



# Duodenoscope-Acquired Infections: Risk Factors to Consider

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## Abstract

In the wake of highly publicized duodenoscope-associated outbreaks caused by multidrug-resistant organisms (MDRO), a herculean effort was made to understand the conditions that led to these transmission events. Although there is now a clearer picture on how these outbreaks happened, there are still significant data gaps when it comes to understanding the rate of duodenoscope-acquired infections (DAIs), especially in nonoutbreak situations. Recent publications indicate that DAIs are still occurring and suggest that infection rates are higher than currently believed. Given this data gap, it is important to identify those patient populations that are most at risk of postprocedure infection, so that appropriate infection control measures may be implemented. Although those patients receiving antibiotic prophylaxis are most at risk for infection, there are additional risk factors that should be considered. For the purposes of this review, risk factors for infection were divided into three broad categories as follows: (1) those that increase patient susceptibility to infection, (2) those related to the endoscopic procedure, and (3) those factors that put reusable duodenoscope inventories at risk of contamination. Infection risk is a complex interaction between the immune status of the patient, the characteristics of the infectious agent (antibiotic sensitivity, virulence factors, and epidemiology), and the environment of care. Because of this complexity, any assessment of the risk of infection should be performed on a case-by-case basis. There is a dearth of information on infection risk for those patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), especially in the context of the development and implementation of new device technology, and new endoscopic procedures that are increasing in complexity. This narrative review was developed using the Medical Subject Heading (MeSH) terms to perform an electronic search in PubMed with the goal of generating a summary of the patient, procedural, and duodenoscope-associated factors that increase the risk of infection in patients undergoing ERCP. This review provides practical information regarding the segmentation of ERCP patients by infection risk, so that endoscopists can make informed decisions about the risk benefits of using enhanced duodenoscope technologies in the care of their patients.

## Keywords

- ▶ ERCP
- ▶ duodenoscope
- ▶ adverse events
- ▶ infection
- ▶ infection risk

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## Introduction

Despite the fact that there have been numerous worldwide outbreaks of duodenoscope-acquired infections (DAIs) in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) with resultant patient deaths, the rate of infection following endoscopic procedures is widely believed to be a rare event.<sup>1-3</sup> The foundational assumptions that form the basis of this belief have been shown to be incorrect but a generally accepted number that reflects the risk of infection remains elusive.<sup>4</sup> The issue is further complicated by the implementation of increasingly complex therapeutic procedures during ERCP and the introduction of new technologies intended to mitigate DAI risks (e.g., single-use duodenoscopes and single-use distal caps) where the risk of infection is unknown. In the face of these data gaps, it is important to identify known risk factors for infection, so that vulnerable patients most susceptible to DAIs may be identified. Segmenting ERCP patients by infection risk allows endoscopists to make more informed decisions about the risk-benefit ratio of using enhanced duodenoscope technology in the care of their patients.

The objective of this narrative review is to summarize patient, procedural, and duodenoscope-associated factors that increase the risk of infection in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). The approach to this review was to identify the medical Subject Heading (MeSH) terms for defined topics and use them to perform an electronic search in PubMed. Topics, search terms, and inclusion criteria are located in ► **Table 1**.

## Identifying Risk Factors for Infection in Patients Undergoing Endoscopic Retrograde Cholangiopancreatography

Understanding the risk factors that facilitate the transmission of infectious agents is important for preventing their spread and can also be used to identify those patients most vulnerable to infection. This review provides a practical list of risk factors that may impact a patient undergoing ERCP with the result of increased susceptibility to infection or colonization. It also defines risk factors that may put reusable duodenoscope inventories at risk for persistent contamination. This list is based on general principles of infection prevention, duodenoscope-associated outbreak investigation literature, clinical literature, and professional association guidelines. Actual post-ERCP infection and colonization rates in clinical practice are unknown,<sup>4,5</sup> therefore not all risk factors are identified, making this list extensive but not comprehensive.

