscopic devices. It has a CMOS imager similar to PillCam® but captures images at a frame rate of three FPS with a wider field of view at 170° and has six white LEDs. A notable difference between MiroCam® and other capsule devices is that it does not use RF to transmit video images to a data recorder but instead uses electric field propagation to transmit data, what has also been described as human body communication (HBC). This technology uses the body's natural conductive capacity to transmit images to the recorder and, as a result, reduces power consumption ordinarily consumed by RF transmission. A second version of this capsule, the MC1000-WM®, has limited steering capabilities using magnetic force. Similar to the Medtronic and Olympus systems, there is a sensor array that is worn by the patient and connected to a data recorder which is housed in a belt around the patient's waist that captures the video images to be downloaded to a workstation for processing and video review. Real-time viewing capabilities are enabled through a USB connection to a notebook or wirelessly to an iPhone or iPad device. The MiroView software has similar reviewing and reporting capabilities compared to other systems but also is designed for interoperability with PACS archiving systems (Fig. 1.11)

Endocapsule



Playback modes



3D Track area and track progress bar

Fig. 1.10 Label Endocapsule EC-10 EC-S10

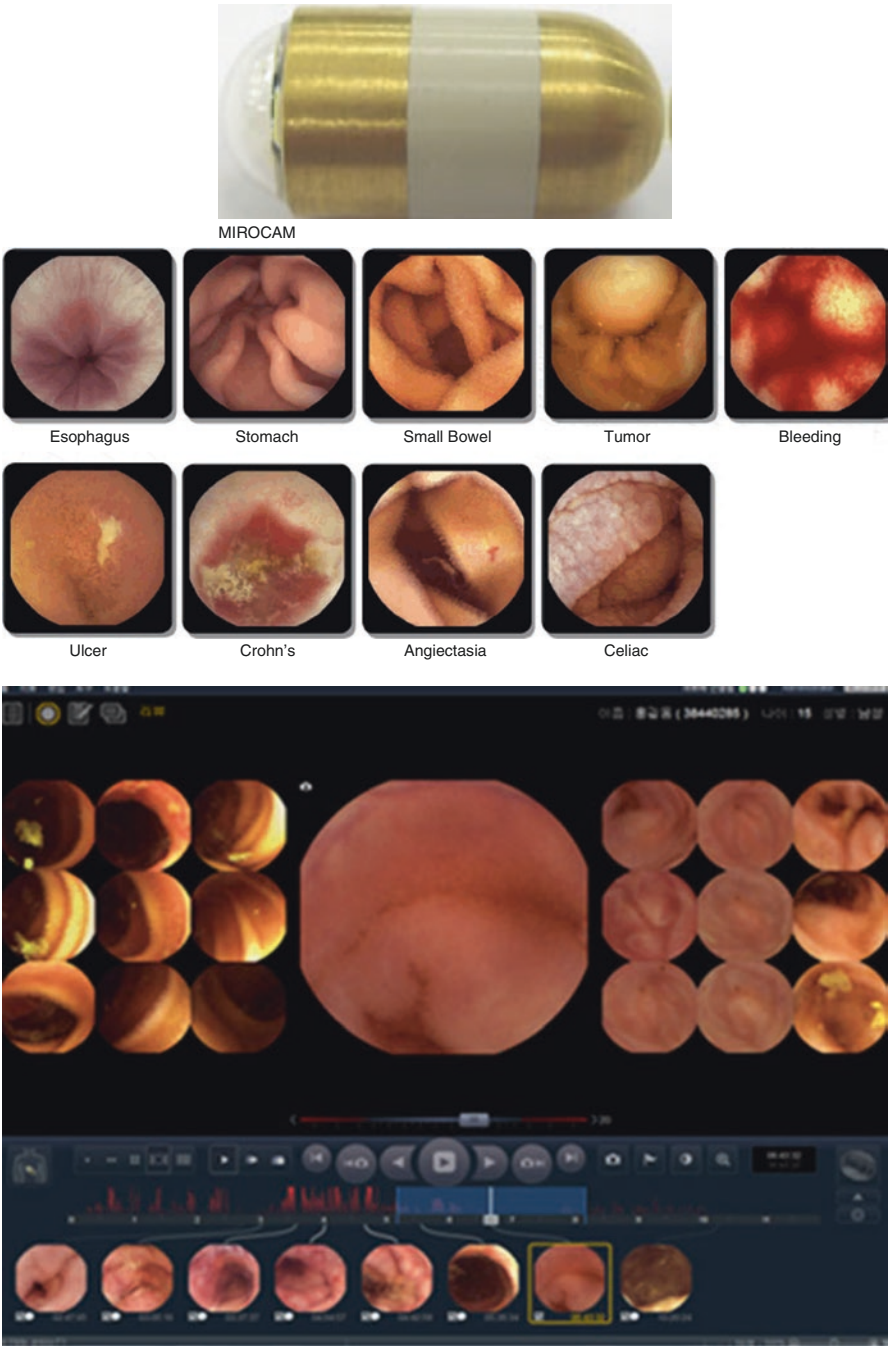


Fig. 1.11 MiroCam system

CapsoCam® SV1 (Capsovision, Saratoga, CA, USA)

The CapsoCam® SV-1 and SV-2 (Capsovision, Saratoga, CA) are not yet approved for use in the USA but are used throughout the rest of world including Central and South America, Europe, Africa, Asia, and Australia. The SV-1 is slightly larger than the other capsules at 31 × 11 mm, weighing 4 g. The SV-1 is a unique capsule that has a CMOS imager, but unlike the other capsules, it has 4 imagers placed around the capsule at 90° angles that allows for a 360° panoramic field of view. It captures 20 FPS (five for each camera) for the first 2 h, followed by 12 FPS for the remainder of the capsules' 15-h battery life. There are a total of 16 white LEDs powered by an automatic light controller that enables the light intensity to vary from low near the walls of the small bowel to high when the capsule is at a distance from the mucosal wall. Another unique feature of this capsule is its smart motion sense technology that activates the cameras only when the capsule is in motion, limiting the number of redundant images acquired and improving capsule battery life. Another unique aspect of the SV1 is that it does not transmit the captured video images via RF to a data recorder/RF receiver. Instead, it stores all of the images on board the capsule in a flash memory card and must be retrieved and connected to a dock to be downloaded to a workstation for review. The lack of RF communication offers the advantage of no potential interference with implanted electronic devices such as pacemakers and defibrillators. This also eliminates the need for the patient to wear a belt carrying the data recorder and sensor array as all data is stored on the capsule. From a physician perspective, the lack of a need for a data recorder reduces capital costs and also eliminates the potential bottle neck of data recorder availability, as all that is required to perform a study is the patient and the capsule. The potential disadvantage to this system is a possible lack of acceptance by the patient, as one has to retrieve the capsule in order to obtain the data. The SV-2 capsule is embedded with a communication device that helps rapid and noncontact data to be downloaded to a workstation. The CapsoView software has similar reviewing and reporting capabilities compared with the other systems, with algorithms that allow for more efficient viewing times and report generation (Fig. 1.12).

OMOM JS-ME-II Capsule (Jinshan Science and Technology, Chongqing, China)

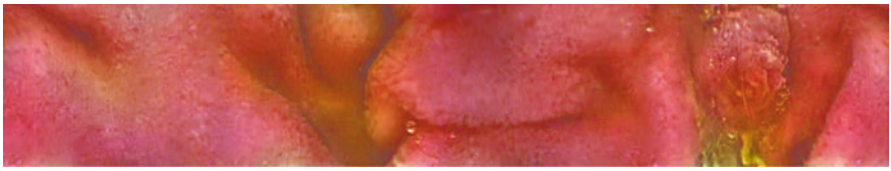
The OMOM JS-ME-II Capsule (Jinshan Science and Technology, Chongqing, China) is not available for use in the USA. It is similar in size, weight, and technical specifications to the PillCam® SB3 but is slightly larger, measuring

CapsoCam System (Capsoview, Capsule, CapsoAccess, CapsoRetrieve)

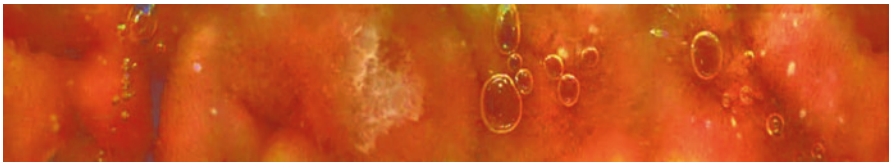
Capsocam

Fig. 1.12 CapsoCam

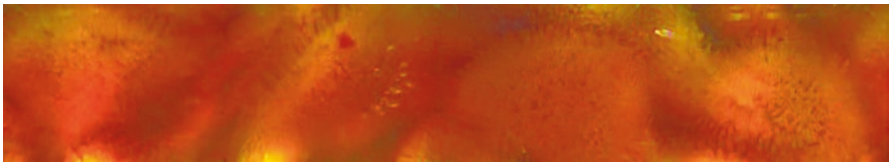
CapsoCam Plus 360° panoramic view of mucosa.



Ampulla



Duodenal Ulcer



Ectasia

Fig. 1.12 (continued)

27.9 × 13 mm. It has a CMOS imager, captures images at two FPS with a field of view of 140°, and has a battery life of about 9 h. One unique and notable difference of the OMOM capsule is that the physician can view the captured images in real time and send a signal to the capsule to change the frame rate from 0.5 to 1 or 2FPS, in order to optimize visualization. Another version of this capsule, the OMOM JS-ME-III, allows for minimal control of the capsule while in the stomach (Fig. 1.13).

Fig. 1.13 OMOM capsule system

Comparison

There is very little data comparing the different capsule systems. Therefore, one cannot endorse the use of one system over another based on data. All systems appear to have similar performance characteristics in terms of imaging and diagnostic yield. Two small studies comparing an older version of PillCam® and Endocapsule did not demonstrate any significant differences in diagnostic yield or definitive

superiority of one capsule over another [15, 16]. Similarly, small comparative studies have not reported any significant differences in terms of diagnostic yield and findings between the MiroCam®, PillCam SB®, and Endocapsule [17–20]. Comparable image quality and diagnostic yields have also been demonstrated between the PillCam® SB, CapsoCam® [21, 22], and OMOM capsule [23, 24].

There is also only a small body of research that has investigated the different software features available across VCE systems that help to decrease reading times and detect abnormal images. In one analysis of RAPID® Quick View, the diagnostic miss rate was 12 %, and in another study looking at its use in the detection of obscure GI bleeding, sensitivity, specificity, and positive and negative predictive values exceeded 90 % [25, 26]. The Rapid® software is optimized to be read in Quad View mode. In one study, Zheng et al. compared detection rates of 24 clips analyzed by 23 experienced endoscopists in four different modes (single view at 15 frames per second, 25 FPS, and Quad View at 20 and 30 FPS).

Detection rates were significantly higher when the studies were read in single-view 15 FPS and Quad View 20 FPS compared with single-view 25 FPS. Increasing the viewing speed from Quad View 20 to 30 FPS had no significant effect on detection. Overall detection rates in this study were lower than previously reported and not influenced by increasing experience [27]. All of the platforms employ algorithms to aid in the detection of bleeding.

While seemingly useful in expediting the diagnosis of a potential bleeding site or finding active bleeding when truly present, the SBI mode is not a substitute for thorough evaluation of all capsule images. In a study on patients with active bleeding, accuracy of the RAPID® SBI was higher in patients who required more blood transfusions [28]. A retrospective review from a single center determined a sensitivity, a positive predictive value, and an accuracy of 81.2 %, 81.3 %, and 83.3 %, respectively, for SBI mode [29]. Other data support the notion that the technology does not result in an increased diagnostic yield and is of overall limited clinical value in its current form with a sensitivity of as low as 28 % in another retrospective study [30, 31]. A recent ex vivo model demonstrated that SBI detection is affected by background color and capsule velocity [32] with detection rates highest for backgrounds that were very pale and lowest for backgrounds that were very dark. The rate of detection decreased at rapid capsule transit velocities.

While there are subtle differences between the various VCE systems, by and large they are all very similar in performance, and there is very little data to suggest any particular advantage of one system over another. The PillCam® system, which was the first system introduced, has the obvious advantage of the majority of the world's market share. Competition however between all of these existing manufacturers and with smaller start-ups is sure to push for further innovation in this exciting technology that has enabled physicians to noninvasively image the small bowel lumen in its entirety. Ongoing research endeavors suggest that at some point in the not so distant future, video capsule endoscopes will not only have diagnostic capabilities but potential therapeutic functionality as well. This is a truly exciting time to be a gastroenterologist.

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Chapter 2
SBCE Indications, Contraindications and Administration: Preps, Prokinetics, and Retention

Michal R. Gross and Daniel S. Mishkin

Indications

In 2001, the FDA approved wireless capsule endoscopy for inspection of small bowel mucosa in patients as young as two years old [1]. The most common indications for the use of the small bowel capsule include:

- *Obscure GI bleeding*, including overt and occult bleeding, as well as unexplained iron deficiency anemia
- *Crohn's Disease*, both suspected and known
- S*uspected small intestinal tumors*
- *Polyposis syndromes*, for diagnosis and surveillance
- *Suspected or refractory malabsorptive syndromes*, including celiac disease [2]

These indications are the most frequent diagnoses and suspected pathologies of the small intestine. While other complementary testing is possible, such as dedicated CT or MR enterography, capsule endoscopy allows for noninvasive, direct visualization of the small intestinal mucosa in an ambulatory setting.

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Table 2.1 Indications for endoscopic delivery of capsule

Indications	Examples
Impaired swallow	Oropharyngeal dysphagia
Esophageal motility disorder	Scleroderma
Altered upper GI anatomy	Zenker's diverticulum, altered surgical anatomy, e.g., gastric resection
Delayed gastric emptying	Gastroparesis

Relative Contraindications

Capsule endoscopy is *relatively* contraindicated in those (1) with swallowing difficulty or motility issues, (2) with cardiac implantable electrical devices (CIEDs), (3) who are pregnant, and (4) with known or suspected obstruction, strictures, or fistulas.

Swallowing difficulties and motility issues limit a patient's ability to deliver the capsule to the small intestine. Endoscopic release of the capsule into the intestine can effectively bypass the anatomic or neurological hindrance to a successful study. Therefore, endoscopic delivery should be considered in patients with limitations of swallowing, esophageal motility disorders, altered upper GI anatomy, or delayed gastric emptying (Table 2.1).

AdvanCE® capsule delivery device is an endoscopic accessory catheter with a plastic holding device at its leading end. The holding device is preloaded with the capsule and the catheter is passed through the biopsy channel of the scope. After the scope is advanced into the small intestine, the video capsule can be deployed via a deployment cable controlled by a handle that moves the cable back and forth to propel the capsule from the holding cup into the intestinal lumen. Overtubes, snares, and even ERCP baskets have also been used to deliver the capsule beyond the pylorus (Figs. 2.1 and 2.2).

Simultaneous with its approval of capsule endoscopy for the study of small bowel mucosa, the FDA issued a warning regarding potential interference between this new technology and CIEDs. In fact, the FDA's warning was based on theoretical concerns, not clinical data. The greatest concern was that the digital radiofrequency signals emitted by the capsule could cause CIEDs to over-sense, causing inappropriate inhibition of pacing by pacemakers and inappropriate delivery of shocks by implantable defibrillators. An additional concern, though with less catastrophic consequence, was that interaction between devices might impede image capture. Numerous case reports, case series, and experimental models that mimic this situation have shown no significant interaction [3–5]. A recent literature review suggests that the use of capsule endoscopy is feasible and safe in patients with implantable cardiac devices, including pacemakers, cardioverter defibrillators, and left ventricular assist devices (LVAD) [6]. There have not been any hemodynamically significant arrhythmias documented in these various published studies. Evaluation of capsule use in patients with LVADs is far more limited, but in one small study, two of 14 patients experienced LVAD dysfunction [7]. Although the overwhelming preponderance of evidence indicates that capsule endoscopy is both

Figs. 2.1 and 2.2 These images of AdvanCE® capsule delivery device demonstrate the loaded video capsule (*left*) and the release of the video capsule (*right*). AdvanCE® capsule delivery device – permission granted by US Endoscopy

safe and effective in patients with CIEDs, larger studies are still necessary. As new capsule models, using different types of image transmission, enter the market, the risk of image interference may eventually be negated. In the interim, cardiology consultation may be useful in addressing the clinical and medical-legal concerns that surrounded this issue in the past. Some cardiologists temporarily convert the pacemaker to forced pace for the duration of the procedure, further minimizing risk.

Pregnancy is a relative contraindication for capsule endoscopy but this is not based on reported adverse outcomes. In the event of retention, the patient may require imaging studies which involve radiation or invasive procedures to retrieve the capsule [8]. Therefore, caution should be used prior to administration of a capsule endoscope in a pregnant woman with suspected stricturing disease [9]. However, given the low likelihood of retention without stricturing disease, the use of video capsule can be considered if necessary in a pregnant woman without suspicion for obstruction [10, 11]. Informed consent must detail all of these risks.

Finally, capsule studies in those with a known or suspected obstruction, stricture, or fistula carry the small but very real and potentially dangerous risks of retention, obstruction, and intestinal perforation. These risks are mitigated by the use of MR enterography/enteroclysis, CT enterography/enteroclysis, and patency capsule, all of which will be detailed further in the section "Prevention of Retention."

Preps

Experts have long debated whether a purgative prep is superior to the more traditional options of a clear liquid diet or fasting. Until recently, data from prospective randomized controlled trials was extremely limited. A few meta-analyses

[12] pointed toward better *visualization* of the bowel after a purgative prep, [13, 14] with variable evidence regarding change in diagnostic yield [15–17]. More recently, a 2016 prospective randomized controlled trial shows that a clear liquid diet is as effective and better tolerated than a PEG or sodium picosulfate preparation for capsule endoscopy. However, this study excluded those at high risk for poor prep, or incomplete examination including inpatients, and those with diabetes, motility issues, or narcotic use [18]. For patients at higher risk for poor quality of study, it may be advisable to continue with purgative preps. Additionally, one Korean prospective study determined that simethicone enhances visualization but could not establish whether it improves diagnostic yield. Some have suggested that the benefit in visualization attributed to simethicone may be limited to the proximal small intestine and to non-Crohn's Disease patients [19].

Prokinetics

The role of a prokinetic agent is to decrease oral-cecal transit time, in order to traverse the desired gastrointestinal tract during the video life span. Prokinetics have been used by many capsule endoscopists to promote motility in those at risk for an incomplete study. Most evaluations of prokinetics show increased completion rate, without increased diagnostic yield, the more clinically significant endpoint [20, 21]. Theoretically, enhancing the completion rate should increase the percentage of complete small bowel evaluations. Unfortunately, speeding up the capsule may propel it through the intestinal lumen at a rate so rapid that the ability to capture the necessary images of potential pathologies will be limited, as it swiftly passes by a small abnormality. Two advances have affected the need for and effect of prokinetics. The longer capsule battery life enhances the completion rate, without the need for prokinetics, and the recently developed Medtronic imaging capsule (PillCam® SB3). This uses the speed of capsule movement to determine the image capture rate, also known as adaptive frame rate technology. When this capsule travels faster, as it does with the use of prokinetics, the device captures more images per second.

Based on the available evidence, practitioners should avoid nonselective use of prokinetics and instead use real-time viewers and capsules designed with longer battery life. As these advances have only partially ameliorated slow-transit issues, the clinician should administer prokinetics to those patients with motility dysfunction severe enough to impede a successful study, despite the best technology. Of note, data presented at the ACG 2014 annual meeting suggests that linaclotide may be a prokinetic that enhances speed *and* quality of visualization when compared with the use of no prokinetic [22]. However, a small study, which compared linaclotide to PEG, showed no significant difference in speed or visualization [23]. Larger studies and a randomized controlled trial are needed to conclude whether linaclotide is in fact useful as a prokinetic.

Table 2.2 Risks of capsule retention based on underlying condition

% capsule retention by indication for SBCE [24, 25]	
Obscure GI bleed	1.2 %
Crohn's disease	2.6 %
Neoplastic lesion	2.1 %
Overall	1.4 %

Retention

Capsule retention is defined as the presence of a capsule endoscope in the digestive tract for two or more weeks after ingestion, and/or the requirement of a medical or procedural intervention to facilitate its passage. The overall risk of retention has been reported at 0.3–2 %, a relatively rare occurrence (Table 2.2). Importantly, none of these cases of retention have been reported in those with healthy, normal bowel. The risk of retention is further stratified by the clinical indication for capsule endoscopy.

The issue of capsule retention is one that concerns patients, and captures the attention of physicians, especially at the beginning of their capsule endoscopy experience. Consequently, it is important to place the risk into perspective when obtaining consent. When discussing this issue, the physician should clarify that the capsule passes naturally in healthy volunteers. Of equal significance, non-passage frequently identifies the presence and probable location of an abnormality, thereby providing a roadmap for determining the source of a patient's signs and symptoms.

Management of retention is determined by the underlying pathology. For example, if the pathology is a tumor, surgery is likely the best approach. In contrast, if the capsule is retained due to Crohn's inflammatory stenosis, medical treatment with steroids and other medications, such as antitumor necrosis factor agents, could be considered as a first-line therapeutic endeavor. Deep enteroscopy either single or double balloon and surgical intervention are also therapeutic options if an obstructive process results from capsule ingestion. Therefore, it is recommended to evaluate each patient individually and to assess if additional testing, such as a patency capsule, should be performed prior to the capsule study.

Prevention of Retention

The first and most crucial step toward decreasing the risk of retention is a thorough medical and surgical history. This identifies higher-risk patients who warrant further testing before proceeding with a capsule study. In fact, the retention rates reported above would be much higher if those study populations had not been pre-screened. In the early days of capsule, the imaging techniques used to determine the safety of the capsule in at-risk populations were mainly limited to small bowel follow-through and small bowel enterography/enteroclysis [26–29]. Unfortunately, these studies were neither sensitive, nor specific, leading to a number of retention cases in patients that had been "cleared" by these studies and preventing a number of patients from using

Figs. 2.3, 2.4, and 2.5 The Pillcam® Patency Capsule is shown prior to ingestion (*top left*), excreted intact suggesting patency (*right*), and degraded suggesting retention or slow motility (*bottom left*)

capsule technology in cases where the capsule would probably have passed without issue [30]. With the advent of MR and CT enterography, sensitivity and specificity for patency did improve, but these studies remain imperfect at prediction of patency.

The Pillcam® Patency Capsule has become a popular and more accurate method to approximate retention risk. Ingestion of a patency capsule evaluates whether the similar sized video capsule will pass through the small intestine lumen or whether it will be retained. This test capsule was designed on the premise that the best and safest predictor of retention would be the use of a capsule identical in shape and size to the capsule endoscope (PillCam® and EndoCapsule) but modified to autolyze and degrade so as not to cause a persistent obstructive process (Figs. 2.3, 2.4, and 2.5).

The original patency capsule was designed as a cellophane coat, capped with one wax end, and perforated to allow entry of intestinal juice for dissolution. The newer version of the patency capsule contains two parylene timer plugs on each end of the capsule which begin to auto-degrade 30 hours after ingestion, thereby preventing prolonged retention. In those patients more likely to have stricturing or obstructing disease, this non-video capsule can be swallowed to predict risk. By beginning dissolution after 30 h, this test capsule enhances the ability to test for patency without incurring the risks that accompany retention. Several studies have shown that patients who are able to pass the patency capsule without issue do not retain the subsequent video capsule endoscope [31, 32]. In contrast, those patients in which the patency capsule causes pain or disintegrates carry higher risk of video capsule retention. Those patients should be counseled about their increased risk.

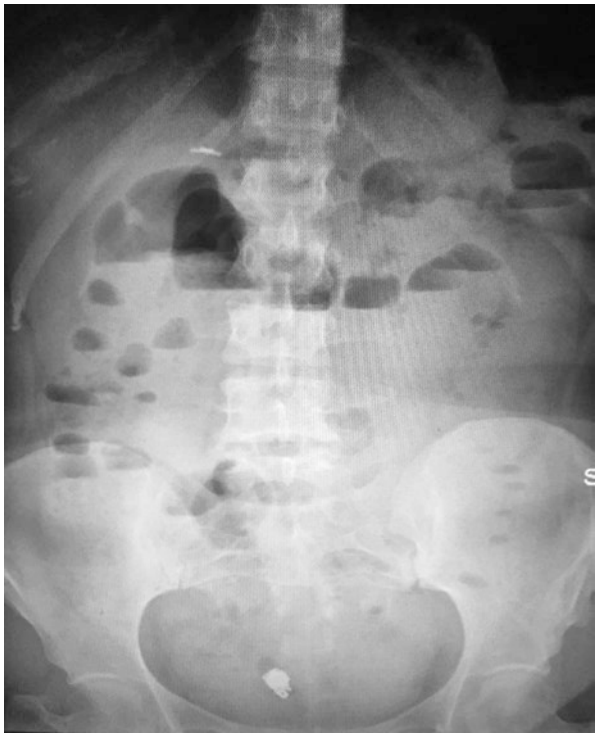
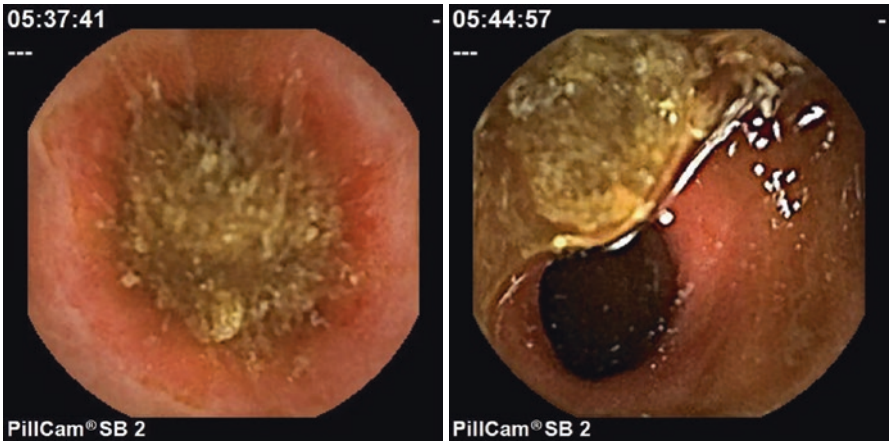


Fig. 2.6 This patient was having symptoms of a partial small bowel obstruction without an obvious transition on CT and MR enterography, and a KUB suggested possible air fluid levels. The patient ingested the Pillcam® Patency Capsule which was retained in the abdomen at 30 h but, as per this abdominal x-ray, had most likely passed into the rectum. This suggested that the video capsule could be ingested and subsequently passed naturally

The patency capsule contains a radiofrequency (RF) ID tag surrounded by a mixture of lactose and barium. This combination facilitates localization of a retained capsule, which aids in localizing the pathology. The presence of the test capsule in the body can be easily determined by passing the RF-ID tag scanner, an RF-ID tag-triggered wand, external to the abdomen. The barium component allows an abdominal x-ray or spot CT scan to localize the test capsule to the small or large intestine until 30–40 h post-ingestion. Thereafter, the patency capsule is designed to self-degrade (see Figs. 2.6, 2.7 and 2.8).

Some clinicians are reluctant to implement patency capsules due to a few accounts of retention requiring emergency surgery. In reality, retention of a patency capsule should not be considered a complication but rather a different means of diagnosing a stricture or obstruction that may require intervention [33]. In one study, during the early days of patency capsule, there were two reports of obstruction requiring emergency surgery. In both cases, surgery would have ultimately been required for the underlying strictures. Retention of the capsule merely indicated the location of the pathology [34]. There have been multiple accounts in which retained patency capsules, prompting nonsurgical retrieval, have actually spared patients the risk of exploratory surgery, by indicating the location of pathology [35]. Moreover, many of these accounts were reported with the older version of the patency capsule that started disintegration after 40 h and only had one perforated wax end. If the single wax tip became buried in a stricture, it prevented intestinal juices from entering and beginning disintegration. Therefore, the newer capsule's



Figs. 2.7 and 2.8 These video capsule images demonstrate the clinically suspected small intestinal stricture (same patient as image 2.1) that could not be seen with a CT or MR enterography. As predicted by the passage of the patency capsule, the video capsule passed naturally

design, with two perforated wax tips and 30 h disintegration time, has vastly improved the safety profile of the capsule [36].

Despite evidence that the patency capsule is the most sensitive and specific tool available, many gastroenterologists use MRI/CT enterography/enteroclysis, alone or in combination with the patency capsule. While the highest sensitivity and specificity are achieved by the combined use of patency capsule and radiology, the indiscriminate use of both screening methods is neither cost-effective, nor time efficient. Additionally, the superior sensitivity and specificity of the patency capsule, compared with radiographic studies, has been based *in part* on the criteria used to define a positive radiographic study. A 2011 study showed that when using SBO criteria to define a positive study instead of the traditional stricture or stenosis, the specificity of radiographic studies significantly improved [37]. Without head-to-head randomized controlled trials of the patency capsule versus MR/CT using these more stringent criteria, evidence still suggests that the patency capsule is the most accurate tool available. However, with the use of more stringent criteria, MR/CT enterography/enteroclysis can be used to replace or supplement patency capsule testing when limited availability, funds, or time prevents the use of it. When considering the proper screening prior to video capsule endoscopy, we recommend using the following systematic approach which has been prepared by the authors of this chapter based on literature reviews and expert opinion:

1. If a patient does not exhibit obstructive signs and symptoms, and the practitioner does not suspect obstruction, the patient may not require screening prior to the SBCE at all.
2. If screening is indicated, choose imaging study versus patency capsule based on availability of test, level of suspicion for obstruction, underlying disease pathology, and comorbidities (e.g., renal failure). *To elaborate further, if the*

patient has Crohn's, retention of patency capsule may be relieved by steroids, and therefore, the practitioner should feel more comfortable starting with patency capsule. However, if retention of patency capsule would necessitate surgical retrieval (which rarely occurs), it would be reasonable for the practitioner to begin with a noninvasive radiographic study.

3. As a patency capsule's negative predictive value is extremely high, if the study does not show retention, it can be followed immediately by SBCE. However, if the exam is positive for retention, it should be followed by an MR/CT enterography/enteroclysis to localize the capsule in order to rule out false positive of "retention" in colon and to localize a potential site of obstructive pathology.
4. If there is no access to a patency capsule, and an MR/CT enterography/enteroclysis is used as the initial screening tool, use proximal dilation as the criterion to rule out the use of SBCE. However, if a seemingly nonobstructive stricture or region of stenosis is seen on radiologic studies, follow up with a patency capsule to ensure uneventful passage prior to attempting an SBCE.

Conclusion

Video capsule endoscopy can be extremely useful in diagnosing and localizing small bowel pathology and is relatively low risk. The only absolute contraindication is complete small bowel obstruction. Most of the relative contraindications, including motility or swallowing disorders, pregnancy, CIEDs, and strictures, can be addressed prior to SBCE and potentially circumvented as needed. The use of preps and prokinetics is based on expert opinion and limited studies. Therefore, their use must be considered on a per-case basis. Although indiscriminate use of MR/CT enterography/enteroclysis has poor sensitivity and specificity, if used in particular cases, or in conjunction with the patency capsule, they can be quite helpful. Additionally, the use of proximal dilation to define a positive study enhances the specificity significantly. However, patency capsules still carry the highest sensitivity and specificity in the evaluation of patency. Unfortunately, much practice in the field of small bowel capsule endoscopy is based on expert opinion and limited studies. Higher-powered studies, particularly randomized controlled trials, are needed to guide our practice further.

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Chapter 3
Difficult Populations: Dysphagia/Partial SBOs/ICDs/Pediatrics

Seth A. Gross, Andrew Dikman, and Jonathan Rosenberg

Pediatric Patient

FDA approval for video capsule endoscopy (VCE) in adult patients older than 18 was granted in 2001. In 2004 VCE became FDA approved for children under age ten and in 2009 for children 2 years and older. Prior to 2004, complete video endoscopic small bowel imaging in the pediatric population necessitated laparoscopy-assisted endoscopy. VCE has since provided for a noninvasive small bowel video imaging option in pediatric patients [1].

One of the most important considerations to address in the pediatric capsule patient is the ability, or lack thereof, for capsule ingestion in the standard fashion. Under age ten, a significant proportion of patients may have difficulty cooperating with swallowing of the actual capsule, though it is certain that there are patients younger than ten who can cooperate with capsule ingestion and those older than ten who cannot. A review by Stanley Cohen found that in a population of nearly 1,000 patients, nearly 90 % were able to swallow the capsule successfully. In clinical practice in younger patients, however, inability to ingest the capsule is more common [13].

Prior to capsule ingestion in the younger range of patients, a trial ingestion with a small candy approximating the size of an actual capsule should be considered in an effort to gauge the patient's ability to swallow the camera. In those who are unable to swallow, or in patients who are considered at high risk for possible capsule aspiration, endoscopic-assisted capsule placement should be employed [47].

There are several available strategies to endoscopically deploy the capsule in the small bowel of the pediatric patient. Regardless of the actual delivery device, the typical protocol for standard esophagogastroduodenoscopy (EGD) should be followed. After an initial complete EGD, the gastroscope should be withdrawn and

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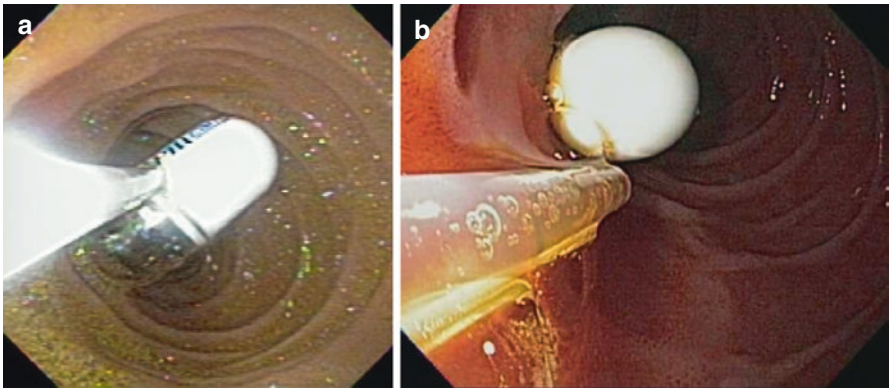

Fig. 3.1 (**a**) Endoscopic view of the small bowel during endoscopic deployment of a capsule endoscope using a standard polypectomy snare. (**b**) Endoscopic view after release of the polypectomy snare with successful endoscopic deployment.

fitted for capsule delivery. Capsule delivery can be accomplished with several tools that should be readily available in any endoscopy suite. A Roth Net catheter (US Endoscopy, Mentor, Ohio) with or without a suction cap can be used. Standard polypectomy snares with the snare cinched securely around the waist of a capsule are a viable option, ideally with an esophageal overtube placed beforehand for airway protection. Some have even reported the use of a Savary dilator to push the capsule through the stomach into the bowel (Fig. 3.1a, b).

While often successful, these techniques may be cumbersome, requiring significant effort and ingenuity to successfully deploy the capsule. In one experience, argon plasma coagulation was needed to burn a hole in the Roth Net in order to release the capsule. In addition, overtube placement in itself can be traumatic and may require increased sedation [24, 38].

A solution to these aforementioned maneuvers was the development of a specific capsule delivery device, the AdvanCE® (US Endoscopy, Mentor, Ohio) [24], which was mentioned in the preceding chapter. The device is disposable. It consists of a catheter, which is advanced through the working channel of an endoscope. The AdvanCE® device has multiple advantages. It has fewer accessory devices, leading to easier use. When the catheter exits the working channel, it is off-center and does not block the light source and lens, thereby facilitating better views and potentially preventing need for multiple passes of the endoscope (Fig. 3.2a, b).

Indications for Pediatric Ingestion

While less data exists in the pediatric population, it appears that indications for VCE are similar to adults. The most common indication for VCE in the pediatric population is for diagnosis of possible underlying inflammatory bowel disease

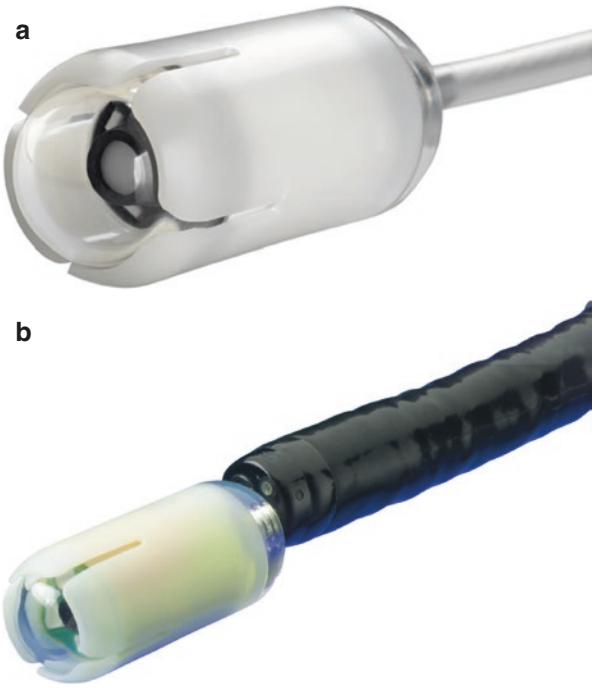

Fig. 3.2 (**a**) AdvanCE® capsule endoscope delivery device fitted into the deployment system. AdvanCE® capsule endoscope delivery device (Courtesy of US Endoscopy). (**b**) AdvanCE® capsule endoscope delivery device with capsule loaded after insertion through the working channel of a standard gastroscope with capsule askew from optics, allowing for better endoscopic viewing. AdvanCE® capsule endoscope delivery device (Courtesy of US Endoscopy)

(IBD), as well as for surveillance of IBD to assess the extent of disease as well as efficacy of a given treatment regimen. VCE for obscure gastrointestinal bleeding is performed less frequently in the pediatric population when compared to adult patients. VCE in the pediatric patient may find a greater role in the future in the diagnosis and management of polyposis syndromes and eosinophilic disorders such as eosinophilic enteritis, cystic fibrosis-related inflammatory enteropathy, graft vs. host disease of the small bowel, chronic recurrent abdominal pain of unclear etiology, protein-losing enteropathies, weight loss and growth failure of unclear etiology, and even eosinophilic esophagitis as physician familiarity and technology for esophageal capsule endoscopy improve [1, 13, 51].

