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Journal

Gastrointestinal Endoscopy, 83(6)

ISSN

0016-5107

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Publication Date

2016-06-01

DOI

10.1016/j.gie.2016.03.790

Peer reviewed

Risk factors associated with the transmission of carbapenem-resistant Enterobacteriaceae via contaminated duodenoscopes

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Background and Aims: The duodenoscopes used to perform ERCP have been implicated in several outbreaks of carbapenem-resistant Enterobacteriaceae (CRE) infection. The risk factors for CRE transmission via contaminated duodenoscopes remain unclear.

Methods: In this retrospective, single-center, case-control study, all patients who underwent ERCP with either 1 of 2 contaminated duodenoscopes were evaluated. We compared the patients who acquired CRE (active infection or colonization) with those who did not.

Results: Between October 3, 2014, and January 28, 2015, a total of 125 procedures were performed on 115 patients by using either of the contaminated duodenoscopes. Culture data were available for 104 of the 115 exposed patients (90.4%). Among these patients, 15 (14.4%) became actively infected (n = 8, 7.7%) or colonized (n = 7, 6.7%) with CRE. On univariate analysis, recent antibiotic exposure (66.7% vs 37.1%; $P = .046$), active inpatient status (60.0% vs 28.1%; $P = .034$), and a history of cholangiocarcinoma (26.7% vs 3.4%; $P = .008$) were patient characteristics associated with an increased risk of CRE infection. Biliary stent placement (53.3% vs 22.5%; $P = .024$) during ERCP was a significant procedure-related risk factor. After adjusting for cholangiocarcinoma, biliary stent placement (odds ratio 3.62; 95% confidence interval, 1.12-11.67), and active inpatient status (odds ratio 3.74; 95% confidence interval, 1.15-12.12) remained independent risk factors for CRE transmission.

Conclusions: In patients undergoing ERCP with a contaminated duodenoscope, biliary stent placement, a diagnosis of cholangiocarcinoma, and active inpatient status are associated with an increased risk of CRE transmission. (Gastrointest Endosc 2016;83:1121-9.)

The side-viewing duodenoscope used to perform ERCP is a complex instrument that is susceptible to bacterial contamination despite standard reprocessing protocols. The presence of an elevator distinguishes duodenoscopes from standard endoscopes, but its architecture and complicated design make it challenging to clean. The recess located under the elevator is difficult to access, leading to the potential for inadequate disinfection and persistent bacterial colonization. Early reports of bacterial transmission during ERCP date back to 1987 when *Pseudomonas*

Abbreviations: CDC, Centers for Disease Control; CRE, carbapenem-resistant Enterobacteriaceae; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

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0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2016.03.790

Received December 17, 2015. Accepted March 8, 2016.

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aeruginosa was isolated from bile cultures in 10 patients who had undergone ERCP.[1] Numerous reports have since implicated the complex design of the duodenoscope and its elevator hinge as the cause of ERCP-associated infections.[2-6]

Carbapenem-resistant Enterobacteriaceae (CRE), a family of gram-negative bacteria resistant to most available antibiotics, has emerged throughout the United States and Europe. Recent outbreaks of CRE have led to epidemiologic investigations to identify the source and prevent further spread. In several published studies, exposure to duodenoscopes contaminated with a CRE organism has been clearly linked to subsequent transmission of the bacteria.[2,3,6] Although ERCP has been well-established to have low rates of infectious adverse events, duodenoscope-transmitted infections may have previously gone largely unnoticed because most patients are asymptomatic or easily treated with periprocedural antibiotics. The emergence of CRE has led to the recognition of the potential for duodenoscope-associated infections. Most concerning is that bacterial contamination of the duodenoscope appears to be possible even when current endoscope reprocessing methods are strictly complied with.

