LESSONS FROM OUTBREAKS OF MULTIDRUG-RESISTANT PATHOGENS ASSOCIATED WITH ENDOSCOPES: POSSIBLE SHORT AND LONG TERM SOLUTIONS

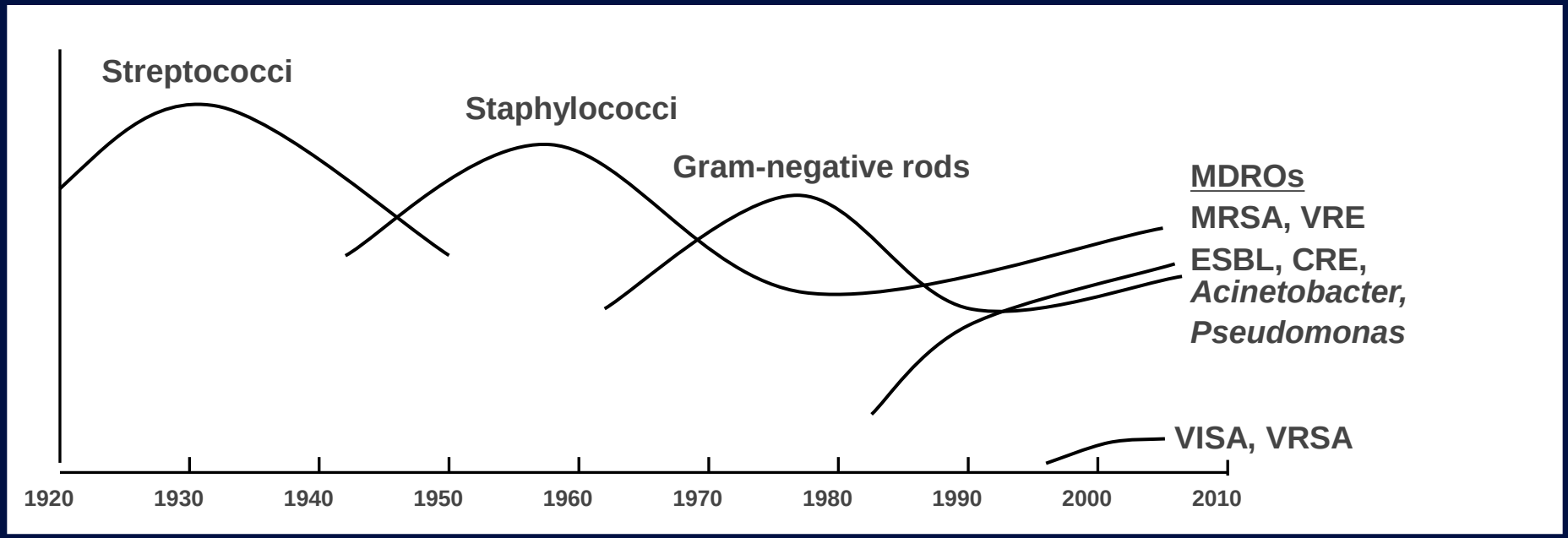
David J. Weber, M.D., M.P.H.
Professor of Epidemiology, Medicine & Pediatrics
Associate Chief Medical Officer, UNC Health Care
UNC Health Care, Chapel Hill, NC

No conflicts or disclosures; Thanks to Dr. William Rutala for some slides

LECTURE GOALS

- Prevalence and impact of multidrug-resistant organisms (MDROs)
- Endoscopy related infections in the past: Frequency and causation
- Reasons endoscopy-associated outcomes occur
- Recent endoscope-associated outbreaks due to MDROs
- Immediate steps that should be taken to reduce endoscope-associated outbreaks
- Long term solutions to endoscope-associated outbreaks

MAJOR NOSOCOMIAL PATHOGENS OF THE 20TH AND 21ST CENTURIES

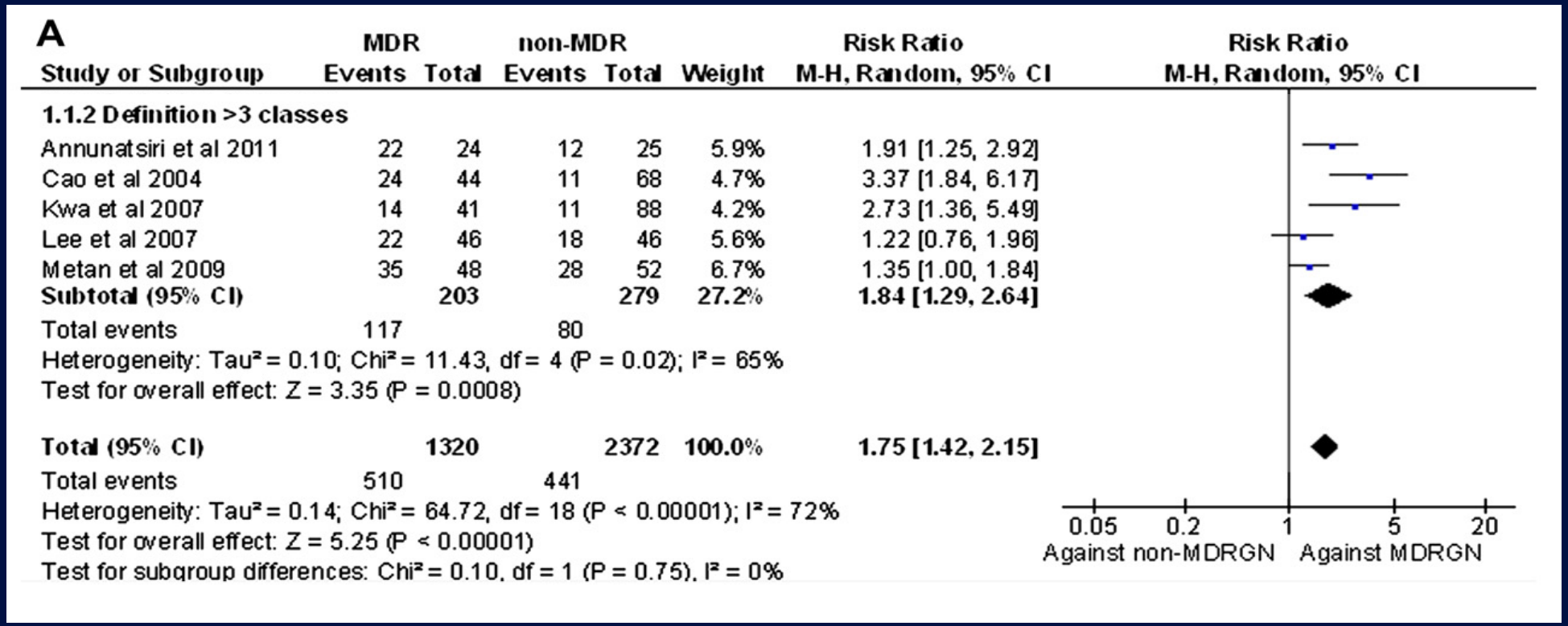


Courtesy of Dr. Robert Weinstein

TABLE 8. Percentage of Pathogenic Isolates Resistant to Selected Antimicrobial Agents, by Location of Patient Reported to the National Healthcare Safety Network, 2009–2010