Gastrointestinal Bleeding

In comparison to adult patients, for whom OGIB is the most common indication for VCE, VCE was less frequently used to investigate the small bowel for causes of OGIB in the pediatric population. However, children are not a uniform population, and when further stratifying children into age subgroups, OGIB is the most common indication for VCE in children 1–6 years old. However, even in this population, the percentage of procedures performed for OGIB is much lower than in the adult population at 36 % [11]. While data evaluating the accuracy of VCE for OGIB in

pediatric patients is limited, meta-analyses as well as several retrospective studies have demonstrated widely varied results. VCE correctly identified causative pathology ranging from less than a third of the time to greater than 75 % of the time. VCE is the most effective diagnostic modality after conventional endoscopy and colonoscopy for evaluating OGIB in the pediatric population. VCE is more effective than angiography and is superior to small bowel follow through (SBFT) as well as push enteroscopy and enterography for identifying vascular anomalies of the small intestine [48]. VCE may be inferior to double-balloon enteroscopy (DBE) in evaluation for symptomatic Meckel's diverticulum [23, 28, 53].

IBD

The most common indication for VCE in patients under the age of 18 is for diagnosis and/or evaluation of small bowel Crohn's Disease (CD). CD is an inflammatory disorder, which can affect the intestinal tract from mouth to anus, often causing small bowel inflammation and ulceration. Evaluating for small bowel CD is essential in both the diagnosis and management of IBD. Differentiating between CD, UC, and indeterminate IBD as well as finding persistent small bowel inflammation despite colonic healing may impact treatment and prognosis significantly. While ileocolonoscopy often reveals the diagnosis, more proximal small bowel involvement beyond the reach of a standard colonoscope is not uncommon. Routine radiologic imaging of the small bowel may be difficult to perform in the pediatric population, inconclusive or fraught with its own practical limitations. CT enterography involves radiation and MR enterography requires significant patient cooperation due to the length of the exam, limiting their utility in the pediatric population. VCE is relatively easy to perform, is approved for the pediatric population, has superior sensitivity for small bowel findings, and can play an integral role in diagnosing small bowel CD [1, 20 , 28, 36].

Comparing VCE with other modalities, a meta-analysis demonstrated that VCE was superior to small bowel follow through (SBFT), CT, and CT enterography [12]. Several studies have reported superior sensitivity and specificity when compared to MR enterography as well [7, 27, 30]. While aphthous ulceration in the small bowel can be multifactorial in adult patients, in children, it may be more indicative of CD when found on VCE, especially when there is a high pretest probability for CD [21, 32].

One of the most significant potential complications of VCE is capsule retention. While the risk of retention is relatively low for all patients undergoing VCE, the risk is higher in those whose indication for VCE is evaluation of CD and IBD. The retention risk may be as high as 5 % in those with a high pretest probability for CD or known CD, especially with a low BMI. While there have been case reports of perforations and small bowel obstruction (SBO), this has yet to be reported in the pediatric population [2, 6, 8, 9 , 33].

In patients with known or suspected CD, especially if they present with a low BMI and a history of SBO or symptoms concerning for intermittent SBO, small bowel imaging and/or patency capsule should be strongly considered prior to administration of VCE. Retrospective and prospective studies have demonstrated the reliability and benefit of the patency capsule prior to VCE in patients with known CD [11, 12, 44].

Dysphagia

In the adult population, VCE is most commonly used in the diagnostic evaluation of OGIB. These patients generally tend to be older. Older patients are at increased risk for stroke and other disorders, which may impair swallowing. The swallowing mechanism is a complex neuromuscular process coordinating the passage of food from the mouth to the stomach. It involves greater than 30 muscles and consists of three phases. The oral phase consists of mastication and positioning of the bolus for swallowing. The pharyngeal phase, the most complex phase, involves protection of the airway, relaxation of the upper esophageal sphincter, and coordination of the oropharynx to allow passage of the bolus past the epiglottis into the esophagus without aspiration. The esophageal phase represents the process distal to the upper esophageal sphincter, allowing passage of food into the stomach. Even a subtle disruption of this intricate process can lead to dysphagia and aspiration. Relying on self-report of dysphagia may be insufficient to identify all those who have dysphagia and aspiration, and thus the importance of obtaining an assessment of the patient's swallowing capacity prior to ingestion cannot be stressed enough [46].

Despite the prevalence of dysphagia in the older adult population, the risk of capsule aspiration or inability to swallow the capsule in VCE is relatively low [45]. Stroke, mechanical obstruction, anatomic anomalies, neuromuscular disorders, mental illness, and inflammatory disorders are among the many etiologies of dysphagia in the elderly. For those patients who are unable to tolerate oral ingestion of the capsule, endoscopic placement will be required.

LVADs/ICDs/Pacemakers (Cardiac Implantable Electronic Devices)

One critical concern that has arisen since the advent of capsule endoscopy is whether the capsule technology has the potential to negatively interact with other devices, particularly cardiac devices. According to the PillCam® (Medtronic) package insert, the presence of an implantable electromagnetic cardiac device represents an absolute contraindication to placement of VCE as a result of theoretical interaction between the capsule and the device. Despite this recommendation within the package insert, as detailed previously in Chap. 2, numerous studies over the last decade have demonstrated the lack of any significant deleterious interactions between the

capsule and cardiac devices such as pacemakers, implantable electromechanical cardiac devices, and left ventricular assist devices (LVADs) [3, 4, 15, 17, 19, 22, 26, 41].

The PillCam® capsule (Medtronic) conducts acquired transmissions as it progresses distally through the small bowel via digital radiofrequencies to a digital recorder at the patient's waist. Capsule endoscopes generally function at radiofrequencies of 434 MHz with 2 or 4 Hz pulses. This frequency equates to a heart rate up to 240 beats/min, which has been postulated to potentially lead to electromagnetic interference (EMI) of the implantable electromechanical device, overlapping with the underlying native cardiac rhythm. This interference could theoretically cause implantable cardiac devices to malfunction. The EMI could cause the cardiac device to sense a tachyarrhythmia that is not actually present, leading to inappropriate therapy. Conversely, it may mask a pathologic cardiac rhythm in need of treatment, which could be life-threatening [3, 17]. This concern was accentuated by previous observations that radiofrequency ablation during gastrointestinal procedures could cause malfunction of pacemakers [49].

Despite these concerns for potential bandwidth overlap between electromagnetic cardiac devices and capsule endoscopes, there have been numerous studies both in vivo and in vitro which have repeatedly demonstrated the safety of capsule endoscopy technology with ICD, PM, and LVADs. This may be due in part to the intensity of the signal. It is likely that the distance between the capsule and device would need to be less than 10 cm to cause interference [17]. In addition to the lack of evidence that capsule technology imparts any negative impact on the cardiac devices themselves, similar studies have also found that capsule image quality was unaffected by any of the implantable cardiac devices (Harris et al. 2003, [4, 15]).

It should also be reemphasized that apart from Medtronic and Olympus capsule devices, other capsule designs, utilizing novel methods of transmission, have been developed. These may mitigate the theoretical radiofrequency interference risk even further [26].

MiroCam capsule endoscope (IntroMedic, Ltd., Seoul, Korea) utilizes human body communication (HBC), using the human body as a conductive medium to propagate electric fields. Even with this technology, there is theoretical risk that these electric fields could disrupt cardiac devices. However, unlike earlier capsule technologies, HBC has a different frequency and frequency intensity, which is so low that it is extremely unlikely to be clinically significant. Prospective evidence has proven the safety of HBC with cardiac devices [10, 26].

Thus, it can be concluded that in patients with implantable cardiac devices, VCE is likely safe. Like any procedure, the risks of the intervention must be weighed against its benefits. In the case of VCE with cardiac devices, the risks appear to be small and the benefits potentially great. By using shared decision making with the patient, VCE can play an integral role in small bowel evaluation for patients with cardiac devices.

Small bowel obstruction (SBO) occurs when the intestinal lumen becomes narrowed to the point that contents within the intestine cannot pass resulting in abdominal distention, pain, nausea, and vomiting. SBOs can be characterized as complete or partial and, when persistent, recurrent, or severe, may necessitate surgical intervention.

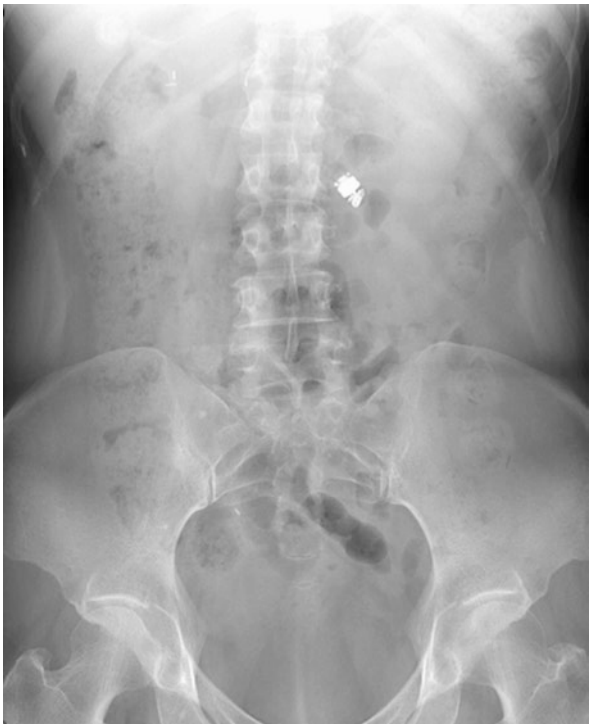

Fig. 3.3 Retained capsule in a 29-year-old patient with known polyposis syndrome without obstructive symptoms

SBOs are relatively common and may be caused by a variety of etiologies. In general, the etiologies can be divided into extrinsic and intrinsic causes. Adhesions, usually related to prior abdominopelvic surgery, causing extrinsic compression of the bowel, represent the causative etiology in the majority of SBOs. Extrinsic compression due to malignancies and hernias are also common. Intrinsic etiologies are less common. Stricture formation related to Crohn's disease (CD), nonsteroidal anti-inflammatory drugs (NSAIDs), metastatic cancer, radiation, and ischemia are the most common causes of intrinsic intestinal obstruction. Even rarer causes include primary small bowel tumors, gallstones, foreign bodies, and Meckel's diverticulum [16].

As described in previous chapters, VCE offers a high-resolution evaluation of the entire small bowel and is the most effective way to evaluate mucosal pathology of the small intestine. Much of the pathology that VCE is used to identify can cause obstruction, such as small bowel CD, NSAID enteropathy, polyps, tumors, ulcerations, Meckel's diverticulum, radiation and ischemic enteropathy, and masses. As a result, it is not surprising that the use of VCE is associated with risk of capsule retention and SBO.

The rates of capsule retention based on indication for the procedure were discussed in the previous chapter (Fig. 3.3). However, an additional concern is the development of a partial or complete small bowel obstruction which can occur with capsule retention. One meta-analysis reported 16 of 88 patients with retained capsules developed symptoms consistent with SBO [31]. Extremely rarely, small bowel

perforation has been reported as a result of small bowel VCE. This complication is exceedingly uncommon with only a few case reports in the literature [39].

Patients with a history of prior SBO or suspected or known CD pose a dilemma for physicians considering VCE. While CD is often diagnosed via ileocolonoscopy, up to 30 % of CD patients present with isolated small bowel inflammation. This percentage is possibly increased in the pediatric population [14, 50].

Prior surgery (particularly lysis of adhesions, gynecologic surgery, colorectal surgery, appendectomy, bowel perforation), leading to adhesive complications, is a major cause of surgical morbidity. It is unclear what percentage of patients with prior abdominopelvic surgery develop adhesions, but some studies have demonstrated that in patients with prior abdominopelvic surgeries, up to 6 % of readmissions were due to complications from adhesions, often SBO [18]. The greatest predictor of adhesive SBO is prior adhesive SBO [5, 35].

It is worth reemphasizing that prior to administering a video capsule endoscope, it is essential to take a careful history and review of symptoms, as well as to perform a comprehensive physical exam to assess for prior abdominal surgeries, intermittent or prior SBO, or evidence of conditions that may predispose the patient to having luminal compromise. Even if no prior history of obstruction or obstructive symptoms can be elicited prior to VCE, a high index of suspicion is needed when evaluating patients for VCE. It is imperative to thoroughly explain the procedure and obtain informed consent for VCE and to fully address the risks, benefits, and alternatives of VCE with the patient prior to capsule administration. Patients who have been deemed inoperable or who would refuse surgery should be especially counseled about the risk of capsule retention, and the benefits and alternatives of the procedure should be reevaluated.

Recently, VCE has been used in patients with a history of SBO in an attempt to identify the pathology that caused the obstruction. This usually occurs after imaging tests, such as CT or MR enterography, have been performed and have been unrevealing. In one retrospective series of 31 patients with prior history of SBO with imaging consistent with partial SBO, pathology was identified in nearly 40 % of capsule procedures and retention was observed in only one patient. This patient had asymptomatic retention without evidence for obstruction [52]. As with all patients undergoing VCE, informed consent must be obtained, especially in this high-risk population.

It is essential to consult with the patient's surgeon prior to administration of VCE in a patient with prior SBO or one who is at higher risk for capsule retention. Given that the greatest risk factor for SBO is a history of prior SBO, involvement of surgical expertise may help to guide the diagnostic and therapeutic plan with regard to VCE. As mentioned above, for a patient whom a surgeon has deemed to be a poor operative candidate, further evaluation for bowel patency may be prudent and noninvasive small bowel imaging, such as enterography, could be considered. Patients with a history of multiple SBOs, history of extensive abdominal adhesions, fibrostenosing small bowel CD, and even extensive NSAIDs use with symptoms concerning for intermittent or partial SBO should be further evaluated. In these complex cases, surgical input is integral to assess the surgical risk and thus better evaluate the

risk-benefit profile of VCE. For those with a prior history of SBO, or for whom there is a high pretest probability for capsule retention, but in whom VCE is deemed necessary, the PillCam® patency capsule is an extremely useful tool to further evaluate the risk of capsule retention.

Excretion of the patency capsule does not guarantee passage of the VCE, nor does retention of the patency capsule guarantee retention. Most study data comes from patients with CD, but up to 2 % of those with successful patency capsule passage can still have retention of the VCE. Up to 89 % of patients with positive patency capsule examinations in one study were able to successfully undergo VCE [37]. This discrepancy may in part be due to motility disorders. While current guidelines advise assessing bowel patency prior to VCE administration [40], indiscriminant use of the patency capsule in patients without obstructive symptoms, even those with known small bowel CD, may not be cost-effective. While judicious use of the patency capsule is important, lack of passage can help to identify potential surgical candidates [37].

When a capsule does not progress through the lumen of the small bowel, attempts at removal should be undertaken. Choice of removal method depends on the location of the retained capsule as well as the local expertise. If amenable, deep enteroscopy can be performed with removal of the retained capsule [33]. In circumstances when this approach is not feasible, surgical enterotomy with removal of the capsule may be necessary.

Double-Balloon Enteroscopy

An alternative and complementary modality to VCE is double-balloon enteroscopy (DBE). DBE is an endoscopic procedure which can be performed either anterograde or retrograde and allows for a more extensive evaluation of the small bowel than deep enteroscopy techniques. DBE consists of a long, flexible enteroscope with a balloon at the tip and an overtube with a balloon at its base (Fig. 3.4). The enteroscope is advanced manually with sequential inflation and deflation of the balloons and advancement of the overtube which causes pleating of the small bowel over the enteroscope, facilitating deeper enteroscopy.

DBE has several benefits when compared to VCE. It allows for therapeutic interventions and tissue acquisition, should pathology be encountered. The small bowel mucosa can be tattooed similarly to standard endoscopy in order to identify the extent of reach in the small bowel and location of pathology on subsequent procedures and/or surgery. While DBE provides more versatile interventions, the limitations of the procedure are predominantly related to the relative invasiveness of the procedure and length of the procedure when compared to VCE. DBE takes significant expertise and should only be performed by gastroenterologists well trained in these procedures. DBE requires sedation and often necessitates deep sedation or general anesthesia when performed via the oral route. Procedure time ranges in length from 73 to 123 min. Up to 20 % of patients experience abdominal pain post-

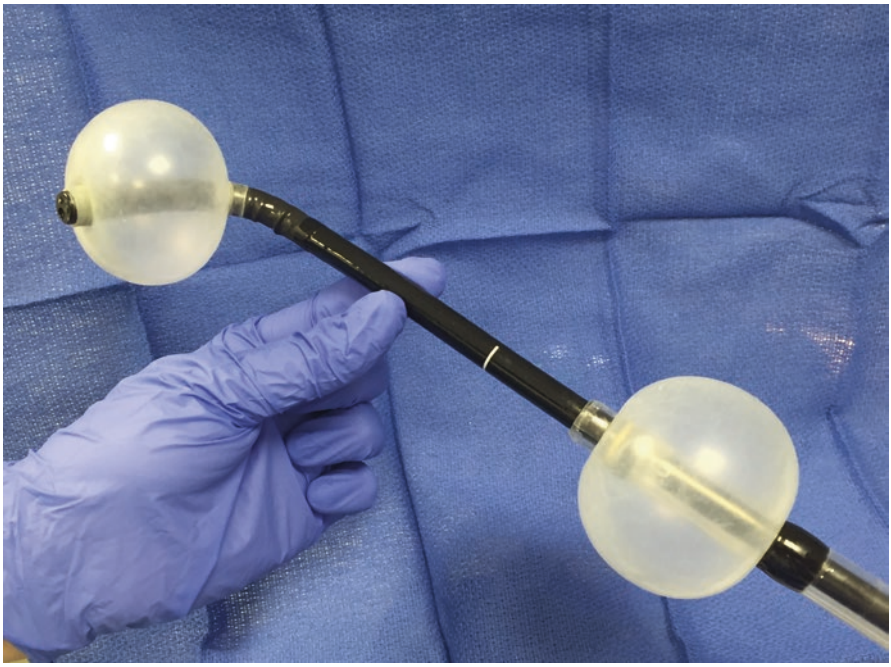

Fig. 3.4 Double-balloon enteroscopy with both distal and proximal balloons inflated over a flexible insertion tube. The overtube is proximal to the proximal balloon inflated in this figure

procedure as a result of prolonged insufflation, and the procedure carries a small, but not insignificant, risk of pancreatitis when performed via the oral route. The exact incidence of procedural pancreatitis is unclear and may be vastly underdiagnosed, but the average incidence from existing case series is roughly 0.3 % [25, 34]. The etiology of DBE-induced pancreatitis is unclear but may be in part due to direct trauma to the papilla during oral insertion [29].

Complete enteroscopy is possible but varies greatly by expertise. Data range widely from 70 to 86 % in Japan to 4–92 % in the West. These results usually reflect utilizing both anterograde and retrograde approaches in the patient. Studies directly comparing VCE and DBE are lacking, and those that have been published are small and heterogeneous in nature. Meta-analyses have demonstrated that both modalities are comparable in terms of diagnostic yield and identification of pathology [42, 43].

As a result, these technologies are often used in a complementary fashion. As a purely diagnostic modality, VCE is generally used to locate and identify pathology. In addition, VCE can influence the route by which DBE is subsequently performed. Very distal pathology in the small bowel may lead an endoscopist to choose to perform DBE via the retrograde route. This can decrease the morbidity of DBE as focusing the exam can decrease the length of procedure, the need for DBE via both anterograde and retrograde routes, and the amount of sedation administered. DBE can be performed to facilitate tissue diagnosis and/or provide therapeutic intervention for the endoscopic finding, if located.

In summary, when considering the implementation of small bowel capsule endoscopy, one must understand the limitations of the procedure, the published risks, and the potential complications. Robust and informed conversation with patients will allow for utilization of this technology, despite the aforementioned challenges so as to ultimately decrease morbidity and mortality of one's patient population.

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Chapter 4
Capsule Endoscopy for Obscure Gastrointestinal Bleeding

Rabia Ali and Seth A. Gross

Introduction/Background

The advent of capsule endoscopy has revolutionized our ability to evaluate the small bowel. A multitude of small bowel pathologies located between the ligament of Treitz and ileocecal valve including malignancy, benign mass lesions, inflammatory bowel disease, and angioectasias are now able to be directly visualized and confirmed leading to proper diagnosis and management. In the case of small bowel bleeding or hemorrhage, video capsule endoscopy has served a significant role in the work-up and subsequent management decision-making for obscure gastrointestinal bleeding, where a source has not been identified with traditional upper endoscopy and colonoscopy.

Obscure GI Bleeding/Background

Gastrointestinal bleeding is a common cause of inpatient hospitalization, with up to 400,000 gastrointestinal bleeding-related admissions per year in the United States [1]. Obscure gastrointestinal bleeding can be classified as "overt" or "occult" after an initial negative endoscopic evaluation including colonoscopy and upper endoscopy [2]. Overt bleeding refers to the presence of blood visible to the human eye, as is seen with hematochezia, hematemesis, and melena. The majority of overt obscure

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gastrointestinal bleeds with negative bidirectional endoscopy are caused by small bowel angioectasias [3, 4]. Occult bleeding is not visible to the naked eye, but reflects previous or ongoing blood loss from the gastrointestinal tract. Occult bleeding is suspected in the presence of iron deficiency anemia (IDA) and can be confirmed in real time by a fecal occult blood test, although it is important to note that fecal occult blood testing has only been studied for the purpose of colorectal cancer screening [3] and may be negative despite previous occult bleeding. Obscure gastrointestinal bleeding has been cited to have an incidence of approximately 5–10 % of all bleeding cases [2, 3, 5–9]. Approximately 75 % of these patients with negative bidirectional traditional endoscopic work-up will have small bowel bleeding sources discovered [3, 10, 11]. Up to 25 % of the remaining patients will have lesions discovered on repeat evaluation of the upper and lower gastrointestinal tracts that had been missed on initial bidirectional endoscopic evaluation [7].

The most recent guidelines published by the American College of Gastroenterology (ACG) have recommended a transition in nomenclature from "obscure gastrointestinal bleeding" to "small bowel bleeding" as the former implies that a source has not been identified despite small bowel evaluation, and therefore, this new terminology should be used to characterize this specific disease entity [7].

History and Physical Presentation

A thorough history and physical exam will provide guidance for the practitioner's management decisions and differential diagnosis. The volume of bleeding (if overt), or degree of anemia (if obscure), duration and frequency of symptoms, and previous work-up all assist in guiding management decisions. If there is a report of overt bleeding, it is important to note that hematemesis suggests the bleeding source is proximal to the ligament of Treitz. Hematochezia typically suggests a bleeding source distal to the ileocecal valve, unless the patient is suffering from a brisk upper gastrointestinal bleed. Melena is more often associated with upper gastrointestinal bleeding sources, but can be seen with bleeding sources throughout the small bowel and even the right colon. Although obscure bleeding sources are more often occult than overt, the latter may present as melena or hematochezia if the volume is significant. Obscure occult gastrointestinal bleeding can be difficult to localize based on history alone. Comorbidities listed in the history, such as hereditary hemorrhagic telangiectasias (HHT), end-stage renal disease, aortic stenosis, or heart failure requiring a left ventricular assist device (LVAD), will direct the gastroenterologist toward specific diagnoses such as angioectasias as a potential bleeding source. Intra-abdominal surgeries involving the small bowel may guide a practitioner to suspect a bleeding marginal ulcer. Medications are also an important aspect of the history that can establish bleeding risk. Nonsteroidal anti-inflammatory drugs may increase the risk of ulceration of the gastrointestinal mucosa, and blood thinners may increase bleeding risk. Family history of gastrointestinal malignancy may increase suspicion for a bleeding tumor or small bowel polyposis syndrome.

Demographics and travel history may increase the likelihood of small bowel tuberculosis or a parasitic infection as the source of blood loss or anemia [12–14].

The majority of patients with obscure gastrointestinal bleeding will be asymptomatic. Iron deficiency is usually detected after patients have been found to be anemic on routine labs. A subset of patients may also present with symptomatic anemia if the volume of blood loss is significant, reporting symptoms of lethargy, fatigue, pica, decreased exercise tolerance, restless leg syndrome, and, in severe cases, shortness of breath and chest pain [15, 16]. Physical exam findings will range from normal to findings suggestive of anemia, such as skin and conjunctival pallor, koilonychia (spoon nails), or alopecia [16, 17]. Unique physical exam findings such as telangiectasias of the lips or oropharynx in a patient with obscure gastrointestinal bleeding could suggest a diagnosis of HHT, and further investigation to identify the location of small bowel telangiectasias with video capsule endoscopy should be performed to plan possible therapeutic interventions [18].

Initial Work-Up

Patients with gastrointestinal bleeding may present with overt and occult bleeding. Those diagnosed with occult bleeding typically initially present with isolated anemia or guaiac-positive stool. Once anemia is detected, an assessment of the mean corpuscular volume of the red blood cells should be measured, as patients with chronic gastrointestinal blood loss will often be microcytic (MCV <80). Iron levels, ferritin, transferrin saturation, and total iron-binding capacity should then be measured to confirm the presence of IDA, which will reveal a low ferritin, a low/normal iron value, an elevated total iron-binding capacity, and a low transferrin saturation [16]. Patients often undergo a fecal occult blood test after the diagnosis of IDA is confirmed, but ultimately this should not alter the management [3], and the patient should undergo both a colonoscopy to screen for colonic pathology and an upper endoscopy to exclude upper tract pathology and to sample the duodenum for possible malabsorptive diseases such as gluten enteropathy to further evaluate the etiology of the IDA [19]. If there is persistent overt bleeding and the bidirectional endoscopy is negative, the next step in management is based on the degree of bleeding and patient stability. If recurrent overt bleeding is present and the patient is hemodynamically unstable, the patient should undergo repeat upper and lower endoscopy to rule out a possible undetected upper or lower gastrointestinal source which occurs in up to 25 % of cases [6, 7]. If the repeat bidirectional endoscopy is negative and the patient remains unstable, suggestive of active bleeding, angiography should be pursued in an attempt to localize the bleeding source [3]. If there is a concern for aorto-enteric fistula, cross-sectional imaging must be performed for diagnosis [3]. Suspicion for a pancreaticobiliary source of bleeding should result in evaluation with a duodenoscope to view the ampulla of Vater/duodenal papilla, and a high suspicion for a proximal small bowel source should prompt a push enteroscopy for improved chance of therapeutic intervention. In most cases, however, a

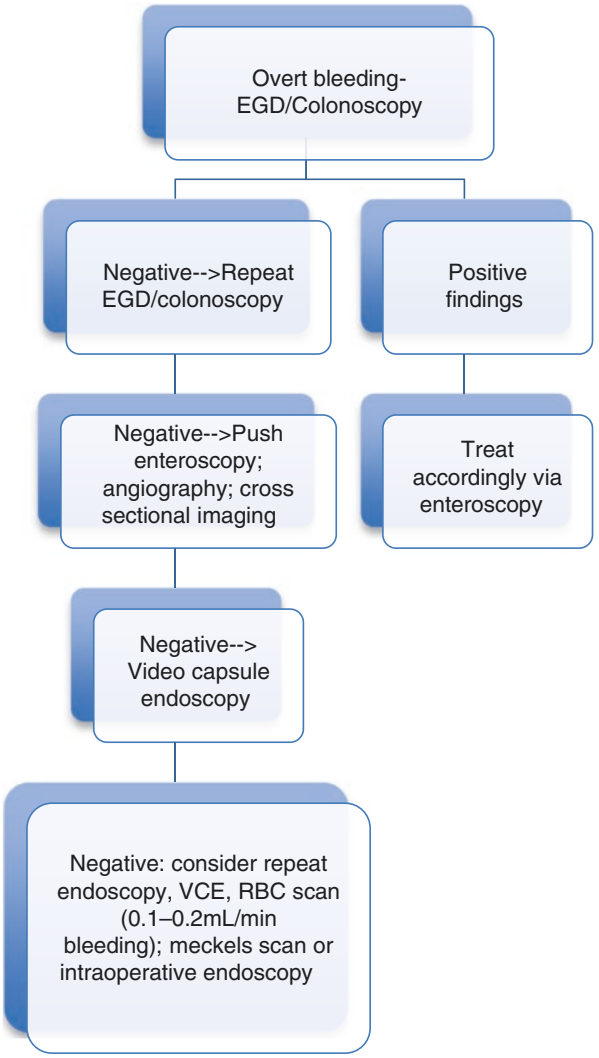

Fig. 4.1 Overt bleeding management [7]

negative bidirectional endoscopic evaluation in the absence of a clear extraintestinal reason for depleted iron stores or blood loss will guide care providers to look to the small bowel as a source, prompting a video capsule endoscopy (Figs. 4.1 and 4.2).

Differential Diagnosis

A thorough history including age of patient, comorbidities, surgical history, active medication list, demographics, and travel history must be obtained to guide the care provider to certain clues that may allude to one diagnosis over another prior to small

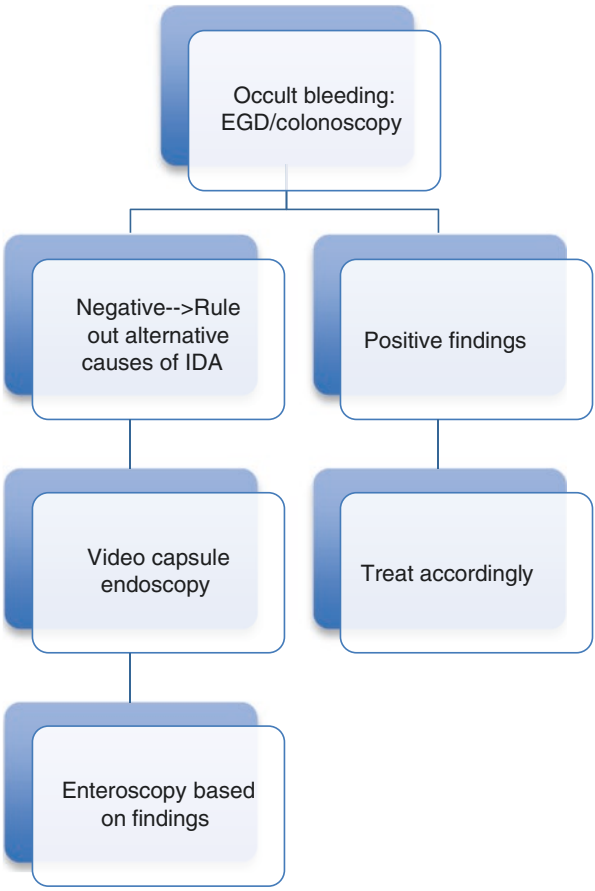

Fig. 4.2 Occult bleeding management [7]

bowel evaluation (Table 4.1). Once a patient is suspected to be suffering from a small bowel gastrointestinal bleed following negative bidirectional endoscopy, the most common sources are vascular lesions, small bowel tumors, or inflammatory lesions of the small bowel [3, 9]. Overall, the most common cause of small bowel bleeding in the United States is small bowel angioectasias. Approximately 30–60 % of overt small bowel bleeding cases are found to have angioectasias on small bowel evaluation [3, 4, 10, 14]. Additional vascular sources of small bowel bleeding include small bowel Dieulafoy lesions, small bowel diverticulosis, mesenteric ischemia, and small bowel varices [21]. Among younger patients, particularly those <40 years of age with small bowel bleeding, overt or occult, the etiology of the bleeding is more commonly inflammatory bowel disease, Meckel's diverticulum, Dieulafoy lesions, or small bowel tumors [3, 7]. Small bowel carcinoid is the most common site for gastrointestinal carcinoid, and additional small bowel tumors that can cause small bowel bleeding are adenocarcinoma, gastrointestinal stromal tumor (GIST), lymphoma, leiomyoma, leiomyosarcoma, lipoma, and metastatic disease (i.e., melanoma). Small bowel tumors will often be visualized on video capsule

Table 4.1 Differential diagnosis for small bowel bleeding

Vascular	Inflammatory/autoimmune	Polyp/mass/tumor	Iatrogenic/drug induced	Infection
AVMs; Heyde syndrome; LVAD; CKD	Crohn's disease ± ulcers	Carcinoid	NSAID enteropathy	Tuberculosis
Dieulafoy ± ulcer	Celiac sprue	Adenocarcinoma	Radiation enteritis	*Mycobacterium avium-intracellulare*
Small bowel diverticulosis	Amyloidosis	Small bowel metastases (melanoma, renal cell, breast, thyroid, Kaposi's sarcoma)	Acute GVHD after BMT	Whipple's disease
Portal hypertensive enteropathy	Sarcoidosis	Small bowel GIST		AIDS/Kaposi's sarcoma
Mesenteric ischemia	Meckel's diverticulum	Lymphoma		CMV
Blue rubber nevus syndrome/HSP	Eosinophilic enteritis	Lipoma		Helminthic infection
Small bowel varices	Small bowel erosions	Leiomyoma		Strongyloides stercoralis
Von Willebrand's disease		Leiomyosarcoma		
Telangiectasias (HHT/Osler-Weber-Rendu syndrome)		Lymphangioma		
Aorto-enteric fistula		Small bowel polyposis syndromes/Gardner syndrome		
Hemobilia/hemosuccus pancreaticus [a]proximal to ligament of Treitz				

[a]*Sources*: ([3, 4, 7, 9, 10, 12–15, 20]);
AVM arteriovenous malformation, *LVAD* left ventricular assist device, *CKD* chronic kidney disease, *HHT* hereditary hemorrhagic telangiectasia, *GIST* gastrointestinal stromal tumor, *GVHD* graft versus host disease, *BMT* bone marrow transplant, AIDS acquired immune deficiency syndrome, *CMV* cytomegalovirus, *HSP* Henoch-Schonlein purpura

endoscopy as submucosal mass lesions. Examples of infectious etiologies that can cause small bowel bleeding include opportunistic infections in immunocompromised individuals, such as gastrointestinal tuberculosis, Kaposi's sarcoma, cytomegalovirus, and *Mycobacterium avium-intracellulare*. Strongyloides stercoralis, a parasitic infection, is a rare cause of occult gastrointestinal bleeding [20]. Other unusual causes of occult small bowel bleeding include infiltrative diseases such as sarcoidosis and amyloidosis, small bowel polyposis syndromes, hereditary hemorrhagic telangiectasias, and blue rubber bleb nevus syndrome. Studies from India reveal small bowel ulcers, erosions, and small bowel tuberculosis, and parasitic worms are the most common findings in the work-up of small bowel bleeding among Indian patients [12–14] (Table 4.1). Figure 4.3 shows clear examples of the differential diagnosis for small bowel intestinal bleeding.

Capsule Endoscopy for Obscure Gastrointestinal Bleeding

First reported in 2000, wireless video capsule endoscopy has revolutionized our ability to visualize the depths of the small bowel in a noninvasive manner, sparing the patient from the risks of sedation and potential discomfort of endoscopy [22]. Approved by the Food and Drug Administration (FDA) in 2001, the patient is required to swallow a disposable white light-emitting capsule endoscope which captures photos of the gastrointestinal tract at a rate of 5–40 photos/s, which are wirelessly transmitted to a recording device that the patient wears during the duration of the capsule's 8–12 h battery life [23]. The recorder device is then used to review the images on a computer with the capsule device software installed, and the procedure is usually performed in the ambulatory setting.

The most common indication for video capsule endoscopy is for the evaluation of bleeding sources within the small bowel following negative bidirectional endoscopy among patients with overt bleeding or occult bleeding (including IDA) [2, 3, 7, 23, 24]. Capsule endoscopy has truly positioned itself as the third test in the work-up of small bowel bleeding, as supported by the AGA Position Statement [3]. Performing a capsule endoscopy for the work-up of overt small bowel bleeding should ideally be within 3 days of the onset of bleeding, as this has been proven to improve diagnostic yield [25, 26] when compared to those who undergo capsule endoscopy more than 3 days after bleeding onset. Capsule endoscopy has also been recommended in the emergent setting for hemodynamically unstable patients with negative upper endoscopy to improve diagnostic yield and the likelihood of successful therapeutic intervention [27].

