Carbapenem-resistant Enterobacteriaceae (CRE) and the Environment: A Pathway to Infection?

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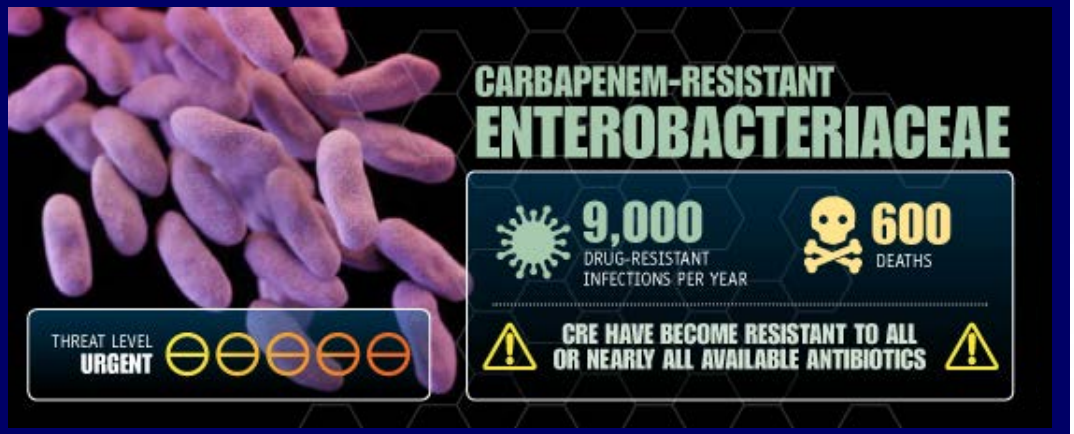
Personal/Professional Financial Relationships with Industry

External Industry Relationships	Company Name	Role
Equity, stock, or options in biomedical industry companies or publishers	None	
Board of Directors or officer	None	
Royalties from Emory or from external entity	None	
Industry funds to Emory for my research	None	
Other	None	

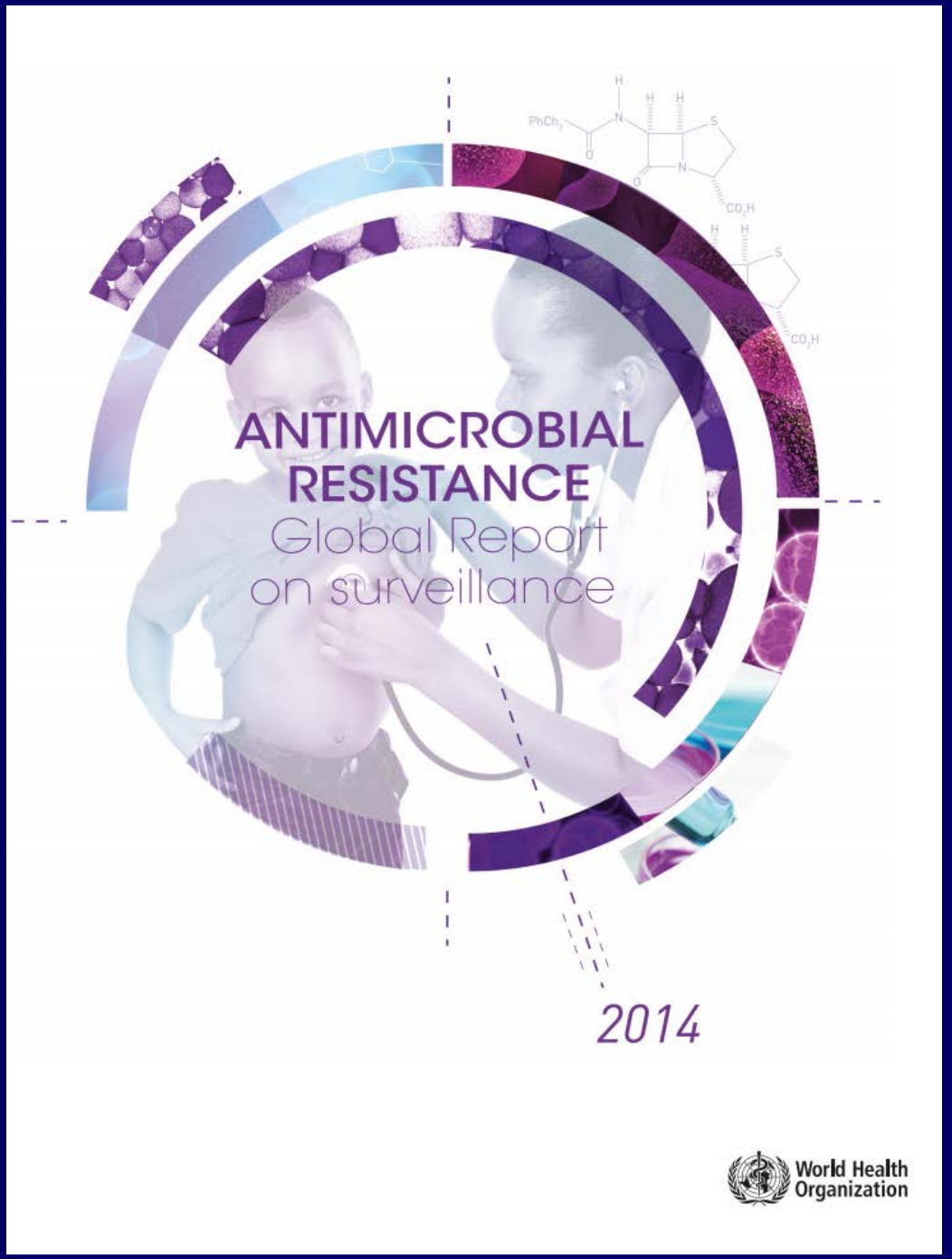
Objectives

- Discuss the increasing recognition of the environment in cross-transmission of pathogens
- Synthesize the evidence for the role of the environment in the transmission of CRE

	Enterobacter cloacae		
Drug	Interp	MIC mcg/mL	Interpreta
Amikacin $			SUSCEPTIBLE
Ampicillin $			Resistant
Ampicillin/Sulbactam $$			Resistant
Aztreonam $$$$			Resistant
Cefazolin $			Resistant
Cefepime $$			Resistant
Cefoxitin $$			Resistant
Ceftazidime $$			Resistant
Ceftriaxone $			Resistant
Cefuroxime $$			Resistant
Colistin $$$		0.064	
Gentamicin $			SUSCEPTIBLE
Levofloxacin $			Resistant
Meropenem $$			Resistant
Piperacillin/Tazobactam $$			Resistant
Tigecycline $$$$	Intermediate		
Tobramycin $			Intermediate
Trimethoprim/Sulfa $			Resistant


CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000
DRUG-RESISTANT
INFECTIONS PER YEAR
600
DEATHS
THREAT LEVEL
URGENT
CRE HAVE BECOME RESISTANT TO ALL
OR NEARLY ALL AVAILABLE ANTIBIOTICS


CRE
VITAL SIGNS
REPORT
CDC
Vitalsigns
www.cdc.gov/vitalsigns


ANTIMICROBIAL
RESISTANCE
Global Report
on surveillance
2014
World Health
Organization

Enterobacteriaceae

- Large family of bacteria
- Normal human (animal) gut microbiota
  - Most common: *E. coli* and *Klebsiella pneumoniae*
- Agents of common and serious infections in both healthcare setting and the community
  - Urinary tract infections, post-operative infections, pneumonia, bloodstream infections, meningitis, typhoid, plague, dysentry

