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Carbapenem Resistant Enterobacteriaceae and Endoscopy: An Evolving Threat

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Abstract

Background—Several clusters of carbapenemase resistant enterococci (CRE) infections associated with contaminated endoscopes have recently been reported. Interim guidelines for mitigating endoscope associated transmission have been proposed, but there has not been a systematic appraisal of CRE prevention practices.

Methods—We conducted a systematic review of endoscope associated CRE infection episodes, abstracting information on outbreak detection, mitigation, outcomes, and corrective steps taken to prevent recurrence.

Results—Seven distinct outbreaks were identified in the published literature and 5 of these were associated with duodenal endoscopy, with the remaining 2 associated with cystoscopy and ureteroscopy. Several investigators noted difficulties in cleaning protocols surrounding difficult to access components, such as the elevator on duodenoscopes.

Discussion—The published investigations did not report any failures of sterilization. It is unclear if routine reprocessing was ineffective, or difficult to execute properly.

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Online supplementary material: 1 appendix

Conclusions—Meticulous cleaning protocols and increased surveillance are necessary to prevent and detect future outbreaks of CRE and to determine whether more stringent measures, such as sterilization are needed for duodenoscopes.

Keywords

CRE; carbapenem resistant enterobacteriaceae; duodenoscope; endoscopy; ERCP

Introduction

Klebsiella pneumoniae carbapenemase (KPC) producing bacteria was originally reported in the United States in 1996.[1] This organism was sporadically reported in the northeastern United States for some years before being detected internationally.[2] Since then, the carbapenemase genes expressed by *Klebsiella* have been identified in a variety of other Gram-negative organisms. Carbapenem resistant Enterobacteriaceae (CRE) healthcare-associated infections have been associated with a number of patient attributes such as acute renal failure, parenteral nutrition, and previous antibiotic exposures. Treatment options for CRE organisms are typically limited, and infections have been associated with more than twice the risk of death. [3, 4] A significant risk factor appears to be procedure and device associated infections, particularly related to endoscopic procedures.[5, 6]

In recent years several cases of endoscope-associated transmission of CRE have been reported. However, optimal prevention strategies to minimize risk of CRE infections associated with contaminated endoscopes are unclear. Considering high morbidity and mortality associated with CRE bacteria, prevention of these healthcare associated infections should be considered a priority for patient safety and quality of care. We report our findings of a systematic review of published outbreaks of endoscope associated CRE infections or colonization and effectiveness of mitigation measures.

Methods

An experienced medical librarian (AF) created the search strategy. Following peer-review by another experienced librarian, the searches were adapted and run in Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Web of Science and Scopus. There were no restrictions to language or publication date. Medical Subject Headings (MeSH) and keywords were utilized; these included endoscopy, Enterobacteriaceae, sterilization and disinfection. Searches were completed in June 2015. See the appendix for the complete search histories.

All abstracts were reviewed by two investigators; data were summarized for narrative review and qualitative synthesis. Inclusion criteria were cases which included a description of an outbreak of a CRE infection in humans. Excluded were all basic science papers, animal models, reviews, editorials and non-English studies. If a report of the same event duplicated in several records, peer reviewed forms (e.g. manuscripts) were preferentially excluded over abstracts and correspondence. When multiple peer reviewed manuscripts reported on the same event, both were included.

Results

Our search yielded 35 non-duplicate articles for screening. Of these, 33 were retrieved for full text review. The typical reasons for excluding articles were for reporting on non-endoscopic routes of KPC infection, or colonization rather than infection. One was excluded as, a case series of bloodstream infections associated with *Klebsiella pneumoniae* where, although 3 of the 7 patients underwent endoscopy, there was insufficient evidence that this was related to the outbreak.[7] Two were excluded as abstract versions of a case series where a manuscript reporting more detail was available.[8, 9] Another was excluded as an MMWR report on a case series reported in greater detail in JAMA.[10, 11]

This is summarized in a PRISMA flow diagram (figure 1). Seven studies were ultimately included, summarized in Table 1.