Infection risk depends on the complex interplay of patient status, characteristics of the infectious agent, and the environment of care (► **Table 2**). Some factors can be controlled, whereas others require the implementation of interventions to mitigate their effect. Because of this complexity, assessment of infection risk is best performed on a case-by-case basis.<sup>6,7</sup>

All pathogenic organisms have a reservoir, a place where they can grow and that facilitates transmission.<sup>7,8</sup> With

**Table 1** Narrative review search strategy and selection criteria

Topic	The Medical Subject Headings terms used to search PubMed	Inclusion criteria
Patient factors: susceptibility to infection	infection, immunocompromised, cancer, transplantation, transplant recipients, bone marrow transplant, neutropenic, neutropenia, malignancies, cholangiocarcinoma, pancreatic neoplasms, liver cancer, hilar cholangiocarcinoma, and cholangitis/sclerosing	Inclusion criteria: English language journals available on PubMed. Randomized controlled studies, nonrandomized, and retrospective studies were included. Papers with limitations were included if more robust studies were not available
Patient factors: risk of post-procedure infection	endoscopy, gastrointestinal endoscopes, ERCP, ERCP/adverse effects, cholangiopancreatography, stents/adverse effects, sphincterotomy, stricture, stricture/malignant, obstruction, bile duct obstruction, cholecystitis, choledocholithiasis, and antibiotic prophylaxis	
Protection of duodenoscope inventory	infection, Enterobacteriaceae/infections, carbapenem-resistant Enterobacteriaceae, antibiotic resistance, drug resistance/bacterial, gram-negative bacteria/pathogenicity, cholangitis, asymptomatic colonization, asymptomatic carrier state, and asymptomatic infections,	
Duodenoscope	duodenoscopes, equipment contamination, disease outbreaks, carbapenems, Enterobacteriaceae, infection control, cross infection/prevention & control, disinfection, device/medical, endoscopes, and biofilms	
Guidelines	NA	International professional gastroenterological societies searched for guidelines on adverse events and antibiotic prophylaxis, and available in English
Reference lists	NA	Reference lists of included peer-reviewed articles were examined for relevant articles to supplement the electronic search

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; NA, not available.

**Table 2** General factors contributing to risk of infection<sup>14</sup>

Patient status	General health, Immune status, disease state, anatomic/physiologic factors, medical history, and immigration/travel history
Infectious agent	Prevalence, transmission route, antibiotic use, pathogen or opportunist, duration of exposure, infectious dose (ID <sub>50</sub> ), virulence factors, antibiotic resistance, and species of microorganism
Environment of care	Type of health care facility (critical, long-term health, and ambulatory surgery center), number and type of procedures performed, staffing ratios, length of stay, adherence to infection prevention protocols, and occupational exposure

respect to patient infection and/or colonization associated with ERCP procedures, there are two significant pathogen reservoirs, the patient and the duodenoscope. A significant patient reservoir is the normal flora of the gastrointestinal (GI) tract. Duodenoscopes become reservoirs due to failures in reprocessing that lead to persistent biofilm formation. Reprocessing failures are common as illustrated in the Federal Drug Administration (FDA) mandated postmarket study conducted in response to DAI outbreaks in the United States which demonstrated up to a 5% contamination rate of patient-ready duodenoscopes after they were reprocessed using best practices.<sup>9</sup> Other studies have shown contamination rates of patient-ready reusable duodenoscopes to be as high as 60%.<sup>10</sup> Infections of endogenous origin are thought to be caused by translocation of normal flora into the blood stream during endoscopic procedures.<sup>2,11,12</sup> It is currently unknown which fraction of ERCP-related infections are endogenous in origin and which fraction results from exogenous bacteria that originate in the environment (e.g., from a contaminated duodenoscope).<sup>10,13</sup> Although there are likely additional reservoirs for those organisms involved in ERCP-related infections, at a minimum, infection risk assessments should consider patient risk factors and factors that put reusable duodenoscope inventories at risk for persistent contamination.<sup>14-16</sup>

For the purpose of this review, risk factors for infection have been divided into three broad categories as follows: (1) those that increase patient susceptibility to infection, (2) those inherent in the type of ERCP procedure being performed that contribute to postprocedure infection, and (3) those factors that put reusable duodenoscope inventories at risk of persistent contamination.

