

## Antibiotic prophylaxis for GI endoscopy

*This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed, supplemented by accessing the "related articles" feature of PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).*

*This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.*

### BACKGROUND

Bacterial translocation of endogenous microbial flora into the bloodstream may occur during an endoscopy because of mucosal trauma related to the procedure. Endoscopy-related bacteremia carries a small risk of localization of infection in remote tissues (ie, infective endocarditis). An endoscopy may also result in local infections in which

a typically sterile space or tissue is breached and contaminated by an endoscopic accessory or by contrast injection. This guideline discusses infectious complications related to an endoscopy and makes recommendations for periprocedural antibiotic therapy.

### BACTEREMIA ASSOCIATED WITH ENDOSCOPIC PROCEDURES

Bacteremia can occur after endoscopic procedures and has been advocated as a surrogate marker for infective endocarditis (IE) risk. However, clinically significant infections are extremely rare. Despite an estimated 14.2 million colonoscopies and 2.8 million flexible sigmoidoscopies, and perhaps as many upper endoscopies, performed in the United States each year,<sup>1</sup> only approximately 15 cases of IE have been reported, with a temporal association with an endoscopic procedure. There are no data that demonstrate a causal link between endoscopic procedures and IE. Similarly, there are no data that demonstrate that antibiotic prophylaxis before endoscopic procedures protects against IE.

#### High-risk procedures

The highest rates of bacteremia have been reported with esophageal dilation and sclerotherapy. In 3 prospective studies, the rate of bacteremia after esophageal bougienage was demonstrated to be 12% to 22%.<sup>2-4</sup> The cultured organisms are usually commensal to the mouth. In 1 study, *Streptococcus viridans* was the organism isolated in 79% of cases.<sup>2</sup> Bacteremia may be more frequent with the dilation of malignant strictures than with benign strictures.<sup>3</sup> Bacteremia may also be more frequent with the passage of multiple dilators rather than with a single dilation.<sup>3</sup>

Estimates of bacteremia associated with variceal sclerotherapy have ranged from 0% to 52%, with a mean of 14.6%.<sup>5-8</sup> Endoscopic variceal ligation, which has largely supplanted sclerotherapy, has been associated with bacteremia rates of 1% to 25%, with a mean rate of 8.8%.<sup>9-14</sup>

Whereas, an ERCP in patients with nonobstructed bile ducts has been associated with a relatively low rate of bacteremia, of 6.4%, it rises to 18% in the setting of obstruction of the biliary tree with stones or a tumor.<sup>15</sup>

#### Low-risk procedures

A gastroscopy, with or without a biopsy, is associated with rates of bacteremia that range from 0% to 8%, with

**TABLE 1. Grades of recommendation\***

Grade of recommendation	Clarity of benefit	Methodologic strength/ supporting evidence	Implications
1A	Clear	Randomized trials without important limitations	Strong recommendation; can be applied to most clinical settings
1B	Clear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Strong recommendation; likely to apply to most practice settings
1C+	Clear	Overwhelming evidence from observational studies	Strong recommendation; can apply to most practice settings in most situations
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Weak recommendation; alternative approaches may be better under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; alternative approaches likely to be better under some circumstances
3	Unclear	Expert opinion only	Weak recommendation; likely to change as data become available

\*Adapted from Guyatt G, Sinclair J, Cook D, et al. Moving from evidence to action: grading recommendation: a qualitative approach. In: Guyatt G, Rennie D, editors. Users' guides to the medical literature. Chicago: AMA Press; 2002. pp. 599–608.

a mean frequency of 4.4%.<sup>16-24</sup> The bacteremia observed was usually short lived (<30 minutes) and not associated with infectious complications. Rates of bacteremia associated with a colonoscopy range from 0% to 25%, with a mean frequency of 4.4%.<sup>15</sup> Rates of bacteremia with a flexible sigmoidoscopy range from 0% to 1%.<sup>25,26</sup>

Prospective studies in patients who are undergoing EUS-guided FNA (EUS-FNA) of cystic or solid lesions along the upper-GI tract indicate a low prevalence of procedure-related bacteremia, which ranges from 4.0% to 5.8%.<sup>27-30</sup> Infectious complications, such as acute febrile illness, abscess, or other infections, are rare. The frequency of bacteremia after an EUS, with or without FNA, therefore, is within the range of that for a diagnostic upper endoscopy.