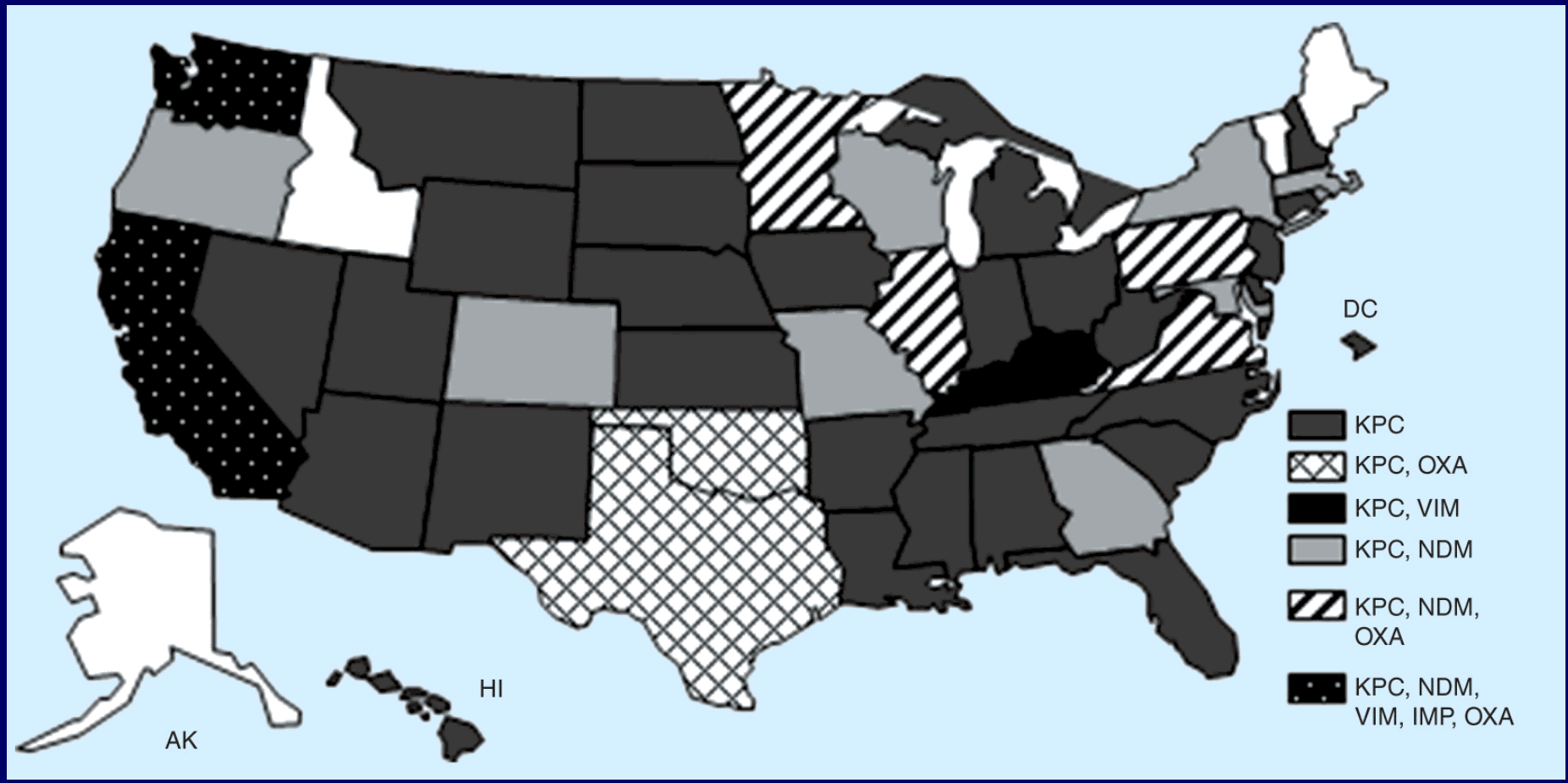
Carbapenems\Carbapenem Resistance

- Carbapenems (i.e. imipenem)
  - One of the broadest spectrum antibiotics
  - “Antibiotics of last resort”
- Carbapenem resistance
  - Potentially transferrable (plasmid mediated)
  - Two major mechanisms
    - Carbapenemase
    - Porin mutation + β-lactamase

CRE in the National Healthcare Safety Network (NHSN), 2009-2010

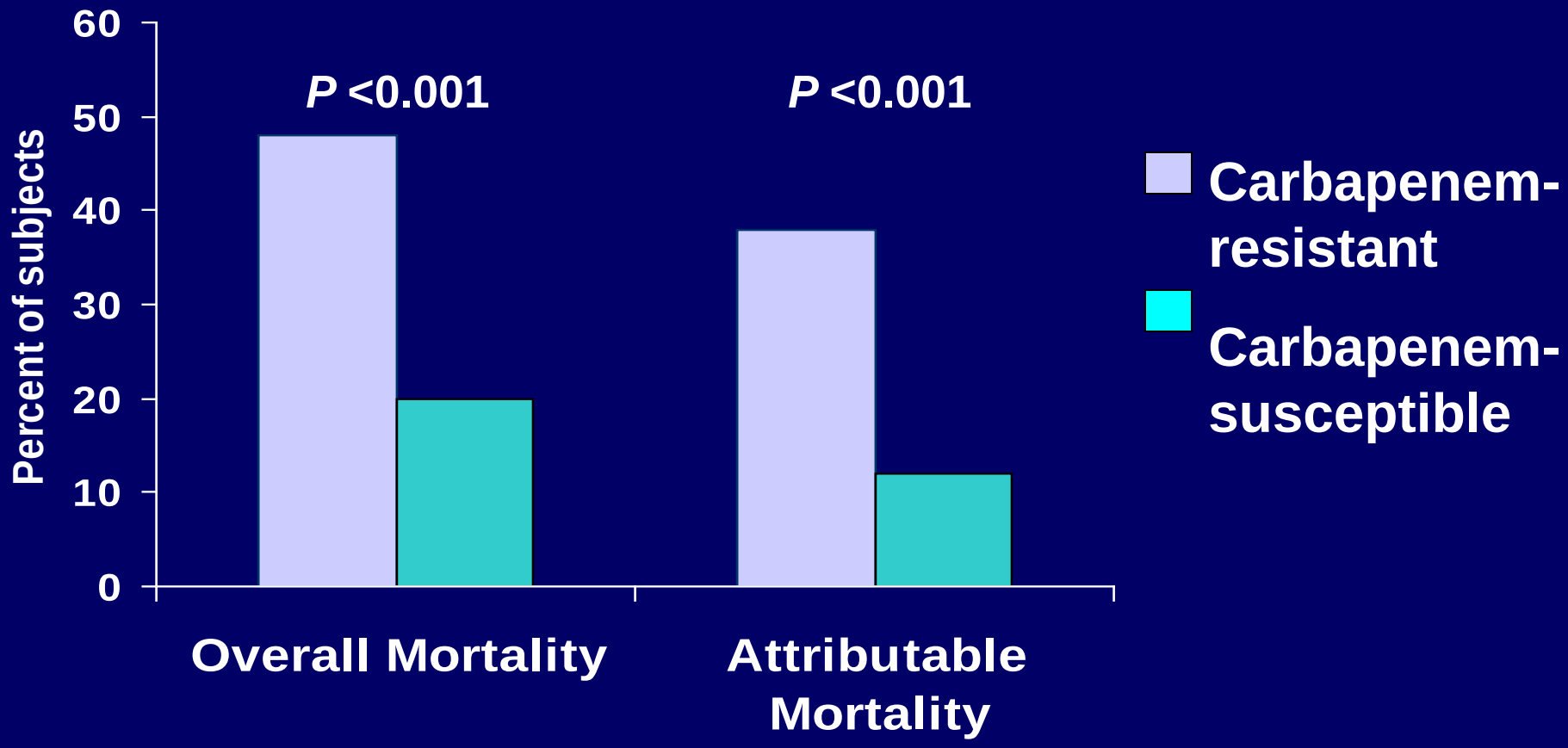
	Central line-associated bloodstream infections	Catheter-associated urinary tract infections	Ventilator-associated pneumonia	Surgical site infections
E. coli	1.9%	2.3%	3.5%	2.0%
Klebsiella spp.	12.7%	12.5%	11.2%	8.2%

CRE in the US, 2013



Guh et al. Expert Rev. Anti Infect. Ther. 2014;12:565–580

Mortality in CRE Bacteremia



Patel G et al. Infect Control Hosp Epidemiol 2008;29:1099-1106.

CRE Spreads Through Contact

	Samples	Samples Contaminated	
	N	n	%
Gown/gloves	96	10	10.4
Environment	19	2	10.5

Rock et al Infect Control Hosp Epi 2014;35:426-429

Variable	Frequency of contamination, % (proportion) of opportunities	*P*
HCW activity in room		
Physical examination	13.3 (21/158)	.59
Wound care	36.4 (4/11)	.05
Manipulation of catheter or drain	37 (10/27)	<.001
Taking vital signs	16.3 (8/49)	.61
Touching intravenous pump or tubing	20 (11/55)	.15
Touching bed rail	22.8 (18/79)	.006
Touching supply cart	17 (14/82)	.33
Longer than 5-minute stay in patient room	16.8 (18/107)	.26
More than 2 patient contacts	25 (25/100)	<.001
More than 2 environmental contacts	23.7 (23/97)	<.001

Rock et al Infect Control Hosp Epi 2014;35:426-429

Relationships between microbial surface contamination and three types of disease, gastrointestinal, cutaneous, and respiratory, are discussed in this presentation. Several outbreaks are described in which contaminated surfaces were involved, and the author points out the need for the epidemiologist to consider the potential implications of such contamination.