### Patient Factors: Increased Susceptibility to Infection

The factors that render a patient more susceptible to infection are complex and have broad application to many disease states.<sup>6,7</sup> This discussion focuses on those patient factors that are relevant to the ERCP patient.

#### Immunocompromised

The immunocompromised patient has defects in the body's normal defense mechanisms that predisposes them to

life-threatening infections that may not otherwise occur. The degree of immune function may vary with time, therapy, and exposure to infectious agents.<sup>6</sup> There are broad categories of host abnormality that are commonly associated with an impaired immune system that may impact the ERCP patient.<sup>2,6</sup> Examples of these categories include cancer, transplant, age, pregnancy, occupation, residence, and travel/immigration status. Comorbidities may also contribute to infection risk in the immunocompromised ERCP patient. Examples include but are not limited to diabetes, eating disorder/poor nutritional status, drug/alcohol/tobacco addiction, chronic liver disease, and disease of the cardio-pulmonary system.<sup>2,6,7</sup> Along with immune system diseases, there are numerous patient factors that increase the risk of infection for the ERCP patient that are listed in **Table 3**. The patient risk factors of most concern to the ERCP patient are malignancies and liver transplant candidates/recipients and are described in more detail below.<sup>1,2</sup>

#### Malignancies

The risk of infection increases in patients with malignancies due to two major concerns, the malignancy itself and the effect of treatment. While all cancer patients are fragile and therefore at risk of infection, they do not all carry the same risk. Patients with acute hematologic cancers are of the greatest concern because they are at increased risk of bacteremia and sepsis after endoscopy.<sup>2,17</sup> In addition, treatment of malignancies often includes use of cytotoxic chemotherapeutic drugs and/or radiation therapy, both of which suppress immune system function leading to a greater risk of infection.<sup>7,17,18</sup> It is important to note that the incidence of bacteremia after ERCP ranges from 6.4% (nonobstructed bile duct) to 18% (with biliary obstruction).<sup>2,11</sup> Such bacteremia in patients with malignancy may become clinically relevant. Bianco et al, in a retrospective study of 47 allogenic bone marrow transplant patients, found that 9 (19%) developed clinically relevant bacteremia 24 hours after EGD.<sup>17</sup> While there is no clinical data on the risk of infection for patients with acute hematologic cancers undergoing ERCP, published guidelines recommend a cautious approach in performing endoscopy in these patients and assessing their infection risk on an individual basis.<sup>1,2,19,20</sup>

**Table 3** Patient factors that may increase susceptibility to infection

Immunocompromised <sup>1,2,6</sup>	Cancer, transplant, bone marrow transplant, disease of immune system, advanced hematologic cancers, and severe neutropenia (absolute neutrophil count <500 cells/mL)
Malignancies <sup>27</sup>	Cholangiocarcinoma, pancreatic cancer, liver cancer, cytotoxic chemotherapy drugs, and radiation treatments
Transplant <sup>7,23-25</sup>	Liver transplant, transplant candidates, transplant recipients, and antirejection drug therapy

### Liver Transplant

The risk of infection in the transplant patient is dependent on the interplay between exposure to infectious agents and their level of immunosuppression.<sup>21</sup> Infection is the most frequent cause of death following liver transplantation, particularly in the first year after transplant.<sup>22</sup> Data from the United Network for Organ Sharing (UNOS) revealed the incidence of mortality for 64,977 first-time liver transplant recipients transplanted between February 2002 and June 2016 ranged between 5 and 10%. Infections were the most frequent cause of death during 30 to 180 days after liver transplantation.<sup>22</sup> Gram-negative infections represent a major complication in liver transplant recipients with a frequency ranging between 20 and 80% of cases. Three-fourths of bacterial infectious episodes occur in the first month after transplantation contributing to longer hospital stays and increased costs.<sup>23</sup>