### BACTEREMIA ASSOCIATED WITH ROUTINE DAILY ACTIVITY

Transient bacteremia occurs frequently during routine daily activity, often at rates exceeding those associated with endoscopic procedures. Brushing and flossing of teeth have been associated with rates of bacteremia of 20% to 68%, use of toothpicks with rates of 20% to 40%, and even activity that might be considered entirely physi-

ologic, eg, chewing food, has been associated with rates of bacteremia that range from 7% to 51%.<sup>31</sup> Given the relative rarity with which most individuals undergo endoscopic procedures, the frequency (and risk) of endoscopy-related bacteremia is trivial compared with the frequency of bacteremia encountered with routine daily activity. This provides a strong rationale for not administering antibiotic prophylaxis for IE before endoscopic procedures.

### ANTIBIOTIC PROPHYLAXIS FOR GI ENDOSCOPIC PROCEDURES

The purpose of antibiotic prophylaxis during GI endoscopy is to reduce the risk of iatrogenic infectious complications. Antibiotic prophylaxis against endoscopically induced local or systemic infections were previously discussed in detail in a guideline published by the ASGE, "Guidelines for antibiotic prophylaxis for GI endoscopy."<sup>32</sup> This guideline is an update of the prior recommendations and is summarized in Table 2. Previous ASGE guidelines recommended antibiotic prophylaxis for IE. These new recommendations represent a substantial change from the prior guidelines.

**TABLE 2. Antibiotic prophylaxis for endoscopic procedures**

Patient condition	Procedure contemplated	Goal of prophylaxis	Periprocedural antibiotic prophylaxis	Grade of recommendation; comments
All cardiac conditions	Any endoscopic procedure	Prevention of infective endocarditis	Not indicated	1C+
Bile-duct obstruction in the absence of cholangitis	ERCP with complete drainage	Prevention of cholangitis	Not recommended	1C
Bile-duct obstruction in absence of cholangitis	ERCP with anticipated incomplete drainage (eg, PSC, hilar strictures)	Prevention of cholangitis	Recommended; continue antibiotics after the procedure	2C
Sterile pancreatic fluid collection (eg, pseudocyst, necrosis), which communicates with pancreatic duct	ERCP	Prevention of cyst infection	Recommended	3
Sterile pancreatic fluid collection	Transmural drainage	Prevention of cyst infection	Recommended	3
Solid lesion along upper-GI tract	EUS-FNA	Prevention of local infection	Not recommended	1C; low rates of bacteremia and local infection
Solid lesion along lower-GI tract	EUS-FNA	Prevention of local infection	Insufficient data to make firm recommendation	Endoscopists may choose on a case by case basis; a single study indicates a low risk of infection
Cystic lesions along GI tract (including mediastinum)	EUS-FNA	Prevention of cyst infection	Recommended	1C
All patients	Percutaneous endoscopic feeding tube placement	Prevention of peristomal infection	Recommended	1A; decreases risk of soft-tissue infection
Cirrhosis with acute GI bleeding	Required for all patients, regardless of endoscopic procedures	Prevention of infectious complications and reduction of mortality	Upon admission	1B; risk for bacterial infection associated with cirrhosis and GI bleeding is well established
Synthetic vascular graft and other nonvalvular cardiovascular devices	Any endoscopic procedure	Prevention of graft and device infection	Not recommended	1C+; no reported cases of infection associated with endoscopy
Prosthetic joints	Any endoscopic procedure	Prevention of septic arthritis	Not recommended	1C+; very low risk of infection

## PREVENTION OF INFECTIVE ENDOCARDITIS

Antibiotic prophylaxis against IE was last discussed in detail in the 2003 ASGE guidelines.<sup>32</sup> Several other professional societies have since published new or updated guidelines on antibiotic prophylaxis for IE.<sup>33,34</sup> Guidelines of different professional societies on antibiotic prophylaxis during GI endoscopy are not uniform, and adherence to these guidelines varies in clinical practice.<sup>35,36</sup> Recommendations for antibiotic prophylaxis against IE were updated in this guideline to reflect the recent major changes in recommendations of the American Heart Association (AHA).