In light of these events, efforts to improve duodenoscope reprocessing and increase patient safety have been initiated.[7] Gas sterilization with ethylene oxide, liquid sterilization with peracetic acid, microbiologic culturing, or repeating high-level disinfection have been recommended as supplemental measures to further reduce the risk of endoscope-associated infection.[8]

The endoscopist must have a heightened clinical suspicion for patients who may be at increased risk for transmission of CRE from contaminated duodenoscopes. Therefore, identifying possible risk factors for bacterial transmission may provide a means to retrospectively identify patients at higher risk of infection in the event that a contaminated duodenoscope is identified. Currently, the patient-related and procedure-related risk factors associated with the transmission of CRE bacteria via a contaminated duodenoscope remain unclear. After a CRE outbreak at our institution, we examined the microbiologic culture data of exposed patients in an effort to elucidate independent risk factors associated with the transmission of CRE during ERCP with a contaminated duodenoscope.

METHODS

Field investigation

In late 2014, a slight increase in the number of hospital inpatients with carbapenem-resistant *Klebsiella pneumoniae* infections was observed, which was attributed to the emergence of a new genotype, $bla_{\text{OXA-232}}$. Full chart review of patients with $bla_{\text{OXA-232}}$ CRE infections was performed and revealed that all infected patients had a common exposure to 1 of 2 duodenoscopes (TJF-Q180V; Olympus America, Center Valley, Pa) used to perform ERCPs between October 3, 2014 through January 28, 2015. These 2 specific duodenoscopes were identified as the likely epidemiologic link for these patients.

The date range was determined retrospectively. On October 3, 2014 the source patient with an active CRE infection underwent an ERCP with a duodenoscope. On October 29, 2014, this same patient underwent another ERCP with a second duodenoscope. When the subtle increase in inpatient CRE infections was detected by the infection prevention team, an investigation was initiated. On January 28, 2015 the infection prevention team—composed of 2 infectious disease physicians and 4 staff members with nursing, epidemiology, and public health training—reported the duodenoscope-associated CRE outbreak within our institution. A summary of the investigation timeline is shown in Figure 1. All ERCPs were canceled immediately and stopped for 8 days, whereas the 2 implicated duodenoscopes were removed from use, and a new protocol for reprocessing the duodenoscopes was implemented.

Active case-finding was performed by evaluating the endoscopic procedure database and automatic endoscopic reprocessor (Custom Ultrasonics Inc, Warminster, Pa) logs to generate a comprehensive list of patients exposed to either duodenoscope. All patients who were exposed to either of the contaminated duodenoscopes during the relevant time period were contacted and offered a screening test to detect CRE colonization. Data were collected on patient demographics, medical history, prior antibiotic exposure and hospitalizations, inpatient status at the time of ERCP, indication for ERCP, duration and number of ERCPs, and techniques used during ERCP such as sphincterotomy, stent placement, stone removal, and cholangioscopy. The study design was approved by the institutional review board at our institution.

Duodenoscope investigation

When the source of the outbreak was identified on January 28, 2015, the 2 implicated duodenoscopes were immediately taken out of service and evaluated for possible sources of contamination. Review of the reprocessing procedure was performed, and the duodenoscopes were deemed to have been cleaned and disinfected according to manufacturer's guidelines. Specimens from the elevator tip and inner channel were collected and cultured for the presence of CRE, following Centers for Disease Control guidelines.[9] Cultures from the 2 implicated duodenoscopes were performed twice, 1 week apart. All cultures were negative for any bacterial growth.

Laboratory analysis

Antimicrobial susceptibility testing was performed on all isolated CRE by the Clinical and Laboratory Standards Institute reference broth microdilution method, on panels prepared in-house.[10] Isolates were defined as CRE if they were

