# CRE in Illinois A Situational Update

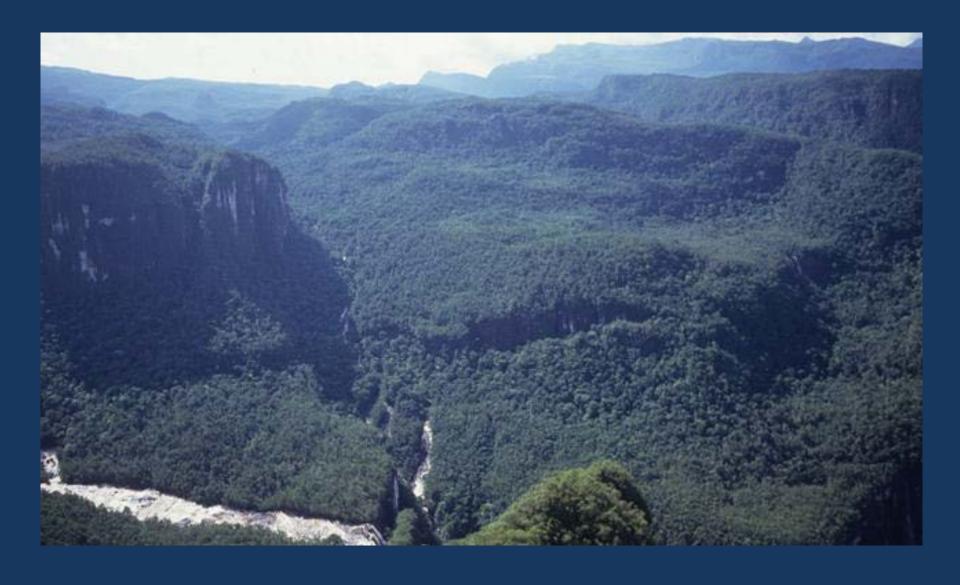
Michael Lin, MD MPH
Rush University Medical Center
Chicago CDC Prevention Epicenter
May 12, 2015

#### Disclosure

• I have nothing to disclose.

#### Overview

- How did we get here?
- The ABC's of CRE
- What's happening in Illinois
  - CRE trends (REALM project, XDRO registry)



High Orinoco area of Amazonas state in Venezuela

#### Yanomami tribe





In 2008, an unmapped village was spotted by army helicopter. In 2009, a medical mission landed.

Scientists encountered a population of hunter-gatherers who ate wild bananas and fruits, plantains, palm hearts, cassava, and small birds/mammals/fish.

#### MICROBIAL ECOLOGY

#### The microbiome of uncontacted Amerindians

Jose C. Clemente,<sup>1,2</sup>\* Erica C. Pehrsson,<sup>3</sup>\* Martin J. Blaser,<sup>4,5</sup> Kuldip Sandhu,<sup>5†</sup> Zhan Gao,<sup>5</sup> Bin Wang,<sup>3</sup> Magda Magris,<sup>6</sup> Glida Hidalgo,<sup>6</sup> Monica Contreras,<sup>7</sup> Óscar Noya-Alarcón,<sup>6</sup> Orlana Lander,<sup>8</sup> Jeremy McDonald,<sup>9</sup> Mike Cox,<sup>9</sup> Jens Walter,<sup>10‡</sup> Phaik Lyn Oh,<sup>10</sup> Jean F. Ruiz,<sup>11</sup> Selena Rodriguez,<sup>11</sup> Nan Shen,<sup>1</sup> Se Jin Song,<sup>12</sup> Jessica Metcalf,<sup>12</sup> Rob Knight,<sup>12,13§</sup> Gautam Dantas,<sup>3,14</sup> M. Gloria Dominguez-Bello<sup>5,7,11¶</sup>

2015 © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC). 10.1126/sciadv.1500183

Most studies of the human microbiome have focused on westernized people with life-style practices that decrease microbial survival and transmission, or on traditional societies that are currently in transition to westernization. We characterize the fecal, oral, and skin bacterial microbiome and resistome of members of an isolated Yanomami Amerindian village with no documented previous contact with Western people. These Yanomami harbor a microbiome with the highest diversity of bacteria and genetic functions ever reported in a human group. Despite their isolation, presumably for >11,000 years since their ancestors arrived in South America, and no known exposure to antibiotics, they harbor bacteria that carry functional antibiotic resistance (AR) genes, including those that confer resistance to synthetic antibiotics and are syntenic with mobilization elements. These results suggest that westernization significantly affects human microbiome diversity and that functional AR genes appear to be a feature of the human microbiome even in the absence of exposure to commercial antibiotics. AR genes are likely poised for mobilization and enrichment upon exposure to pharmacological levels of antibiotics. Our findings emphasize the need



### Key findings

- Highest diversity of microbiome ever found!
- Their E. coli were ancient, reflecting divergence 11,000 years ago (100 million bacterial generations)
- All E. coli were pan-susceptible
- Yet, the microbiome also carried 28 antibiotic resistance genes to man-made antibiotics, including ceftazidime, cefepime, aztreonam

# Antibiotic resistance is a natural phenomenon...





#### An un-natural creation

BLOOD CULTURE (PERIPHERAL) (Abnormal): PROCEDURE: BLOOD CULTURE (PERIPHERAL) SOURCE: BLOOD COLLECTED: ----- FINAL REPORT FINAL REPORT GROWTH OF GRAM NEGATIVE RODS FINAL IDENTIFICATION: KLEBSIELLA PNEUMONIAE This isolate demonstrates carbapenemase production. Carbapenems, cephalosporins, and penicillins are unlikely to be effective in treatment of serious infections. Contact precautions required. ----- SUSCEPTIBILITY TESTING ------K PNEUMO MIC mcg/ml MIC INTERP MIC mcg/ml ET INTERP RESISTNT TRIMETH/SULFA >2/38 CEFAZOLIN >16 RESISTNT TIGECYCLINE 1.00 SUSCEPT LEVOFLOXACIN RESISTNT >4 CEFOXITIN 16 INTERMED PIP/TAZOBACTAM >64 RESISTNT TICARCIL/K CLAV >64 RESISTNT CEFTRIAXONE >32 RESISTNT GENTAMICIN <=4 SUSCEPT TOBRAMYCIN >8 RESISTNT AMIKACIN 16 SUSCEPT IMIPENEM 8 RESISTNT MEROPENEM RESISTNT >8 CEFEPIME 16 RESISTNT COLISTIN .38 SUSCEPT

RESISTNT

>4

A ERTAPENEM

#### Antibiotic use: key driver

- In 2010 alone:
  - 73 billion units of antibiotics used in humans
    - 10 antibiotic units for every man, woman, and child on earth; 36% increase from 2000
    - India and China were largest consumers by country
      - Though had half of per-capita use compared to US (22 units/person)
  - 63,151 tons of antibiotics used in livestock
    - Van Boeckel et al. The Lancet 2014
    - Van Boeckel et al. PNAS 2015



### The ABCs of CRE

Class	Enzyme
A	KPC
B (metallo-β-lactamases)	NDM-1, VIM, IMP
D	OXA

### KPC – quick facts

- "Klebsiella pneumoniae carbapenemase"
- Origin: USA
- First identified: 1996
- Associated bacteria:
  - Klebsiella pneumoniae >>> E. coli > Enterobacter
- Primarily found in debilitated hospitalized patients. No significant community spread.

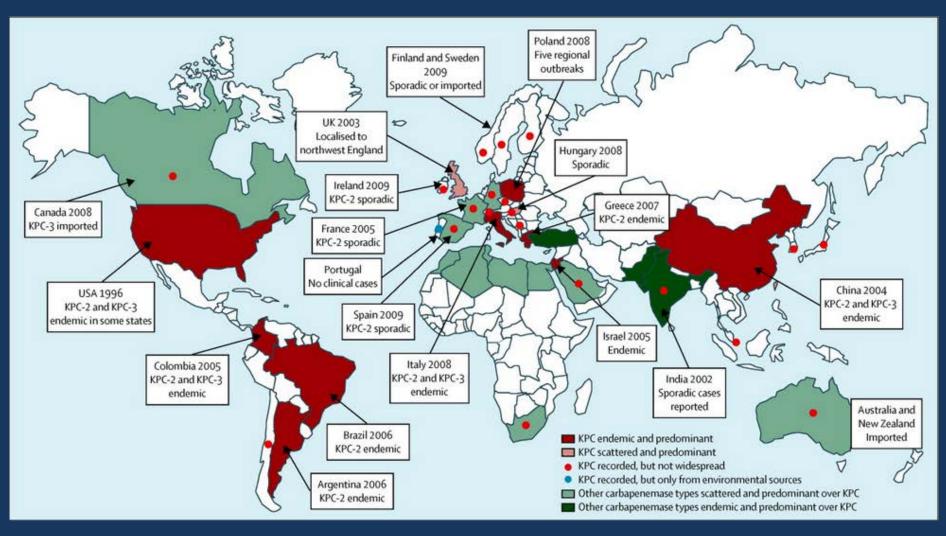
# Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection

#### Benjamin A. Rogers, <sup>1</sup> Zohreh Aminzadeh, <sup>1,2</sup> Yoshiro Hayashi, <sup>1,3</sup> and David L. Paterson<sup>1</sup>

<sup>1</sup>University of Queensland Centre for Clinical Research, The University of Queensland, Herston, Brisbane, Australia; <sup>2</sup>Infectious Diseases Research Centre, Shaheed Beheshti University M. C., Tehran, Iran; <sup>3</sup>Department of Intensive Care Medicine, the Royal Brisbane & Women's Hospital, Herston, Brisbane, Australia



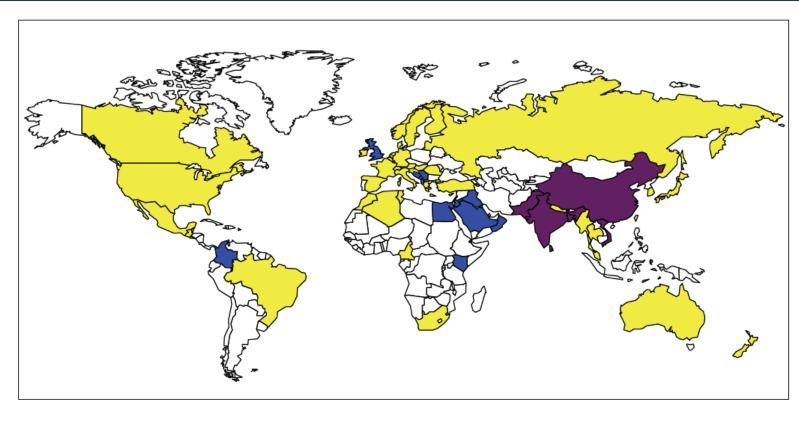
## KPC global spread



### NDM – quick facts

- "New Delhi metallo-β-lactamase"
- Origin: South Asian continent
- First identified: 2008
- Species: Klebsiella pneumoniae = E. coli, others (Enterobacter, Citrobacter, Proteus, Salmonella, Providentia, Acinetobacter, Pseudomonas)
- Found in both in hospitalized pts and in the community

## NDM global distribution



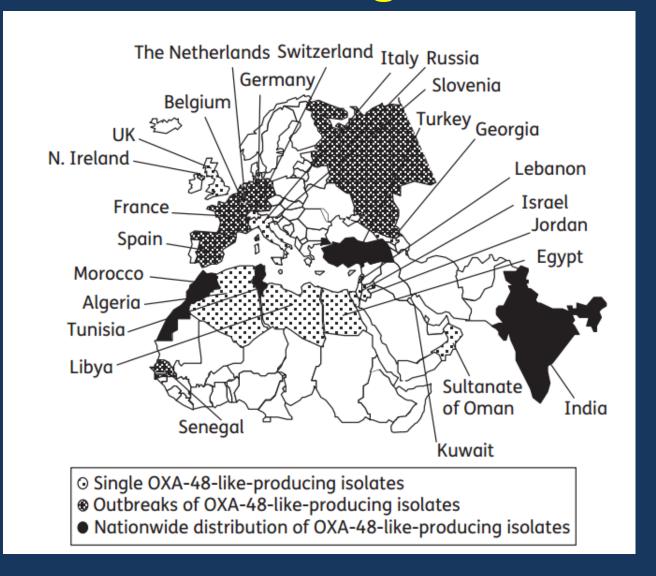
- High prevalence of NDM producers (endemicity)
- Outbreaks and interregional spread of NDM producers
- Sporadic description of NDM producers

Figure 2: Geographical distribution of NDM producers.

### OXA-48 quick facts

- OXA = "Oxacillinase"
- Origin: Turkey
- First identified: 2001
- Claim to fame: is a <u>weak</u> carbapenemase, and does not have cephalosporin resistance.
   (However, some OXA-48 have co-expressed ESBLs + outer membrane protein changes = high level resistance)
- Species: Klebsiella pneumoniae >>> E. coli, others

### OXA-48 global



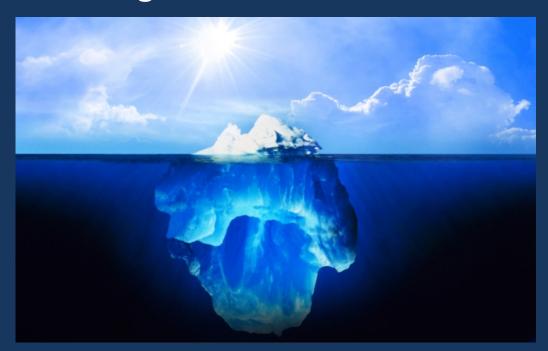
## CRE: 3 important types for Illinois

	КРС	NDM	OXA-48
Bacteria	K. pneumo > E. coli	E. coli = K. pneumo	K. pneumo > E. coli
Prevalence	Most common CRE	Rare but emerging	Rare but emerging
Take-home point	Most prevalent CRE in US	Most concerning CRE given propensity to spread among bacterial species and into community	A 'sneaky' CRE that can be difficult to recognize

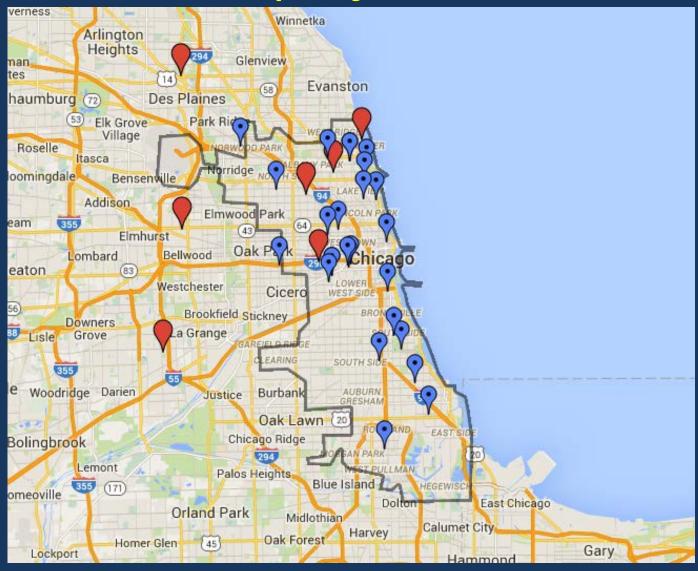
### What's happening in Illinois?

### REALM project

- Is a CDC-sponsored twice-yearly point prevalence survey for MDROs (CRE, since 2010)
  - Main advantage: tests for colonization

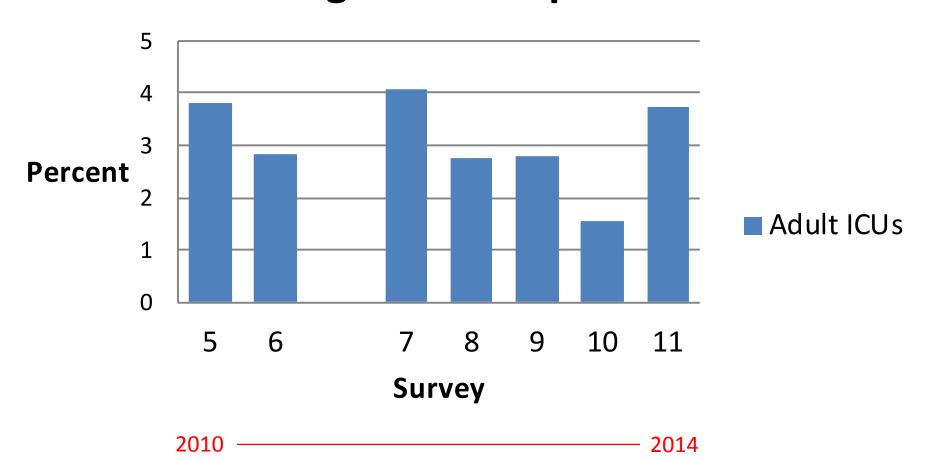


#### REALM project - KPC

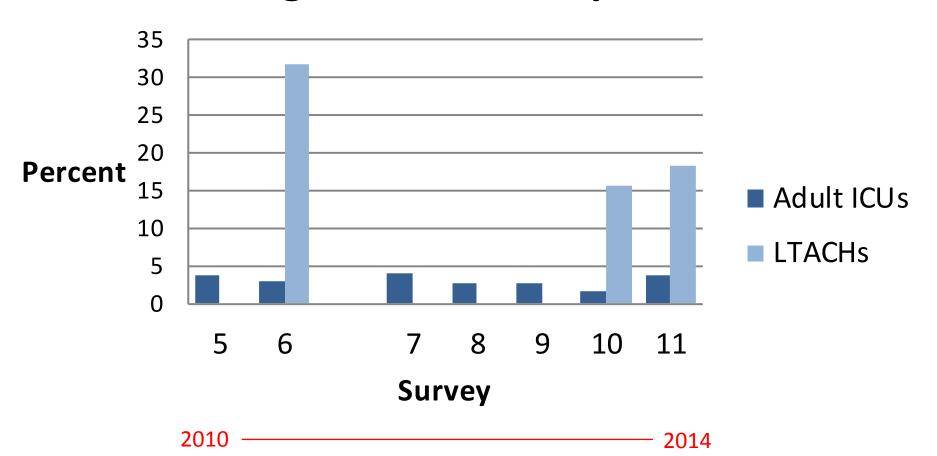


Hospital ICUs (blue), LTACHs (red):

# Prevalence of KPC colonization among adult ICU patients



# Prevalence of KPC colonization among ICU vs. LTACH patients



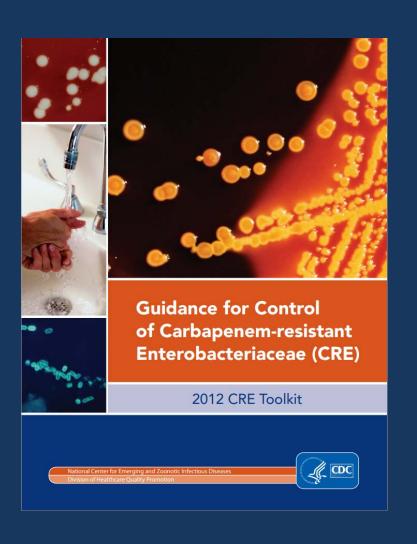
### REALM project 2015 update

- Survey #12 is underway
  - We will now test for <u>all 5 major carbapenemases</u>
     (KPC, NDM, OXA-48, VIM, IMP)

Thank you to REALM hospitals for continued participation

# Illinois' CRE Control efforts: Detect and Protect

#### "Detect and Protect"



- <u>Detect</u>: Identify all patients with CRE
- Protect: Maintain CREcolonized patients in isolation precautions throughout the healthcare system