The AHA recently revised their guidelines for prophylaxis of IE,<sup>31</sup> and their new recommendations depart significantly from their prior 1997 guidelines. For endoscopic practice, a landmark change is that administration of prophylactic antibiotics solely to prevent IE is not recommended for patients who undergo GI-tract procedures.

The AHA bases its new recommendations on several lines of evidence, including the following: (1) cases of IE associated with GI procedures are anecdotal, (2) no data demonstrate a conclusive link between GI procedures and the development of IE, (3) no data exist that demonstrate that antibiotic prophylaxis prevents IE after GI-tract procedures, (4) IE is more likely to be caused by

bacteremia that results from usual daily activities, eg, brushing teeth, and (5) only an extremely small number of cases of IE may be prevented, even if antibiotic prophylaxis were 100% effective.

The AHA further lists cardiac conditions associated with the highest risk of an adverse outcome from IE, including the following: (1) a prosthetic cardiac valve, (2) a history of previous IE, (3) cardiac transplant recipients who develop cardiac valvulopathy, and (4) patients with congenital heart disease (CHD), including (a) those with unrepaired cyanotic CHD (including palliative shunts and conduits), (b) those with completely repaired CHD with prosthetic material or device, placed surgically or by catheter, for the first 6 months after the procedure, and (c) those with repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device. For patients with these cardiac conditions who have established infections of the GI tract in which enterococci may be part of the infecting bacterial flora (such as cholangitis) and particularly for those who are about to undergo an endoscopic procedure that will increase the risk of bacteremia in these patients (such as an ERCP), the AHA suggests that it may be reasonable that the antibiotic regimen include an agent active against enterococci. Although GI-tract infections are often polymicrobial, coverage for enterococci is recommended, because only enterococci are likely to cause IE. However, the AHA reiterates that no studies demonstrate that such therapy would prevent enterococcal IE.

## Recommendation

Antibiotic prophylaxis solely to prevent IE is no longer recommended before endoscopic procedures (Grade 1C+). For patients with established GI-tract infections in which enterococci may be part of the infecting bacterial flora (such as cholangitis) and with one of the above-listed cardiac conditions associated with the highest risk of an adverse outcome from endocarditis, amoxicillin, or ampicillin should be included in the antibiotic regimen for enterococcal coverage (Grade 3). Vancomycin may be substituted for patients allergic to or unable to tolerate amoxicillin or ampicillin.

## PREVENTION OF INFECTIONS OTHER THAN IE

Antibiotic prophylaxis may be useful for the prevention of infection related to some endoscopic procedures, before placement of prosthetic devices, and in specific clinical scenarios. These are addressed in this section.

### ERCP

Cholangitis and sepsis are known complications of an ERCP, and occur in up to 0.5% to 3% of cases.<sup>37-41</sup> Several studies evaluated the role of antibiotic prophylaxis in preventing post-ERCP cholangitis. Although antibiotic

prophylaxis was shown to reduce the incidence of bacteremia associated with an ERCP,<sup>42,43</sup> preprocedural antibiotic prophylaxis has not clearly been shown to be of benefit in the prevention of cholangitis. A meta-analysis of 5 randomized, placebo-controlled trials published up to 1999 failed to show benefit in decreasing the incidence of cholangitis and/or sepsis from routine use of antibiotic prophylaxis.<sup>44</sup> Similar conclusions were drawn in another review.<sup>45</sup> However, some of the trials in these analyses included a mix of diagnostic and therapeutic procedures.