Description of the studies

Naas *et al.* 2010 and Carbonne *et al.*, 2010 both reported on the same outbreak in a French medical intensive care unit associated with a duodenoscope. Following endoscopy for a patient with severe gastrointestinal bleed who had screened positive for extended spectrum beta lactamase producing *E. coli*, repeat surveillance screening found an MDR *K. pneumoniae* isolate. The isolate was imipenem intermediate, and a subsequent blood culture screening found a KPC-producing *Klebsiella pneumoniae*. The same isolate was cultured from the endoscope along with enteric flora and *Pseudomonas aeruginosa*. Further screening of all contact patients via rectal swab found two patients who screened positive for KPC. Aggressive infection control measures were enacted, including awareness campaigns, reinforced hand hygiene precautions and dedicated nursing staff. However, further investigation identified 17 patients that had undergone endoscopy with the contaminated endoscope before the outbreak was identified. Ten of these patients could be screened, and six were colonized with KPC-*Klebsiella pneumoniae*. Of those colonized, one developed bloodstream infection and another infected biloma. Cross transmission was observed at an outside hospital from a patient who had transferred for further care. No deaths were attributed to KPC organisms. Investigation into cleaning practices found two potential deficiencies to explain the persistence of organisms on the device; endoscope pre-washing may have been delayed for unclear reasons, allowing for drying and adherence of debris and post-peracetic acid washing with an automated device may not have had a long enough drying cycle. The drying process was adequate per guidelines at the time, but the institution determined that the drying was not completed in the prescribed time frame. The institution made new local guidelines for reprocessing including an extended drying time to ensure complete drying after each disinfection cycle and increased the frequency of surveillance cultures of endoscopes to monthly.[9, 12]

Koo et al, 2012 reported a series of infections with New Delhi metallo-beta-lactamase NDM-1 *Klebsiella* and *E. coli* associated with a urologic endoscopic camera. A series of five cases- four urine and one blood culture- positive for NDM-1 *E. coli* triggered an investigation; all had undergone cystoscopy in the preceding 34 days. Although the manufacturer recommends glutaraldehyde decontamination or ethylene oxide (ETO) sterilization, the device was being cleaned with cloth detergent wipes only (detergent

unspecified). The video camera head was not subject to routine high level disinfection as it was deemed a non-critical item that did not usually come into direct patient contact. A swab of the camera head grew *Klebsiella*, and four additional cases were identified. The device was ultimately sterilized with ETO. Routine use of a disposable plastic sheath was also put into place, and a protocol for preoperative antibiotics for known NDM colonized patients enacted. [13]

Alrabaa et al, 2013 described an outbreak in Florida where seven patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) developed infection with carbapenemase-producing *Klebsiella pneumoniae*. Five were bloodstream infections, one hepatobiliary infection and one urinary tract infection. Investigation into the endoscopy practices found inadequate ERCP cleaning procedures related to technical challenges of cleaning an angled part of the ERCP channel, the elevator. Debris recovered from the elevator was cultured and demonstrated grow of carbapenemase producing *E. coli*. Subsequent screening of 46/51 patients who had been instrumented with the implicated scope found 3 to be colonized with carbapenemase producing organisms. One of the 7 infected patients expired and 2 were discharged to hospice care. The facility began retraining in cleaning, handling and scrubbing of the ERCP scope with particular attention to the elevator, as well as alerting providers about screening and isolation procedures for ERCP. [14]

Chang et al. 2013 reported on an outbreak associated with a contaminated ureteroscope. A single case of carbapenem-resistant *E. cloacae* was isolated in October 2010, followed by 7 urinary isolates over the next month in urology patients. An investigation began, and epidemic curve suggested a common source. By the end of this outbreak, 15 cases were identified, with 2/3 requiring hospitalization for treatment. All devices were inspected, and sterilization practices reviewed. These were felt to be adequate, and the devices continued to be used throughout the investigation. Ultimately, surveillance cultures from the ureteroscopes yielded CRE *E. cloacae*. This scope was determined to have been the most frequently used device, and was associated with all infections. It was removed from use, and all ureteroscopes were washed using a new protocol of washing with tap-water, irrigation of channels with a diluted enzymatic cleaner followed by ortho-phthaldehyde (OPA), immersion in 0.55% OPA for 15 minutes and thorough rinsing with sterile water. Despite this, repeat culture still isolated CRE *E. cloacae*. Weekly ethylene oxide sterilization was added to the disinfection protocol, with no further isolation of the organism. [15]