From its inception, capsule endoscopy has been found to have improved sensitivity and diagnostic yield compared with its predecessors, namely, push enteroscopy (26 %) and small bowel barium radiography (6 %) [2, 21, 23, 28, 29]. Capsule endoscopy has also been found to have higher diagnostic yield than angiography (56 %) and CT angiography (26 %) for work-up of small bowel bleeding [22, 30–33]. The diagnostic yield of capsule endoscopy has been reported to range from 35

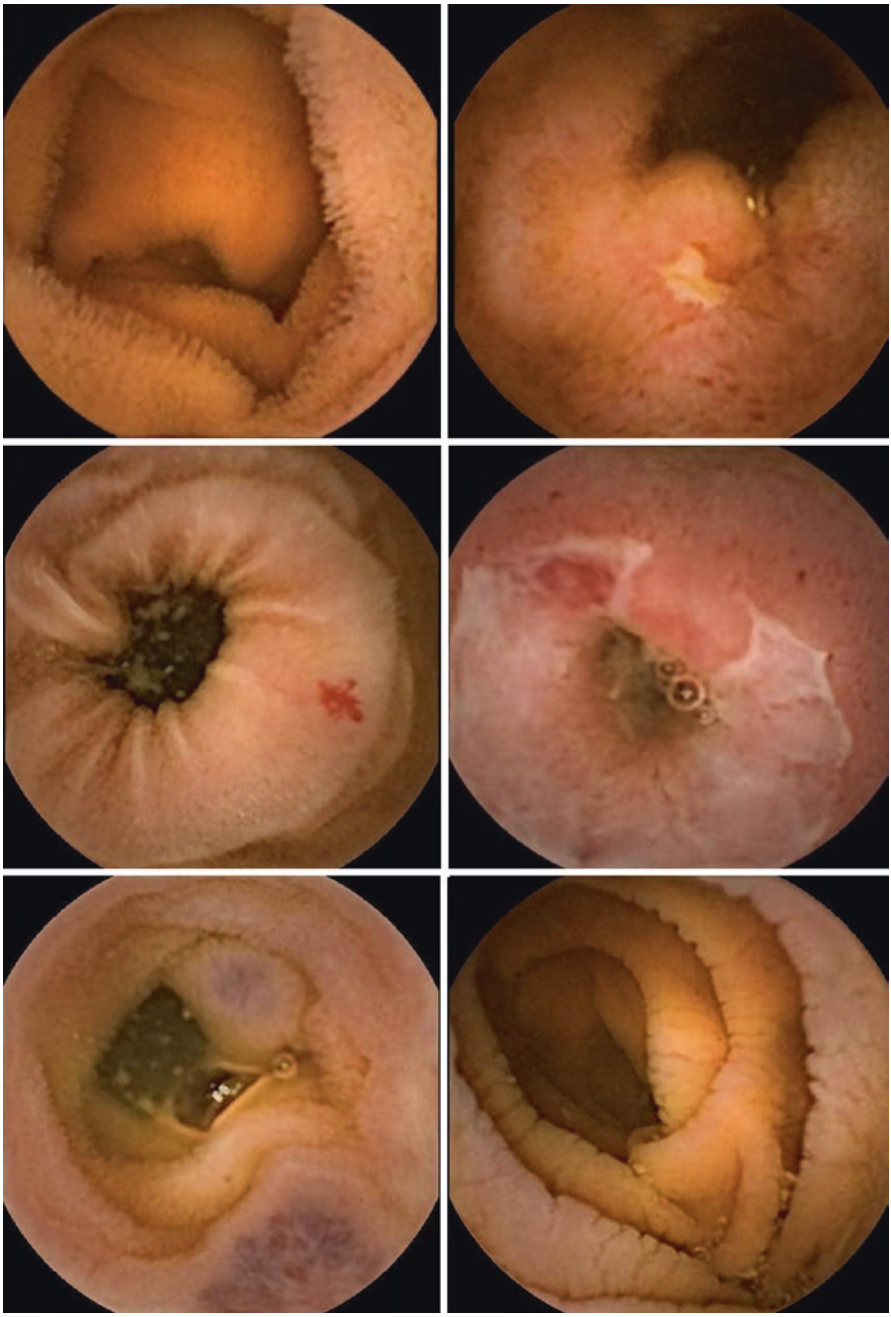

Fig. 4.3 Small bowel bleeding (Sources from Video Capsule Endoscopy). *First row:* normal small bowel; ulcer. *Second row:* angioectasia, Crohn's disease ulceration. *Third row:* blue rubber nevus; celiac sprue scalloping. *Fourth row:* submucosal mass; small bowel polyp. *Fifth row:* Meckel's diverticulum; small bowel varices. *Sixth row:* small bowel active bleeding; bleeding ulcer. *Seventh row:* small bowel melanoma (metastatic); CMV enteritis. *Eighth row:* small bowel diverticulum; NSAID-induced ulceration

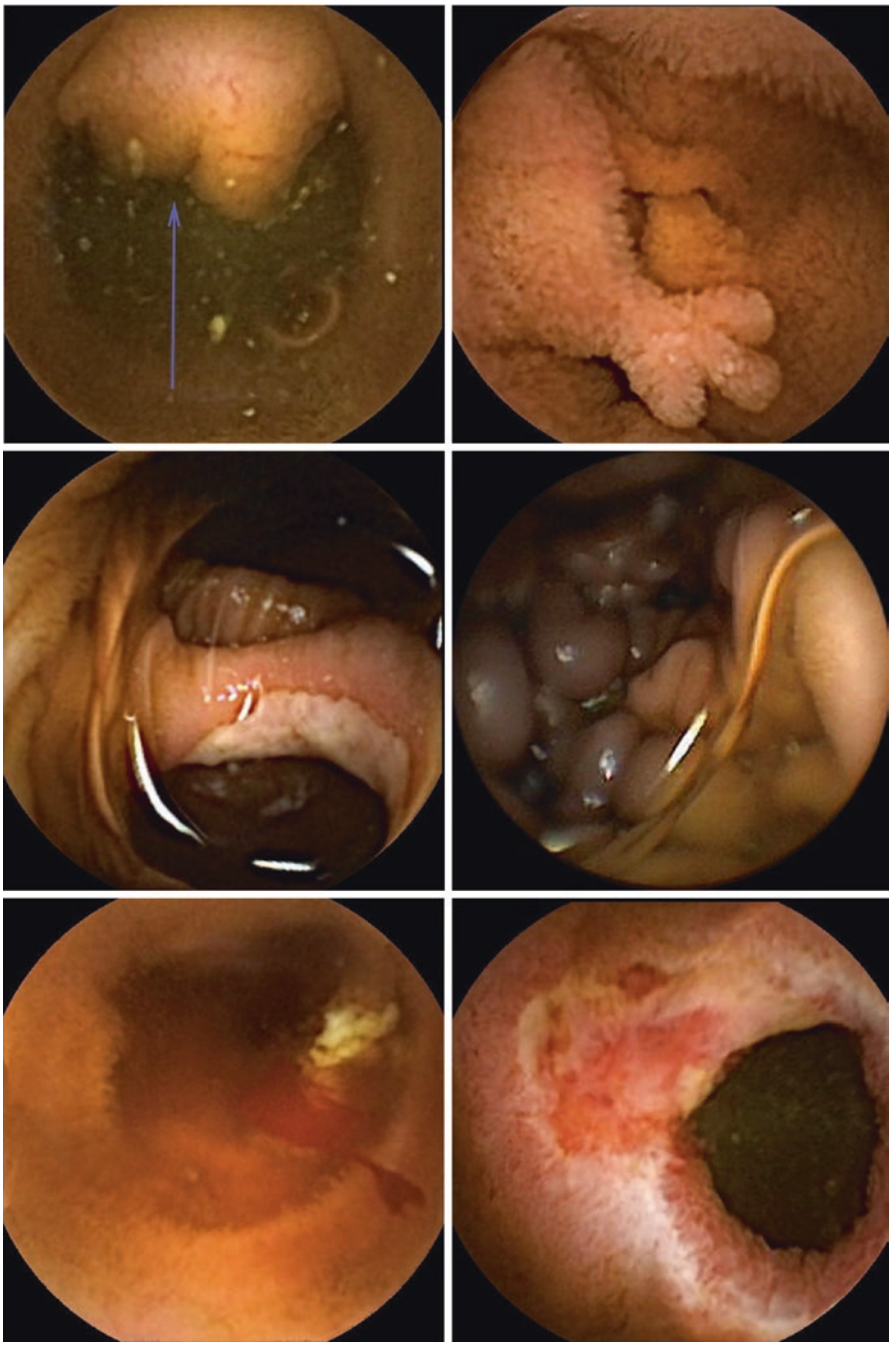

Fig. 4.3 (continued)

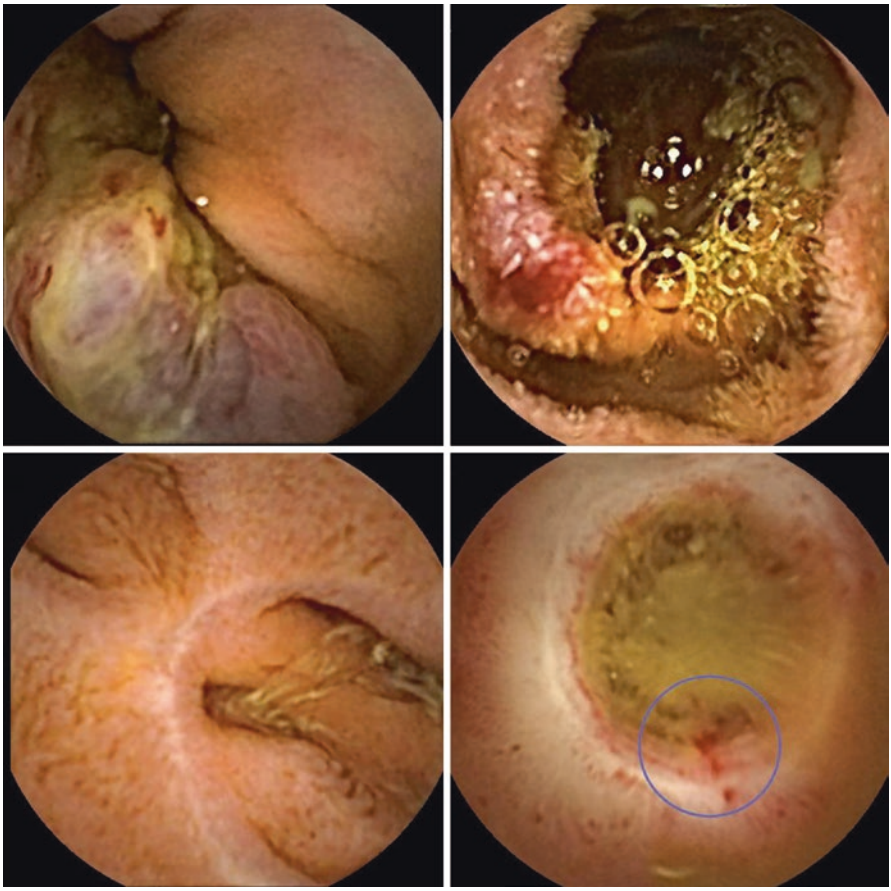

Fig. 4.3 (continued)

to 83 % [7, 14, 23], and the sensitivity and specificity of capsule endoscopy have been reported as high as 95 % and 75 %, respectively, when compared to the "gold standard," intraoperative enteroscopy for which diagnostic yield is reported as 70–100 % [2, 8, 34, 35]. The diagnostic yield of capsule endoscopy in detecting a source of bleeding among patients with overt bleeding has been reported to be as high as 91.9 % if performed within 48 h of the onset of the bleeding episode [2, 13, 25]. Among patients with IDA only, capsule endoscopy diagnostic yield was found to be 77.8 % compared with a yield of 22.1 % for CT enteroclysis or enterography [23, 36]. As one may expect, the diagnostic yield of capsule endoscopy is noted to be lower in patients with occult gastrointestinal bleeding (36.4–46 %) versus overt bleeding (64.7–87 %) [7, 13, 23]. Additional factors that have resulted in an increased diagnostic yield include anemia with hemoglobin <10 g/dL, inpatient status, recurrent bleeding episodes, and shorter duration of time from bleeding onset to capsule endoscopy (<3 days), which was also linked to an increased therapeutic yield and shorter length of hospitalization [7, 23, 25, 26].

Capsule endoscopy has also been compared to double balloon enteroscopy as the initial test in the work-up of small bowel bleeding. Capsule endoscopy and double balloon enteroscopy have been found to have similar diagnostic yields, but capsule endoscopy is the preferred first-line test given the less invasive nature of the study, as well as the avoidance of procedural risks associated with enteroscopy in the case of negative capsule endoscopy [7, 11, 37]. Double balloon enteroscopy has been found to have a better negative predictive value when compared to capsule endoscopy [38]. Capsule endoscopy followed by double balloon enteroscopy in the evaluation of positive or indeterminate results is a safe strategy to work up suspected small bowel bleeding [38–41]. Initial capsule endoscopy is also indicated to determine an anterograde versus retrograde approach for double balloon enteroscopy [11]. Lesions found within the first 60 % of the total small bowel transit time of capsule endoscopy should be further investigated with anterograde enteroscopy and oral insertion route, and lesions found within the last 40 % of the total small bowel transit time should be evaluated via a retrograde enteroscopy [42].

As previously stated, the true benefits of video capsule endoscopy over alternative forms of small bowel endoscopy are the lower side effect and risk profile. It is a noninvasive test that markedly reduces risk of perforation and bleeding that can be seen with invasive endoscopy. It requires no sedation and thereby eliminates the risks associated with anesthesia. Small bowel enteroscopy is invasive and time-consuming, owing to the length of the small bowel (>6 m) [7]. Capsule endoscopy is successful in evaluating the entire small bowel in up to 90 % of patients and results in a change in the management or therapeutic intervention in 37–87 % of patients [7, 43]. Benefits over radiologic testing for small bowel bleeding are the absence of radiation exposure and lack of contrast administration needed for capsule endoscopy, making it a safer alternative for patients with impaired renal function.

The primary shortcoming of capsule endoscopy in the work-up of small bowel bleeding is its inability to perform therapeutic intervention. Active bleeding that is detected on capsule endoscopy is revealed to the care provider at least 8–12 h after the fact. Unlike traditional endoscopy, capsule movement cannot be controlled by the practitioner, and therefore a lesion that is incompletely viewed cannot be further visualized if passed by the capsule endoscope. Furthermore, small lesions (i.e., arteriovenous malformations (AVMs), polyps, tumors) may be missed altogether. Additionally, exact localization of lesions remains a challenge given the long length of the small bowel, and although an estimation can be made based on the location of the lesion from the estimated small bowel transit time, it remains an inaccurate science [42]. Battery life has previously posed as a problem for capsule endoscopy, especially in patients with motility disorders. A capsule examination during which the endoscope ceases to record images prior to reaching the ileocecal valve is deemed incomplete and must be repeated, occurring in up to 15 % of cases [44]. Patients with poor gastric motility and emptying who require a capsule endoscopy should have the capsule placed by a delivery device which delivers the capsule to the small bowel using a traditional adult gastroscope [3, 45].

Risks of capsule endoscopy are capsule retention, and the incidence of capsule retention is thought to be up to 1–2 % [2, 7, 46–49] when performed for the indication of obscure gastrointestinal bleeding. Although capsule endoscopy markedly reduces perforation risk, it has been reported in patients with fibrostenotic, stricturing Crohn's disease and should be carefully considered in this patient population where capsule retention has been reported to be as high as 13 % [7, 50]. Additional potentially high-risk population for capsule retention include patients with previous surgery with potential for anastomotic strictures, NSAID enteropathy and resultant ulceration or stricture, and small bowel neoplasms [47, 51].

Management of Capsule Endoscopy Findings

Once a bleeding source has been identified on capsule endoscopy, a management decision must be made owing to the lack of therapeutic capability of the capsule endoscope. Supportive management with transfusions and crystalloid replacement should be administered as clinically necessary. Active bleeding sources are typically pursued with small bowel enteroscopy as mentioned above. Options include push enteroscopy if the lesion is thought to be in the proximal small bowel within reach of a pediatric colonoscope, single or double balloon enteroscopy. Innovative on demand through the scope single-balloon enteroscopy tools may be utilized to evaluate the small bowel using traditional adult gastroscope and colonoscope for anterograde and retrograde enteroscopy, respectively [52]. Double balloon enteroscopy and capsule endoscopy result in similar diagnostic yields as mentioned above, and double balloon enteroscopy as a therapeutic endeavor for small bowel bleeding is an accepted part of the treatment algorithm [7, 11, 37]. The exact therapeutic modality depends on the characteristics of the bleeding lesion. Enteroscopy will allow for direct thermal therapy for prevention of bleeding and treatment of actively bleeding AVMs with argon plasma coagulation. Alternative methods of hemostasis include hemostatic clip placement, injection therapy with epinephrine, and cautery [3]. Deep enteroscopy also allows for biopsy of suspicious lesions or polyps that may be intermittently bleeding.

In a subset of patients with suspected small bowel bleeding, capsule endoscopy will be negative. These patients are diagnosed with obscure gastrointestinal bleeding, owing to the lack of diagnosis despite visualization of the entire gastrointestinal tract. Rates of rebleeding among these patients have been reported as ranging from 6 to 26.7 % [2, 53, 54]. A repeat capsule endoscopy should be considered if suspicion for small bowel bleeding source persists. The diagnostic yield for a repeat capsule endoscopy after initial negative results has been reported and can be as high as 55 % [55]. Similar characteristics increase diagnostic yield in the repeat capsule endoscopy that were associated with higher diagnostic yield during initial capsule endoscopy (overt bleeding, shorter duration of time from bleeding to procedure, and significant anemia) [2].

Conclusion

Capsule endoscopy is a safe and effective tool for the work-up of small bowel bleeding. With diagnostic yield on par with double balloon enteroscopy, it is an excellent option to visualize the small bowel to identify and localize bleeding sources prior to planned therapeutic intervention.

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Chapter 5
The Utility of Capsule Endoscopy in Crohn's Disease

Steven Naymagon and David Greenwald

Introduction

Over the past decade small bowel capsule endoscopy (CE) has emerged as an invaluable tool in the evaluation of patients with inflammatory bowel disease (IBD). In particular, CE has expanded the ability to effectively diagnose Crohn's disease (CD), which involves the small bowel in the majority of patients, as well as monitor disease activity [1]. CE allows for visualization of the entire small bowel mucosa, thereby improving diagnostic capabilities and informing therapeutic decisions. In this chapter, we review the clinical utility and evidence for the use of CE in patients with CD.

Capsule Endoscopy Findings in Crohn's Disease

There is no pathognomonic lesion on capsule endoscopy that defines Crohn's disease. However, several characteristic CE findings have been identified that may support the diagnosis in the appropriate clinical setting. Findings associated with CD include aphthous lesions, deep ulcers, mucosal erythema and edema, loss of normal villi and vascular pattern, mucosal fissures, and luminal strictures (Fig. 5.1). Any or all of these findings may be present in a patient with active small bowel CD. If the disease is severely active, the findings are not subtle and a diagnosis can be readily established. However, making the diagnosis can be challenging when disease activity is mild. Early studies defined active CD by the presence of three or more small bowel aphthous lesions [2]. However, there is little evidence to support this practice.

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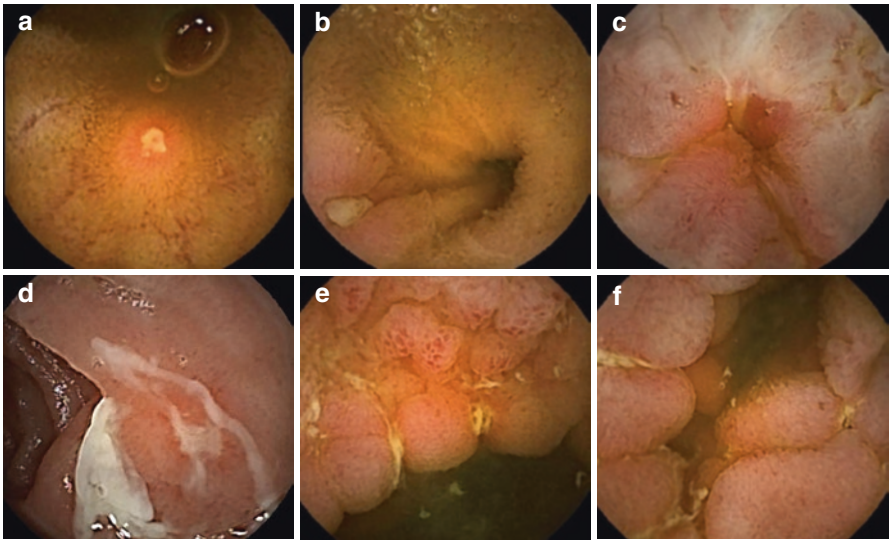

Fig. 5.1 Endoscopic findings in Crohn's disease. (**a**) Superficial aphthous ulcer demonstrating a yellow base and a pink or red collar. (**b**) Deeper ulcer with surrounding mucosal edema. (**c**) Ulcerated stricture that could not be traversed by the capsule. (**d**) Linear ulcers with exudate. (**e**) Edematous and erythematous villi with associated longitudinal lineal ulcers. (**f**) Linear ulcers with associated mucosal edema partially occluding the small bowel lumen

Currently, defined indices of inflammation are commonly used to help diagnose and monitor small bowel CD.

In an effort to create uniformity in describing the findings on small bowel capsule, a capsule endoscopy structured terminology (CEST) was proposed [3]. In describing CE findings as they pertain to suspected or established CD, certain descriptive terms are recommended (Table 5.1). Stenosis and strictures should be noted and characterized, as well as whether the capsule was able to traverse the stenotic areas. Evidence of previous surgery, including anastomoses and suture material, should be described. Abnormalities in the small bowel mucosa should be described, including erythema, edema (congestion), pallor, granularity, nodularity, and atrophy. The nature of these findings should be further characterized by noting their distribution and longitudinal extent. Abnormalities in the shape and color of the villi should be recorded, and the distribution, number, and longitudinal extent of any aphthae, erosions, and ulcers should be described. Active bleeding or stigmata or recent hemorrhage should be noted. Polyps or masses should be described with their size, number, and location. The use of a common nomenclature allows for a decrease in the interobserver variability when interpreting CE findings.

Since CE findings commonly seen in CD are nonspecific, it is important to use the findings judiciously, and always in context with other clinical data, when considering a diagnosis of CD. In fact, mucosal breaks and aphthae have been noted in approximately 10 % of individuals without any apparent underlying disorder [4]. In patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), mucosal

Table 5.1 Common capsule endoscopy findings and descriptors in patients with Crohn's disease

	Findings	Description
Lumen	Stenosis Stricture	Extrinsic or intrinsic? Traversed?
	Prior surgery	Type of surgery? Suture material present?
Mucosa	Erythematous Pale Edematous (congested) Granular Nodular	Localizes, patchy, or diffuse? Short or long segment?
Villi	Abnormal shape Discoloration	Convoluted or swollen? Blunted or absent? Whitish or yellow? Localizes, patchy, or diffuse? Short or long segment?
Excavated lesions	Aphthe Erosion Ulcer	Single, few, or multiple? Localized, patchy, or diffuse? Short or long segment? Bleeding? Stigmata of recent hemorrhage?
Protruding lesions	Polyp Mass Tumor	Single, few, or multiple? Small, medium, or large? Sessile or pedunculated? Ulcerated or bleeding?

Adapted from the capsule endoscopy structured terminology (CEST) [3]

breaks are seen in nearly 70 % [5]. NSAID avoidance is therefore critical in patients with suspected CD planning to undergo CE. Similar findings may also be seen in patients with celiac disease, ulcerative jejunoileitis, small bowel lymphoma, lymphoid hyperplasia, radiation enteritis, HIV-related opportunistic infections, intestinal tuberculosis, and Behcet's disease [6].

Capsule Endoscopy Severity and Diagnostic Scores

The adoption of a uniform terminology in describing capsule endoscopy findings allowed for the development of an objective measure of disease severity. The most commonly used disease severity score was developed by Lewis and colleagues [7]. The Lewis score (LS) assigns a numerical severity rating to each tertile of the small bowel (proximal, middle, distal). The score is based on findings of mucosal ulceration, villous edema, and the presence of stenosis (Table 5.2). The score assigned to the worst affected tertile is taken as the overall score for the study. A score <135 is considered normal, 135–790 is considered mild inflammation, and greater than 790 is considered moderate-to-severe inflammation.

The Lewis score has been validated as a valuable and reproducible clinical tool in reporting small bowel inflammatory activity. In one large retrospective study,

Table 5.2 The Lewis score

Parameters	Number	Longitudinal extent	Descriptors
First tertile			
Villous appearance	Normal = 0 Edematous = 1	Short segment = 8 Long segment = 12 Whole segment = 20	Single = 1 Patchy = 14 Diffuse = 17
Ulcer	None = 0 Single = 3 Few = 5 Multiple = 10	Short segment = 5 Long segment = 10 Whole segment = 15	<¼ = 9 ¼ to ½ = 12 >½ = 18
Second tertile			
Villous appearance	Normal = 0 Edematous = 1	Short segment = 8 Long segment = 12 Whole segment = 20	Single = 1 Patchy = 14 Diffuse = 17
Ulcer	None = 0 Single = 3 Few = 5 Multiple = 10	Short segment = 5 Long segment = 10 Whole segment = 15	<¼ = 9 ¼ to ½ = 12 >½ = 18
Third tertile			
Villous appearance	Normal = 0 Edematous = 1	Short segment = 8 Long segment = 12 Whole segment = 20	Single = 1 Patchy = 14 Diffuse = 17
Ulcer	None = 0 Single = 3 Few = 5 Multiple = 10	Short segment = 5 Long segment = 10 Whole segment = 20	<¼ = 9 ¼ to ½ = 12 >½ = 18
Stenosis – rated for whole study			
Stenosis	None = 0 Single = 14 Multiple = 20	Ulcerated = 24 Non-ulcerated = 2	Traversed = 7 Not traversed = 10

Adapted from Gralnek et al. [7]

small bowel capsule examinations for 70 patients with Crohn's disease were read by both an investigator and a central reader. The interobserver agreement between the investigators and the central reader was very high for both the individual tertiles and for the global score ($r = 0.745–0.928$, $p < 0.0001$) [8].

Several studies have evaluated the diagnostic accuracy of the Lewis score in patients with suspected CD undergoing capsule endoscopy. A retrospective study of 95 patients who underwent CE for suspected CD over a 6-year period found that a Lewis score of ≥135 had an overall diagnostic accuracy of 83.2 % for Crohn's disease. The sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of CD were 89.5 %, 78.9 %, 73.9 %, and 91.8 %, respectively. In patients with a LS <135, the probability of having CD confirmed on follow-up was very low [9]. Similar performance characteristics were found in another large retrospective study which yielded a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of CD of 82.6 %, 87.9 %, 82.6 %, and 87.9 %, respectively [10]. Given these findings, the Lewis score may be a useful tool for diagnosis, staging, and therapeutic assessment of patients with small bowel Crohn's disease.

The Lewis score has also been assessed as a prognostic tool in patients with Crohn's disease. One retrospective study included 53 patients with small bowel CD who underwent CE and subsequently had at least 12 months of follow-up. In multivariate analysis, moderate-to-severe disease at CE (Lewis score ≥790) was independently associated with a need for corticosteroid therapy (RR = 5, $p = 0.011$) and hospitalization (RR = 13.7, $p = 0.028$) during the follow-up period. Thus, stratifying the degree of small bowel inflammatory activity using the Lewis score at the time of diagnosis may provide valuable prognostic information [11].

An alternative scoring system called the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) grades disease activity based on the severity of inflammation, extent of disease, and presence of strictures in each half of the small bowel (proximal and distal) [12]. The final score is calculated by compiling the inflammation, disease extent, and stricture subscores for each segment. CECDAI scores of 3.8 and 5.8 have been shown to correspond to the Lewis score thresholds of 135 and 790, respectively [13]. A study in which four experienced endoscopists used the CECDAI to review CE images for 20 patients with Crohn's disease yielded a strong correlation between observers (0.867; $p < 0.0001$) [14].

While it is difficult to directly compare the performance of the CECDAI with that of the Lewis score, indirect comparisons have been made. One study assessed the performance of the two scoring systems by correlating them with fecal calprotectin levels. Overall, the Lewis score appeared to correlate better with fecal calprotectin level. The strength of the correlation was driven by the subgroup of patients with a fecal calprotectin level <100 μg/g [13]. In 2016, a Lewis score calculator is a standard feature of commonly used CE software platforms.

The Utility of Capsule Endoscopy in Various Clinical Settings

Capsule endoscopy has several clinical applications in patients with small bowel Crohn's disease. First, it may help establish the diagnosis, determine the disease location, and define the disease phenotype. Second, it may help monitor response to therapy by assessing for mucosal healing. Third, it may help assess for postoperative recurrence in patients who have undergone small bowel resection. Fourth, it may help clarify the diagnosis in patients with indeterminate colitis. Finally, there may be a role for capsule endoscopy in patients with ulcerative colitis.

Diagnosis of Small Bowel Crohn's Disease

As discussed above, there is no pathognomonic lesion, or combination of lesions, diagnostic for Crohn's disease of the small bowel. For study purposes, a minimum requirement of three aphthous lesions on capsule endoscopy has been adopted by many investigators for the diagnosis of active small bowel Crohn's disease [2]. However, it should be noted that this diagnostic threshold has not been prospectively

validated [15]. Using this definition, the performance characteristics of capsule endoscopy have been studied in various clinical settings and have been compared to other modalities used to evaluate Crohn's disease of the small bowel. The most commonly used radiologic modalities for assessing the small bowel are conventional small bowel follow-through (SBFT), computed tomography enterography (CTE), and magnetic resonance enterography (MRE). The gold standard technique for small bowel evaluation in patients with suspected or established Crohn's disease remains ileocolonoscopy or deep enteroscopy with biopsy.

In one of the few studies using histopathology (terminal ileum biopsy or surgical specimens) as the gold standard, the yield of CE was compared with SBFT for the evaluation of small bowel CD. Thirty-nine patients with suspected or established CD underwent SBFT, CE, and histologic evaluation of the small bowel. A final histologic diagnosis of active Crohn's disease was made in 29/39 patients (74.4 %). In these patients, CE yielded a sensitivity, specificity, positive predictive value, and negative predictive value of 89.6 %, 100.0 %, 100.0 %, and 76.9 %, respectively. These performance characteristics were significantly better than those for SBFT [16].

As SBFT has been largely replaced by cross-sectional imaging, several studies have compared CE with CTE and MRE. In one study, 56 consecutive patients with Crohn's disease underwent CTE followed by CE if small bowel patency was confirmed. In the 41 patients who underwent both studies, jejunal or ileal lesions were found in 25 patients by CE compared with 12 by CTE ($p = 0.004$). The difference was mainly driven by mucosal lesions (villous denudation, aphthae, erosions) in the proximal small bowel. There was no significant difference in the detection of lesions in the terminal ileum [17].

Similar findings were demonstrated in a study of 18 patients with known or suspected CD undergoing both CE and MRE. CE detected significantly more lesions in the small bowel compared with MRE (12 vs. 1 patient, $p = 0.016$). The difference was again driven by the detection of mucosal defects in the proximal and middle parts of the small bowel [18].

In a larger study, investigators prospectively enrolled 93 patients with Crohn's disease scheduled to undergo colonoscopy, MRE, CTE, and CE (if stenosis was excluded). The gold standard was considered colonoscopy, ileoscopy, or surgery. Overall, the sensitivity and specificity for the diagnosis of Crohn's disease of the terminal ileum were 100 % and 91 % by CE, 81 % and 86 % by MRE, and 76 % and 85 % by CTE, respectively. The sensitivity of CE was significantly higher compared with CTE ($p = .03$), and there was a trend toward higher sensitivity compared with MRE ($p = 0.1$). As was the case in other studies, significantly more proximal lesions were detected by CE than by the cross-sectional imaging modalities (18 vs. 8 patients, $p < .05$) [19]. It is important to note that the identification of proximal lesions in CD may have clinical significance. A database study of thousands of patients with CD showed that patients with jejunal disease were more likely to develop stricturing complications and require surgery [20]. In a prospective study of 108 patients with Crohn's disease, jejunal lesions were detected in over half of patients who underwent CE, and the presence of jejunal lesions was a predictor of disease relapse at a median follow-up of 24 months [21].

Table 5.3 Meta-analyses comparing capsule endoscopy with other modalities for the diagnosis of Crohn's disease

		Triester et al. [22]		Dionisio et al. [23]	
		Diagnostic yield %	Incremental yield %	Diagnostic yield %	Incremental yield %
CE vs. SBFT	All CD	64 vs. 24	*40*[a]	58 vs. 22	*37*[a]
	Suspected CD	43 vs. 13	30	52 vs. 16	*32*[a]
	Established CD	78 vs. 32	*46*[a]	71 vs. 36	*38*[a]
CE vs. C + IL	All CD	61 vs. 46	*15*[a]	64 vs. 48	*15*[a]
	Suspected CD	33 vs. 26	*7*	47 vs. 25	*22*[a]
	Established CD	86 vs. 60	*26*[a]	70 vs. 57	13
CE vs. CTE	All CD	69 vs. 30	*39*[a]	70 vs. 31	*39*[a]
	Suspected CD	70 vs. 21	49	68 vs. 21	*47*[a]
	Established CD	68 vs. 38	*30*[a]	71 vs. 39	*32*[a]
CE vs. MRE	All CD	72 vs. 50	22	50 vs. 43	7
	Suspected CD			55 vs. 45	10
	Established CD			70 vs. 79	−6

CE capsule endoscopy, *SBFT* small bowel follow-through, *C + IL* colonoscopy with ileoscopy, *CTE* CT enterography, *MRE* MR enterography, *CD* Crohn's disease
[a]Statistically significant result

In an effort to overcome the limitations of several small studies, Triester et al. performed a meta-analysis of prospective trials comparing CE with other diagnostic modalities (Table 5.3). In nine studies comparing CE to SBFT, the yield for CE was significantly higher (63 vs. 23 %, incremental yield (IY) = 40 %, $p < 0.001$). In four trials comparing the yield of CE to colonoscopy with ileoscopy, the yield for CE was higher (61 vs. 46 %, IY = 15 %, $p = 0.02$). In three studies comparing CE to CTE, the yield for CE was higher (69 vs. 30 %, IY = 39 %, $p = 0.001$). Finally, in one trial comparing CE to MRE, the yield of CE was higher (IY = 22 %, $p = 0.16$). Subgroup analyses were further carried out to assess the utility of CE in patients with established CD with suspected small bowel recurrence and those with a suspected initial diagnosis of CD. In the subgroup of patients with established CD, there was a statistically significant difference in yield in favor of CE compared with other modalities. However, in evaluating the subgroup of patients with a suspected initial presentation of CD, while there was a trend toward significance in favor of CE, there was no statistically significant difference between the yield of CE and the other modalities [22].

A larger meta-analysis by Dionisio et al. again compared the diagnostic yield of CE with other modalities in patients with suspected or established CD (Table 5.3). The authors identified 12 trials comparing the yield of CE with SBFT, eight trials comparing CE with ileocolonoscopy, four trials comparing CE with CTE, and four trials comparing CE with MRE. In the subgroup of patients with suspected CD, the diagnostic yields for CE were significantly higher than other modalities: CE vs. SBFT, 52 vs. 16 % (IY = 32 %, $p < 0.0001$); CE vs. CTE, 68 vs. 21 % (IY = 47 %, $p < 0.00001$); and CE vs. ileocolonoscopy, 47 vs. 25 % (IY = 22 %, $p = 0.009$). Similarly, in the subgroup of patients with established CD, statistically significant yields were seen in CE vs. SBFT, 71 vs. 36 % (IY = 38 %, $p < 0.00001$), and in CE vs. CTE, 71 vs. 39 % (IY = 32 %, $p < 0.0001$) [23].

Thus, review of the available data comparing CE with other small bowel imaging modalities seems to show that CE has superior sensitivity for CD. However, a major limitation of many of these studies is the lack of a gold standard tissue diagnosis. In addition, the convention of using three or more aphthous ulcers to define a positive study has never been validated. This calls into question the specificity of CE in diagnosing CD. These limitations should be kept in mind when reviewing the data on the utility of CE for the diagnosis of CD.

Assessing Disease Activity and Mucosal Healing

The therapeutic target in Crohn's disease has shifted from achieving symptomatic control to aiming for complete healing of the gastrointestinal mucosa in hopes of preventing irreversible bowel damage. This target of achieving clinical, serologic, and endoscopic remission (termed deep remission) has been shown to lead to favorable long-term outcomes [24]. Ileocolonoscopy has been the standard method for assessing mucosal healing for decades. However, mucosal healing in the colon does not necessarily correlate with mucosal healing in the small bowel. To that end, capsule endoscopy offers a unique and highly sensitive method of assessing response to therapy in patients undergoing treatment for small bowel Crohn's disease. It should be noted that the definition of mucosal healing has not been established for CE. Some studies, however, have defined a normal small bowel as one with a Lewis score of <135.

The utility of CE in tracking response to therapy and mucosal healing has been formally evaluated. In one prospective study, 40 patients with known or suspected active small bowel CD underwent CE prior to the initiation of any treatment and again after clinical response was achieved. The follow-up CE demonstrated an improvement in the number of large ulcers but no significant change in more subtle mucosal lesions such as aphthae [25]. In another study, sequential CE was performed in 19 patients with known active small bowel CD undergoing therapy, in an effort to correlate the CE findings with clinical and laboratory parameters of inflammation. Interestingly, clinical response over time did not correlate with changes in the Lewis score [26]. Finally, in a long-term prospective trial of patients with active small bowel CD commencing therapy, baseline and 52-week clinical and CE scores were calculated. Twenty-eight patients underwent the 52-week assessment, and only 12 (42 %) participants achieved complete mucosal healing which was paralleled by clinical remission [27]. These studies demonstrate that CE may serve as a sensitive tool for assessing response to therapy and also underscore the lack of correlation between clinical and endoscopic remissions.

The incongruence of clinical and endoscopic findings in patients with CD was recently demonstrated in a large prospective study by Kopylov et al. Patients with small bowel CD in clinical remission or with mild symptoms underwent CE, and inflammation was quantified using the Lewis score. Fifty-six patients were enrolled; 52 (92.9 %) patients were in clinical remission. Mucosal healing was demonstrated

in only eight of 52 (15.4 %) patients in clinical remission. A striking finding was that 11 of 52 (21.1 %) patients had moderate-to-severe inflammation demonstrated by CE. Only seven of the 52 (13.5 %) patients in clinical remission had deep remission as defined by Lewis score <135 and normal biomarkers [28].

Detecting endoscopically active disease in patients in clinical remission allows clinicians to alter medical therapy. The impact of capsule endoscopy findings on clinical decision-making has been assessed. In a large retrospective cohort of 907 capsule studies done for IBD patients at a tertiary-care center, nearly two-thirds of patients had their therapy altered based on CE findings. Severe findings on CE, as compared to no or minimal findings, resulted in significant differences in the addition of medications (58.5 vs. 22.2 %, $p < 0.01$) and surgeries (21.9 vs. 4.4 %, $p = 0.01$) [29]. Another study assessing the impact of CE on the clinical management of 187 patients with CD demonstrated active disease in 71.6 % of patients. A change in management was recommended in 52.3 % of the patients based on CE findings. This study also demonstrated a poor correlation between biomarkers and small bowel inflammation seen on CE [30].

Based on available evidence to date, CE may be a valuable tool for assessing mucosal healing in patients with small bowel CD. Importantly, findings on CE provide information on mucosal changes that do not correlate strongly with clinical remission or serologic markers. Symptomatic and biochemical response to treatment appears to be mirrored by mucosal healing seen on CE in under half of individuals. Thus, CE is an independent and objective therapeutic monitoring tool in patients with CD. Importantly, capsule endoscopy findings have been demonstrated to influence treatment decisions as clinicians aim to achieve mucosal healing in their CD patients. However, it should be noted that while achieving mucosal healing and deep remission have been shown to improve long-term outcomes, whether therapeutic changes guided by CE will lead to improved clinical outcomes is still unknown.

Assessing for Postoperative Recurrence

Postoperative recurrence is the rule rather than the exception in patients with Crohn's disease who undergo resection of diseased bowel segments. The gold standard for assessing for postoperative recurrence is ileocolonoscopy with use of the Rutgeerts score to grade disease. Capsule endoscopy has been proposed as an alternative modality for postoperative surveillance of disease activity in Crohn's disease.

The accuracy and therapeutic impact of capsule endoscopy was prospectively studied in 24 patients with Crohn's disease who had undergone ileocolic resection. All patients were asymptomatic and did not receive any prophylactic treatment. A colonoscopy was performed in all patients, although the neo-terminal ileum could not be reached in three of them. Capsule endoscopy was performed in 22 of the patients. Recurrence in the neo-terminal ileum was visualized with colonoscopy in six patients and with capsule endoscopy in five. In addition, capsule endoscopy was

able to detect proximal lesions outside the reach of the colonoscopy in 13 patients [31]. A second prospective trial of 32 postoperatively enrolled patients also demonstrated a significant gain in detection of lesions outside the reach of ileocolonoscopy. However, in this study the sensitivity of CE in detecting recurrence in the neo-terminal ileum was inferior to that of ileocolonoscopy [32].

At this time, it does not appear that CE will replace ileocolonoscopy as the primary modality for assessing postoperative recurrence in CD. There have been mixed results in assessing the sensitivity of CE for lesions in the neo-terminal ileum. While CE detects more lesions in the proximal small bowel, the precise clinical relevance of these lesions is yet to be determined.