For patients on a transplant waiting list, development of an infection may rapidly change their suitability for a transplant.<sup>23-25</sup> Transplant candidates may be temporarily suspended from the list until the infection is resolved or can be delisted if the infection is caused by a multidrug resistant organism (MDRO) or results in multiple organ failure.<sup>23-25</sup> In a retrospective analysis of consecutive patients listed for liver transplantation between 2007 and 2014 those with an infection were 5.2 times more likely to become delisted than noninfected patients. Infections occurred in 144 of 327 studied patients (44%) with 23.4% of the patients on the liver transplantation waiting list delisted or deceased before transplantation.<sup>24</sup>

Interestingly, infectious complications and infection-associated acute-on-chronic liver failure (I-ACLF) seem to be increasing in potential transplant candidates. This is illustrated in a study conducted by 15 transplant centers that compose the North American Consortium for the Study of End-Stage Liver Disease (NACSELD). These centers enrolled patients in a prospective study structured to follow those admitted with cirrhosis who also had or developed one or more infections during hospitalization.<sup>25</sup> Of the 136 patients enrolled, 57 (42%) were delisted or deceased within 6 months of infection illustrating that infections can rapidly change a patient's survival in time for transplant or suitability for transplant.<sup>25</sup> Because infection is the primary cause for delisting a transplant candidate, infection prevention, including efforts to prevent duodenoscope mediated cross-contamination, is critical.

The goal of preventing infections in transplant candidates and recipients faces multiple hurdles including the shifting worldwide epidemiology of infections, increasing prevalence of antimicrobial resistance, suboptimal assays for the microbiologic screening of organ donors, virus-associated malignancies, and persistently contaminated reusable duodenoscopes used in ERCP procedures.<sup>5,21,26</sup>

### Procedure Factors Associated with Increased Infection Risk

ERCP is considered a high-risk endoscopic procedure because it has one of the highest rates of postprocedure bacteremia

ranging from 6.4 to 18%.<sup>1,2</sup> In comparison, other endoscopic procedures that have known high rates of postprocedure bacteremia include esophageal dilation (12–22%) and sclerotherapy of esophageal varices (up to 52%).<sup>2,12</sup> Factors that increase the risk of post-ERCP infection are listed in ►Table 4 and discussed in detail below.

### Obstruction

Obstruction or stricture of a body passage is a recognized risk factor for infection.<sup>7</sup> Incomplete drainage of an obstructed biliary system is the major predictor of post-ERCP biliary sepsis and cholangitis occurring in up to 3% of ERCP cases. Incomplete biliary drainage was predictive of 91% of all cases of sepsis associated with ERCP with the risk of post-ERCP cholangitis dependent on the nature and site of the obstruction (►Table 3) and the highest in patients with incomplete biliary drainage (e.g., hilar cholangiocarcinoma and primary sclerosing cholangitis) and prior history of liver transplantation.<sup>1</sup>

Although cholangitis is the most common infection that occurs after ERCP,<sup>1,2,27</sup> ERCP-associated infections can occur in systems remote to the GI tract.<sup>2,26,28</sup> During the course of a carbapenem-resistant *Enterobacteriales* (CRE) outbreak associated with ERCP procedures, Kim et al found that 53.3% of CRE colonized patients who became actively infected had cultures positive for the outbreak strain coming from blood, bile, wound, the peritoneum, and the urinary tract.<sup>15</sup> In a risk evaluation for duodenoscope-associated infections in the Netherlands, Kwakman et al reviewed three outbreak investigations involving MDROs.<sup>26</sup> They also found that DAIs presented in locations remote from the GI system. Combining the numbers from all three outbreaks, they identified seven blood stream infections, three abdominal infections, one

**Table 4** Patient and procedural factors that contribute to post-ERCP infection risk

Obstruction <sup>2,7,15</sup>	Cholangiocarcinoma with hilar stricture, cholangitis, malignant biliary stricture, multiple strictures, acute cholecystitis, and choledocholithiasis with incomplete stone clearance
Prior procedures <sup>1,7,15,34,60</sup>	ERCP, prior stent placement, stent replacement, and biliary sphincterotomy
Multiple concurrent procedures <sup>1,7,15,34,41,60</sup>	Choledochoscopy during ERCP, laparoscopic-assisted ERCP, tumor ablation, EUS with biopsy, percutaneous hepatic stent placement, and percutaneous intervention in radiology + endoscopy procedures
Antibiotic prophylaxis - ASGE recommendations and suggestions <sup>1,2</sup>	Known or suspected biliary obstruction, where there is a possibility of incomplete biliary drainage to include primary sclerosing cholangitis, hilar cholangiocarcinoma, biliary complications post-liver transplant, patients with high-risk cardiac conditions and established gastrointestinal tract infections (for prevention of infective endocarditis), EUS-fine needle aspiration for pancreatic and mediastinal cysts/pseudocysts