	CLABSI		CAUTI	
Pathogen, antimicrobial agents[a]	ICU	Non-ICU	ICU	Non-ICU
Staphylococcus aureus, oxacillins	51.5	59.3	52.0	63.3
Enterococcus species				
E. faecium, vancomycin	83.6	80.7	81.8	83.1
E. faecalis, vancomycin	9.4	9.5	5.5	11.8
Klebsiella (*pneumoniae/oxytoca*)				
ES cephalosporins 4	29.7	27.7	24.6	29.0
Carbapenems	14.2	10.9	12.4	12.6
Multidrug resistant 1	19.1	13.7	15.2	17.0
Escherichia coli				
ES cephalosporins 4	18.6	19.5	11.5	13.2
Fluoroquinolones 3	36.5	47.1	29.1	33.5
Carbapenems	1.9	2.0	1.7	2.9
Multidrug resistant 1	3.4	4.0	1.6	2.3
Enterobacter species				
ES cephalosporins 4	38.0	36.2	38.8	38.2
Carbapenems	4.9	2.2	5.5	3.5
Multidrug resistant 1	4.0	3.1	4.6	5.0
Pseudomonas aeruginosa				
Aminoglycosides	11.6	7.5	11.8	9.9
ES cephalosporins 2	28.3	22.6	22.5	28.3
Fluoroquinolones 2	30.3	30.8	31.8	35.5
Carbapenems	26.8	24.9	20.6	22.3
Piperacillin/tazobactam	19.6	13.8	16.1	17.1
Multidrug resistant 2	16.8	13.3	12.6	15.6
Acinetobacter baumannii				
Carbapenems	64.5	56.1	73.8	75.0
Multidrug resistant 3	69.7	60.4	78.6	76.1

IMPACT OF MDRO ON MORTALITY



Vardakas et al. J Infect 2013;66;401

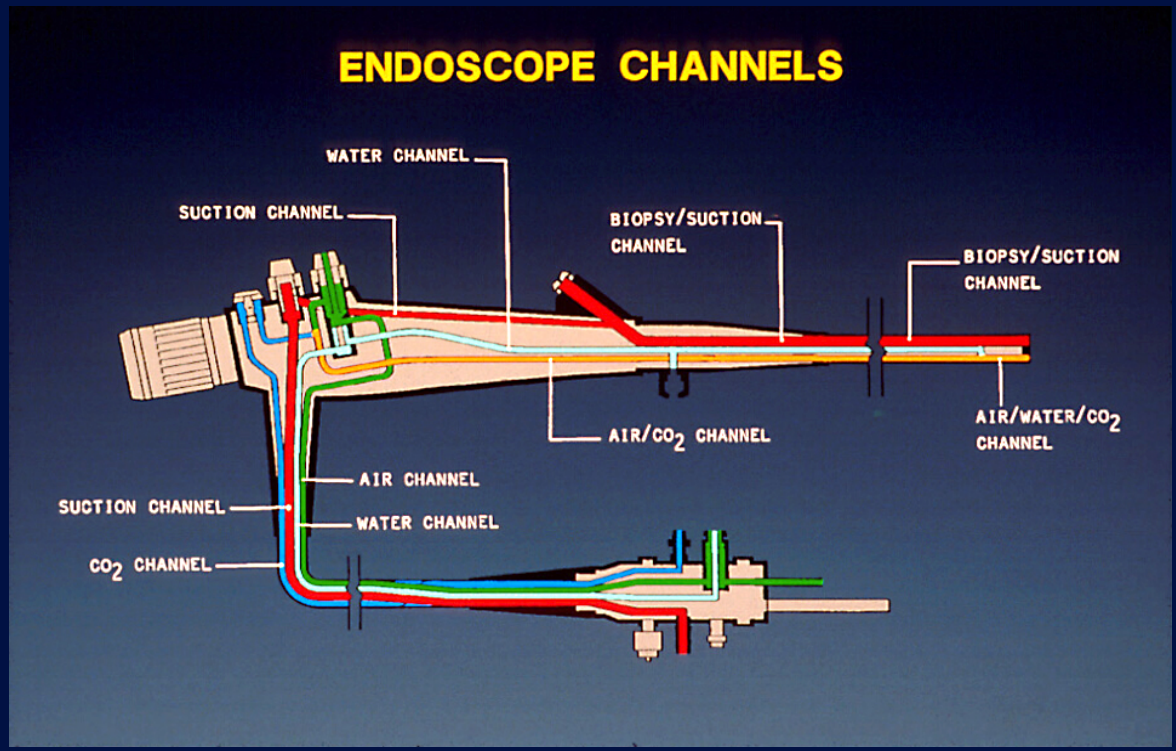
GI ENDOSCOPES

- Widely used diagnostic and therapeutic procedure (~20 million GI procedures annually in the US; ~500,000 ERCPs/year)
- GI endoscope contamination during use (10^{7-10} inside/10^{5} outside)
- Semicritical items require high-level disinfection minimally
- Inappropriate cleaning and disinfection has led to cross-transmission
- Although the incidence of post-procedure infection remains very low, endoscopes represent a significant risk of disease transmission. In fact, more outbreaks of infection associated with endoscopes than any reusable medical device in healthcare.