Patient selection, together with continuation of antibiotics after the procedure for a few days may improve the chances of benefit. In 1 study, incomplete biliary drainage was predictive of 91% of all cases of sepsis.<sup>46</sup> Antibiotic therapy, therefore, may have particular value where drainage achieved at an ERCP is incomplete<sup>46</sup> or is achieved with difficulty, such as with hilar cholangiocarcinoma<sup>47</sup> and primary sclerosing cholangitis (PSC). Even in high-risk patients, ie, those suspected of having either a bile-duct stone or stricture, 1 study indicated that single-dose preprocedural antibiotic prophylaxis did not reduce the risk of post-ERCP cholangitis.<sup>48</sup> In one of the few trials that indicated a benefit of antibiotics in patients who were undergoing an ERCP for biliary obstruction, "prophylactic" antibiotics were continued after the procedure, in some cases for several days, until complete drainage was obtained.<sup>49</sup> Similarly, a low rate of cholangitis in patients with hilar strictures managed with only unilateral stenting was attributed to antibiotic coverage continued for 5 days after the procedure.<sup>47</sup>

It is possible that combined preprocedural and postprocedural antibiotic use may reduce infectious complications in patients with incomplete biliary drainage (including PSC) or in patients with inadvertent filling of pancreatic pseudocysts with contrast at an ERCP. Similarly, when transpapillary or transmural endoscopic drainage of a pancreatic-fluid collection (pseudocyst or necrosis) is undertaken, given the potential seriousness of complicating local infections, antibiotics are usually administered before the procedure and are continued for a variable period after the procedure, depending on the adequacy of drainage and the presence of necrosis.<sup>50</sup> However, no randomized data exist on the risk of infection in these situations or of the usefulness of antibiotic prophylaxis.

A recent large retrospective analysis of the role of antibiotics in preventing cholangitis in 11,484 patients who were undergoing an ERCP was published.<sup>51</sup> Over an 11-year period, the investigators changed their practice sequentially, from administering antibiotics to all patients with evidence of biliary or pancreatic obstruction, immunosuppression, or a need for therapeutic intervention (95% of all procedures), to limiting therapy to patients in whom endoscopic drainage was predicted to be incomplete (PSC, pancreatic pseudocyst, gallbladder stones, and hilar tumor) and those patients with immunosuppression (26% of all procedures). No difference was noted in

infection rates, with infectious complications developing in 0.28% of the first group and in 0.23% of the latter group. The overall rate of infection was 0.28% of all 11,484 procedures. Multivariate analysis of clinical variables indicated that only patients with a prior history of liver transplantation were at significantly greater risk of developing infection. Even in this group, the overall risk was low, with an infection rate of 1.2%. Also noteworthy is the fact that infection developed in 27 of 33 patients, despite antibiotic prophylaxis. No cases of ERCP-induced endocarditis were noted in this patient group, which included 77 patients documented as being "at risk" for endocarditis.

**Recommendation.** Antibiotic prophylaxis should be considered before an ERCP in patients with known or suspected biliary obstruction, in which there is a possibility that complete drainage may not be achieved at the ERCP, such as in patients with a hilar stricture and PSC (Grade 2C). When biliary drainage is incomplete despite an ERCP, continuation of antibiotics after the procedure is recommended (Grade 3). Antibiotics that cover biliary flora, such as enteric gram-negative organisms and enterococci, should be used. When biliary drainage is complete, continuation of antibiotics is not recommended (Grade 3). An exception is patients with posttransplant biliary strictures who are undergoing an ERCP; in these patients, continuation of antibiotics after the procedure may be beneficial (Grade 3), even when drainage is achieved. Antibiotic prophylaxis is not recommended in patients with biliary obstruction when it is likely that an ERCP will accomplish complete biliary drainage (Grade 1C). Antibiotic prophylaxis is not recommended before an ERCP when obstructive biliary-tract disease is not suspected (Grade 1C). Antibiotic prophylaxis is recommended before an ERCP in patients with communicating pancreatic cysts or pseudocysts and before transpapillary or transmural drainage of pseudocysts (Grade 3).

