Update on CRE: epidemiology, emerging mechanisms, and duodenoscopes

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- No disclosures
- The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

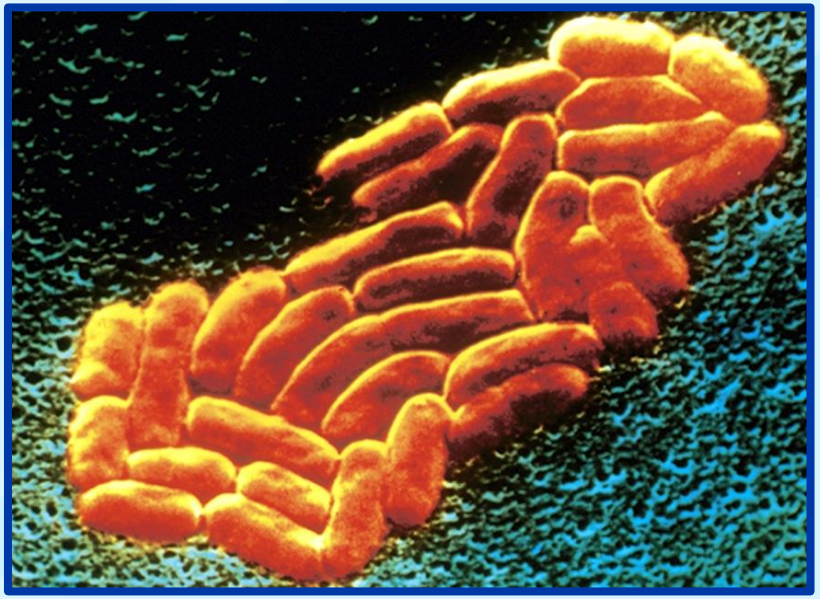
Objectives

- Summarize recent epidemiologic trends for CRE
- Describe epidemiology of key resistance mechanisms
- Discuss duodenoscope-associated outbreaks and processes and procedures for ensuring adequate cleaning and disinfection

EPIDEMIOLOGY

Enterobacteriaceae

- Large family of gram negative rods
- Includes *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
- Normal gut flora & opportunistic pathogens
- Most common family encountered in clinical microbiology labs



***K. pneumoniae*, scanning electron micrograph**
http://www.ppdictionary.com/bacteria/

Carbapenem-Resistant Enterobacteriaceae (CRE)

- Carbapenems sometimes considered antibiotics of last resort
- Often multidrug resistant
- Cause infections with high mortality rates
- Multiple resistance mechanisms - some with potential for epidemic spread

How Common are CRE?

- **Among HAIs submitted to NHSN**
  - Percentage of Enterobacteriaceae NS to a carbapenem increased from 1.2% (2001) to 4.2% (2011)
  - Percentage of *Klebsiella* NS to a carbapenem increased from 1.6% to 10.4%
- **Percentage of facilities doing surveillance for CAUTI or CLABSI with at least one CRE**
  - 2013: 9.6% (7.1% short stay acute care, 30.1% LTACH)*

*Data are preliminary and subject to change

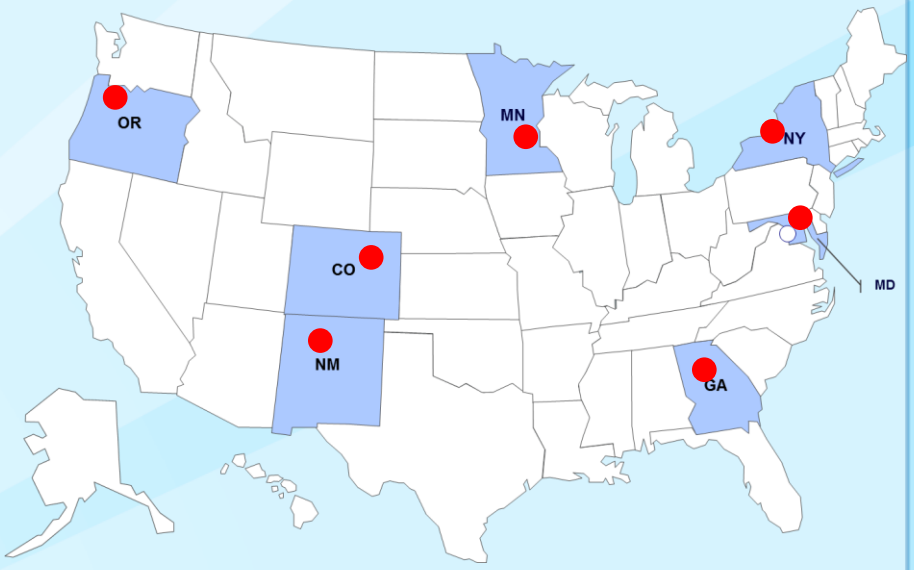
Incidences of CRE and Other Well-Characterized Multidrug-resistant Organisms

- **CRE: 3.08 per 100,000 population**
- **Methicillin-resistant *Staphylococcus aureus*: 25.1 per 100,000 population**
- ***Clostridium difficile*: 147.3 per 100,000 population**

Source: CDC Emerging Infections Program

Multisite Gram Negative Surveillance Initiative (MuGSI)

- *E. coli, E. aerogenes, E. cloacae, K. pneumoniae, K. oxytoca*
- NS to doripenem, imipenem, or meropenem and R to all third-generation cephalosporins tested
- Population-based surveillance in seven metropolitan areas
- 12.5 million persons under surveillance in 2013



Annual Crude Incidence Rates, by MuGSI site

Emerging Infections Program site	Crude annual CRE incidence rates (per 100,000 population)	
	2012[a]	2013
Colorado	-	1.05
Georgia	4.58	4.68
Maryland	-	4.80
Minnesota	1.82	2.32
New Mexico	-	0.89
New York	-	3.60
Oregon	0.35	0.82
Total	2.94	3.08

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Number of CRE Organisms by MuGSI Site, 2012-2013

Site	Number of CRE isolates (%)					
	Total	*E. aerogenes*	*E. cloacae*	*E. coli*	*K. pneumoniae*	*K. oxytoca*
Colorado	27	7 (25.9)	10 (37.0)	3 (11.1)	7 (25.9)	0 (0)
Georgia	356	22 (6.2)	38 (10.7)	56 (15.7)	235 (66.0)	5 (1.4)
Maryland	92	8 (8.7)	6 (6.5)	9 (9.8)	69 (75.0)	0 (0)
Minnesota	71	29 (40.9)	16 (22.5)	10 (14.1)	16 (22.5)	0 (0)
New York	27	3 (11.1)	2 (7.4)	5 (18.5)	17 (63.0)	0 (0)
Oregon	20	4 (20.0)	7 (35.0)	3 (15.0)	6 (30.0)	0 (0)
Total	599	75 (12.5)	79 (13.2)	89 (14.7)	351 (58.6)	5 (0.8)

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CRE Collection Site, 7 U.S. Sites, 2012-2013 (N=584)

Collection site	Number (%)
SS Acute Care Hospital	198 (33.9%)
Community	386 (66.1%)
Outpatient or ED	253 (65.5%)
LTCF	104 (26.9%)
LTACH	29 (7.5%)

Prior Healthcare Exposures, 7 U.S. Sites, 2012-2013 (N=575)

Exposure	Number (%)
Healthcare exposure	531 (92.3%)
Hospitalization	399 (75.1%)
LTCF	259 (48.8%)
Surgery	194 (36.5%)
LTACH	59/392 (15.1%)
Current chronic dialysis	60 (11.3%)
Presence of indwelling device (in 2 days prior)	413 (71.9%)
No healthcare exposure	44 (7.7%)

CRE Source, 7 U.S. Sites, 2012-2013 (N=599)

Source	Number (%)
Urine	520 (86.8%)
Blood	68 (11.4%)
Peritoneal fluid	8 (1.3%)
Pleural fluid	3 (0.5%)
Other	7 (1.2%)

Note: MuGSI collects isolates from sterile sites and urine only

Outcome of Carbapenem-Resistant Enterobacteriaceae Cases

Outcome	Number (%)
Hospitalization within 30 days of initial positive culture (n=569)	371 (65.2)
Intensive care unit stay in 7 days after positive culture (n=368)	128 (34.8)

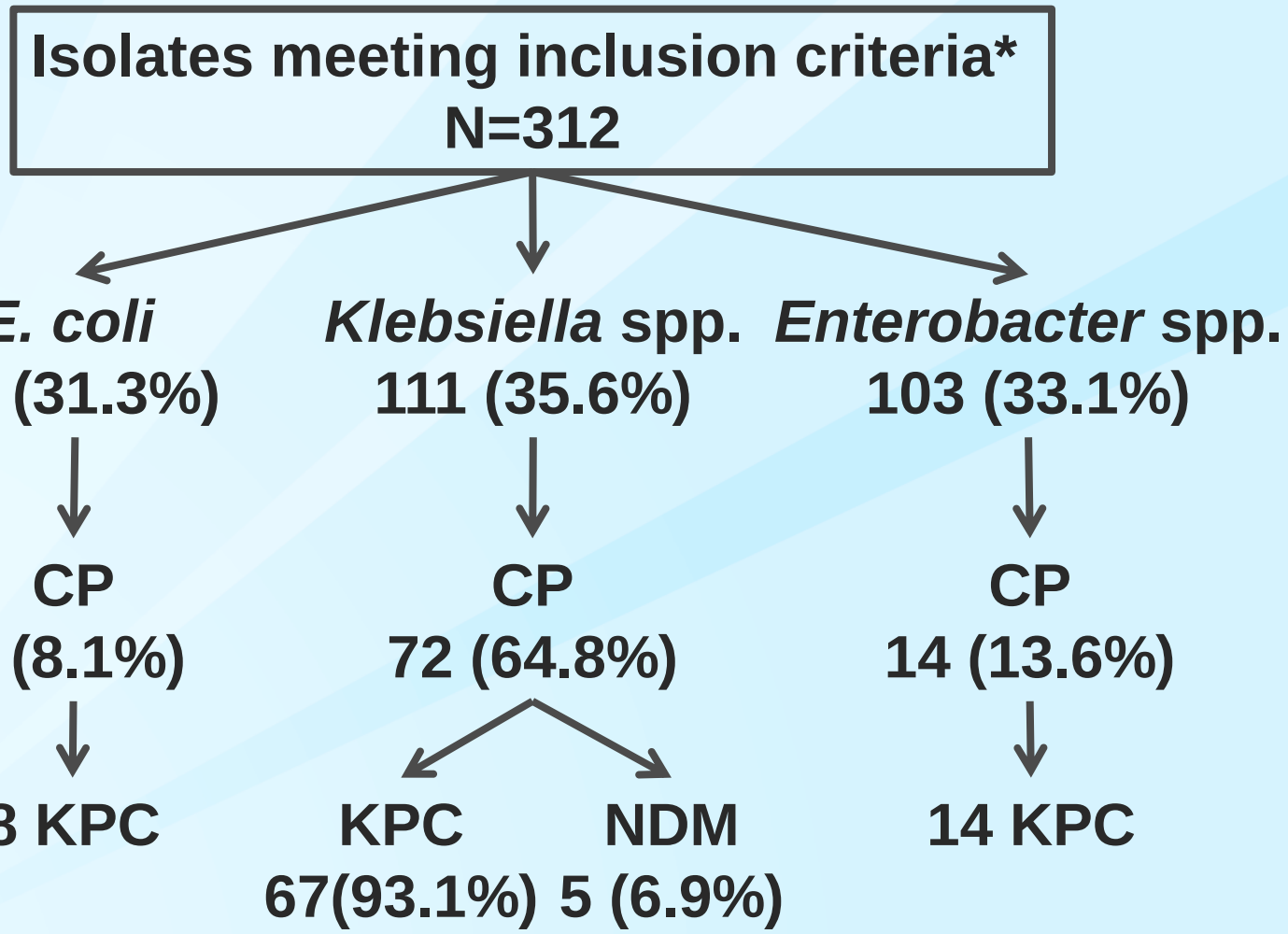
Mortality among Carbapenem-Resistant Enterobacteriaceae Cases