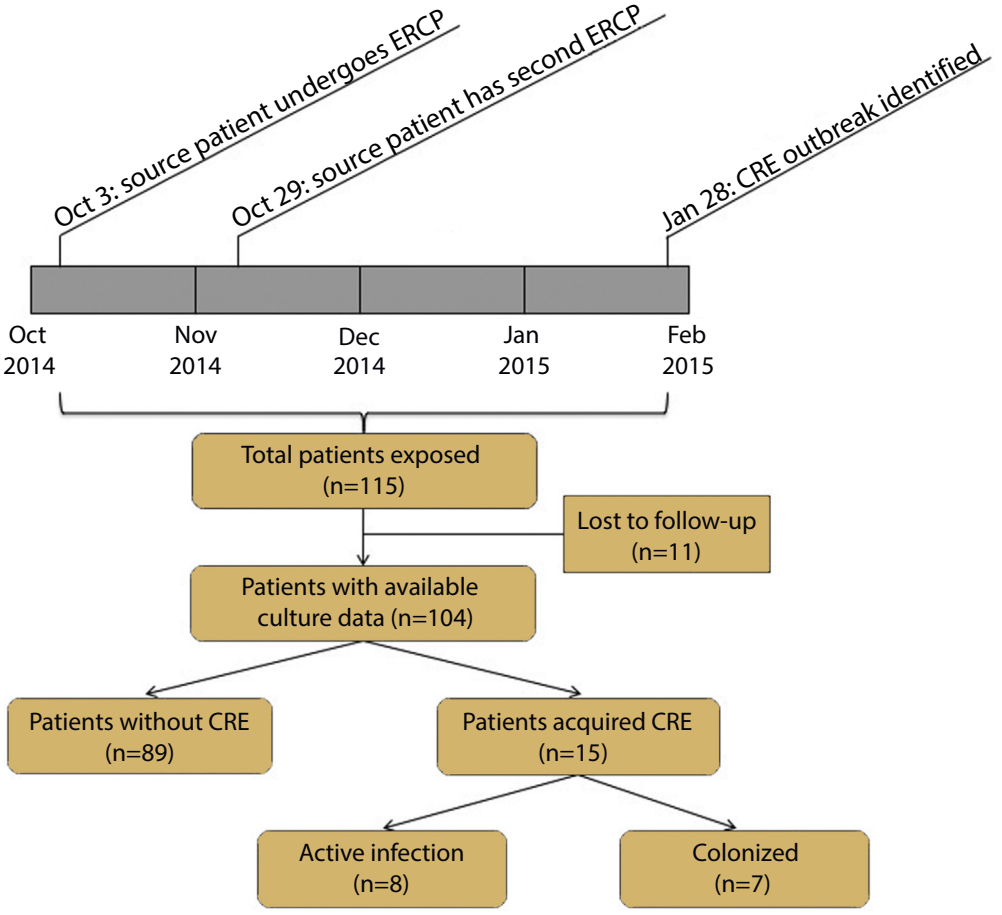

Figure 1. Timeline of events during the carbapenem-resistant Enterobacteriaceae outbreak and flow sheet of patients exposed to either of the 2 contaminated duodenoscopes. *CRE,* carbapenem-resistant Enterobacteriaceae.

not susceptible (intermediate or resistant) to meropenem (ie, minimum inhibitory concentration [MIC] >1 μg/mL) and/or imipenem (MIC >1 μg/mL). CRE isolated from patients who underwent ERCP were tested by using a multiplex real-time polymerase chain reaction (PCR) assay to determine the presence of carbapenemase genes (bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{NDM-1}, bla_{SME}, bla_{OXA-48}).[11] Isolates that were negative for all of these genes were further tested by using a LunaProbe PCR with high-resolution melt analysis to determine the presence of the $bla_{OXA-232}$ gene.[12] For rectal surveillance cultures, home self-collect rectal swab kits were sent to exposed patients, and the specimen was mailed to the laboratory for CRE culture. Rectal swabs were collected by using the CultureSwab with Amies transport (Becton, Dickenson Diagnostics, Sparks, Md).

Case and control definitions

A case was defined as a patient who had undergone an ERCP with a contaminated duodenoscope at our institution from October 3, 2014 to January 28, 2015 in whom carbapenem-resistant *Klebsiella pneumoniae* (CRE) carrying the $bla_{OXA-232}$ gene was recovered. Patients were further characterized as having an active infection if they were symptomatic with signs and symptoms of CRE infection including leukocytosis, fevers, intra-abdominal abscess, and septic shock. Actively infected patients were found to have positive CRE cultures in the blood, abdomen, bile, wound, and/or sputum. Patients were considered to be colonized with CRE if they were asymptomatic and found to have a positive CRE culture on the rectal swab screening test.