### EUS-FNA

Clinical infection or sepsis after an EUS-FNA is infrequent. There are few data about the development of local infectious complications after an EUS with FNA of solid lesions. In 2 large series that comprised a total of 672 patients who were undergoing an EUS-FNA of a variety of lesions, sepsis developed in only 3 patients.<sup>52,53</sup> Thus, prophylactic antibiotics are not recommended before an EUS-FNA of solid lesions.

The main rationale for antibiotic prophylaxis before a FNA of cystic lesions along the GI tract is to prevent cyst infection. A subgroup analysis of patients with cysts who were undergoing a FNA indicated a 14% risk of infectious complications.<sup>54</sup> However, the number of cystic lesions in this series was small. Sing et al<sup>55</sup> developed an *in vitro* cystic environment model, with conical tubes filled with blood culture media and covered with sterilized bovine tripe, to study the incidence of transmucosal microbial transmission during an FNA of cystic lesions.

In their contaminated controls, in which the tripe was inoculated with bacteria, the investigators were able to demonstrate a 100% rate of transmission of bacterial agents with an FNA through the tripe into the culture media within the conical tube. Despite the alarming extrapolations that can be made from the above study, reports of infection of cystic lesions after an FNA are sparse. Two isolated reports document infection of mediastinal cysts after an EUS-FNA.<sup>56,57</sup> In a large retrospective analysis of 603 patients who were undergoing an EUS-FNA of pancreatic cysts, possible infection developed in only a single patient.<sup>58</sup> The majority of patients in this series (90%) received antibiotic prophylaxis, most commonly a fluoroquinolone given for 3 days after the procedure, and this may possibly explain the low infection rate. The benefit of prophylactic antibiotics before an FNA of cystic lesions has not been evaluated by prospective randomized studies. However, most expert opinion currently favors administration of antibiotics before and often for 3 to 5 days after an EUS-FNA of cystic lesions.<sup>50</sup>

Although some experts recommend preprocedural and postprocedural antibiotics for an EUS-FNA of the perirectal space,<sup>59</sup> a recent prospective study on 100 patients who underwent a total of 471 FNAs of solid lesions in the lower-GI tract indicated low rates of bacteremia, with none of the patients developing signs or symptoms of infection.<sup>60</sup>

**Recommendation.** Antibiotic prophylaxis is not recommended before a diagnostic EUS or EUS-FNA of solid lesions along the upper-GI tract (Grade 1C). Prophylaxis with an antibiotic such as a fluoroquinolone administered before the procedure is recommended before an EUS-FNA of cystic lesions along the GI tract. Antibiotics may be continued for 3 to 5 days after the procedure (Grade 1C). There are insufficient data to make recommendations on antibiotic prophylaxis before an EUS-FNA of solid lesions along the lower-GI tract. The endoscopist may consider prophylaxis on a case-by-case basis. When antibiotic prophylaxis is administered, a fluoroquinolone administered before the procedure and continued for 3 days after the procedure is a reasonable regimen.

### PEG

Patients who were undergoing PEG-tube placement are often vulnerable to infection because of age, compromised nutritional intake, immunosuppression, and underlying diseases. A systematic review of randomized controlled trials, from the Cochrane Database, that evaluated the use of prophylactic antimicrobials for PEG placement identified 10 eligible trials of a total of 1100 patients.<sup>61</sup> A pooled analysis indicated a statistically significant reduction in the incidence of peristomal infection with administration of prophylactic antibiotics. An antibiotic that provides optimal coverage of cutaneous organisms, such as cefazolin 1 g IV, should be administered 30 minutes before the procedure.<sup>62</sup> When methicillin-

resistant *Staphylococcus aureus* (MRSA) is endemic, pre-procedural screening for MRSA with the culture of swabs obtained from the nose, throat, perineum, and broken skin areas, with decontamination in patients who test positive, appears to be effective in reducing MRSA peristomal infection.<sup>63</sup>

**Recommendation.** Parenteral cefazolin (or an antibiotic with equivalent coverage) should be administered to all patients 30 minutes before they undergo PEG-tube placement (Grade 1A).