### 'Detect & Protect' Challenges

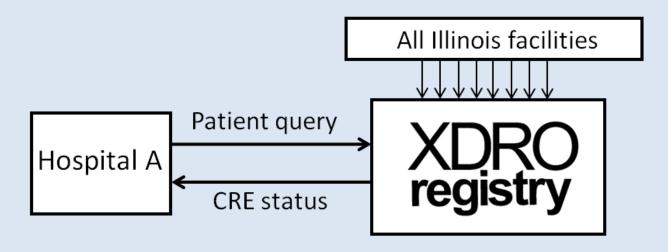
- Laboratory identification of CRE can be tricky
- Patients move around a lot
  - During 1 year after ICU discharge, median 4 facility transitions (2/3 with re-admission)
    - Unroe, Annals Int Med, 2010; 153(3)
- Information can be lost at time of hospital transfer
- Many patients go home before going to another hospital



- Public health infection control tool created to facilitate the Detect and Protect strategy
- Partnership
  - Illinois Department of Public Health
  - Chicago CDC Prevention Epicenter
  - Medical Research Analytics and Informatics
     Alliance (MRAIA)

#### XDRO registry overview

#### 1. Mandatory CRE reporting



2. CRE information exchange (inter-facility communication)

Participants: All Illinois hospitals, including LTACHs (142), nursing homes (784), laboratories

# Illinois CRE definition: Enterobacteriaceae with one of the following test results:

1. Molecular test (e.g., PCR) specific for carbapenemase OR

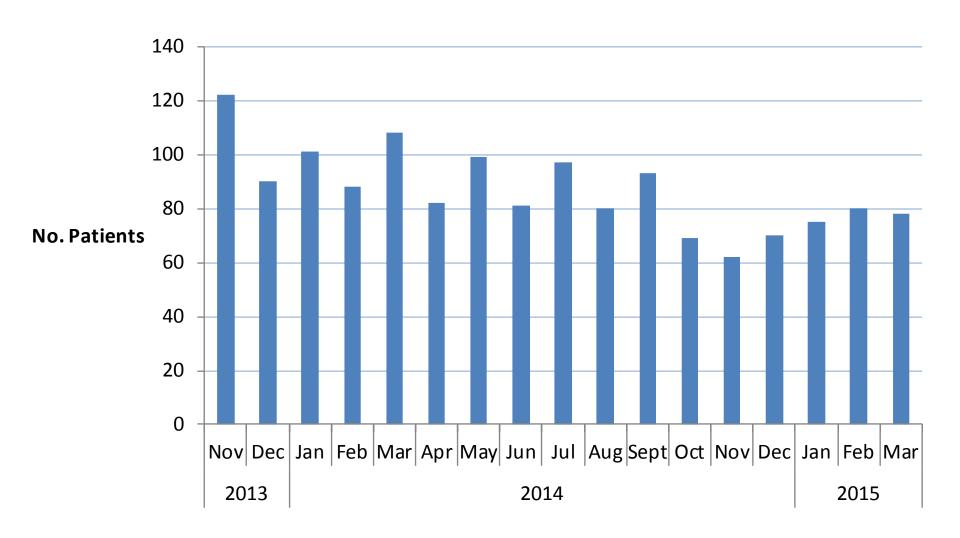
2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production

OR

3. For *E. coli* and *Klebsiella* species only: non-susceptible to ONE of the carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).

Report 1<sup>st</sup> CRE event per patient per encounter

#### Unique patients reported to XDRO registry



#### XDRO registry, year 1

#### Reporting

- Unique reports: 1,557 reports
- Unique patients: 1,095
- Reporting facilities: 175

```
115 Acute hospitals
```

5 LTACHs

46 SNFs

7 reference labs

2 Outpatient clinics

#### Querying

30 unique facilities query the registry/month

# XDRO registry summary, 2014



Characteristics of ALL submitted reports		%		
Culture Type				
Clinical	1254	80		
Screening	301	20		
Organism				
Klebsiella spp.	1347	86		
E. coli	103	7		
Enterobacter spp.	77	5		

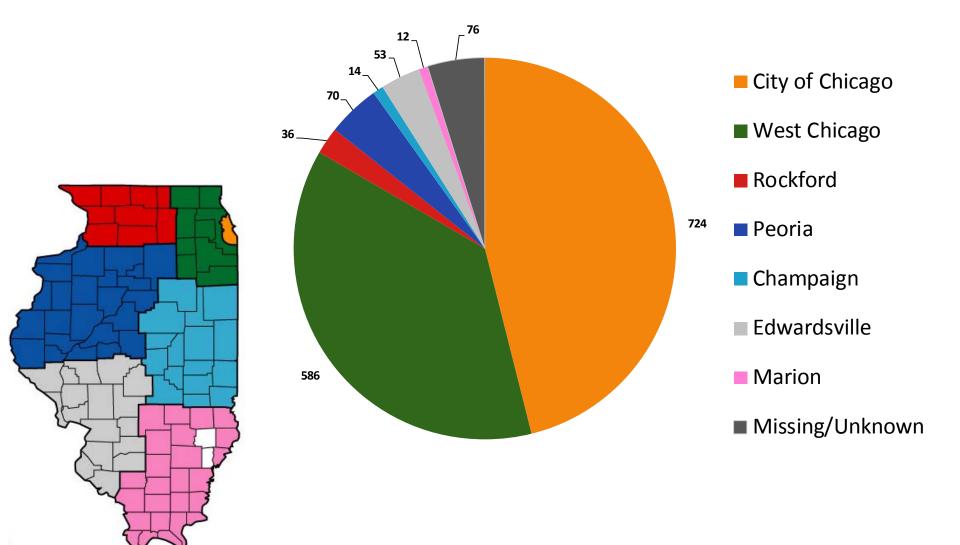
## XDRO registry summary, 2014 (cont)



Characteristics of ALL submitted reports		%		
Type of testing performed*				
1) Molecular test*	_ 397	25		
2) Phenotypic test*	751	48		
3) Susceptibility test ONLY	449	29		
Unknown	29	2		
Mechanism of resistance (applies only to reports with molecular test)				
KPC	363	91		
NDM	11	3		
Other/Unknown	23	6		

### All XDRO reports by region

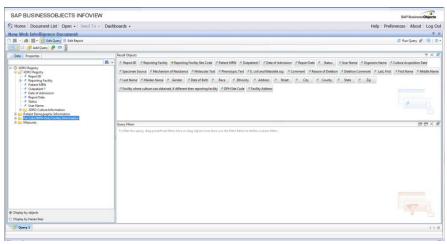




Data and adapted slide from IDPH (A. Tang)

#### XDRO data access for LHDs

- Local health departments can obtain access to XDRO data through I-NEDSS Business Objects
- Must fill out a user agreement form
- E-mail <u>dph.xdroregistry@illinois.gov</u> for the form or questions about XDRO data access



### XDRO registry: Future Directions

- 1. CRE validation
- 2. Automated CRE alerts
- 3. Cluster detection

### **Laboratory Validation**

- First 5 consecutive CRE isolates from each lab should be sent to IDPH (Jan 1, 2015 - )
  - Identification to species
  - Antibiotic susceptibility testing
  - $bla_{KPC}/_{NDM} PCR$
  - Additional phenotypic and genotypic evaluation if necessary

# Validation preliminary results, 134 isolates (1/1/15 – 4/25/15)

- 115 (86%) Carbapenemase-producing Enterobacteriaceae
  - 111 (97%) KPC PCR+
  - 2 (2%) NDM PCR+
  - 2 (2%) OXA-48-like
- 10 (8%) carbapenem-resistant *Enterobacteriaceae* 
  - 9 Enterobacter spp, 1 E. coli

- 3 (2%) carbapenem-resistant *Acinetobacter/Pseudomonas*
- 6 (5%) carbapenem-susceptible *E. coli*

### Lab validation – moving forward

- Current protocol:
  - Labs should continue to send their first 5 <u>consecutive</u>
     CRE isolates of 2014 to IDPH until they meet their quota
- Proposed protocol for next year (<u>contingent on</u> <u>CDC support</u>)
  - Every lab sends 5 consecutive CRE isolates for 2015
  - For confusing CRE isolates, every lab can send an additional 5 CRE isolates

#### **CRE** automated alerts

In a REALM survey, 96% of hospitals indicated interest in receiving automated CRE alerts from the XDRO registry

### Query strategy

**Hospital A firewall** 

1

Patient admission list (inpatient only)

- 1. Smith, John 1/5/1967
- 2. Doe, Jane 1/1/1989
- 3. Patient, Test 1/2/1977

**XDRO** hashing software

- 23425252434325
- 3. 62624535363466

#### **XDRO** registry

registry

(identifiers

hashed using

same algorithm)

Query against

1. 15234234235235

2. 23425252434325

3. 62624535363466

4. 26236346345345

5. 24572457456554

6. 35683734564547

7. 34573453456456

#### Hospital A infection control dept

Infection preventionist logs into XDRO registry to retrieve alert and patient information

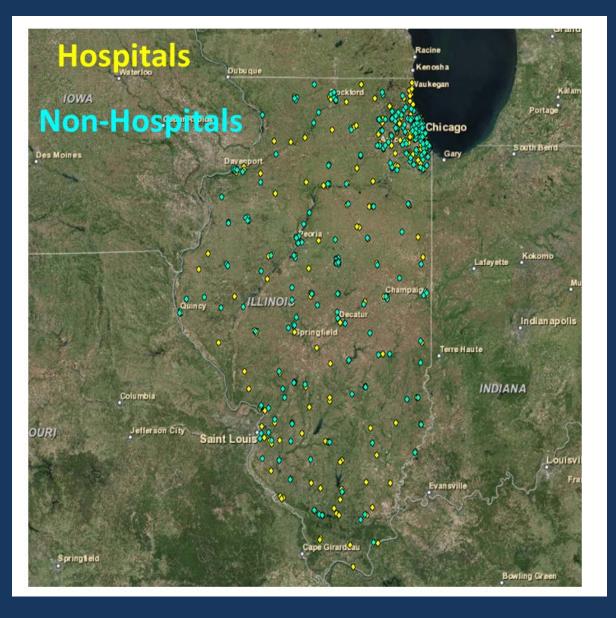
Positive match generates a generic email (no PHI)

### Piloting automated CRE alerts

- Pilot 1 (convenience sample)
  - 1 hospital (Stroger) active since Jan 2015
  - 2 hospitals (RUMC, ROPH) in next month

- Pilot 2 (MedMined hospitals)
  - Plan for 2 hospitals to trial alerts
  - MedMined represents 60+ Illinois hospitals (~42% of hospital beds in state)

### Detection of CRE Clusters in Illinois



#### Cluster detection

- Only consider clinical cultures
- Run SaTScan software (www.satscan.org)
- Investigate clusters to determine if there are indications of a clonal outbreak
  - Same species/susceptibility pattern?
  - If isolates available, similar by whole genome sequencing?

### Summary

- KPC is still most predominant in Illinois, but NDM, OXA-48 are emerging
- CRE prevalence is highest in Chicago region
- Overall CRE rates are stable but transmission is on-going
- We still need to improve CRE detection and inter-facility communication (XDRO registry).
   Antibiotic stewardship too!

### Thank you

Illinois Dept. of Public Health

Allison Arwady

**Craig Conover** 

Mary Driscoll

Mary Alice Lavin

Robynn Leidig

Erica Runningdeer

**Angela Tang** 

**CDC** 

John Jernigan

Alex Kallen

Chicago Dept. of Public Health

Stephanie Black

Sarah Kemble

**UIC School of Public Health** 

Michael Ray

**CDC Prevention Epicenter** 

Laura Bardowski

Mary Hayden

William Trick

Robert Weinstein

# Antimicrobial Stewardship at the Front Lines

David Schwartz, MD
Stroger Hospital of Cook County
May 12, 2015

Nothing to disclose

#### Outline

Stewardship rationale

Resources to/from stewardship

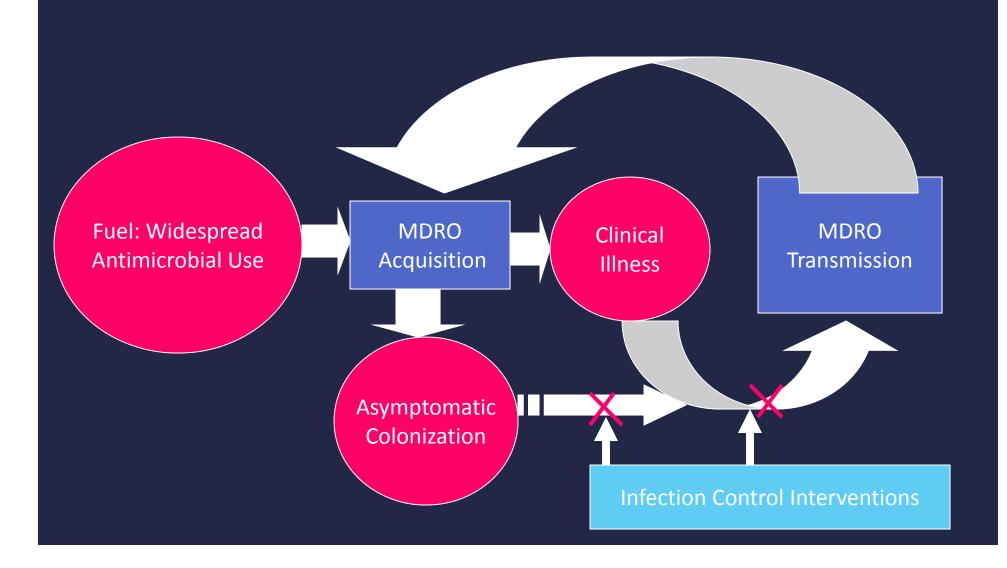
Necessary procedural attributes

Examples

# The Primary Aim of Antimicrobial Stewardship Is...

- A. To conserve the fuel driving antimicrobial resistance and other unintended consequences of antimicrobial use
- B. To save money
- C. To improve patient care and outcomes
- D. All of the above

# Fueling the Fire: MDRO Transmission Dynamics



# Ingredients Necessary for Changing Behavior

Compelling rationale

Resources

- Procedures that are:
  - Comprehensive and comprehensible
  - Feasible given limits of workflow and competence

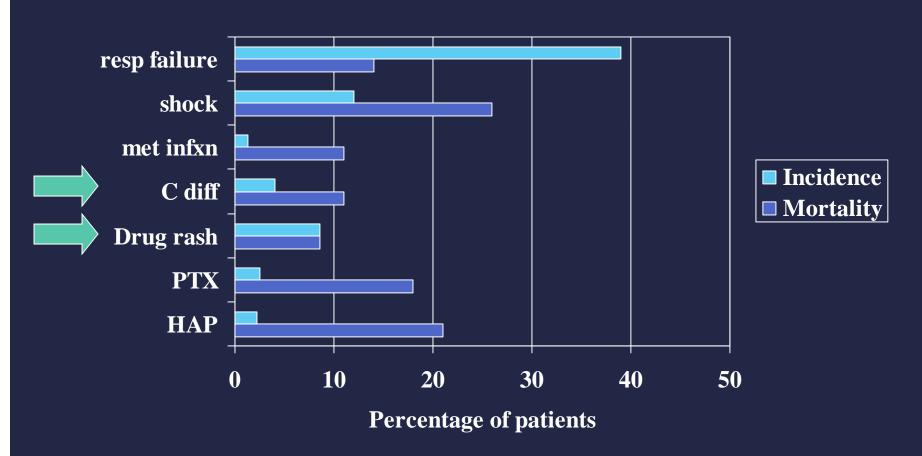
#### Antimicrobial Stewardship Rationale

- Antimicrobial use is unnatural:
  - Disrupts normal physiologic function
  - Characterizes other "restorative care" modalities:
    - Surgery
    - Cancer treatment
  - (Long-term intensive care: "beyond restorative" begets "beyond resistant"?)
- Antimicrobial exposure breadth of spectrum, duration – should be limited to the extent possible

# Antibiotic-Associated Adverse Drug Reactions

- "Allergic" reactions:
  - IgE-mediated
  - Fever, rash, hepatitis, nephritis, pneumonitis, etc.
- Dyspepsia, diarrhea
- Pill esophagitis
- Seizures, neuropathy
- Stevens-Johnson, TEN
- Bone marrow dyscrasias

### Complications Among 1339 Inpatients with CAP



Arch Intern Med 1999;159:970-81

# Antibiotic Use Begets Resistance in the Population and the Person

 Adjusted hazard ratios for development of specific resistance pattern after prior use:

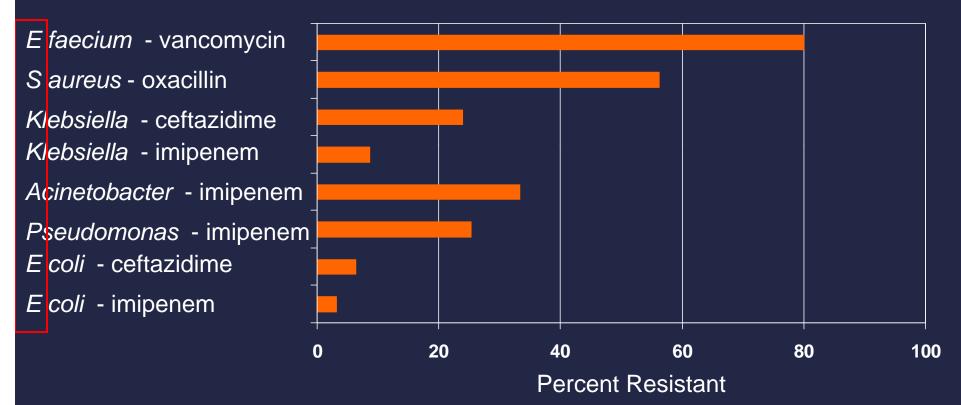
Fluoroquinolones:4.0

- 3<sup>rd</sup>-generation cephalosporins: 3.5

– Ampicillin-sulbactam: 2.3

– Imipenem:
<u>5.7</u>

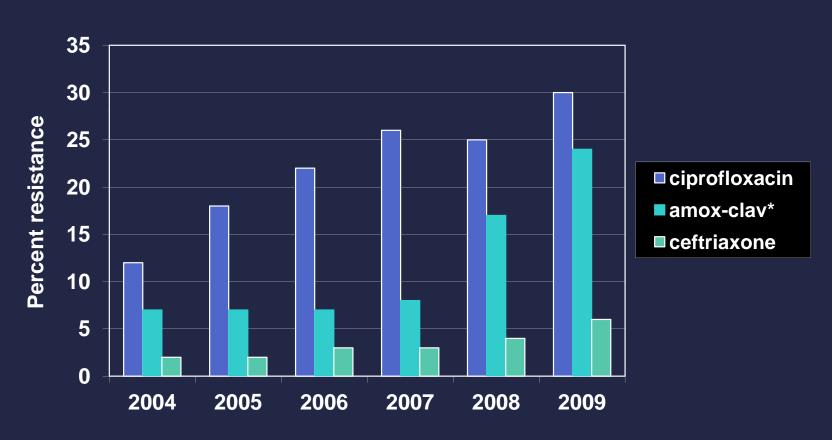
# Antimicrobial Resistance Prevalence in Hospital-Acquired Infections\*, NHSN-Reporting U.S Hospitals, 2006-7



\*Central-line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia only

Infect Control Hosp Epidemiol 2008;29:996-1011

# Prevalence of Antibiotic Resistance Among Community-Onset Isolates of *E coli*, Stroger Hospital



\* Percent intermediate or resistant Schwartz DN, unpublished data

### Resources for/from Antimicrobial Stewardship

- Resources needed:
  - Multidisciplinary staff:
    - MD/RN/PharmD
    - IT/IC/microbiology
  - Authority
    - Provider respect
    - Administrative support
  - Niche within QA infrastructure
  - Capacity for multimodal interventions
  - Process, outcome data

- Expected return:
  - Reduced medication acquisition costs
    - Big-ticket items
    - In aggregate
  - Reduced ancillary costs
    - Lab testing
    - Diapers
  - Better informed, more harmonious staff
  - Improved outcomes(?)