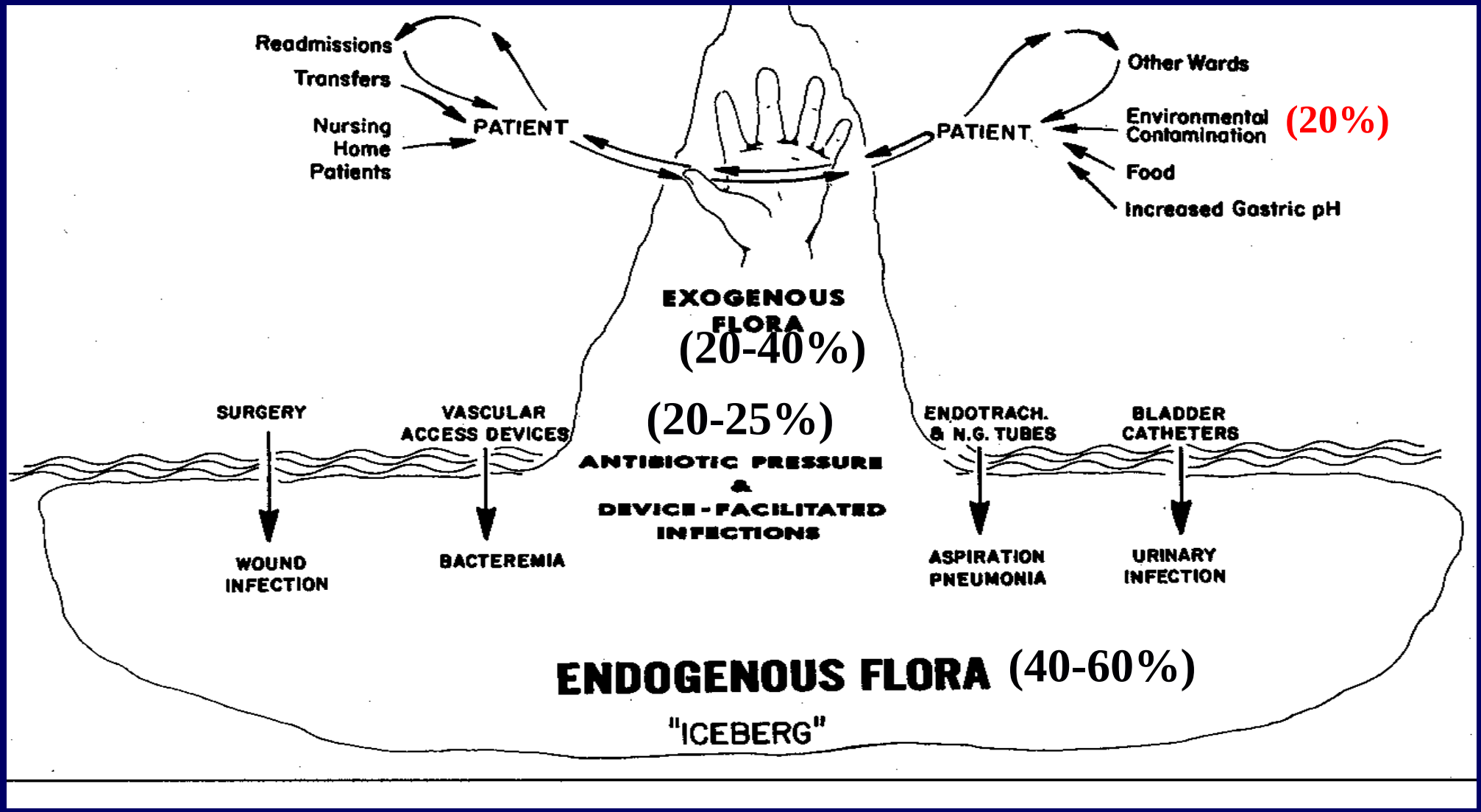
THE RELATION OF SURFACE CONTAMINATION TO THE TRANSMISSION OF DISEASE

Lieutenant Warren R. Sanborn, MSC, USN

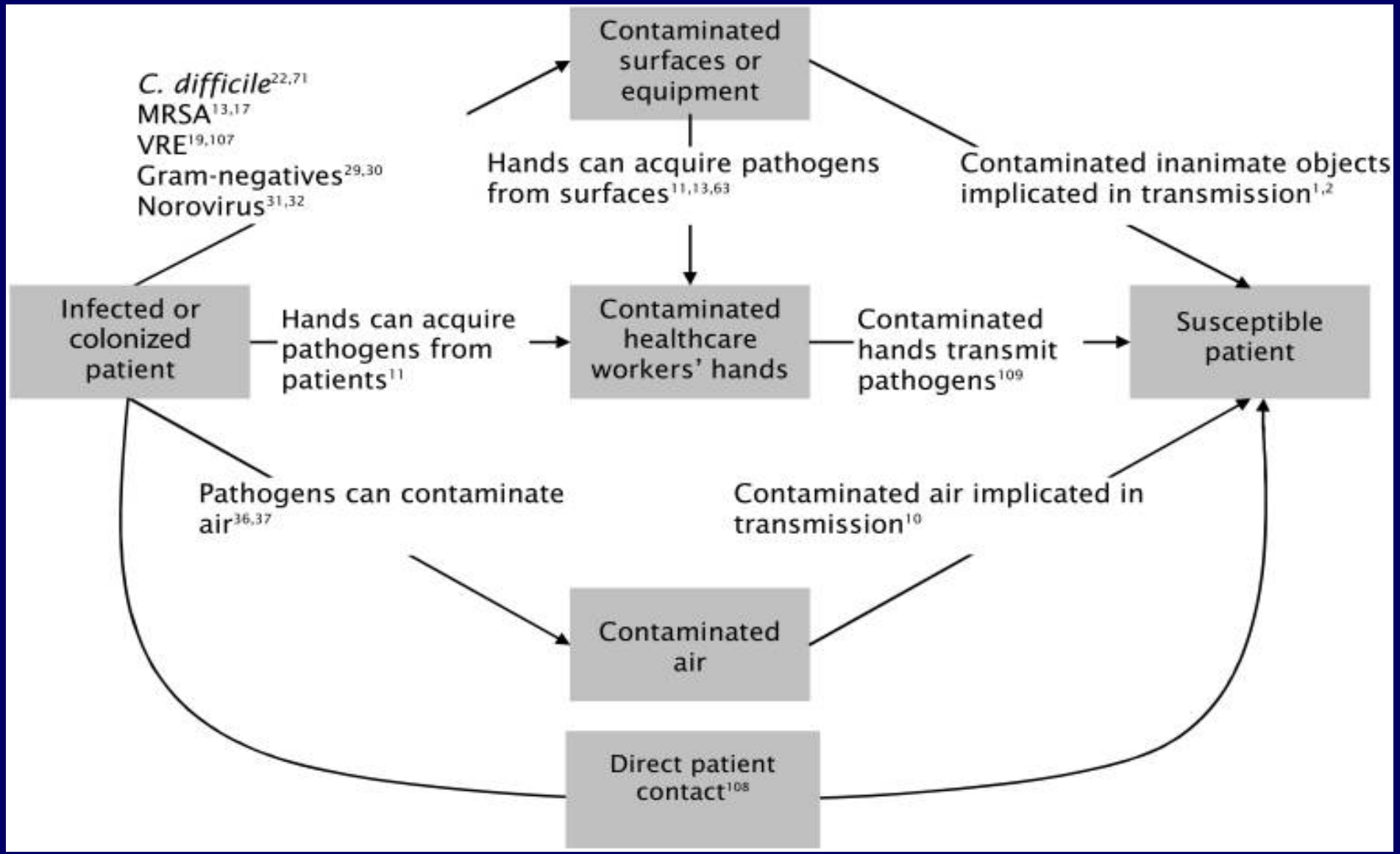
VOL. 53, NO. 8, A.J.P.H. AUGUST, 1963

Modes of Transmission of Infectious Agents

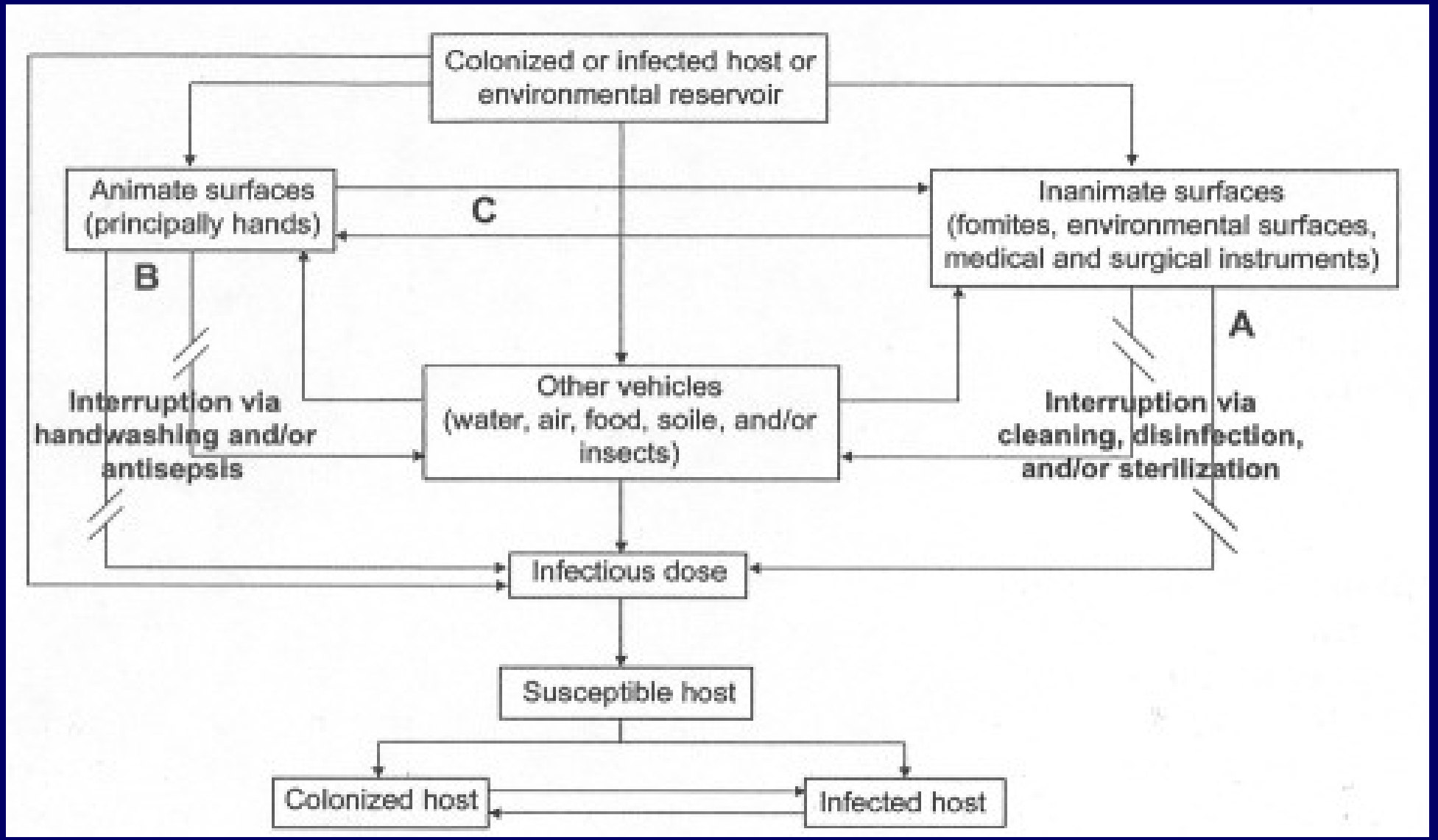
- Contact
  - Direct (body-to-body)
  - Indirect (e.g., fomites/environment, HCWs' hands)
- Air
  - Large Droplet (>5µm; travel 3 feet)
  - Small "Droplet" (≤5µm; airborne)
- Common source (Water)
- Endogenous