Outcome	Number (%)
Died (during hospitalization or at the end of 30-day evaluation) (n=566)	51 (9.0)
Among any sterile-site positive culture	25 / 91 (27.5)
Among nonsterile-site positive culture only (i.e., urine)	26 / 475 (5.5)

Carbapenemase-producers vs non-carbapenemase producers

- **Carbapenemase producers (CP-CRE)**
  - KPC, NDM, OXA-48, VIM, IMP
  - Resistance encoded on plasmids
  - Plasmids transferred across genera
  - Often acquired during healthcare exposures outside the U.S.
  - Thought to drive increasing spread of CRE in U.S.
- **Non-carbapenemase producers (nonCP-CRE)**
  - Chromosomal changes confer resistance (AmpC, porin mutations)
  - Epidemic spread of less concern

Carbapenemase Production

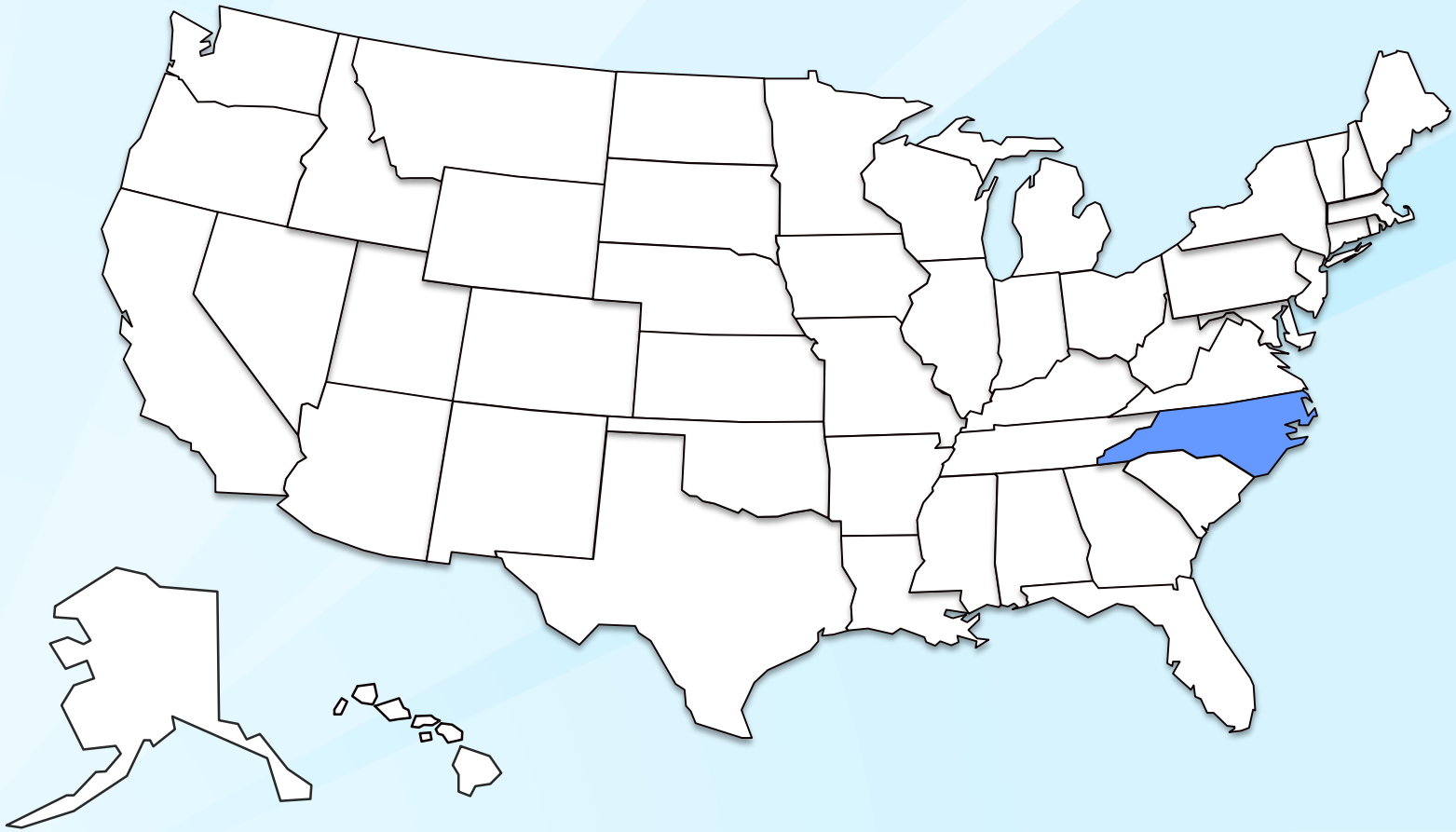


*Nonsusceptible to any carbapenem based on 2013 CLSI breakpoints

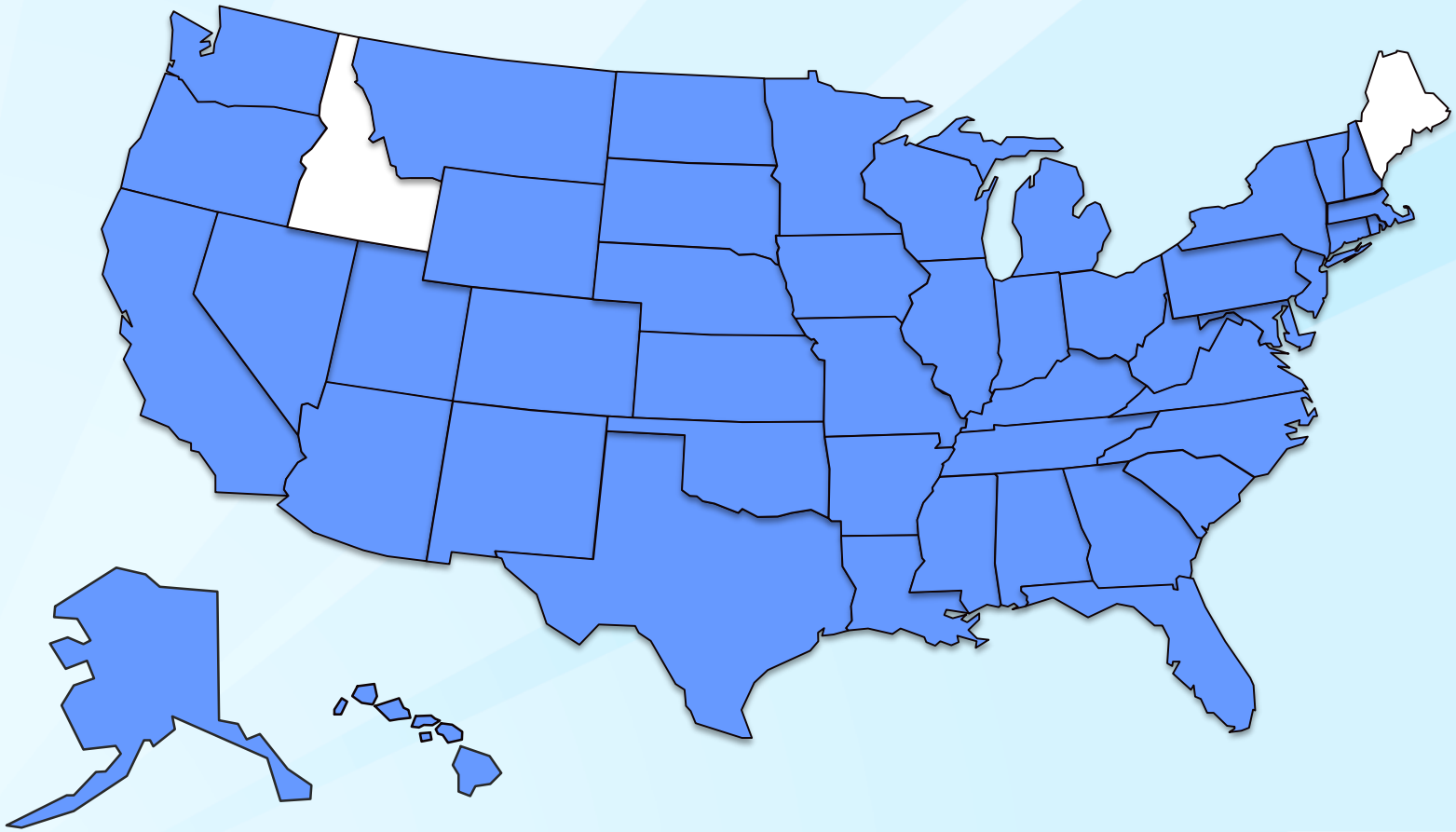
Number and Proportion of Carbapenemase-producing CRE by Site

State	CP-CRE (%)
MD	43 (73.8)
MN	33 (29.6)
TN	13 (18.8)
NY	3 (5.6)
NM	1 (6.6)
CO	0 (0)