### Antimicrobial Stewardship Procedures Must Be...

- Clearly (and repeatedly) communicated
- Easy for providers to access and understand
- Within provider and staff competence
- Minimally intrusive on established workflows
- More informative/persuasive than coercive
- Self-evidently promote improved patient care

Might he be infected?
I'll give VANC &
ZOSYN!



God, were the Bears awful – AGAIN?!! wonder what's on TV tonight?



### The 6 Ds: Operational Goals of Antimicrobial Therapy <u>and</u> Stewardship

#### 1. Right **D**iagnosis

- What infection syndrome is being treated?
- Is it responsive to antibiotics?
- Have appropriate diagnostic tests been collected?

#### 2. Right **D**rug(s)

- Demonstrated effective
- Safest
- Narrowest spectrum

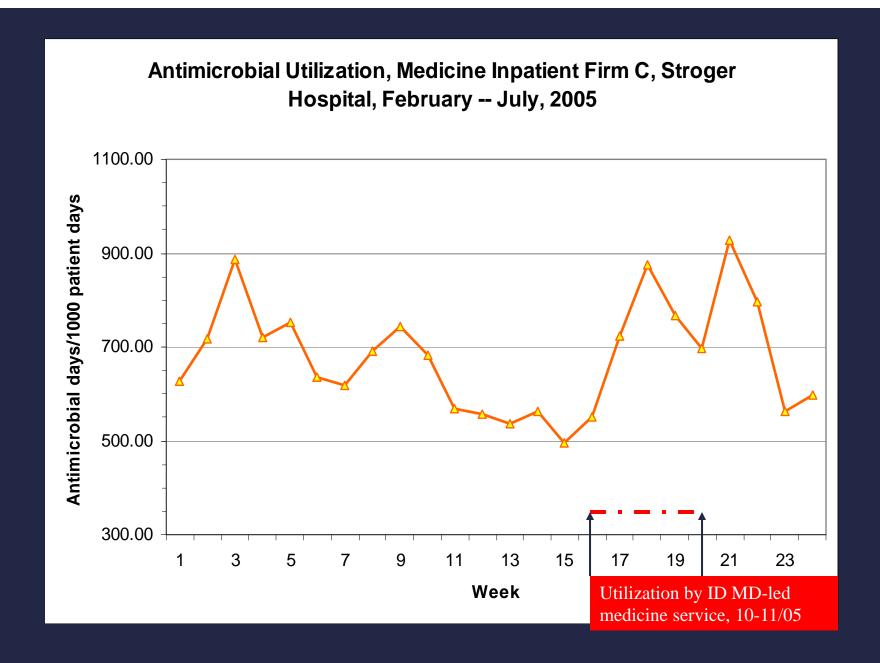
#### 3. Right **D**ose

### The 6 Ds: Operational Goals of Antimicrobial Therapy and Stewardship

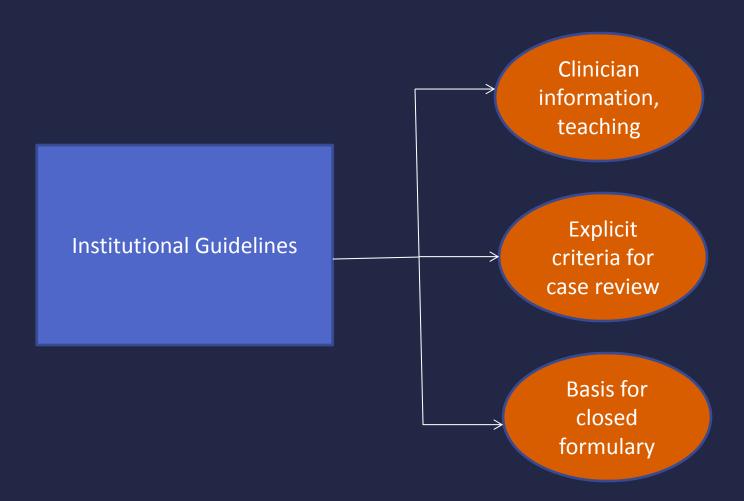
- 4. Right <u>D</u>e-escalation: right Drug(s) redefined when:
  - Justified by culture results (positive or negative)
  - Clinical improvement (e.g., IV to PO switch)
- 5. Right **D**uration:
  - Minimum necessary
  - Defined infections requiring prolonged therapy
- 6. Right **D**ebridement or source control

# Antimicrobial Use Is Best When Thoughtful and Well Informed

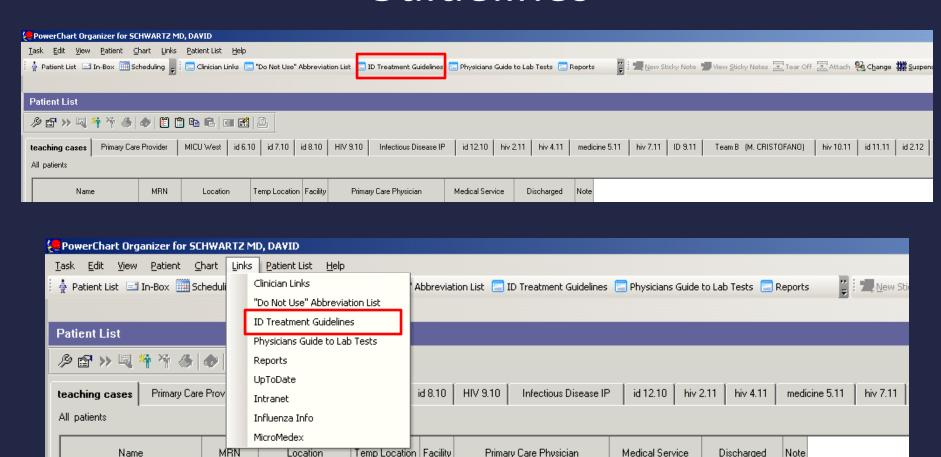
- 40 syndromes, 40 drugs (antibacterials)
- How many bugs and resistance phenotypes?
- Variation by institution, over time
- "When will it get through to you ID guys that we need you to explain how we should treat common infections? Is that so hard to understand?"

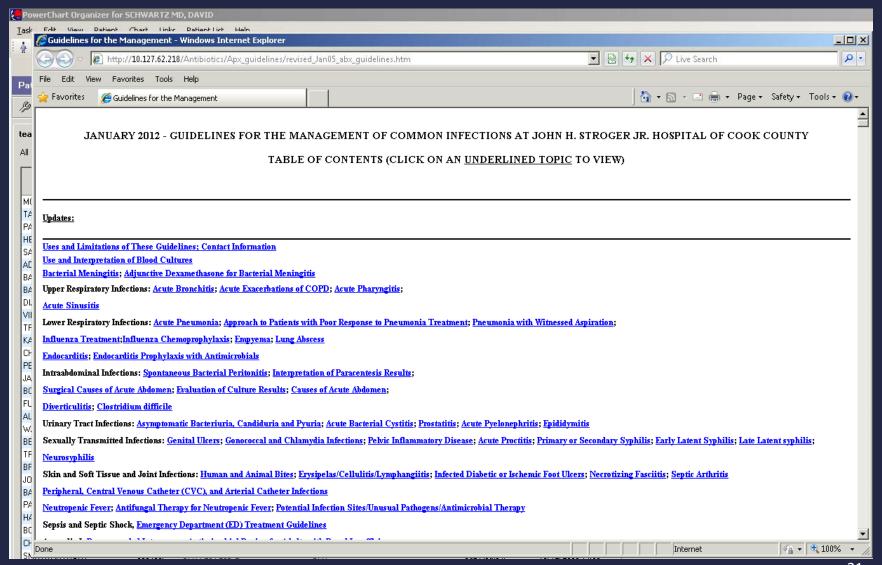


#### The Heart of the Matter



### Stroger Hospital ID Treatment Guidelines





### Guidelines for the Management - Windows Internet Explorer → ► http://10.127.62.218/Antibiotics/Apx\_guidelines/revised\_Jan05\_abx\_guidelines.htm#pneu File Edit View Favorites Tools Help → Favorites ← Guidelines for the Management

#### PNEUMONIA, ACUTE (SEE IDSA GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA AT:

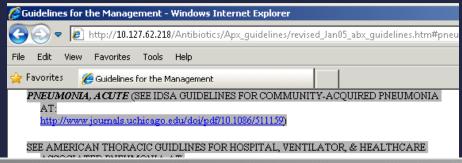
http://www.journals.uchicago.edu/doi/pdf/10.1086/511159)

#### SEE AMERICAN THORACIC GUIDLINES FOR HOSPITAL, VENTILATOR, & HEALTHCARE ASSOCIATED PNEUMONIA AT:

http://ajrccm.atsjournals.org/cgi/reprint/171/4/388)

- · Risks for tuberculosis and HIV should be assessed in all patients
- Empiric coverage for atypical pathogens has not been shown to confer benefit to pneumonia patients
  hospitalized in areas where Legionella is rare like Chicago see "Why Pneumonia Treatment Needn't Be
  Atypical" or page Dr. Schwartz (839-4584)
- . Obtain a PA/lateral rather than portable chest xray unless the patient is too ill to travel to radiology
- Obtain two sets of blood cultures from different sites (10ml blood in each bottle) prior to antibiotics for all patients requiring hospitalization
- For hospital-acquired pneumonia, also obtain sputum or endotracheal aspirate for gram stain and culture
- Clinical criteria for starting antibiotics: new or progressive radiographic infiltrate plus at least two of
  the following: fever greater than 38 degrees centigrade, leukocytosis or leucopenia, and purulent secretions.
- Up to 30% of inpatients treated for pneumonia lack fever and diagnostic radiographic changes, according to
  previous audits. Careful observation instead of antibiotics should be considered when:
  - Underlying cardiopulmonary disease (asthma, COPD, lung cancer, CHF) is the primary reason for hospitalization: AND
  - 2. X-ray findings for pneumonia are equivocal; AND
  - 3. Systemic abnormalities fever, leukocytosis are absent
- <u>Clinical improvement</u> usually becomes apparent after the first 48-72 hours of treatment. The responding
  patient should have de-escalation of antibiotic therapy to the most focused regimen possible on the basis of
  culture data. Non-response is usually evident by Day 3.
- Conversion from IV to oral antibiotic therapy should be considered when fever and tachycardia have resolved and the patient is subjectively improved
- If improvement is delayed, see "Approach to Patients with Poor Response to Pneumonia Treatment"
- These recommendations are for empiric therapy; antibiotics should be tailored to the recovered
  pathogen(s) when cultures are positive.

	ETIOLOGY	RECOMMENDED EMPIRIC REGIMENS				
INFECTION		DRUG OF CHOICE (DAILY DRUG COST)	PCN-ALLERGIC/ ALTERNATIVE			
$\underline{A}$ = ID APPROVAL REQUIRED; $\underline{I}$ = DRUG INTERACTION; $\underline{R}$ = DOSAGE REDUCTION FOR RENAL INSUFFICIENCY						
Community- acquired, outpatient	S. pneumoniae H. influenzae Mycoplasma Chlamydia Influenza (ucnter	doxycycline 100mg PO q12h (\$0.08) x 7-10 days <u>OR</u> - amoxicillin/clavulanate <u>R</u> 500/125mg PO q8h (\$0.12) x 7-10 days	Levofloxacin  I A R 500mg PO q24h  (\$2.35) x 7-10 days			
Community- acquired, inpatient (non-ICU)		ceftriaxone 1g IV q24h (\$3.60), with oral conversion <sup>a</sup> to amoxicillin/clavulanate <u>R</u> 500/125mg PO q8h (\$0.12) x 10-14 days total	levofloxacin R 500mg IV q24h (\$13), with oral conversion to levofloxacin I A R 500mg PO q24h			





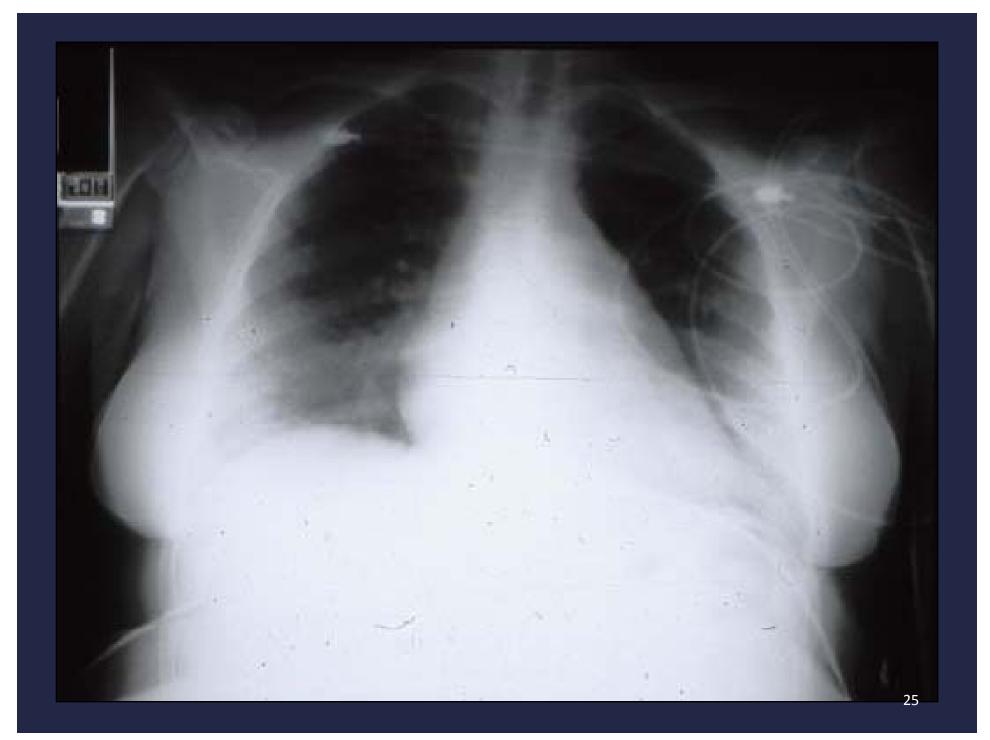
#### RECOMMENDED DOSAGES FOR ORAL ANTIMICROBIAL DRUGS FOR ADULTS WITH RENAL INSUFFICIENCY

DDUC NAME	NORMAL DOSE	REGIMEN IF CREATININE CLEARANCE (ML/MIN)		
DRUG NAME		50-31	30-10	<10 (DIALYSIS)
Levofloxacin (PO)	250mg q24h	No adjustment	250 mg q48h	250 mg q48h
	500mg q24h	500mg LD <sup>a</sup> then 250 mg q24h	500mg LD <sup>a</sup> then 250 mg q48h	500mg LD <sup>a</sup> then 250 mg q48h
	750mg q24h	750mg LD <sup>a</sup> then 500mg q48h	750mg LD <sup>a</sup> then 500mg q48h	750mg LD <sup>a</sup> then 500mg q48h
	For M. tuberculosis: 500 – 1000mg daily	500 – 1000mg daily	750-1000mg per dose three times per week (not daily)	

		COST)	ALTERNATIVE				
A = ID APPROVA	$\underline{A}$ = ID APPROVAL REQUIRED; $\underline{I}$ = DRUG INTERACTION; $\underline{R}$ = DOSAGE REDUCTION FOR RENAL INSUFFICIENCY						
Community- acquired, outpatient	S. pneumoniae H. influenzae Mycoplasma Chlamydia Influenza (winter	doxycycline 100mg PO q12h (\$0.08) x 7-10 days <u>OR</u> - amoxicillin/clavulanate <u>R</u> 500/125mg PO q8h (\$0.12) x 7-10 days	Levofloxacin  I A R 500mg PO q24h  (\$2.35) x 7-10 days				
Community- acquired, inpatient (non-ICU)		ceftriaxone 1g IV q24h (\$3.60), with oral conversion <sup>a</sup> to amoxicillin/clavulanate <u>R</u> 500/125mg PO q8h (\$0.12) x 10-14 days total	levofloxacin R 500mg IV q24h (\$13), with oral conversion to levofloxacin I A R 500mg PO q24h				

# Case Report

- 29-year-old woman presents to the ER with a one-week h/o dyspnea, palpitations and anxiety; dysphagia for six months
- Denies cough, fever, chest pain
- Prior hyperthyroidism; stopped propylthiouricil 4 weeks ago after rash, now on no medications
- In no distress T 100.1 179/69 HR 138 RR 20;
   large goiter; otherwise normal exam



# Case Report – continued

 Levofloxacin begun in the ER, continued by the admitting ward service

# Case Report – continued

- Levofloxacin begun in the ER, continued by the admitting ward service
- Antibiotics were discontinued after the clinical and chest radiograph findings (normal breast shadowing) were reviewed
- The patient did well with management of her hyperthyroidism

## How Did We Do That?

- Prospective audit and feedback implemented in patient's hospital ward
- Pharmacist reviewed charts of each antimicrobial recipient
- Guidelines served as reference standard
- Prescribing MD contacted when potential improvements were identified
- ID physician called to adjudicate clinical questions ("Does she have pneumonia?")

# Guidelines for the Management - Windows Internet Explorer Apx\_guidelines/revised\_Jan05\_abx\_guidelines.htm#pneu File Edit View Favorites Tools Help Appropries Guidelines for the Management

#### PNEUMONIA, ACUTE (SEE IDSA GUIDELINES FOR COMMUNITY-ACQUIRED PNEUMONIA AT:

http://www.journals.uchicago.edu/doi/pdf/10.1086/511159)

#### SEE AMERICAN THORACIC GUIDLINES FOR HOSPITAL, VENTILATOR, & HEALTHCARE ASSOCIATED PNEUMONIA AT:

http://ajrccm.atsjournals.org/cgi/reprint/171/4/388)

- · Risks for tuberculosis and HIV should be assessed in all patients
- Empiric coverage for atypical pathogens has not been shown to confer benefit to pneumonia patients
  hospitalized in areas where Legionella is rare like Chicago see "Why Pneumonia Treatment Needn't Be
  Atypical" or page Dr. Schwartz (839-4584)
- Obtain a PA/lateral rather than portable chest xray unless the patient is too ill to travel to radiology
- Obtain two sets of blood cultures from different sites (10ml blood in each bottle) prior to antibiotics for all patients requiring hospitalization
- For hospital-acquired pneumonia, also obtain sputum or endotracheal aspirate for gram stain and culture
- Clinical criteria for starting antibiotics: new or progressive radiographic infiltrate plus at least two of
  the following: fever greater than 38 degrees centigrade, leukocytosis or leucopenia, and purulent secretions.
- Up to 30% of inpatients treated for pneumonia lack fever and diagnostic radiographic changes, according to
  previous audits. Careful observation instead of antibiotics should be considered when:
  - Underlying cardiopulmonary disease (asthma, COPD, lung cancer, CHF) is the primary reason for hosvitalization: AND
  - 2. X-ray findings for pneumonia are equivocal; AND
  - 3. Systemic abnormalities fever, leukocytosis are absent
- Clinical improvement usually becomes apparent after the first 48-72 hours of treatment. The responding
  patient should have de-escalation of antibiotic therapy to the most focused regimen possible on the basis of
  culture data. Non-response is usually evident by Day 3.
- Conversion from IV to oral antibiotic therapy should be considered when fever and tachycardia have resolved and the patient is subjectively improved
- · If improvement is delayed, see "Approach to Patients with Poor Response to Pneumonia Treatment"
- These recommendations are for empiric therapy; antibiotics should be tailored to the recovered
  pathogen(s) when cultures are positive.