Weinstein RA. Am J Med 1991;91(suppl 3B):179S



Otter JA, et al. Infect Control Hosp Epidemiol 2011;32:687-699



Rutala WA, Weber DJ. In:"SHEA Practical Healthcare Epidemiology", 3rd ed, 2010.

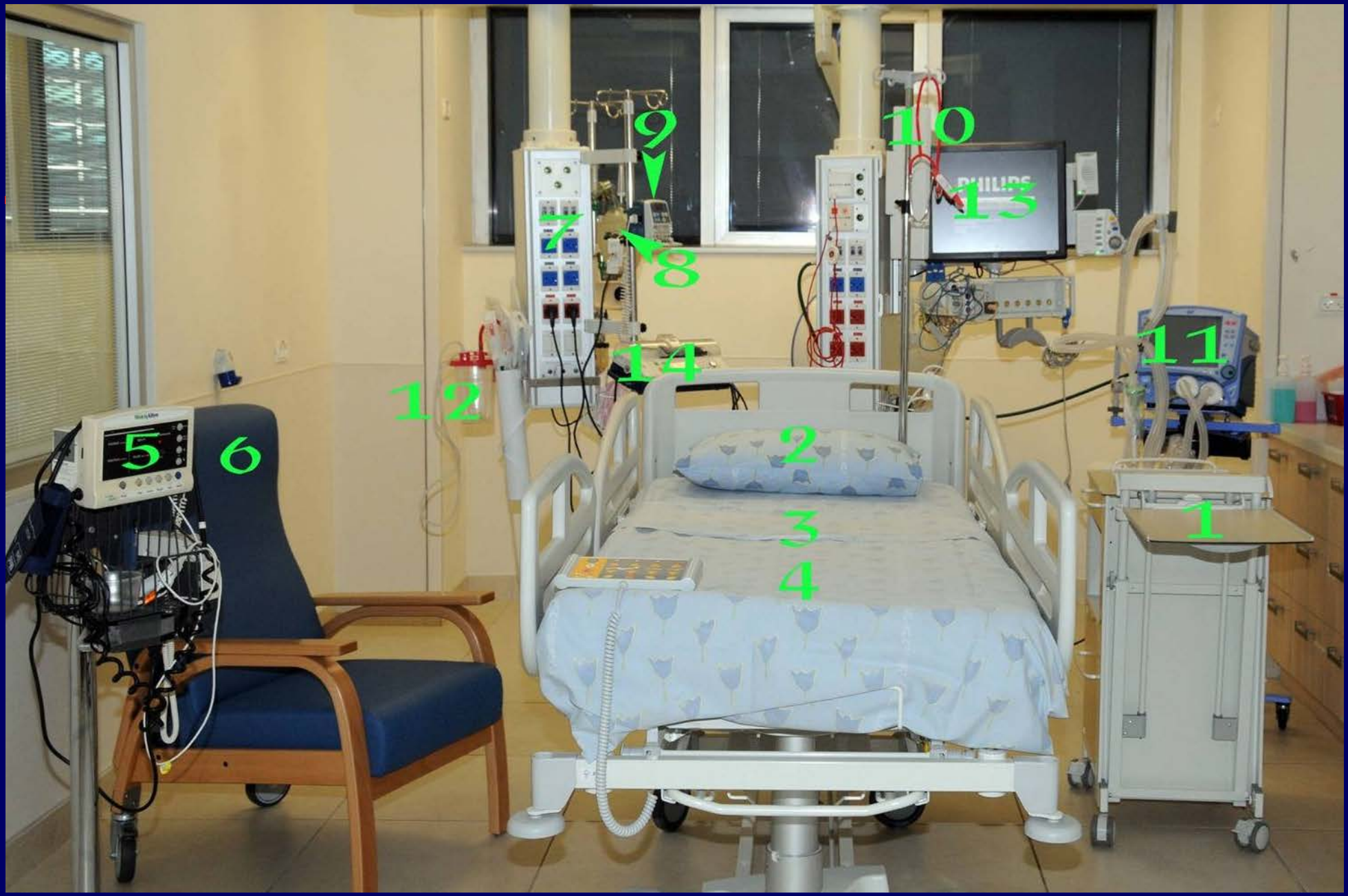
A Framework

- Environmental contamination frequent
- Persists in the environment
- HCW hand contamination
  - Correlated to environmental burden
- Viability preserved
- Increased acquisition risk if prior room occupant +
- Molecular link of environmental and clinical isolates
- Improved cleaning/disinfection reduces infection

VRE and Environmental Contamination

X represents VRE culture positive sites

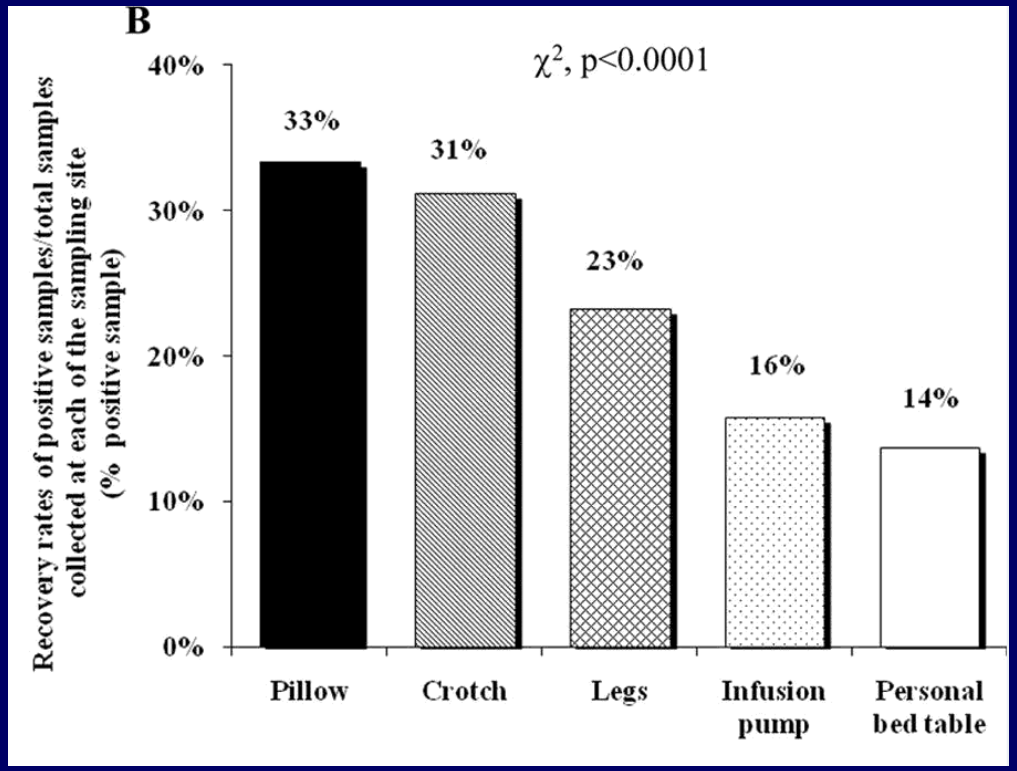
Hayden et al. ICAAC, 2001. Abstract K-1334