Rutala WA, Weber DJ. JAMA 2014;312:1405-06

FEATURES OF ENDOSCOPES THAT PREDISPOSE TO DISINFECTION FAILURES

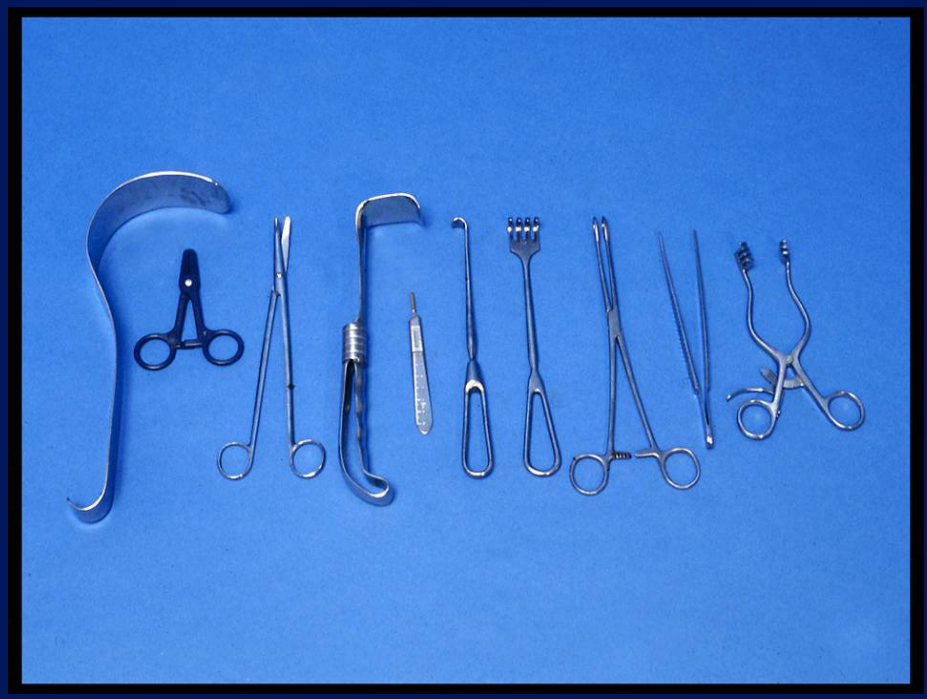
- Require low temperature disinfection
- Long narrow lumens
- Right angle turns
- Blind lumens
- May be heavily contaminated with pathogens
- Use of AERs has led to a new set of problems
- ?Biofilm formation



ENDOSCOPE REPROCESSING: CHALLENGES

Complex [elevator channel]-~10^9 bacteria

Surgical instruments-<10^2 bacteria



Transmission of Infection by Endoscopy

Scope	Outbreaks	Micro (primary)	Pts Contaminated	Pts Infected	Cause (primary)
Upper GI	19	Pa, *H. pylori*, *Salmonella*	169	56	Cleaning/Dis-infection (C/D)
Sigmoid/ Colonoscopy	5	*Salmonella,* HCV	14	6	Cleaning/Dis-infection
ERCP	23	Pa	152	89	C/D, water bottle, AER
Bronchoscopy	51	Pa, Mtb, *Mycobacteria*	778	98	C/D, AER, water
Totals	98		1113	249	

Based on outbreak data, if eliminated deficiencies associated with cleaning, disinfection, AER , contaminated water and drying would eliminate about 85% of the outbreaks.
Kovaleva et al. Clin Microbiol Rev 2013. 26:231-254

Nosocomial Infections via GI Endoscopes

- Infections traced to deficient practices
  - Inadequate cleaning (e.g., failure to clean all channels)
  - Inappropriate/ineffective disinfection (e.g., inadequate time exposure, failure to perfuse all channels or test concentrations, ineffective disinfectant, inappropriate disinfectant)
  - Failure to follow recommended disinfection practices (e.g., tapwater rinse)
  - Flaws and complexity in design of endoscopes or AERs

MULTISOCIETY GUIDELINE ON REPROCESSING GI ENDOSCOPES, 2011

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY JUNE 2011, VOL. 32, NO. 6

ASGE-SHEA GUIDELINE

Multisociety Guideline on Reprocessing Flexible GI Endoscopes: 2011

Bret T. Petersen, MD, FASGE; Jennifer Chennat, MD; Jonathan Cohen, MD, FASGE; Peter B. Cotton, MD, FASGE; David A. Greenwald, MD, FASGE; Thomas E. Kowalski, MD; Mary L. Krinsky, DO; Walter G. Park, MD; Irving M. Pike, MD, FASGE; Joseph Romagnuolo, MD, FASGE; for the ASGE Quality Assurance in Endoscopy Committee; and William A. Rutala, PhD, MPH; for the Society for Healthcare Epidemiology of America

The beneficial role of GI endoscopy for the prevention, diagnosis, and treatment of many digestive diseases and cancer is well established. Like many sophisticated medical devices, the endoscope is a complex, reusable instrument that requires reprocessing before being used on subsequent patients. The most commonly used methods for reprocessing endoscopes result in high-level disinfection. To date, all published occurrences of pathogen transmission related to GI endoscopy have been associated with failure to follow established cleaning and disinfection/sterilization guidelines or use of defective equipment. Despite the strong published data regarding the safety of endoscope reprocessing, concern over the potential spread gaps in infection prevention practices.[10] Given the ongoing occurrences of endoscopy-associated infections attributed to lapses in infection prevention, an update of the multisociety guideline is warranted.

This document provides an update of the previous guideline, with additional discussion of new or evolving reprocessing issues and updated literature citations, where appropriate. Specific additions or changes include review of expanded details related to critical reprocessing steps (including cleaning and drying), reprocessing issues for various endoscope attachments such as flushing catheters, discussion of risks related to selected periprocedural practices including

Petersen et al. ICHE. 2011;32:527

Endemic Transmission of Infections Associated with GI Endoscopes May Go Unrecognized

- Inadequate surveillance of outpatient procedures for healthcare-associated infections
- Long lag time between colonization and infection
- Low frequency of infection
- Pathogens “usual” enteric flora
- Risk of some procedures might be lower than others (colonoscopy versus ERCP where normally sterile areas are contaminated in the latter)

Rapid indicator and microbial growth findings by endoscope component and sampling time