Assessing Patients with Indeterminate Colitis

A subset of patients with inflammatory bowel disease of the colon have features suggestive of, but not meeting full criteria for, Crohn's disease. These patients are labeled as having inflammatory bowel disease unspecified (IBDU) or indeterminate colitis (IC) [33]. Capsule endoscopy has been proposed as a tool for clarifying the diagnosis in patients with IC and IBDU.

In one prospective study, 18 patients with long-standing IBDU or IC were enrolled to undergo capsule endoscopy and were followed prospectively for a median of nearly 3 years. The capsule findings were normal in 11 patients leading to no change in the diagnosis. On long-term follow-up, one of these patients was ultimately diagnosed with CD. In seven patients, criteria for CD were met and the patients were diagnosed with CD [34]. A larger multicenter study of 30 patients with IBDU found capsule endoscopy features suggestive of CD in five (17 %) patients leading to a change in diagnosis. Over the next year, five (17 %) other patients who had a normal CE were diagnosed with CD based on repeated ileocolonoscopy with biopsies. Two patients were diagnosed with UC on follow-up. Overall, 18 patients (60 %) remained with a diagnosis of IBDU at 16 months follow-up [35].

When interpreting the above studies, it bears noting that small bowel findings are not uncommon in patients with IBD of the colon. In a large retrospective cohort of 120 patients with UC or IBDU who underwent capsule endoscopy, 19 (15.8 %) had small bowel findings suggestive of Crohn's disease [36]. In a prospective study that had 23 well-documented UC patients and 23 control volunteers who underwent CE, small bowel lesions were found in significantly more UC patients than healthy controls (57 vs. 35 %, $p < 0.001$). Interestingly, the capsule endoscopy score correlated with clinical disease activity ($r = 0.718$, $p < 0.001$) [37].

Thus, based on currently available data, while CE may help clarify the diagnosis in some patients with IBDU, a negative CE does not exclude a future diagnosis of CD. Additionally, small bowel lesions seen on CE in patients with colitis may not signify a diagnosis of CD. Finally, the clinical implications of small bowel findings in this subset of patients are unclear, since therapy often remains unchanged despite the capsule findings.

Assessing Disease Activity in Ulcerative Colitis

The advent of colon capsule endoscopy (CCE) has led investigators to assess the utility of this technology in ulcerative colitis (UC) patients as a means of staging disease and assessing inflammation. This will also be discussed in a subsequent chapter.

In one prospective study, 40 patients with UC underwent bowel preparation followed by both CCE and conventional colonoscopy. In patients with complete exams, endoscopic severity scores determined by CCE showed a strong correlation with scores obtained by conventional colonoscopy [38]. A similar study of 25 patients with UC also found a significant correlation in the severity and extent of UC between CCE and conventional colonoscopy [39]. A study of 100 patients with UC found that as compared with colonoscopy, the sensitivity, specificity, positive predictive value, and negative predictive value of CCE to detect active colonic inflammation were 89 %, 75 %, 93 %, and 65 %, respectively [40].

A major limitation of CCE in the above studies is the relatively high rate of incomplete examinations due to inadequate bowel preparation or failure of the capsule to visualize the entire colon in the allotted time. In the study by Hosoe et al., the CCE procedure was completed in only 69% of patients, and the proportion of patients with good or excellent bowel cleansing was below 50% [38]. In addition, CCE does not allow for tissue sampling, which remains standard practice for dysplasia surveillance in UC. At this stage, CCE does not appear ready to replace conventional colonoscopy for the evaluation and management of ulcerative colitis.

Capsule Retention in Crohn's Disease

The most feared complication of capsule endoscopy is capsule retention, defined as failure of the capsule to pass within 14 days of ingestion and requiring direct intervention [41]. It should be noted that most patients do not visualize capsule passage in the stool. If capsule passage is not witnessed by the patient, and the colon is not visualized on the captured video imaging, an abdominal radiograph can reliably diagnose or exclude capsule retention [42]. Although capsule retention is a rare event, it can have significant consequences. In one case series of patients undergoing CE, capsule retention occurred in eight of 904 patients (0.88 %). Six of the eight patients suffered acute small bowel obstruction requiring hospitalization. In this series, all retained capsules were successfully retrieved using double-balloon enteroscopy [43].

As demonstrated in the abovementioned study, the risk of capsule retention is low in the general population of patients undergoing CE. This was confirmed in a systematic review of 227 original articles involving 22,840 patients wherein the retention rate for CE done for all indications was 1.4 %. However, the study also clearly demonstrated that retention rate depends on the study indication. The rates were

lowest (1.2 %) in patients being evaluated for occult bleeding. On the other hand, retention rates in patients being investigated for Crohn's disease (2.6 %) or small bowel neoplastic lesions (2.1 %) were significantly higher [44]. In various studies, capsule retention rates specific to IBD populations are in the range of 1.4–6.7 % [45].

The risk of capsule retention in Crohn's disease was further dissected by Cheifetz et al. Capsule endoscopy was performed in 64 patients with suspected CD and 38 patients with known CD. Capsule retention occurred in only one patient (1.6 %) with suspected CD, very similar to the rate reported in the general population. In contrast, five of the 38 patients (13 %) with established CD had a retained capsule proximal to a stricture. In four of these cases, the patients underwent uncomplicated resection of the strictured segment. One patient opted to defer surgery and did well for over 3 years of follow-up [46].

As demonstrated by Cheifetz et al., capsule retention can potentially act as a marker of major pathology that requires intervention to address a patient's symptoms. Thus, some have argued that retention may not always be an adverse event. In a retrospective database of 568 capsule endoscopies, 19 cases were identified in which capsule endoscopy was used in the setting of suspected small bowel obstruction either based on symptoms or imaging findings. Capsule endoscopy made a definitive diagnosis in five of the 19 cases (26 %): two Crohn's strictures, one radiation-induced stricture, one NSAID-induced stricture, and one MALT lymphoma. The capsule was retained proximal to a stricture in four cases in which the obstructing lesions were electively resected without complications. Thus, retention of the capsule may provide valuable diagnostic information and indicate the presence of a lesion requiring surgery [47].

The risk of capsule retention in Crohn's disease is not insignificant and should be discussed with all patients. In particular, patients with long-standing CD or those with known strictures must be explicitly counseled. Patients must understand that although capsule retention rarely leads to acute obstruction, surgery may be required for an obstruction that may have otherwise been treated medically. If the patient is high risk for retention and refuses to consider the possibility of surgery, it may be necessary to avoid offering CE.

The Utility of the PillCam® Patency Capsule in Crohn's Disease

As discussed earlier in this book, patency capsule systems have been designed to identify patients at risk for capsule retention. Several generations of patency capsules have been used. An older system, the M2A patency capsule (Given Imaging), was identical in size to the PillCam® SB but was made of lactose and barium, thus allowing it to dissolve in the bowel over a period of 40–100 h. The capsule contained a chip that could be detected if the capsule failed to be excreted. Unfortunately, there was a significant rate of retention of the M2A capsule, including cases of acute obstruction necessitating emergent surgery. Overall, the complication rate of the M2A patency capsule was 3–13 %, similar to the retention rates of the video capsule

itself. It was suggested that the significant complication rate was a result of the long dissolution time of the M2A patency capsule [45].

As a result of the limited success of the M2A system, a newer product was introduced. The PillCam® Patency System (Medtronic) is composed of a capsule that has the same dimensions as the PillCam® SB2. To again review, the capsule is composed of a radio-opaque, dissolvable shell and two time plugs that begin to erode and dissolve in under 30 h, significantly faster than the aforementioned M2A system. The PillCam® patency capsule core contains a radio-frequency identification tag that can be sensed by a handheld scanner if present in the GI tract. The radio-frequency tag is small enough to pass through most strictures [48]. Despite these safety measures, it is worth noting that administration of the patency capsule itself may cause symptoms or complications. However, this may be valuable information as well, since patients in whom passage of the patency capsule is painful may have a higher risk of video capsule retention or high-grade stenosis requiring surgery [49].

The PillCam® Patency System was tested in a prospective study of 106 patients with known small bowel strictures. Fifty-nine (56 %) excreted the patency capsule intact and subsequently underwent CE. The remaining 47 patients (44 %) excreted a disintegrated capsule and were deemed ineligible for CE. There were no confirmed episodes of patency capsule retention or related complications. Of the patients who underwent CE, there were no cases of capsule retention [48]. In a systematic review of five studies including 203 patients with suspected small bowel strictures, the pooled sensitivity and specificity of the patency capsule were 97 % and 83 %, respectively [50].

It must be noted that successful passage of a patency capsule does not definitively exclude the possibility of capsule retention. A large retrospective study included 406 patients with established Crohn's disease referred for CE for various clinical indications. CE was performed in 132 of 406 patients (32.5 %) without a prior patency capsule test. A patency capsule test was performed in 274 of 406 patients (67.5 %) and was negative in 193 patients (70.4 %), who then went on to undergo CE. An additional 18 patients with a positive patency capsule also underwent CE. Overall, CE was performed in 343 patients and was retained in the small bowel in 8 (2.3 %). In this cohort, the risk of capsule retention in the small bowel was not significantly different between patients who had not undergone a patency capsule as compared to those who had a negative patency capsule (1.5 vs. 2.1 %, $p = 0.9$). However, in the 18 patients who underwent CE after a positive patency capsule test, the retention rate was significantly higher (11.1 %, $p = 0.01$). Thus, while a negative patency capsule test does not ensure successful passage of the video capsule endoscopy, a positive patency test appears to predict patients at highest risk of capsule retention [51].

Where Does Capsule Endoscopy Fit in Diagnostic and Management Algorithms?

The role of capsule endoscopy in the diagnosis and staging of small bowel Crohn's disease is still in flux. Based on recommendations adapted from two recent consensus statements, we propose the approach outlined in Fig. 5.2 [52, 53]. If Crohn's

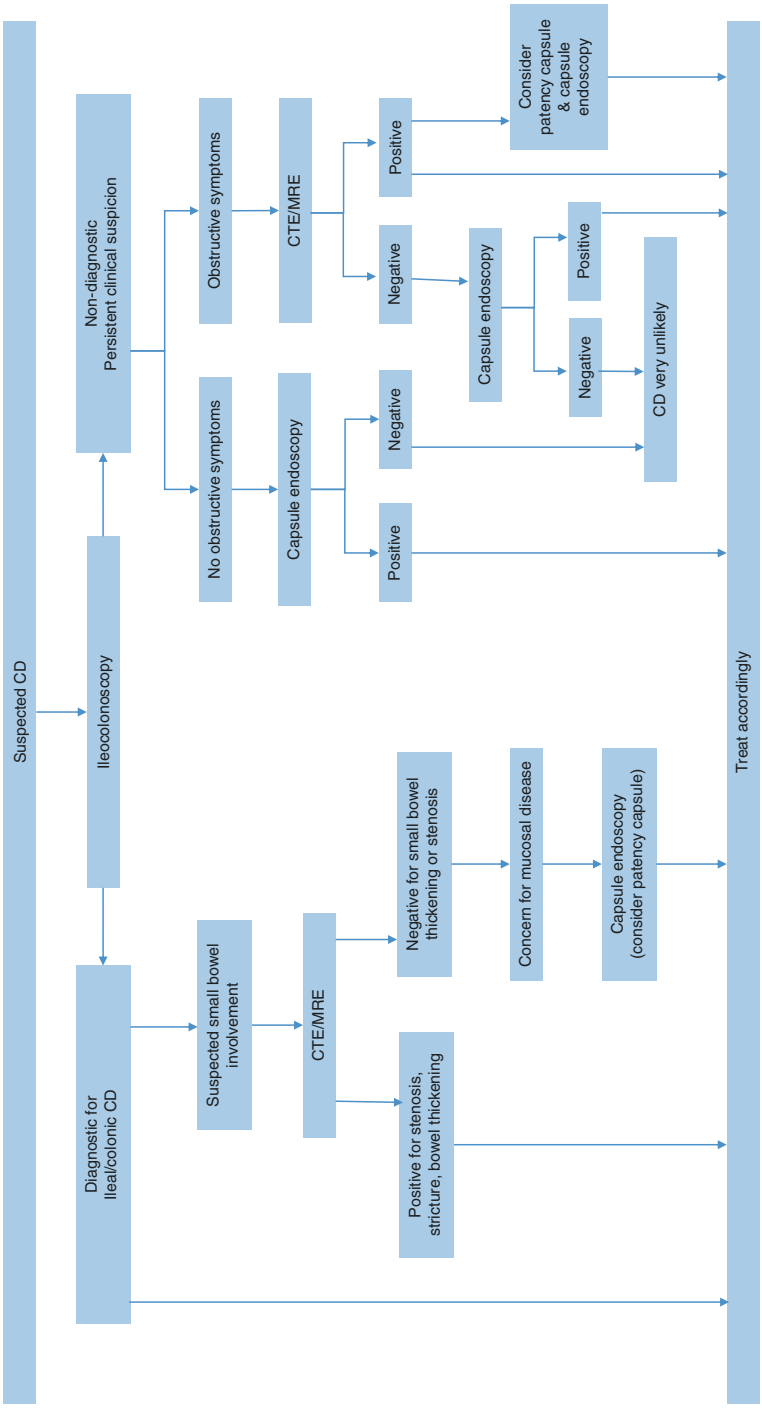

Fig. 5.2 The role of capsule endoscopy in the evaluation of Crohn's disease. Ileocolonoscopy remains the best initial study in patients with suspected Crohn's disease. As outlined above, capsule endoscopy serves as an important adjunct to help stage disease when colonoscopy is positive or further evaluate the patient when colonoscopy is nondiagnostic

disease is suspected based on gastrointestinal symptoms and other supporting evidence (anemia, elevated inflammatory markers, extraintestinal manifestations, imaging), the initial test of choice is ileocolonoscopy with biopsies.

If ileocolonoscopy is diagnostic for Crohn's disease, the appropriate therapy can be initiated. However, if there is concern for small bowel disease beyond the reach of the colonoscope, dedicated small bowel imaging should be performed with CT or MR enterography and any positive findings managed accordingly. If no significant disease is uncovered on enterography, capsule endoscopy can be considered due to its increased sensitivity for mild, proximal mucosal lesions. Administration of a patency capsule can be considered prior to capsule endoscopy if there is concern for capsule retention. Use of NSAIDs should be avoided for at least 4 weeks prior to capsule endoscopy.

In the event of a normal ileocolonoscopy but persistent suspicion for Crohn's disease, dedicated investigation of the small bowel is indicated. If the patient does not exhibit obstructive symptoms, the next best test is capsule endoscopy due to its high negative predictive value. Again, NSAIDs should be avoided for at least 4 weeks prior to the exam. In the event that obstructive symptoms are present, cross-sectional imaging can be performed with MR or CT enterography. Once patency of the small bowel is confirmed, capsule endoscopy can be performed to exclude mild disease. If enterography is positive, capsule endoscopy can be considered to better define disease location and severity. A patency capsule is recommended in the latter situation to exclude a stenosis missed on enterography.

Conclusion

The role of capsule endoscopy in the care of patients with Crohn's disease will continue to evolve in the coming years. CE has the unique capability of detecting subtle small bowel mucosal lesions that may be missed by other modalities. The sensitivity of CE will become increasingly valuable as the paradigm of IBD management shifts toward achieving deep remission and mucosal healing. There are already data to support the use of CE in confirming the diagnosis of CD in patients with suspected disease as well as restaging patients with established disease. Other applications of CE, including its utility in assessing for postoperative recurrence and classifying indeterminate colitis, are being investigated. As studies emerge and more reliable indices for calculating disease activity and severity are developed, CE may become the gold standard for complete small bowel assessment in the IBD population.

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Chapter 6
The Role of Capsule Endoscopy in the Diagnosis and Management of Celiac Disease and Refractory Diarrhea

Amir Eshag Soumekh and Fouad Otaki

Introduction

Celiac disease represents an immune-mediated intestinal injury as a result of intolerance to gluten, a protein found in wheat, rye, and barley. It affects genetically susceptible individuals with a prevalence ranging from 0.7 to 2 % in various communities [1–3]. Symptoms vary from persistent and daily to subclinical, vague, and variable. They can include abdominal pain, diarrhea, bloating, as well as signs and symptoms of malabsorption, such as fatigue, nutritional deficiencies, anemia, osteoporosis, and ataxia. Other associated autoimmune phenomena include dermatitis herpetiformis, alopecia, and infertility. The majority of patients have clinical response to dietary restrictions, and persistent symptoms are most commonly secondary to gluten contamination.

Diagnosis

Diagnosis involves a multifactorial approach and includes a combination of endoscopic, histopathologic, and serologic evaluations. Multiple serologic tests are available. Currently, anti-tissue transglutaminase (TTG) antibody is the preferred test from a diagnostic standpoint, with a sensitivity and specificity of >90 %. IgA and IgG antibodies to deaminated gliadin peptide (DGP) can be measured, with somewhat lower sensitivity compared with TTG. Anti-endomysial antibody (EMA) is highly accurate, but expensive and technically difficult to perform. It is

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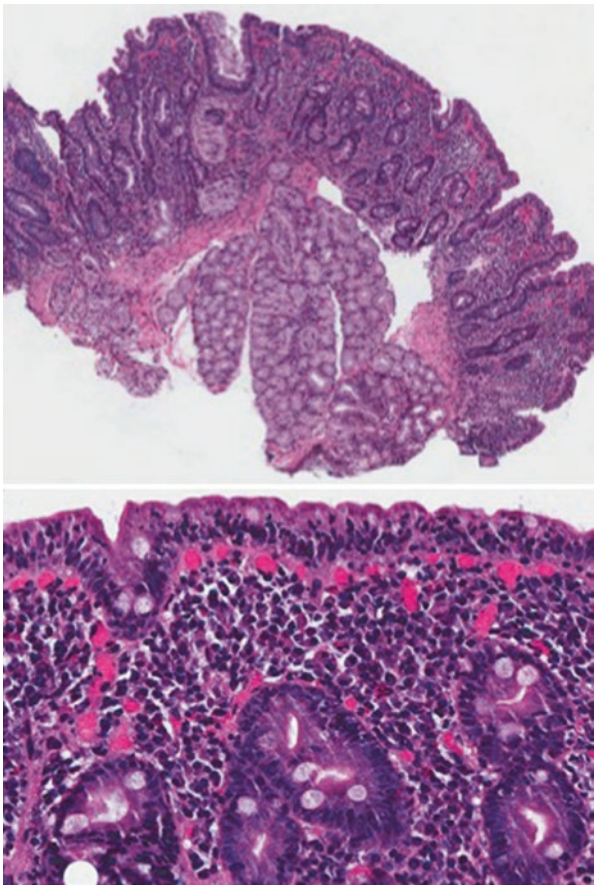

Fig. 6.1 Duodenal biopsy under low power (*upper panel*) and high power (*lower panel*) revealing flattened villi and relative crypt hyperplasia, increased intraepithelial lymphocytes, and numerous plasma cells within the lamina propria

considered nearly 100 % specific, with variable sensitivity due to the technical difficulty in performing this test. Regardless of the serologic test performed, serum immunoglobulin A (IgA) levels are drawn with serologies as IgA deficiency is more common in patients with celiac disease and may result in false negative values [4]. Genetic testing can also be performed for the HLA DQ2 and DQ8 alleles in patients already on a gluten-free diet with negative serologies. This testing is only useful to exclude celiac disease, as it has a negative predictive value of 97 %, but a much lower positive predictive value.

Histopathologic findings include villous atrophy, increased intraepithelial lymphocytes, and crypt hyperplasia, but they are not unique to celiac disease (Fig. 6.1). Endoscopically, common findings are a reduction in folds, scalloping, mucosal fissuring, crevices/grooves, and mosaic patterns [5]. Diagnosis with endoscopy can be difficult. Only a limited portion of the small intestine is typically examined in an upper endoscopy, and the histopathologic findings can be patchy and missed on biopsy. Moreover, endoscopy is an invasive test with inherent risks. It is also associated with significant costs, including anesthesia and days missed from work. Finally,

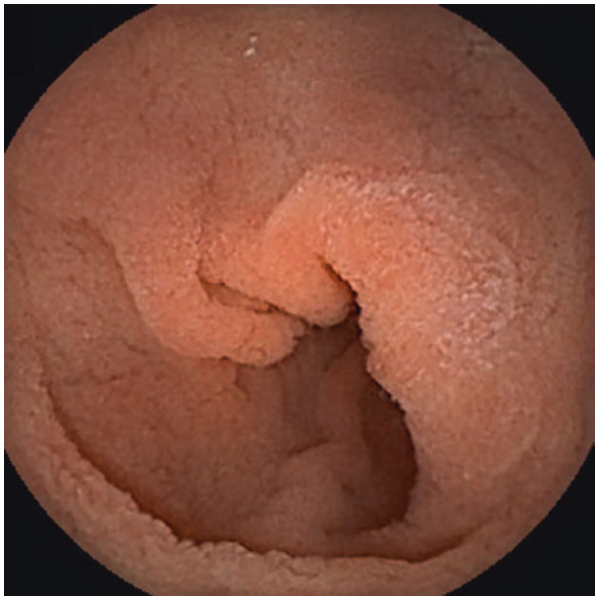

Fig. 6.2 Capsule image revealing villous blunting or atrophy. Villi may be completely absent or shortened

endoscopy and histology are only as accurate as the expertise of the endoscopist, and dedicated training programs to identify features when they are subtle are lacking. Nonetheless, the combination of upper endoscopy and histology currently represents the gold standard in the diagnostic algorithm [6, 7].

The majority of mucosal findings are found in the proximal small bowel [8]. However, given the limitations of endoscopic diagnosis, evaluation of the remainder of the small intestine is often required. Capsule endoscopy provides a second diagnostic option for celiac disease. In addition to identifying mucosal and luminal changes previously missed with conventional endoscopy, it can identify the extent of enteropathy, evaluate for complications, and assess refractory symptoms, which could suggest more concerning pathologies. Randomized trials are sparse but are expected to increase as the technology advances.

An international consensus guideline recommends capsule endoscopy in patients unable to undergo upper endoscopy or in patients where a biopsy would pose significant risk. Patients with positive serologies and an incomplete study or negative endoscopy, as well as patients with established disease with warning signs or refractory Type 2 disease, are also candidates for capsule endoscopy in the evaluation of gluten enteropathy [9].

Several features on capsule endoscopy are suggestive of celiac disease. Mild disease can present as villous blunting (Fig. 6.2), while more severe disease can present with scalloping of folds (Fig. 6.3), mucosal fissures (Fig. 6.4), a mosaic pattern (Fig. 6.5), and layering or "stacking" of folds (Fig.6.6). Although these findings are often severe and quite obvious, subtle changes (especially partial villous atrophy) can be difficult to detect.

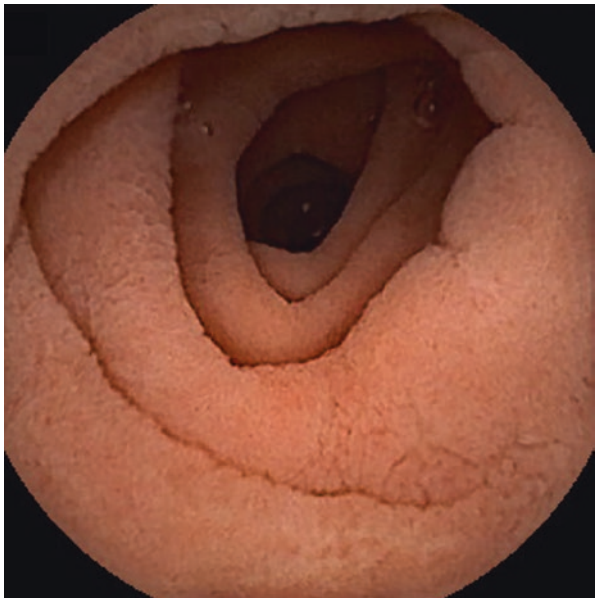

Fig. 6.3 Capsule image revealing scalloping. As villi are lost, the edges of mucosal folds take on a scalloped appearance

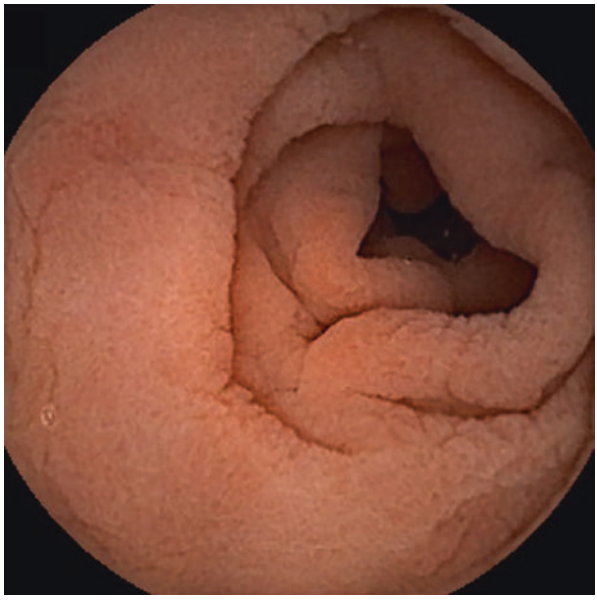

Fig. 6.4 Capsule image revealing mucosal fissures. Fissures are also due to loss of villi and are manifested as breaks in the mucosa seen on the edges of mucosal folds

In the sentinel multicenter trial of 43 patients, authors reported capsule endoscopy sensitivity of 87.5 % (95 % CI 76.1–98.9 %) and specificity of 90.9 % (95 % CI 81.0–100 %) in the diagnosis of celiac disease when compared to the gold standard of duodenal histological evaluation during upper endoscopy [10]. Most centers have been able to replicate similar results, and a subsequent meta-analysis of six

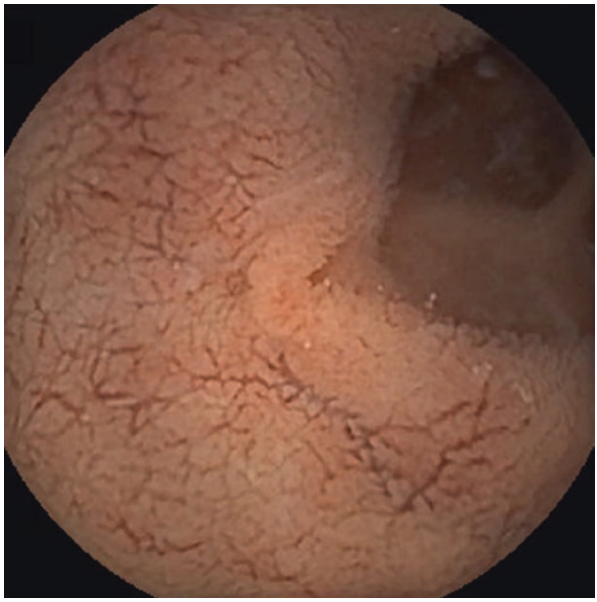

Fig. 6.5 Capsule image revealing mosaic pattern or mosaicism. Fissures seen on flat portions of the mucosa (as opposed to folds) create a cobblestone or mosaic pattern

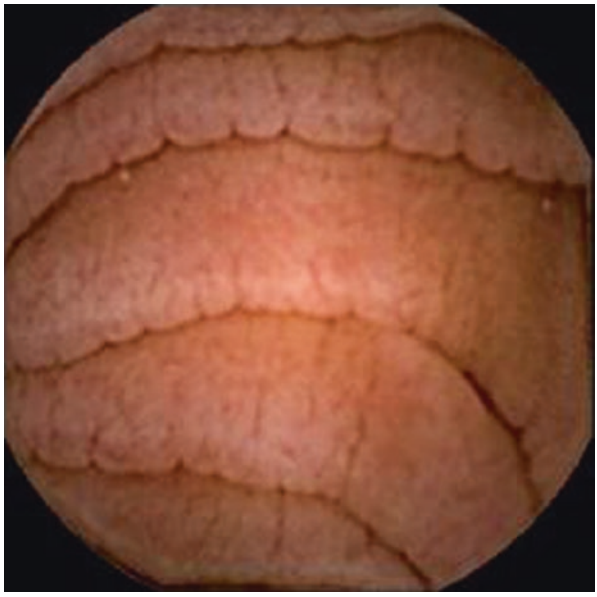

Fig. 6.6 Capsule image revealing stacking. Folds of atrophied, fissured mucosa lay (or "stack") on top of one another

studies evaluating a total of 166 untreated celiac disease patients in centers from across the world identified a pooled sensitivity and specificity of 0.89 (0.82–0.94, $p = 0.4523$) and 0.95 (0.89–0.98, $p = 0.0022$), respectively [11].

Unfortunately, the literature detailing interobserver agreement regarding the evaluation of capsule endoscopy varies widely. Interobserver concordance between

histology and capsule endoscopy was 78 % with a kappa statistic measuring 0.65 (95 % CI 0.36–0.95) in celiac disease patients not responding to a 12-month trial of a gluten-free diet [12]. In another study, the concordance of capsule endoscopy was better than conventional endoscopy, κ coefficient = 0.45 (95 % CI 0.23–0.67) vs. κ coefficient = 0.24 (95 % CI 0.02–0.45) in 47 patients with refractory celiac disease compared to 47 controls [13].

Assessing Disease Severity

The ability to predict the extent and distribution of small bowel involvement in celiac disease is limited. Histological findings do not appear to reliably predict severity or extent of disease. By allowing for visualization of the entirety of the small bowel, capsule endoscopy can determine the distribution and extent of disease.

In one study, 37 patients from a single tertiary care center with positive serology and Marsh III histology (intestinal villous atrophy) were compared to 38 age- and sex-matched controls with normal histology and negative serology. Over 90 % of celiac patients had villous atrophy on capsule endoscopy: 59 % had some involvement of the jejunum (patchy distribution); 32 % limited to the duodenum alone; and only one patient had isolated patchy jejunal disease. The nature of findings in descending order were fissuring, scalloping, and mosaicism. Collectively these findings were more frequently noted in the duodenum compared with the distal small bowel, 92 vs 62 % ($p = 0.0034$) [14].

Monitoring

The ideal endpoint of celiac disease management is resolution of symptoms, normalization of serologies, normalization of histopathology, and prevention of complications. However, meeting such a strict target is difficult in reality, and changes in symptoms, serologies, and pathology do not always concur. Normalization of serologies does not necessarily reflect histological recovery, and patients often have persistent symptoms that may be due to an overlap of a secondary process such as irritable bowel syndrome, small intestinal bacterial overgrowth, or non-gluten dietary intolerances [15, 16].

Prior to the advent of capsule endoscopy, relatively little was known on what occurs throughout the small bowel after treatment of celiac disease. Treatment responses were evaluated almost exclusively based on serologies and duodenal biopsies. Capsule endoscopy has shed light on what occurs in the treated small bowel. Studies have identified recovery of villous features in the duodenum and jejunum of patients 6 months post implementation of treatment. Murray and associates have reported 79 % improvement of which 31 % had complete endoscopic healing. The authors also noted that the healing occurred in distal to proximal direction

and speculated that this was due to the concentration-dependent exposure of the proximal small bowel [14]. In another prospective study, 12 patients with serology-confirmed celiac disease with duodenal villous atrophy were reevaluated after a strict 12-month gluten-free diet. Seven patients achieved histological "response." Compared to the "nonresponders," there was no significant difference in extent of villous atrophy when assessed by capsule endoscopy. Their data also noted a distal to proximal healing pattern and associated extent of healing with symptom score improvement [17].

Outside of research protocols, the role of capsule endoscopy in patients with symptom and serologic improvement or resolution is limited. Duodenal biopsies can confirm mucosal healing, and evaluation of the remainder of the small bowel is generally not warranted.

Refractory Celiac Disease

Refractory celiac disease (RCD) is defined as the presence of symptoms and villous atrophy after 6 or more months of strict gluten avoidance. The most common cause of persistent symptoms is nonadherence (intentional or unintentional) and gluten contamination. A gluten-free diet may be very restrictive and, to certain patients, unpalatable. As a result, some patients may knowingly ingest gluten-containing foods. Commonly, however, patients unwittingly consume foods they believe are gluten-free but that may contain hidden gluten, for example, soups, sauces, or dressings that are thickened with bread or other gluten-containing components or contamination of gluten-free foods during the cooking process in which gluten-containing foods are also made. Finally, certain nonfood items may contain gluten, such as medications, vitamins/supplements, or beauty products. Clinicians must exclude other causes of symptoms such as bacterial overgrowth, non-gluten dietary intolerances (such as lactose or fructose), microscopic colitis, inflammatory bowel disease, medication-induced mucosal injury (e.g., olmesartan), and pancreatic insufficiency.

True RCD is classified into Type 1 and Type 2 disease based on the phenotype of intraepithelial lymphocytes (IELs) on biopsy. In Type 1 disease, there is a normal population of IELs on duodenal biopsy. In Type 2 disease, the intraepithelial lymphocytes are aberrant, with clonality analysis of T-cell receptors and immunophenotyping revealing a loss of surface CD3 and CD8 and a monoclonal T-cell receptor rearrangement [18]. Patients with ongoing symptoms despite a strict gluten-free diet should be evaluated for refractory celiac disease or occult malignancy [19]. Capsule endoscopy may have a role in these patients.

Barret and colleagues retrospectively evaluated capsule endoscopy findings on patients with symptomatic CD, Type 1 and Type 2 RCD, and patients without celiac disease. They found that mucosal abnormalities such as villous atrophy and ulcers were more frequent in celiac patients than controls, and the finding of villous atrophy on capsule endoscopy had a higher concordance with histology than optical endoscopy (κ coefficient = 0.45 vs. 0.24, $p < 0.001$). Distal disease (a finding that

would be missed on optical endoscopy) was seen more frequently in Type 2 disease than Type 1 RCD or symptomatic celiac disease ($p = 0.02$) [13].

Atlas et al. evaluated CE in 42 consecutive patients with nonresponsive CD and compared them to 84 age- and sex-matched controls. Villous atrophy was detected in 31 % of RCD, compared to 0 % of controls. However, a post hoc comparison revealed that 47 % of 30 uncomplicated CD patients also had this finding ($p = 0.13$). Notably, two severe complications (ulcerative jejunoileitis and adenocarcinoma) were detected by capsule endoscopy in nonresponsive CD [19]. In another prospective review, a single case of lymphoma and one case of ulcerative jejunoileitis were noted in seven patients with Type 2 RCD, while none was identified in the comparator group of seven patients with Type 1 RCD. Of note, only one of the findings was also documented by magnetic resonance imaging [20].

Taken together, this data suggests that capsule endoscopy may have a limited role in the evaluation of patients with known celiac disease. In a select subset of patients, such as those with refractory disease and/or alarm symptoms, capsule endoscopy may identify active disease or even malignancy [21]. These patients may need to be referred to specialty centers for possible immunosuppressive therapy.

Capsule Endoscopy Advanced Techniques

Although some small bowel mucosal changes in celiac disease are easily visible and fairly obvious, many patients can have subtle changes that are difficult to detect. This can be especially true in treated patients where shortening of villi or even villous atrophy can be mild. In response, recent efforts have attempted to develop automated, quantitative measures of mucosal changes to rapidly, accurately, and reproducibly identify mucosal changes consistent with ongoing celiac disease.

A few methods have been described. In one technique, the variance of the brightness and color of any given capsule endoscopy image is measured. As normal small intestinal mucosa is rather uniform, a high variance is suggestive of celiac changes. Another measure is the computer-generated average fissure length using automated image processing techniques. Computer-aided analysis can also use images to recreate three-dimensional models of the mucosa and allow for digital measurements of villous protrusions [23].

Together, these techniques may allow for rapid, unbiased analysis of capsule images in patients with known or suspected celiac disease. Although early data suggests each technique may be accurate, studies are small and have yet to bring the technology to routine use [23–25].

One widely available advanced imaging technique does currently exist in capsule endoscopy. The use of chromoendoscopy and narrowband imaging ("virtual chromoendoscopy") has been well described in optical endoscopy. Similar virtual chromoendoscopy has been incorporated in capsule endoscopy. Flexible spectral imaging color enhancement (FICE) and blue mode (BM) are two such systems. These techniques adjust the white light images to provide enhanced imaging. The

literature on the added yield for the detection of mass lesions or sources of bleeding has been mixed, ranging from 7.7 to 87.7 % depending on the indication, and is limited by high false positivity [26]. The utility of these images in celiac disease is unknown.

Limitations of Capsule Endoscopy

Despite its appeal as a safe and noninvasive study, capsule endoscopy has some notable limitations. The most important drawback is the inability to acquire tissue for histology with the current generation of capsule devices. Drug delivery and tissue acquisition capsule devices are currently being developed. The implementation of these devices may occur in the not-too-distant future pending further studies and regulatory approval. A second limitation in all capsule studies is the potential failure to examine the entire bowel. The rate of incomplete examinations does not appear to be higher in celiac disease compared to controls, and newer capsules with longer recording times may decrease the number of incomplete studies [19].

Summary

Capsule endoscopy is a revolutionary new technology that allows for the exploration of the small bowel in a noninvasive manner. The quality of acquired data is improving as the hardware and software advances. The main role of capsule endoscopy in celiac disease is the diagnosis of patients unable to undergo upper endoscopy, in patients where a biopsy would pose significant risk, or in patients with a positive serology and an incomplete study or negative endoscopy. Capsule studies may play a further role in patients who have known celiac disease unresponsive to dietary treatment or with alarm signs or symptoms concerning for possible occult malignancy. Future changes in capsule technology may allow for automated analysis of images to detect mucosal changes suggestive of gluten enteropathy and may even afford the ability to acquire tissue for histopathology.

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Chapter 7
Becoming an Efficient and Effective Reader of Capsule Endoscopy in Screening and Surveillance of Small Bowel Polyposis Syndromes and Masses

Amit P. Desai and Felice Schnoll-Sussman

Introduction

Capsule endoscopy (CE) has become a powerful tool for endoscopic evaluation of the small bowel since FDA approval in 2001. The most common indications for CE include evaluation of obscure gastrointestinal bleeding, suspected Crohn's disease [1], and detection of small bowel tumors. This chapter will focus specifically on the use of CE in the identification of small bowel lesions in patients with familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), and small bowel masses. This chapter will focus on the efficient and effective application of CE in the evaluation and management of patients with small bowel polyposis and masses.

Familial Adenomatous Polyposis (FAP): Epidemiology

FAP is an autosomal dominant syndrome caused by mutations in the adenomatous polyposis coli (APC) gene located on chromosome 5q21–q22 with a prevalence of approximately 1 in 10,000–1 in 30,000. It is known that patients with FAP have a significantly increased lifetime risk of developing adenomas and carcinomas of the stomach, duodenum, and colon. These patients are additionally at risk for extraintestinal malignancies, such as follicular or papillary thyroid cancer and childhood hepatoblastoma and central nervous system tumors, mostly medulloblastomas. Polyposis can develop in the second to third decade of life, and more than one hundred adenomatous colorectal polyps are typically diagnostic of FAP.