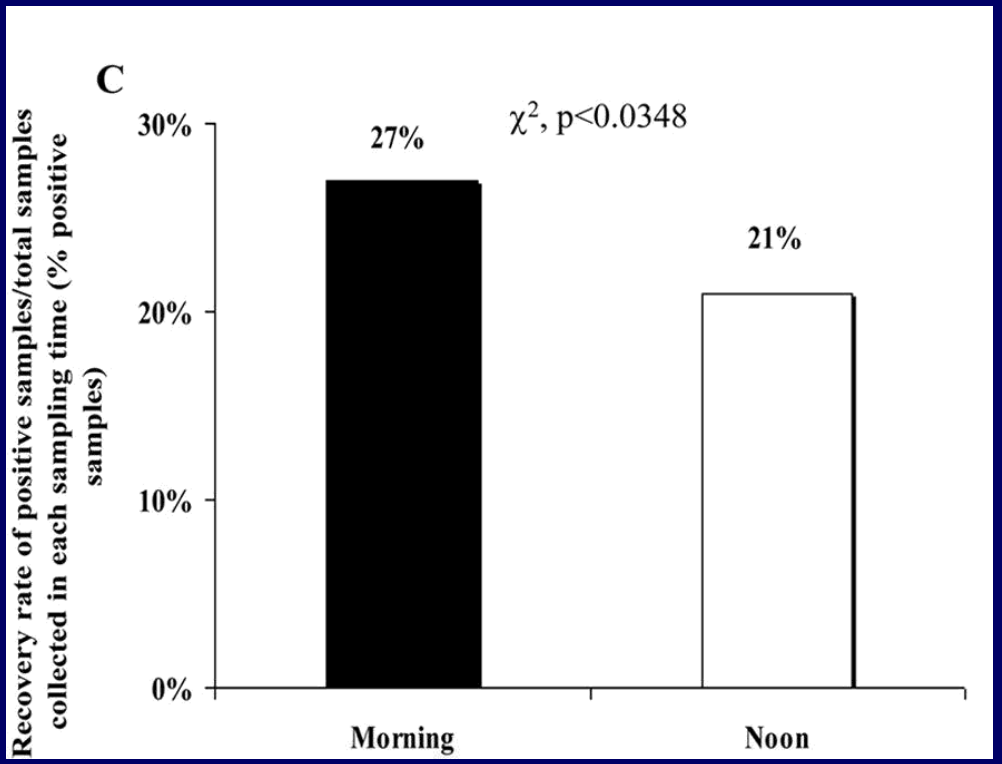


Lerner et al. J Clin Microbiol. 2013;51: 177–181.

KPC in 298 Environmental Samples from Vicinity of 34 Known Carriers

224/928 (24%) positive for CRE





Lerner et al. J Clin Microbiol. 2013;51: 177–181.

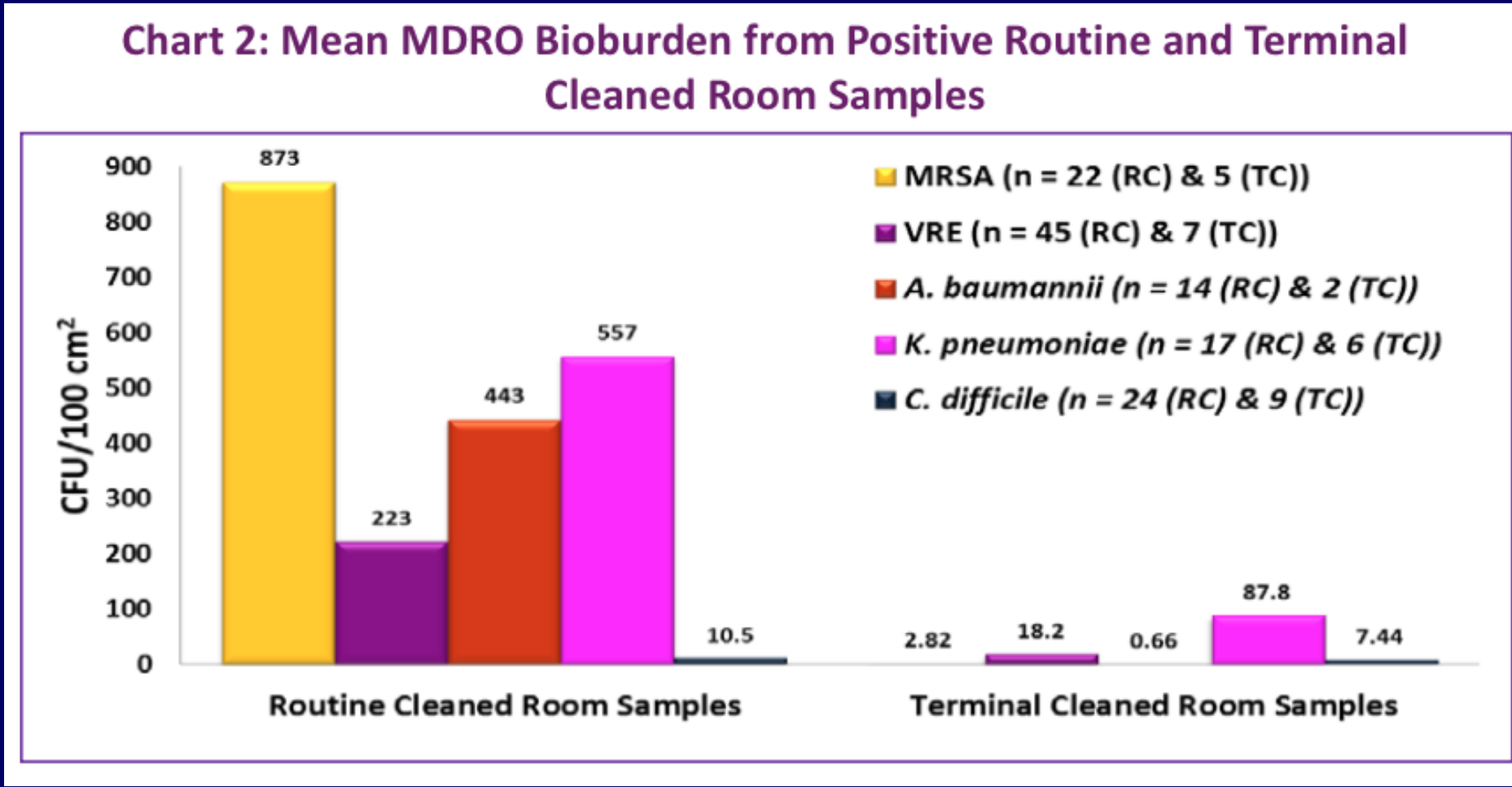
CRE from 11 Facilities in 4 States

Table 1: Percent Recovery of MDROs from Routine & Terminal Cleaned Rooms (n = total rooms positive)

	All MDROs	MRSA	VRE	*A. baumannii*	*K. pneumoniae*	*C. difficile*
Routine (n = 113)	52.2 (59)	12.4 (14)	25.7 (29)	9.7 (11)	11.5 (13)	16.8 (19)
Terminal (n = 53)	34.0 (18)	9.4 (5)	9.4 (5)	3.8 (2)	9.4 (5)	13.2 (7)
All Rooms (n = 166)	**46.4** (77)	11.5 (19)	**20.5** (34)	7.8 (13)	10.8 (18)	15.7 (26)

Shams et al. IDWeek 2014 Abstact #1366

When Present, CRE Burden is High



Shams et al. IDWeek 2014 Abstact #1366

CRE in the Environment of 15 Rooms of Colonized Patients

TABLE 1. Contamination on Surfaces in Rooms Housing a Patient with CRE

Room Site Cultured (No.)	CRE Positive, No. (%)[a]	CRE, mean CFU (range)[b]
Bed rail (15)	2 (13.3)	45 (43–47)
Overbed table (15)	1 (6.7)	3
Chair #1 arm (12)	0 (0.0)	...
Sink (15)	2 (13.3)	14.5 (11–18)
Toilet (11)	2 (18.2)	7 (4–10)
Bathroom floor (10)	1 (10.0)	5
Supply cart (11)	1 (9.1)	2
Linen hamper (12)	0 (0.0)	...
Mobile computer (3)	0 (0.0)	...
Chair #2 arm (3)	0 (0.0)	...
Bedside table (3)	0 (0.0)	...
Toilet cabinet (4)	0 (0.0)	...
Floor outside toilet cabinet (4)	1 (25.0)	2
Ventilator counter (1)	0 (0.0)	...
Total (119)[c]	10 (8.4)	5.1 (2–47)

CFU, colony forming units; CRE, carbapenem-resistant *Enterobacteriaceae*.

[a]Considered positive if ≥1 of the 5 Rodac plates had positive growth (ie, area sampled = 120 cm^2).

[b]Mean and range calculated only for CRE culture positive sites.

[c]For one site cultured, technical difficulties prevented assessing growth. Thus total was 119 sites instead of 120 sites.