INFECTION	ETIOLOGY	RECOMMENDED EMPIRIC REGIMENS		
		DRUG OF CHOICE (DAILY DRUG COST)	PCN-ALLERGIC/ ALTERNATIVE	
$\underline{A} = ID$ APPROVAL REQUIRED; $\underline{I} = DRUG$ INTERACTION; $\underline{R} = DOSAGE$ REDUCTION FOR RENAL INSUFFICIENCY				
Community- acquired, outpatient	S. pneumoniae H. influenzae Mycoplasma Chlamydia Influenza (ucinter	doxycycline 100mg PO q12h (\$0.08) x 7-10 days OR - amoxicillin/clavulanate R 500/125mg PO q8h (\$0.12) x 7-10 days	Levofloxacin  I A R 500mg PO q24h (\$2.35) x 7-10 days	
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# Case Report

- 58-year-old man underwent right hemicolectomy and ileal resection for obstructing cecal carcinoma
- Complex surgery; prolonged recovery
- PICC for post-operative TPN
- 8<sup>th</sup> post-operative day: fever (102.2° F)
- Single blood culture: *Enterococcus faecalis*

# Case Report – continued

- Given 3 doses vancomycin on 9<sup>th</sup> and 10<sup>th</sup> post-operative days
- PICC removed
- Fever resolved
- Discharged on no antibiotics

# Case Report – continued

- Readmitted 3 months later with fever, confusion
- Found to have aortic valvular endocarditis caused by Enterococcus faecalis
- Required mitral and aortic valve replacement
- Prolonged ICU course, then rehab, with IV antibiotics
- Died of recurrent cancer months later

# Infectious Diseases Surveillance for Positive Blood Cultures

- Computer program identifies all newly positive blood culture gram stains
- ID fellow on consult service reviews chart:
  - Calls primary provider when opportunities for improvement detected
  - Reviews cases with ID attending

# Clinician Training, Cohort Review/Feedback at Oak Forest Hospital

- 600-bed long-term/acute care hospital
- Bulk of care by 20 salaried internists
- Series of 2-hour trainings, guidelines issued
- Some of the lessons conveyed:
  - No abx for asymptomatic bacteriuria
  - Cultures, abx only useful for acutely ill patients
  - Avoid empiric levofloxacin (> 50% resistance)
- Cohorts reviewed, results given to clinicians

# Fever Algorithm

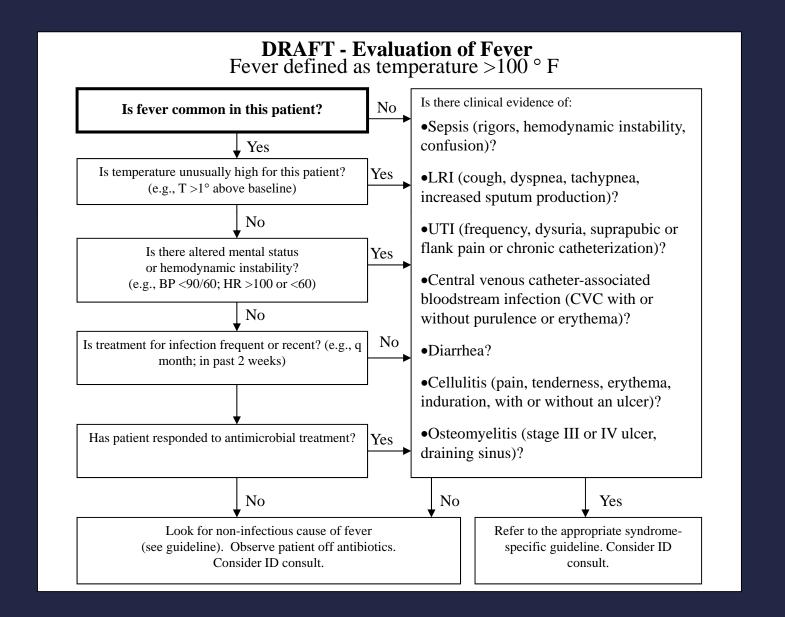
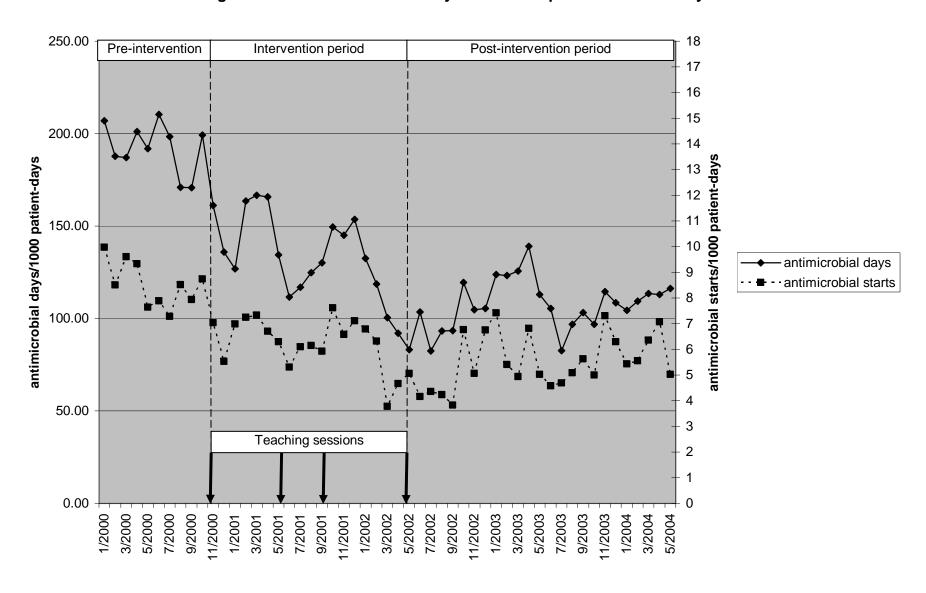
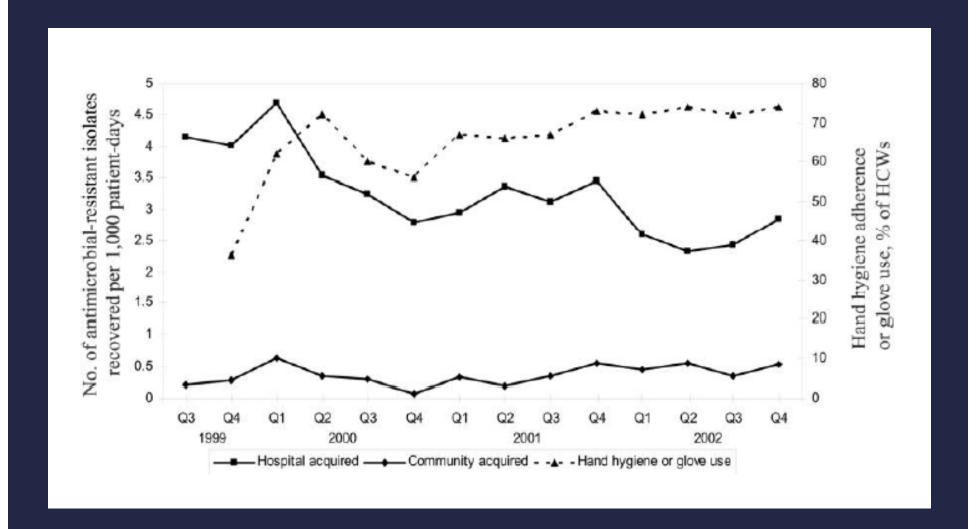


Figure 1a. LTC Antimicrobial Days and Starts per 1000 Patient-Days



Schwartz DN, et al. J Amer Geriatr Soc 2007;55:1236-42



# Additional Stewardship Strategies

- Surveillance and intervention for error-prone regimens:
  - Redundant antimicrobial spectra
  - Regimen-indication mismatch
  - Prolonged use with negative cultures
- Leverage computer support
  - Provider order entry
  - Decision support
- Optimize dosage regimens (e.g., piperacillintazobactam)
- Restriction with prior approval targeted only

## We Can Do This

- Stewardship is amenable to centralized resources, oversight, remote (computer-based) applications
- General goals, paradigm apply equally to other areas of medical care:
  - Analyses of surgical volume, procedures and outcomes
  - Procedural checklists
  - Patient-centered medical homes
  - Infection control

# Questions?

312-864-4559 office dschwartz@cookcountyhhs.org



# CRE Surveillance and Prevention in Acute Care Hospitals

Maureen K. Bolon, MD, MS Northwestern University Feinberg School of Medicine

Northern Illinois Infection Prevention and CRE Workshop May 12, 2015

## **Objectives**

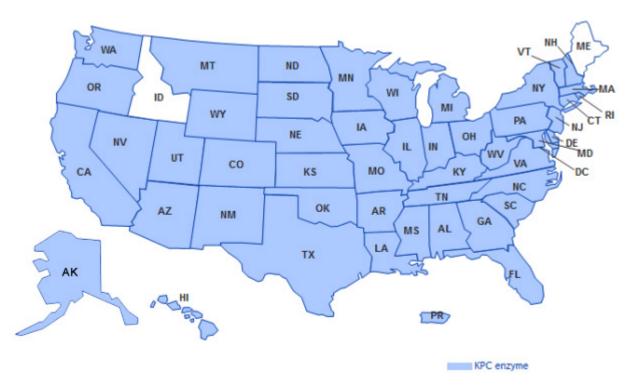
- Demonstrate examples of ways to prevent CRE transmission
- Explain how to implement CRE surveillance in an acute-care facility
- List the steps involved in an outbreak investigation



\*No Disclosures



## Carbapenemase-producing CRE in the United States, 2015



This map was last updated in February 2015



#### None or Rarely Detected (e.g., 1 case per month or less)

- Review preceding 6-12 months of microbiology records to detect previously unrecognized CRE cases.
- If review identifies previously unrecognized CRE cases, perform point prevalence survey (a single round of perirectal or rectal active surveillance cultures) in high-risk units to identify CRE cases (e.g., units where previously unrecognized cases were identified, ICU, and units with high antimicrobial utility).
- Conduct perirectal or rectal surveillance testing of patients with epidemiologic links to previously unrecognized CRE cases (e.g., patients in same unit or who were provided care by same healthcare personnel).

#### Periodically Detected (e.g., 2-3 cases per month)

- Conduct perirectal or rectal surveillance testing of patients with epidemiologic links to previously unrecognized CRE cases.
- If repeated rounds of perirectal or rectal surveillance testing show no evidence of transmission, consider shifting the surveillance strategy to periodic point prevalence survey in high-risk units (e.g., units where previously unrecognized cases were identified, ICU, and units with high antimicrobial utility).



- None or Rarely Detected (e.g., 1 case per month or less)
  - Review preceding 6-12 months of microbiology records to detect previously unrecognized CRE cases.
  - If review identifies previously unrecognized CRE cases, perform <u>point</u> <u>prevalence survey</u> (a single round of perirectal or rectal active surveillance cultures) in high-risk units to identify CRE cases (e.g., units where previously unrecognized cases were identified, ICU, and units with high antimicrobial utility).
  - Conduct perirectal or rectal <u>surveillance</u> testing of <u>patients with epidemiologic</u> <u>links to previously unrecognized CRE</u> cases (e.g., patients in same unit or who were provided care by same healthcare personnel).

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#### Endemic

Implement one or more of the interventions described in the Tier recommendations of the 2006 "Guidelines for Management of Multidrug-Resistant Organisms in Healthcare Setting".\* These interventions may include:

- Implement preemptive Contact Precautions for all patients admitted from settings/facilities with high prevalence of CRE or with risk factors for CRE until perirectal or rectal surveillance cultures are negative.
- Conduct serial (e.g., weekly) unit-specific point prevalence culture surveys of CRE to assess efficacy of intensified control interventions.
- Monitor cleaning performance to ensure consistent environmental cleaning and disinfection of surfaces frequently touched by patients and healthcare personnel (e.g., bedrails, tray table, etc.).

If CRE rates do not decrease, implement additional interventions as needed to reduce and eliminate transmission.



- All hospitals should implement the following prevention measures regardless of their CRE prevalence:
  - Place all CRE-colonized or –infected patients on Contact Precautions.
  - Place all CRE-colonized or –infected patients in single-patient rooms when possible.
  - Conduct perirectal or rectal active surveillance testing of patients with epidemiologic links to previously unrecognized CRE cases, especially those patients who are not in Contact Precautions for another reason and thus may be contributing to further transmission.
  - Ensure a mechanism is in place for microbiology laboratory to alert infection prevention staff immediately whenever a CRE isolate is identified.

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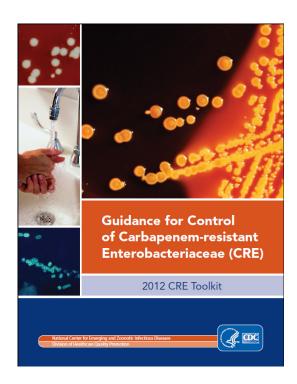


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  - Ensure a mechanism is in place for <u>microbiology laboratory to alert infection</u> <u>prevention</u> staff immediately whenever a CRE isolate is identified.



#### Core Measures for All Acute and Long-term Care Facilities

#### 1. Hand hygiene

- Promote hand hygiene
- Monitor hand hygiene adherence and provide feedback
- · Ensure access to hand hygiene stations

#### 2. Contact Precautions

#### Acute care

- Place CRE colonized or infected patients on Contact Precautions (CP)
  - Preemptive CP might be used for patients transferred from high-risk settings
- Educate healthcare personnel about CP
- Monitor CP adherence and provide feedback
- No recommendation can be made for discontinuation of CP
- Develop lab protocols for notifying clinicians and IP about potential CRE

#### Long-term care

 Place CRE colonized or infected residents that are high-risk for transmission on CP (as described in text); for patients at lower risk for transmission use Standard Precautions for most situations

#### 3. Patient and staff cohorting

- When available cohort CRE colonized or infected patients and the staff that care for them even
  if patients are housed in single rooms
- If the number of single patient rooms is limited, reserve these rooms for patients with highest risk for transmission (e.g., incontinence)

#### 4. Minimize use of invasive devices

#### Promote antimicrobial stewardship

#### 6. Screening

 Screen patient with epidemiologic links to unrecognized CRE colonized or infected patients and/or conduct point prevalence surveys of units containing unrecognized CRE patients

#### Supplemental Measures for Healthcare Facilities with CRE Transmission

#### 1. Conduct active surveillance testing

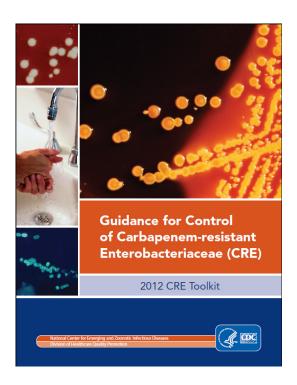
- Screen high-risk patients at admission or at admission and periodically during their facility stay for CRE. Preemptive CP can be used while results of admission surveillance testing are pending
- · Consider screening patients transferred from facilities known to have CRE at admission

#### 2. Chlorhexidine bathing

Bathe patients with 2% chlorhexidine



# General Approach to CRE Control in Facilities that Rarely or Have Not Identified CRE



New CRE-colonized or CRE-infected patient identified



- · Notify appropriate personnel (i.e., clinical staff, infection prevention staff)
- Notify public health if indicated



- · Place patient on Contact Precautions in single room (if available)
- · Reinforce hand hygiene and use of Contact Precautions on affected ward/unit
- · Educate healthcare personnel about preventing CRE transmission



- Screen epidemiologically-linked patient contacts (e.g., roommates) for CRE with at least stool, rectal, or peri-rectal cultures and/or consider point prevalence survey of affected unit
- Consider preemptive Contact Precautions of these patients pending results of screening cultures



- If screening cultures or further clinical cultures identify additional CREcolonized or -infected patients, consider additional surveillance cultures of contacts or point prevalence surveys of affected units (if not already done)
- · Consider cohorting patients and staff



- Ensure if patient transferred within the facility that precautions are continued
- Ensure if patient transferred to another facility CRE information is shared with accepting facility



## **Today's Talk: How is the Toolkit being Implemented?**

- Review of recent publications regarding management of CRE in acute care hospitals
  - Both routine measures and outbreak control measures
- Most of Core Measures from Toolkit utilized
  - Limited discussion of stewardship
  - In depth discussion of screening



## **Survey: What are we doing for CRE?**

- Survey of SHEA Research Network, Nov 2012-Feb 2013
- Infection control practices for MDROs
- 52% had encountered CRE
- Isolation practices for CRE:
  - 93.9% would use contact precautions
  - Duration of contact precautions (43.5% indefinitely; 29% until negative surveillance cx; 12.9% current hospitalization; 6.5% during active illness)
  - 72% would isolate on readmission
  - 21% perform active surveillance in at least one area of the hospital



## SHEA survey: CDC Toolkit implementation

- 37% use CHG bathing
- 24% conduct point prevalence surveys
- 39% use epidemiology-based screening
- 22% use active surveillance testing
- 61% had implemented updated CLSI breakpoints for GNB
- 61% performed modified Hodge test



## **Contact Precautions & CRE**



- Evaluation of gown & glove contamination following care of CRE patient
- 14% of HCW-patient interactions resulted in contamination of gloves or gowns
  - No difference between KPC and non-KPC-producers
- Activities most associated with HCW contamination
  - Wound care
  - Manipulating catheter or drain
  - Caring for patient with ETT or tracheostomy
- 3 "super-spreaders" identified who caused contamination of HCW or environment in 50% or more observations
  - All 3 were actively bacteremic and had sacral ulcers



## When to Discontinue Contact Precautions?

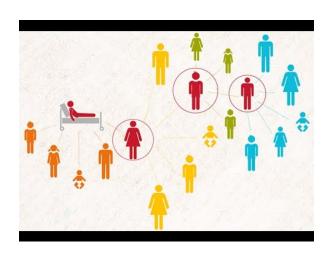
- Retrospective review of CRE surveillance program
  - Follow-up perirectal cultures obtained on CRE-colonized patients not on antibiotics and no sooner than 8 weeks after positive culture
- Evaluated for recurrence, defined as a positive culture following at least one negative perirectal culture

### Results: Predictive Value of Negative Cultures

Previous Sequential Negative Cultures	Next Culture Negative/No. at Risk (%)
0 (first culture)	51 of 95 (54%)
1	24 of 31 (77%)
2	17 of 20 (85%)
≥3	6 of 8 (75%)



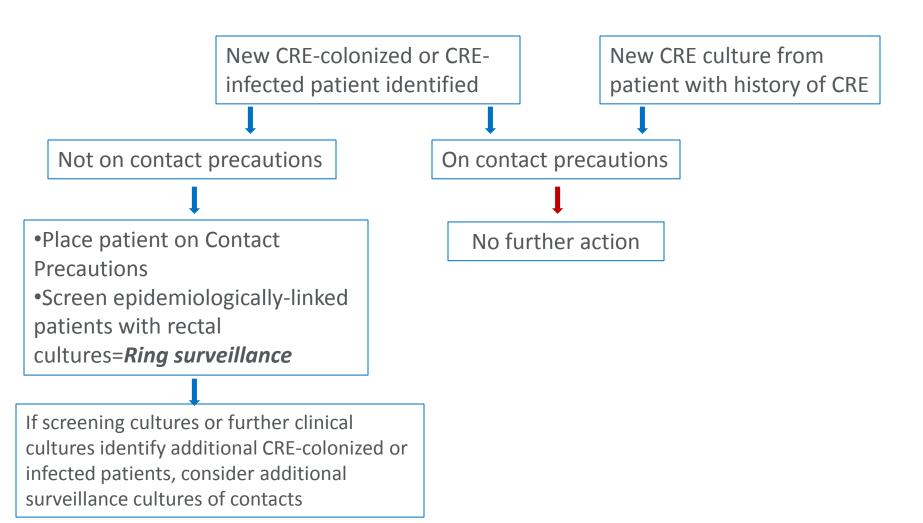
# Screening Epidemiologically-Linked Contacts: How productive is it?