Epstein et al., 2014 reported an outbreak of NDM-1 associated with a duodenoscope. Eight clinical cultures and one surveillance culture triggered an investigation over a six-month period. A case-control investigation found ERCP to be a significant risk factor, and cultures obtained from the duodenoscope after high level disinfection with OPA found both NDM=1 *E. coli* and KPC *Klebsiella* from the elevator channel. Ninety-four potential exposures were notified, and 58 returned for screening, with 23 screening positive for colonization. However, 2 of those with clinical infection had subsequent ERCP with a second duodenoscope, 16/39 patients who had ERCP with the second device were screened, with one additional case screening positive for colonization. One more colonized patient from the first duodenoscope had another duodenoscopy with a third endoscope; 2 clinical cases and 3

surveillance positive cases were identified from that particular endoscope. Reviewing sterilization and cleaning procedures, no recorded breaches of protocol were identified. The outbreak terminated with implementation of ETO gas sterilization.[11]

Smith *et al.*, 2015 reported 4 cases of clinical infection with NDM-1 *E. coli* over a six-month period related to the same duodenoscope used for ERCP. Post exposure cultures found one exposure patient who was colonized, and 13 patients exposed with negative surveillance cultures. The majority of patients underwent ERCP for malignancies such as pancreatic cancer, cholangiocarcinoma, and metastases to the biliary tree. The device was removed from use, and distal tip sonicated, and channels cultured with the elevator channel both open and closed. No organisms were isolated from the endoscope, and the device was sterilized with ETO before being returned to use. The authors note that in the six-month lag between the first case and final culturing, the endoscope had undergone several high level disinfections with ETO, which may have cleared the organism.

Discussion

The recent CRE outbreaks have prompted new guidance from the Federal Drug Administration (FDA) with particular attention to ERCP duodenoscopes, such as following all manufacturer instructions for cleaning and reprocessing, reporting failures of reprocessing to the FDA, and paying meticulous attention to the elevator mechanism with hand cleaning even if otherwise using an automatic endoscope reprocessor (AER). The FDA additionally recommends discussing with patients worrisome symptoms which should prompt follow up, and prompt notification and follow up for potential exposures.[16] The Centers for Disease Control and Prevention (CDC) has released interim surveillance guidelines in response to the recent outbreaks, recommending cultures approximately after every 60 uses of the duodenoscope, or weekly on Fridays for busy centers, to give the weekend for cultures to finalize. The CDC recommendations also specify that surveillance cultures should be obtained after the endoscope is completely reprocessed, and should be obtained from the instrument channel, the elevator mechanism, recess and channel, and other sites as deemed appropriate.[17]

Chang et al. observed with their outbreak that there was delayed recognition because of the infections occurring relatively early in hospitalization, and thus not being recognized as healthcare associated infection (HAI). They advocated more specific screening for infection after endoscopy or procedures, as this, in retrospect, was easily recognized as a common-source outbreak associated with a single ureteroscope.[15]

Chang et al. concluded that OPA sterilization alone was insufficient for removing the CRE organisms. They hypothesized this to be related to formation of bacterial biofilm on device surfaces or resistance to OPA, and necessitated ETO for effective sterilization.[15] A subsequent review by Muscarella *et al.* suggested that high level disinfection is a reliable method to destroy CRE organisms, and that evidence was insufficient to require routine ETO sterilization to prevent CRE transmission from GI endoscopes.