Weber et al. Infect Control Hosp Epidemiol 2015 (pub ahead of print)

Anatomic Sites of Patient Colonization and Environmental Contamination with *Klebsiella pneumoniae* Carbapenemase–Producing Enterobacteriaceae at Long-Term Acute Care Hospitals

Sterile, moistened double Dacron swabs were also used to culture environmental sites in occupied patient rooms and in common areas. Sites varied according to facility but included dresser, call button, bed rails, overbed table, infusion pump control panel, ventilator control panel, toilet flusher, computer keyboard, and medicine cabinet door. Common-area sites included equipment in the physical therapy gym and the hemodialysis room and items in staff break rooms. A 10 × 10-cm area of the surface of each site was swabbed when feasible. For smaller surfaces, the entire site was swabbed. For large surfaces, high-touch regions were swabbed. Rooms and common areas were cleaned daily with a quaternary ammonium compound. The time from cleaning to environmental sampling was not recorded.

Infect Control Hosp Epidemiol 2013;34(1):56-61

Lancet Infect Dis 2011;
11: 355–62

Figure 1: Map of NDM-1-positive samples from New Delhi centre and surroun

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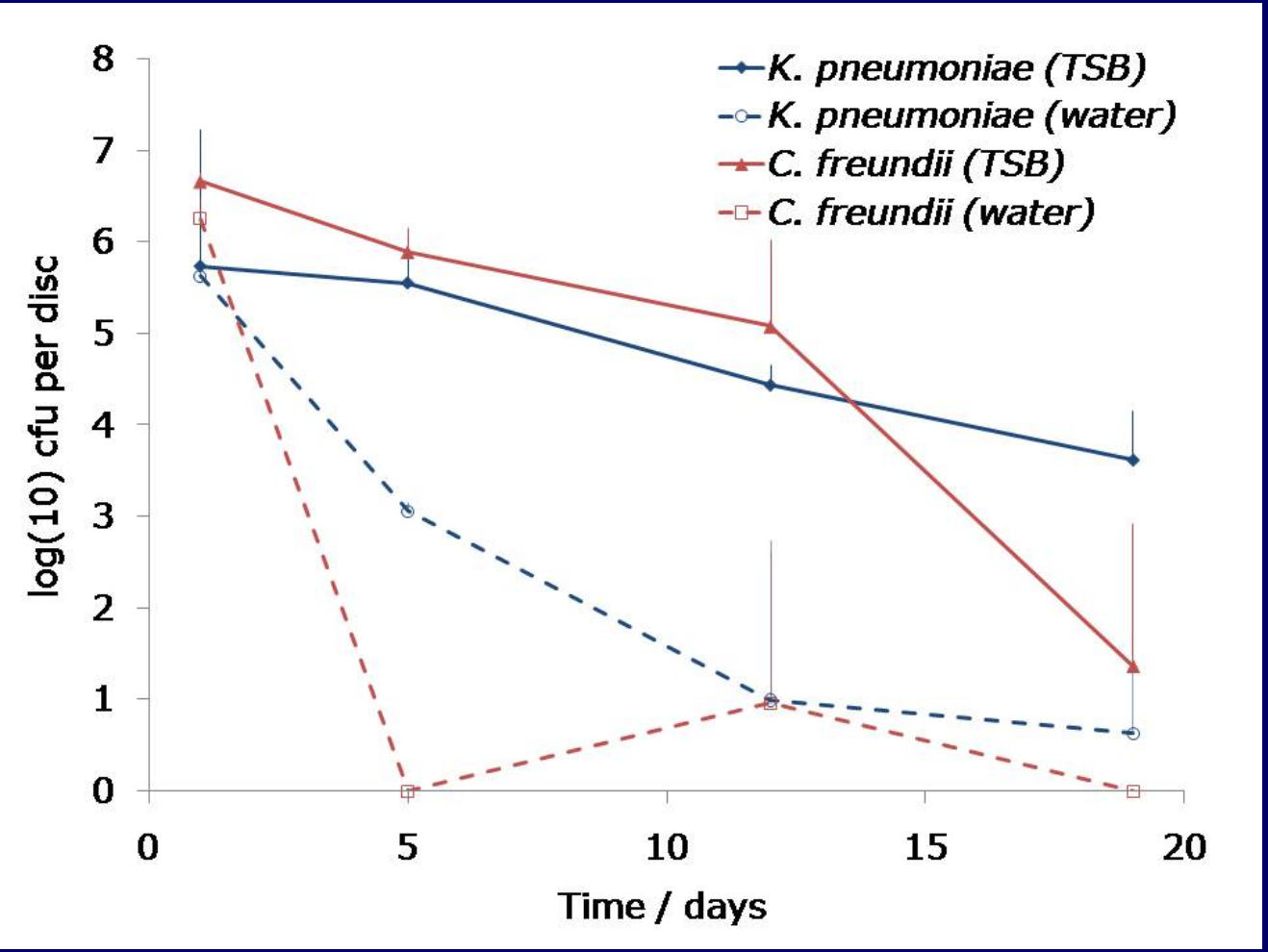
Survival of CRE on Dry Surfaces



Havill et al. ICHE 2014; 35:445-447

“Down the Drain”: CRE ICU Sinks

- Patients
  - 10 clinical isolates and 1 surveillance isolate with bla_{IMP-4} gene over 30 months
- Environment
  - *S. marcescens* in grate/drain of 8 sinks
    - Molecular typing relatedness to clinical isolates
  - Tap water cultures negative.
  - Failed 6 attempts to clean and decontaminate sinks using detergents and steam

Kotsanas et al. Med J Aust 2013; 198 (5): 267-269.

A Suboptimal Process

- Aged (2005), deteriorating porcelain
- Shallow sink with water over drain
- Sink used for clinical waste
- One brush used to clean all drains without disinfection

Kotsanas et al. Med J Aust 2013; 198 (5): 267-269.

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INVITED ARTICLE HEALTHCARE EPIDEMIOLOGY

Robert A. Weinstein, Section Editor

Managing Transmission of Carbapenem-Resistant Enterobacteriaceae in Healthcare Settings: A View From the Trenches

Tara N. Palmore and David K. Henderson

Hospital Epidemiology Service and the Office of the Deputy Director for Clinical Care, Clinical Center, National Institutes of Health, Bethesda, Maryland

In 2011, the National Institutes of Health Clinical Center experienced a cluster of infection and colonization caused by carbapenem-resistant *Klebsiella pneumoniae* among profoundly immunocompromised inpatients. This manuscript describes the approach and interventions that were implemented in an attempt to curtail the cluster. Interventions employed included engagement of all stakeholders involved in care of at-risk patients; detailed and frequent communication with hospital staff about issues relating to the outbreak; aggressive microbial surveillance; use of techniques that facilitate rapid identification of resistant organisms; rapid characterization of resistance mechanisms; whole-genome sequencing of outbreak isolates to characterize the spread and to investigate mechanisms of healthcare-associated spread; implementation of enhanced contact precautions for all infected or colonized patients; geographic and personnel cohorting; daily chlorhexidine gluconate baths; dedicating equipment to be used solely for cohorted patients and aggressive decontamination of equipment that had to be reused on uncohorted patients; monitoring adherence to infection control precautions, including unwavering attention to adherence to appropriate hand hygiene procedures; and attention to the details of environmental decontamination. In addition, the manuscript discusses some of the challenges associated with managing such an event, as well as a few of the unanticipated consequences associated with the aftermath of the case cluster.

Table. **Interventions Used to Combat the Spread of CRE at the NIHCC**

Intervention	Basis	Comment
Careful engagement of all stakeholders involved in the care of infected and colonized patients	Guideline (1)	Critical to successful implementation of prevention and control measures
Communication with hospital staff, campus staff, local and state public health authorities, and patients about issues relating to the outbreak that are relevant to each group	Guideline (1)	Critical to successful engagement of stakeholders
Aggressive microbial surveillance		
Microbial surveillance of all patients who are admitted to medical, surgical, or pediatric wards of the hospital, with empirical isolation and additional surveillance of patients who have been hospitalized in the United States in the past week or abroad in the past 6 mo	Guideline (1)	Crucial for identifying new cases and preventing transmission from patients who have had potentially high-risk exposures
Targeted, twice-weekly microbial surveillance of patients hospitalized in the highest-risk units	Empirical	Frequency driven by the severity of illness/immunosuppression
Monthly whole-house microbial surveillance of all medical–surgical patients	Guideline (1)	Crucial for identifying new cases/transmission
Use of selective media to identify resistant pathogens	Guideline (1)	Selective media are expensive
Sampling multiple sites on each patient to decrease sampling error and capture different pathogens in their respective niches	Empirical	Driven by local microbiology; prior outbreaks of other multidrug-resistant organisms
Rapid identification of resistant organisms (e.g., MALDI-TOF MS)	Routine at NIHCC	Equipment expensive; output extremely rapid and remarkably useful
Rapid characterization of resistance mechanisms (for example, PCR testing for carbapenemase genes)	Guideline (1)	–
Whole-genome sequencing to characterize the spread and investigate mechanisms of health care–associated spread	Investigational	Did not "unravel" our outbreak but identified silent transmission and changed our strategy (see text for details)
Implementation of enhanced contact precautions for all infected or colonized patients	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression
Geographic and personnel cohorting	Guideline (1)	Difficult to implement for some categories of personnel
Equipment dedicated to be used solely for cohorted patients, to the extent possible	Guideline (1)	–
Daily chlorhexidine baths for patients	Guideline (1)	Unable to determine efficacy in our setting
Monitoring adherence to all infection control precautions, including unwavering attention to performance of appropriate hand hygiene procedures	Empirical	Strategy was useful in prior outbreak (6), and implementation was associated with improved adherence
Attention to the details of environmental disinfection, including consideration of use of new decontamination technologies (e.g., hydrogen peroxide vapor or ultraviolet light)	Empirical	Intensity of the intervention due to the severity of illness/immunosuppression of our patients; a minuscule inoculum may ultimately prove lethal

CRE = carbapenem-resistant Enterobacteriaceae; MALDI-TOF MS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NIHCC = National Institutes of Health Clinical Center; PCR = polymerase chain reaction.