- Comparison of two methods of identifying transmission to contacts of CRE-colonized or –infected patients.
- "Ring surveillance" vs. retrospectively identified CRE contacts
- 900 bed, academic institution in Chicago
- 3-4 new CRE patients identified/month



## **CRE Ring Surveillance Protocol**





## **CRE Ring Surveillance Findings**

- 14 episodes of ring surveillance
  - September 2011 January 2013
  - 173 patients had rectal cultures done for ring surveillance
  - Median 12 patients per episode (range 6-22)
  - 5 episodes (36%) in ICUs and 9 on general wards
    - [2 surgical, 3 medical, 4 heme/onc]



#### **New CRE Identified by Ring Surveillance**

- 3 patients identified as CRE-positive on ring surveillance
  - All colonization
  - All were colonized with different species than the source patient
  - One of patients was screened on day of admission and thus was felt to be pre-existing
  - None felt to represent transmission
- Duration between index culture obtained and ring surveillance initiated: median 5 days (range 3-7)



### Looking for Transmission Under the Radar: Retrospectively-identified CRE Contacts

- Source = Any CRE-positive patient who spent at least 24 hours on a ward with the case patient prior to the case-patient's acquisition of CRE
- Possible transmission if case patient and source share a CRE with 0 to 3 band PFGE difference
- 7 potential transmissions identified involving 6 CRE-positive source patients



#### **Summary of Possible CRE Transmissions**

Culture Type of Source Patient	Shared Days	Source Patient in Isolation?	Case Patient in Isolation?
Blood	3	Yes	Yes
Wound	2	Yes	Yes
Respiratory	3	No	No
Urine	3	Yes	No
Respiratory	3	Yes	No
Urine	9	Yes	No
Respiratory	3	Yes	No



#### **Ring Surveillance Conclusions**

- Ring surveillance failed to identify transmissions
- Epidemiologic review and PFGE typing of retrospectively-identified source-case pairs did identify 7 transmissions in 17 month study period
- Flaws of ring surveillance
  - Ring surveillance done at single point in time, therefore limited in capturing transmissions
  - Time lag between obtaining CRE cultures and implementing RS allows patients to be missed d/t discharge, moving between wards
  - Decision to only perform ring surveillance for source patients not in contact isolation may have led to missed opportunities
- Regular point prevalence in high risk areas may be more fruitful



#### **Risk-Based Screening for CRE: LTACH Patients**

- Screened patients with a history of LTACH facility stay in the past year upon admission to hospital
- And screened patients upon admission to LTACH following discharge from hospital
- 48 new carriers identified in 2.5 years of study
  - 42% on admission to acute care and 58% on admission to LTAC
- Predictors of CRF colonization
  - High comorbidity score
  - Immunosuppression
  - Indwelling devices



#### **Risk-Based Screening for CRE: International Travel**



- Questionnaire to guide CRE admission screening
- Administered by admitting clerk or nurse
- Infection Prevention reviewed questionnaires and ordered screening cultures for all patients with Out of Country Medical Care
- 48% of admissions completed questionnaires
- 3.1% had Out of Country Medical Care
  - 59% outpatient care; 18% inpatient care;
    16% both
- 34% traveled to US; 23% to Asia; 15% to Europe; 11% to Central/South America
- 49% of those with Out of Country Medical
   Care were screened, no positive results



### **Effectiveness of Active Surveillance Testing for Uncovering Unidentified Carriers**

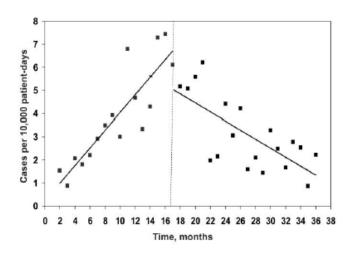


- In Calfee study, admission & weekly screening introduced in ICUs
  - 2% of patients found to be colonized or infected
  - When screening fully implemented, 53% of patient were first identified by AST
  - Median time from admission to positive AST—18 days
  - 46% of patients positive by AST later had clinical culture
  - 21% of patients positive by AST later became bacteremic
  - AST prompted contact precautions and prevented 1396 days of unprotected patient & staff exposure
- In Swaminathan study, AST is done at admission and weekly in ICUs, med-surg units and acute rehab units
- 68% of CRE carriers would have gone undetected without active surveillance



#### **Active Surveillance Testing to Control a CRE Outbreak**

#### Rates of CRE Infection



- AST culturing as an intervention during an outbreak of CRE
  - ICUs and step-down units
  - Admission & weekly
- 52% of patients identified by AST
  - 26% of these subsequently had clinical cultures
- Colonization detected a median of 9 days sooner
- 38% of days on contact precautions due to AST identification
- Clinical infections decreased 4.7 fold following intervention



### Chlorhexidine Bathing: Microbiologic and Pharmacologic Outcomes

- CHG bathing performed as part of a bundle of interventions at LTACHs
- Measured CHG concentrations on patient skin pre- and post-bath
- Also cultured skin for KPC
- CHG bathing reduced the proportion of patients colonized with KPC
  - 56% of patients pre-bath  $\rightarrow$  32% of patients post-bath (p = 0.01)
- Also led to a 51% reduction in the skin sites colonized (p <0.001)</li>

% KPC positive	Inguinal	Back	Antecubital	Axilla	Neck
Before bath	37	8	10	39	8
After bath	15	5	5	11	15



#### CHG bathing, continued

- Median concentration of CHG on skin higher after bathing
  - -312.5 vs. 78 mcg/mL; p < 0.001
- Inguinal and axillary sites had the highest concentrations
- Controlling for skin site, a CHG concentration of 128 mcg/mL or greater halved the risk of KPC colonization
- Other findings:
  - Diarrhea increased the risk of KPC colonization in the inguinal region
  - No patients without a tracheostomy had neck colonization

CHG concentration	Inguinal	Back	Antecubital	Axilla	Neck
Median pre-bath	312.5	19.5	58.6	156.3	14.7
Median post-bath	1250.0	234.4	312.5	625.0	78.0
≥ 128 mcg/mL pre-bath	81%	23%	27%	61%	6%
≥ 128 mcg/mL post-bath	97%	66%	77%	84%	47%

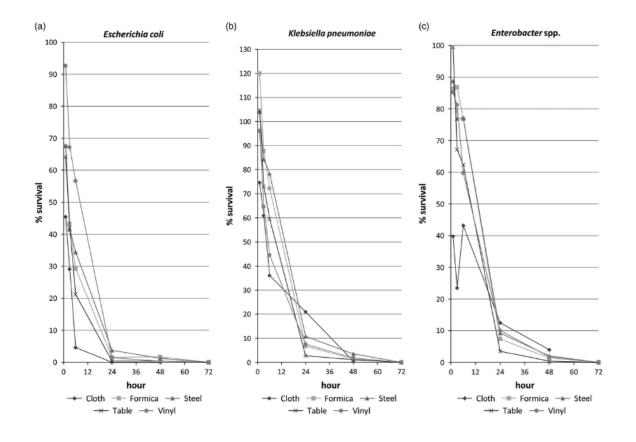


#### **CRE in the Environment—Perhaps not a Major Concern**

- Aim: describe the frequency & location of CRE contamination of hospital rooms and assess survival of CRE on surfaces
- Sampled surfaces in occupied CRE patient rooms
- 8.4% of surfaces are contaminated in occupied patient rooms
  - Sites more frequently contaminated: bed rail, sink, toilet
- Inoculated test surfaces: overbed table, vinyl, stainless steel, Formica, cloth
- Survival was < 15% at 24 hours; < 5% at 48 hours</li>
  - No cultures positive at 72 hours



#### **Survival of CRE on Environmental Surfaces**





#### Focus on Super-spreaders of CRE?

- Quantified environmental contamination from the vicinity of known
   CRE carriers
- 18% of carriers were responsible for 79% of environmental colonies detected
  - High rectal CRE concentrations
  - Admitted with respiratory disease



#### **NIH Outbreak**

- Cluster of CRE infections at NIH
  - 18 patients acquired single strain over 15 month period
  - 7 died
- Interventions
  - Surveillance
    - Admission & twice weekly rectal, throat, inguinal swabs in ICU and neighboring medical wards
    - Monthly point prevalence hospital-wide
    - Rapid identification of organisms
      - Growth on KPC- CHROMager → MALDI-TOF → PCR for KPC gene
  - Isolation Precautions
    - "Enhanced contact precautions": patients confined to room, visitors gown/glove, disposable dishes/trays, staff cannot touch pagers or phones
  - Geographic & Staff Cohorting



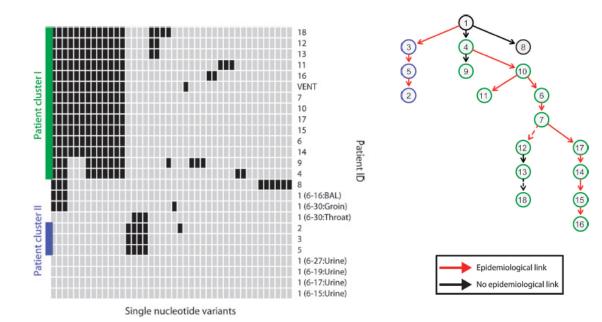
#### **NIH Outbreak**

- Hand Hygiene
  - Improved from 80-85% to 100%
  - "Two pumps, 20 seconds"
  - Around the clock monitors, 3 positions: HH, contact precautions, and environmental disinfection
- Daily CHG Bathing
  - Improved adherence from <70% to > 90%
- Environmental Decontamination
  - For routine cleaning—double disinfection of high touch surfaces with bleach wipes
  - At discharge—double cleaning, disinfection with bleach, & decontamination with hydrogen peroxide vapor
  - Removal of sink drains for cleaning



#### **NIH Outbreak**

- Extensive communication, engagement of stakeholders, education
- Whole genome sequencing





Palmore T et al. CID 2013; 57: 1593-9. Snitkin ES et al. Sci Transl Med 2012; 4 (148):

#### **CRE Surveillance & Prevention Conclusions**

- Active surveillance testing is clearly useful
  - Also resource-intensive
  - Will depend upon institutional priorities
- Risk-based screening may allow focused use of resources
  - Will still need personnel and IT commitments
- Concept of super-spreader
  - Should interventions be tailored based on patient characteristics?
- Tried and true interventions still work for outbreak control
  - Primary benefit of new technologies may be speed



#### **Acknowledgements**

- NMH HEIP Team
  - Chris Silkaitis
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  - Kim Schelling
  - Anessa Mikolajczak
  - Autumn Duggan
  - Maryanne Sotelo
  - Sandra Reiner
  - Larysa Fedoriw
  - Sharon Ward-Fore
- Teresa Zembower, MD, MS
- Margaret Fitzpatrick, MD, MSCI

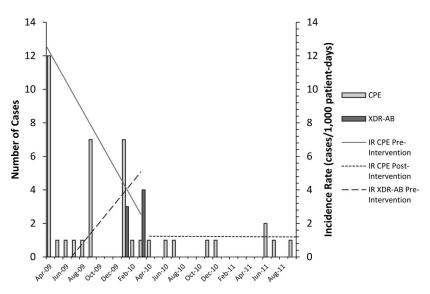




### Questions?



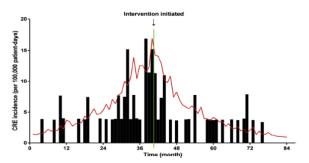
### Point Prevalence Screening Effective for Outbreak of CRE and XDR-Acinetobacter



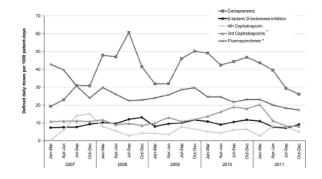
- Weekly education and status update meetings
- Cohort patients, nursing and respiratory care staff
- HH monitoring
- Pre-emptive contact precautions
- Weekly point prevalence screening; increased to twice weekly
- Restricted carbapenems
- Daily CHG bathing (wipes)
- ATP testing to assess room cleaning



#### **CRE Control without Active Surveillance**



ig 1. Monthly CRE incidence rates (per 100,000 patient days) during the study period, CRE, carbapenem-resistant Enterobacteria



- CRE incidence rose from 1.6 to 9.8 per 100,000 pt-days
- Returned to baseline following interventions
- Improvement of HH from 35% to 70%
- Enhanced antimicrobial stewardship of carbapenem



# Infection Prevention in Nursing Homes

Dheeraj Mahajan, MD, CMD, CIC

Nothing to disclose.

#### **TOPICS**

- Effective infection control and prevention program in PA-LTC
- Barriers and challenges in our setting
- Isolation conundrum, medical care Vs. quality of life
- Safety Culture, Facility acquired and potentially preventable infections
- Anti-microbial Stewardship, our time has come

#### **Burden of Infections**

- Range 1-5 infections/1,000 resident days
  - Single day, point prevalence = 3-5%
    - 25% had devices; 10% of them with infection
  - Prospective study (MI):
    - No device: 5.7/1,000 days
    - Device: 9-11/1,000 device-days
- Nationwide estimates: 765K-2.8 million/year
- UTIs, pneumonia, skin and soft tissue, GI infections
  - 12%-30% treated for a UTI annually; more females than males

#### Consequences of Nursing Home Infections

- Leading cause of mortality and morbidity
- 150,000-300,000 hospital admissions each year
  - 26-50% of transfers due to infections
- Costliest of all adverse event related hospitalization

This means your resident might get sick, transfer to the hospital or even die of an HAI.

The goal of infection prevention is to prevent these infections from occurring and promote resident safety.

### Effective Infection Control and Prevention Program

- Establishing a core team, with IP at the center
- Ensuring person in IP role has optimum training and qualification
- Ensuring reasonable and fixed FTE is dedicated to IP activities
- Medical director as clinical resource, Infectious diseases specialist if needed.
- Integration into Laboratory , Pharmacy, Nutritional and Environmental services Work Flow

#### Suggested Team Structure

# Infection Prevention & Control Team

- Establish infection prevention & control priorities
- Design & implement plans, policies
- Allocate resources
- Assess program efficiency

#### Infection Preventionist

- Report to Infection & Prevention Control Team
- Surveillance, data collection & analyses
- Staff education
- Communication with other stakeholders

#### Barriers and challenges in our setting

- Lack of formal and structured program
- High staff turn over
- IP pulled in different directions
- IP lack of training and knowledge
- Lack of ownership and administration buy-in
- Fear of survey citations
- Poor medical director involvement
- Over all poor resource allocation, including IT

# Isolation conundrum, medical care Vs. quality of life

- Long-term residents 'live' in nursing homes and deserve quality of life as if its their home
- Many residents are colonized and remain in prolonged contact isolation, further isolating them from social interactions
- Many facilities still follow arbitrary policies of repeated negative cultures prior to discontinuing isolation precautions (including but not limited to C-diff, MRSA, ESBL)

# Safety Culture, Facility acquired and potentially preventable infections

- Resident safety culture is still not standard continued efforts on way (AHRQ,CMS)
- National action plan highlights the urgency of reducing HAIs
- Several national initiatives addressing HAIs (AHRQ-CUSP-CAUTI, QIN-QIO – NH Collaborative)
- Lack of robust hand hygiene programs

# ANTIBIOTIC USE (ABUSE) in Nursing Homes

- Antimicrobials account for approximately 40% of all systemic drugs prescribed in LTCFs
- 50-70% of the residents will receive at least one course of a systemic antimicrobial agent during a one-year period.
- Studies estimate that 25-75% of systemic antibiotic use may be inappropriate in the long-term care setting

### Anti-microbial Stewardship, our time has come

- Understanding AMS
- Getting leadership Buy-in
- Getting facility "antibiogram"
- Compiling a list of common infections and appropriate treatment guidelines
- Poor Man's ATO
- Working with lab on timely microbiology reports
- Working with pharmacy on timely antibiotic reports

#### AMS Contd.

- "Choosing wisely" the UAs and other cultures
- IT/EMR integration for lab/MAR reporting
- Using minimum criteria for infection diagnosis
- Medical Director engagement for medical staff education
- Using data to identify any outliers for unnecessary testing or prescribing

#### **DISCUSSION**



Northern Illinois Infection Prevention and CRE Workshop, Addison, IL

May 12, 2015

# "What every Laboratory Should be Doing to Detect CRE's"

Paul C. Schreckenberger, Ph.D.,
D(ABMM), F(AAM)
Professor of Pathology
Director, Clinical Microbiology Laboratory
Loyola University Medical Center
pschrecken@lumc.edu



#### **Financial Disclosures**

<b>Type of Financial Interest</b>	Name of Commercial Interest
Salaried Employee	Loyola University Medical Center
Stocks/Stock Options	None
Independent contractor/Speaker's Bureau	Accelerate Dx., Beckman Coulter, bioMerieux, BioFire, Cepheid, Hardy Diagnostics, Merck, Thermo Fisher Scientific
Consultant/Advisory Committees	BioFire, Cepheid, GenMark, Quidel, Thermo Fisher Scientific, Theravance
Research Grants	Accelerate Dx, Becton-Dickinson, Beckman Coulter, BioFire, bioMerieux, Bruker, Cepheid,

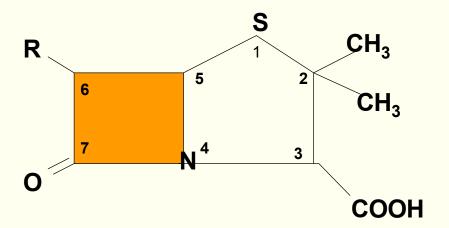
## **Learning Objectives**

At the conclusion of this session, participants will be able to:

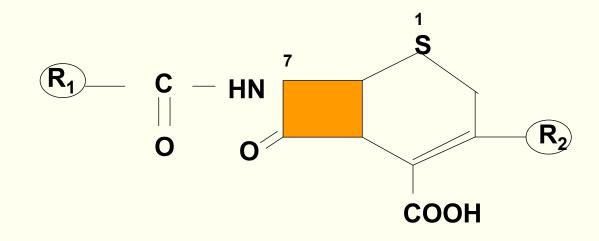
- 1. Describe the five major types of CRE
- 2. Review conventional and new approaches to detecting CRE
- 3. Explain the CSTE CRE definition proposal and its implications for labs
- 4. Evaluate their own laboratories readiness for detecting and reporting CRE



#### Penicillin nucleus



### Cephalosporin nucleus



## MODE OF ACTION OF BETA LACTAMS IN GRAM NEGATIVES

#### **SUSCEPTIBLE**

RESISTANT

β-Lactam Antibiotic



Diffusion through

**Outer Membrane** 



Diffusion through

Peptidoglycan



Penicillin Binding Proteins



Cell Death

- ← Porin Blocks Entry
- ← Efflux Pump
- Beta-LactamaseHydolyzes Beta-Lactam
- Changes in PBP results in Failure to Bind to β-Lactam