Controls were defined as all patients who underwent ERCP with 1 of the 2 implicated duodenoscopes during the relevant time period who did not develop an active infection with CRE and had a negative culture on the subsequent screening test.

Statistical analyses

Continuous variables were summarized as means, standard deviations, and ranges, and categoric variables were summarized in terms of frequencies and percentages. Continuous variables were compared between patient groups by using 2 sample *t* tests, and categoric variables were compared by using the chi-square or the Fisher exact test, as appropriate. Logistic regression models were used

to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for predicting case and control status. The Firth bias correction was used to address issues of quasi-complete separation. P values < .05 were considered statistically significant. All analyses were performed by using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Overall rate of transmission

A total of 125 ERCP procedures were performed on 115 patients by using either of the 2 implicated duodenoscopes during the study period. Ten patients underwent 2 ERCP procedures. Clinical bacterial culture and colonization data were collected on 104 (90.4%) of the 115 exposed patients. Among patients with available culture data, the mean age was 59.0 years (range 7-89), and there were 64 men (61.5%). Fifteen patients (14.4%) were infected with carbapenem-resistant *Klebsiella pneumoniae* (CRE) as identified by culture data, which were confirmed as $bla_{\text{OXA-232}}$ by PCR. Of the 15 CRE-infected patients, 8 (7.7%) were actively infected, requiring urgent treatment (Fig. 1). The average time between duodenoscope exposure and acute CRE infection, as defined by clinical symptoms and positive culture, was 44 days (range 4-90 days). The remaining 7 patients (6.7%) were asymptomatic and identified as being colonized with CRE during the screening process. Surveillance cultures available for 3 patients demonstrated spontaneous decolonization of CRE at an average of 255 days (range 201-298 days).

Risk factors for transmission—univariate analysis

The 15 cases/patients who acquired CRE were similar in age and sex to the group of patients who remained uninfected after ERCP with a contaminated duodenoscope. Recent antibiotic exposure within the 90 days before the ERCP (73.3% vs 37.1%; $P = .019$) was associated with an increased risk of CRE acquisition (Table 1). Inpatients who underwent ERCP were more likely to develop CRE infection than outpatients (60.0% vs 28.1%; $P = .034$). In addition, patients with cholangiocarcinoma (26.7% vs 3.4%; $P = .008$) were at higher risk of acquiring CRE during ERCP. No other patient-related risk factors were determined to be significant.

During ERCP, biliary stent placement (53.3% vs 22.5%; $P = .024$) was the only procedure-related risk factor that was associated with an increased risk of CRE transmission. ERCP with direct cholangioscopy (20.0% vs 4.5%; $P = .060$) appeared to increase the risk of CRE infection, although it did not reach statistical significance.

Risk factors for transmission—multivariate analysis

Patients with cholangiocarcinoma often are managed with antibiotics for cholangitis and stent placement for biliary decompression. A multivariate analysis was performed, adjusting for cholangiocarcinoma as a possible confounding variable. On logistic regression analysis, active inpatient status (OR 3.74; 95% confidence interval [CI], 1.15-12.12) and biliary stent placement (OR 3.62; 95% CI, 1.12-11.67) were observed to be independent risk factors for the transmission of CRE during ERCP (Table 2). Prior antibiotic exposure (OR 3.31; 95% CI, 0.97-11.31) did not maintain a significant association with the risk of CRE transmission after multivariate analysis.

Comparison of actively infected versus colonized patients

Among the 15 patients who acquired CRE after ERCP, active infection was more common in men (87.5% vs 14.3%; $P = .010$) as compared with those who were colonized. Patients who developed active CRE infection also underwent biliary stent placement (87.5% vs 14.3%; $P = .010$) more often than those who were colonized. No other significant differences were observed between the patients who were actively infected or colonized (Table 3).