Palmore and Henderson. Ann Intern Med. 2014;160(8):567-569.

What environmental interventions did the NIH Clinical Center make?

- Double disinfection of all high-touch surfaces with bleach wipes
- Hydrogen peroxide vapor decontamination
- Sink drains were removed and cleaned thoroughly, and bleach sprayed daily down drains on affected wards
- Built a wall to allow cohorting

Palmore and Henderson. Clin Infect Dis 2013;57(11):1593–9

Why such aggressive cleaning?

- Bed ?source in 1 transmission
- Ventilator grew KPC despite 3 prior rounds of manual cleaning and disinfection
- Cultures from 4 sink drains grew KPC
- 7/260 (3%) of environmental cultures KPC +
- Small inocula might transmit lethal infection to immunosuppressed patients

Palmore and Henderson. Clin Infect Dis 2013;57(11):1593–9

What worked at NIH?

"We emphasize that much of what we did in managing this outbreak is not evidence-based...We attempted to mitigate literally every risk we could identify and took the most conservative approach that was feasible in virtually every instance...We are not suggesting that our use of any of these interventions implies efficacy and underscore that we implemented all of them virtually simultaneously, so we have no way of knowing which of them were effective. "

Palmore and Henderson. Clin Infect Dis 2013;57(11):1593–9

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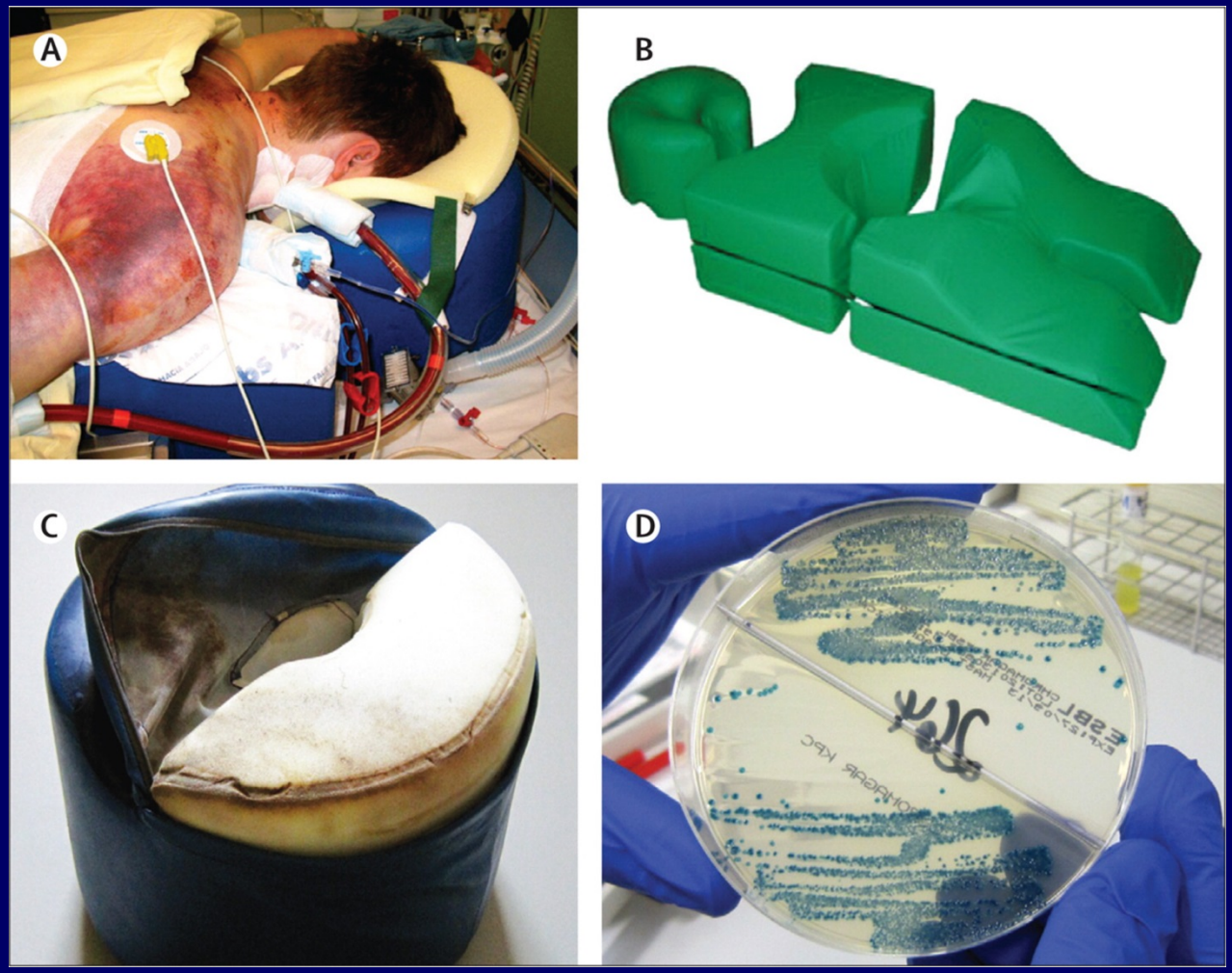
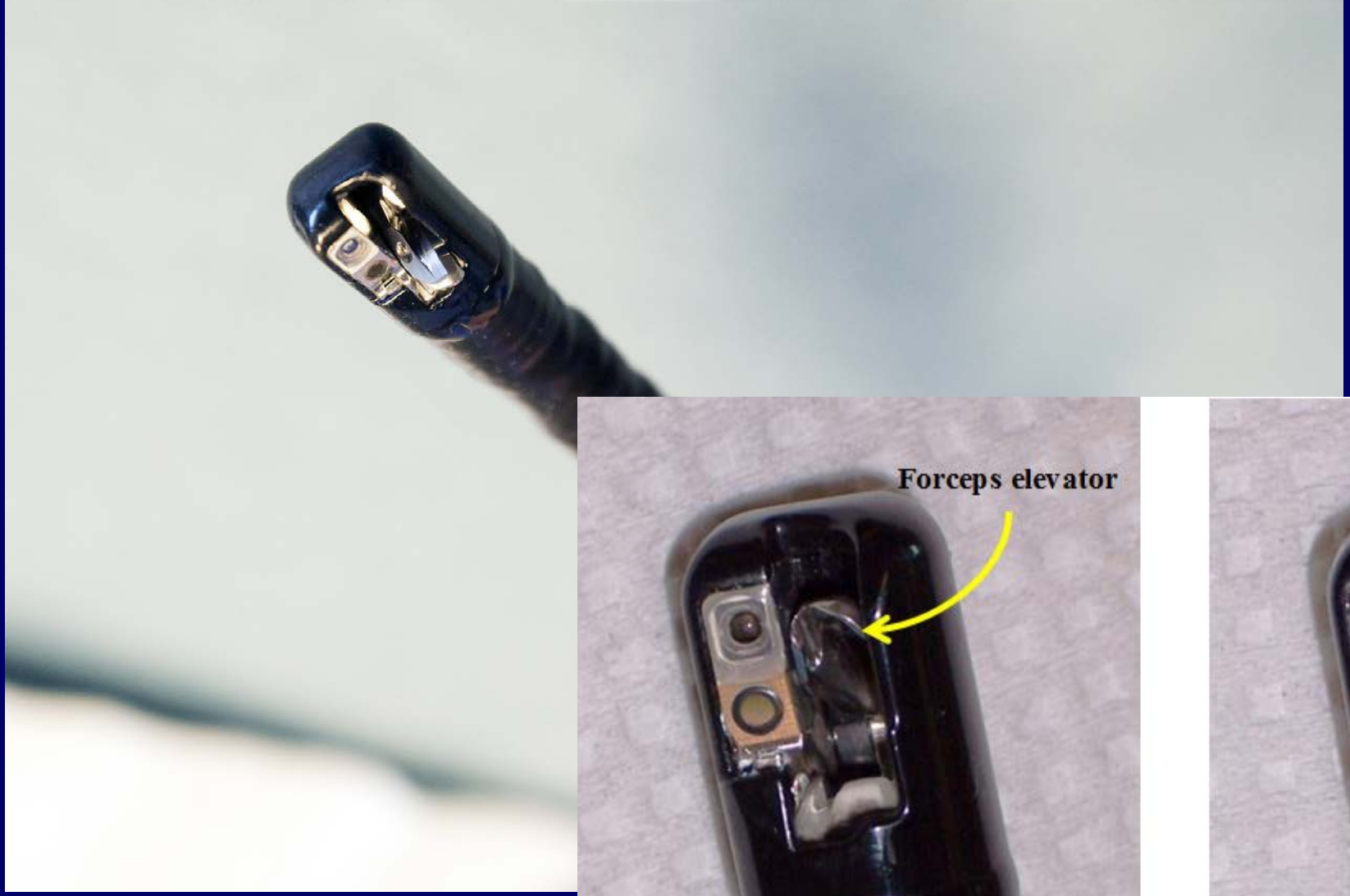
CRE Outbreak Linked to Contaminated Pillows



Lippmann et al. Lancet ID 2014;14:271-272



(a) Lowered/ closed forceps elevator

(b) Raised/ open forceps elevator

Deadly bacteria outbreak inflames disinfection concerns

Peter Eisler, 11:25 p.m. EDT March 18, 2015

(Photo: Melissa Brower, AP)

The contaminated medical scopes linked since 2013 to a series of deadly superbug outbreaks in at least eight hospitals across the country all had been cleaned and disinfected using high-tech appliances cleared by the government to kill the bacteria behind such infections.