**Penicillins** 

Cephalosporins

Cephamycins Carbapenems

Monobactams

Benzylpenicillin

Cephalothin 1st

Cefoxitin

Imipenem

Meropenem

**Aztreonam** 

Methicillin

Cefamandole 2<sup>rd</sup>

Cefotetan

Ertapenem

**Ampicillin** Cefuroxime 2<sup>nd</sup>

Cefmetazole

Doripenem

Carbenicillin | Cefotaxime 3rd

Mezlocillin

**Ticarcillin** 

Ceftazidime 3<sup>rd</sup>

Ceftriaxone 3<sup>rd</sup>

Cefepime 4th

Penicillins Cephalosporins Cephamycins

ephamycins Carbapenems

Monobactams

Benzylpenicillin Cephalothin 1st

Cefoxitin

**Imipenem** 

**Aztreonam** 

Methicillin

Cefamandole

2nd

Cefotetan

**Ertapenem** 

Meropenem

**A**mpicillin

Cefuroxime

2<sup>nd</sup>

**Cefmetazole** 

Doripenem

Carbenicillin Cefotaxime 3rd

Mezlocillin

Ceftazidime

3rd

**Ticarcillin** 

Ceftriaxone 3<sup>rd</sup>

Cefepime 4<sup>th</sup>

ESBLs hydrolyze all

**Penicillins** 

Cephalosporins

**Monobactams** 



**Penicillins Cephalosporins** 

Cephamycins Carbapenems

Monobactams

Benzylpenicillin Cephalothin 1st

in 1<sup>st</sup> Cefoxitin

**Imipenem** 

**Aztreonam** 

Methicillin Cefamandole 2<sup>n</sup>

Cefotetan

**Ertapenem** 

Meropenem

Ampicillin Cefuroxime 2<sup>nd</sup>

Cefmetazole

**Doripenem** 

Carbenicillin Cefotaxime 3rd

Mezlocillin Ceftazidime 3<sup>rd</sup>

Ticarcillin Ceftriaxone 3<sup>rd</sup>

ampCs hydrolyze all

**Penicillins** 

1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> Cephalosporins

**Cephamycins** 

**Monobactams** 

Cefepime 4th



Penicillins Cephalosporins

Cephamycins Carbapenems

ems Monobactams

Benzylpenicillin

**Ampicillin** 

Cephalothin 1st

Cefoxitin

**Imipenem** 

**Aztreonam** 

Methicillin Cefamandole 2<sup>n</sup>

Cefuroxime

**9**nd

Cefotetan

Ertapenem

Meropenem

Cefmetazole

**Doripenem** 

Carbenicillin Cet

Cefotaxime 3<sup>rd</sup>

Mezlocillin

Ceftazidime 3<sup>rd</sup>

**Ticarcillin** 

Ceftriaxone 3<sup>rd</sup>

Cefepime 4<sup>th</sup>

Metallo BL hydrolyze all

**Penicillins** 

**Cephalosporins** 

**Cephamycins** 

**Carbapenems** 



Penicillins	Cephalosporins	Cephamycins	Carbapenems	Monobactams
Benzyl- penicillin	Cephalothin 1 <sup>st</sup>	Cefoxitin	Imipenem	Aztreonam
Methicillin	Cefamandole 2 <sup>r</sup>	<sup>l</sup> Cefotetan	Meropenem	
		Gerotetari	Ertapenem	
Ampicillin	Cefuroxime 2 <sup>nd</sup>	Cefmetazole	Doripenem	
Carbenicillin	Cefotaxime 3 <sup>rd</sup>	KPCs hydrol		

Mezlocillin Ceftazidime 3<sup>rd</sup>

Ticarcillin Ceftriaxone 3<sup>rd</sup>

Cefepime 4<sup>th</sup>

Penicillins
Cephalosporins
Cephamycins
Carbapenems
Monobactams



### Carbapenem-Resistance in Enterobacteriaceae

- Two mechanisms of resistance
  - Carbapenemase (β-lactamase that can hydrolyze carbapenems)
  - Cephalosporinase combined with porin loss
    - Some cephalosporinases (e.g., AmpC-type β-lactamases or certain ESBLs i.e. CTX-M) have a low-level carbapenemase activity
    - Porin loss limits entry of the carbapenem into the periplasmic space



## Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Carbapenemase
  - Isolate likely to be resistant to all carbapenems and other β-lactam agents
  - May need to change susceptible reports to resistant for β-lactam drugs
  - Need to implement infection control measures such as contact precautions and possibly active surveillance testing
  - These are an Infection Control Emergency

## Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Cephalosporins combined with porin-loss
  - Class A ESBL's (CTX-M) + reduced permeability
  - Class C High AmpC + reduced permeability
- These hydrolyze ertapenem more than meropenem or imipenem
  - Not necessarily resistant to all carbapenems (i.e., would not need to change susceptible results to resistant reports for β-lactam drugs
- These isolates are clearly MDR and infection control measures are recommended. Healthcare institutions may reserve more aggressive measures for carbapenemase-producing isolates

### 5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac- teriaceae	Non- fermenters
<b>A</b> <sup>1</sup>	KPC <sup>2</sup>	+++	+
B (metallo)	NDM <sup>3</sup> , IMP, VIM,	+++	+++
D	OXA-48-like	+++	+/-

<sup>1</sup>also includes SME; <sup>2</sup>most common in USA; <sup>3</sup>increasing in USA

....but several types within 5 groups and other types of carbapenemases

## Strategy for Laboratory Detection of Carbapenemases

- Antibiogram CDC approach: if any Enterobacteriaceae tests non-susceptible to any carbapenem call it CRE.
- Phenotypic testing
  - Modified Hodge Test
  - Boronic Acid Synergy Test
  - EDTA inhibition test (MBL Etest)
- Rapid Colorimetric
  - Carba NP
  - NEO-Rapid CARB Kit by Rosco Diagnostica (Hardy, Key Scientific)
  - RAPIDEC® CARBA NP (bioMerieux)
  - EPI-CRE® (Pilots Point, Sarasota, FL)
- MALDI-TOF MS
- Molecular PCR



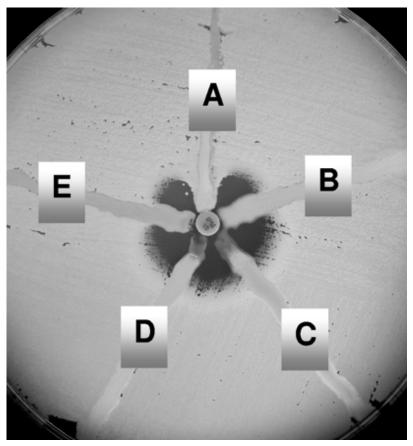
## Strategy for Laboratory Detection of Carbapenemases

- CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  - "Laboratories should perform the modified Hodge test (MHT), the Carba NP test, and/or a molecular assay when isolates of *Enterobacteriaceae* are suspicious for carbapenemase production"

## Strategy for Laboratory Detection of Carbapenemases

- CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  - Disk zone of < 22 mm for ertapenem or meropenem</li>
  - MIC of >1 µg/ml for imipenem, ertapenem or meropenem
- Procedure Notes
  - Imipenem disk test is <u>not</u> a good screen
  - Imipenem MIC does <u>not</u> work as a screen for *Proteus/ Providencia/Morganella* due to slightly elevated MICs in this group by mechanisms other than carbapenemases

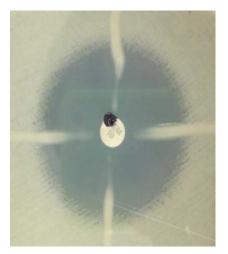
## **Modified Hodge Test**



- Inoculate MH agar with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streak for confluent growth using a swab.
- Place 10-µg ertapenem or meropenem (best) disk in center
- Streak each test isolate from disk to edge of plate
- Isolate A is a KPC producer and positive by the modified Hodge test.

Anderson KF et al. JCM 2007 Aug;45(8):2723-5.

### **Modified Hodge Test**



Neg Control



KPC





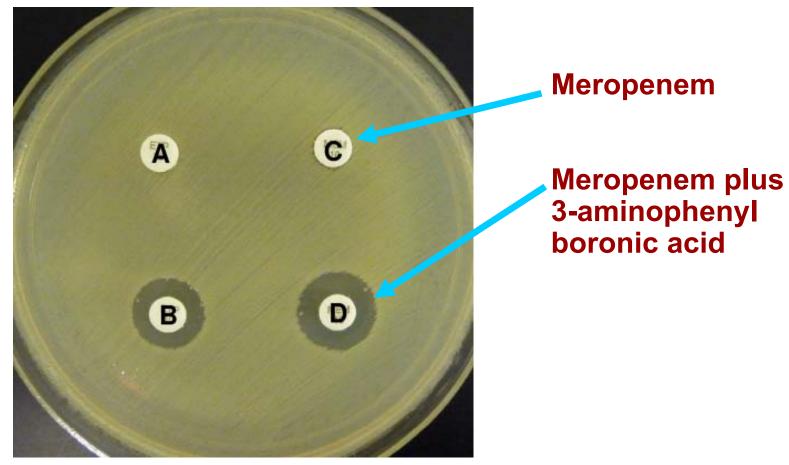




**UCLA** 

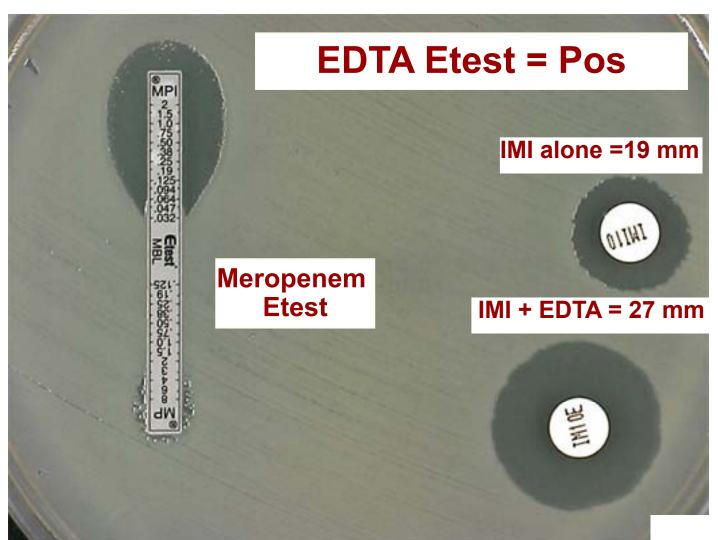


### **Boric Acid Synergy Test**



Potentiation of carbapenems by APB in *K. pneumoniae* producing KPC-2. (A) Ertapenem (10 μg); (B) ertapenem plus APB (300 μg); (C) meropenem (10 μg); (D) meropenem plus APB (300 μg).

## Rosco Diagnostica IMI/EDTA Disks MBL Etest bioMerieux

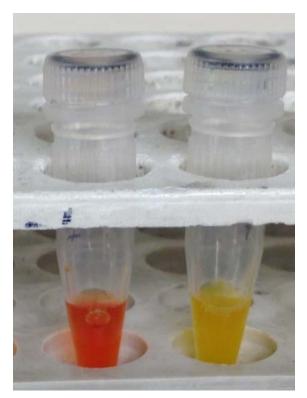


## What is the Carba NP test?

- A colorimetric test for carbapenemase production by Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter
  - Uses imipenem as the target substrate, phenol red as the pH indicator; positive hydrolysis turns yellow
  - Color usually turns fast, test ends at 2 hours
  - Good at detecting KPC, NDM, VIM, SPM, and SME, not so good at OXA
  - Will pick up carbapenem resistance if the MIC is 2 or 4 and you haven't changed your breakpoints

# Carba NP Test for Carbapenemase Production

- ♦ Isolated colonies (lyse)
- ♦ Hydrolysis of imipenem
- Detected by change in pH of indicator (red to yellow/orange)
- ♦ Rapid <2h
- Microtube method



NO + imipenem

Nordmann et al. 2012. Emerg Infect Dis. 18:1503.

Tijet et al. 2013. Antimicrob Agents Chemother. 57:4578.

Vasoo et al. 2013. J Clin Microbiol. 51:3092.

Dortet et al. 2014. J Med Microbiol. 63:772.

Dortet et al. 2014. Antimicrob Agents Chemother. 58:2441.

#### Results for Patient and QC Tubes Tube "a": Solution A Tube "b": Solution B (serves as internal control) Interpretation Red or red-orange Red or red-orange Negative, no carbapenemase detected Red or red-orange Light-orange, dark yellow, or Positive, yellow carbapenemase producer Red or red-orange Orange Invalid Orange, light-orange, dark Any color Invalid yellow, or yellow

#### Solution A

Red

Red

Red

Red-orange

Red-orange



Orange Invalid

Light Orange

Dark Yellow

Yellow

Yellow

M100-S25. p.120-126.

(slide courtesy Janet Hindler)

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### Carba NP Test Materials/Reagents



- Testing simple
- Reagent Preparation takes time

#### Reagents Must be Prepared Fresh

10 mM Zinc sulfate heptahydrate

Phenol red solution

0.1 N NaOH

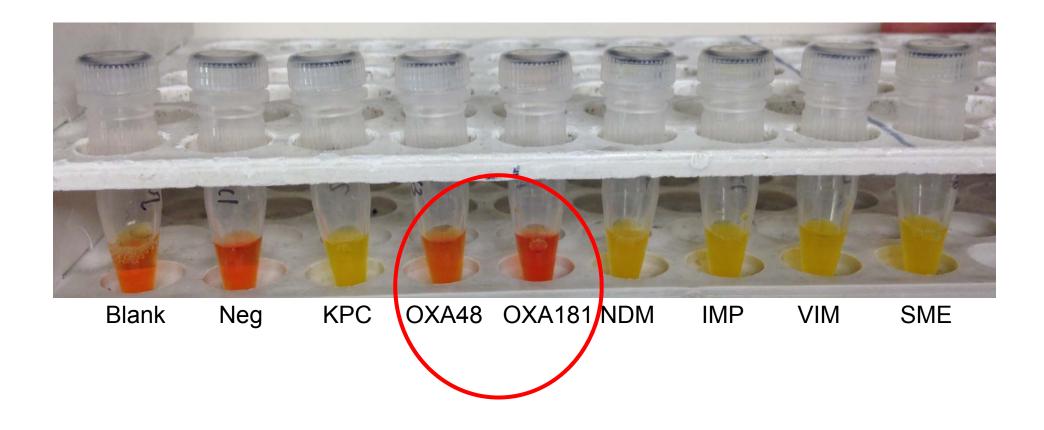
Carba NP Solution A

(phenol red + zinc solutions)

Carba NP Solution B

(Carba NP Solution A + imipenem)

## **Carba NP Test**



**UCLA** 

## **Commercial Test** Rapid CARB Screen Kit

Commercial kit; similar to Carba NP

Enterobacteriaceae and P. aeruginosa

- Tablets
  - Imipenem + indicator
  - Negative control
- ≤2 hours
- CLSI study isolates UCLA results:
  - More difficult to read than Carba NP
  - Good agreement with Carba NP but more initial invalids that required repeating
  - Most problems with Acinetobacter baumannii NDM (not indicated for this species)

www.rosco.dk NOT FDA cleared

neg

cntrl

nea

pos

pos



## **Enterobacteriaceae Carbapenemase Detection**

Study	N	Carba NP	Rapid CARB Screen Kit	MHT
1	235	97% sens 100% spec	98% sens 83% spec	-
2	92	91% sens 100% spec	73% sens 100% spec	-
3	150	<b>-</b>	98% sens 100% spec	75% sens 91% spec

- 1 Huang et al. 2014. J Clin Microbiol. 52:3060.
- 2 Yousef et al. 2014. Eur J Clin Microbiol Infect Dis. Jul 10 epub.
- 3 Simner et al. 2015. J Clin Microbiol. 53:105.

Rapid CARB Screen Kit discontinued !!!!
Reformatted Product is Neo-Rapid CARB Screen Kit

### Commercial Test RAPIDEC® CARBA NP

1) Phenol red: pH indicator

A carbapenem: imipenem
 (carbapenemase substrate)
 + Zinc, required for the detection of metallodependent carbapenemase-producing strains



Detects (without distinction)
Class A, B and D Carbapenemases

bioMerieux

**NOT FDA cleared** 



### **EPI-CRE®**

#### Enterobacteriaceae (CRE)

#### It's Easy to See...





#### **Specifications**

Time to Results: **Positive** – as soon as

the sample changes from

gold to magenta.

**Negative** – after 24 hours if no color change

from gold occurs.

Storage: From 2 to 28 °C under

dry conditions, EPI-CRE® is stable for 1 year

from date of manufacture.

Sensitivity & Specificity:

EPI-CRE® detects ONLY

living bacteria. It is

100% specific.

Regulatory: CE/IVD approved.

Pilots Point, Sarasota, FL www.pilotspoint.net

**NOT FDA cleared** 



### **EPI-CRE®**

	Carbapenemases		Cehpalosporinases						
Organism	KPC	MBL	OXA	Total	EPI-CRE Positive Results	ESBL	AmpC	Total	EPI-CRE Negative Results
C.freundii	0	0	0	0	0	0	2	2	2
E.aerogenes	2	0	0	2	2	0	5	5	5
E.cloacae	3	0	0	3	3	3	6	9	9
E.coli	2	24	1	27	27	12	0	12	12
K.oxytoca	0	0	0	0	0	1	0	1	1
K.pneumoniae	9	2	1	12	12	2	0	2	2
M.morganii	0	0	0	0	0	0	1	1	1
P.mirabilis	0	0	0	0	0	1	0	1	1
P.stuartii	0	0	0	0	0	1	1	2	2
S.marcesens	0	0	0	0	0	0	6	6	6
Total	16	26	2	44	44	20	20	40	40
				Sens- itivity	100%			Speci- ficity	100%

#### **EPI-CRE** inoculated with 50 μl 0.5 McFarland suspension

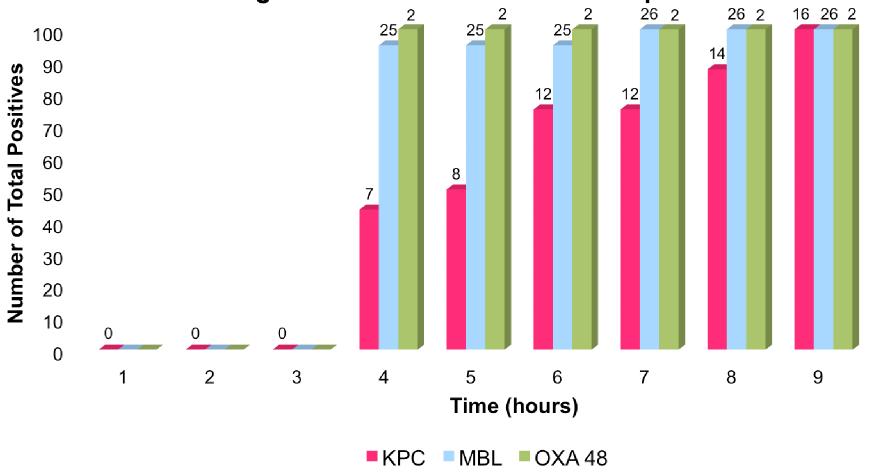
Slesar AJ, Schreckenberger PC. Evaluation of Modified EPI-CRE Tet for Rapid Carbapenemase Detection. Abstr. 115<sup>th</sup> Gen. Mtg. Am. Soc. Microbiol, New Orleans, LA, June 2, 2015.



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### **EPI-CRE®**

#### Percentage of Cumulative Positive Samples vs. Time



Slesar AJ, Schreckenberger PC. Evaluation of Modified EPI-CRE Tet for Rapid Carbapenemase Detection. Abstr. 115<sup>th</sup> 32 Gen. Mtg. Am. Soc. Microbiol, New Orleans, LA, June 2, 2015.