Abbreviations: ASGE, the American Society for Gastrointestinal Endoscopy ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

respiratory infection, one cholangitis, and nine cases of sepsis. In another ERCP-associated outbreak investigation, Epstein et al reported that intestinal colonization can lead to remote sites of infection as evidenced by finding the outbreak strain in the urinary tract, pulmonary tree, bloodstream, and abscesses weeks to months after the initial ERCP procedure.<sup>16</sup>

#### Prior and/or Multiple Concurrent Procedures

Increased infection risk is seen in those patients who are having selected advanced, multiple, or concurrent procedures (► **Table 4**). Instrumentation and mechanical manipulation of tissues provides opportunities for the occurrence of transmission events.<sup>7</sup> For example, biliary sphincterotomy is a risk factor for cholangitis.<sup>1</sup> Freeman et al identified cholangitis in 1% of patients undergoing biliary sphincterotomy. Other significant risk factors include combined percutaneous endoscopic procedures ( $p < 0.001$ ), stenting of malignant strictures ( $p < 0.001$ ), and failed biliary access or drainage ( $p < 0.001$ ).<sup>29</sup>

Placement of in-dwelling biliary stents to relieve obstruction from stones or malignancies may increase the risk of infection.<sup>15</sup> Biofilm formation on stents is of concern as colonized stents provide a conduit for microbes to migrate to other ducts and tissues.<sup>1</sup> An occluded stent, as it is pulled through a reusable duodenoscope, may seed the working channel of a reusable duodenoscope putting the duodenoscope inventory at risk for cross-contamination and transmission events. There is an increased risk of life-threatening acute cholangitis and sepsis in patients experiencing a sudden obstruction of bile flow due to stent occlusion.<sup>30,31</sup> Occlusions of the stent lumen may be from stone fragments, bacterial biofilm, sludge, tumor and/or tissue ingrowth, and overgrowth.<sup>1,31</sup> Occlusion and cholangitis may also occur because of stent migration in the setting of an obstructed bile duct.<sup>1,32</sup> While investigating an ERCP-associated CRE outbreak, Kim et al found that, in patients undergoing ERCP with a contaminated duodenoscope, biliary stent placement was the only independent procedure-related risk factor associated with an increased risk for CRE infection (odds ratio [OR] = 3.62; 95% confidence interval [CI]: 1.12–11.67).<sup>15</sup> When comparing patients who were actively infected versus colonized patients, they found that those with an active infection also underwent biliary stent placement (87.5 vs. 14.3%;  $PZ = 0.010$ ) more often than those who were colonized.<sup>33</sup>

In addition, the ERCP patient undergoing multiple or concurrent procedures may be at increased risk for infection. In a study that examined 72 patients who underwent single-operator choledochoscopy, 19% of patients had sustained bacteremia following ERCP or choledochoscopy.<sup>34</sup> Despite the use of postprocedure intravenous antibiotic administration, seven patients (9.7%) required further antibiotic treatment for infectious complications with three hospitalizations required to receive intravenous antibiotic therapy. Sethi et al examined 4,214 ERCPs, 402 of which included cholangioscopy or pancreatoscopy.<sup>35</sup> Compared with the ERCP-only cohort, patients undergoing cholangioscopy or pancreatoscopy had higher rates of adverse events (2.9 vs. 7%,

OR = 2.50; 95% CI: 1.56–3.89), and significantly higher rates of cholangitis (0.2 vs. 1%, OR = 4.98; 95% CI: 1.06–19.67).<sup>35</sup> In an analysis of surgical site infection (SSI) surveillance data, Loor et al found that patients undergoing ERCP within 60 days of a cholecystectomy had an increased SSI rate (4.1 vs. 1.8%) compared with those procedures where ERCP was performed in the same setting. These findings underscore the principle that multiple procedures increase the risk of infection and suggest that pathogen transmission during ERCP may remain undetected until later invasive procedures.<sup>5,36</sup>