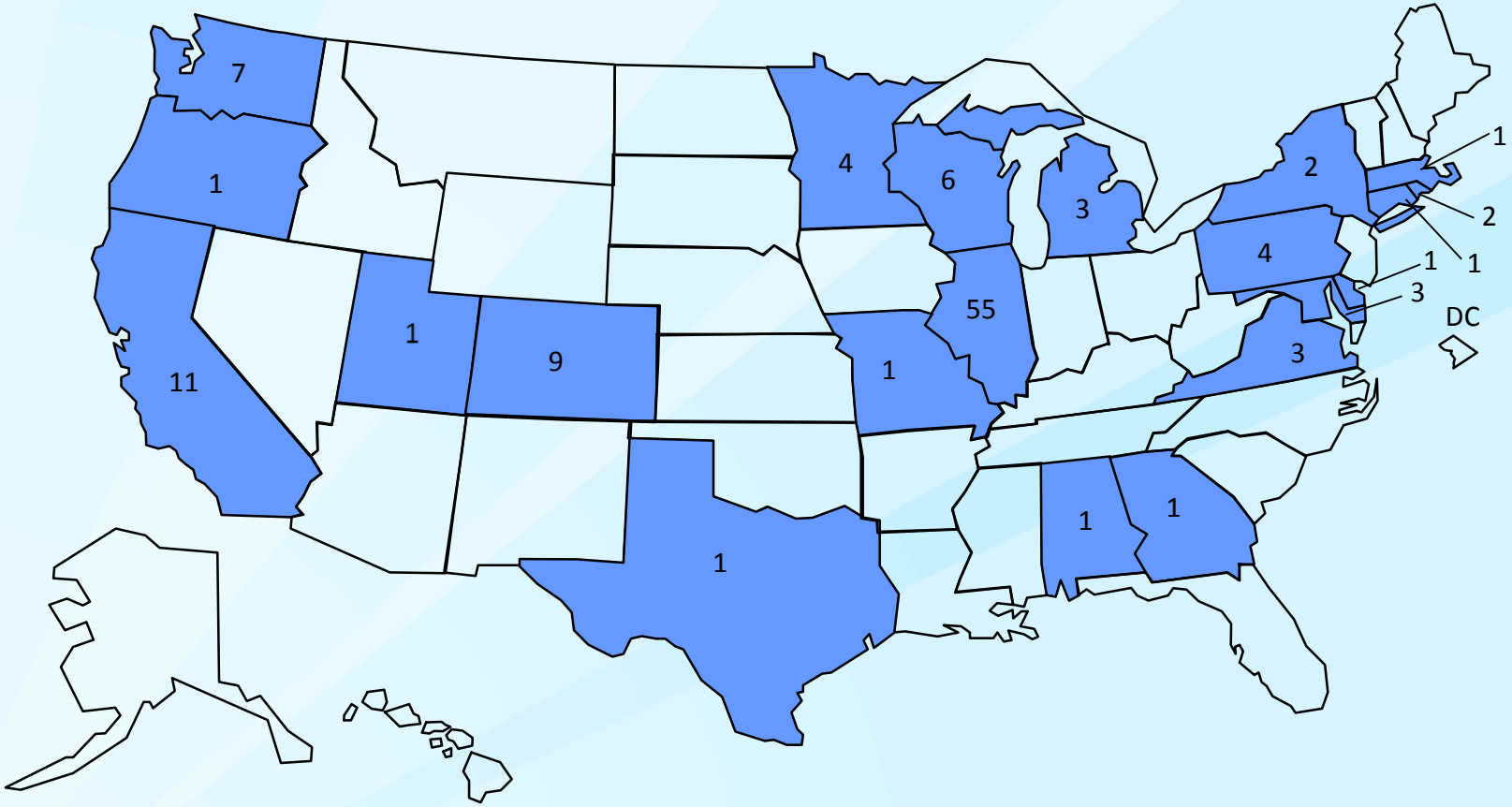
First Report of CP-CRE, 2001



Carbapenemase-producing CRE isolates reported to the Centers for Disease Control and Prevention (CDC) as of January 2015



NDM-producing CRE isolates reported to CDC as of January 2015, by state, n=118

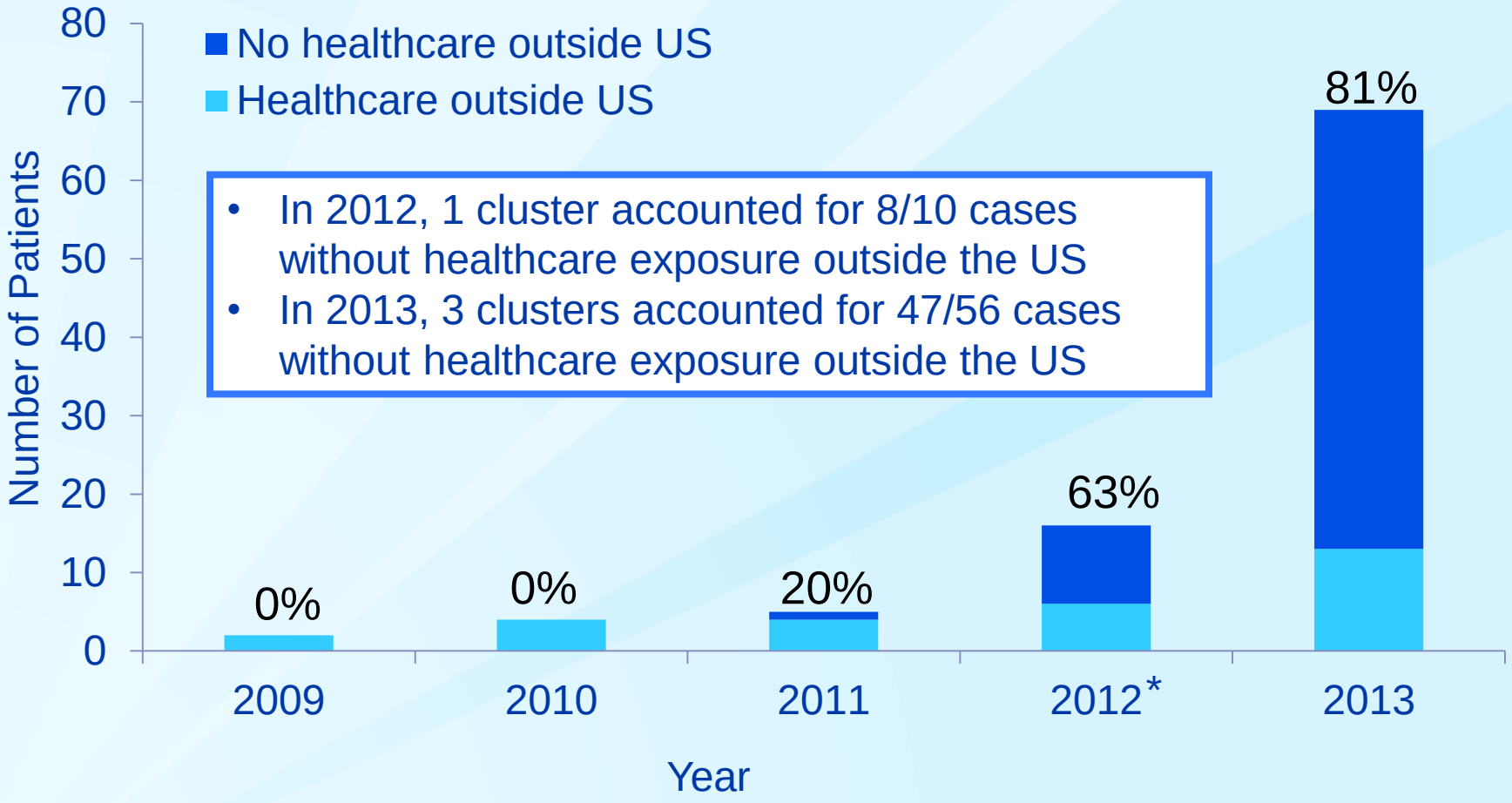


*Isolates were identified by CDC from isolates either sent for reference carbapenemase testing or as part of a CDC surveillance program for CRE.

These isolates are likely an underestimation of the true number of NDM-producing CRE because CRE mechanism testing is not routinely performed in US clinical laboratories and, if performed, isolates might not be sent to CDC for this testing.

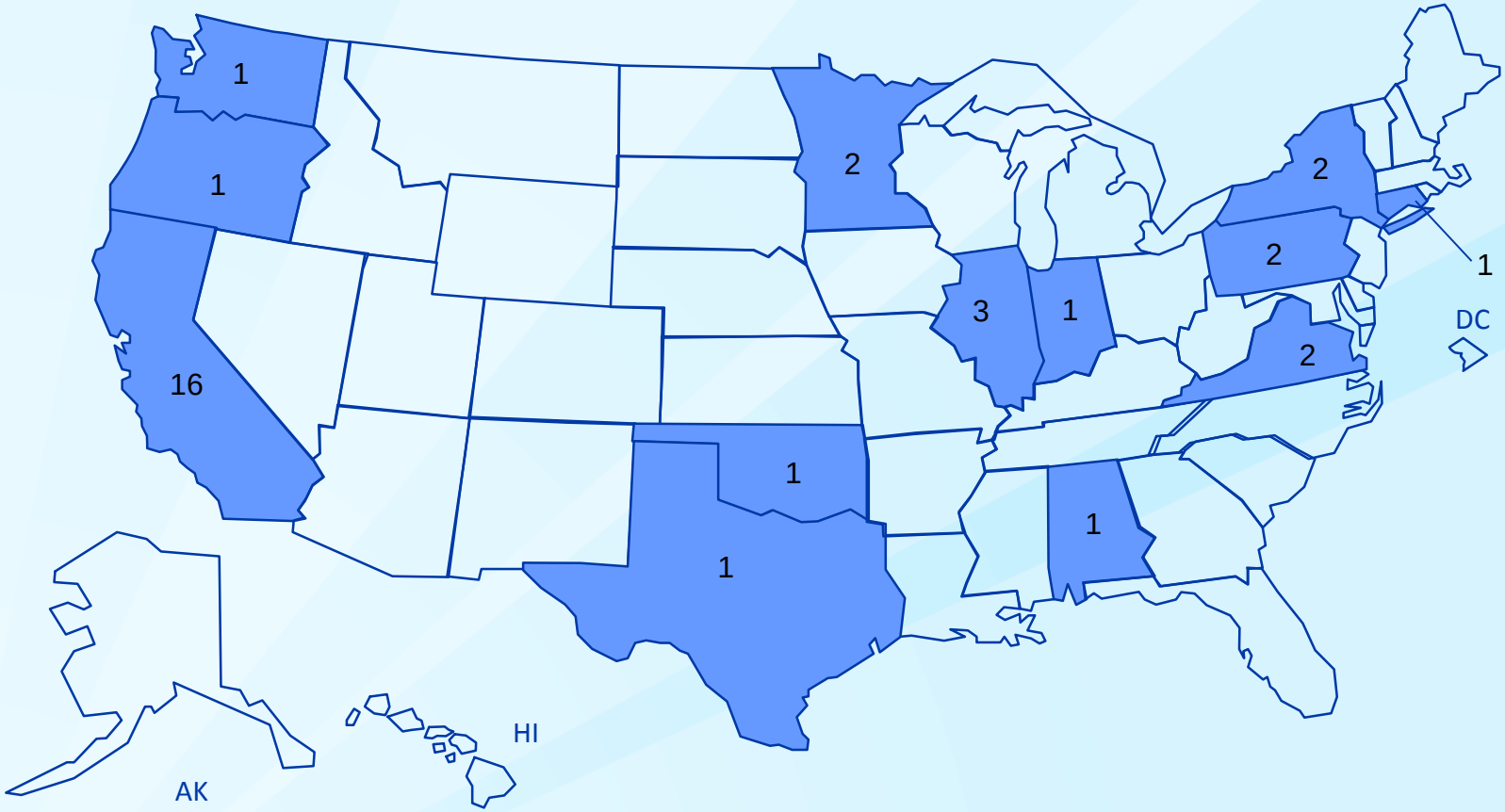
Number of Patients with NDM-producing CRE Reported to CDC, by Year

