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Major article

Outbreaks of carbapenem-resistant *Enterobacteriaceae* infections associated with duodenoscopes: What can we do to prevent infections?

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Recent outbreaks with carbapenem-resistant *Enterobacteriaceae* (CRE) in patients who have undergone endoscopic retrograde cholangiopancreatography (ERCP) have raised concerns of whether current endoscope reprocessing guidelines are adequate to ensure a patient-safe endoscope. Unlike previous outbreaks, these CRE outbreaks occurred even though manufacturer's instructions and professional guidelines were followed correctly. This article reviews why outbreaks associated with endoscopes continue to occur; what alternatives exist that might improve the margin of safety associated with duodenoscope reprocessing; and how to prevent future outbreaks associated with ERCP procedures. The advantages and disadvantages for the proposed enhancements for reprocessing duodenoscopes are reviewed as well as future strategies to prevent GI endoscope-related outbreaks.

In the last 2 years, multiple reports of outbreaks have led the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and national news to raise awareness among the public and health care professionals that the complex design of duodenoscopes (used primarily for endoscopic retrograde cholangiopancreatography [ERCP]) may impede effective reprocessing.[1,2] Several recent publications have associated multidrug-resistant (MDR) bacterial infections, especially those caused by carbapenem-resistant *Enterobacteriaceae* (CRE), in patients who have undergone ERCP with reprocessed duodenoscopes.[3-5] Unlike other endoscope outbreaks, these recent outbreaks occurred even when the manufacturer's instructions and professional guidelines were followed correctly.[3,4] The purpose of this article, which is adapted from recent publications,[6,7] is 3-fold: (1) why do outbreaks associated with endoscopes continue to occur; (2) what alternatives exist today that might improve the safety margin associated with duodenoscope reprocessing; and (3) how to prevent future outbreaks associated with ERCP endoscopes and other gastrointestinal (GI) endoscopes.[6]

The key concern raised by these outbreaks is that current reprocessing guidelines are not adequate to ensure a patient-safe GI endoscope (one devoid of potential pathogens) because the margin of safety associated with reprocessing endoscopes is minimal or nonexistent. There are 2 (and possibly 3) reasons for this reprocessing failure and why outbreaks continue to occur. First, studies have shown that the internal channel of GI endoscopes, including duodenoscopes, may contain $10^{7\text{-}10}$ (7-10 $\log_{10}$) enteric microorganisms.[8,9] Investigations have demonstrated that the cleaning step in endoscope reprocessing results in a 2-6 $\log_{10}$ reduction of microbes, and the high-level disinfection (HLD) step results in another 4-6 $\log_{10}$ reduction of mycobacteria, for a total 6-12 $\log_{10}$ reduction of microbes.[8-10] Therefore, the margin of safety associated with cleaning and HLD of GI endoscopes is minimal or nonexistent (level of contamination: 4 $\log_{10}$ [maximum contamination, minimal cleaning/HLD] to -5 $\log_{10}$ [minimum contamination, maximum cleaning/HLD]). Therefore, any deviation from proper reprocessing (eg, crevices associated with the elevator channel) could lead to failure to eliminate contamination, with a possibility of subsequent patient-to-patient transmission. This low (or nonexistent) margin of safety associated with endoscope reprocessing compares with the 17 $\log_{10}$ margin of safety associated with cleaning and sterilization of surgical instruments (ie, 12 $\log_{10}$ reduction via sterilization and at least a net 5 $\log_{10}$ reduction based on

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microbial load on surgical instruments [2 $\log_{10}$] and microbial reduction via a washer disinfector [7 $\log_{10}$]).

Second, GI endoscopes not only have a heavy microbial contamination (10^7-10^{10} bacteria), but they are complex, with long, narrow channels and right angle turns and have difficult to clean and disinfect components (eg, elevator channel). The elevator channel in duodenoscopes is unique to side-viewing endoscopes. It has a separate channel and provides orientation of catheters, guidewires, and accessories into the endoscopic visual field.[6,7] This channel is complex in design and has crevices that are difficult to access with a cleaning brush and may impede effective reprocessing.[2] Based on this and other recent studies, it is likely that MDR pathogens are acting as a marker or indicator organism for ineffective reprocessing of the complex design of duodenoscopes, which is an infectious risk to patients. It is unclear if echoendoscopes that have an elevator channel for the same reasons as ERCP scopes (directing accessories) pose the same disinfection challenges and similar infectious risks because these scopes are used to violate otherwise sterile spaces when used to obtain diagnostic samples and for therapeutic interventions.

The third issue that could impact endoscope reprocessing failure and continued endoscope-related outbreaks is the development of a biofilm.[11] Biofilms are multilayered bacteria plus exopolysaccharides that cement cells to surfaces. They develop in a wet environment. If reprocessing is performed promptly after use and the endoscope is dry, the opportunity for biofilm formation is minimal.[12] It is unclear if biofilms contribute to failure of endoscope reprocessing.