Sampled component by test performed	Bedside cleaning	Manual cleaning 1	Manual cleaning 2	Manual cleaning 3	Automated*	HLD	Stored	HLD 2†	Controls: New	Controls: Automated‡
Surface ATP§										
Control handle	85 (11/13)	0 (0/13)	0 (0/6)	0 (0/1)	0 (0/1)	0 (0/11)	9 (1/11)	0 (0/2)	0 (0/1)	0 (0/1)
Distal end	100 (13/13)	15 (2/13)	0 (0/6)	0 (0/1)	0 (0/1)	0 (0/11)	18 (2/11)	50 (1/2)	0 (0/1)	100 (1/1)
Suction button	100 (13/13)	23 (3/13)	0 (0/6)	NA	NA	0 (0/10)	NA	NA	NA	NA
Air-water button	77 (10/13)	8 (1/13)	0 (0/6)	NA	NA	0 (0/8)	NA	NA	NA	NA
Biopsy cap	100 (13/13)	46 (6/13)	17 (1/6)	NA	NA	20 (2/10)	NA	NA	NA	NA
Biopsy port	100 (13/13)	46 (6/13)	50 (3/6)	100 (1/1)	0 (0/1)	18 (2/11)	27 (3/11)	50 (1/2)	0 (0/1)	0 (0/1)
AUX port	43 (3/7)	0 (0/7)	0 (0/1)	NA	NA	0 (0/6)	0 (0/6)	NA	0 (0/1)	NA
Water ATP§										
SB channel	100 (13/13)	23 (3/13)	33 (2/6)	0 (0/1)	100 (1/1)	9 (1/11)	9 (1/11)	0 (0/2)	0 (0/1)	0 (0/1)
AUX channel	0 (0/7)	0 (0/7)	0 (0/1)	NA	NA	0 (0/6)	0 (0/6)	NA	0 (0/1)	NA
Surface protein										
Suction and air-water ports	100 (5/5)	20 (1/5)	50 (1/2)	NA	NA	33 (1/3)	0 (0/3)	NA	NA	NA
Control handle	92 (12/13)	75 (9/12)	83 (5/6)	100 (1/1)	100 (1/1)	55 (6/11)	78 (7/9)	0 (0/2)	100 (1/1)	100 (1/1)
Channel dipstick										
SB channel										
Protein	0 (0/13)	0 (0/13)	0 (0/6)	0 (0/1)	0 (0/1)	0 (0/11)	0 (0/11)	0 (0/2)	0 (0/1)	0 (0/1)
Carbohydrate	0 (0/13)	0 (0/13)	0 (0/6)	0 (0/1)	0 (0/1)	0 (0/11)	0 (0/11)	0 (0/2)	0 (0/1)	0 (0/1)
Hemoglobin	38 (5/13)	0 (0/13)	0 (0/5)	0 (0/1)	0 (0/1)	0 (0/11)	0 (0/10)	0 (0/2)	0 (0/1)	0 (0/1)
AUX channel										
Protein	0 (0/7)	0 (0/7)	0 (0/1)	NA	NA	0 (0/6)	0 (0/6)	NA	0 (0/1)	NA
Carbohydrate	0 (0/7)	0 (0/7)	0 (0/1)	NA	NA	0 (0/6)	0 (0/6)	NA	0 (0/1)	NA
Hemoglobin	0 (0/7)	0 (0/7)	0 (0/1)	NA	NA	0 (0/6)	0 (0/5)	NA	0 (0/1)	NA
Aerobic plate growth										
SB channel	79 (41/52)	13 (7/52)	8 (2/24)	0 (0/4)	0 (0/4)	16 (7/44)	2 (1/44)	0 (0/8)	0 (0/4)	0 (0/4)
AUX channel	11 (3/28)	4 (1/28)	0 (0/4)	NA	NA	4 (1/24)	0 (0/24)	NA	0 (0/4)	NA

Ofstead CL, et al. Am J Infect Control 2015;43:794-801

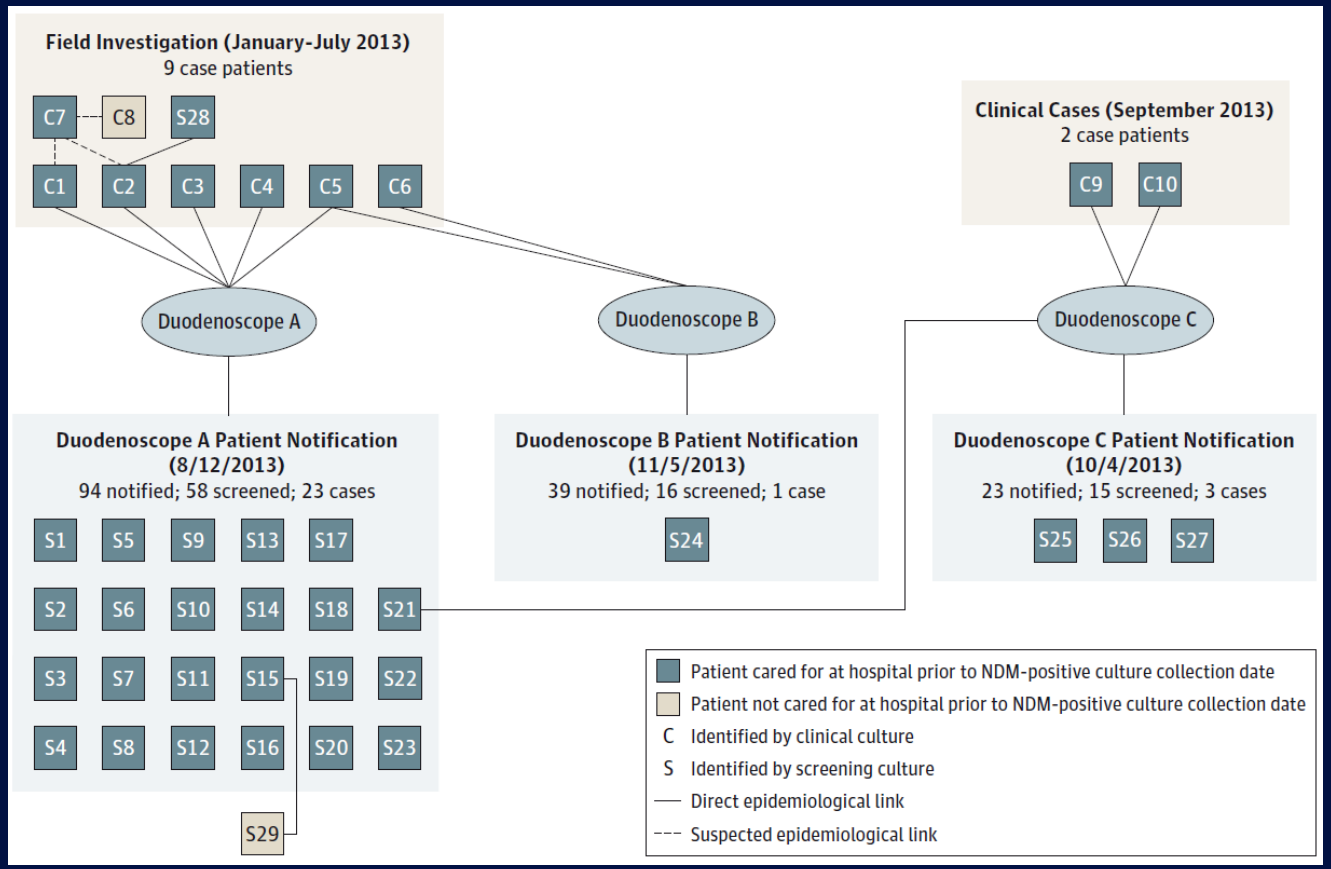
RECENT ENDOSCOPY-RELATED OUTBREAKS OF MRDO WITHOUT REPROCESSING BREACHES

MDRO	Scope	No.	Recovered From Scope	Molecular Link	Reference
P. aeruginosa (VIM-2)	Duodenoscope	22	Yes, under forceps elevator	Yes	Verfaillie CJ, 2015
E. coli (AmpC)	Duodenoscope	7	Yes (2 scopes)	Yes (PFGE)	Wendort, 2015
K. pneumoniae (OXA)	Duodenoscope	5	No		Kola A, 2015
E. Coli (NDM-CRE)	Duodenoscope	39	Yes	Yes (PFGE)	Epstein L, 2014