Patients lost to follow-up

Of the 115 patients exposed to a contaminated duodenoscope during ERCP, 11 patients (9.6%) were lost to follow-up. The indication for the procedures and the interventions performed are listed in Table 4.

DISCUSSION

This study represents an initial attempt to identify clinical risk factors for the transmission of CRE infection after exposure to a contaminated duodenoscope. During the CRE outbreak at our institution, 2 duodenoscopes were epidemiologically linked to the transmission of the multi-drug resistant bacteria among exposed patients. The ensuing investigation resulted in the collection of culture data and screening samples on over 90% of the patients who underwent ERCP with 1 of the 2 contaminated duodenoscopes during the time period. This provided a unique opportunity to closely examine the clinical risk factors that may have a role in the transmission of CRE during ERCP.

The complex design of the duodenoscope leads to difficulty in reprocessing, and previously reported outbreaks were attributed to breaches in duodenoscope reprocessing and to damaged devices.[4,13-15] However, the recent wave of duodenoscope-related CRE outbreaks has occurred despite strict adherence to reprocessing guidelines.[3,6,16,17] The apparent epidemiologic link between CRE infections

TABLE 1. Univariate analysis of demographics and clinical characteristics of patients exposed to the contaminated duodenoscopes (n = 104)

Characteristics	Cases (n = 15)	Controls (n = 89)	*P* value
Age, mean (range), y	57.7 (18-77)	59.3 (7-89)	.755
Men, no. (%)	8 (53.3)	56 (62.9)	.675
Exposures within 90 days before ERCP			
Antibiotics	11 (73.3)	33 (37.1)	.019
Prior hospitalization	12 (80.0)	44 (49.4)	.055
Invasive procedures*	8 (53.3)	34 (38.2)	.412
Indication for ERCP			
Malignant biliary stricture	5 (33.3)	17 (19.1)	.302
Benign biliary stricture	3 (20.0)	23 (25.8)	.756
Bile duct stone	3 (20.0)	21 (23.6)	1.0
Pancreatic duct stone	0	5 (5.6)	1.0
Bile leak	0	4 (4.5)	1.0
Other	4 (26.7)	19 (21.3)	.738
Patient-related			
Active inpatient status	9 (60.0)	25 (28.1)	.034
Prior MDR organism	0	3 (3.4)	1.0
Cirrhosis	2 (13.3)	2 (2.2)	.099
Immunosuppression	5 (33.3)	26 (29.2)	.765
Diabetes	2 (13.3)	15 (16.9)	1.0
Solid organ transplant	1 (6.7)	17 (19.1)	.459
Active cancer	5 (33.3)	20 (22.5)	.348
Pancreatic adenocarcinoma	1 (6.7)	7 (7.9)	1.0
Cholangiocarcinoma	4 (26.7)	3 (3.4)	.008
Procedure-related			
Biliary stent placement	8 (53.3)	20 (22.5)	.024
Cholangioscopy	3 (20.0)	4 (4.5)	.060
Biliary sphincterotomy	6 (40.0)	17 (19.1)	.093
Bile duct stone removal	3 (20.0)	27 (30.3)	.545
Multiple ERCPs	3 (20.0)	7 (7.9)	.156
Total duration, mean (range), min	48.6 (10-148)	40.1 (3-169)	.333

MDR, Multidrug-resistant.
*Any procedure involving a break in the skin (surgery, percutaneous, etc) or endoscopy.