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Emerging Concepts in the Use of Capsule Endoscopy for Small Bowel

Screening/Surveillance in FAP

The American Society for Gastrointestinal Endoscopy (ASGE) has issued recommendations for screening and surveillance of the upper gastrointestinal tract [2] which state that patients with FAP should undergo upper endoscopy with both end-viewing and side-viewing instruments, suggesting that optimal timing is unknown, but can be performed around the time that the patient is considered for colectomy or early in the third decade of life. It should be noted that there are currently no official recommendations for evaluation of the small bowel distal to the ligament of Treitz. With the growing prevalence of CE use, there is an emergent literature base exploring the utility of CE for detection and surveillance of small bowel polyps in patients with FAP**.**

Several studies [3] have explored the use of CE for the detection of small bowel polyps in patients with FAP; however, given the lack of a gold standard for visualization of the small bowel in the setting of a polyposis syndrome, the comparative exam was variable among studies and included push enteroscopy, magnetic resonance imaging (MRI), and barium small bowel follow through (SBFT) or was solely observational without exploring other imaging in contrast to the CE. The use of Spigelman classification (Table 7.1) of duodenal polyposis [4] was a common thread in the literature. The Spigelman classification is a five-grade scale of duodenal polyposis based on polyp number, size, histology, and severity of dysplasia published in 1989 and has since been incorporated into routine endoscopy assessment in patients with FAP. Given that there are no guidelines that dictate when and how often the small bowel must be examined in FAP, studies have used Spigelman criteria in an attempt to stratify the findings on CE and ideally predict the need for and timing of small bowel evaluation in FAP.

Table 7.1 Spigelman classification for duodenal polyposis in FAP [4]

Criterion	1 point	2 points	3 points
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe
Stage 0: 0 points,			
Stage I, 1–4 points			
Stage II, 5–6 points			
Stage III, 7–8 points			
Stage IV, 9–12 points			

Burke and colleagues [5] found that patients with Spigelman stage II, III, or IV polyposis notably had jejunal and ileal polyps detected with CE, while polyps distal to the ligament of Treitz in patients with stage 0 or I polyposis were not identified with CE. The practice of these authors is to use CE as a standard small bowel visualization modality prior to duodenectomy in patients with Spigelman stage IV polyposis. They do not recommend routine small bowel surveillance in patients with stage 0 to II disease. Similarly, Katsinelos et al. found an association between Spigelman stage of duodenal polyposis and the presence of jejunal and ileal polyps in their study of a Greek FAP cohort of 14 patients published in 2009 [6]. In this study, patients with Spigelman stage 0 did not have any detectable small bowel polyps, while patients with stage III and IV polyposis tended to have small bowel polyps, but it should be noted that the majority of these were in the duodenum. Conversely, another study [7] found the presence of duodenal adenomas, regardless of Spigelman stage, to be the only statistically significant parameter associated with small bowel polyps. Whether Spigelman staging can accurately be predictive of jejunal or ileal polyposis remains to be determined as these studies all consist of small cohorts of patients. However, it is clear that the mere presence of duodenal polyposis should prompt further small bowel investigation. One conclusive finding in these studies however was that CE was inferior to side-viewing endoscopy at visualization of the ampulla of Vater and as such should be only used as an adjunctive surveillance tool to complement standard side-viewing endoscopy of the ampulla.

While the previously discussed studies have demonstrated a relationship between the incidences of duodenal polyps as a predictor of the presence of small bowel polyps distal to the ligament of Treitz, Schulz et al. explored the relationship between small bowel polyps and the occurrence of adenomas of the ileoanal pouch in patients with FAP who have undergone proctocolectomy [8]. In this study, 35 patients with ileoanal pouch construction after proctocolectomy underwent standard pouch endoscopy at 3 months following surgery and then annually. CE was performed in patients who were noted to develop ileoanal pouch adenomas, regardless of histology, size, and number. Pouch adenomas were found in 8 of the 35 patients (22.8 %), and those patients subsequently underwent CE. All of these patients had small bowel polyps identified at CE. Given that patients without pouch adenomas did not undergo CE, the presence of small bowel polyps in the absence of pouch adenomas is unknown, questioning whether the incidence of pouch adenomas is predictive of small bowel polyps or just a correlative finding.

Natural History of Small Bowel Polyps in FAP

With improved detection of small bowel polyps in FAP by CE, the question remains as to clinical impact of these polyps. Established guidelines as to the mode and frequency of small bowel surveillance do not exist for FAP. Furthermore,

the prevalence and natural progression of small bowel adenomas in FAP is undefined presently. Günther and colleagues explored the use of capsule endoscopy in 15 patients with FAP over a 7-year period, where five of those patients had repeat capsule endoscopies, thus incorporating the component of a time continuum into their study [9]. Two of the patients that had undergone repeat CEs continued to exhibit multiple small-sized polyps over the entire length of the small bowel, while another patient was found to have medium-sized polyps in the proximal jejunum when his previous two CEs had shown only small polyps. In yet another patient, CE revealed a large-sized flat polyp in the upper third of the small intestine, which had not been identified on previous CE. This polyp was subsequently removed by double-balloon enteroscopy and was histologically determined to be a tubular adenoma with low-grade dysplasia. This finding supports the use of CE as a surveillance tool with repeated CE exams over time.

Possible/Suggestive Recommendations

Despite a well-established adenocarcinoma sequence, the natural history of duodenal polyposis is variable among FAP patients [3, 10, 11]. There is even less data documenting the disease course of distal small bowel lesions. A surveillance strategy was suggested by Plum and colleagues based on data from their 2009 article [1, 2]. They recommended that if the CE (or push enteroscopy) showed only polyps <10 mm, CE should be repeated after 2 years. If polyps ≥10 mm and other suspicious mucosal abnormalities were found, a double-balloon enteroscopy (DBE) is recommended to localize and biopsy or resect the found polyps. If a DBE is not feasible, an intraoperative endoscopy and surgical resection of the lesions should be done. On the other hand, if no lesions or concerning polyps were seen on the CE, an interval of 4 years is suggested for the next CE. One can additionally infer that with the correlation between the presence of duodenal polyps and polyps seen distal to the ligament of Treitz [6, 9, 13], the *standard* practice should be to complete a CE in a patient with duodenal polyps, particularly those with higher-grade Spigelman score [11, 12]. As such, our center routinely incorporates CE in the surveillance of FAP patients with Spigelman grade II and above.

Pearls and Pitfalls of CE in FAP

Given the need to evaluate the small bowel, CE can be useful to evaluate the stomach and small intestine in FAP. Gastric polyps, duodenal adenomas, ampullary lesions, small bowel polyps, and small bowel adenocarcinoma are among the more common lesions that may be seen in FAP.

Gastric Polyps

Fundic gland polyps are common and typically located in the proximal stomach (Fig. 7.1). These polyps are not thought to have malignant potential; however, dysplasia can occur in them. On the other hand, antral polyps are usually adenomatous and should be resected endoscopically when possible. Although evaluation for gastric polyps is better performed during an upper endoscopy, the CE reader should pay careful attention to the appearance of gastric polyps in FAP patients particularly when identifying large, abnormal, multi-lobulated, or adenomatous-appearing polyps, in which resection would be required.

Duodenal and Periampullary Adenomas

Duodenal adenomas can occur in up to 90 % of adult patients with FAP [12] with up to a 4 % risk of development of periampullary cancer [13]. Duodenal adenomas can appear as flat to raised, multifocal, and nodular lesions (Fig. 7.2). Periampullary adenomas can appear as flat to raised, multinodular lesions surrounding the ampulla**.** After colorectal cancer, duodenal/periampullary cancers are the second most common cause of cancer deaths in patients with FAP [14].

At times CE may be able to identify suspicious ampullary or duodenal lesions; however, it is imperative to realize that the capsule will often times pass very quickly through the duodenal sweep without any images of the ampullary region. As such, the use of CE in the surveillance of patients with FAP is *not* a reasonable alternative to a standard upper endoscopy with side viewing capability to visualize the duodenum and ampulla, resect any obvious duodenal polyps, and take empiric biopsy samples of the ampulla.

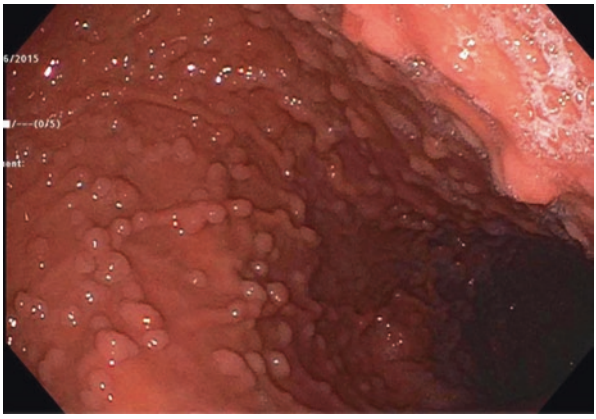

Fig. 7.1 Multiple fundic gland polyps

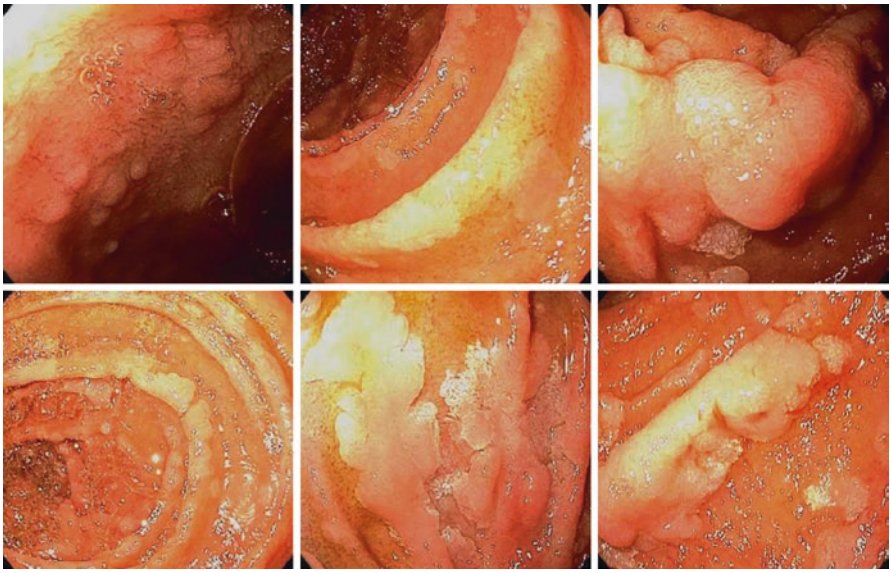

Fig. 7.2 Images of duodenal adenomas

Jejunal and Ileal Polyps

Patients with Spigelman stage 0 or I polyposis are less likely to have jejunal or ileal polyps as compared to patients with stage II, III, or IV disease. Jejunal and ileal polyps appear similar in appearance to duodenal polyps. They can be flat to raised, multifocal, and nodular in appearance [5].

Small Bowel Adenocarcinoma

Please see Sect. Small Bowel Masses.

Peutz-Jeghers Syndrome (PJS): Epidemiology

PJS is an autosomal dominant syndrome caused by mutations in the *STK11* gene with a prevalence of 1 in 8000–1 in 200,000. PJS is characterized by multiple hamartomas, gastrointestinal polyps, and mucocutaneous pigmentation. Additionally, it is known that affected patients have increased risks of gastrointestinal and extraintestinal malignancies including breast, cervical, ovarian, and testicular cancer. Polyposis can develop in the first decade of life with a higher proportion of polyps in the jejunum [15].

Screening and Surveillance in Peutz-Jeghers Syndrome

In these patients, baseline endoscopy, colonoscopy, and CE are recommended to be performed starting at age 8. Subsequent follow-up endoscopies and colonoscopies can be performed starting at the age of 18 and continued every 3 years if no alarm symptoms are noted. Surveillance interval should be shortened to every 1–2 years after the age of 50. CE should be performed every 3 years starting at the age of 8. The goal of surveillance is to identify larger polyps, which could be the source for anemia and the cause of intussusception and obstruction [16]. Cumulative intussusception risk may be as high as 50 % at the age of 20 years and is caused by polyps with an average diameter of 35 mm. PJS polyps have easily recognizable features such as long stalks, arborizing structure, and intact surface.

Pearls and Pitfalls of CE in PJS

The small bowel can be the most common site of polyp occurrence in patients with Peutz-Jeghers [16]. The goal of CE in individuals with PJS is to identify larger polyps (>10–15 mm) for endoscopic resection.

The long stalk is a characteristic attribute of the Peutz-Jeghers hamartomatous polyp. Histologically, they all show smooth-muscle hyperplasia and an elongated, arborized pattern of polyp formation, resulting in the formation of islands of epithelium within the underlying smooth muscle. There is morphologic characterization of hamartomatous gastrointestinal polyps in Cowden syndrome, PJS, and juvenile polyposis syndrome. Those that are bleeding, ulcerated, and/or large (>10–15 mm) would be indications for endoscopic resection.

Suggestive Recommendation for FAP and PJS

In conclusion, CEs are a safe, effective, and noninvasive technique for the detection and surveillance of small bowel polyps in FAP and PJS. It is recommended that the CE study be performed as an adjunctive imaging modality to standard endoscopic evaluation of the stomach and duodenum, including the use of a side-viewing endoscope for visualization of the ampulla of Vater. Studies have shown the inferiority of radiographic studies, such as MRI and enteroclysis, in detection of small bowel polyps when compared to CE, further supporting the incorporation of capsule endoscopy in polyposis syndromes.

Small Bowel Masses: Pearls and Pitfalls of CE

A variety of tumors, both malignant and benign, may arise from within the small intestine. Malignant small intestinal tumors include adenocarcinomas, carcinoids, stromal tumors, gastrointestinal stromal tumors (GIST), and non-GIST soft tissue sarcomas and lymphomas. Benign lesions include adenomas, leiomyomas, fibromas, and lipomas. The diagnosis of small bowel tumors is often made late in the disease course, given the rarity of the condition. Additionally, the patients typically present with nonspecific symptoms such as generalized abdominal pain, weight loss, nausea, vomiting, or occult GI bleeding.

CE is a useful adjunctive tool for the evaluation of the small intestine. This was affirmed by a retrospective review of 562 patients who underwent CE for a variety of indications. Of these, 50 patients were diagnosed with small bowel tumors (8.9 %) of which 48 % were malignant. Among patients younger than 50 undergoing CE for obscure gastrointestinal bleeding (OGIB), a small bowel tumor was identified in nine (13 %) patients, demonstrating that small bowel tumors continue to be a significant finding in the workup for OGIB. CE also identified tumors at an earlier stage, which is expected to improve the prognosis for patients [17, 18].

Interpreting CEs

Capsule endoscopy images are different than traditional endoscopy given there is no air distension of the bowel wall and the capsule is located at times within millimeters of the mucosal surface. This can lead to difficulties in interpreting the images. The following tips can be helpful when evaluating suspicious findings [19]:

- *Look at the surrounding mucosa for clues of abnormality.*
- *If possible, do not base a diagnosis on a single capsule image.*
- *View the video flow of images to see the intestinal lining and similar abnormalities before or after the lesion in question.*
- *Look for similar abnormalities in the images before or after the images in question.*
- *Always use a mouse to read images so that one may scroll through the images.*

One of the findings in CE that is most difficult to interpret is discerning a bulge from a submucosal process. Bulges in the bowel wall may be created by another loop of bowel overlying the loop being observed during the CE (Fig. 7.3). These need to be differentiated from submucosal processes (Fig. 7.4).

A simple bulge may be suspected when the impression on the bowel is seen to move with continued peristaltic activity. On the other hand, overlying bowel edema and inflammation may indicate the presence of a submucosal lesion. In this scenario, the following tips will be useful:

- *View the full video stream instead of single images.*
- *Adjacent loops (forming simple bulges) will move with peristalsis.*

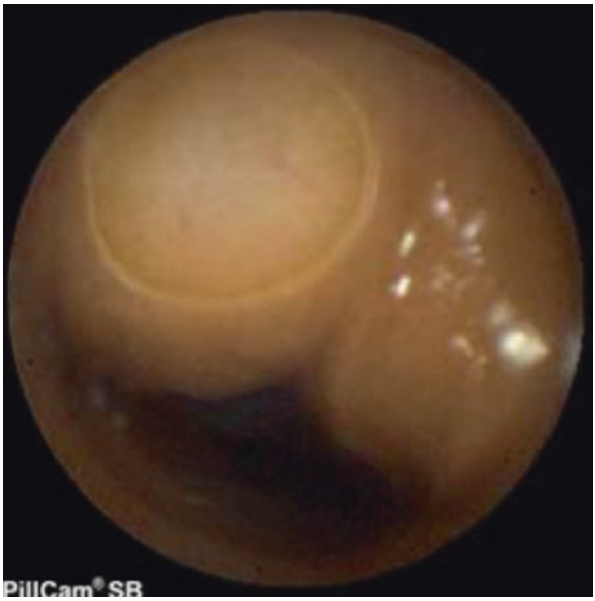

Fig. 7.3 Loop of bowel overlying another loop with a halo effect from the capsule touching the surface of bowel lumen

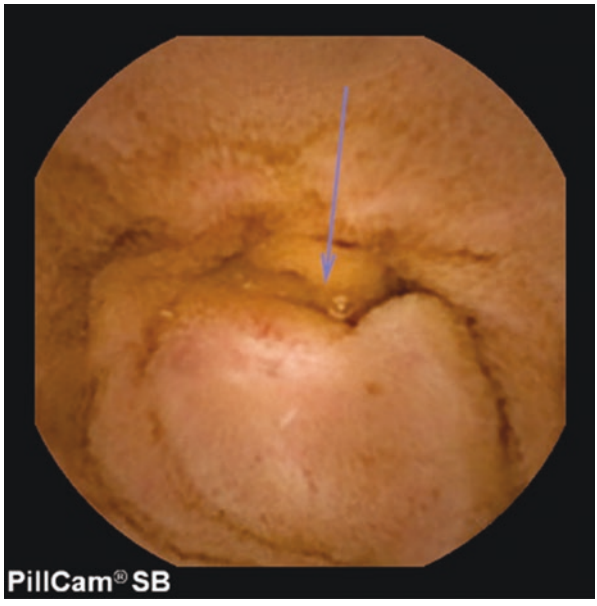

Fig. 7.4 Arrow points to submucosal process

- *Simple bulges will not change the appearance of the overlying villi.*

Given the difficulty in discerning bulge from a mass on CE, a simple index was derived from Girelli et al. in 2011 [20].

The smooth protruding lesion index on capsule endoscopy (SPICE) was devised to help in the discrimination of innocent bulges from submucosal masses. SPICE scores range from 0 to 4. The index was derived from a single, center prospective trial where 25 of 424 consecutive CEs had findings of smooth, round, and protruding lesions [20].

The clips were blinded for the readers. The following criteria were used by the readers:

Criterion	No	Yes
Ill-defined boundary with the surrounding mucosa	1	0
Diameter larger than its height	1	0
Visible lumen in the frames in which it appears	0	1
Image of the lesion lasting more than 10 min	0	1

A value >2 was predictive of a submucosal mass with 83 % sensitivity and 89 % specificity. In addition to the SPICE, various characteristics of lesions can be suggestive of a submucosal process. These include central umbilication, white appearance of stretched mucosa and lobulation (Fig. 7.5), and bridging folds, which are folds that come up to but not across the process (Fig. 7.6).

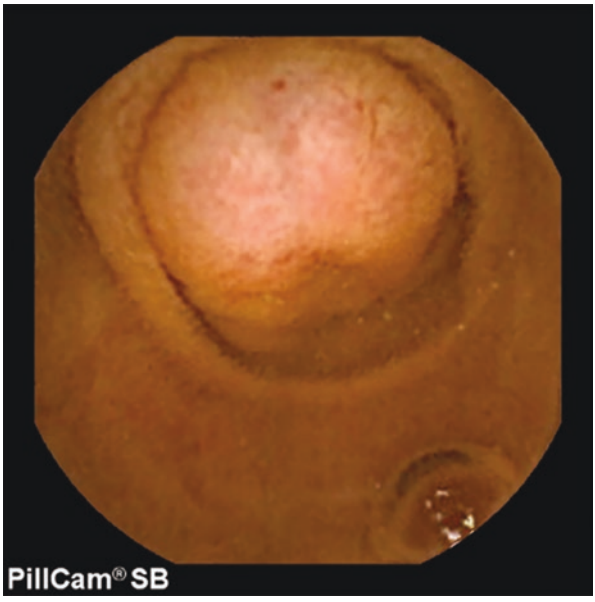

Fig. 7.5 White appearance of stretched mucosa and lobulation as opposed to single bulge

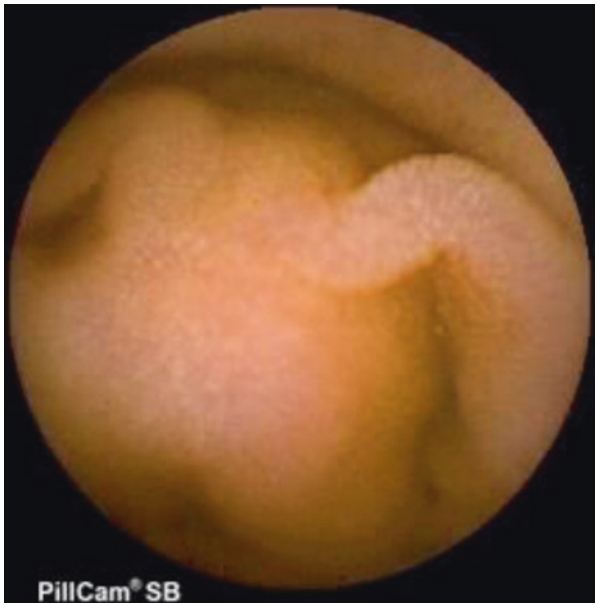

Fig. 7.6 Bridging folds

If clinical suspicion is high, further testing should be considered. These may include a repeat CE, intraoperative endoscopy, CT enterography (CTE), or deep enteroscopy. CTE allows for the detection of both vascular lesions and masses. The technique optimizes luminal distension by the use of oral contrast. CTE has the additional advantage of the identification of small bowel strictures and obstruction prior to CE and provides information on mural and extramural findings not examinable by CE. CTE can be a complementary imaging tool for patients with negative CE.

In conclusion, CE remains an important diagnostic tool in the evaluation of small bowel masses. Small bowel masses can be identified by careful examination of the mucosal surface and by the identification of suspicious features.

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Chapter 8
How to Read a Small Bowel Capsule Endoscopy Study

David W. Wan and David J. Hass

Introduction

Reading a capsule can be a daunting endeavor. The responsibility of the reviewer is to know the difference between normal and abnormal images, find and recognize pathology when present, and then guide management. Without the ability to control the capsule, flush the mucosal surface with water, insufflate the lumen, or obtain biopsy samples, it is indeed a challenging task. Moreover, when reviewing over 50,000 images, there may be only one image with the pivotal finding. Fortunately, with a critically trained eye, an effective methodology, and experience, you can become an adept reader. In the previous chapters, you have seen the diverse panoply of pathologies that can be discovered on a capsule endoscopy. In other words, you have learned *what* to look for. Here in this chapter, you will learn *how* to look for it!

Before Reading the Capsule: Preparation and Foundation

Before one even views the first image, there are three basic foundational principles (Table 8.1) that need to be followed. With a solid foundation, adherence to core principles, and the development of these skills, you will maximize your ability to read small bowel capsules.

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Table 8.1 Basic principles of capsule reading

1. Understand the patient (i.e., clinical history, endoscopic history, indication for capsule endoscopy)
2. Understand the software
3. Understand key features of various GI pathologic conditions

Understanding the Patient

It is a well-known mantra that taking a good history is the key to making a diagnosis. This is no different for reading and interpretation of capsules. One must be a capsule endoscopic clinician, not just an endoscopist. Reviewing the patient's chart and knowing the indication are mandatory, but sometimes obtaining one's own focused but thorough history and even physical exam may yield important clues that will make the diagnosis. Having a pretest probability of various GI pathologies helps sharpen the endoscopists' eye when reviewing the images. Depending on the reason for referral and the indication for the procedure, certain pertinent positives and negatives emerge. Lastly, many correctly identified findings are nonspecific and need to be placed in a clinical context.

For obscure gastrointestinal bleeding, now called small bowel bleeding, one needs to know the nature of the bleed [1]:

1. Is the patient hemodynamically stable? If unstable, the patient may need angiography instead [1].
2. What is the time frame of the bleeding? Is it acute, subacute, or chronic?
3. Was it melena, maroon stool, or bright red blood per rectum?
4. When and what endoscopic procedures were performed (i.e., EGD, colonoscopy, push enteroscopy, deep enteroscopy, capsule endoscopy)? What were the findings and quality of the tests? If a colonoscopy was done, what was the quality of the prep? If a capsule was done, did it completely traverse the small bowel and was the visualization adequate?
5. Does the patient have aortic stenosis or end-stage renal disease, making angioectasias more likely? Does the patient have a history of NSAID use? Does the patient have weight loss, abnormal imaging, or risk factors to suggest a malignancy?

For iron-deficiency anemia, in addition to the elements above, one needs to know:

1. Is the patient taking iron? When did he/she stop?
2. Has the patient been tested for celiac disease?
3. Has the patient been tested for Helicobacter pylori and/or atrophic gastritis?

For suspected Crohn's disease, one might ask:

1. What are the symptoms (i.e. diarrhea, abdominal pain, obstruction, weight loss)?
2. Are there extraintestinal manifestations of Crohn's present (i.e. erythema nodosum, uveitis)?

3. What medical therapy is the patient on?

For celiac disease, reasonable inquiries might include:

1. Is the patient on a gluten-free diet? If so, how long have they been gluten-free?
2. Is the patient losing weight or anemic?

For suspected polyposis syndromes, one needs to know:

1. What is the family history?
2. What syndrome do we suspect or have confirmed (i.e., Peutz-Jeghers, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer)?

Understanding the Software

There are several commercially available capsule platforms. This was described previously in Chap. 1. There are subtle differences between the programs, but the basic functions are the same. It is worthwhile to read the accompanying instruction manual or Quick Reference Guides [2–4]. After a brief familiarization, learning how to check-in patients, download files, and open studies should be straightforward. However, navigating the viewing modes requires more attention. Ultimately, each program will allow one to select the desired viewing mode, control the viewing speed, and capture individual images.

Using the Medtronic platform as an example, the user interface for the view screen (Fig. 8.1) has the following features. On the menu bar, one can select different viewing modes and layouts with preview modes such as suspected bleeding indicator (SBI) or QuickView settings (Fig. 8.2). The middle panel displays the images. The bottom panel contains the localization and small bowel progress bar, the color bar, and thumbnails (Figs. 8.1 and 8.4).

As part of our reading algorithm (Figs. 8.3 and 8.4), we begin by annotating anatomic landmarks (first gastric, first duodenal, and first cecal image). After these are selected, the software becomes optimized. The SBI mode will highlight images with the presence of red color. The QuickView settings condense the video by altering the playback speed based on image variation and removing redundant images. It markedly shortens the view time but should not be used as the sole reviewing mode given its miss rate of up to 8 % [5, 6]. Once a preview or review mode is selected, one can choose between one, two, four, and mosaic image viewing layouts (Fig. 8.5). However, the mosaic image layout should not be used for reading the study. This is used primarily to help the reader determine persistence of abnormalities that distinguish true pathology versus artifact.

Below the image, there is a scroll bar that allows one to select the speed from 1 to 40×. There are also buttons that allow one to rewind, pause, fast-forward, and skip to the beginning or end of the video. Lastly, one can capture images by right-clicking and create thumbnails displayed on the bottom of the screen. These images can be labeled as anatomic landmarks or with free-text descriptions.

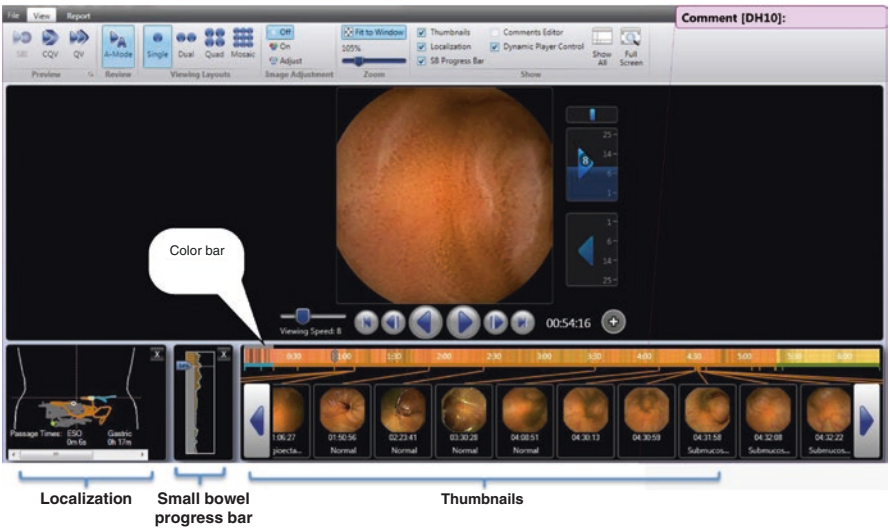


Fig. 8.1 Medtronic interface (All rights reserved. Used with the permission of Medtronic)

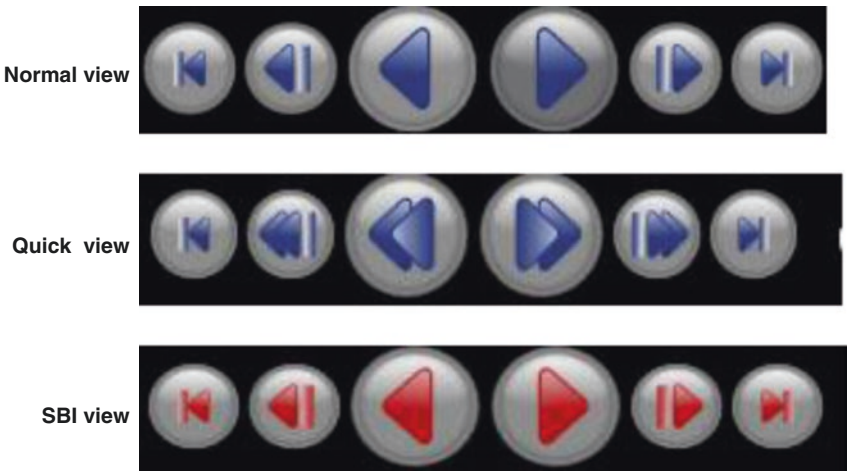


Fig. 8.2 Different preview and viewing modes (All rights reserved. Used with the permission of Medtronic)

Using Localization Software

Knowing the approximate location of a finding within the small bowel will determine how to approach it from a diagnostic and/or therapeutic standpoint subsequent to the capsule endoscopy. One needs to determine whether an endoscopy, push enteroscopy, deep enteroscopy from the oral or rectal approach, or surgery should be attempted. Thankfully, with the help of the localization and small bowel progress bar (Fig. 8.6), the relative location within the small bowel can be inferred by the passage time from the pylorus to the lesion and from the lesion to the ileocecal valve, the capsule

Step 1. Read capsule in a comfortable setting with an alert mindset.

Step 2. Determine if the study is a complete exam. Did the capsule reach the colonic lumen?

Step 3. Identify landmarks (1st gastric, 1st duodenal, 1st cecal image).

Step 4. Review the Suspected Blood Indicator Images once software activated by identifying landmarks.

Step 5. Preview the study with QuickView if desired. (DO NOT SUBSTITUTE THIS FOR INTERPRETING THE ENTIRE STUDY).

Step 6. On review mode, toggle through esophageal images manually and view gastric images at selected speed.

Step 7. With preferred small bowel viewing mode and speed, view video and cruise and capture images of interest to review at completion for more analysis.

Step 8. View colonic images at increased viewing speed that you are comfortable with contingent upon preparation. Remember, small bowel capsule endoscopy is not meant to evaluate colonic images.

Step 9. Review all captured thumbnails to better characterize findings and label thumbnails. Compare images to atlas images for additional guidance if necessary. For small bowel findings, mark small bowel transit time so as to estimate location of small bowel findings in terms of percentage of small bowel transit and thus direct further endoscopic evaluation if necessary.

Step 10. Complete report.

Fig. 8.3 HASS-WAN small bowel capsule reading algorithm

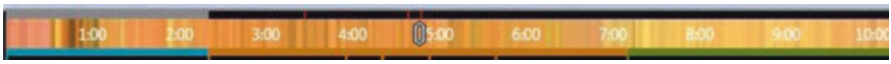


Fig. 8.4 Color bar indicating average regional image color. Designated current image position and thumbnail positions are marked. If areas of red are seen, they are displayed above the color bar in SBI mode (All rights reserved. Used with the permission of Medtronic)

velocity, and amount of bowel traversed. The localization bar contains a small diagram of the abdomen divided into four quadrants and gives an approximate visual position. The small bowel progress bar indicates what percentage of small bowel has been traversed to reach the finding of interest (i.e., 30 % of small bowel transit time). When a lesion is within 30 min of the pylorus or the left abdomen, a push enteroscopy is usually adequate to reach the pathology with conventional endoscopic techniques. If a lesion is noted 30 min post-pylorus, but within the proximal 60 % of the small bowel, an oral approach for deep enteroscopy would be recommended. If it is more distal, a rectally approached deep enteroscopy would be recommended [7].

Using Spectral Color Selection

With post-processing of images, mucosal and vascular patterns can be enhanced. One can customize sharpness, color, and brightness. Medtronic uses a blue mode analogous to narrow-band imaging on traditional endoscopes that may

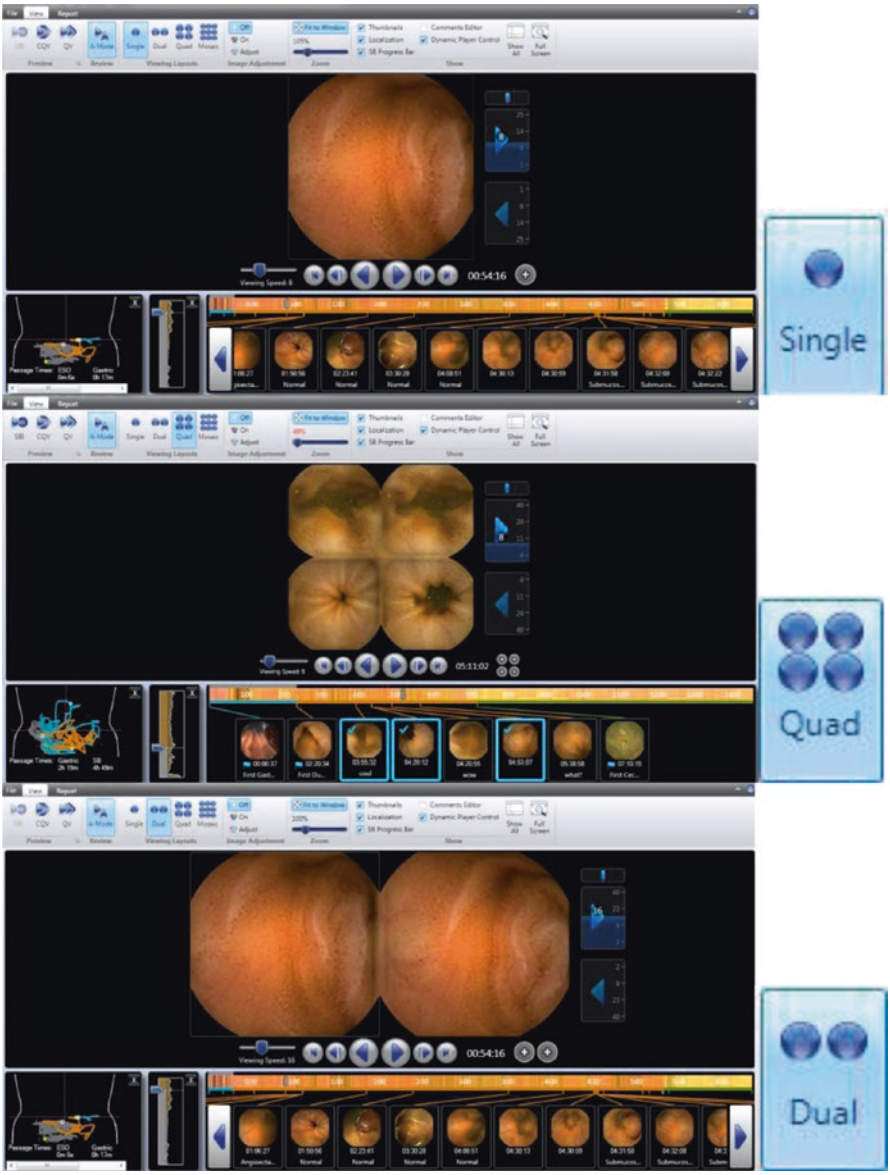


Fig. 8.5 Different viewing modes with representative display (All rights reserved. Used with the permission of Medtronic)

improve detection and image quality [8]. Olympus uses the flexible spectral imaging color enhancement (FICE) module, which has been shown to improve image quality and detection of erosive and vascular lesions, but not for tumors or polyps [9, 10].

Fig. 8.6 Localization and small bowel progress indicator. This assists in identifying anatomic localization of the capsule (All rights reserved. Used with the permission of Medtronic)

Other Clinical Tools

The Lewis Score is a tool that measures the small bowel inflammatory activity level in Crohn's patients [11]. It provides an approximate measure and way of standardizing inflammatory mucosal damage based on direct visual imaging of the small intestine. It is tabulated by inputting data on characteristics of the villi, the number and extent of ulcers, and the number and severity of stenoses. The small bowel is broken into tertiles. The higher the score, the more severe the endoscopic disease. Of note, the Lewis Score allows for a common vernacular of scoring to be achieved so that gastroenterologists who do not read capsule endoscopies can understand the severity of disease based on the score. This may alter clinical management or lead a physician to escalate therapies if small bowel disease is severe.

An endoscopic atlas is also available to review and compare images of interest. It is a useful compendium with small descriptors of a variety of different images. It can enable a side-by-side comparison of a captured image to known pathology. It is catego-

rized and searchable by Capsule Endoscopy Structured Terminology, anatomic locations, characteristic findings (i.e., protruding lesions, ulcers, etc.), or specific diseases.

Understanding the Key Features of Various GI Pathologic Conditions

There are a plethora of potential findings in the GI tract. Some are relatively esoteric (i.e., diffuse white villi in Whipple's disease), while others are more common (i.e., angioectasia, ulcers, etc.). It is important to distinguish the salient features of all these different processes, or else the diagnosis may be missed. Fortunately, after reading the previous chapters, you will be better prepared to recognize and interpret these capsule findings.