Side viewing duodenoscopes used for ERCP have been implicated in several studies, and authors repeatedly identified the difficulty of reprocessing the elevator wire hinge component.[11, 14, 18, 19] Only two studies did not include duodenoscopes, and of these, one noted the disinfection practices in place to be inadequate. It is possible that high level disinfection is sufficient for destroying the CRE organisms (as these organisms should retain susceptibility to disinfectants) if properly executed, but the mechanical difficulty of cleaning the elevator makes failure more likely. If so, improved protocols for high level disinfection may be possible and present a more cost effective alternative to sterilization. However, no such standardized protocols exist at this time. ETO sterilization failure was not noted in any investigation, but this strategy is not typically considered viable for routine prevention because of its complexity, cost and time.

This systematic review is limited by the small number of reports to date on this emerging problem. Further, as published data are primarily limited to small case series, there is significant heterogeneity in reporting methodologies across studies. Strain typing and molecular studies were not reported in the majority of these studies, and thus it is difficult to confirm if all of the reported cases of colonization detected on subsequent screening were truly linked to the original case. Moreover, detailed reporting on the sterilization techniques was not available in most of the studies, making it difficult to compare ETO and OPA protocols. While several studies reported no lapse in their institutional sterilization protocols, the method by which this was established was reporting of known breaches rather than direct observation. As such, breaches in protocol may be more frequent and severe than the authors estimate. Finally, while few studies provide outcome data such as mortality, given that a majority of these patients were receiving endoscopy for terminal malignancies such as pancreatic cancer, it is difficult to determine the attributable morbidity and mortality due to CRE infection in these cases.

Overall, there is insufficient evidence at present to determine whether or not sterilization should be routinely undertaken for duodenoscopes. While ETO and OPA protocols are effective, issues of endoscope inventory and resource allocation make them difficult to implement and it is not known whether these approaches are necessary beyond high level disinfection. However, improvement in methods to reliably clean difficult to access components, like the duodenoscope elevator, are needed. Periodic culturing as recommended by national guidelines may be useful to detect and prevent procedure-related outbreaks due to CRE.