TABLE 2. Multivariate analysis adjusting for cholangiocarcinoma

Characteristic	Cases (n = 15)	Controls (n = 89)	Adjusted OR (95% CI)	*P* value
Antibiotic exposure before ERCP, no. (%)	11 (73.3)	33 (37.1)	3.31 (0.97-11.31)	.057
Active inpatient status	9 (60.0)	25 (28.1)	3.74 (1.15-12.12)	.028
Biliary stent placement	8 (53.3)	20 (22.5)	3.62 (1.12-11.67)	.032

OR, Odds ratio; *CI,* confidence interval.

and duodenoscope exposure has suggested an inherent challenge in the endoscope's design leading to an inability to adequately clean the device. More specifically, the unique elevator channel of the duodenoscope has been implicated as the source of transmission. A previous study showed that up to 19% of elevator channels were inadequately cleaned despite proper manual cleaning.[18] In a detailed examination of the tip of the duodenoscope, Verfaillie et al[2] found that the recess under the elevator was difficult to access both by manual cleaning and

TABLE 3. Clinical characteristics of patients actively infected and colonized with CRE

Characteristic	Active infection, (n = 8)	Colonized, (n = 7)	*P* value
Age, mean (range), y	58.4 (18-77)	57 (36-74)	.884
Men, no. (%)	7 (87.5)	1 (14.3)	.010
Exposures within 90 days before ERCP, no. (%)			
Antibiotics	6 (75.0)	4 (57.1)	.608
Prior hospitalization	7 (87.5)	5 (71.4)	.569
Invasive procedures*	4 (50.0)	4 (57.1)	1.0
Indication for ERCP			
Malignant biliary stricture	3 (37.5)	2 (28.6)	1.0
Benign biliary stricture	1 (12.5)	2 (28.6)	.569
Bile duct stone	2 (25.0)	1 (14.3)	1.0
Patient related			
Active inpatient status	6 (75.0)	3 (42.9)	.315
Prior MDR organism	0 (0)	0 (0)	1.0
Cirrhosis	0 (0)	2 (28.6)	.200
Immunosuppression	2 (25)	3 (42.9)	.608
Solid organ transplant	0 (0)	1 (14.3)	.608
Pancreatic adenocarcinoma	1 (12.5)	0	1.0
Cholangiocarcinoma	2 (25.0)	2 (28.6)	1.0
Procedure-related			
Biliary stent placement	7 (87.5)	1 (14.3)	.010
Cholangioscopy	2 (25.0)	1 (14.3)	1.0
Biliary sphincterotomy	3 (37.5)	3 (42.9)	1.0
Bile duct stone removal	1 (12.5)	2 (28.6)	.569
Multiple ERCPs	1 (12.5)	2 (28.6)	.569
Total duration, mean (range), min	42.2 (19-81)	55.9 (10-148)	.509

CRE, Carbapenem-resistant Enterobacteriaceae; *MDR,* multidrug-resistant.
*Any procedure involving a break in the skin (surgery, percutaneous, etc) or endoscopy.

TABLE 4. Patients lost to follow-up: indications for ERCP and interventions performed

	Indication for ERCP	ERCP intervention
1	Malignant biliary stricture	Failed ERCP due to distorted ampulla
2	Bile duct stone	ERCP with stone removal, biliary stent placement
3	Malignant biliary stricture	ERCP with biliary stent placement
4	Suspected bile leak	ERCP—no leak identified
5	Suspected bile leak	ERCP with biliary stent placement
6	Benign biliary stricture	ERCP with biliary stent placement
7	Ampullary adenoma	ERCP with biopsy of the ampulla
8	Bile duct stone	ERCP with stone removal
9	Ampullary adenoma	ERCP with biopsy of the ampulla
10	Prior gallstone pancreatitis	ERCP with biliary stent removal
11	Bile duct stone	ERCP with stone removal

high-level disinfection. The authors ultimately identified the source of a carbapenem-resistant *Pseudomonas aeruginosa* outbreak when a verona integron-encoded metallo-β-lactamase (VIM-2) strain of *Pseudomonas aeruginosa* was isolated from a swab collected from the elevator channel.