Nonetheless, while you can review "textbook" examples of these findings available in reference books and a software electronic atlas, the images that are available to review seldom are of textbook quality. A finding may appear ambiguous or there may be suboptimal quantity or quality of images to review. Thus, this is when reading a capsule becomes an art and a rigorous methodology becomes crucial. The key is to develop an algorithm and adhere to a systematic approach.

The Process of Reading a Capsule Video

Reading a capsule requires ample patience and attentiveness. There are hours of real-time video to review amounting to over 50,000 images. The challenge is to stay alert (and awake) and give continuous attention to a task that at times can lead one to potentially become distracted. Coupled to the tedious nature of the job is the stress of trying to find a lesion or definitely rule out any pathology. Calling a capsule normal requires a high level of confidence in one's reading ability.

Each individual reads capsule video in a different way. Some readers prefer a dual viewing mode, while others prefer a quad-viewing mode. Some clinicians opt for a frame viewing speed of 8 frames per second, while others prefer 10 or 20. Nevertheless, no matter what methodology one employs, one should develop a consistent, systematic process when reading capsules. We will describe our algorithm to maximize your ability to competently read capsules (Fig. 8.3). If you apply these steps and read more and more capsules, you will become a confident and accurate capsule endoscopic clinician.

Setting the Stage: Preliminary Steps

The first step is to create a comfortable reading environment. One needs to wisely choose a place with the preferred level of noise, light, and privacy. Ideally, it should be a place where you can have some privacy without interruptions. The background

noise should suit the reader, whether it is quiet like a library or with more ambient noise or even music as in a cafe. Lewis has summarized how to create an ideal reading environment [12]. He recommends a darkened but not black room, comfortable seating and clothing, carbohydrates or caffeine prior to evaluation, auditory distraction (i.e., music), sessions limited to 1 h, and the self-awareness to interrupt a session in the case of restlessness or distraction.

Previewing and Marking the Anatomic Landmarks

With the newest software versions, one can use the preview modes before dedicating a full review of the entire capsule. The QuickView is a useful tool to employ initially to capture and label all of the relevant landmarks (i.e., first gastric image, first duodenal image, ileocecal valve, or first colonic image). Once a landmark is set, then the SBI is activated and used to survey any areas suspicious for active bleeding. Lastly, one may choose to use the mosaic or QuickView review to rapidly identify interesting images. Alternatively, looking at the color bar at sites of major color shifts can help identify transition areas from stomach and duodenum and ileum and cecum.

Viewing the Capsule Video

When viewing the capsule, one must choose the mode, viewing layout, and speed at which one is most comfortable. With current small bowel capsules, two images are captured per second. At the maximal reading speed of 40×, that would equate to 25 ms per image. Finding the ideal view mode and speed is highly individual. A low-image view mode and slow frame rate allow more time for scanning individual images but may make the experience too slow and monotonous for readers to sustain attention. When increasing the frame rate or number of images that are viewed simultaneously, one is able to navigate through the video faster, but less viewing time per image. Each reader needs to find their own personal comfort zone for speed and viewing layout. A consensus of capsule endoscopy experts has recommended that the fastest acceptable speed is 15 frames per second; however, there is limited evidence to support this approach. One study suggested that SingleView 15 and QuadView 20 was better than SingleView 25, but the detection rates overall were unexpectedly low [13]. Another study showed that the two- and four-view modes were superior to single-view mode and that a rate of ten frames per second had the best sensitivity [14].

If we estimate that the average capsule is 8 h with 57,600 images, it would take 64 min to read a full capsule at 15 frames per second rate. For the small bowel portion, typically about 4 h in length, it would take approximately 32 min to read. For beginners, we recommend using an initial reading rate of 8–10 frames per second. As one becomes more experienced, one should adjust his/her reading speed but avoid a frame speed faster than 20 frames per second when possible.

Capturing Images of Interest

If any image looks unusual, that picture should be captured. The series of images before and after should be reviewed carefully to see if the finding is preserved. Other angles and views may show different features of the lesion that may be elucidating. Conversely, the other neighboring images may help suggest that the "lesion" is simply an extrinsic bulge or floating debris.

Basic Capsule Endoscopic Benchmarks

As one is reviewing the video for small bowel pathology, these are some basic questions one needs to ask and answer:

Are There Any Incidental Esophageal or Gastric Findings?

After the capsule is swallowed, there may be a few images of the esophagus that may show findings such as esophagitis, Barrett's esophagus, or varices. However, without a dedicated esophageal capsule such as Pillcam ESO©, the number of images is limited and carries poor sensitivity and specificity. The capsule evaluation of the stomach, on the other hand, is more useful and may occasionally reveal pathology, most commonly gastropathy, erosions, ulcers, tumors, angioectasias, or even GAVE that may have been mislabeled endoscopically.

When Does the Capsule Reach the Duodenum? What Is the First Duodenal Image?

The capsule typically spends most of its gastric transit time in the antrum as it awaits passage through the pylorus. The folds and contractions of the antrum are readily apparent and after the stellate shaped-appearing pylorus is seen, it is usually a short matter of time (average of 10 min and usually less than 30 min) before the capsule enters the duodenum. However, sometimes a total gastric time may be longer. Prolonged gastric passage would appear to suggest gastroparesis, but one study demonstrated this finding had no clinical correlation to gastroparesis symptoms and no clinical significance [15]. Of note, there are times when the capsule may enter the duodenum and then fall back into the antrum. The first duodenal image should be labeled as the image when the capsule enters the duodenum and stays in the duodenum. If this is not followed, it is possible that the recorded small bowel transit time may be overestimated.

The duodenum has a paler mucosal color and is frequently stained with yellow bile. The hallmark feature is the presence of villi. Rarely, the pylorus can be seen on "retrograde view," and the small nodules of Brunner's glands can be appreciated. One must become comfortable recognizing normal anatomic structures such as the pylorus in retrograde view as well as the ampulla, so as not to mislabel these normal findings as abnormalities.

Does the Capsule Traverse the Entire Length of the Small Bowel and Reach the Cecum?

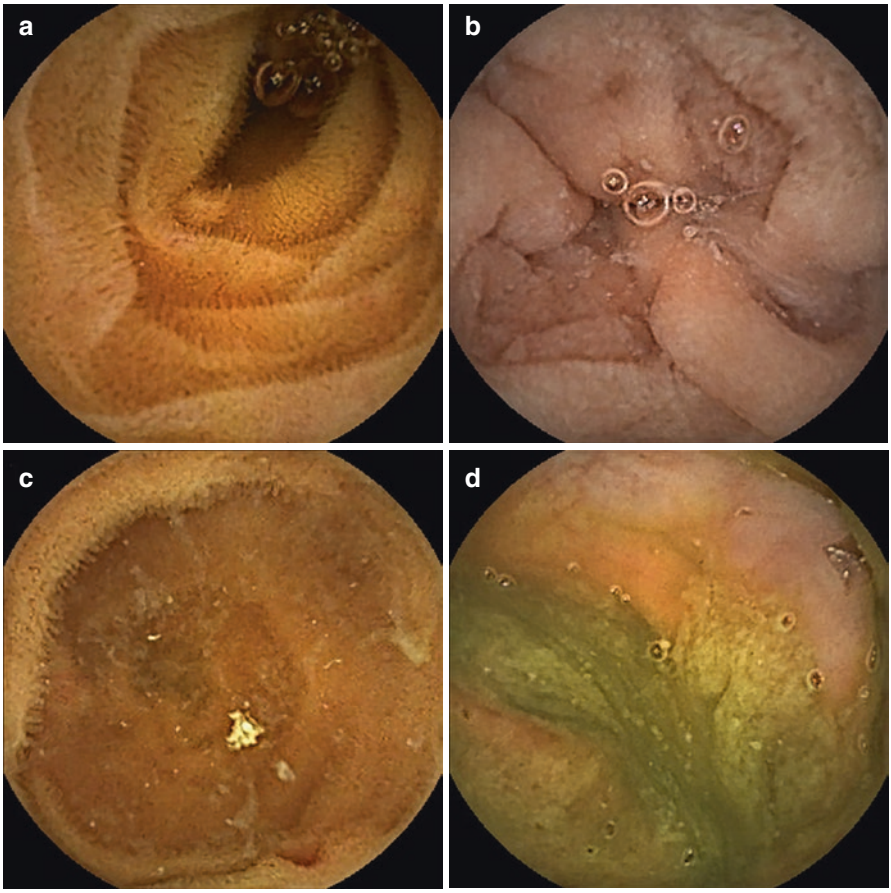
To answer this question, one needs to accurately identify the first colonic image. The ileocecal valve can only be seen up to 20 % of the time, as the capsule briskly traverses it [16]. At this transition from small to large bowel, the terminal ileum is characterized by more prominent and elongated superficial vessels and lymphoid hyperplasia. When seen, the ileocecal valve can have the appearance of a keyhole with radiating creases in a spoke-like pattern. Shortly after its visualization, the cecum is verified by the presence of green or brown stool. The colonic mucosa has a pink appearance with more obvious surface vessels and a distinct lack of villi.

How Is the Prep? Are There Pill or Food Residue or Bubbles that Preclude Adequate Visualization? Is the Bowel Contracted?

Unlike in colonoscopy prep grading using the Aronchick scale (i.e., inadequate, poor, fair, good, excellent) or Boston Bowel Preparation Scale (score from 0 to 9), there are no validated or even generally accepted standards for grading the preparation in a small bowel capsule endoscopy. Some capsule endoscopists do not even use bowel preparations. Nonetheless, it is important to document how adequate the prep is. Bubbles, food and pill residue, as well as bowel contractions can easily interfere with visualization, and one cannot use water jets, flushes, or insufflation to improve views. The yield of capsule endoscopy is dependent on the prep quality, so it is important to communicate the visual limitations present. Most people use a system analogous to the Aronchick scale (Fig. 8.7).

Scanning the Small Bowel

As the capsule progresses through the small bowel, one needs to constantly ask oneself whether there are any abnormal luminal contents, mucosal abnormalities, or pathologic bulges. The next section will review the various scenarios and provide examples to help illustrate the differences between normal and abnormal findings.



Figs. 8.7 (**a**–**d**) Quality of preparation as listed sequentially. (**a**) Excellent; (**b**) good; (**c**) fair; (**d**) poor. All rights reserved (Used with the permission of Medtronic)

Interpreting Capsule Findings: Commonly Encountered Scenarios

Is Anything in the Lumen (i.e., Blood, Foreign Bodies, Parasites)?

Intraluminal contents appear as an object that seems to break the continuity of the mucosa. It can be difficult to discern whether the object is part of the mucosa or freely floating. Often, it takes review of the series of images that bookend the finding to see how the object moves through space and time relative to the mucosa to determine its nature (Fig. 8.8). Contents such as blood are usually the most important to identify. Sometimes the suspected blood indicator can help but can miss critical images so a thorough review of the entire study is essential [17].

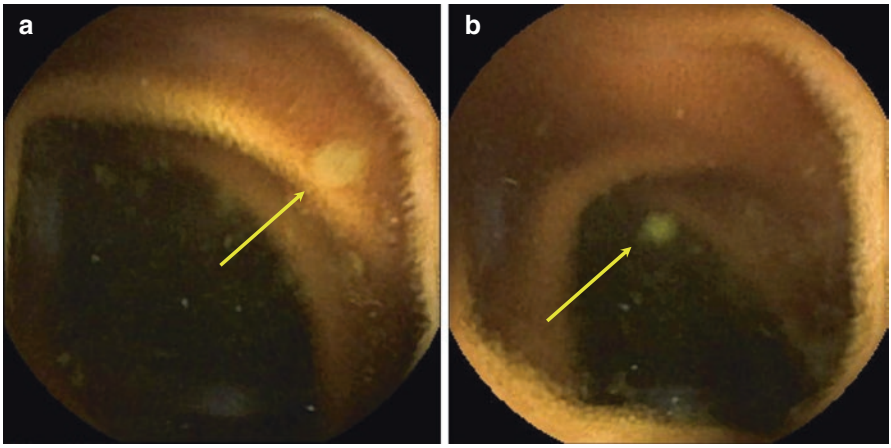


Fig. 8.8 Intraluminal object. From one image to the next, what appears to be an ulcer (**a**) becomes a floating piece of debris (**b**) All rights reserved (Used with the permission of Medtronic)

How Do the Villi Appear? Are There Any Breaks in the Mucosa?

The villi should carpet the surface of the small bowel. It even has the appearance of a shag carpet or sea anemone-like projections into the lumen. Normal small bowel is characterized by villi, yellow-orange mucosa, circular folds, occasional small vessels and veins, and occasional contractions (Fig. 8.7a). Frequently, one sees small or medium-sized white or yellow plaques with or without a "fluffy" appearance. These are usually benign lymphangiectasias.

If there is a break or absence of villi, one may be seeing an erosion or ulcer (Fig. 8.9).

Is There Any Bulge? Does This Bulge Harbor Any Features That Suggest a Potential Submucosal Lesion?

One of the most difficult tasks is to differentiate whether a bulge is pathologic. It has been reported that capsule endoscopy finds that up to 11 % of small bowel bleeding is due to a tumor [18]. Finding a tumor is one of the most challenging tasks in capsule endoscopy. Is that bulge an adjacent bowel loop or a submucosal tumor? To do so requires viewing the video stream instead of single images. Normal adjacent loops will move with peristalsis and simple bulges will not change the appearance of villi.

In contrast, the features suggesting tumor (Fig. 8.10a, b) include [19]:

- Change in villus pattern
- Surface ulceration
- Central umbilication

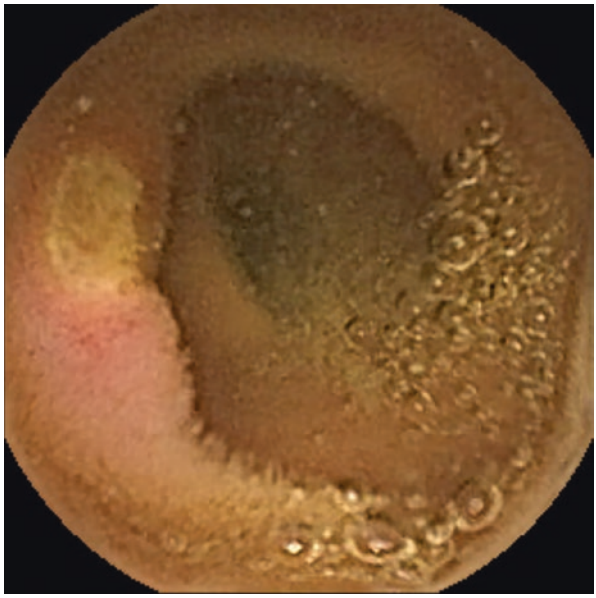


Fig. 8.9 Jejunal ulcer (Courtesy of Charles Maltz MD, PhD). Note loss of villi

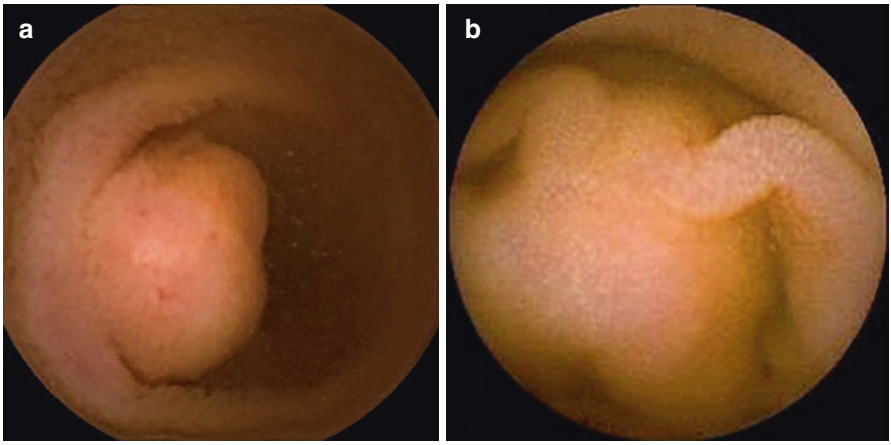


Fig. 8.10 Submucosal lesions noted on capsule endoscopy. Image (**a)** reveals a protruding mass with "stretched mucosa" and evidence of mild surface hemorrhage. Image (**b)** reveals an infiltrative process interrupting the folds of the small bowel suggesting a small bowel submucosal lesion (All rights reserved. Used with the permission of Medtronic)

- Stretched mucosa and white appearance
- Lobulated mucosa
- Thickened folds
- Nonbridging folds ("turkey sign")

Table 8.2 SPICE index for distinguishing submucosal lesions

Criteria
Lack of ill-defined borders with the surrounding mucosa
Height > diameter
Visible lumen in frames in which lesion appears
Image present for >10 min

[a]If >2 criteria seen, high likelihood of submucosal lesion being neoplastic

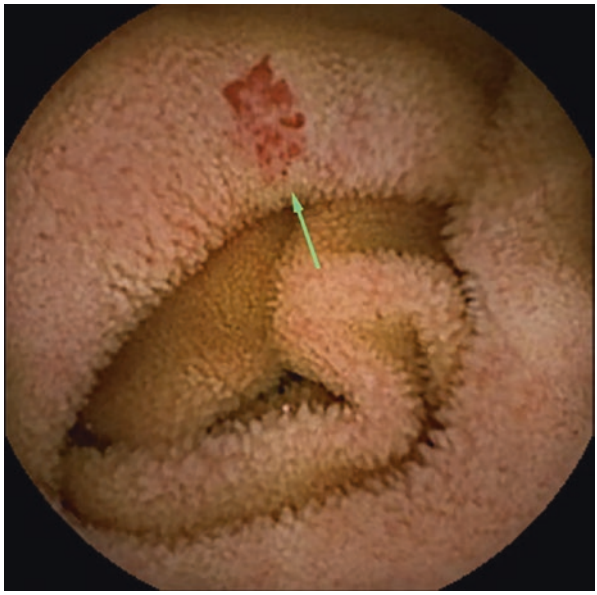


Fig. 8.11 Small bowel angioectasia. Note the feathery and delicate appearance of the lesion to distinguish it from incidental "red spots" or petechiae

To help distinguish a submucosal lesion from a benign finding, a smooth, protruding lesion index on capsule endoscopy (SPICE) was developed (Table 8.2). It is based on lack of ill-defined borders, a height larger than the diameter, visible lumen, and visibility for more than 10 min. If there are two or more of these features, there is a high likelihood that the submucosal lesion is neoplastic. The SPICE index yields a sensitivity of 83 % and a specificity of 89 %.

What Are These Red Spots?

A common dilemma is determining whether a red spot represents an abnormality. First, they should be classified as localized or isolated or diffuse and petechial-like. Classic angioectasias have a sharply demarcated border and feathery appearance and are bright red (Fig. 8.11). They are usually found in isolation, unless there is a history suggestive of hereditary hemorrhagic telangiectasia. Occasionally, a lone red spot can appear when the capsule lens compresses the surface. Understanding

the clinical context such as NSAID use and previous radiation can be helpful. Moreover, understanding the endoscopic context of coexisting capsule findings such as abnormal villi, fibrotic appearance, ulcers, or masses will lend support to a suspected abnormal diagnosis.

Conclusion

With colonoscopy, while every endoscopist has a different technique or style, there are still accepted colonoscopy quality benchmarks (i.e., cecal intubation rate, withdrawal time, adenoma detection rate, prep quality rate). In contrast, capsule endoscopists do not have widely accepted quality indicators. There is no preparation quality rate, ampulla detection rate, gastrointestinal bleeding source detection rate, nor small bowel tumor detection rate. Thus, it is up to the individual capsule endoscopic clinician to maintain a high standard. By applying our algorithm (Fig. 8.3), one is equipped with a systematic approach to reading capsules. By consistently applying this rigorous methodology, with experience one can become a proficient capsule endoscopic clinician.

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Chapter 9
Distinguishing Normal Anatomy from Abnormal Capsule Endoscopic Images: A Challenging Task

Jonathan A. Erber and Grigoriy E. Gurvits

Introduction

Video capsule endoscopy (CE) received Food and Drug Administration (FDA) clearance in 2001 to evaluate the small bowel for the indication of obscure gastrointestinal (GI) bleeding [1, 2]. Since then, the indications for its use have expanded to include suspected and known Crohn's disease (CD) and to evaluate the small bowel for other potential causes of iron deficiency anemia (IDA) not detected by standard upper or lower endoscopy, including suspected and known celiac disease and tumors.

Reading and interpreting capsule endoscopic images is a skill similar to interpreting standard video endoscopic images. First, it requires the reader to understand and recognize what is normal before being able to detect, identify, and interpret what is abnormal. In addition, the reader should have a thorough understanding of the various diseases of the small bowel and their respective endoscopic/capsule endoscopic presentations. If one does not know what to look for, then one will never find it. However, unlike conventional endoscopy that enables the gastroenterologist to not only observe but to also touch and sample pathologic findings, with capsule endoscopic evaluation, the endoscopist is simply an observer without the ability to manipulate the movement of the capsule, insufflate the bowel lumen, lavage the mucosa, or sample a suspicious finding. This chapter aims to familiarize the reader with normal anatomy, with common pathologies, and also with common findings that one may see that are not pathologic, but rather incidental, yet important to recognize.

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In order to provide some form of standardization, the ASGE submitted its guidelines in 2005 (reviewed and reapproved in February 2011) on credentialing and granting privileges in CE [3]. The minimum training requirements for interpreting CE are generally based on this societal guideline and expert opinion which suggests that either the reader (1) complete formal training in CE during GI fellowship or (2) that a practicing gastroenterologist complete a hands-on course with a minimum of 8 h of CME credit, endorsed by a national or international GI or surgical society, and read at least 10-proctored capsule endoscopy studies in order to be deemed competent. Many gastroenterologists who perform CE have learned to do so through short training courses offered by the various professional societies including the ASGE and ACG and sponsored by industry. Over the past 10 years, some gastroenterology fellowship programs have developed a formal curriculum for teaching the interpretation of capsule endoscopy studies. In 2013, a group in Rochester developed a structured CE training curriculum, and based on their findings, it was suggested that trainees should complete more than 20 CE studies before assessing competence regardless of previous endoscopic experience [4].

Normal

The images obtained with capsule endoscopy are slightly different from traditional endoscopy since there is no air distension of the bowel lumen as the capsule is propelled by peristalsis (physiologic endoscopy). More detail of the mucosa can also be achieved and seen due to magnification (8x). In addition, the capsule is, at times, located within millimeters of the mucosa, and because the capsule passively moves through the GI tract, sometimes only a few images or even a single frame of an abnormality is visualized. Therefore, vigilance is necessary when reviewing a capsule study. The reader should also be cautious so as not to overly ascribe significance to a small single frame abnormality. Reading and interpreting capsule images is purely a descriptive endeavor. Unlike standard endoscopy, one cannot insufflate air to see if something is an artifact and flattens with air, nor can one poke or prod with a forceps to feel if the lesion is hard or soft, mucosal or submucosally based, and importantly, one cannot biopsy. Hence, context is important and capsule images should be described and a diagnosis only made after a thorough review of the patient's history and prior endoscopy and imaging findings. It is not an infrequent occurrence to recommend follow-up enteroscopy and/or imaging in order to confirm a capsule finding.

There are specific problems when interpreting some capsule images. These include proper identification of vascular lesions, submucosal processes, and differentiating dark blood from bile. Useful strategies to distinguish normal from abnormal and artifact are to look at the surrounding mucosa for clues and findings to support or refute one's conclusion. In addition, viewing the video flow of images both immediately before and after the intestinal abnormality in question will assist the reader in better characterizing true pathology and differentiating it from benign findings or artifact.

Normal anatomical landmarks and structures that should be readily identified by the reader include the tongue (Fig. 9.1) and teeth (Fig. 9.2) in the oropharynx as well as the vocal cords, Z-line at the junction of the distal esophagus and stomach (Fig. 9.3), the antral folds and prominent rugae, the pylorus, Brunner's glands in the duodenal bulb, the ampulla/papilla in the duodenum, and nodular lymphoid hyperplasia in the terminal ileum.

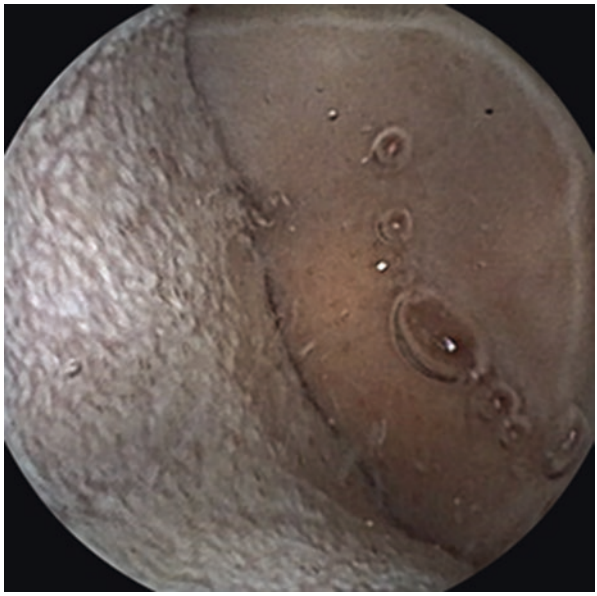

Fig. 9.1 Tongue

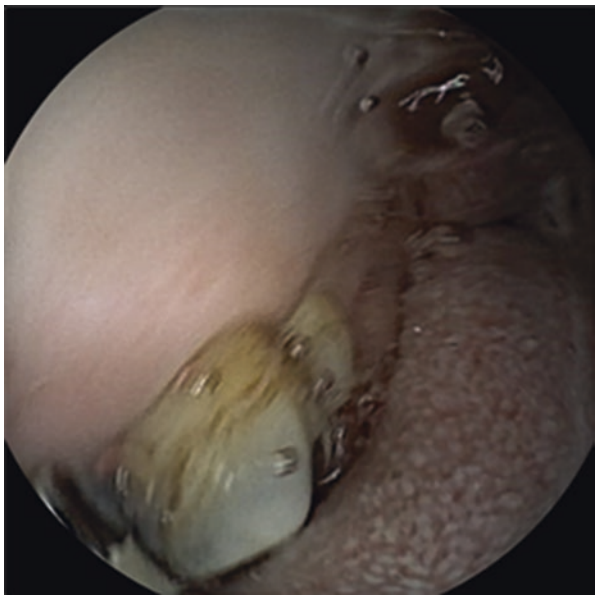

Fig. 9.2 Teeth

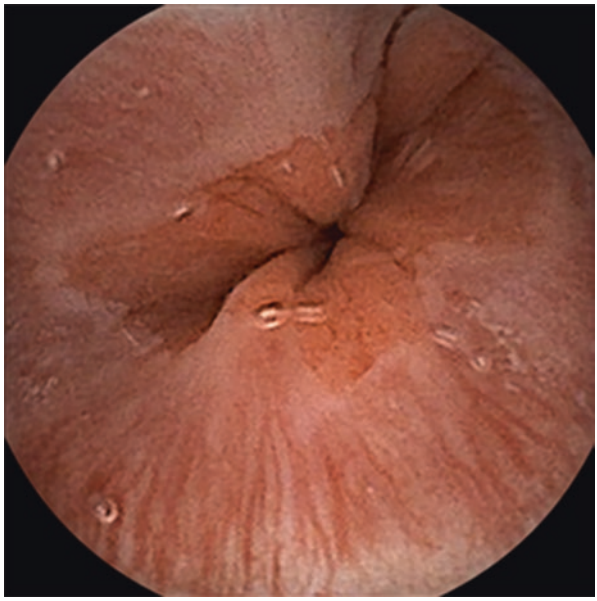

Fig. 9.3 GE junction

Orientation and the capsule trajectory are both important to note as well. The capsule does not necessarily pass through the bowel in a straight and linear orientation. The capsule at times may be pointed caudally (down/forward) or cranially (up/backward) and can also tumble upon itself and at times remain in a segment of bowel for a period of time before being propelled forward. Valvulae conniventes or mucosal folds populated by numerous villi are characteristic of the small bowel and decrease in frequency and number caudally as the capsule moves distally.

The capsule generally resides in the mouth and esophagus for only a few seconds, so limited views are obtained here; however the Z-line can often be identified. Rapid passage through the esophagus is not uncommon, and hence the Z-line may not be imaged in all studies. If the capsule is oriented with the lens pointed in the proximal direction, i.e., cranially, the Z-line may not be noted in the usual fashion. In the case of a large hiatal hernia, the capsule may hesitate and remain at the junction of the esophagus and stomach for a period of time, and this should be noted. A careful review of these images may uncover the presence of pathology such as Cameron's lesions that may have been missed or underappreciated at the time of upper endoscopy and often can be an occult source of iron deficiency anemia. On occasion, esophagitis and Barrett's esophagus may also be identified (Fig. 9.4). A normal variant of the esophagus includes trachealization (Fig. 9.5) which may be seen if the patient coughs during capsule ingestion or may also be an indication of underlying pathology such as eosinophilic esophagitis (EoE). If this is visualized and one has elicited a history in a young patient with seasonal allergies and a history of recurrent food impaction, one may suspect a diagnosis of EoE.

Once the capsule reaches the stomach, one can expect to obtain several minutes to hours of video images as the capsule moves back and forth secondary to the nor-

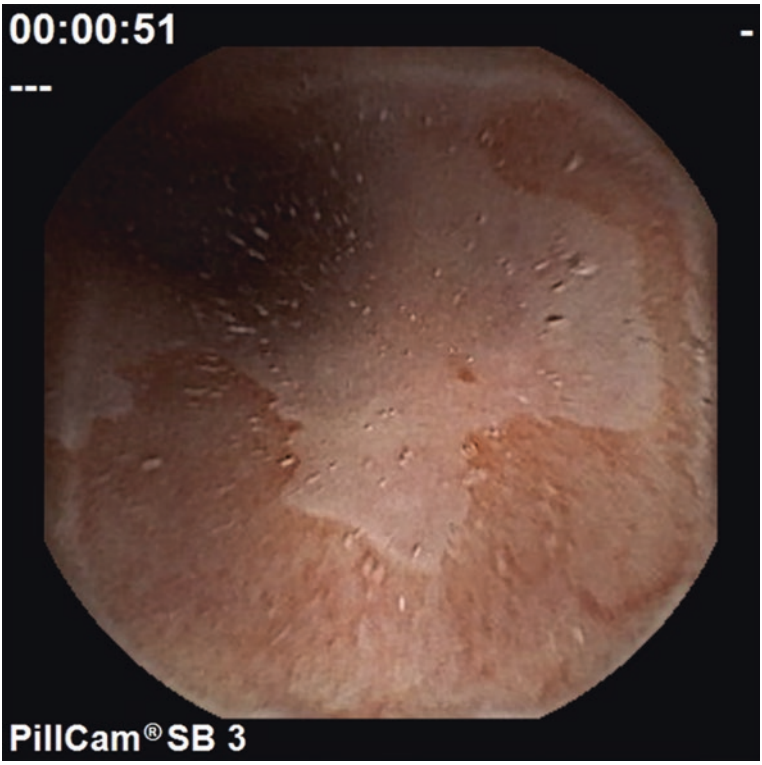

Fig. 9.4 Barrett's esophagus

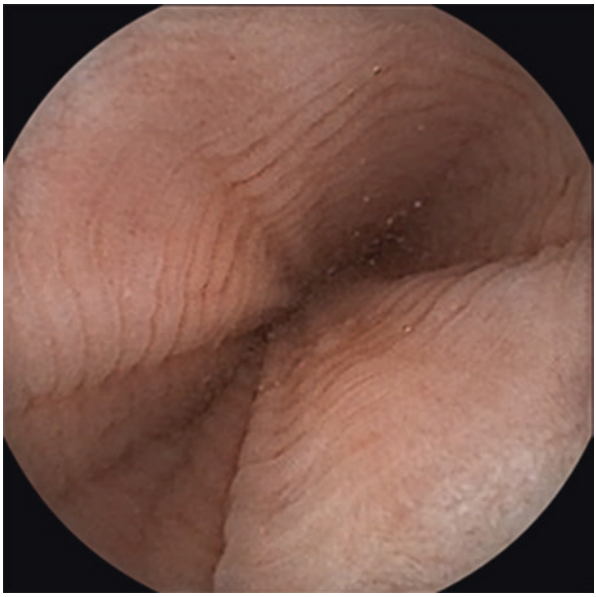

Fig. 9.5 Eosinophilic esophagitis

mal motility of the gastric musculature. Images may tend to be darker in this area due to the larger diameter of the gastric lumen in comparison with the esophagus. All of the usual findings that can be seen on standard upper endoscopy can be seen with the capsule endoscopic images of the stomach as well, such as erosions, ulcers, tumors, and polyps. Importantly however, detailed exams of the stomach are lacking with the typical small bowel capsule endoscope. New techniques and technology are currently being developed that may allow for future control of capsule movement in order to perform a more thorough exam of the stomach and entire upper GI tract. Antral folds often appear more prominent compared to traditional optical endoscopy, as the lumen is not distended with air. Magnification and close visualization of the mucosa may highlight and exaggerate subtle mucosal findings in the stomach, and tiny erosions may seem quite large on capsule. White adherent food particles in the stomach may mimic small erosions or ulcers from peptic ulcer disease, and care should be taken to identify similar free-floating objects and note apparent absence of an erythematous halo around the ulcer edges. Erosions may also be seen on CE after recent endoscopic biopsies and should be differentiated from conventional ulcer disease in the appropriate clinical setting (Fig. 9.6). Frequently bile, other fluids, and debris are noted and can obscure the gastric lumen as well. The typical view of the pylorus as seen with the capsule oriented caudally as it approaches and passes through the pylorus is that of a "cloverleaf" (Fig. 9.7). If the capsule lens however is positioned looking in a retrograde fashion as it passes from the stomach into the duodenum, the pylorus may not be imaged at all or only imaged in a retrograde fashion as it sits in the bulb of the duodenum (Fig. 9.8). It is not uncommon for the capsule to obtain these retrograde views of the pylorus and for this to be mistakenly interpreted as a tumor or submucosal mass. It is also not

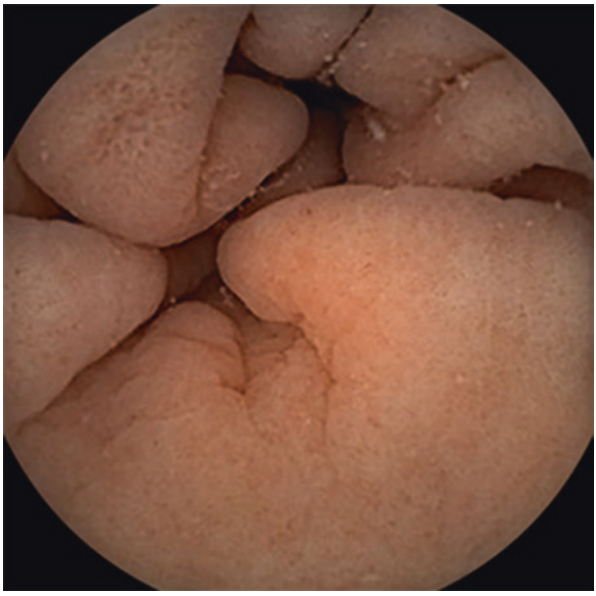

Fig. 9.6 Post-biopsy gastric erosions

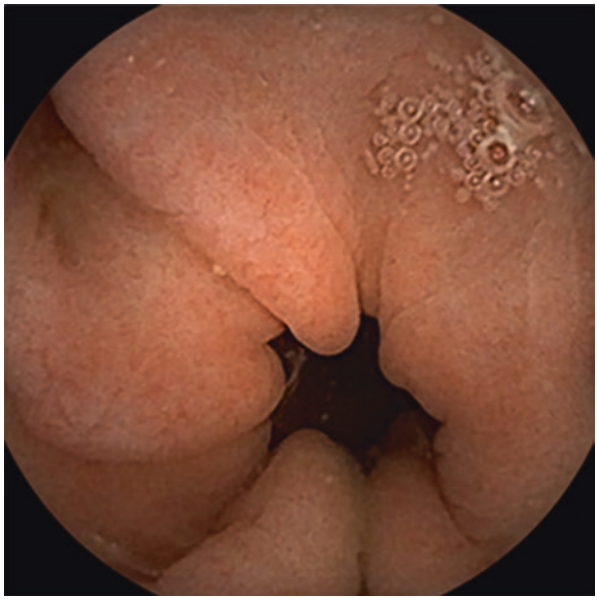

Fig. 9.7 Pylorus

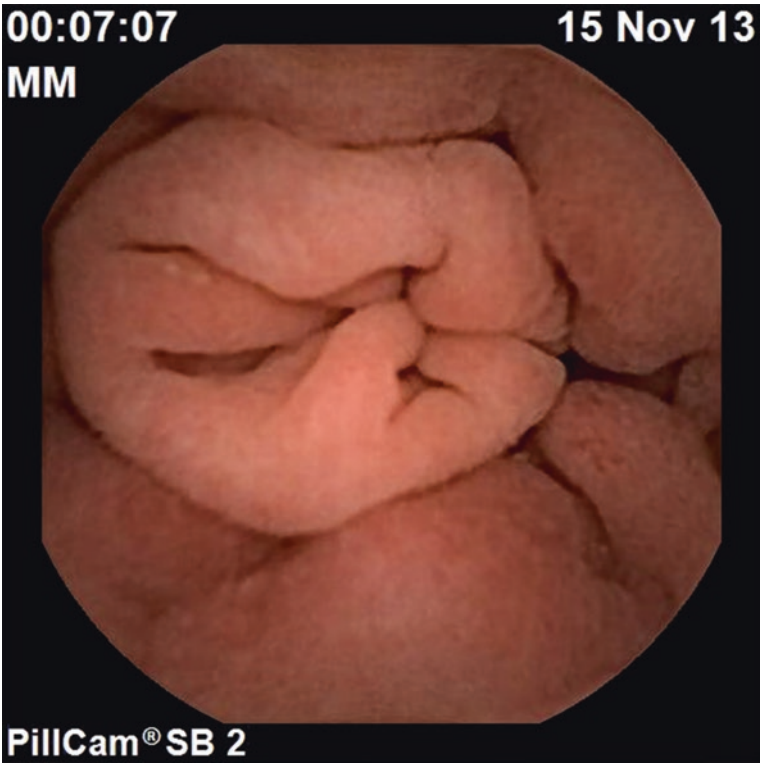

Fig. 9.8 Pylorus, looking from the bulb (retrograde/cranial)

uncommon for the capsule to pass back and forth from the bulb to the stomach multiple times before completing passage through the duodenum and into the jejunum.