Proportion of Patients Without Overnight Healthcare Stay Outside the US, by Year



*2 unknown exposure outside US

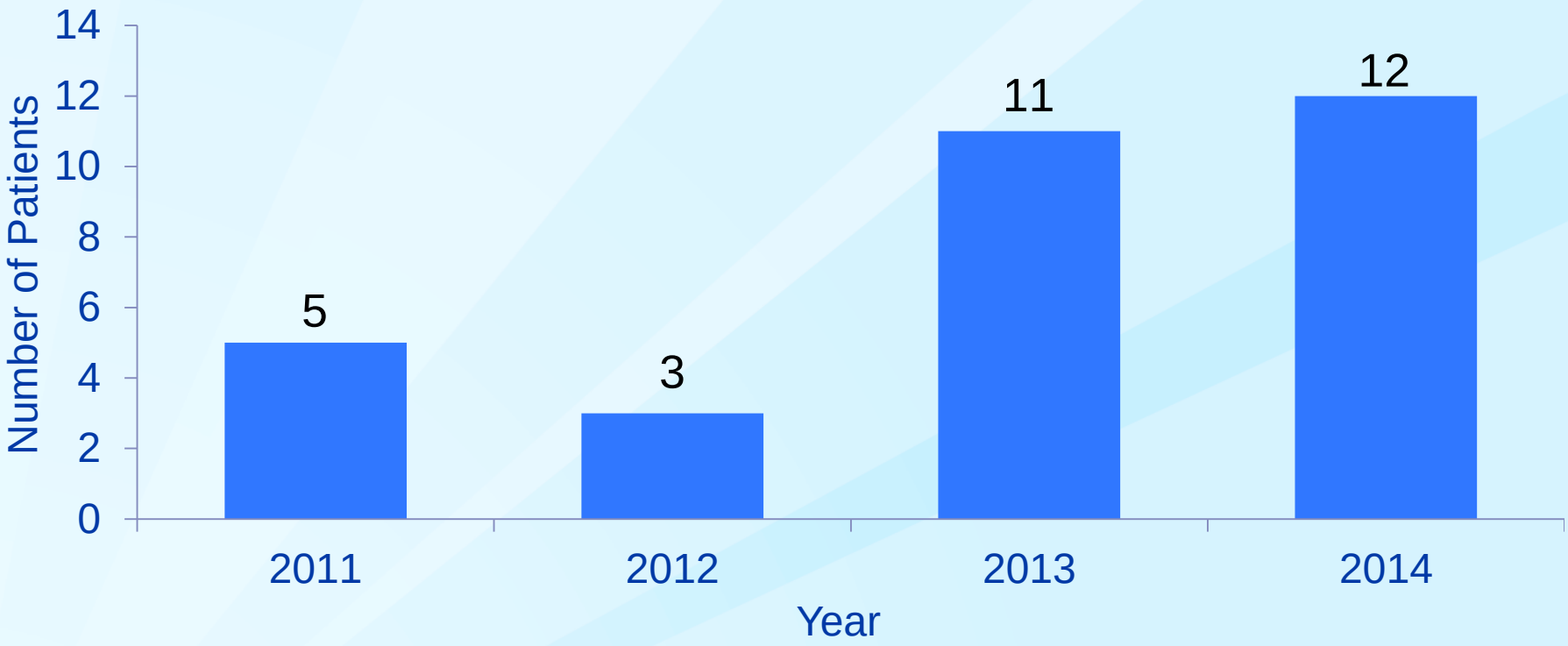
OXA-48-Type-producing CRE isolates reported to the CDC as of January 2015, by state, n=34



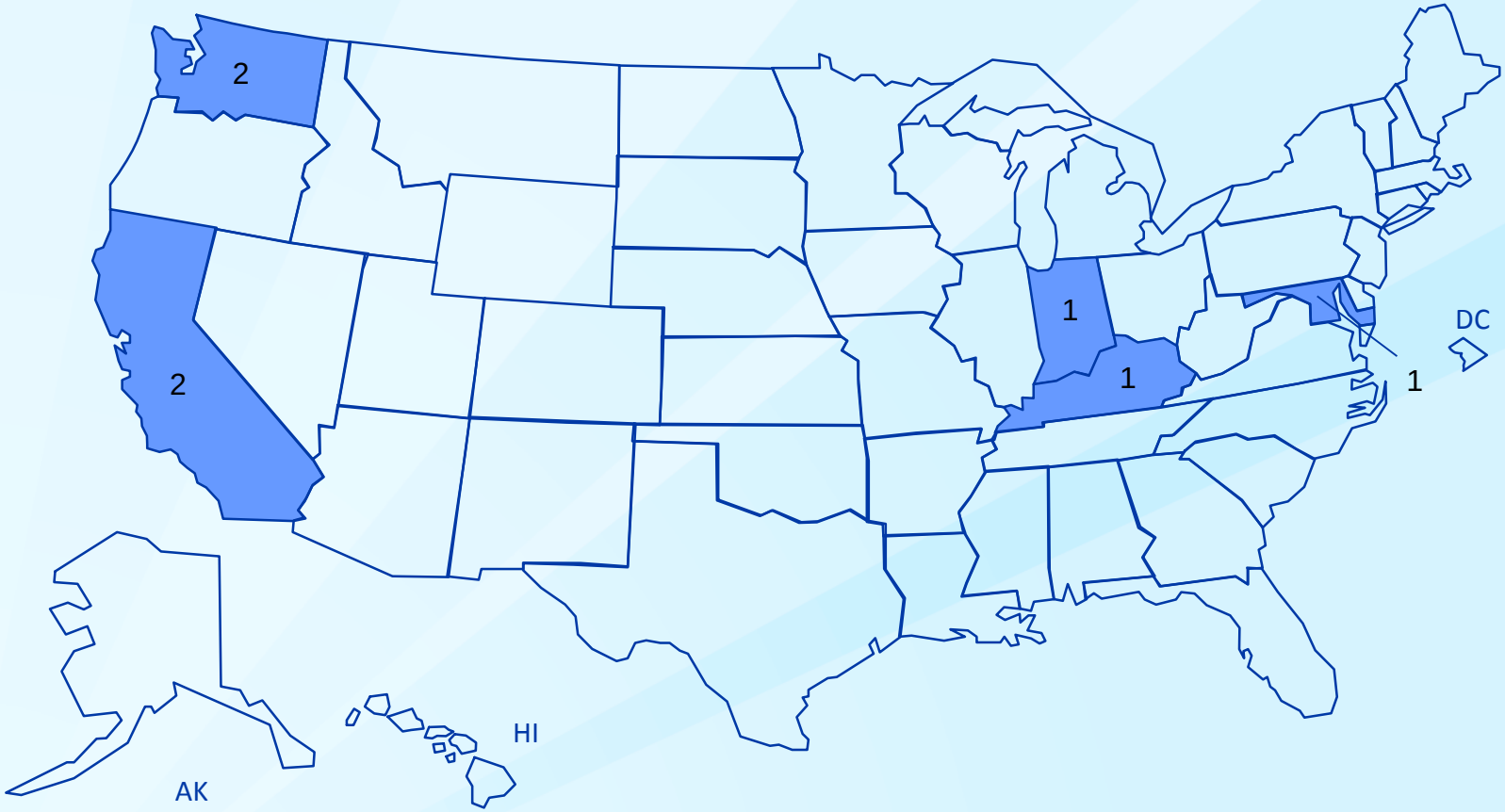
*Isolates were identified by CDC from isolates either sent for reference carbapenemase testing or as part of a CDC surveillance program for CRE.

These isolates are likely an underestimation of the true number of OXA-48--producing CRE because CRE mechanism testing is not routinely performed in US clinical laboratories and, if performed, isolates might not be sent to CDC for this testing.

Number of Patients with OXA-48-like-producing CRE Reported to CDC, by Year



VIM-producing CRE isolates reported to the CDC as of January 2015, by state, n=7



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These isolates are likely an underestimation of the true number of VIM--producing CRE because CRE mechanism testing is not routinely performed in US clinical laboratories and, if performed, isolates might not be sent to CDC for this testing.

CDC HAN February 14, 2013

- **When a CRE is identified in a patient with a history of an overnight stay in a healthcare facility (within the last 6 months) outside the United States, send the isolate for confirmatory susceptibility testing and test to determine the resistance mechanism; at a minimum this should include evaluation for KPC and NDM**
- **For patients admitted to healthcare facilities in the US after recently being hospitalized (within the last 6 months) in countries outside the US, consider the following:**
  - Rectal screening for CRE
  - Contact precautions pending results of the screening cultures

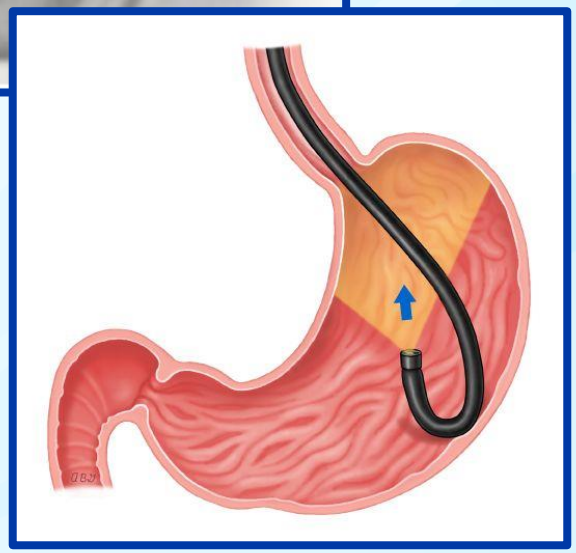
DUODENOSCOPES

Duodenoscopes

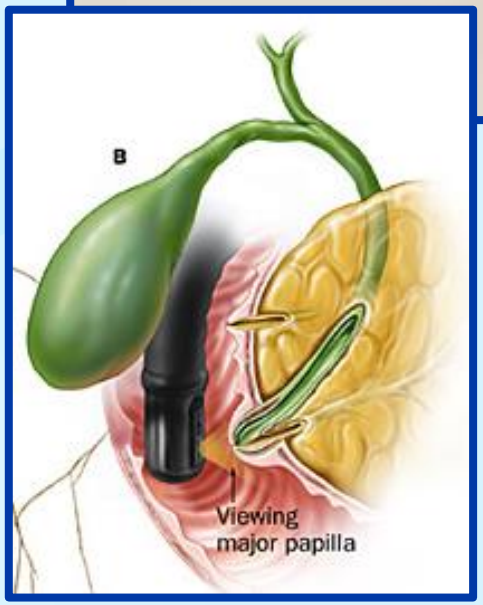
- Flexible, lighted tubes threaded through top of throat into esophagus, stomach, and small intestine
- Used for endoscopic retrograde cholangio-pancreatography (ERCP)
- Diagnostic and therapeutic interventions involving the pancreas and biliary tree
- ~600,000 procedures performed annually in the U.S.
- Implicated in multiple outbreaks

Flexible Endoscope Design

Most flexible endoscopes
Forward viewing



Duodenoscopes
Side-viewing



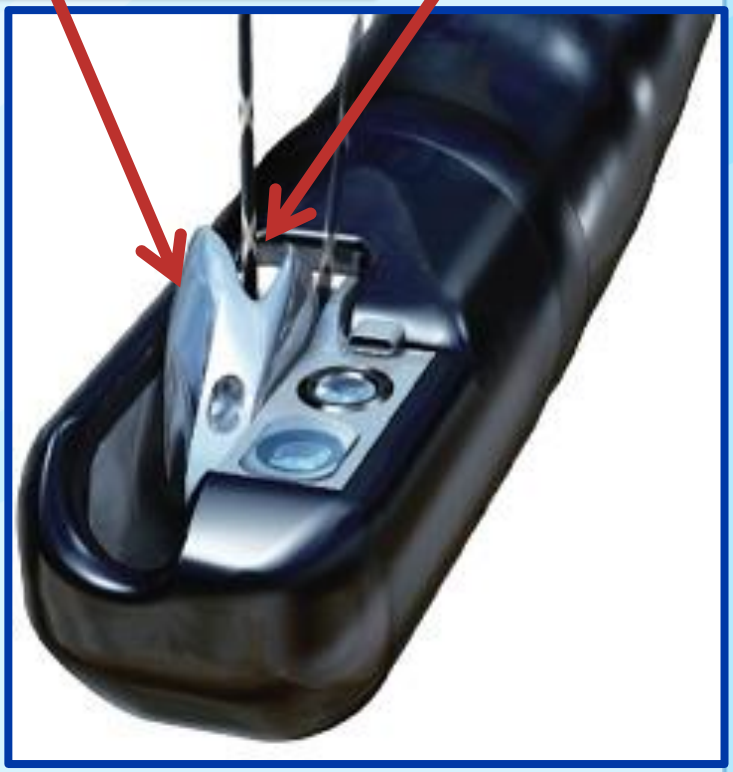
http://www.endoscopy.com
https://www.jhmicall.org/GDL_Disease.aspx
http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?8/0/8196