World Journal of Gastrointestinal Endoscopy

World J Gastrointest Endosc. 2014 Oct 16; 6(10): 457-471. PMCID: PMC4198301
Published online 20

Risk of tran
"superbugs

Lawrence F Mus

Notes from the Field: New Delhi Metallo-β-Lactamase–Producing *Escherichia coli* Associated with Endoscopic Retrograde Cholangiopancreatography — Illinois, 2013

Weekly
January 3, 2014 / 62(51);1051-1051

Infections with carbapenem-resistant *Enterobacteriaceae* (CRE)* are increasing among patients in medical facilities (*1*). CRE that produce *Klebsiella pneumoniae* carbapenemase (KPC) have been responsible for much of the increase in the United States. However, New Delhi metallo-β-lactamase (NDM)–producing CRE have the potential to add to this burden. Since first reported in 2009, through 2012, 27 patients with NDM-producing CRE have been confirmed by CDC from isolates submitted by state laboratories. Since January 2013, a total of 69 patients with NDM-producing CRE have been identified in the United States; 44 patients were from northeastern Illinois.

From March to July 2013, nine patients with positive cultures for NDM-producing *Escherichia coli* (eight clinical cultures and one rectal surveillance culture) were identified in northeastern Illinois. An investigation was conducted to understand and prevent the transmission of NDM-producing CRE. A case was defined as an NDM-producing *E. coli* isolate, recovered from a patient in northeastern Illinois, with >85% similarity by pulsed-field gel electrophoresis (PFGE) to the outbreak strain, detected after January 1, 2013. Of the nine cases, eight were treated at the same hospital (hospital A). To determine risk factors for acquiring NDM-producing CRE, a case-control study was conducted. The eight patients cared for at hospital A were selected as case-patients; 27 controls were randomly selected from among 131 hospital A patients with negative surveillance cultures. A history of undergoing endoscopic retrograde cholangiopancreatography (ERCP)† at hospital A was strongly associated with case status (six of eight [75%] versus one of 27 [4%]; odds ratio = 78.0; 95% confidence interval = 6.0–>999.99).

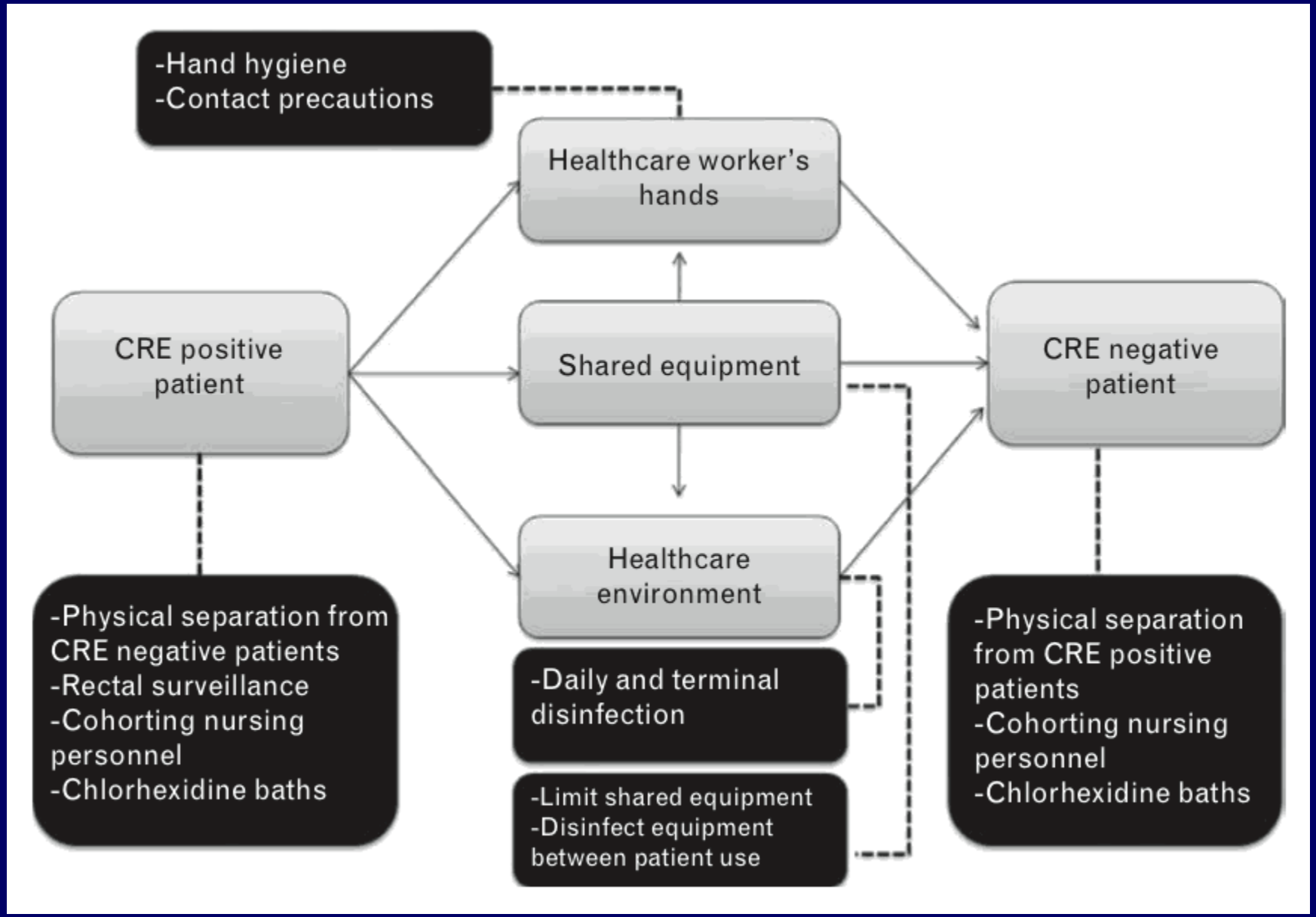
After manual cleaning and high-level disinfection in an automated endoscope reprocessor, cultures were obtained from the ERCP endoscope used on five of the case-patients. NDM-producing *E. coli* and KPC-producing *K. pneumoniae* were recovered from the terminal section (the elevator channel) of the device.§ The *E. coli* isolate was highly related (>95%) to the outbreak strain by PFGE. Retrospective review and direct observation of endoscope reprocessing did not identify lapses in protocol. Previous studies have shown an association between ERCP endoscopes and transmission of multidrug-resistant bacteria; the design of the ERCP endoscopes might pose a particular challenge for cleaning and disinfection (*2,3*).

Among 91 ERCP patients who were initially notified that they had potential exposure to a culture-positive endoscope, 50 returned for rectal surveillance cultures. NDM-producing *E. coli* were recovered from 23 (46%). An additional 12 patients with NDM-producing CRE have been identified in northeastern Illinois, bringing the total during January–December 2013 to 44. In September 2013, as a result of the investigation, hospital A changed ERCP endoscope reprocessing from automated high-level disinfection to gas sterilization with ethylene oxide; no new cases with exposure to a gas-sterilized ERCP endoscope have been identified.

This investigation highlights the potential for CRE transmission following ERCP. Health-care facilities with CRE outbreaks should consider the possibility of ERCP-related transmission. If ERCP-related transmission of CRE is suspected, reprocessing and preventative maintenance procedures for ERCP endoscopes should be evaluated in consultation with the manufacturer of the endoscope and automated endoscope reprocessor, if used. In addition, expertise in the evaluation and prevention of CRE transmission are available at CDC and can be accessed via state and local health departments.

A Framework

- Environmental contamination frequent
- Persists in the environment
- HCW hand contamination (gap)
  - Correlated to environmental burden
- Viability preserved
- Increased acquisition risk if prior room occupant +
- Molecular link of environmental and clinical isolates
- Improved cleaning/disinfection reduces infection



Munoz-Price and Quinn. Curr Opin Infect Dis 2013, 26:378 – 387

Conclusions

- Environment important in CRE transmission
  - Extent and importance unclear since mostly based on outbreaks
- Environmental cleaning (including devices) should be a focus
- Ascertaining which intervention(s) works best should be a priority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"The patient in the next bed is highly infectious. Thank God for these curtains."