Additional Outbreaks (Not published; news media reports)

- UCLA, 2015, CRE, 179 patients exposed (2 deaths), 2 colonized duodenoscopes
- CMC, 2015, CRE, 18 patients exposed (7 infected), duodenoscopes
- Cedars-Sinai, 2015, CRE, 67 patients exposed (4 infected), duodenoscopes
- Wisconsin, 2013, CRE, (5 infected), duodenoscopes
- University of Pittsburgh, 2012, CRE, 9 patients, duodenoscopes

E. coli (NDM CRE) ASSOCIATED WITH EXPOSURE TO DUODENOSCOPES



Culture Site

- Urine 3
- Abscess 2
- Blood 2
- Catheter tip 2
- Sputum 2
- Wound 2

Epstein L, et al. JAMA 2014;312:1447-1455

ROLE OF ENDOSCOPY IN PROPAGATING A CRKP OUTBREAK

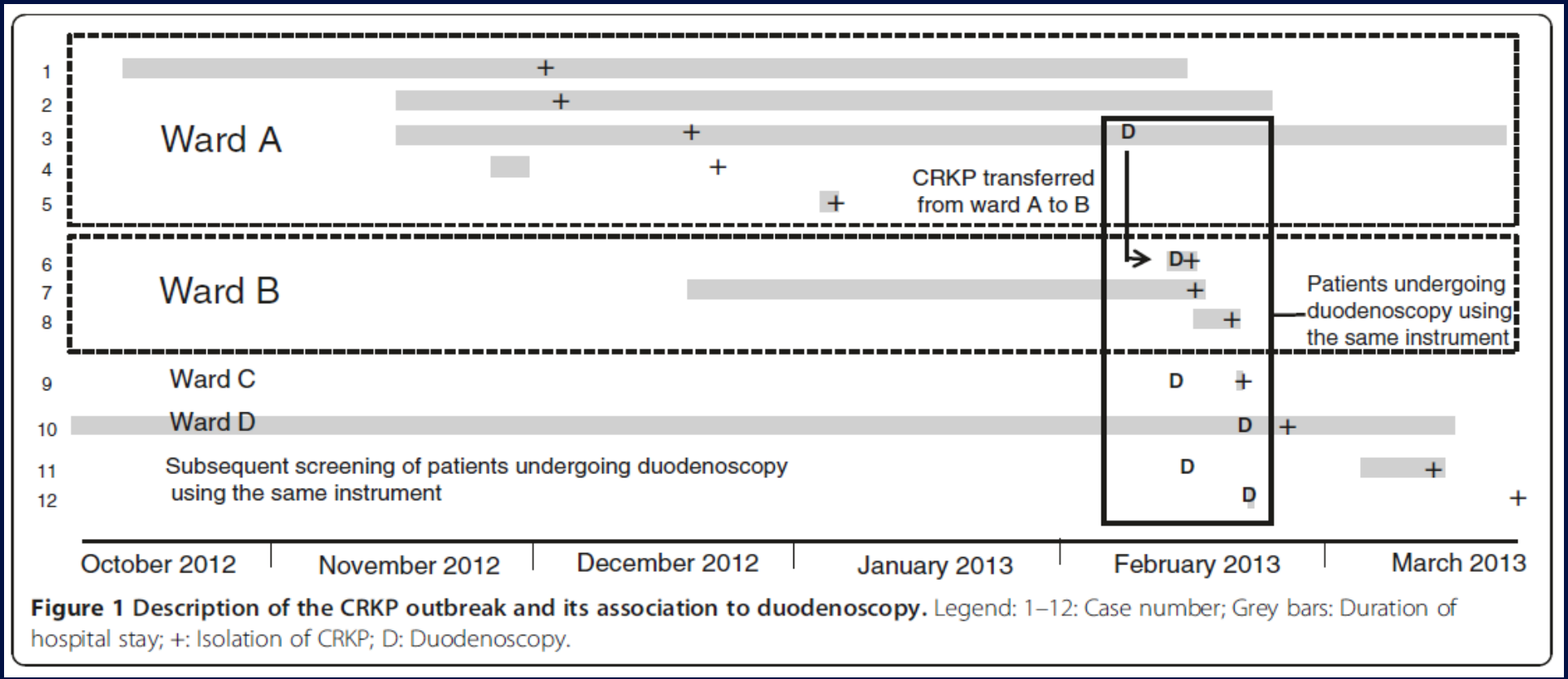
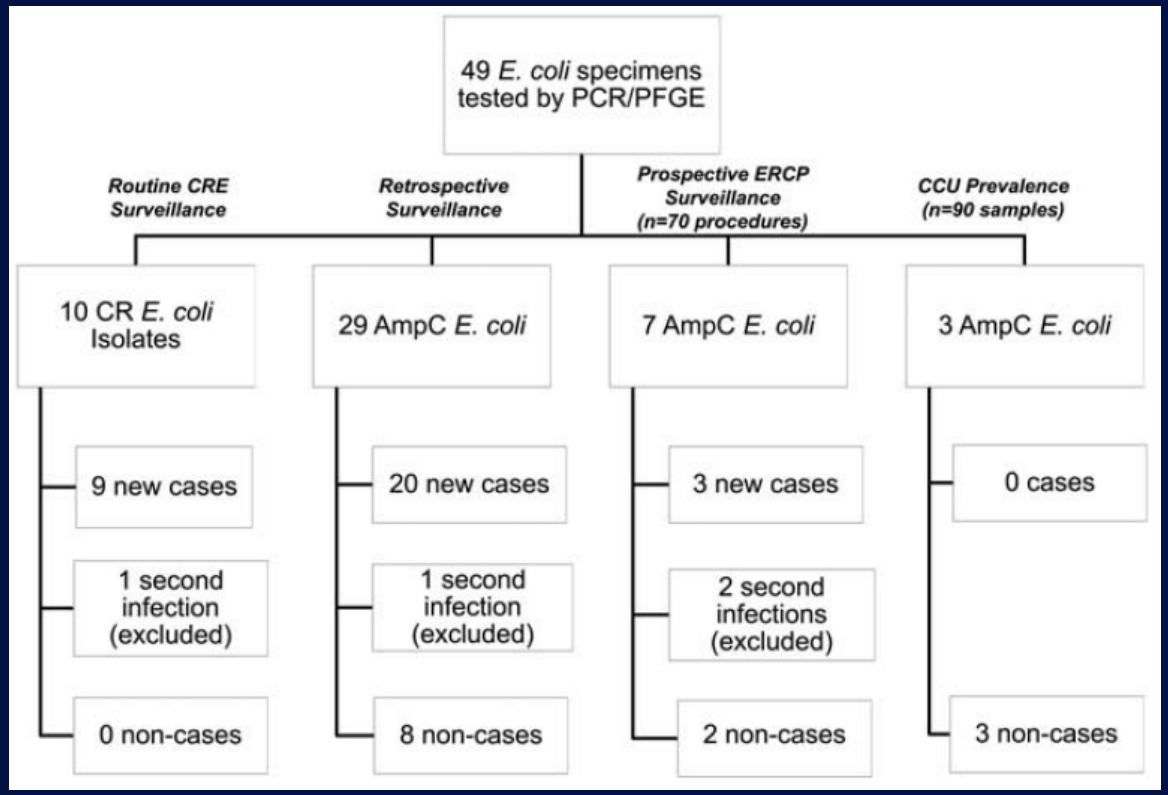