Duodenoscope Design

Tip, Elevator Mechanism

Elevator Mechanism

Instrument channel



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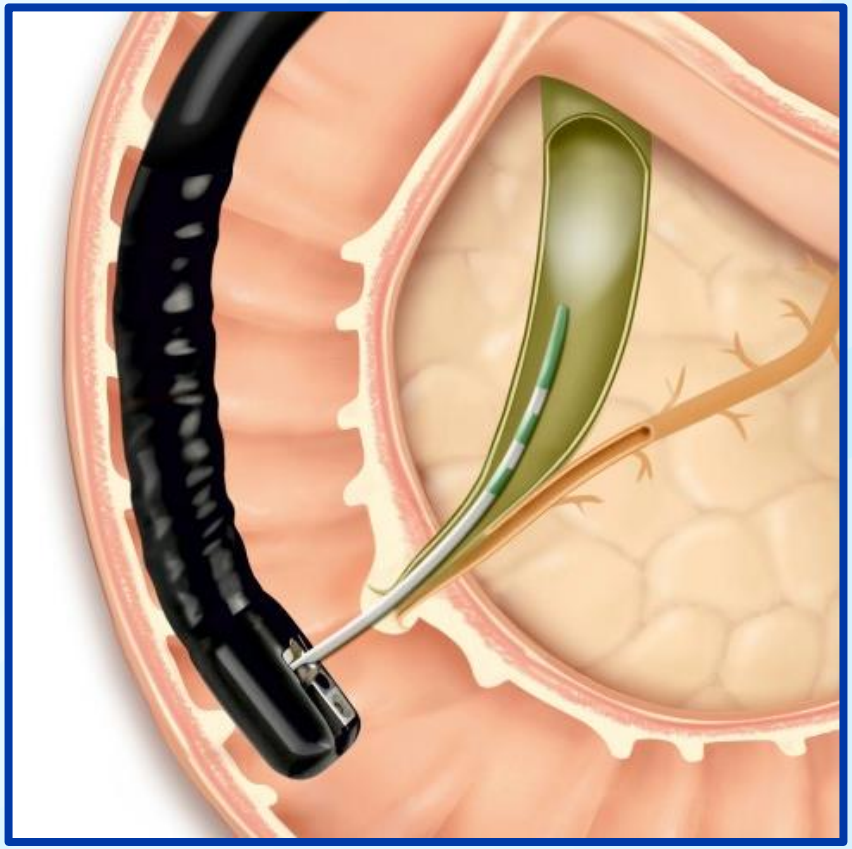
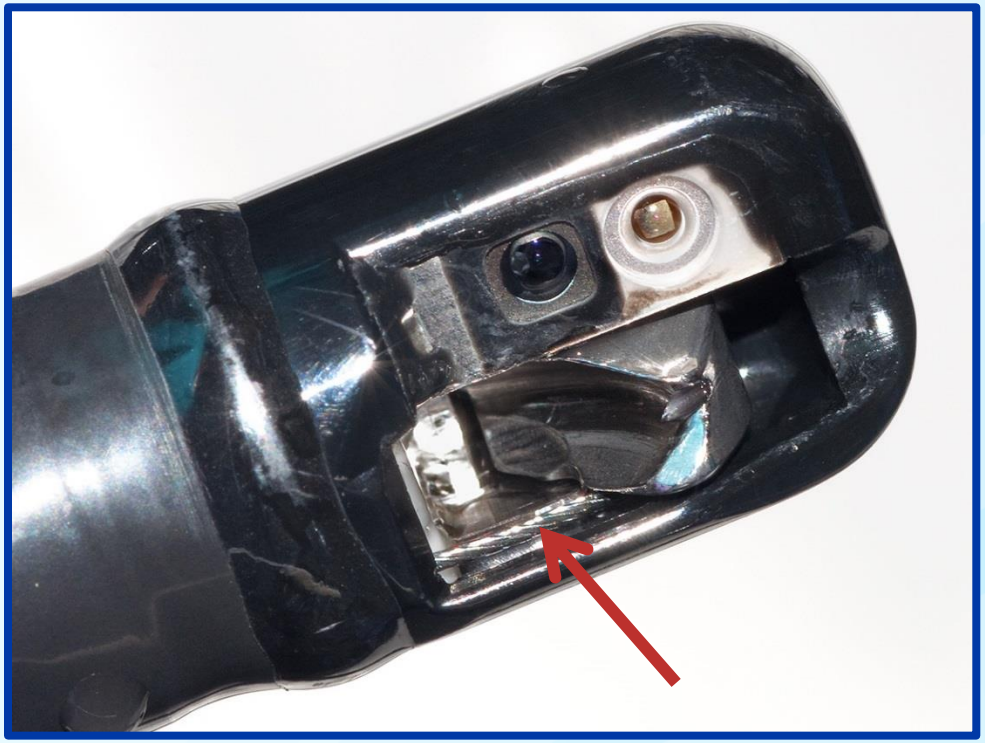


Open vs. Closed Elevator Wire Channel



Open elevator wire channel

Closed elevator wire channel

Reported Causes of Endoscopy-related Outbreaks

- Not following recommended cleaning and/or disinfection steps
- Inadequate disinfection: substandard disinfectant, insufficient exposure of the endoscope
- Contaminated water bottles and irrigating solutions
- Contaminated or improperly used automated endoscope reprocessor (AER)
- Damaged equipment (endoscopes or reprocessing equipment)

Nelson DB. Gastrointestinal Endoscopy 2003; 57:695-711
Kovaleva J, et al. Clin Microbiol Rev 2013; 26:231-253

PIVOTAL OUTBREAK

Illinois NDM Cluster

- **March 2013**
  - Single patient with NDM *E. coli* who was hospitalized in Illinois
  - No international travel history
- **March–July 2013, identified 8 additional cases**
  - 7 from diagnostic testing
  - 1 from screening culture, nursing home roommate
- **No NDM detected from 131 patients with shared room or ward at hospital**

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

Case-Control Study Results

Exposure – since January 2013 (unless otherwise marked)	% Cases (N=8)	% Controls (N=27)	Odds Ratio	*P*-value
ERCP*	**75**	**4**	**78**	**<0.001**
Antibiotics	**100**	**56**	**9.5**	**0.047**
Anesthesia	88	44	8.8	0.056
Other Endoscopy	25	11	2.7	0.34
Interventional radiology	25	30	0.8	0.80
Surgical procedure (operating room)	63	41	2.4	0.29
Radiology – MRI	13	0	6.0	0.34

*Timeframe for ERCP: Prior 6 months

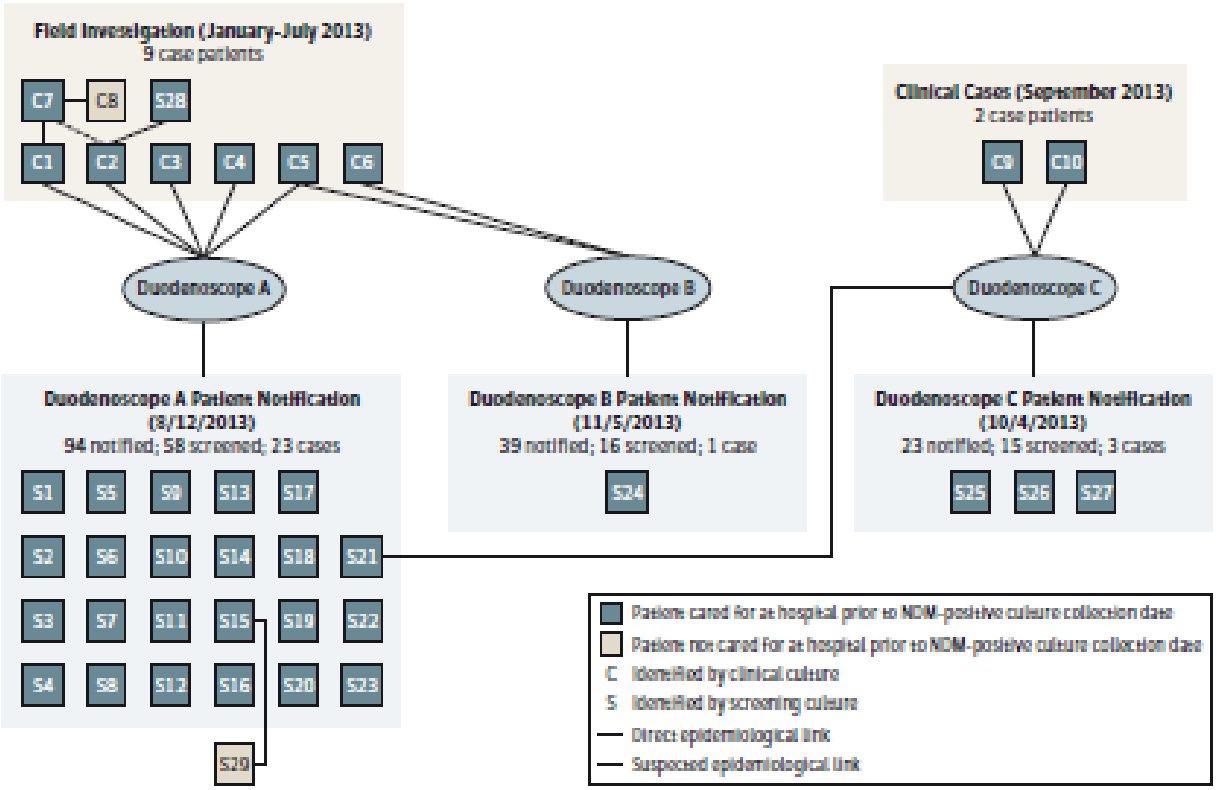
Subsequent Case Finding

- **Patient notification**
  - Exposure to a duodenoscope from January 1–September 30, 2013
  - Recommend return to hospital for CRE rectal screening
- **Diagnostic testing**
- **Screening roommates**
- **38 NDM colonized or infected patients identified**