Similar to another duodenoscope-associated CRE outbreak,[16] cultures performed on the implicated

duodenoscopes in our outbreak did not grow any bacteria, let alone CRE. The 2 contaminated duodenoscopes were identified based solely on a clear epidemiologic link between the infected patients and their shared exposure to 1 of these 2 duodenoscopes. Our institution's infection prevention team did not identify any other common exposures among the infected patients, and no further CRE infections have occurred since removal of the 2 duodenoscopes and the institution of an enhanced duodenoscope reprocessing protocol. The discouraging reality that duodenoscopes can be contaminated with bacteria such as CRE whereas being culture-negative has important repercussions on the reprocessing and reuse of these duodenoscopes. We posit that the inability to identify positive cultures on contaminated duodenoscopes may either be related to the inaccessibility of the bacteria within the elevator channel of the duodenoscope or the inhibition of bacterial growth from the bacteriostatic effects of residual disinfectant used during duodenoscope reprocessing.

Another institution recently disclosed details of an investigation of their own CRE outbreak and their adoption of a culture and quarantine method for 48 hours after reprocessing of their duodenoscopes.[19] Under this protocol, if the culture result is negative for pathogens at 48 hours, the duodenoscope is released for reuse. Although the authors should be commended for their novel approach to combat this issue, the question remains as to whether this method can truly be effective in preventing future CRE outbreaks if CRE is not routinely able to be cultured from contaminated instruments. Given the inability of culturing to identify bacterial duodenoscope contamination at our institution, we enhanced our reprocessing protocol by adding gas sterilization with ethylene oxide after standard high-level disinfection for all endoscopes with an elevator channel including duodenoscopes and linear echoendoscopes.

In our study, we found that biliary stent placement, cholangiocarcinoma, and active inpatient status are independent risk factors associated with an increased risk of CRE infection after duodenoscope exposure. Biliary stent placement would appear to be a biologically plausible risk factor as the central lumen of these stents may serve as a conduit for the transmission of bacteria into the bile duct. The prolonged dwell time of the stent may further increase both the risk of bacterial transmission as well as the risk of developing clinical infection. Patients with a history of cholangiocarcinoma also were observed to be at increased risk, possibly because of inadequate drainage of proximal bile ducts injected with contrast material during ERCP. Biliary stasis upstream of the obstructing tumor could facilitate bacterial colonization and infection. Overall, our findings suggest that patients with biliary obstruction are more likely to develop infectious adverse events during ERCP. This is consistent with previous studies that have evaluated the risk factors for post-ERCP bacteremia in retrospective analyses.[20-22] We suspect that active inpatient status is a surrogate marker for sicker patients with multiple comorbidities who may be more susceptible to nosocomial infections such as CRE. We were unable to perform additional multivariate analyses to further investigate this because of the small cohort of infected patients.

In a previous CRE outbreak in Illinois, Epstein et al[6] similarly found that CRE-infected patients were more likely to have undergone biliary stent placement (risk ratio 2.8; 95% CI, 1.7-4.5) during ERCP, although culture data were available only for half of the exposed patients. Multiple duodenoscope exposures also were found to be associated with case patients, although we did not find this to be statistically significant in our study.

Patients exposed to a contaminated duodenoscope should be followed closely for months after ERCP. Among the 8 patients who became actively infected with CRE in our study, the average time between the inciting ERCP and the development of symptoms was 44 days. Notably, there was a wide range with the earliest clinical presentation at 4 days after the procedure whereas another patient presented with symptoms 90 days after the ERCP. Of the CRE-colonized patients, 3 patients had spontaneous clearance at an average of 255 days, ranging from 201 to 298 days. In a study tracking the natural history of CRE infection and colonization after a large outbreak in Germany, most patients had spontaneous decolonization within the first 6 months.[23] However, a small minority of patients was still colonized with CRE after 1 year, and 1 patient continued to be CRE positive after more than 3 years. Based on our study results and limited published data, it appears that patients can develop an acute CRE infection up to 3 months after exposure to a contaminated duodenoscope, and colonized patients should be closely observed for the first 6 months or until decolonization is achieved.