Given the heavy microbial contamination (10^7-10^{10}) and endoscope components that are difficult to clean and disinfectant (eg, elevator channel), are current endoscope reprocessing guidelines adequate to ensure a GI endoscope devoid of potential pathogens? To examine this question we briefly review the current knowledge on endoscope reprocessing and then offer recommendations. First, endoscopes are semicritical items that require at least HLD.[13,14] Because flexible GI endoscopes are currently heat labile, only HLD with FDA-cleared high-level disinfectants or low-temperature sterilization technologies (LTSTs) are possible.[13] Unfortunately, at present, no solution exists that has been proven to eliminate the risk of microbial contamination associated with duodenoscopes. For example, there is no LTST that achieves a sterility assurance level (SAL) of 10^{-6} for GI endoscopes such as duodenoscopes. Second, there have been more health care–associated outbreaks linked to contaminated endoscopes than to any other reusable medical device.[13,15] However, until recently, these outbreaks have been traced to deficient practices, such as inadequate cleaning, inappropriate disinfection (eg, failure to perfuse all channels), and damaged endoscopes or flaws in the design of endoscopes (eg, duodenoscope elevator channel) or automated endoscope reprocessors.[13,15] Reprocessing failures have led to patient notifications and bloodborne pathogen testing in dozens of instances.[16] Third, evidence-based endoscope reprocessing guidelines have been prepared by professional organizations and the CDC, and past data suggested that rigorous adherence to these guidelines would result in a patient-safe endoscope.[13,14] Unfortunately, there are also data that demonstrate that all of the steps associated with manual endoscope reprocessing are rarely performed and some essential steps (eg, brushing all endoscope channels and components) are uncommonly performed.[17] Endoscope reprocessing was improved with the use of automated endoscope reprocessors because most steps were automated.[17] Fourth, endemic transmission of infections associated with GI endoscopes may go unrecognized because of inadequate surveillance of outpatient procedures, the long lag time between colonization and infection, and a low frequency of infection. Additionally, the risk for some procedures might be lower than others (eg, colonoscopy vs ERCP, where normally sterile areas are contaminated in the latter). In the outbreak reported by Wendorf et al, it was the presence of an unusual pathogen (AmpC-producing *Escherichia coli*) that resulted in an investigation and recognition that duodenoscopes were the source of the outbreak.[3]

What should we do now? Unfortunately, there is currently no single, simple, and proven technology or prevention strategy that hospitals can use to guarantee patient safety. Of course, we must continue to emphasize the enforcement of evidence-based practices, including equipment maintenance and routine audits, with at least yearly competency testing of reprocessing staff.[13,14] All reprocessing personnel must be knowledgeable and thoroughly trained on the reprocessing instructions for duodenoscopes. This includes the new recommendations to use a small bristle cleaning brush and for additional flushing and cleaning steps of the elevator channel (http://medical.olympusamerica.com/sites/default/files/pdf/150326_TJF-Q180V_Customer_letter.pdf). Although these steps were described as validated, no public data are available on the ability of these new cleaning recommendations to yield an ERCP scope devoid of bacteria. However, we must do more or additional outbreaks will likely continue. We must obtain additional information on the frequency and level of microbial contamination of endoscopes that have been cleaned and high-level disinfected with strict adherence to current guidelines. If endoscopes are found to be contaminated with potential pathogens (eg, enteric gram-negative bacilli), the clinical impact of such contamination needs to be quantified. In addition, based on the study by Wendorf et al and others,[3-5] it would be reasonable to consider periodic microbiologic surveillance of duodenoscopes to assess microbial contamination as a component of a prevention strategy; however, culture results are delayed 2-3 days, and there are many questions related to microbiologic surveillance.[1] These include the following: what cutoff should be used to define proper disinfection (eg, 0 pathogens or a higher number, such as <10 colony forming units [CFU] of enteric pathogens per channel)?; should there be a separate cutoff based on relatively nonvirulent pathogens, such as coagulase-negative *Staphylococcus*?; what sampling scheme should be used to evaluate GI endoscopes (eg, all scopes or a sample of endoscopes)?; if a hospital cultures 2 endoscopes of 10 and 1 endoscope is positive, do they reprocess all 10 endoscopes because 50% of the sampled endoscopes are positive?; if a hospital does periodic microbiologic culturing and 20% of sampled endoscopes are positive, what actions should an endoscopy unit undertake (eg, patient notification with an offer of bloodborne pathogen testing, stool examination for CRE, ethylene oxide [ETO] sterilization of positive endoscopes, or HLD followed by ETO sterilization of all duodenoscopes)?; has the staff been trained on culturing the duodenoscope channels and the elevator channel?; and is the trigger for further action based on the level of contamination or the frequency of contamination (ie, percent of endoscopes contaminated) or infection?[6,7] In addition, if a hospital decides to culture all endoscopes and quarantine endoscopes for 48-72 hours while awaiting culture results before using the scope, it must be recognized that the sensitivity of culturing the elevator channel of the scope or the scope is unknown (ie, how many microbes must contaminate the endoscope to yield a positive culture?). Until there are evidence-based guidelines, individual hospitals should base their decisions on best available information (eg, clinical risk) and what is feasible for theirhospital.

Real-time, monitoring methods need to be developed and validated to assess the effectiveness of cleaning and HLD and the risk of infection. Adenosine triphosphate (ATP) detection of effluent has been offered as a monitoring tool[18,19] for assessing cleaning because it detects organic residuals. Although ATP may be used to assess endoscope cleaning, it is neither a good indicator of microbial contamination nor validated as a method to assess the risk for patient-to-patient transmission. A validation study of ATP used to audit cleaning of flexible endoscope channels used a benchmark for