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

Transmission Relatively Efficient and Sustained

Figure 1. Network Diagram of Case Patients



48% screened positive

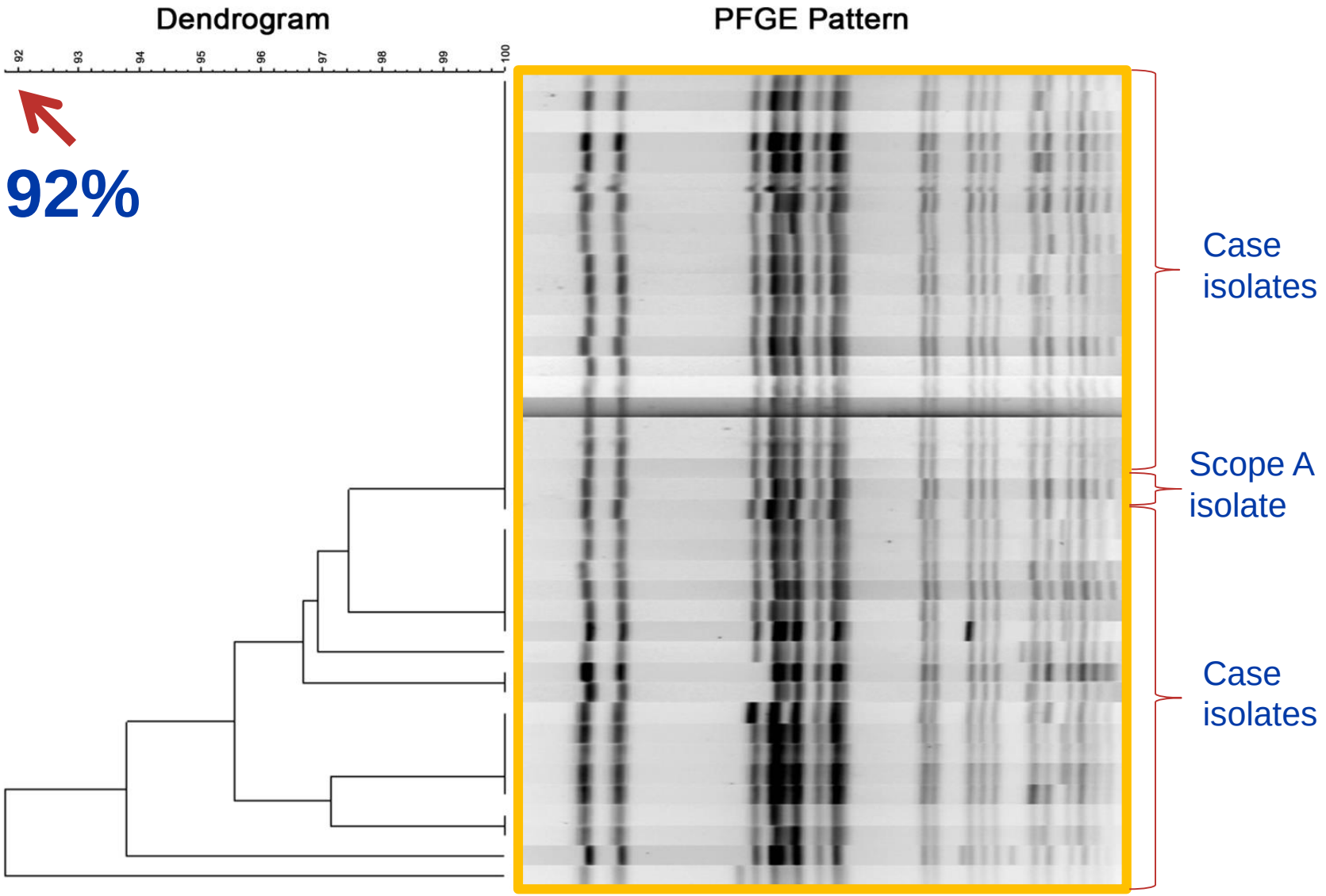
Epstein L, et al. JAMA 2014; 312:1447-1455

Laboratory Results

- NDM *E. coli* and KPC-producing *K. pneumoniae* recovered from area around elevator mechanism of Scope A (nearly 2 months after last use)
- NDM not recovered from other parts of duodenoscope
- Cultures of AER and of reprocessing areas did not reveal CRE
- CRE isolates appeared sensitive to disinfectants

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

PFGE to Assess Relatedness



Reprocessing and Duodenoscope Assessment

- **No errors in reprocessing identified**
  - AER and duodenoscope manufacturer also reviewed
- **No duodenoscope defects found**
- **Deviations from manufacturer instructions**
  - Enzymatic cleaner and disinfectant not on manufacturer's list of compatible reagents
    - Cleaner commonly used
    - Disinfectant considered identical to product on list
  - One channel brush compatible although not that recommended by manufacturer

Duodenoscope Clusters (as of April 2015)

CDC Notification Dates	Manufacturer	Organism
July 2013	Pentax	NDM-Producing *E. coli*
November 2013	Olympus	NDM-producing *E. coli*
November 2013	Olympus	Plasmid AmpC-producing *E. coli*
May 2014	FujiFilm	KPC-producing *K. pneumoniae*
June 2014	Olympus	KPC-producing *K. pneumoniae*
February 2015	Olympus	OXA-48-type-producing *K. pneumonia*
March 2015	Olympus	KPC-producing K. *pneumoniae*
March 2015	Olympus	ESBL-producing *E. coli*

Common Themes from CDC Duodenoscope Investigations

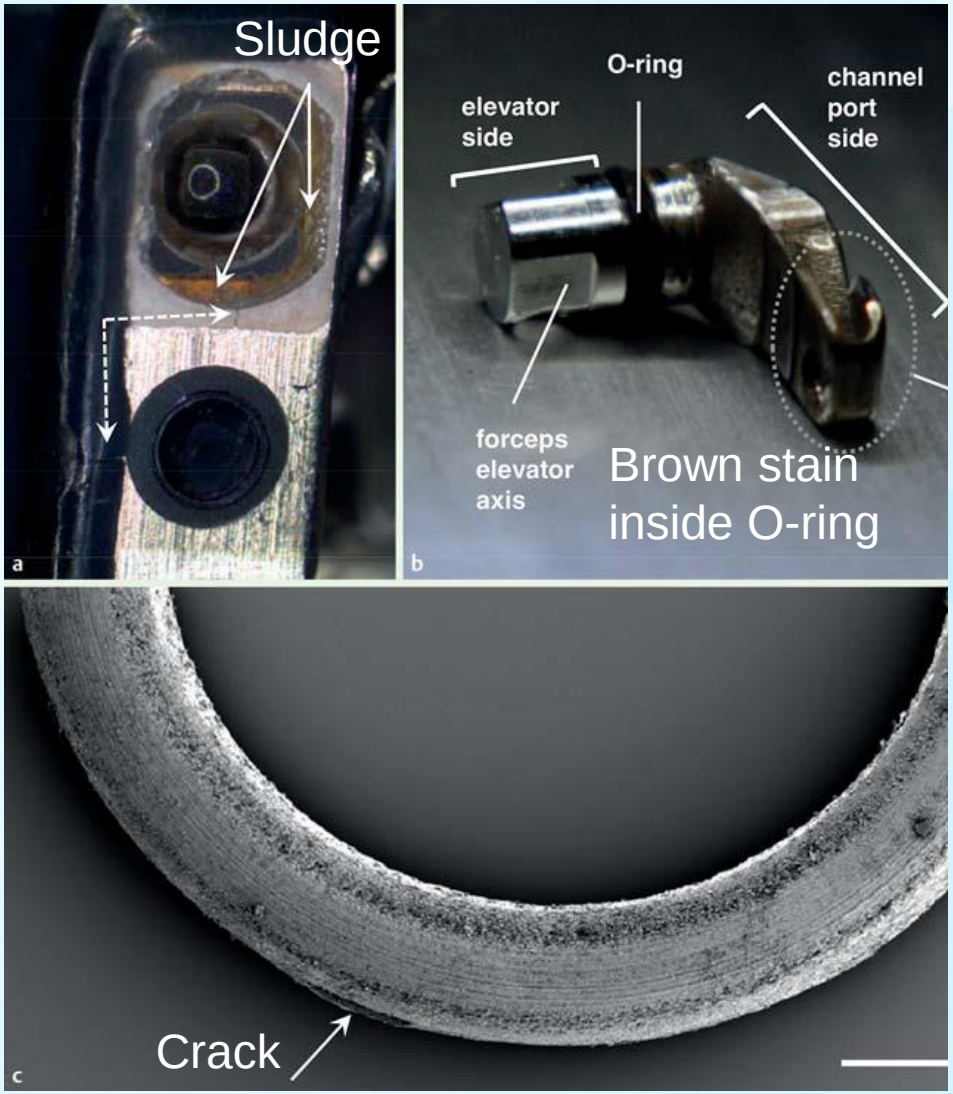
- **Clusters detected due to presence of very unusual organisms**
  - No reason CDC aware of that CRE would be more likely to persist than other organisms
- **Duodenoscopes linked to transmission have been of variable ages (weeks old to years old)**
  - Have involved open and closed elevator wire endoscopes although closed more common
- **Perceived problems removing debris with what facilities felt were manufacturer recommended procedures**
  - Employed other brushes or steps
- **Some deviations from recommended practice**
  - Additional brushes
  - Detergents or disinfectants not on manufacturers list
- **Scope cultures positive months after last use**

Where is persistent contamination? Outbreak of VIM-producing *P. aeruginosa*

- **2012: 30 patients with related VIM-producing *P. aeruginosa* identified (22 had ERCP)**
  - Olympus TJF-180V (closed elevator wire channel)
- **Duodenoscope and sink cultures in endoscopy suite positive**
  - Elevator recess
  - Distal cap

Verfaillie CJ, et al. Endoscopy 2015;epub

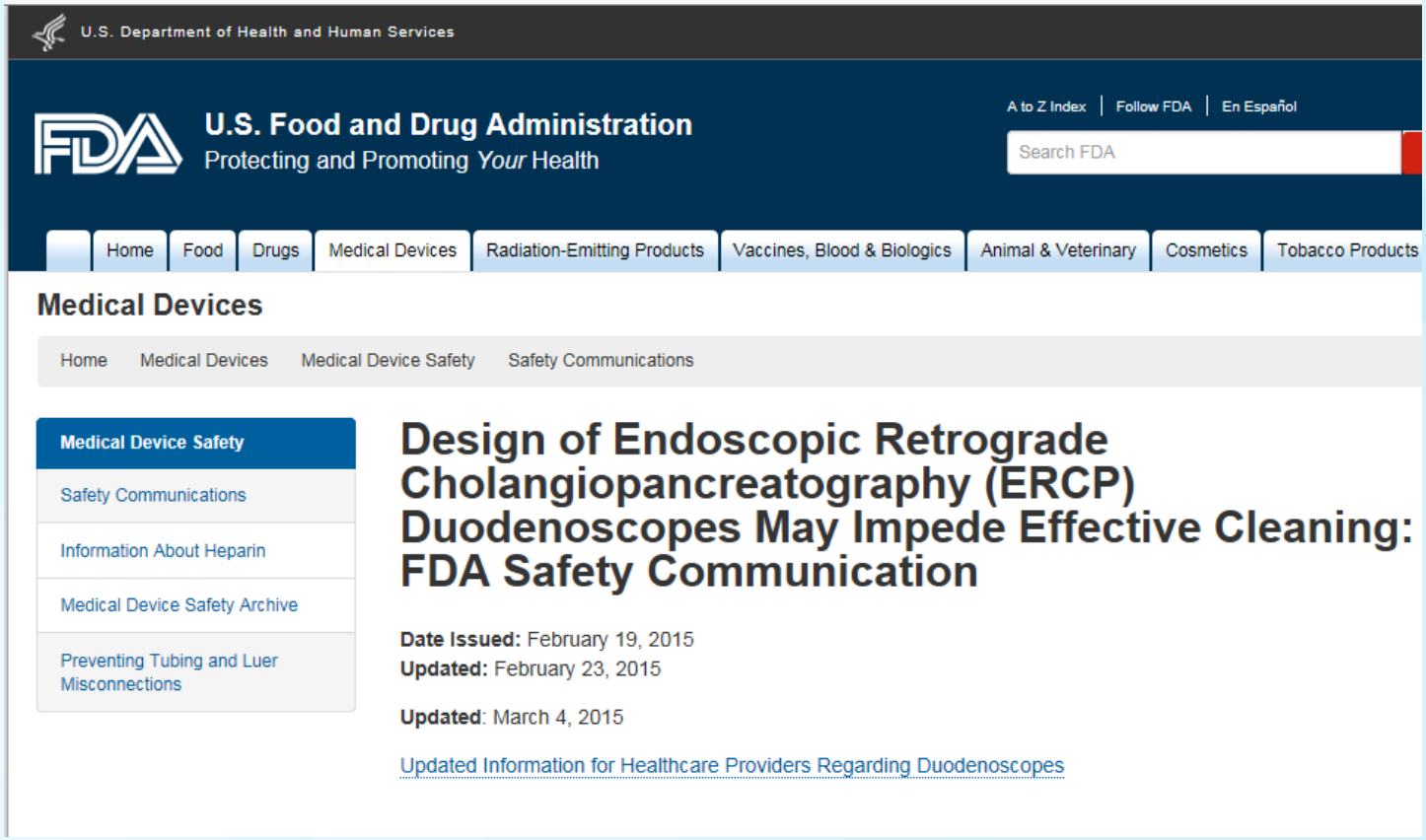
Dismantling of 13 month-old Duodenoscope



Verfaillie CJ, et al. Endoscopy 2015;epub

POTENTIAL SOLUTIONS?