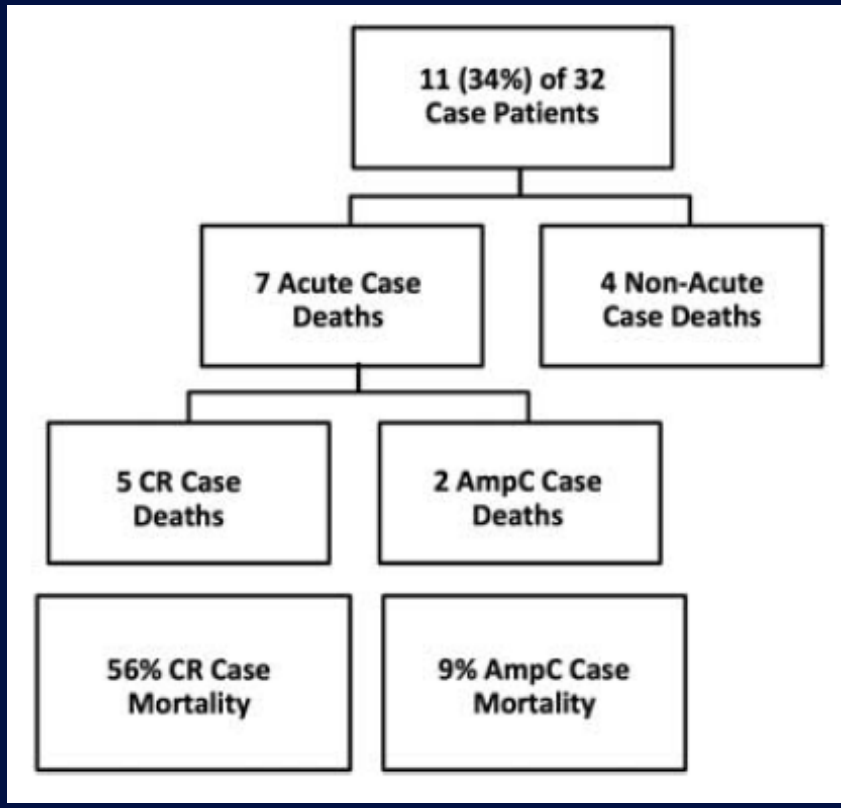
Figure 1 Description of the CRKP outbreak and its association to duodenoscopy. Legend: 1–12: Case number; Grey bars: Duration of hospital stay; +: Isolation of CRKP; D: Duodenoscopy.

Consequences 0f 5 endoscopy-associated transmission events: Sepsis 2, SSI 1, RTI 1

Kola A, et al. Antimicrobial Resistance and Infection Control 2015,4:8

ERCP-ASSOCIATED AmpC *E. coli* OUTBREAK





Wenforf KA, et al. Infect Control Hosp Epidemiol 2015 (epub)

Reason for Endoscope-Related Outbreaks

- Margin of safety with endoscope reprocessing minimal or non-existent for two reasons:
- Complexity of endoscope
- Microbial load
  - GI endoscopes contain $10^{7\text{-}10}$ bacteria
  - Cleaning results in 2-6 $\log_{10}$ reduction
  - High-level disinfection results in 4-6 $\log_{10}$ reduction
  - Cleaning plus disinfection results in a total 6-12 $\log_{10}$ reduction of microbes
  - Level of contamination after processing: 4-$\log_{10}$ (maximum contamination, minimal cleaning/HLD)

Infection Control and Hospital Epidemiology

ERCP Scopes: What Can We Do To Prevent Infections

--Manuscript Draft--

Manuscript Number:	35439
Full Title:	ERCP Scopes: What Can We Do To Prevent Infections
Short Title:	ERCP Scopes
Article Type:	Review
Corresponding Author:	William A Rutala, PhD MPH UNC School of Medicine Chapel Hill, NC UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	UNC School of Medicine
Corresponding Author's Secondary Institution:	
First Author:	William A Rutala, PhD MPH
First Author Secondary Information:	
Order of Authors:	William A Rutala, PhD MPH
	David Weber, MD, MPH

Current Enhanced Methods for Reprocessing Duodenoscopes

Hospitals performing ERCPs should do one of the following (priority ranked); doing nothing is not an option:

1. Ethylene oxide sterilization after high level disinfection with periodic microbiologic surveillance
2. Double high-level disinfection with periodic microbiologic surveillance
3. High-level disinfection with scope quarantine until negative culture
4. Liquid chemical sterilant processing system using peracetic acid (rinsed with extensively treated potable water) with periodic microbiologic surveillance
5. High-level disinfection with periodic microbiologic surveillance