#### Antibiotic Prophylaxis

There is no clearer indication of infection risk than those situations where antibiotic prophylaxis is already recommended as part of society guidelines. Patients who meet the criteria for receiving pre-ERCP antibiotic prophylaxis based on existing guidelines should be considered at a higher risk for infection overall. The recommendations for antibiotic prophylaxis in ERCP patients from selected professional organizations are summarized in ► **Table 5**. All associations recommend against the routine use of antibiotic prophylaxis for ERCP.<sup>2,19,20</sup> There are varying strengths of recommendations for certain high-risk patient populations and procedures. Of note are the disparities on recommendations for patients who are immunocompromised such as those with severe neutropenia or advanced hematologic malignancy. Acknowledging the lack of clinical evidence, the British and European guidelines recommend prophylactic antibiotics prior to endoscopy if the absolute neutrophil count (ANC) is less than 500/mm<sup>3</sup> and the patient is undergoing a high-risk procedure, such as ERCP for an obstructed system.<sup>19,20</sup> The American Society for Gastrointestinal Endoscopy (ASGE) recommendation is less clear. Citing insufficient evidence to recommend for or against administration of antibiotic prophylaxis before routine endoscopic procedures in patients with severe immunosuppression (absolute neutrophil count of <500 cells/mL, advanced hematologic malignancies, and bone marrow transplantation), they state that the use of antibiotic prophylaxis in these scenarios may be beneficial and should be individualized.<sup>2</sup> Citing a lack of data, all guidelines agree that that patients with immunocompromised status but normal neutrophil counts (e.g., organ transplant recipients and patients with HIV) are at increased risk for GI endoscopy-related infections but do not recommend routine administration of prophylactic antibiotics in this setting (► **Table 5**).

► **Table 5** records the variations in recommendations for antibiotic prophylaxis to prevent infectious endocarditis (IE). ASGE is the only professional society to recommend antibiotic prophylaxis for IE but only in those patients with high-risk cardiac conditions that also have active GI infections such as cholangitis. The rationale is that ERCP patients may be especially vulnerable because of the high rate of postprocedure bacteremia. The British guideline does not recommend antibiotic prophylaxis for infective endocarditis and the topic is not addressed in the European guideline on adverse events.

**Table 5** Antibiotic prophylaxis recommendations

Recommendation	American Society for Gastroenterology, 2015 <sup>2</sup>	European Society for Gastrointestinal Endoscopy, 2020 <sup>19</sup>	British Society of Gastroenterology, 2009 <sup>20</sup>
Against routine use of antibiotic prophylaxis before ERCP	Yes	Yes, strong recommendation, moderate quality of evidence	Yes
Known or suspected biliary obstruction, where there is a possibility of incomplete biliary drainage to include primary sclerosing cholangitis, hilar cholangiocarcinoma	Yes	Yes, weak recommendation, moderate quality of evidence	Yes
Biliary complications post liver transplant	Yes	Not addressed	Yes
Endoscopic ultrasound–fine needle aspiration for pancreatic and mediastinal cysts/pseudocysts	Yes, suggested	Not addressed	Yes
Patients with high-risk cardiac conditions and established gastrointestinal tract infections (for prevention of infective endocarditis)	Yes	Not addressed	No, patients with known cardiac risks should be followed closely for signs of infection
Severely immunocompromised patients	No, prophylactic antibiotics also may benefit patients with severe neutropenia (absolute neutrophil count of 500 cells/mL) and/or advanced hematologic malignancy.	Yes, weak recommendation, moderate quality of evidence	Yes, patients with severe neutropenia (0.56109/L) and/or advanced hematological malignancy
When performing cholangioscopy	Not addressed	Yes, weak recommendation, moderate quality of evidence	Not addressed

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.