FDA Safety Communication
Improved Reprocessing Review & Adherence



FDA Safety Communication

Recommendations for Facilities and Staff that Reprocess ERCP Duodenoscopes:

- **Follow closely all manufacturer instructions for cleaning and processing.**
  - The FDA recommends adherence to general endoscope reprocessing guidelines and practices established by the infection control community and endoscopy professionals, as described in the Additional Resources section, below. In addition, it is important to follow specific reprocessing instructions in the manufacturer's labeling for each device.
  - Even though duodenoscopes are inherently difficult to reprocess, strict adherence to the manufacturer's reprocessing instructions will minimize the risk of infection. Deviations from the manufacturer's instructions for reprocessing may contribute to contamination. The benefit of using cleaning accessories not specified in the manufacturer's instructions, such as channel flushing aids, brushes, and cleaning agents, is not known.
- **Report problems with reprocessing the device to the manufacturer and to the FDA, as described below.**
- **Follow these additional general best practices:**

Meticulously clean the elevator mechanism and the recesses surrounding the elevator mechanism by hand, even when using an automated endoscope reprocessor (AER). Raise and lower the elevator throughout the manual cleaning process to allow brushing of both sides.

program should include written procedures for monitoring training and adherence to the program, and documentation of equipment tests, processes, and quality monitors used during the reprocessing procedure.

  - Refer to the Multisociety Guideline on Reprocessing Flexible Gastrointestinal Endoscopes: 2011 consensus document for evidence-based recommendations for endoscope reprocessing.

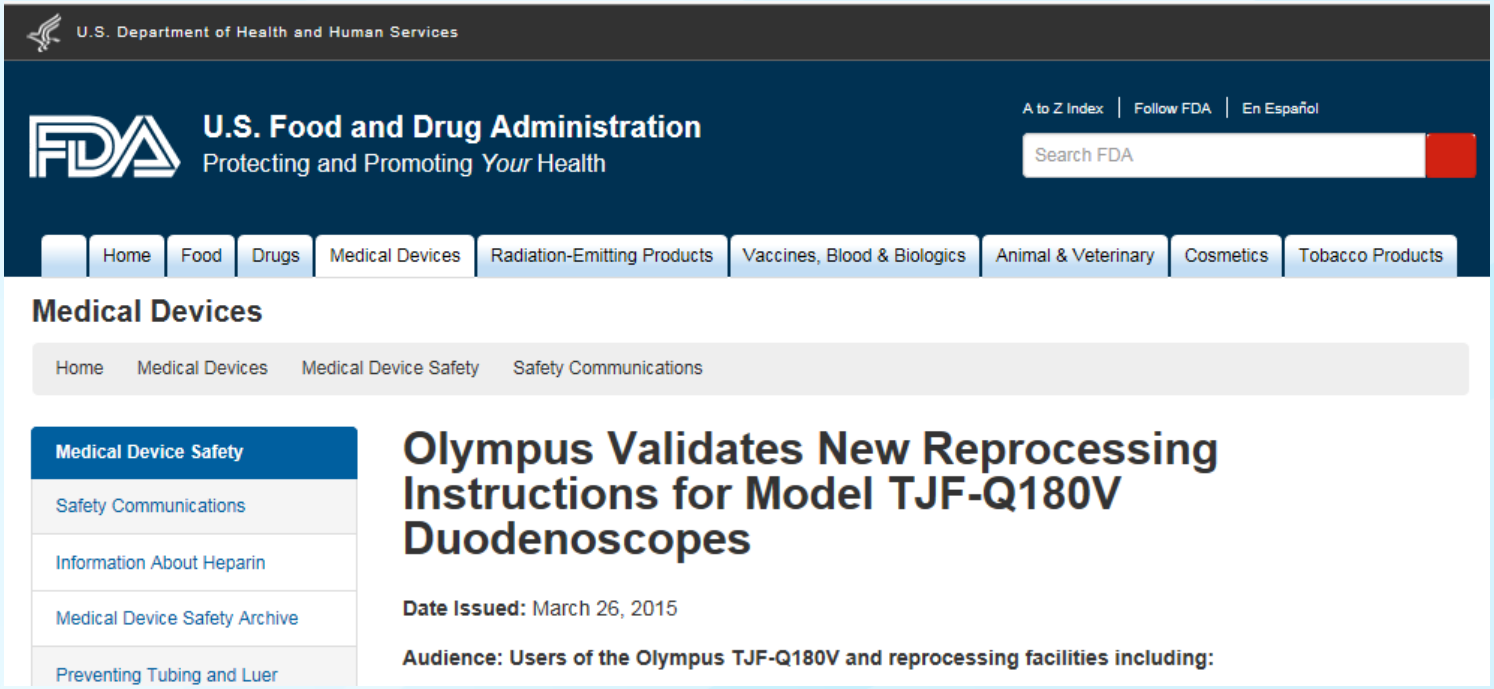
CDC Duodenoscope Algorithm

Duodenoscope Reprocessing: Facilities should review all steps in duodenoscope reprocessing several times a year (e.g., quarterly) and ensure strict adherence to the manufacturer's instructions, paying particular attention to the following:

- ***Inspection and manual cleaning***: Ensure that the elevator mechanism located at the distal tip of the duodenoscope is thoroughly cleaned and free of all visible debris. The visible inspection is to be done with the elevator in the "open/raised" position as well as with the elevator in the "closed/lowered" position to ensure there is no visible debris above or below the elevator mechanism. Consideration should be given to use of a magnifying glass (e.g., 10x) to improve detection of residual debris around the elevator mechanism.
- ***Drying***: Ensure that the channels of the duodenoscope and elevator mechanism are thoroughly dried prior to storage. This should include an alcohol flush followed by forced air drying if these procedures are compatible with the duodenoscope per the manufacturer's instructions. If channels and the elevator mechanism are not completely dry, bacterial growth can occur, forming a biofilm that is difficult to remove and could result in persistent contamination.

http://www.cdc.gov/hai/organisms/cre/cre-duodenoscope-surveillance-protocol.html

Validated Reprocessing Instructions



- Focus on cleaning elevator recess area
- Increased flushing of each channel
- Train staff on changes to procedures

High-level Disinfection vs Sterilization

- **High-level Disinfection**
  - Kills vegetative bacteria, viruses, fungi, mycobacteria
  - Recommended for semicritical devices such as duodenoscopes
- **Sterilization**
  - Complete elimination of all microbial life
  - Recommended for critical items that enter sterile body cavities
  - Only low temperature methods available
  - Not clear how effective sterilization will be if cleaning difficulties are root of problem

Low-Temperature Sterilization Methods

- **Ethylene oxide (EtO)**
  - Most commonly used procedure
  - Not available everywhere
  - Potential toxicities for workers
  - Longer reprocessing times (> 12 hour off-gassing)
  - Unknown long-term impact on device

- **Liquid chemical sterilization (peracetic acid) AER**
  - End product might not be sterile because rinse water might not be sterile
  - Approved for immediate use only

Surveillance Cultures

- **Culture of duodenoscopes to identify bacteria remaining after reprocessing**
- **Identify contaminated duodenoscopes during outbreaks**
- **Routinely assess adequacy of reprocessing**
- **Current protocols not yet validated**
  - Negative culture result does not exclude contamination of duodenoscope
  - Optimal frequency of culturing not established
- **Many challenges to implementation**
  - Requires discussion and coordination at facility-level
- **Part of guidelines in Europe, Canada, Australia, and New Zealand**

Surveillance Cultures Rationale - Australia

"Poor compliance with guidelines for endoscope reprocessing, occult endoscope damage and faulty or contaminated automated flexible endoscope reprocessors will continue to threaten the safety of patients undergoing endoscopy. Endoscope and AFER cultures have identified breakdowns in infection control before they were otherwise detected or that would not have been detected by other quality control measures."

Gastroenterological Society of Australia. 2010 Guidelines on Infection Control in Endoscopy, 3rd Edition

Highlights: CDC Protocol

- **Timing: Recommends minimum of every 4 weeks or 60 procedures for each duodenoscope**
  - Other options include after each procedure or weekly (on Friday)
  - Option to hold duodenoscopes prior to culture results
- **Organisms: Defines high-concern and low-concern organisms**
  - High-concern – more often associated with disease (*e.g.*, enteric gram-negative bacilli, *Enterococcus* spp.)
  - Low-concern – less often associated with disease; potentially a result of contamination during collection (e.g., coagulase negative staphylococci)
- **Areas to target (minimum)**
  - Area around elevator mechanism
  - Instrument channel

FDA Gastroenterology and Urology Devices Panel Meeting, May 2015

- Duodenoscopes that are properly cleaned and disinfected based on current recommendations for reprocessing do not provide “reasonable assurance of safety and effectiveness”
- The benefit of therapeutic ERCP outweighs the risks of infection

Potential Long-term Solutions

- **Duodenoscope redesign**
  - Removable distal end caps
  - Single-use parts
- **New or modified reprocessing**
  - Validated high-level disinfection instructions
  - Sterilization
  - Use of forced air drying cabinets
- **Improved/validated reprocessing assessment**
  - Surveillance cultures
  - ATP or other non-culture methods

Thank you.