Despite all of the recent attention focused around duodenoscope-associated CRE outbreaks, it is imperative to understand that the risk of transmitting CRE infections via duodenoscope remains extremely low. In order for a patient to acquire a multidrug-resistant organism such as CRE via ERCP, 5 requisite events must occur. First, an index patient must be colonized with CRE, which still remains an uncommon infection in the United States. The incidence rate of CRE infection has been documented to be as low as 1.4 cases per 100,000 patient-days in the inpatient setting.[24] Second, a colonized patient would need to undergo an ERCP with a duodenoscope. It is estimated that approximately 500,000 ERCPs are performed each year.[25] Third, the duodenoscope used to perform the ERCP on the index patient would need to become contaminated with CRE during the ERCP procedure and remain contaminated despite postprocedure disinfection. Ross et al[19] demonstrated that duodenoscopes become colonized with a pathogenic bacterial species in

Requisite Events	Probabilities/Rates
1. Index patient is colonized with CRE	1.4 cases per 100,000 inpatient days[22]
2. CRE-colonized patient undergoes ERCP	500,000 ERCPs performed per year in the U.S.[23]
3. Duodenoscope becomes colonized with CRE despite disinfection	1.9% of duodenoscopes colonized with pathogenic bacteria despite disinfection[18]
4. Patient has ERCP via contaminated duodenoscope and acquires CRE	14.4% transmission rate
5. Colonized patient becomes actively infected with CRE	53.3% of CRE-transmitted cases

Figure 2. Five requisite events that must occur to transmit a carbapenem-resistant Enterobacteriaceae infection via duodenoscope along with the probabilities/rates of each event. *CRE,* carbapenem-resistant Enterobacteriaceae.

approximately 1.9% of all ERCP cases. Fourth, subsequent patients would need to undergo ERCP with the contaminated duodenoscope and acquire CRE. The observed transmission rate of CRE from duodenoscope exposure from our study was 14.4%. Fifth, and finally, the colonized patient would need to become actively infected with systemic dissemination of CRE into the blood stream, peritoneum, or urinary tract, which occurred in just over half of our CRE-transmitted cases (8/15 patients, 53.3%) (Fig. 2). Based on these calculations, the probability that a patient undergoing ERCP with a contaminated duodenoscope will develop a clinically relevant CRE infection is approximately 7.7%. Although this risk is not insignificant, we believe ERCP is a critical, life-saving procedure that is safe for patients and remains the least-invasive means of treating pancreaticobiliary diseases.

We acknowledge that there are several limitations to our study. Due to the small number of CRE-infected patients in our cohort, we combined both the actively infected and colonized patients when performing our statistical analyses. Even after combining all of the case patients, we were limited in performing multivariable analyses due to our small sample size. Second, our study cohort was followed for up to 1 year after being exposed to a contaminated duodenoscope during ERCP. As the natural history of CRE infection and colonization is unknown, it is possible that more patients may turn out to be colonized on subsequent screening tests or that asymptomatic patients originally colonized with CRE who undergo delayed testing may have spontaneously cleared the organism. Although we were able to collect culture data on over 90% of the exposed patients, we acknowledge that any missing data in a small study may have implications on the overall statistical results. Of the 11 patients who were lost to follow-up, 4 of these patients underwent ERCP with biliary stent placement for biliary obstruction. The culture results from these patients may have further impacted our study results.

In conclusion, it has become increasingly apparent that duodenoscope exposure has been associated with outbreaks of multidrug-resistant bacterial infections. These outbreaks have highlighted the difficulty in adequately disinfecting these complicated devices and bacterial contamination can persist, despite strict adherence to reprocessing guidelines. Until more definitive processes for duodenoscope cleaning are developed, physicians must rely on enhanced high-level disinfection techniques and their clinical judgment regarding specific patients and procedures that may be at increased risk for CRE transmission. Our study reveals that biliary stent placement, a history of cholangiocarcinoma, and active inpatient status are independent risk factors for CRE transmission during ERCP by using a contaminated duodenoscope. For circumstances in which a concern for CRE transmission via contaminated duodenoscopes were to arise, patients with these high-risk clinical risk factors and the duodenoscopes used in these patients should be monitored closely to aid in early recognition and prevention of future outbreaks of ERCP-related CRE infection.

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