As the capsule passes into the duodenum, first the bulb is noted. Once again the images may be darker because of the larger lumen, presence of bile, and other debris. The capsule may quickly pass through this segment or can lay there for several minutes. Often, only a few images of the bulb and the rest of the duodenum are obtained with a very high frame to finding ratio. The reader should consider toggling carefully with the mouse to advance the flow of video images slowly in order to carefully review each image and not miss a finding. Brunner's glands are typically noted and may seem very prominent due to the lack of air distension and magnified views imaged by the capsule. Brunner's gland hyperplasia should not be mistaken for pathological polyposis (Fig. 9.9). The papilla/ampulla (Fig. 9.10) in the second portion of the duodenum may only be seen in up to 50 % of cases [5]. Bile may be seen emanating from the orifice. It is not uncommon even for a more experienced reader to misinterpret the ampulla as a polyp or mass, and the novice reader should heed this closely. As a benchmark of competency and to test one's prowess as a reader, one should document how often the major papilla is seen on CE.

The capsule typically views the small bowel for about 3–4 h. Views of the jejunum are typically brighter than the darker appearing ileum, due to the presence of more copious bile in the ileum. In addition, submucosal vascularity is typically more prominent in portions of the jejunum and the ileum and may almost resemble the typical normal vascular pattern of the large bowel (Figs. 9.11 and 9.12). Phlebectasias are dilated veins that are typically seen in the rectum and small bowel and are not a source of bleeding (Fig. 9.13). One should not misinterpret this normal vascular pattern or vasculature as abnormal. Magnification and closeup imaging of

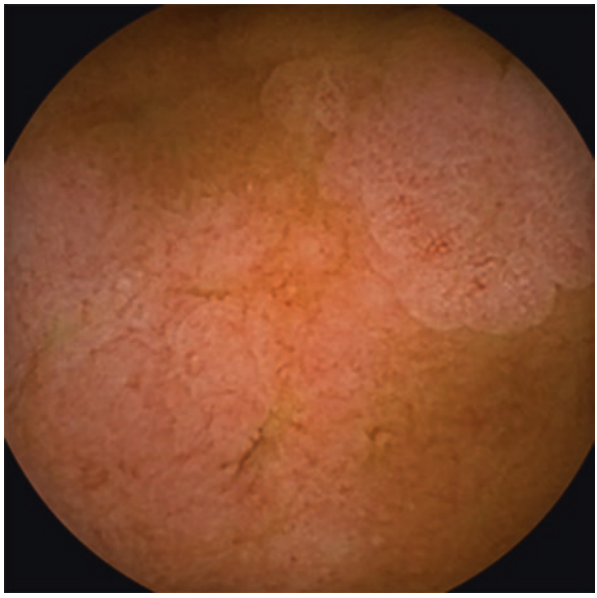

Fig. 9.9 Brunner's gland hyperplasia

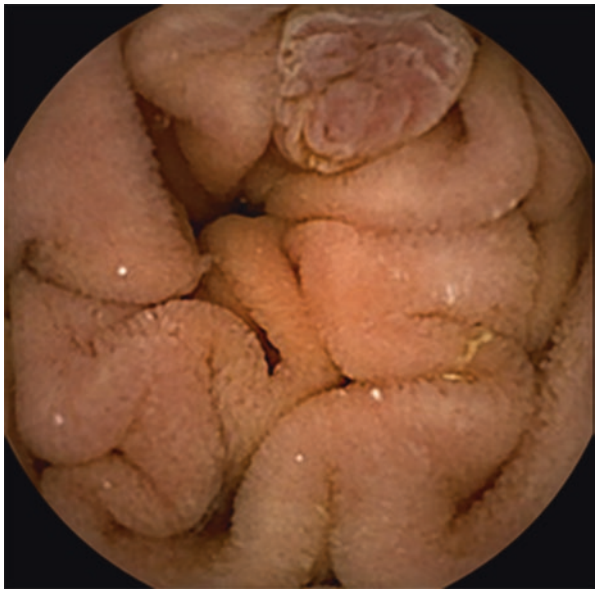

Fig. 9.10 Duodenal papilla, not to be confused with a polyp

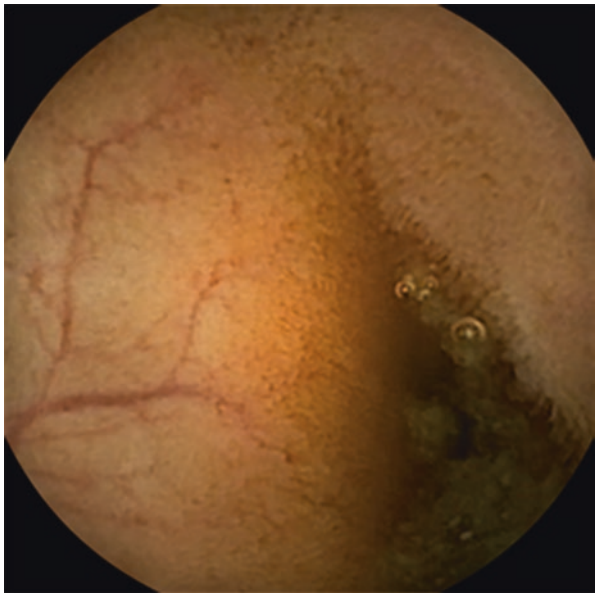

Fig. 9.11 Small bowel vascularity

the mucosa allow for a detailed view of the villi that may appear to stand upright and have a shaggy appearance (Fig. 9.14). Once the capsule reaches the distal ileum/IC region, it is not uncommon for the capsule to bounce at the valve and image this region for several minutes before passing into the colonic lumen. Darker images with bubbles and fluid are often the norm because of the presence of more copious

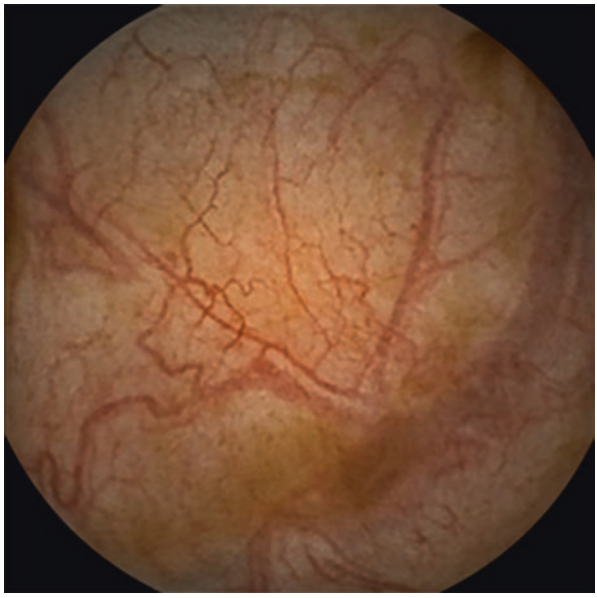

Fig. 9.12 Colon vascularity (normal)

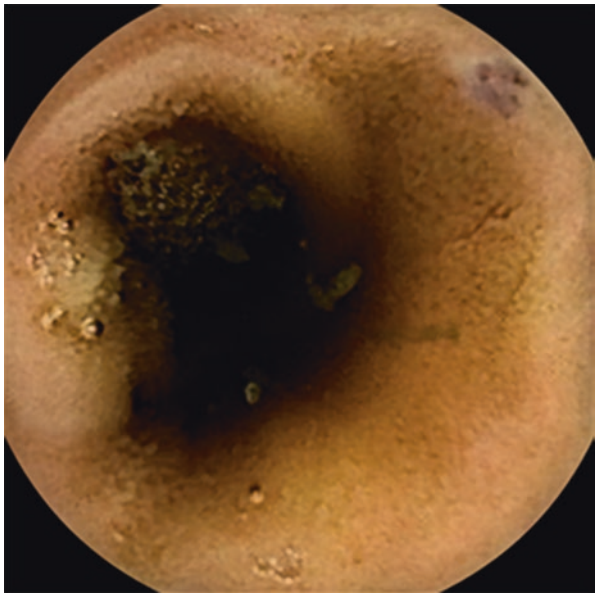

Fig. 9.13 Phlebectasia

bile. Small intestinal landmarks end with the lymphoid nodular hypertrophy of the terminal ileum. These nodules are normally present in the terminal ileum (nodular lymphoid hypertrophy), especially in the younger patient. Compared to the view obtained on ileoscopy during conventional colonoscopy, they appear more prominent on capsule owing to the lack of air distension (Fig. 9.15). The reader should not consider this clinically significant unless found in more significant number in more

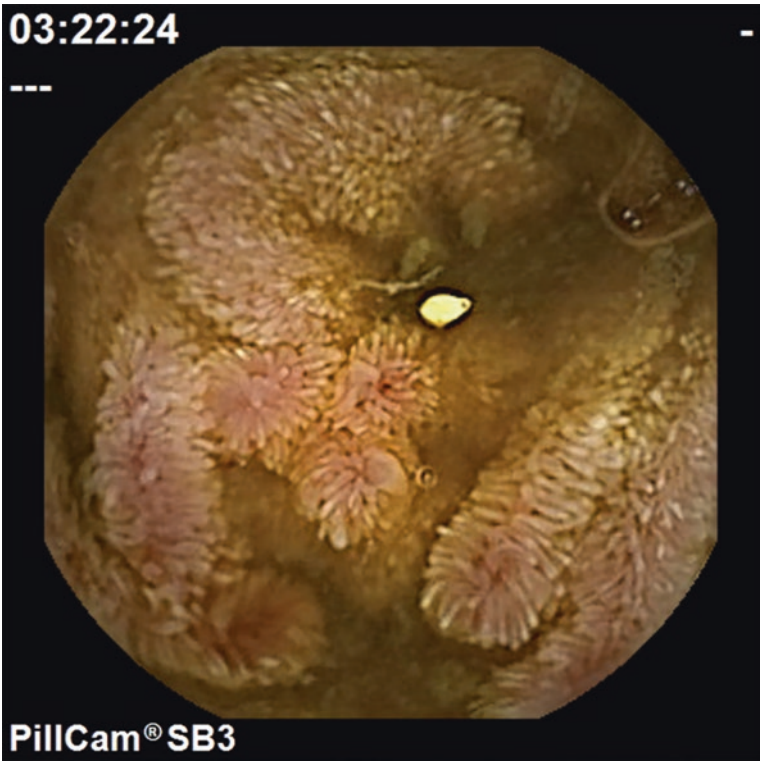

Fig. 9.14 Normal appearance of small bowel villi. One can appreciate the "shag carpet" appearance that is typical

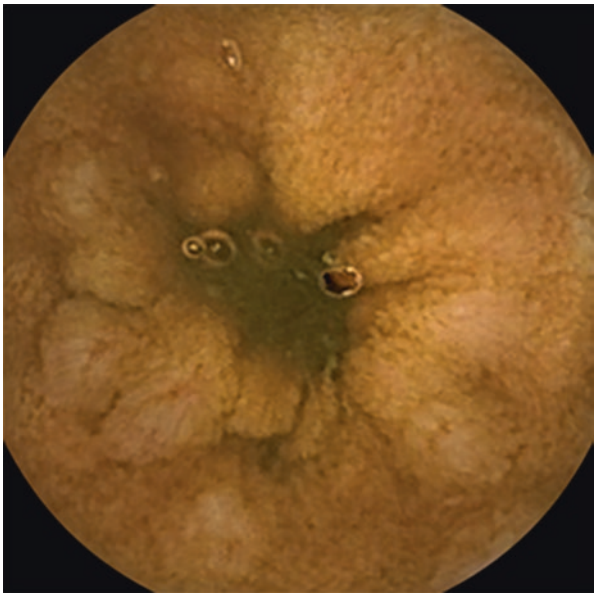

Fig. 9.15 Nodular lymphoid hypertrophy (hyperplasia)

proximal portions of the small bowel or in significant number in an elderly patient. On occasion, significant nodular hyperplasia may also be seen in the setting of inflammatory bowel disease (IBD). These nodules should also not be mistaken for polyps. The presence of darker bile and the presence of these nodules are a clue that the capsule has likely reached the distal ileum and distinguishes itself from the more featureless jejunum.

Once the cecum is entered, colonic haustral folds are typically seen along a paler mucosal background as compared to the ileum along with the presence of solid stool. In addition, the images in the colon may be much darker owing to the larger lumen of the colon. Much less movement may also be apparent (Fig. 9.16). On occasion, views of the colon may be good, and on rare occasions, an angioectasia, a polyp, or even a missed neoplasm may be detected (Fig. 9.17).

Failure of the capsule to reach the cecum may indicate a pathological process in a given part of the gastrointestinal tract that warrants further investigation. A thorough history and physical examination including a complete medical and surgical history is crucial prior to the performance of CE. Inability to identify the GE junction and gastric folds suggests capsule retention in or above the esophagus, such as in a Zenker's diverticulum, esophageal stenosis, stricture, or possible motility disorder such as achalasia. Passage of the GE junction but non-visualization of the pyloric channel and repeated images of the gastric cardia may be seen in the patient with a history of gastric surgery such as gastric bypass or lap band surgery. Similarly, the reader should be able to recognize a situation where capsule does not reach duodenal landmarks and remains in the stomach, indicating delayed gastric emptying in the setting of gastroparesis, mechanical stenosis such as hypertrophic pyloric stenosis, or a structural abnormality such as peptic ulcer disease or neoplasm.

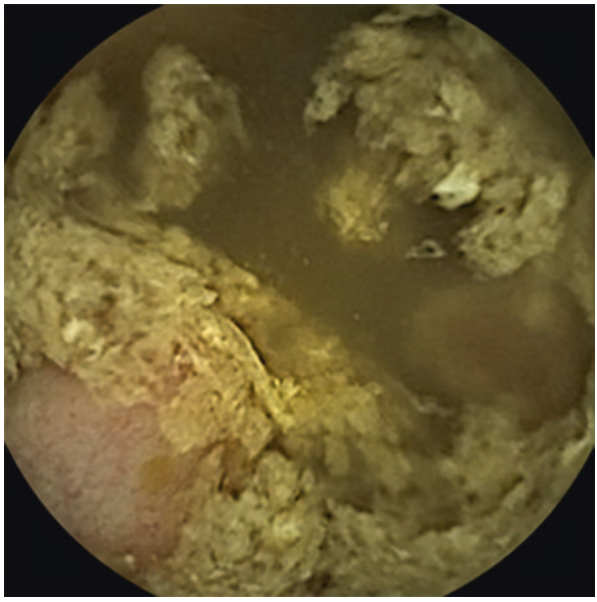

Fig. 9.16 Cecum

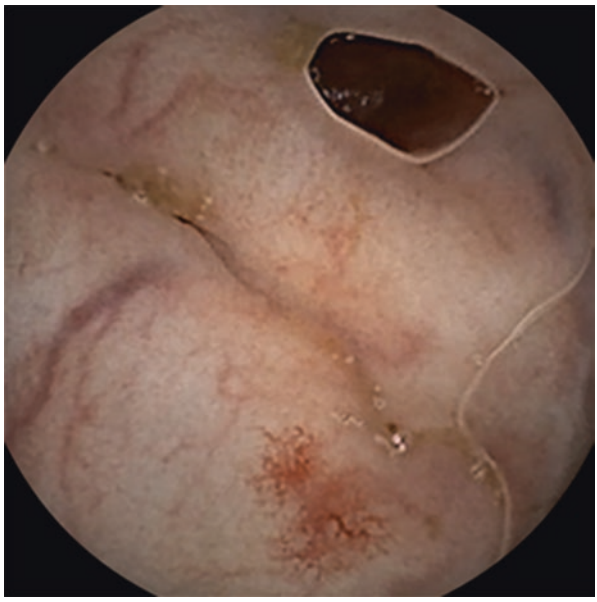

Fig. 9.17 Colonic angioectasia

Finally, failure of the capsule to reach the cecum after successfully passing duodenal landmarks is abnormal but not necessarily pathologic. Regional transit delay in the setting of inflammatory disease of the small bowel is one common scenario. Small bowel strictures in the setting of Crohn's disease, NSAID enteropathy, or neoplasm may also be a cause for an incomplete capsule endoscopy. This scenario, less commonly seen with newer, 12-h capsules however, should raise concern for a delayed passage anywhere in the proximal tract and warrants further investigation of areas of suspected pathology.

Artifacts

In addition to normal anatomy that should not be confused with an abnormality, it is important not to misinterpret the presence of debris as true pathologic findings. A very common occurrence is the presence of white lines that course between normal villi, thought to represent parting of the villi by pressure exerted by the optical dome of the capsule, almost like a part in one's hair (Fig. 9.18). However this artifact/normal pattern should be distinguished from NSAID induced semi- or fully circumferential diaphragms (Fig. 9.19). Sometimes finding these suspected diaphragms may reveal surreptitious NSAID use.

Another common occurrence is the presence of fluid and bubbles (Fig. 9.20). Due to the presence of fluid and bubbles, the bowel wall may be obscured (unlike standard endoscopy where one can wash and suction fluid/bubbles away with a water jet). The fluid and bubbles may also create a light artifact and reflect the white

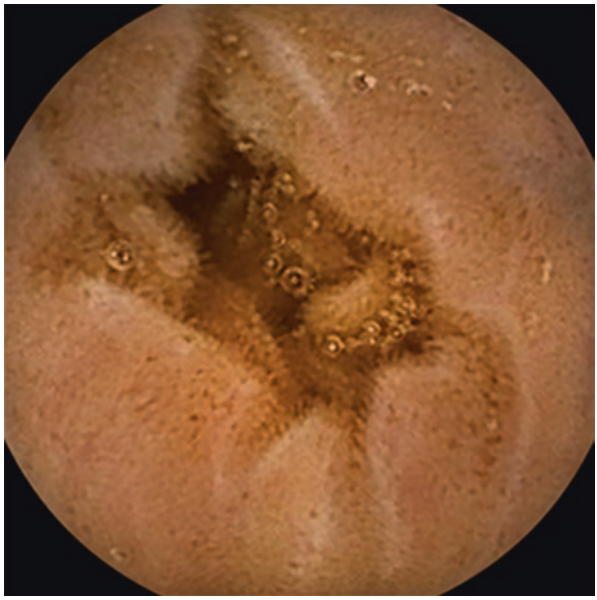

Fig. 9.18 Normal white lines

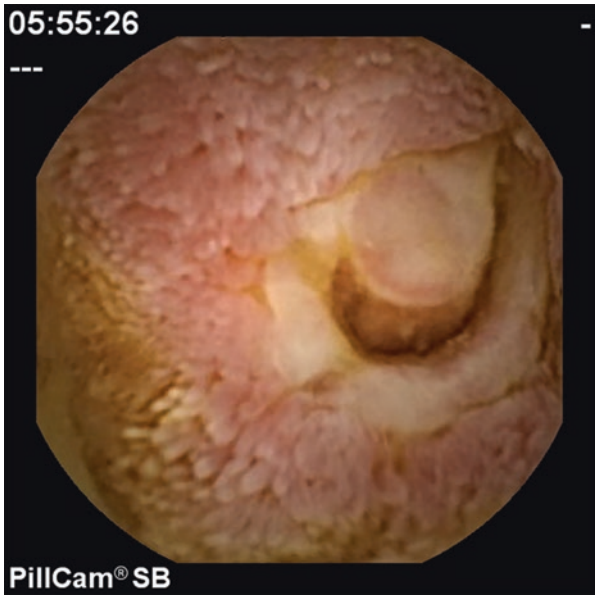

Fig. 9.19 NSAID induced circumferential diaphragms

LEDs of the capsule (Fig. 9.21). Visualization of the mucosa through fluid may magnify a finding even more causing one to overestimate the size and significance of a lesion. In addition, visualization through fluid bubbles may alter the view of the villi, giving a false sense of a smooth mucosal surface with absent villi that can be misinterpreted for pathology such as gluten enteropathy.

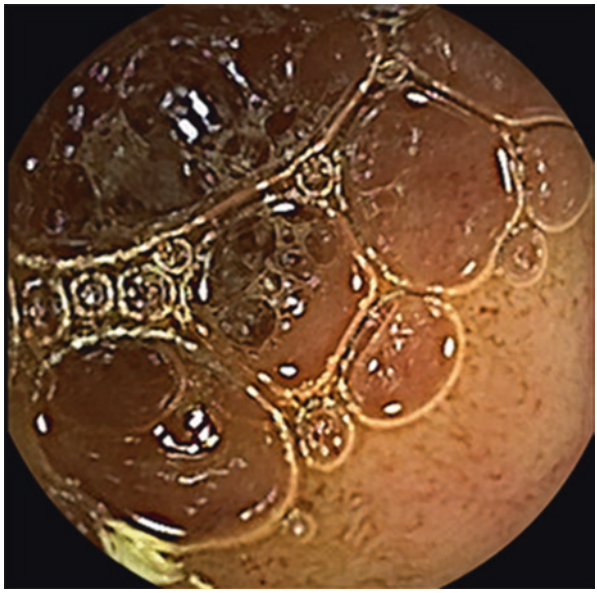

Fig. 9.20 Bubbles; effaced villi

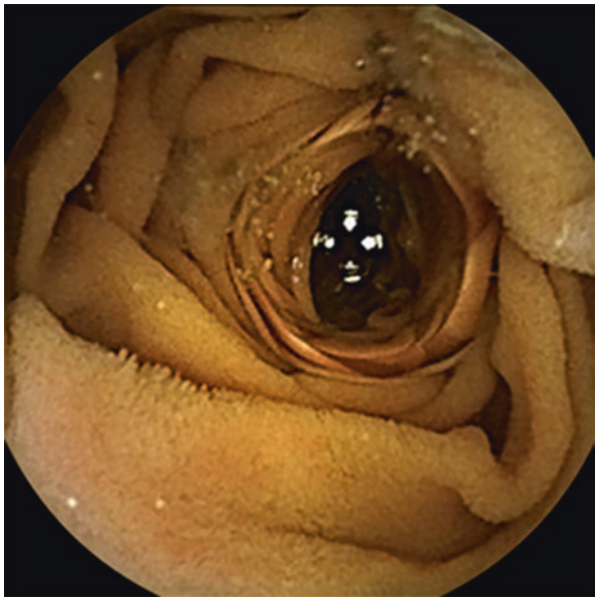

Fig. 9.21 Capsule LED light reflection

Special attention should be paid to the appearance/presence of a "double lumen" in the video images seen on CE. Here too, it is very important to have a detailed knowledge of patient's clinical presentation and medical and surgical histories. The capsule may travel an angulated loop of bowel (Fig. 9.22) where a central fold divides a tunneled appearance of the intestinal passage, find a surgical anastomosis

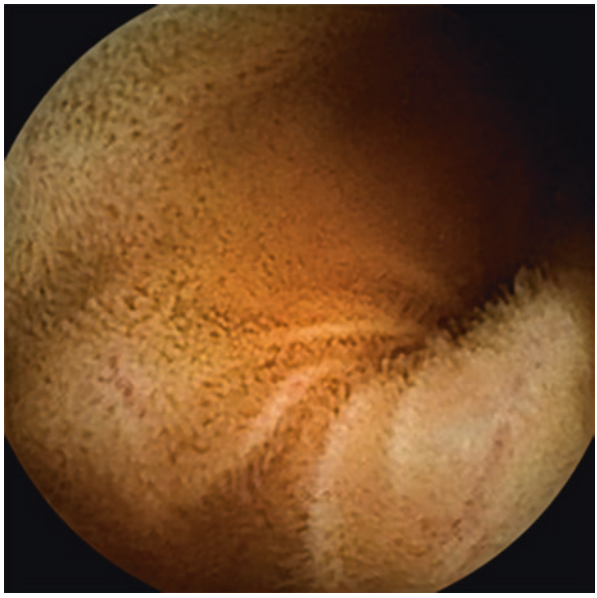

Fig. 9.22 Angulated loop of bowel

(Fig. 9.23) where suture material or a scar would be encountered along the way of perpendicular appearing folds, or come across a small intestinal diverticulum (Fig. 9.24) where a diverticular septum, radial fold pattern, a back wall, or a thin line of a diverticular orifice may be seen. The presence of this "double lumen" in the ileum however should raise the suspicion for Meckel's diverticulum (Fig. 9.25). Rarely, a foreign object such as pill (Fig. 9.26) or other foreign body may be seen within or in proximity of a diverticulum.

Bulges

As discussed in previous chapters, distinguishing a bulge due to extrinsic impression or peristalsis from a loop of small bowel (non-pathologic) from a pathological submucosal mass can be one of the most challenging tasks when interpreting capsule endoscopy images. Typically, innocent bulges have an overlying normal appearing mucosal pattern or vascularity and move with peristalsis (Fig. 9.27). Lipomas, another benign type of bulge lesion, may appear as yellow mobile submucosal well-rounded lesions. A true submucosal mass such as a stromal tumor may have a changed mucosal appearance with splaying, thinning, or stretching of the mucosa (Fig. 9.28). Central umbilication and ulceration may also be present. Adjacent thickened folds and diffuse lymphangiectasia may also attest to the submucosal process. Non-bridging folds are another sign suggesting a submucosal

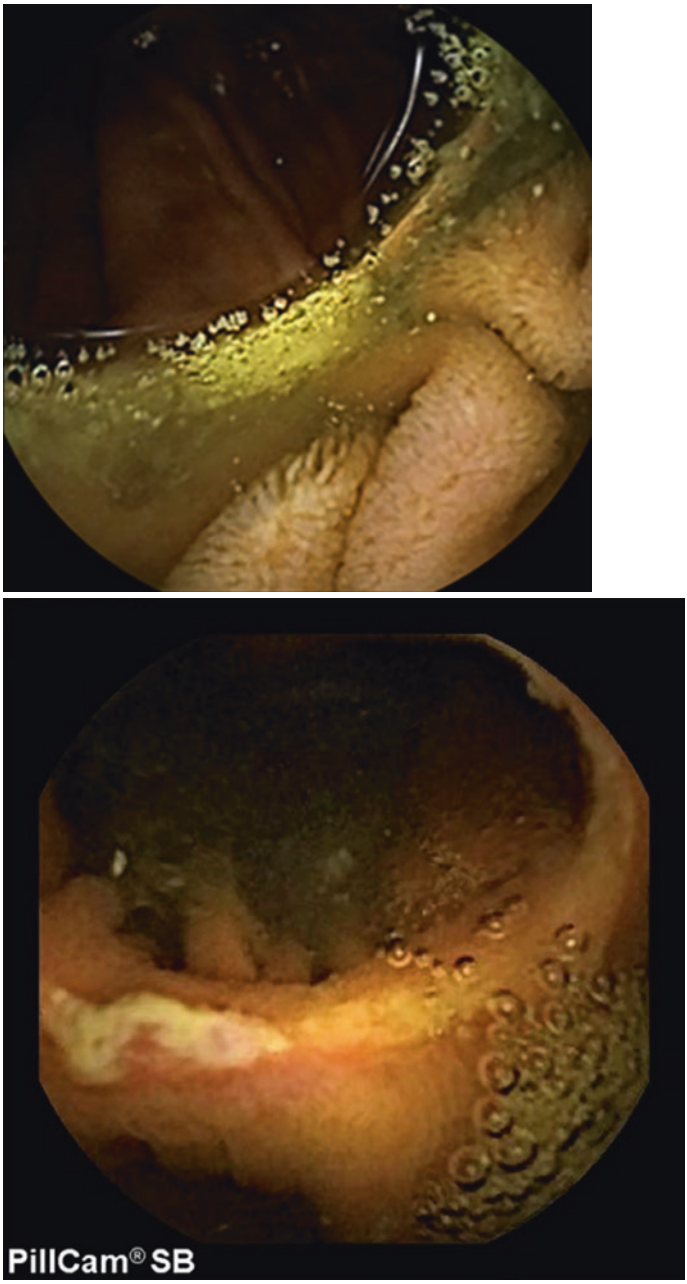

Fig. 9.23 Anastomosis

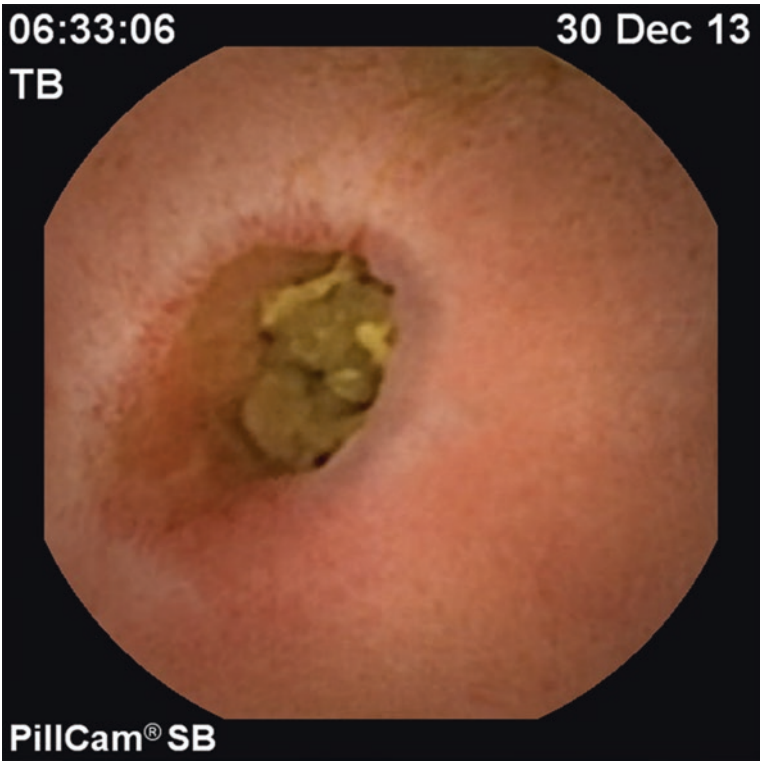

Fig. 9.24 Small intestinal diverticulum

process (folds that come up to but not across the bulge). Development of the SPICE (Smooth Protruding Lesion Index on Capsule Endoscopy) classification, as discussed earlier in this text, may further aid in discriminating submucosal malignant masses from innocent bulges [6], with index >2 carrying 83 % sensitivity and 89 % specificity, as discussed in a previous chapter.

Non-pathological Lesions

The normal and prominent vasculature of the jejunum and ileum should not be mistaken for the presence of an abnormality such as a vascular ectasia. Phlebectasias which are dilated veins are also a normal finding of the small bowel and rectum and are not a cause for bleeding and should be distinguished from varices that can be associated with cirrhosis in the setting or portal hypertension. Nodular lymphoid hyperplasia is typically a normal finding in the terminal ileum, especially in the young. Lymphoid hyperplasia may also take several

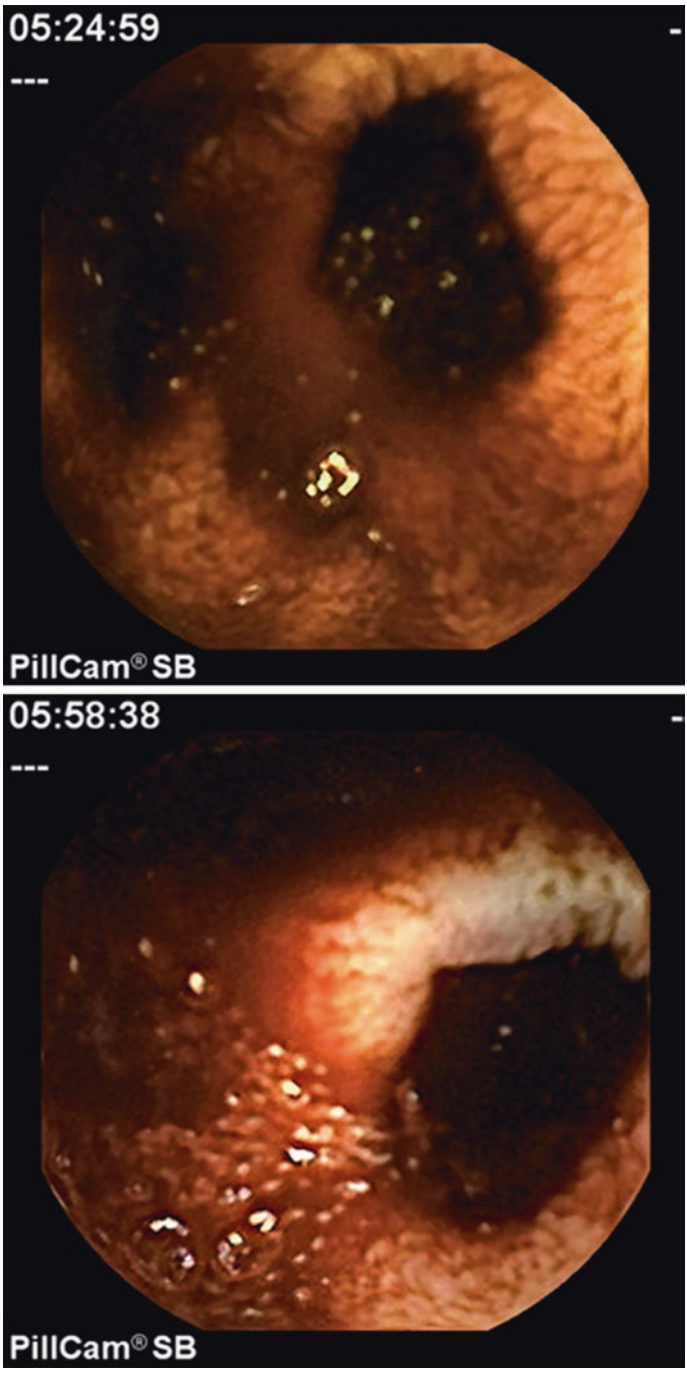

Fig. 9.25 Meckel's diverticulum

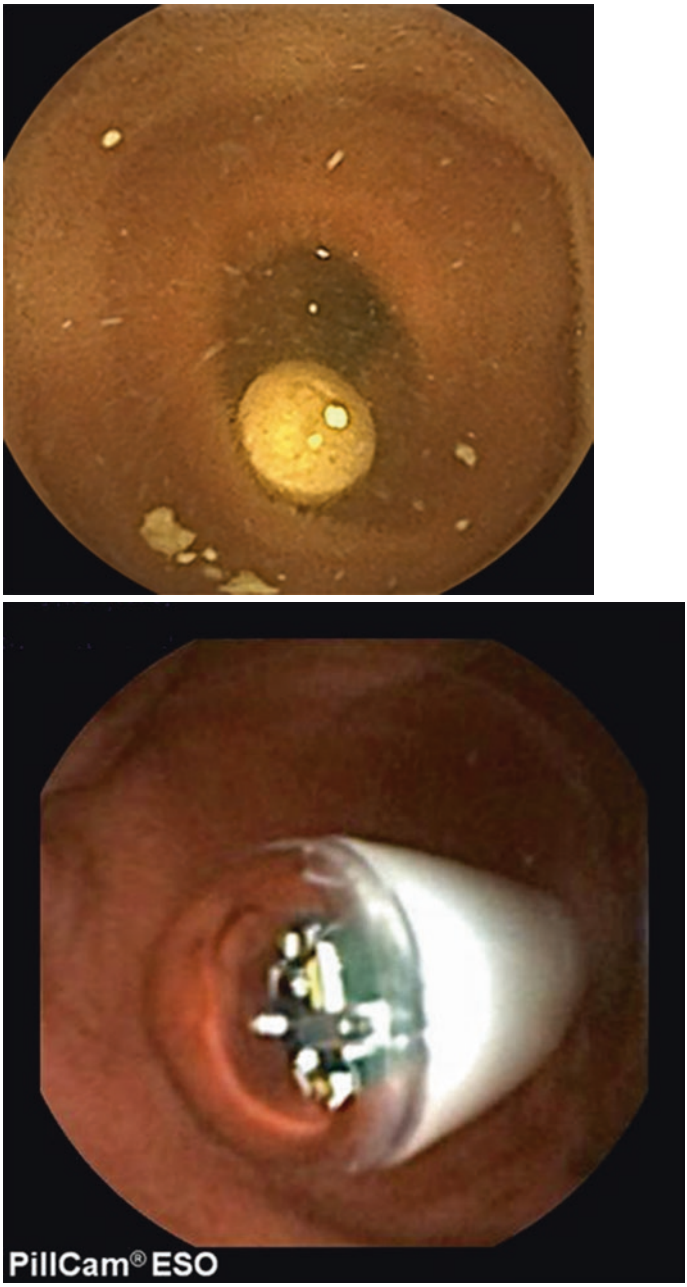

Fig. 9.26 Examples of foreign bodies such as retained pill or capsule

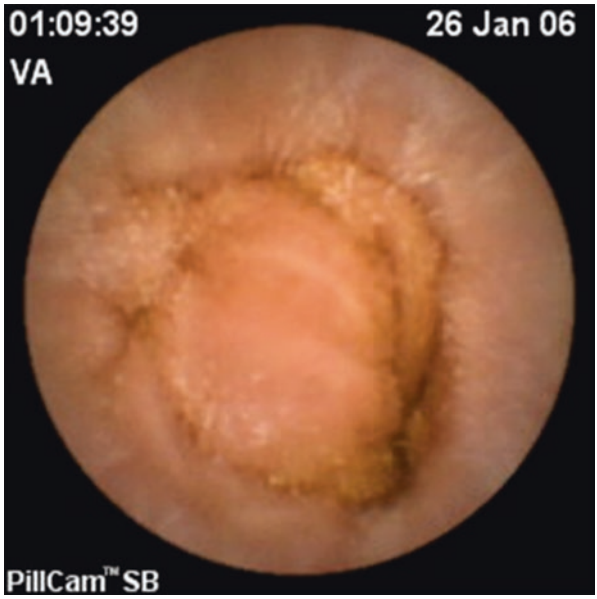

Fig. 9.27 Innocent bulge

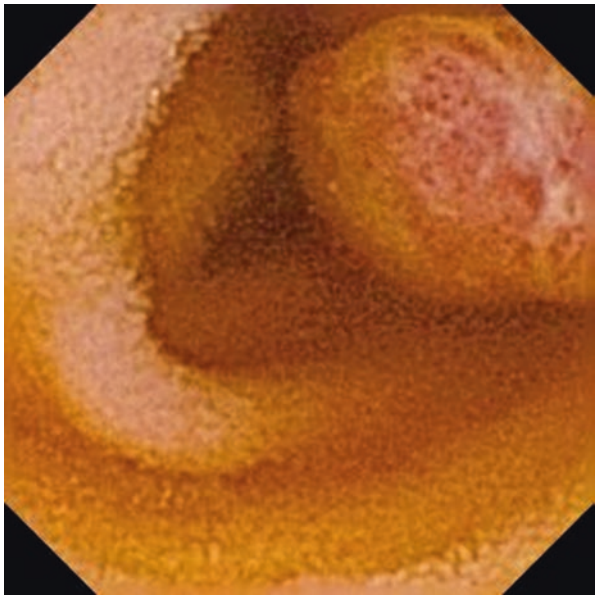

Fig. 9.28 Submucosal mass

other forms. Chylous cysts or cholesterol cysts are yellow submucosal lesions that can be smooth with a normal vascular pattern that may occasionally cross their surface. Lymphangiectasias are dilated lymphatic vessels and that can appear as multiple small white nodules clustered all together or even polypoid

and may be seen throughout the small bowel (Figs. 9.29, 9.30, and 9.31). Chylous cysts and lymphectasias seem to particularly catch the attention of the novice reader due to their high prevalence in the small bowel, especially in the elderly. This should be distinguished from the pathologic presentation of diffuse intestinal lymphangiectasia syndrome, which is represented by diffuse lymphangiectasias seen in the clinical context of a malabsorption syndrome with abdominal