### **MALDI-TOF MS**

Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry

Method	Sensitivity	Specificity
MALDI-TOF Assay	77%	100%
Carb NP Test	76%	100%
MALDI-TOF BIC Assay	98%	100%



BIC Assay includes addition of 50 mM NH<sub>4</sub>HCO<sub>3</sub> to reaction buffer

Both methods experienced problems with subset of 19 isolates producing OXA-48 carbapenemase

Papagiannitsis CC et al. J Clin Microbiol. 2015 May;53:1731-5.



## Molecular Tests for Carbapenemases

- ◆ Biofire \*
  - KPC
- ♦ Nanosphere \*
  - KPC, NDM, OXA, IMP, VIM
- ♦ BD Max
  - KPC, NDM, OXA-48
- ◆ Cepheid
  - KPC, NDM, OXA-48, IMP-1, VIM
- ◆ Check-Points
  - KPC, NDM, OXA-48, IMP, VIM
- ♦ Others?
  - \* FDA cleared



## Tests for Carbapenemases in *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

	MHT	Carba NP	Molecular
Use	Enterobacteriaceae	Enterobacteriaceae P. aeruginosa Acinetobacter	Enterobacteriaceae P. aeruginosa Acinetobacter
Strengths	Simple	Rapid	Determines type of carbapenemase
Limitation	Some false pos (eg, ESBL/ampC + porin)	Special "fresh" reagents	Special reagents
	Some false neg (eg NDM)	Some invalid results  False neg for OXA-	Specific to targeted gene
	Enterobacteriaceae only	type carbapenemase	High Cost

## Why is Carbapenem Resistance a Public Health Problem?

- Significantly limits treatment options for lifethreatening infections
- No new drugs for gram-negative bacilli
- Emerging resistance mechanisms, carbapenemases are mobile
- Detection of Carbapenem Producing Organisms (CPO's) and implementation of infection control practices are necessary to limit spread

## Alphabet Soup: CRE, CPE, CPO

- What is the difference between CPO, CPE and CRE?
  - The differences depend on type of bacteria being included and the mechanisms of resistance to carbapenem antibiotics.
  - Carbapenem Resistant Enterobacteriaceae (CRE) refers to bacteria in the family of Enterobacteriaceae (e.g. E.coli, Klebsiella, etc) that are resistant to carbapenem antibiotics regardless of the method of resistance, as there are a number of different ways.

## Alphabet Soup: CRE, CPE, CPO

- What is the difference between CPO, CPE and CRE?
  - Carbapenemase Producing Enterobacteriaceae (CPE) refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli, Klebsiella*, etc) that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.

# Alphabet Soup: CRE, CPE, CPO

- What is the difference between CPO, CPE and CRE?
  - Carbapenemase Producing Organisms (CPO) refers to bacteria in the family of Enterobacteriaceae (e.g. E.coli, Klebsiella, etc) and those that do not belong to this family such as Pseudomonas and Acinetobacter, that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.

# Alphabet Soup: CRE, CPE, CPO

- Why are other countries using the term CPO?
  - Genes for carbapenem resistance can be transferred to bacteria in the Enterobacteriaceae family and to bacteria not within this family
  - The term CPO includes the larger group of potentially affected bacteria. This is important for surveillance purposes so that we do not miss any groups of bacteria that may be carrying and spreading these antibiotic resistant genes.
  - CPO's are what laboratories should be looking for and what Infection Preventionists should be reporting.

#### **CSTE Definition of CRE**

- The 2012 definition for CRE was: E. coli, Klebsiella spp., and Enterobacter spp. nonsusceptible to imipenem, meropenem, or doripenem and resistant to all 3rd-generation cephalopsporins tested (e.g., ceftriaxone, cefotaxime, ceftazidime) Ertapenem was excluded.
- Proposed 2015 definition for CRE is: *E. coli, Klebsiella* spp., and *Enterobacter* spp. resistant to imipenem, meropenem, doripenem, or ertapenem or production of a carbapenemase (eg. KPC, NDM, VIM, OXA-48) demonstrated by a recognized test (e.g. PCR, MBL test, MHT, Carba NP

#### **Problems with CSTE Definition**

- MYSPACE Bugs (Morganella, Yersinia, Serratia, Providencia, Aeromonas, Citrobacter, Enterobacter, posses chromosomal AmpC beta-lactamase) may test ertapenem nonsusceptible if also have porin mutation. These are not CPO's and are not an IC threat.
- At LUMC, 12% of *E. cloacae* test non-susceptible to ertapenem.
- In 2014, 40 patients would have been called CRE (that were not CPO's) and would have been placed in isolation and reported to XDRO registry

#### **Problems with CSTE Definition**

- Imipenem vs. Proteeae (i.e., Morganella morganii, Proteus spp., Providencia spp.)
- MIC<sub>90</sub> of imipenem ≤ 1 ug/mL for most Enterobacteriaceae, but is 4-8 ug/mL for Proteeae and may test non-susceptible to imipenem using new CLSI/FDA BPs
- Some P. mirabilis are more resistant, with imipenem MICs ranging from 16 to 64 ug/mL
- Higher MICs seen with imipenem vs. *P. mirabilis* are not due to carbapenemases but rather diminished expression of penicillin-binding protein (PBP) 1a and reduced binding of imipenem by PBP2

#### **Problems with CSTE Definition**

- Proteeae that are non-susceptible to imipenem are not CPOs and are not an IC threat.
- These patients should not be placed in isolation and should not be reported to the XDRO registry
- P. aeruginosa and Acinetobacter baumannii have both been reported to have CPO's yet these are not reported using the CSTE definition.

# **Creation of XDRO Registry**

- In response to the CRE public health threat, IDPH has amended the Control of Communicable Diseases Code (77 III. Adm. Code 690) Rules (see addendum) to require reporting of CREs to IDPH.
- All hospitals, hospital-affiliated clinical laboratories, independent or free-standing laboratories, longer-term care facilities, and longterm acute care hospitals in Illinois will be required to report CRE isolates that meet surveillance criteria to IDPH through a tool called the XDRO registry, effective November 1, 2013.

# Report CRE Isolates to XDRO Registry with <u>one</u> of following test results:

1. Molecular test (e.g., PCR) specific for carbapenemase OR

2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production

#### OR

3. For *E. coli* and *Klebsiella* species only: non-susceptible to ONE of the carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).

Report 1<sup>st</sup> CRE event per patient per encounter

# Why labs should continue to perform MHT and EDTA Inhibition Test on isolates that test Non-Susceptible to carbapenems

- Knowing the resistance mechanism is important
- The following cases demonstrate 4 different mechanisms of carbapenem resistance. Some require changes in antibiotic reporting, some require infection control notification, some require reporting to XDRO registry, and some require no action
- Can you tell the difference between them by MIC alone?

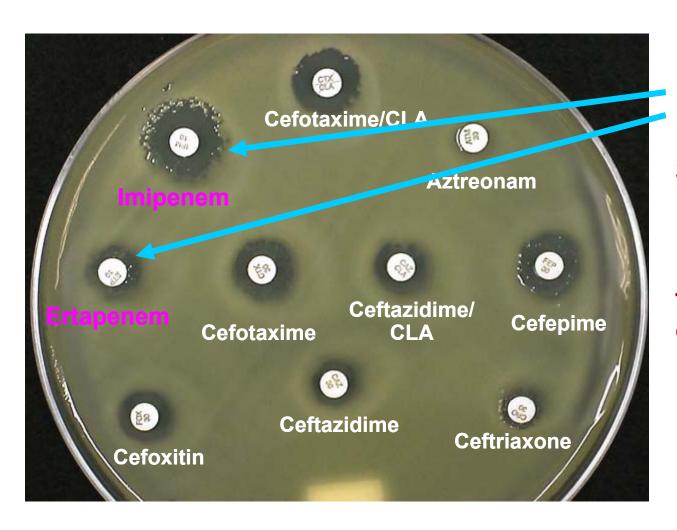
# **Patient History Case 1**

- 58 y/o male, morbidly obese (>500 lbs)
- Presented to ER with episode of hypoxia and hypotension during dialysis
- PMH
  - Pt has trach for hypercapnea (COPD and OSA), vent dependent
  - Chronic foley catheter
  - Diabetes mellitus type 2
  - ESRD
- Exam:
  - Afebrile
  - Multiple decubitus ulcers (sacrum, spine, right leg)
  - Urine is grossly dirty
- Concerned that septic => Pan-cultures
  - Urine: Klebsiella...



Vitek ID:	PARTICIPATION OF THE SEC.	Oxidase -	- The same of the	
Type:		General Susce	tibility 143 (	GNS-143)
Status:	Final			
Elapsed Time:	13 hours			
Organism:	Klebsiella pr	neumoniae		
Source:	Manual			
Demographics:				
		MIC	Instrument	Expert
Ampicillin		>=32	R	- C.
Ampiciliin/Sult		>=32	K	
Piperacillin/Ta	azobactam	>=128	R	
Cefazolin		>=32	R	100
Ceftriaxone		>=64	R	
Ceftazidime		>=38	R	
Cefepime		8	R	
Aztreonam		>=32	R	
Imipenem		<=4	- 5	
Gentamicin		4	S	
Tobramycin		>=16	R	
Ciprofloxacin		>=4	R	
Levofloxacin		>#B	R	
Trimeth-sulfa		>=320	R	
Nitrofurantoin		64	1	
ESBL		1	Negative	
MIC values in a	ncg/ml ( Mi )	Wait for All		
The presence of production.	f other Beta-la	ctamases (e.g.	AmpC, IR9) may	mask ESB

#### **Double Disk Potentiation Method – Case 1**



Imipenem - S Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation

# Case 1-MHT **Patient** Positive **Positive control Negative control** 51 51

#### And the Answer is .....

### 5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac- teriaceae	Non- fermenters		
<b>A</b> <sup>1</sup>	KPC <sup>2</sup>	+++	+		
B (metallo)	NDM <sup>3</sup> , IMP, VIM,	+++	+++		
D	OXA-48-like	+++	+/-		

<sup>1</sup>also includes SME; <sup>2</sup>most common in USA; <sup>3</sup>increasing in USA

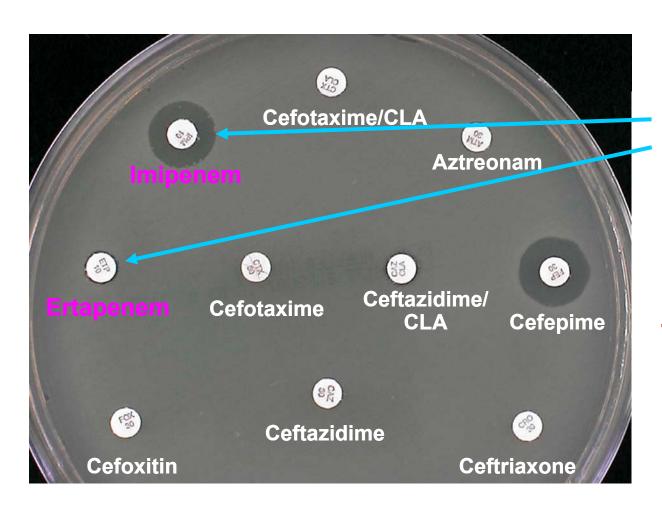
....but several types within 5 groups and other types of carbapenemases

# **Patient Report Case 1**

- If using former CLSI/FDA breakpoints change all carbapenems to resistant
- If using new CLSI/FDA breakpoints report interpretations as tested
- Add following statement to report:
   "Carbapenem resistant Enterobacteriaceae (CRE) detected by Modified Hodge Test –probable KPC type. Implement infection control measures according to facility policy."
- REPORT TO XDRO REGISTRY

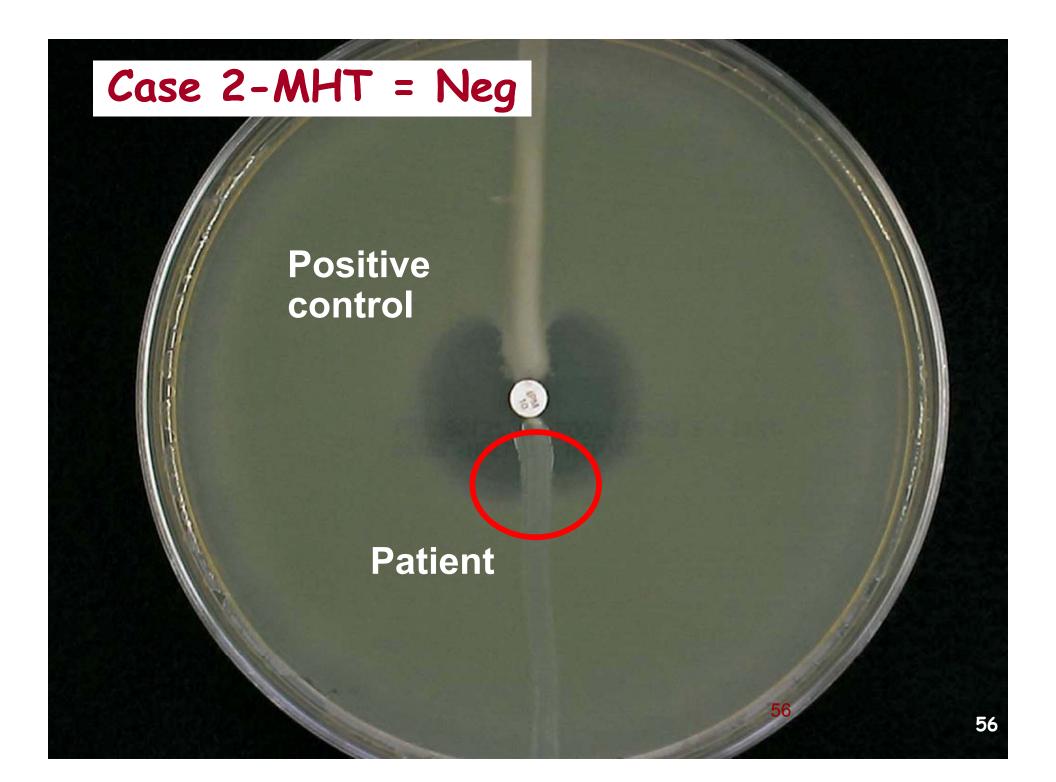


# **Double Disk Potentiation Method – Case 2 Blood Culture with** *Enterobacter cloacae*



Imipenem - S Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation



### And the Answer is .....

And the Answer is .....

<u>Chromosomal AmpC\_(Derepressed mutant) + Porin mutation</u>

# **Patient Report Case 2**

- Susceptibility pattern in Case 2 is identical to susceptibility pattern in Case 1, except in Case 2 we have a chromosomal AmpC that is not MDRO, is not an infection control risk, and does not require modification of susceptibility report.
- Add following statement to report:
   "This organism is known to possess an inducible ß-lactamase. Isolates may become resistant to all cephalosporins after initiation of therapy. Avoid ß-lactam-inhibitor drugs"
- DO NOT REPORT TO XDRO REGISTRY

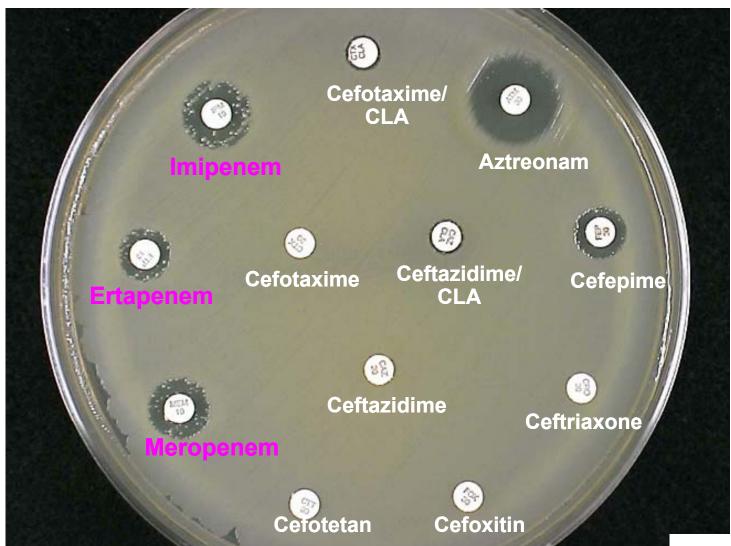
#### Case 3

 Patient is a 40 Y.O. male paraplegic who traveled to New Dehli India for a surgical procedure. 3-4 months after returning to the U.S. patient presents to outpatient center in Chicago with multiple decubitus ulcers and urinary tract infection. Urine collected from foley cath is submitted for culture.

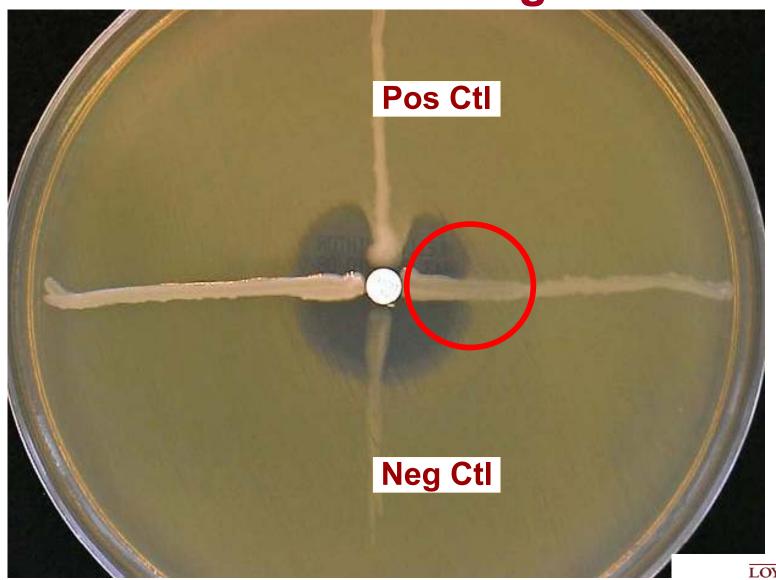
# MicroScan Report – Case 3

							Panel D	)ata ́						
Biotype	e:		7	3115012										
organi	sm Identif	ication:	-0000000 NOVO											
0	rganism				% Proba	bility F	ootnotes	S	pecial Cha	racteristics				
1 E	. coli				9	9.99								
o' a a b a	aria d Dan	······································												
					olded and u					organism)				
					TDA - C			E - K4		+				
						IAL - C								
SOR	+ ARA +	+ MEL +	IND +	ORN +	VP - 0	NPG + C	XI FD	64 - OF	/G + TO4	+				
AIC R	esults: (An	timicrobic	s marked	with "Ø" a	re suppress	ed from L	and S	hort Form	at Patient	Reports)				
M	A/S	P/T	CFZ	CAX	CAZ	CPE	MER	GM	ØTE	TO	CP	T/S	Ø FD	AK
16	>16/8	>64	>16	>32	>16	>16	>8	>8	>8	>8	>4	>2/38	<=32	>3
	R	R	R	R	R	R	R	R	R	R	R	R		R
AZ/CA	CFT	CFT/CA	ETP	IMP	Ø AUG	Ø CRM	Ø LVX	Ø MXF	Ø TIM					
2	>32	>4	>4	4	>16/8	>16	>4	>4	>64					
~	R		R	S	, ale	R	R	R	R					
<b>.</b>														
Extra T	ests:	ESBL -												