100% ETHYLENE OXIDE (ETO) AFTER HLD

Advantages

- Ideally, should be used after standard disinfection
- Major endoscope manufacturer offers ETO as a sterilization option
- Single-dose cartridge and negative pressure chamber minimizes the potential for gas leak and ETO exposure
- Simple to operate and monitor
- Compatible with most medical materials
- Some data demonstrate reduced infection risk with HLD followed by ETO

Disadvantages

- Requires aeration time to remove ETO residue
- Only 20% of hospitals have ETO on site
- Lengthy cycle/aeration time
- No microbiocidal efficacy proving SAL 10^{-6} achieved for endoscopes
- Studies question microbiocidal activity in presence of organic matter/salt
- ETO is toxic, a carcinogen, and flammable
- May damage endoscopes

DOUBLE HLD (BACK TO BACK), MICROBIOLOGIC SURVEILLANCE

Advantages

- High-level disinfectants inactivate MDR organisms including CREs
- Wide availability
- A second HLD cycle may reduce or eliminate microbial contaminants remaining from first cycle
- Microbiologic surveillance offered as supplement by CDC

Disadvantages

- Based on recent ERCP outbreaks, infection risk related to device complexity and microbial load
- Some high-level disinfectants (e.g., aldehydes) may cross-link proteins

HLD WITH MICROBIOLOGIC SURVEILLANCE

Advantages

- High-level disinfectants inactivate MDR organisms including CREs
- Wide availability
- A second HLD cycle may reduce or eliminate microbial contaminants remaining from first cycle

Disadvantages

- Based on recent ERCP outbreaks, infection risk related to device complexity and microbial load
- No data demonstrating reduce infection risk
- Sensitivity of microbiologic surveillance unknown
- 48-72 hours before culture results known
- No consensus regarding sampling scheme; 100% or 10% of scopes per week/per month?
- No cutoff to define effective disinfection (0 GNR?)

MONITORING CLEANING WITH ATP

Advantages

- High-level disinfectants inactivate MDR organisms including CREs
- Real-time monitoring tool
- Monitors cleaning effectiveness
- Simple to conduct
- Detects organic residue

Disadvantages

- Does NOT monitor disinfection
- No data demonstrating reduced infection risk
- Does not detect microbial contamination
- ATP not validated as risk factor for patient-to-patient transmission
- Unknown cut-off level to assure safety

Adenosine Triphosphate (ATP) Validation

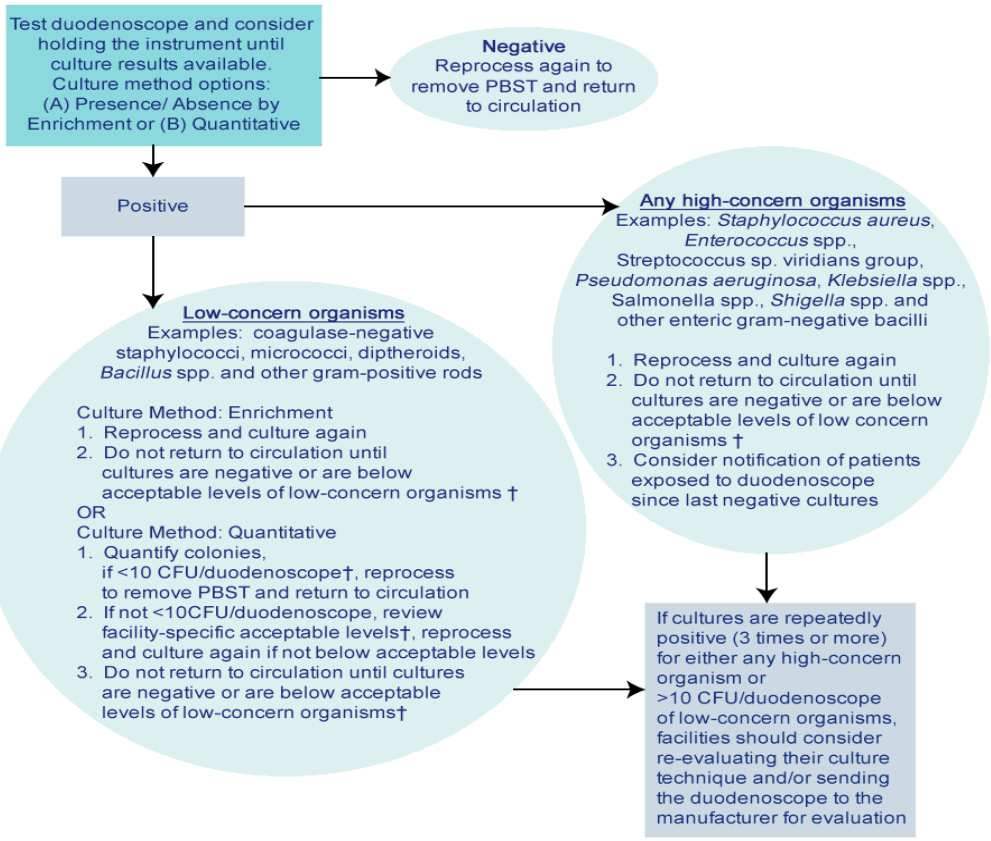
- Validated as a monitoring tool for assessing cleaning because it detects organic residuals
- ATP is not a good indicator of microbial contamination and has not been validated as a method to assess the risk of patient-to-patient transmission
- ATP <200 RLU benchmark for clean, equates to <4 $\log_{10}$ CFUs/cm^2 or 10^6 CFUs per endoscope
- Thus, an endoscope assessed as clean using ATP could still have a significant microbial load (e.g., 10^6)

Alfa et al. Am J Infect Control 2013;41:245

MICROBIOLOGICAL CULTURES

- CDC recommendations (accessed 11 may 2015)
  - Limited information to guide the use of surveillance cultures to assess reprocessing outside of recognized outbreak settings
  - Culturing should supplement and not replace or modify manufacturer's reprocessing recommendations ("negative cultures do NOT exclude possibility of contamination")
  - Cultures should be obtained after duodenoscope reprocessed and should include at least the instrument channel and the distal end of the duodenoscope (elevator channel)
- Olympus revised disinfection (26 March 2015)
  - No mention of culturing scopes
- ASM, Laboratory Practices Committee (9 April 2015)
  - "At this time, it seems that clinical microbiology laboratories should not perform routine cultures of reprocessed duodenoscopes due to lack of data on the utility of such culturing."