### Infections with Multidrug-Resistant Organisms

Antibiotic prophylaxis recommendations are guided by the goal of providing information on the use of antibiotics, in part, to prevent the overuse and misuse of antibiotics that leads to the development of antibiotic-resistant bacteria.<sup>8</sup> MDROs have been involved in over 32 ERCP-associated outbreaks.<sup>3,14,37,38</sup> The most common MDRO involved were CRE bacteria which are becoming more prevalent, have few treatment options, and are associated with a high mortality rate.<sup>8</sup> Reuken et al analyzed 1,764 isolates from bile cultures taken from ERCP patients and found that 24 of 89 patients were cultured positive for MDR bacteria.<sup>39</sup> The univariate risk factors for these biliary MDR bacteria were male sex, nosocomial acute cholangitis, prior antibiotic exposure, and prior biliary stenting. Biliary stenting was the only independent risk factor according to multivariate analysis (OR = 3.8; 95% CI: 1.3–11.0,  $p = 0.013$ ).<sup>39</sup>

ERCP patients are at risk for MDRO infection from contaminated duodenoscopes. The infection rate has been under debate ever since Ofstead et al published a commentary in 2013 showing that the oft-quoted infection rate of 1 in 1.8 million for endoscopic procedures was incorrect.<sup>4</sup> Since 2013, the GI community has not come to a consensus on the rate of infection after ERCP mainly due to the fact that there is a paucity of solid data on the topic. A study out of the Netherlands performed a systematic literature search to identify all DAI outbreaks between 2008 and 2018.<sup>26</sup> They calculated a minimum risk of duodenoscope-associated

infection as 0.01% which was at least 180 times higher than previously published risk estimates of infection after endoscopy.<sup>26</sup> The risk of becoming colonized with an MDRO was calculated at being at least 0.023 to 0.029%.<sup>26</sup> They proposed that the actual risk is likely to be much higher due to underreporting of both MDRO infections and those caused by sensitive bacteria.

Du et al used automated surveillance to identify infections that occurred after ERCP in one of the largest tertiary hospitals in China between 2012 and 2015.<sup>28</sup> Infection control personnel and physicians confirmed all identified healthcare-associated infections (HAIs; e.g., cholangitis and bacteremia). From the 1,743 ERCP procedures that were included in the study, 132 HAIs were identified. The most prevalent HAI was biliary tract infection (4.02%), followed by transient bacteremia (1.14%). The most prevalent bacterial isolates were *Enterococcus faecium* and *Escherichia coli*. A large proportion (73%) of the *E. coli* isolates and all of the *E. faecium* isolates were resistant to ciprofloxacin. In addition, only 37% of the *E. coli* isolates were susceptible to ceftriaxone.<sup>28</sup>

Ofstead posits that evidence-based calculations of DAI risk can be made from estimates of pathogen transmission using duodenoscope contamination rates.<sup>5</sup> Contamination rates from different sources were used that ranged from 0.3% in academic centers to 5% in FDA postmarket surveillance studies to 22% in 67 Dutch hospitals and 60% in other high-volume settings. With approximately 750,000 annual ERCP procedures

in the United States, the predicted number of ERCPs performed annually with contaminated patient-ready reusable duodenoscopes was calculated to range from 2,250 to 412,500. Using an average attack rate of 18.9% Ofstead then calculated a range of per-procedure pathogen transmission, resulting in rates of 1 in 1,765 (0.3% contaminated) to 1 in 106 (5% contaminated), 1 in 24 (22% contaminated), and 1 in 10 ERCP procedures (60% contaminated) depending on which contamination rate is used.<sup>5</sup>