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References

1. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 2001; 45:1151–61. [PubMed: 11257029]
2. Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis*. 2011; 17:1791–8. [PubMed: 22000347]
3. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol*. 2008; 29:1099–106. [PubMed: 18973455]
4. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis*. 2013; 13:785–96. [PubMed: 23969216]
5. Orsi GB, Garcia-Fernandez A, Giordano A, Venditti C, Bencardino A, Gianfreda R, et al. Risk factors and clinical significance of ertapenem-resistant *Klebsiella pneumoniae* in hospitalised patients. *Journal of Hospital Infection*. 2011; 78:54–8. [PubMed: 21450365]
6. Orsi GB, Venditti M. Carbapenem-resistant *Klebsiella pneumoniae* transmission associated to endoscopy. *Am J Infect Control*. 2013; 41:849–50.
7. Nadkarni AS, Schliep T, Khan L, Zeana CB. Cluster of bloodstream infections caused by KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Manhattan. *Am J Infect Control*. 2009; 37:121–6. [PubMed: 19249638]
8. Sanderson R, Braithwaite L, Ball L, Ragan P, Eisenstein L. An outbreak of carbapenem-resistant *klebsiella pneumoniae* infections associated with endoscopic retrograde cholangiopancreatography (ERCP) Procedures at a hospital. *Am J Infect Control*. 2010; 38(5):E141.
9. Naas T, Cuzon G, Babics A, Fortineau N, Boytchev I, Gayral F, et al. Endoscopy-associated transmission of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-2 beta-lactamase. *Journal of Antimicrobial Chemotherapy*. 2010; 65:1305–6. [PubMed: 20382724]
10. Notes from the Field: New Delhi metallo-beta-lactamase-producing *Escherichia coli* associated with endoscopic retrograde cholangiopancreatography - Illinois, 2013. *MMWR Morb Mortal Wkly Rep*. 2014; 62:1051. [PubMed: 24381080]
11. Epstein L, Hunter JC, Arwady MA, Tsai V, Stein L, Gribogiannis M, et al. New Delhi metallo-beta-lactamase-producing carbapenem-resistant *Escherichia coli* associated with exposure to duodenoscopes. *Jama*. 2014; 312:1447–55. [PubMed: 25291580]
12. Carbonne A, Thiolet JM, Fournier S, Fortineau N, Kassis-Chikhani N, Boytchev I, et al. Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009. *Euro Surveill*. 2010; 15.
13. Koo VS, O'Neill P, Elves A. Multidrug-resistant NDM-1 *Klebsiella* outbreak and infection control in endoscopic urology. *BJU Int*. 2012; 110:E922–6. [PubMed: 23107243]
14. Alrabaa S. Early identification and control of carbapenemase-producing *Klebsiella pneumoniae*, originating from contaminated endoscopic equipment. *Am J Infect Control*. 2013; 41:850.
15. Chang CL, Su LH, Lu CM, Tai FT, Huang YC, Chang KK. Outbreak of ertapenem-resistant *Enterobacter cloacae* urinary tract infections due to a contaminated ureterscope. *Journal of Hospital Infection*. 2013; 85:118–24. [PubMed: 23954065]
16. FDA. , editor. Effective Reprocessing of Endoscopes used in Endoscopic Retrograde Cholangiopancreatography (ERCP) Procedures. Washington, DC: 2015.
17. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), (DHQP) DoHQP. Interim Protocol for Healthcare Facilities Regarding Surveillance for Bacterial Contamination of Duodenoscopes after Reprocessing. Services HaH. , editor. Centers for Disease Control and Prevention; Atlanta, GA: 2015.
18. Smith ZL, Oh YS, Saeian K, Edmiston CE, Khan AH, Massey BT, et al. Transmission of carbapenem-resistant Enterobacteriaceae during ERCP: Time to revisit the current reprocessing guidelines. *Gastrointestinal Endoscopy*. 2015; 81:1041–5. [PubMed: 25638508]
19. Banerjee S, Shen B, Nelson DB, Lichtenstein DR, Baron TH, Anderson MA, et al. Infection control during GI endoscopy. *Gastrointestinal Endoscopy*. 2008; 67:781–90. [PubMed: 18355826]

Figure 1.
PRISMA diagram detailing search strategy

Table 1

Included studies.

Study	Location	Type(s) of equipment	Number of cases	Organisms involved	Disinfection/sterilization notes
Naas et al., 2010(9) and Carbone et al., 2010(12)	France	Duodenoscope	3 infected, at least 10 colonized	<i>Klebsiella pneumoniae</i> , ST258 clone with SHV-11 and SHV 12 plasmid elements	The hospital changed to a glutaraldehyde decontamination bath followed by automated peracetic acid washer because of concern about Creutzfeldt-Jacob transmission; there may have been deficiencies in cleaning associated with the change in protocol
Koo et al., 2012(13)	UK	Cystoscope	5 infected, 4 colonized	<i>Klebsiella pneumoniae</i> , NDM-1	Deficiencies noted in cleaning protocol of head of device; outbreak stopped with ETO sterilization
Alrabaa et al., 2013(14)	United States	Duodenoscope	7 infections 3 colonized	<i>Klebsiella pneumoniae</i> ; <i>Escherichia coli</i>	Found to have a deficiency in mechanical removal of debris
Chang et al., 2013(15)	China	Uteroscope	15	<i>E. cloacae</i> , mostly with SHV-12 and IMP-8 genes	OPA sterilization alone failed to clear the device; required weekly ETO treatments
Epstein et al., 2014(11)	United States	Duodenoscope	10 cases, 28 colonized out of 100 screened/ cultured	NDM-1 <i>E. coli</i>	HLD with OPA; outbreak terminated when changing to sterilization with ETO
Smith et al., 2015(18)	United States	Duodenoscope	4 infections, 1 colonization	NDM-1 <i>E. coli</i>	Routine HLD; exact methodology not specified

ETO=Ethylene oxide, OPA=Ortho-phthaldehyde