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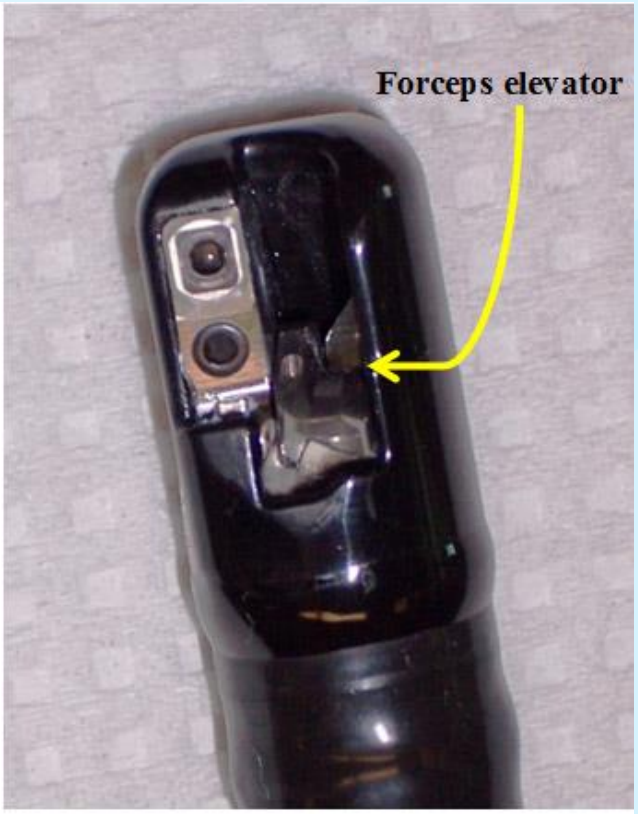
Proposed Enhanced Methods for Reprocessing Priority Ranking

- Ethylene oxide sterilization after high level disinfection with periodic microbiologic surveillance
- Double high-level disinfection with periodic microbiologic surveillance
- High-level disinfection with scope quarantine until negative culture
- Liquid chemical sterilant processing system using peracetic acid and rinsed with extensively treated potable water, with periodic microbiologic surveillance
- High-level disinfection with periodic microbiologic surveillance

Rutala WA and Weber WA, ICHE, 2015, in press.

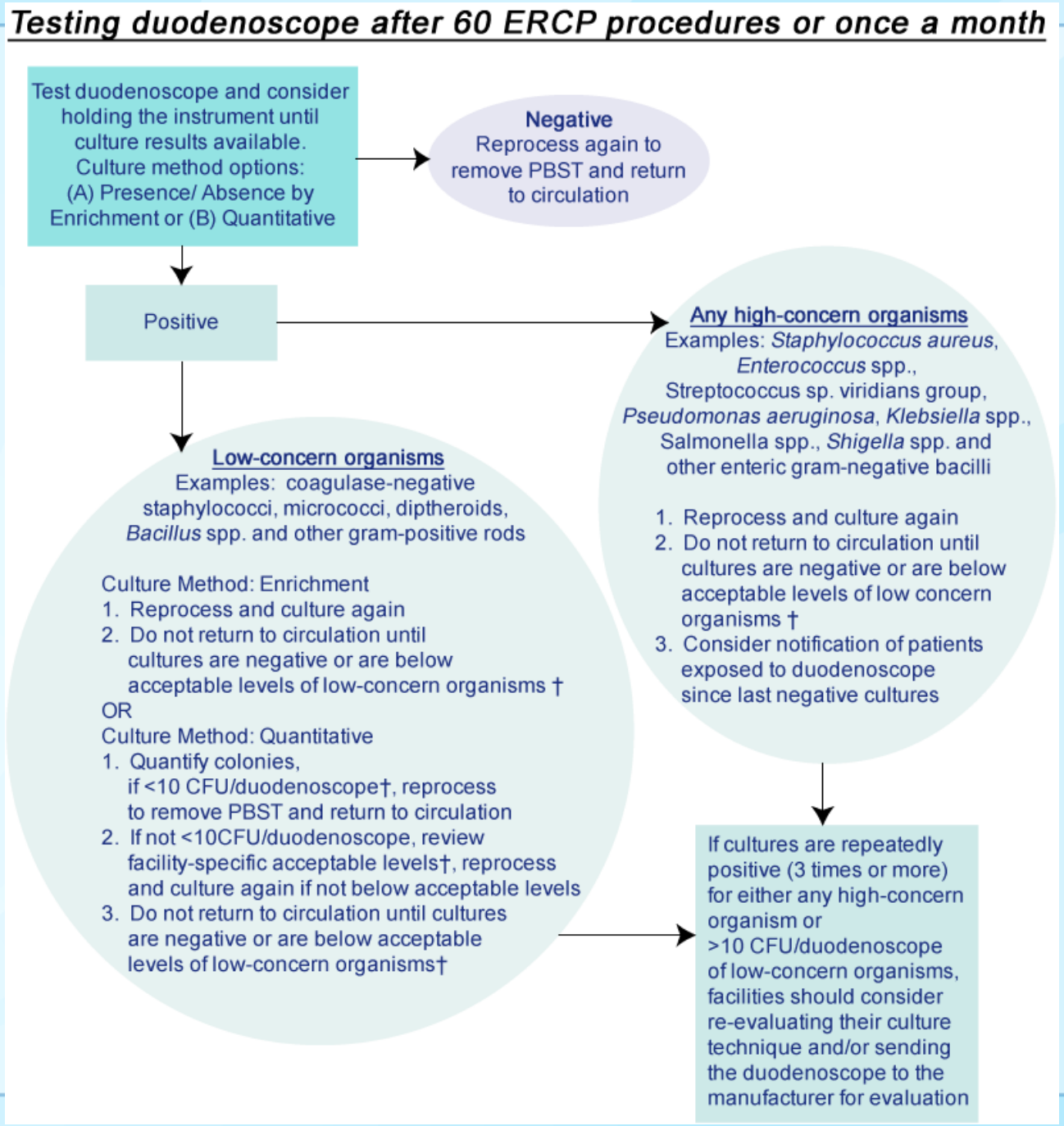
Closed Elevator Wire Channel

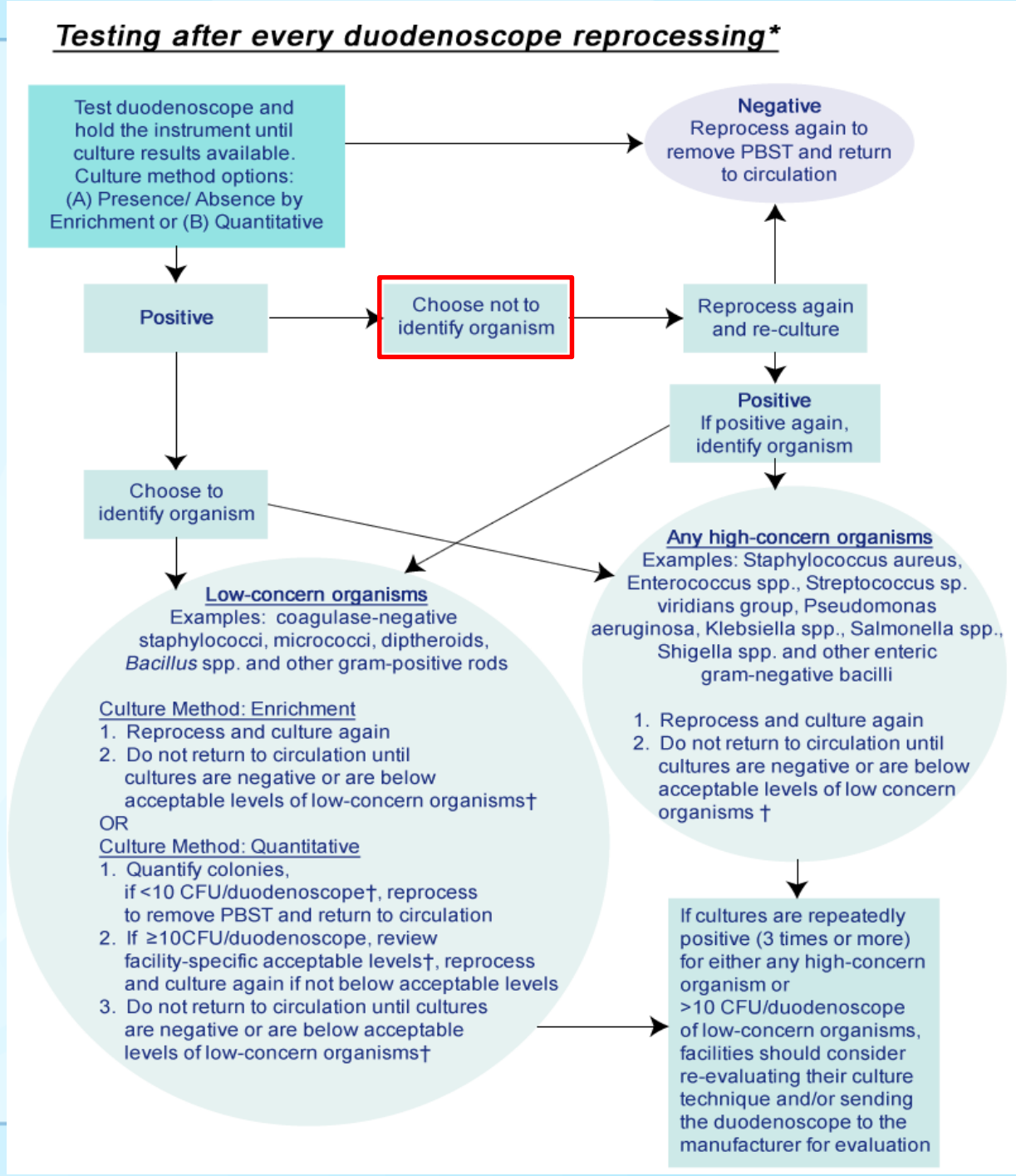
(a) Lowered/ closed forceps elevator



(b) Raised/ open forceps elevator

Testing duodenoscope after 60 ERCP procedures or once a month




Testing after every duodenoscope reprocessing*
Test duodenoscope and hold the instrument until culture results available. Culture method options: (A) Presence/ Absence by Enrichment or (B) Quantitative
Negative
Reprocess again to remove PBST and return to circulation
Positive
Choose not to identify organism
Reprocess again and re-culture
Positive
If positive again, identify organism
Choose to identify organism
Low-concern organisms
Examples: coagulase-negative staphylococci, micrococci, diptheroids, Bacillus spp. and other gram-positive rods
Culture Method: Enrichment
1. Reprocess and culture again
2. Do not return to circulation until cultures are negative or are below acceptable levels of low-concern organisms†
OR
Culture Method: Quantitative
1. Quantify colonies, if <10 CFU/duodenoscope†, reprocess to remove PBST and return to circulation
2. If ≥10CFU/duodenoscope, review facility-specific acceptable levels†, reprocess and culture again if not below acceptable levels
3. Do not return to circulation until cultures are negative or are below acceptable levels of low-concern organisms†
Any high-concern organisms
Examples: Staphylococcus aureus, Enterococcus spp., Streptococcus sp. viridians group, Pseudomonas aeruginosa, Klebsiella spp., Salmonella spp., Shigella spp. and other enteric gram-negative bacilli
1. Reprocess and culture again
2. Do not return to circulation until cultures are negative or are below acceptable levels of low concern organisms †
If cultures are repeatedly positive (3 times or more) for either any high-concern organism or >10 CFU/duodenoscope of low-concern organisms, facilities should consider re-evaluating their culture technique and/or sending the duodenoscope to the manufacturer for evaluation

CRE Definition

- **Old CDC definition**
  - NS to imipenem, meropenem or doriopenem AND R to all third-generation cephalosporins tested
- **New CDC definition**
  - R to imipenem, meropenem, doripenem, or ertapenem

Advantages

- Simpler, easier to apply
- OXA-48
- Captures some KPC-producing CRE missed by old definition

Applying CRE Interventions