## Protection of Duodenoscope Inventory

### Active Patient Infection and Colonization

Reusable duodenoscopes (with or without removable end-caps) exposed to patients with active infections are at risk of becoming persistently contaminated with pathogenic organisms. These contaminated scopes increase the risk of patient infection and colonization in each patient in which they are used.<sup>15,40</sup> The emphasis on protection of duodenoscope inventory has evolved as the GI community has become aware of pathogen transmissions and outbreaks associated with ERCP procedures. Currently, the focus is on the emerging MDROs involved in these outbreaks but there should also be concern for infections caused by pan-sensitive pathogens with a less remarkable profile, as they also result in significant patient morbidity and mortality.<sup>10</sup> Active infections, such as cholangitis, cholecystitis, localized infection, and septicemia, all present risk for contamination of a duodenoscope inventory.<sup>15,16,41,42</sup> Patients colonized with pathogenic organisms are of concern as well because they may be asymptomatic or present with subclinical symptoms making them undetectable unless active screening is performed. A small number of facilities in the United States have reported patient MDRO screening results on ERCP patients. Positive MDRO results ranged from 0.6 to 3.2%.<sup>43-45</sup> Colonization also poses a risk to the patient as conversion to active infection may happen over a period of weeks to years.<sup>46</sup> Public health studies that screen healthy individuals for carriage of MDROs are lacking. Current estimates of the prevalence of asymptomatic carriage in the United States are largely based on estimates of community-onset infections.<sup>8</sup> Jernigan et al reported on community-onset infections for both CRE and extended spectrum  $\beta$ -lactamase (ESBL)-producing *Enterobacteriales* and found an increase from 19.1 to 64.1% between 2012 and 2017. Travel history and immigration status may be an important factor, as well as there are many regions of the world where MDROs are endemic.<sup>47,48</sup>

### Persistent Contamination of Duodenoscopes

Persistent contamination of a duodenoscope results from the interplay of events involving exposure to infected/colonized patients, ineffective reprocessing protocols, and complex duodenoscope design.<sup>5,15,41,49</sup> Despite the best efforts to follow current reprocessing guidelines, an endoscope that is known to be contaminated can remain contaminated despite multiple rounds of reprocessing.<sup>5,15,41,49</sup> Persistent contamination indicates that duodenoscope processing is

ineffective.<sup>9</sup> The primary culprit that impedes effective reprocessing is the presence of biofilm which can be extremely difficult or impossible to remove even with adherence to the best practice reprocessing protocols.<sup>50,51</sup> The primary factors that contribute to persistent biofilm formation and microbial contamination are mentioned below:

- Normal use of an endoscope results in damage to the working channel that may include luminal shredding, scratches, gouges, staining, and persistent debris, all of which provide a “safe harbor” for biofilm.<sup>52-54</sup>
- Inadequate manual cleaning impedes high-level disinfection/sterilization.<sup>49</sup>
- Incomplete drying resulting in storage of wet endoscopes which promotes biofilm formation.<sup>55,56</sup>
- Complex endoscope design impedes proper reprocessing.<sup>49</sup>

Based on data from FDA postmarket surveillance studies, up to 1 in 20 patient-ready duodenoscopes may be contaminated with pathogenic organisms.<sup>9,57-59</sup> Contributing to this persistent contamination problem is the ongoing issue of lack of adherence to manufacturer instructions for use (IFU) for reprocessing reusable duodenoscopes. The FDA mandated observational study on the ability of users to adhere to IFUs showed high failure rates (25–94%) when performing the manual cleaning steps for duodenoscope reprocessing. Due to these ongoing challenges, contaminated duodenoscopes are now recognized as a risk factor for transmission of infection to ERCP patients.<sup>1</sup>

## Conclusion

A patient's risk of developing an infection after ERCP involves contributions from patient and procedural factors, pathogen characteristics, and environmental factors (e.g., a contaminated duodenoscope), and therefore should be assessed on a case-by-case basis. While data on the true risk of infection after ERCP is evolving, what is known is that the risks are significant. Reducing this risk of infection for ERCP patients will require the generation of robust data from studies focused on post-ERCP infection and colonization rates. Studies are also needed to assess the impact on infection risk after adoption of new technologies (device and device processing) and implementation of new, more complex procedures. Given that DAIs can be severe and life-threatening, infection prevention efforts are critical to providing high-quality patient care for these common procedures.

### Disclosures

G.T. and B.D. are full-time employees of Boston Scientific. Brian Dunkin has ownership interest in Allotrope Medical.

### Authors' Contributions

G.T. conceptualized, researched, and prepared the manuscript and compiled the tables. B.D. conceptualized, edited, and reviewed the manuscript.

### Conflict of Interest

None declared.

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