## CIRRHOSIS WITH GI BLEEDING

A meta-analysis of 8 trials indicated a significant beneficial effect of antibiotic prophylaxis in decreasing the incidence of bacterial infections and mortality in patients with cirrhosis who develop GI bleeding.<sup>64</sup> Antibiotic therapy, therefore, should be instituted at admission. Although oral norfloxacin is a common choice of antibiotic, a recent study indicated that IV ceftriaxone is superior to norfloxacin in preventing infections in the setting of GI-tract bleeding.<sup>65</sup> IV antibiotics have an advantage when the patient is actively vomiting.

### Recommendation

All patients with cirrhosis who are admitted with GI-tract bleeding should have antibiotic therapy instituted at admission, preferably with IV ceftriaxone (Grade 1B). In patients allergic to or intolerant of ceftriaxone, oral norfloxacin may be used.

## SYNTHETIC VASCULAR GRAFT AND OTHER NONVALVULAR CARDIOVASCULAR DEVICES

The same rationale for not administering antibiotic prophylaxis for IE before GI endoscopic procedures applies also to synthetic vascular grafts and other nonvalvular cardiovascular devices, such as pacemakers, defibrillators, coronary artery stents, peripheral vascular stents, and vena cava filters. There are no reported cases in the literature of a vascular graft infection related to GI endoscopic procedures. In 2003, the AHA stated that there was no evidence that microorganisms associated with GI endoscopic procedures caused infection of nonvalvular cardiovascular devices, including synthetic vascular grafts, at any time after implantation.<sup>66</sup> Infections of these grafts are most often caused by staphylococci, Gram-negative bacteria, or other microorganisms in association with implantation of the graft or that result from wound or other active infections. Accordingly, the AHA does not recommend antibiotic prophylaxis after vascular graft or other nonvalvular cardiovascular device placement for patients who undergo GI endoscopic procedures.

## Recommendation

Antibiotic prophylaxis before GI endoscopic procedures is not recommended for patients with synthetic vascular grafts or other nonvalvular cardiovascular devices (Grade 1C+).

## ORTHOPEDIC PROSTHESIS

Infection of prosthetic joints related to endoscopy is extremely rare, with only 2 case reports that describe pyogenic arthritis after an endoscopy.<sup>67,68</sup> In a survey of program directors of infectious disease fellowships, most respondents agreed that antibiotic prophylaxis is not indicated at any time for patients with orthopedic prosthesis who are undergoing GI endoscopic procedures. There, however, was an equal recommendation for and against antibiotics for a patient who is undergoing colonic polypectomy within 6 months of a prosthesis insertion.<sup>69</sup>

### Recommendation

Antibiotic prophylaxis is not recommended for patients with orthopedic prosthesis who are undergoing GI endoscopic procedures (Grade 1C+).

## NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

The use of a transluminal route to access the peritoneal cavity increases the risk for intraperitoneal contamination and infection. At the present time, there are insufficient data to make recommendations on the prevention of infection for natural orifice transluminal endoscopic surgery (NOTES). However, precautions, including the use of endoscopes that have been gas sterilized with ethylene oxide, the use of sterile overtubes, and decontamination of the gut lumen before transluminal puncture may reduce the risk of intraperitoneal infection. Prophylactic antibiotic use may be beneficial.<sup>70</sup>

### Recommendation

There are insufficient data to make recommendations on antibiotic prophylaxis before NOTES. However, at this time, antibiotic prophylaxis seems reasonable.

*Abbreviations:* AHA, American Heart Association; ASGE, American Society for Gastrointestinal Endoscopy; CHD, congenital heart disease; EUS-FNA, EUS-guided FNA; IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; NOTES, natural orifice transluminal endoscopic surgery; PSC, primary sclerosing cholangitis.

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