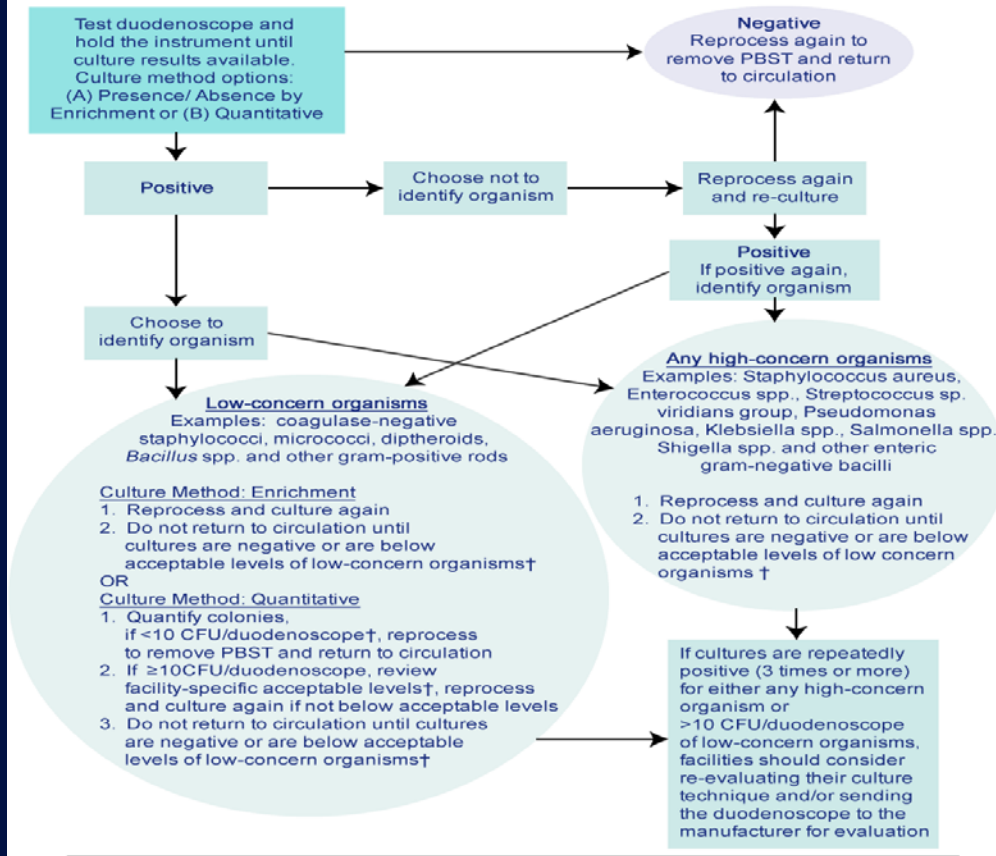
Testing duodenoscope after 60 ERCP procedures or once a month



† The levels of low-concern organisms on a duodenoscope may vary depending on the reprocessing, handling, and culturing practices in a facility. Therefore, the acceptable level of these organisms can vary. Facilities can monitor the levels of low-concern organisms during the first month of surveillance testing to develop an appropriate baseline for those organisms. Typically, fewer than 10 CFU of these microbes does not require intervention; interpretation of culture results with ≥ 10 CFU of non-pathogenic microbes should be considered in the context of expected culture results at the facility

Definitions
Negative – A liquid enriched culture is not turbid
Positive – A liquid enriched culture is turbid
CFU – colony forming units
PBST – Phosphate buffered saline with Tween®-80 solution

*Testing after every duodenoscope reprocessing**



*This approach could be reserved specifically for patients known to be colonized or infected with or felt to be at high risk for multidrug-resistant organisms (e.g., carbapenem-resistant *Enterobacteriaceae)*
†The levels of low-concern organisms on a duodenoscope may vary depending on the reprocessing, handling, and culturing practices in a facility. Therefore, the acceptable level of those organisms present after reprocessing can vary. Facilities can monitor the levels of low-concern organisms during the first month of surveillance testing to develop an appropriate baseline for those organisms. Typically, fewer than 10 CFU of these microbes does not require intervention; interpretation of culture results with ≥ 10 CFU of low-concern organisms should be considered in the context of expected culture results at the facility

Definitions
Negative – A liquid enriched culture is not turbid
Positive – A liquid enriched culture is turbid
CFU – colony forming units
PBST – Phosphate buffered saline with Tween®-80 solution

UNC Hospitals
Interim Response to ERCP Outbreaks

- Ensure endoscopes are reprocessed in compliance with national guidelines (CDC, ASGE, etc)
- Evaluate CRE culture-positive patients for ERCP exposure
- In the short term, enhance reprocessing of ERCP scopes: Reprocess ERCP scopes by HLD followed for ETO sterilization
- Microbiologic surveillance, 5-10% of scopes monthly
- When new recommendations are available from ASGE, CDC, FDA, etc. = comply

What Is the Public Health Benefit?
No ERCP-Related Infections

Margin of Safety-currently nonexistent; sterilization will provide a safety margin. To prevent infections, all duodenoscopes should be devoid of microbial contamination.

HLD (6 $\log_{10}$ reduction)

vs

Sterilization (12 $\log_{10}$ reduction=SAL 10^{-6})

Potential Future Methods to Prevent GI-Endoscope Related Outbreaks

- Steam sterilization for GI endoscopes
- Disposable sterile GI endoscopes (disposable bronchoscopes available)
- Improved GI endoscope design (to reduce or eliminate challenges noted earlier)
- Use of non-endoscope methods to diagnosis or treat disease (e.g., capsule endoscopy, blood tests to detect GI cancer, stool DNA test)
- New low temperature sterilization methods proving SAL 10^{-6} achieved (or optimizing current LTST)

Rutala WA, Weber WA. Infect Control Hosp Epidemiol 2015, In press

Some Potential Sterilization Technologies for Duodenoscopes

- Optimize existing low-temperature sterilization technology
  - Hydrogen peroxide gas plasma
  - Vaporized hydrogen peroxide
  - Ethylene oxide
- Potential new low-temperature sterilization technology
  - Ozone plus hydrogen peroxide vapor
  - Nitrogen dioxide
  - Supercritical CO_2
  - Peracetic acid vapor

Rutala WA, Weber WA. Infect Control Hosp Epidemiol 2015, In press

CONCLUSIONS

- Endoscopes represent a nosocomial hazard. Narrow margin of safety associated with high-level disinfection of semicritical items due to microbial load and complexity (biofilms?).
- Hospital should select 1 of the 5 enhanced methods for duodenoscope reprocessing. Doing nothing is not an option.
- To protect the public health and prevent ERCP-related outbreaks, there is an urgent need to shift from HLD to sterilization.

THANK YOU!!