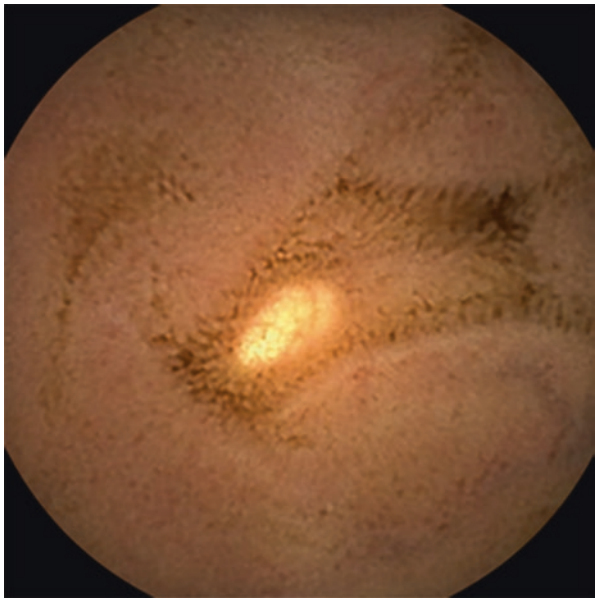

Fig. 9.29 Chylous cyst

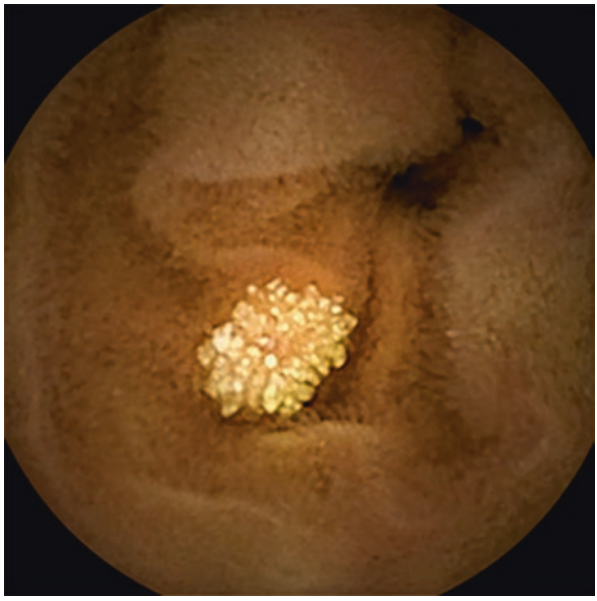

Fig. 9.30 Lymphangiectasia

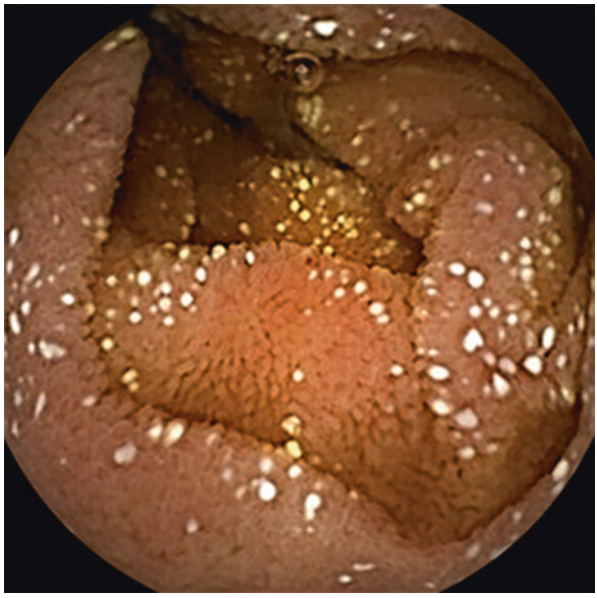

Fig. 9.31 Lymphangiectasia

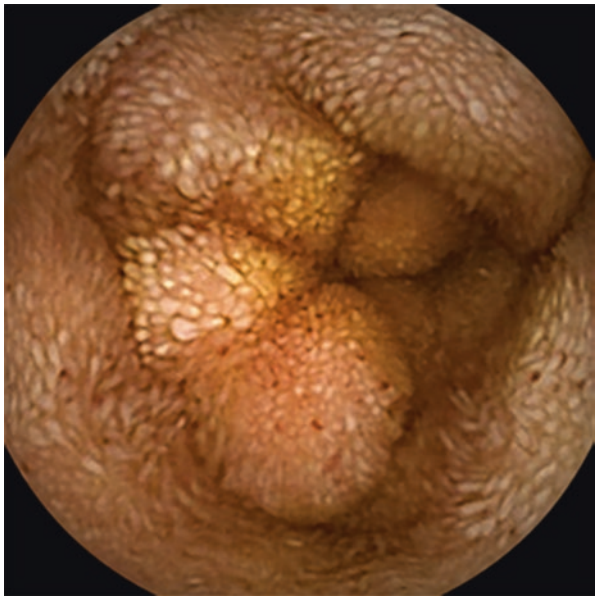

Fig. 9.32 Lymphangiectasia in multiple myeloma

pain, diarrhea, edema, weight loss, hypoproteinemia, lymphocytopenia, and hypogammaglobulinemia. This can be an idiopathic process or secondary to an infectious, inflammatory, or infiltrative pathology such as sarcoidosis and multiple myeloma (Fig. 9.32). Lipomas and xanthomas, which are deposits of lipids and other fat, can be seen as yellow nodules in the small bowel and have no clinical significance (Fig. 9.33).

Small mucosal breaks or erosions even ulcers can be seen in the small bowel and may have no clinical consequence (Figs. 9.34 and 9.35). Some theorize that the healthy bowel may harbor these findings and that their presence may be due to the everyday consequence of minimal inflammation and housekeeping of the GI tract immune system. In Graham's study on NSAIDs, 10 % of healthy controls had

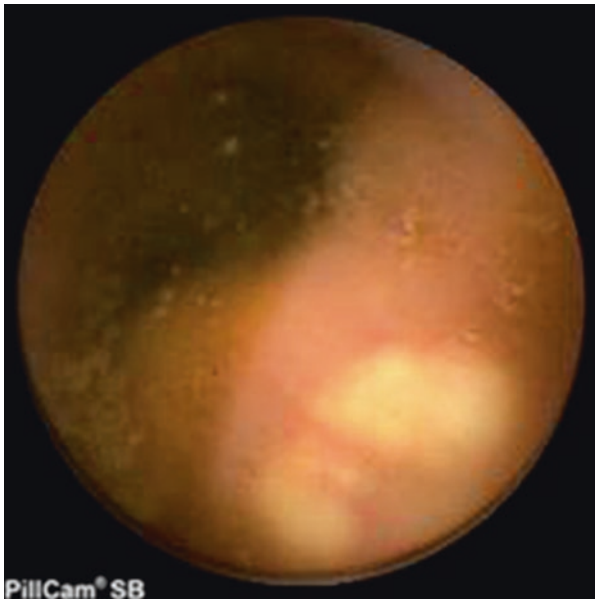

Fig. 9.33 Xanthoma

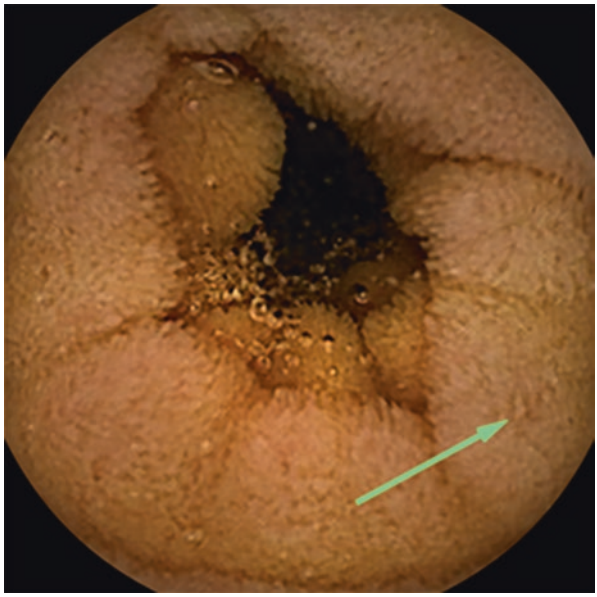

Fig. 9.34 Small erosion

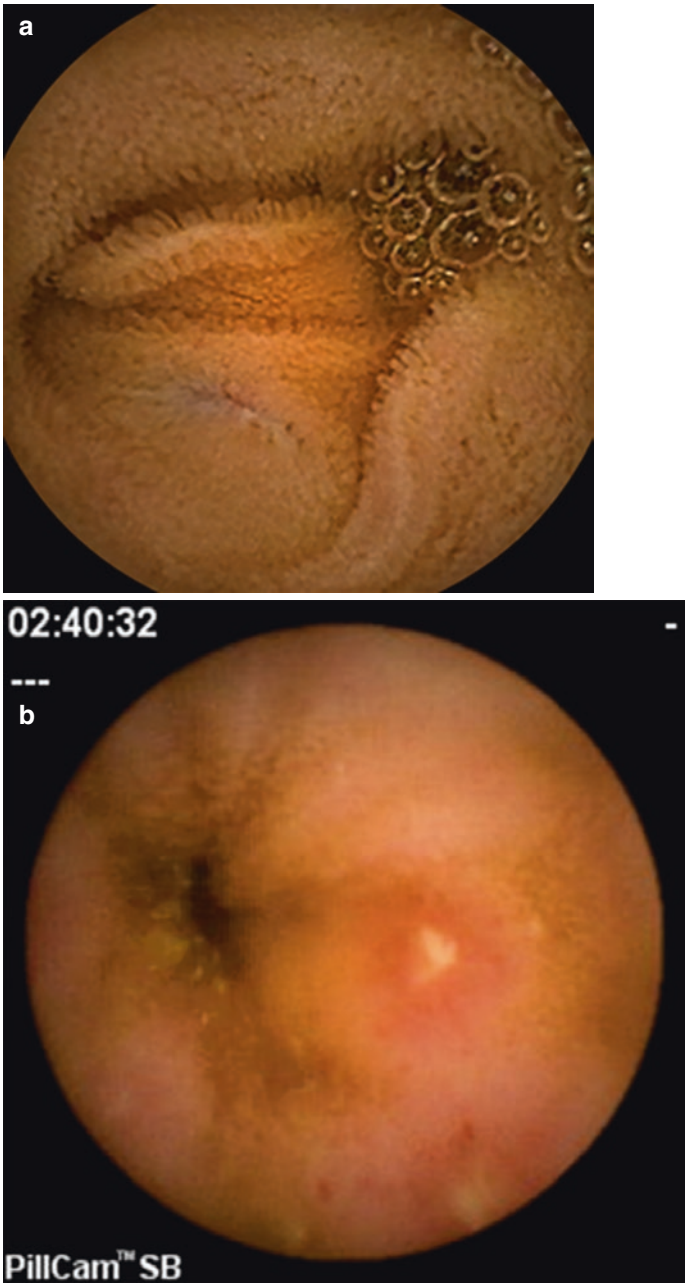

Fig. 9.35 (**a**, **b**) Mucosal breaks

mucosal breaks or erosions at baseline [7]. In addition, 71 % of chronic NSAID users display some degree of small bowel injury when visualized endoscopically. A common problem in evaluating small bowel capsule images is distinguishing

between the normal finding perhaps of a few mucosal breaks and erosions versus that of clinically significant NSAID injury and small bowel Crohn's disease.

Red spots or red dots are another very common finding and are often of no clinical significance. They usually appear similar to that of retinal flame hemorrhages seen on ophthalmic exams and may be related to localized trauma or inflammatory change. These red spots and dots should not be confused with vascular lesions such as angioectasias (Fig. 9.36). Typically angioectasias appear as red, round, serpigi-

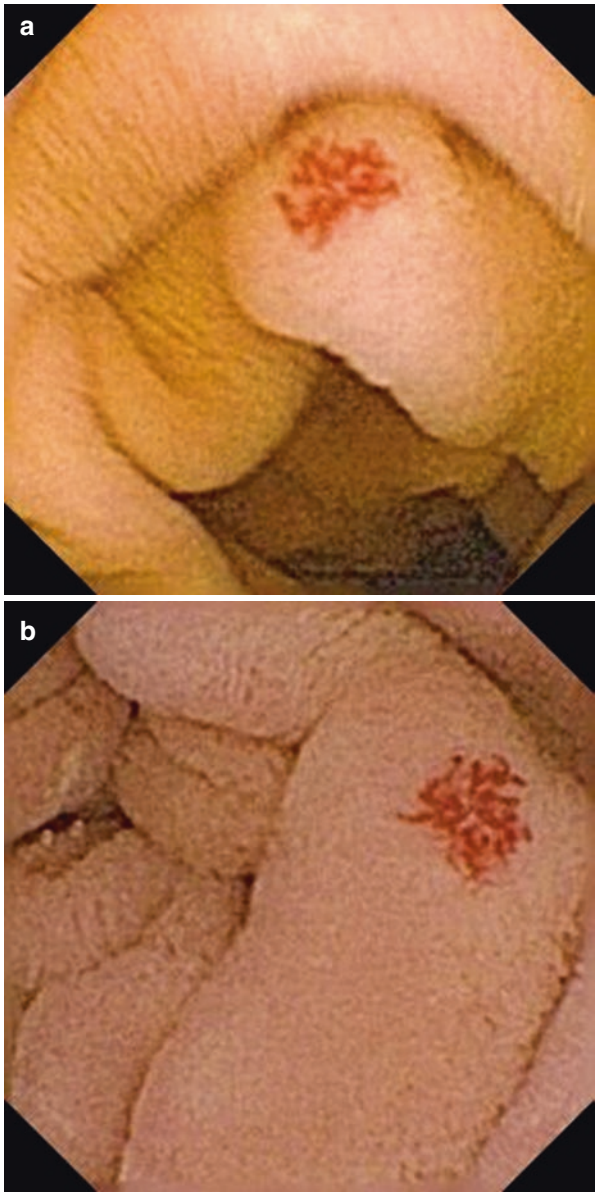

Fig. 9.36 (**a**, **b**) Angioectasias

nous spiderlike lesions. They may be raised or flat. Occasionally, blood vessels can be seen within the lesion. No villi are seen within the vascular structure and usually they are larger than a single villus.

In conclusion, it is important for the capsule endoscopist to become familiar with normal anatomic structures, as well as common artifacts and benign findings that can be seen throughout the small bowel lumen. As one gains more experience reading small bowel studies, comfort level increases and false-positive interpretations of luminal findings can be avoided. In addition, one must always remember to call upon resources, such as online atlas images, local colleagues, as well as regional and national experts, so that together images can be interpreted properly and patient pathology can be diagnosed in an efficient, thorough, and timely manner.

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Chapter 10
Colon Capsule and the Future of Capsule Endoscopy

David J. Hass

In the preceding chapters, we have reviewed the clinical applications and important impact that small bowel capsule endoscopy has had in revolutionizing visualization of the small bowel mucosa. This has allowed for refinement of treatment algorithms, earlier therapeutic interventions in the treatment of small bowel diseases, as well as reclassification of disease and decreased morbidity and mortality. While small bowel capsule endoscopy has established a clear benefit in the treatment and evaluation of obscure gastrointestinal bleeding, inflammatory bowel disease, refractory malabsorption and diarrheal illness, and surveillance in polyposis syndromes, newer devices and technologies are poised to catapult capsule endoscopy technology to the next level. This will allow for even more patients to reap the benefits of this technology.

Several reports have described newer innovations that will potentially allow capsule endoscopy to be even more impactful. As an example, 3-dimensional reconstruction may allow an individual to interpret a capsule study more effectively. Data suggests that this software enhancement can allow for improvement of mucosal textural changes and demarcation of pathology. This allows for better visualization and characterization of ulcerated lesions, angioectasias, and even neoplastic pathology [1, 2]. There are also newly developed software enhancements that allow for novice video capsule endoscopy readers to better distinguish masses from external bulges and bowel peristaltic waves, one of the most challenging skills when interpreting small bowel endoscopy videos [3].

Numerous technical interventions have been introduced in recent years to allow for capsule endoscopes to gain potential therapeutic capacity. Recently, active manipulation of capsule devices has been investigated to allow for more careful evaluation of a particular area of concern. Potential tissue acquisition via a retractable biopsy forceps and targeted drug delivery systems within the capsule are also

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enhancements that will further the impact of capsule technology. With the development of real-time viewing and external manipulation, these concepts of obtaining tissue samples and delivering pharmacologic intervention could become potential realities in the very near future.

Cecal intubation is defined as passage of the colonoscope to a point proximal to the ileocecal valve so the entire cecal caput, including the medial wall of the cecum between the ileocecal valve and the appendiceal orifice, is visible [4]. The rate of successful cecal intubation is critical because interval colon cancers are often thought to localize to the proximal colon [5]. Rates of incomplete colonoscopy can range from 2 to 19 % [6–9]. This number can vary, depending on the population being studied. Broader-based public health populations (i.e., studies sampling an entire regional population) often have higher rates of incompletion [10, 11]. Populations studied in a veterans' hospital and corporate screening programs reveal much higher rates of completion, approximating 97 % [10, 11].

There are many reasons why an individual patient's colonoscopy may result in an incomplete study. Prior abdominal surgeries leading to adhesions within the abdominal cavity can make advancement of the colonoscope challenging. Other factors that could lead to an incomplete study would include looping of the colonoscope during the procedure due to a redundant colon; patient discomfort; obstructing luminal lesions such as a stricture, stenosis, or neoplasm of the colonic lumen; or poor preparation. Population-based studies have shown that women are more likely than men to have incomplete colonoscopic exams [12–14]. The likelihood of an incomplete colonoscopy increases with older age and is more strongly associated with private office setting (vs. academic hospital setting) [7] Given that there are significant risk factors for incomplete colonoscopy, a technology that will allow for complete visualization of the mucosa that is beyond the reach of the conventional colonoscope would be a welcome addition to the arsenal of endoscopic diagnostic tools.

Colon capsule endoscopy (CCE) is a novel technology that has been developed to enable complete endoscopic imaging of the colonic mucosa in a minimally invasive fashion. First introduced in 2006, the colon capsule has undergone multiple programmatic and design changes since that time. The role of CCE in the algorithm for colorectal cancer screening and its clinical niche are still developing. Currently, there are two FDA-approved indications for CCE. The capsule is intended to provide visualization of the colon, and it may be used for detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, when a complete evaluation of the colon was not technically possible.

Second, it is indicated for the detection of colon polyps in patients with evidence of gastrointestinal bleeding of lower gastrointestinal origin. This applies to patients with major risks for colonoscopy or moderate sedation, but who could tolerate colonoscopy and moderate sedation in the event that a clinically significant colonic abnormality is identified on colon capsule endoscopy. These two indications provide a tool for physicians to ensure a comprehensive visualization of the colonic mucosa so as to detect pathology earlier in order to decrease morbidity and mortality from lower gastrointestinal tract lesions.

Fig. 10.1 Pillcam Colon 2 capsule (All rights reserved. Used with the Permission of Medtronic)

There have been two generations of colon capsule endoscopy (CCE) technology. Today, the second-generation colon capsule system, i.e., Pillcam Colon2™ (Medtronic), which was first introduced in 2009, is the device presently being implemented in the United States and abroad (Fig. 10.1). The capsule measures 11.6 × 31.5 mm, similar to that of a large prenatal vitamin. It is coated with a smooth casing, thereby providing ease of ingestion. The device is a dual-headed capsule featuring two cameras. Each camera has an expanded field of view measuring 172 °, enabling a near 360 ° view of the colonic lumen. In addition, the colon capsule is equipped with an adaptive frame rate. This allows for different rates of image capturing to occur depending upon the transit speed of the capsule. The device alternates between 4 and 35 frames per second and is dynamic in its ability to adjust this image capturing. This allows for conservation of the battery power when the capsule is fixed in a single position.

The preparation for CCE is slightly more extensive than traditional small bowel capsule endoscopy and that of traditional optical colonoscopy (Fig. 10.2). In clinical trials and in practice, this preparation though it appears daunting, has been well tolerated. Quality preparation prior to capsule ingestion is critical to adequate mucosal visualization in CCE given the inability to lavage, suction, and insufflate the colonic lumen as one would with conventional optical colonoscopy. In clinical trials when the preparation detailed above is adhered to, an 89 % excretion rate has

Before ingestion of PillCam COLON :

- 4 (12mg) Senna tablets- 2 days prior to the procedure
- 2 liters PEG the evening prior to the procedure
- 2 liters PEG the morning of the procedure

After ingestion of PillCam COLON :

- Reglan: If necessary during procedure for gastric emptying*
- 2 boosts of SUPREP® -to enhance capsule propulsion and maintain adequate cleansing
  - 6 oz. SUPREP** solution
  - 3 oz. SUPREP** solution*
- Suppository, if needed*
- Light meal, if needed*

***Indicates *potential* procedure requirements**

****** SUPREP © Braintree Laboratories Inc., Braintree, MA.**

Fig. 10.2 Bowel preparation for the CCE as used in the U.S. Registration Trial

been achieved. Figures 10.3, 10.4, and 10.5 detail the impressive image quality that is obtained with the current CCE technology. Examples of diverticular disease, ulcerative colitis, polypoid lesions, and tumors are seen in these impressively clear optics. Of note, sessile lesions can appear more prominent on CCE due to the lack of air insufflation that could potentially flatten lesions as is seen with optical colonoscopy.

Prototypes of a newer capsule implement a drug delivery system that is magnetically controlled with two compartments containing components that create a chemical reaction and production of carbon dioxide when mixed, thereby allowing for air insufflation and theoretical better visualization of the colonic mucosa [15]. As technology continues to evolve, there will no doubt be continual improvements and refining of this exciting technology that will only enhance its capabilities.

While the role of CCE continues to evolve, it has become clear from the literature that CCE appears to have increased sensitivity and specificity compared with both barium-based and cross-sectional imaging in terms of diagnostic yield and impact for the detection of neoplastic lesions of the colon. Thus, CCE could be poised to replace these technologies in the realm of colorectal mucosa visualization if further studies yield similar clinical results. Spada et al. have demonstrated in the cases of incomplete colonoscopy that CCE demonstrated an increased sensitivity

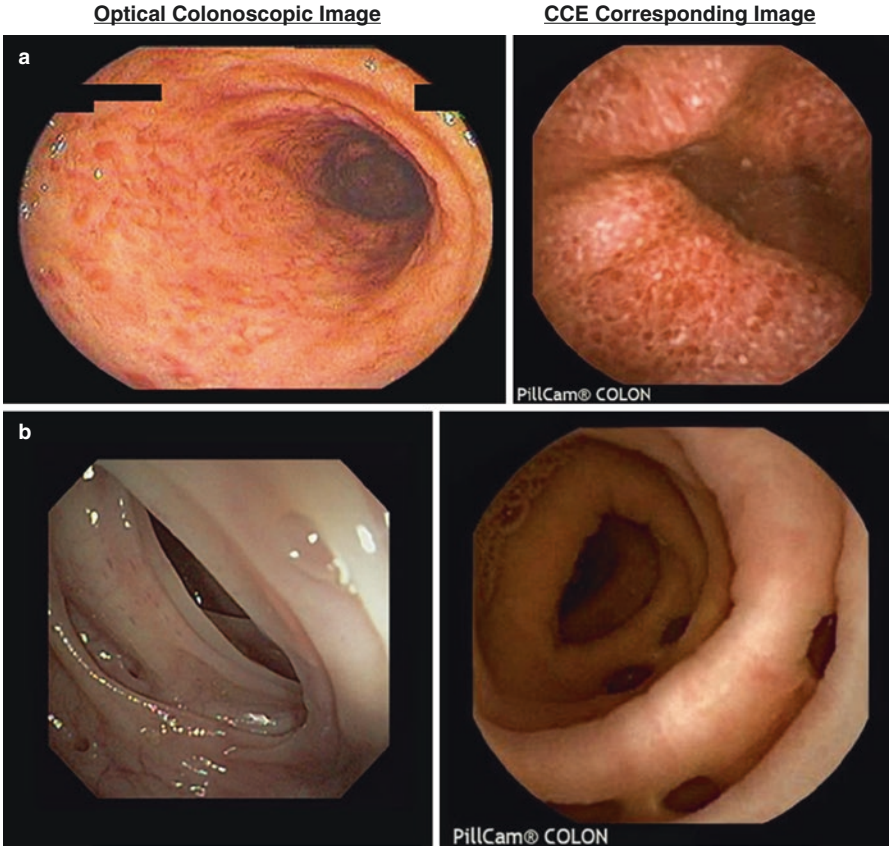

Fig. 10.3 CCE versus optical colonoscopy images—examples of ulcerative colitis and diverticular disease, as seen on the two different modalities (All rights reserved. Used with the Permission of Medtronic)

for polyps both 6 and 10 mm in size compared with CT colonography, thereby implying that the overall diagnostic yield of CCE is improved and that CCE is a feasible and safe tool, superior to that of CTC. CCE demonstrated visualization of polyps in more than twice the patients than did CT colonography [16].

There are contraindications to the ingestion of the colon capsule technology. Patients with known or suspected GI obstruction, strictures, or fistulae based on the clinical picture or pre-procedural testing and profile should not use the device. Patients with cardiac pacemakers (PPM) or other implanted electro-medical devices are also contraindicated from partaking in the technology. This is based on the theoretical concern of electromagnetic interference between programmable implanted devices and the capsule itself. While this is technically considered a "black box warning" on the capsule packet insert, to date there have been no in vivo reports of cardiac pacemaker or implantable defibrillator malfunction. Importantly, with the indication for CCE recently having been expanded to evaluate for colonic

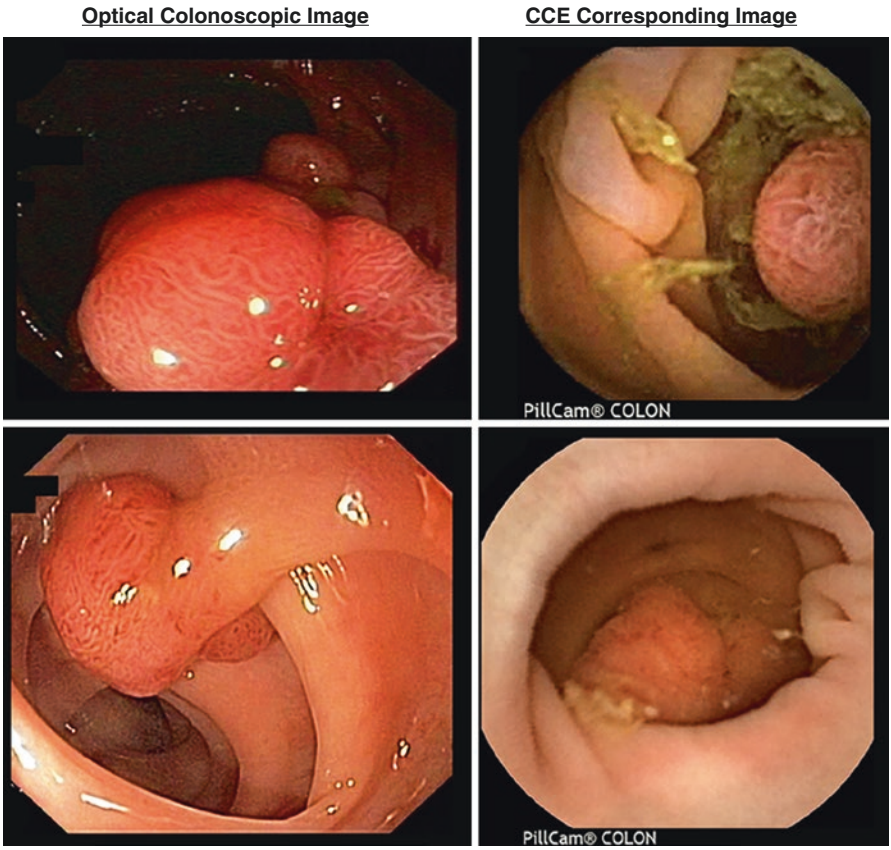

Fig. 10.4 Examples of both sessile and pedunculated polyps as seen on both optical colonoscopy (*left column*) and CCE (*right column*) (All rights reserved. Used with the Permission of Medtronic)

pathology as a source of lower gastrointestinal bleeding, it may stand to reason that this patient population with PPMs or ICDs may be a population that would derive significant benefit clinically from the technology, as these patients are more prone to requiring anticoagulants, antiplatelet agents, or direct thrombin inhibitors secondary to their underlying cardiac pathology. A risk/benefit discussion with the patient's electrophysiologist and an informed discussion with the patient are both paramount in determining if implementation may be appropriate in this clinical situation.

Another population of patients who have a technical contraindication to oral ingestion of CCE technology would be those with swallowing disorders or intestinal transit difficulties. Mechanical intraluminal impediments such as Schatzki rings, esophageal webs, strictures, or Zenker's diverticulum preclude oral ingestion. Motility disorders such as achalasia also would prevent the capsule from passing through the esophageal lumen. In addition, oropharyngeal dysphagia related to conditions such as dementia, cerebrovascular events, or neuromuscular disorders such as Parkinson's disease or multiple sclerosis would prevent oral ingestion similar to

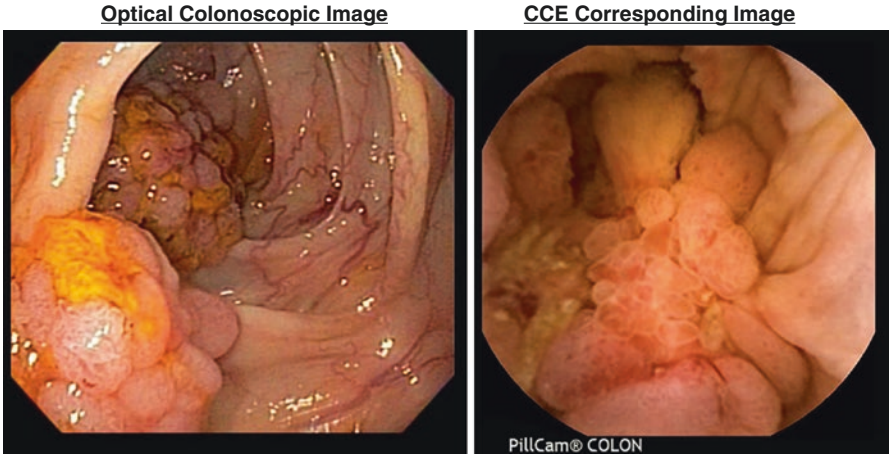

Fig. 10.5 Additional examples of sessile polypoid lesions as seen on the two different modalities (All rights reserved. Used with the Permission of Medtronic)

that of the small bowel capsule. Pediatric or elderly patients also may have a difficult time ingesting the capsule. Finally, intestinal dysmotility transit issues due to narcotics and psychotropic drugs or gastroparesis may present an issue to ensure that oral ingestions will result in a complete study. Therefore, similar to the small bowel capsule, the CCE device may be placed endoscopically with similar techniques as described in previous chapters.

A final contraindication for CCE would be in patients with known allergies or contraindications to the medications and preparation agents used in the standard protocol, as described in the relevant instructions for use. Thus, one must be mindful when administering the preparation for CCE.

The efficacy of CCE has been studied in multiple trials and continues to be evaluated in a variety of patient populations. Two prospective multicenter studies comparing Pillcam Colon2™ to optical colonoscopy demonstrated impressive sensitivity, specificity, and negative predictive values. Sensitivity of 84–89 % and specificity of 89–95 % were demonstrated in polyps greater than 10 mm. Importantly, the capsule was also noted to have a negative predictive value of 95 % for colonic polyps >10 mm and 100 % sensitivity for colorectal cancer (Table 10.1). The explanation for the low specificity of CCE for colonic polyps ≥6 mm is due to the rigorous nature of the study in terms of scrutinizing size matching of polyps. Polyps that measured on CCE greater than 6 mm but were considered <6 mm on optical colonoscopy were considered false positives and therefore impacted the specificity values.

CCE has also been studied in a multicenter prospective study to evaluate its accuracy in detecting colorectal adenomatous polyps in a screening population. Rex et al. [19] studied 884 patients, of which 695 were included in the final analysis. This was a prospective multicenter trial, involving 16 sites, ten in the United States and six in Israel. This was performed in an average-risk screening population, those aged 50 or older with a limited family history of colorectal cancer. Colon capsule

Table 10.1 Comparative sensitivities and specificities of Pillcam Colon™ to Optical Colonoscopy in Clinical Studies

	# of pts	>6 mm	>6 mm	>10 mm	>10 mm
		Sensitivity (%)	Specificity (%)	Sensitivity	Specificity (%)
Eliakim [17]	98	89	76	88	89
Spada [18]	109	84	64	88	95

endoscopy was performed first, and then one of five central readers interpreted the study. Then, conventional optical colonoscopy (OC) was performed several weeks later by a blinded endoscopist. The value of a delay between studies was that the results of the CCE were known and allowed one to determine if false positives or true positives were then to be noted on optical colonoscopy. Lesion size was determined using the forceps and size estimation tool during OC and CCE, respectively.

As previously mentioned, 884 patients were enrolled and 695 patients were included in the polyp analysis. The mean age of subjects was 57, and 56 % of the study participants were female. From an analysis perspective, the colon was divided into five segments and capsule per segment analysis was performed, which was more rigorous than in previous trials evaluating CCE efficacy [19]. Sensitivity and specificity of the capsule for adenomatous polyp detection ≥6 mm were 88 % (95 % CI 82–93) and 82 % (95 % CI, 81–83 %), respectively. For polyps ≥10 mm, the sensitivity and specificity were 92 % (95 % CI, 82–97 %) and 95 %, (95 % CI, 94–95 %), respectively [19]. Importantly, as in previous studies, all cases of colorectal cancer were detected as well. This trial also revealed a lower sensitivity for sessile serrated polyps with CCE. The reasons for this are unclear and this remains an active area of research. CCE has also been evaluated as a screening filter test in patients with a positive fecal immunohistochemical test (FIT). Holleran et al. evaluated individuals with a positive FIT and compared CCE with optical colonoscopy [20]. CCE demonstrated effectiveness in detecting both significant polyps and cancer in FIT-positive patients and a negative predictive value for any polyp and significant lesions of 90 % and 96 %, respectively [20]. The authors suggest that CCE could serve as an initial screening test based on this data so as to improve access to patients for colorectal screening. Based on the aforementioned studies, CCE displays tremendous potential in becoming an impactful tool in the arsenal of weaponry for detecting and preventing colorectal polyps and malignancies, respectively, to thereby decrease their morbidity and mortality.

CCE has also been evaluated in the assessment of inflammatory bowel disease. As endoscopy-driven treatment algorithms have emerged, CCE is poised to play a significant role in establishing the diagnosis of IBD, disease monitoring, assessing for mucosal healing, and evaluating for postsurgical disease recurrence. As mucosal healing is associated with sustained clinical remission, lower hospitalization rates, and lower surgical resection rates, CCE can be implemented as a noninvasive, clinically relevant tool that will help to assess efficacy of a given treatment regimen. Sung et al. evaluated CCE in assessing colonic inflammation. This study reported a sensitivity of 89 % in the detection of active colonic inflammation and a specificity of 75 % [21]. Oliva et al. recently published a prospective study looking to determine the accuracy of CCE in assessing disease activity of the small bowel and colon

in a pediatric Crohn's disease patient population [22]. Forty consecutive patients were enrolled with a mean age of 13.1 years. Patients underwent an extensive evaluation inclusive of magnetic resonance enterography, CCE, and optical colonoscopy with ileal intubation. Sensitivity of CCE to detect colonic inflammation was 89 % and specificity was 100, thereby demonstrating, albeit in a small study, the high diagnostic accuracy of this technology [22]. Another study was performed to evaluate the role of CCE in IBD-evaluated 30 consecutive pediatric patients with ulcerative colitis. In this trial, the sensitivity of CCE for IBD was 96 % and the specificity was 100 % [23]. Positive and negative predictive values for CCE were 100 % and 85 %, respectively. In addition, CCE was more favorably tolerated [23].

Though CCE is truly an exciting and promising technological advance, several limitations still exist. First, the device is only a diagnostic device. There is not currently the ability to sample an abnormal area or deliver a therapeutic treatment regimen to a diseased segment of bowel with the current technology. However, this is only a matter of time before developments are refined and the aforementioned becomes a potential reality. In addition, from a practicality standpoint, CCE does require a significant investment of time to read one study as well as to become trained to understand the nuances of the software.

As the future of capsule endoscopy evolves, one can postulate that this technology will become more utilized globally. CCE is deemed to be a safe procedure, and to date, there have been no serious adverse related events reported with ingestion. An inability to swallow the capsule has been reported in less than 1 % of patients, but this can be easily overcome by implementing a capsule endoscopy delivery system (US endoscopy). Currently, the European Society of Gastrointestinal Endoscopy (ESGE) has proposed guidelines suggesting that CCE can be used in average-risk patients, in patients with a history of previous incomplete colonoscopy, in patients unwilling to undergo a conventional optical colonoscopy, or for those in whom optical colonoscopy is not possible or contraindicated [24]. The notion that this technology yields effective sensitivity and specificity for adenomatous polyps, and the efficiency and convenience of CCE, in that it can be performed in an outpatient setting without the need for sedation, in a patient-safe and patient-friendly manner, highlights the attractiveness of this technology for the general population. These features further add to the utility of the technology to potentially increase patient compliance with the evaluation of bowel pathology such as obscure gastrointestinal bleeding and colorectal cancer screening. The cost-effectiveness of CCE still warrants further evaluation and this will likely be the subject of ongoing research.

The continued new advancements in the realm of both small bowel and colon capsule endoscopy have afforded gastroenterologists the opportunity to evaluate areas of both the small bowel and colon in a more comprehensive and clinically meaningful manner. As these technologies allow for noninvasive visualization of areas that conventional enteroscopy and colonoscopic evaluation may not be able to see, in a sedation free manner with minimal risk, the potential for implementation and utilization of these technologies is tremendous. One can hope that in the not so distant future, the new frontier of capsule endoscopy will be reached, in that the device will become not only diagnostic but therapeutic as well.

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