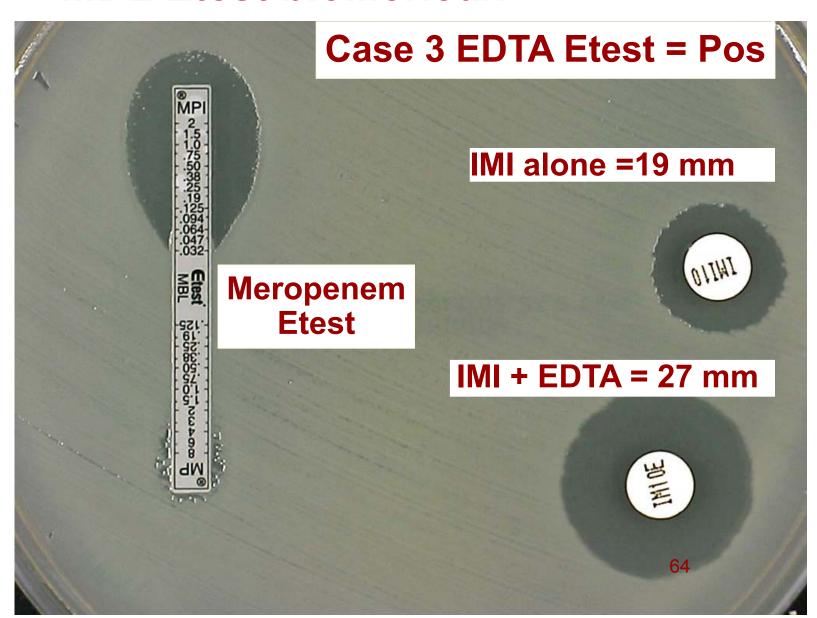
#### Case 3. 12 Disk



# **Case 3 - Modified Hodge Test**



# Rosco Diagnostica IMI/EDTA Disks MBL Etest bioMerieux



### And the Answer is .....

### 5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac- teriaceae	Non- fermenters
<b>A</b> <sup>1</sup>	KPC <sup>2</sup>	+++	+
B (metallo)	NDM <sup>3</sup> , IMP, VIM,	+++	+++
D	OXA-48-like	+++	+/-

<sup>1</sup>also includes SME; <sup>2</sup>most common in USA; <sup>3</sup>increasing in USA

....but several types within 5 groups and other types of carbapenemases

# MicroScan Report

						P	anel D	ata				- 1		
Biotype:	:		73	3115012										
Organis	m Identifi	cation:								90004	100			
Org	ganism				% Probab	oility Foo	otnotes	Spe	ecial Char	acteristics				
1 E.	coli				99	9.99				-				
Riochem	nical Pasi	ulter (Bioch	omicals f	hat are hal	ded and un	dodinad a	ro otunical	for the fire	t abains a	:				
					TDA - CI			For the firs	+ P4					
	RHA +					AL - CF			+ TAR	+				
				ORN + V		NPG + OX		4 - OF/G						
MIC Res	sults: (An	timicrobics	marked v	vith "Ø" are	suppresse	ed from La	ing and Sh	ort Forma	t Patient F	Reports)				
AM	A/S	P/T	CFZ	CAX	CAZ	CPE	MER	GM	ØTE	то	CP	T/S	Ø FD	AK
>16	>16/8	>64	>16	>32	>16	>16	>8	>8	>8	>8	>4	>2/38	<=32	>3
R	R	R	R	R	R	R	R	R	R	R	R	R		R
CAZ/CA	CFT	CFT/CA	ETP	IMP	Ø AUG	Ø CRM	Ø LVX	Ø MXF	Ø TIM					
>2	>32	>4	>4	4	>16/8	>16	>4	>4	>64					
	R		R	S		R	R	R	R					
Extra Te	ata.	ESBL -												

#### Case 4

 Patient presenting with UTI grows K. pneumoniae. MHT, MBL Etest both negative.

### 5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac- teriaceae	Non- fermenters		
<b>A</b> <sup>1</sup>	KPC <sup>2</sup>	+++	+		
B (metallo)	NDM <sup>3</sup> , IMP, VIM,	+++	+++		
D	OXA-48-like	+++	+/-		

<sup>1</sup>also includes SME; <sup>2</sup>most common in USA; <sup>3</sup>increasing in USA

....but several types within 5 groups and other types of carbapenemases

# **OXA-48 Carbapenemases**

- Chromosomal gene from Shewanella spp. that moved via plasmid to Enterobacteriaceae (not yet to Pseudomonas or Acinetobacter)
- OXA-48 confers resistance or reduced susceptibility to carbapenems and penicillininhibitor combinations, but 3<sup>rd</sup> and 4<sup>th</sup> gen cephs remain susceptible unless have ESBL or AmpC
- Problem for detection by some automated systems that tend not to believe carbapenem-R, cephalosporin-S phenotypes
- Most reports from Turkey and North Africa. Only recently reported in US

#### **OXA-48-Like\*** in Illinois

- On March 13, 2015, IDPH was notified two cases of OXA-48 like-producing CRE in suburban Chicago area.
- OXA-48 is an emerging mechanism for bacterial resistance to carbapenem antibiotics. These are the first CRE cases associated with OXA-48-like carbapenemases reported into Illinois XDRO Registry.

\* OXA-48-like refers to a family of similar OXA enzymes and includes: OXA-48, OXA-163, OXA-181, OXA-204, OXA-232, OXA-244

#### **OXA-48-Like in Illinois**

- Both cases were detected from urine cultures; one was *Klebsiella pneumoniae* other was *Escherichia coli*.
- Patients had healthcare encounters at multiple facilities, including an acute care hospital, rehabilitation facility, assisted living, and skilled nursing facility. Neither patient had any known international travel or invasive medical procedures within the last six months.
- No epidemiological link between the cases

#### **OXA-48-Like in Illinois**

- Because these two patients had several transitions of care, they are examples of the importance of reporting CRE-positive patients into the XDRO Registry and indicating the mechanism of resistance (if available).
- The Registry data help inform the regional prevalence of CRE, identify the introduction of less common mechanisms of resistance, and enhance inter-facility communication.

# **CDC Lab Training Resources**

- 5 e-learning courses in the basic curriculum—direct link: <a href="http://www.cdc.gov/labtraining/basic\_courses.html">http://www.cdc.gov/labtraining/basic\_courses.html</a>
- Curriculum on antimicrobial susceptibility testing called MASTER – 3 e-learning courses offered: <a href="http://www.cdc.gov/labtraining/master\_courses.html">http://www.cdc.gov/labtraining/master\_courses.html</a>
- E-learning course on Packaging and Shipping Division 6.2 Materials. Relevant for facilities who need to send specimens to other labs for testing. Individuals who pass this course are eligible to be certified to pack and ship by their employer. <a href="http://www.cdc.gov/labtraining/course\_listing/">http://www.cdc.gov/labtraining/course\_listing/</a>

employer. <a href="http://www.cdc.gov/labtraining/course\_listing/1043824.html">http://www.cdc.gov/labtraining/course\_listing/1043824.html</a>

# ANTIBIOTIC RESISTANCE:

Darwin, Semelweis, & The Never Ending Story

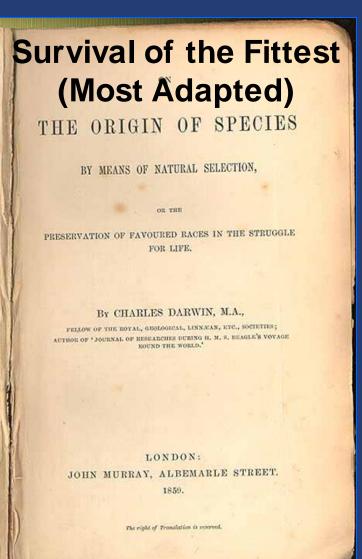
Robert A. Weinstein, MD
May 12, 2015
Rush University Medical Center
Cook County Health & Hospitals System

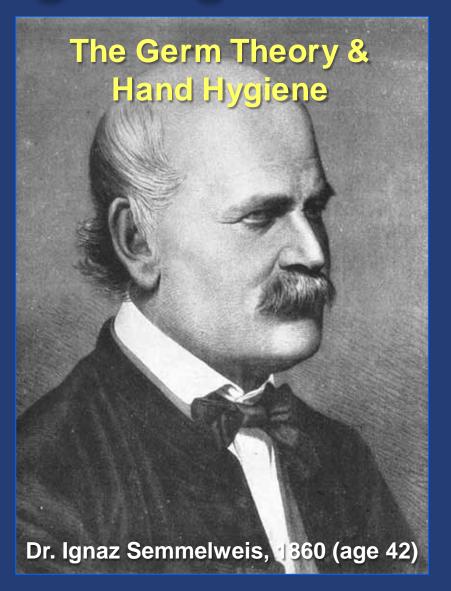
Disclosures: Sage Inc (Remote) & CDC (Current) Funding

# **TOPICS**

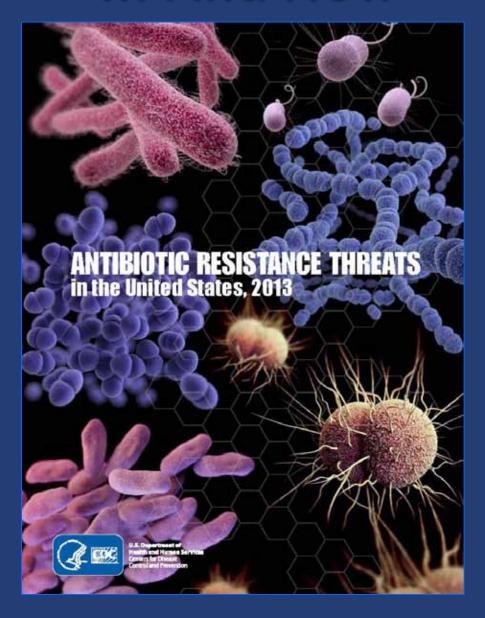
- Background & Six Inconvenient Truths
- Trumping Low Hand Hygiene Rates
- Antibiotic Stewardship
- Microbiomes & Networks
- The National Action Plan

# In the "Beginning"...





# ... And Now



### **Urgent Threats**

- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae

#### Serious Threats

- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococcus (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant Non-typhoidal Salmonella
- Drug-resistant Salmonella Typhi
- Drug-resistant Shigella
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Drug-resistant Streptococcus pneumoniae
- Drug-resistant tuberculosis

### **Concerning Threats**

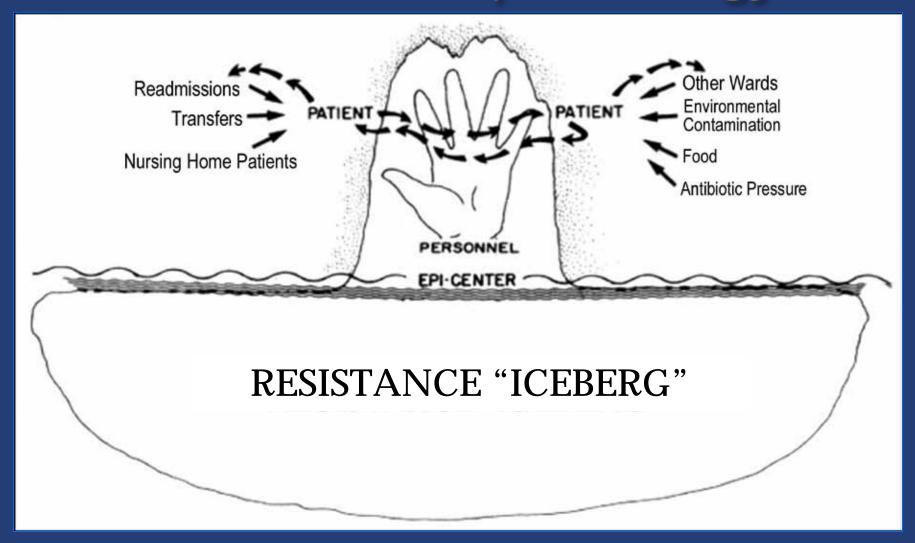
- Vancomycin-resistant Staphylococcus aureus (VRSA)
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

Estimated minimum number of illnesses and deaths caused by antibiotic resistance\*:

At least **2,049,442** illnesses, **23,000** deaths

\*bacteria and fungus included in this report

# Resistance Bad — Control Measures Are Based on Epidemiology

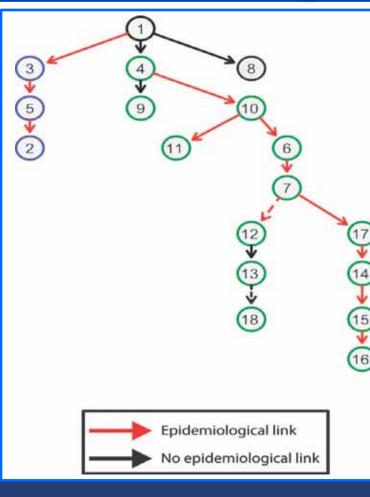


# Putative map of *K. pneumoniae*Transmission During Outbreak

### Tracking a Hosp Klebsiella pneun

Evan S. Snitkin, Adrian M. NISC Comparative Sequenc Tara N. Palmore, Hulia A.

The Gram-negative bacteria *Klet* munocompromised patients. The making infection containment or outbreak of carbapenem-resistal quencing was performed on *K. p* implementation of infection collisted to three independent case became clinically apparent. routes, with subsequent mining Our analysis demonstrates that if facilitate the control of nosocom



# nem-Resistant ne Sequencing

ifections, primarily among imas left few treatment options, Clinical Center experienced an hom died. Whole-genome sepreak progressed despite early hiological analysis traced the rged 3 weeks before the next e for unexpected transmission ations for these transmissions. In yield actionable insights and

Snitkin et al, *Sci Transl Med* 2012; <a href="http://stm.sciencemag.org/content/4/148/148ra116.full.html">http://stm.sciencemag.org/content/4/148/148ra116.full.html</a>

# The Epidemiology of Healthcare-associated Infections is Generally Understood

Epidemiology of Endemic Nosocomial Resistance		
Factor leading to resistance	Relative contribution	
	Gram (-)	Gram (+)
Cross-infection via hands of hospital personnel	30-40%	60-80%
Antibiotic pressures	30-40%	10-20%
"Community" acquired	20-25%	10-50%
Other (contamination of environment, food, air: personnel carriers; unknown)	20+%	10-20+%

# Six Inconvenient Truths About Antibiotic Resistance

- Hand hygiene often lacking
- Physicians believe antibiotic resistance is real but not in their hospital/practice
- Physicians view "antibiotic stewardship" as taking too much time and annoying patients
- Judicious antibiotic use in animal husbandry largely voluntary
- Bacterial "genetic barriers" to resistance vary greatly
- Repeated Federal Plans to control resistance

## ATTACKING THE ICEBERG

Hand Hygiene –
Appealing to Our
Basic Instincts to
Control Healthcareassociated Infections
and Antibiotic
Resistance



# The Inanimate Environment Can Facilitate Transmission



### Source Control of MDROs — Remove the Fecal Patina

# Chlorhexidine Gluconate to Cleanse Patients in a Medical Intensive Care Unit

The Effectiveness of Source Control to Reduce the Bioburden of Vancomycin-Resistant Enterococci

Michael O. Vernon, DrPH; Mary K. Hayden, MD; William E. Trick, MD; Robert A. Hayes, BSc; Donald W. Blom, RN; Robert A. Weinstein, MD; for the Chicago Antimicrobial Resistance Project (CARP)

**Background:** Historically, methods of interrupting pathogen transmission have focused on improving health care workers' adherence to recommended infection control practices. An adjunctive approach may be to use source control (eg, to decontaminate patients' skin).

Methods: We performed a prospective sequential-group single-arm clinical trial in a teaching hospital's medical intensive care unit from October 2002 to December 2003. We bathed or cleansed 1787 patients and assessed them for acquisition of vancomycin-resistant enterococci (VRE). We performed a nested study of 86 patients with VRE colonization and obtained culture specimens from 758 environmental surfaces and 529 health care workers' hands. All patients were cleansed daily with the procedure specific to the study period as follows: period 1, soap and water baths; period 2, cleansing with cloths saturated with 2% chlorhexidine gluconate; and period 3, cloth cleansing without chlorhexidine. We measured colonization of patient skin by VRE, health care worker hand

or environmental surface contamination by VRE, and patient acquisition of VRE rectal colonization.

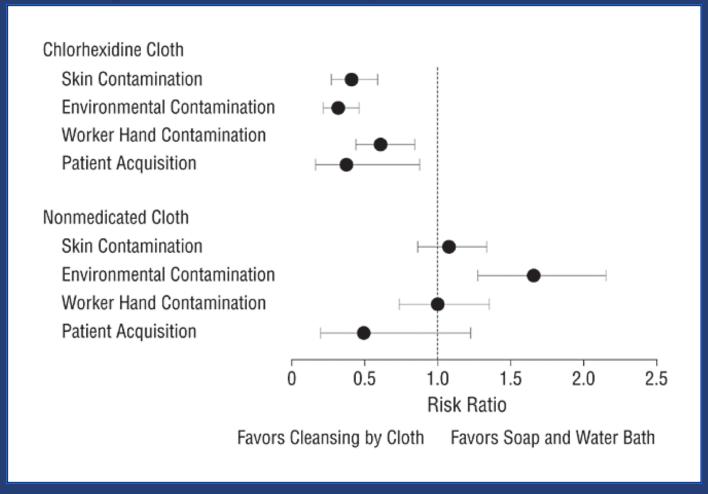
**Results:** Compared with soap and water baths, cleansing patients with chlorhexidine-saturated cloths resulted in 2.5 log<sub>10</sub> less colonies of VRE on patients' skin and less VRE contamination of health care workers' hands (risk ratio [RR], 0.6; 95% confidence interval [CI], 0.4-0.8) and environmental surfaces (RR, 0.3; 95% CI, 0.2-0.5). The incidence of VRE acquisition decreased from 26 colonizations per 1000 patient-days to 9 per 1000 patient-days (RR, 0.4; 95% CI, 0.1-0.9). For all measures, effectiveness of cleansing with nonmedicated cloths was similar to that of soap and water baths.

**Conclusion:** Cleansing patients with chlorhexidinesaturated cloths is a simple, effective strategy to reduce VRE contamination of patients' skin, the environment, and health care workers' hands and to decrease patient acquisition of VRE.

Arch Intern Med. 2006;166:306-312

MDRO, Multi-drug resistant organism

### Risk Ratios for Skin Contamination and Environmental or Healthcare Worker Contamination by or Patient Acquisition of VRE



VRE, Vancomycin-resistant enterococci

Vernon et al, *Arch Intern Med* 2006; 166:306-12

### Effectiveness of Chlorhexidine Bathing to Reduce Catheter-Associated Bloodstream Infections in Medical Intensive Care Unit Patients

Susan C. Bleasdale, MD; William E. Trick, MD; Ines M. Gonzalez, MD; Rosie D. Lyles, MD; Mary K. Hayden, MD; Robert A. Weinstein, MD

**Objective:** To determine whether patients bathed daily with chlorhexidine gluconate (CHG) have a lower incidence of primary bloodstream infections (BSIs) compared with patients bathed with soap and water.

Methods: The study design was a 52-week, 2-arm, crossover (ie, concurrent control group) clinical trial with intention-to-treat analysis. The study setting was the 22bed medical intensive care unit (MICU), which comprises 2 geographically separate, similar 11-bed units, of the John H. Stroger Jr (Cook County) Hospital, a 464-bed public teaching hospital in Chicago, Illinois. The study population comprised 836 MICU patients. During the first of 2 study periods (28 weeks), 1 hospital unit was randomly selected to serve as the intervention unit in which patients were bathed daily with 2% CHG-impregnated washcloths (Sage 2% CHG cloths; Sage Products Inc, Cary, Illinois); patients in the concurrent control unit were bathed daily with soap and water. After a 2-week washout period at the end of the first period, cleansing methods were crossed over for 24 more weeks. Main outcome measures included incidences of primary BSIs and clinical (culture-negative) sepsis (primary outcomes) and incidences of other infections (secondary outcomes).

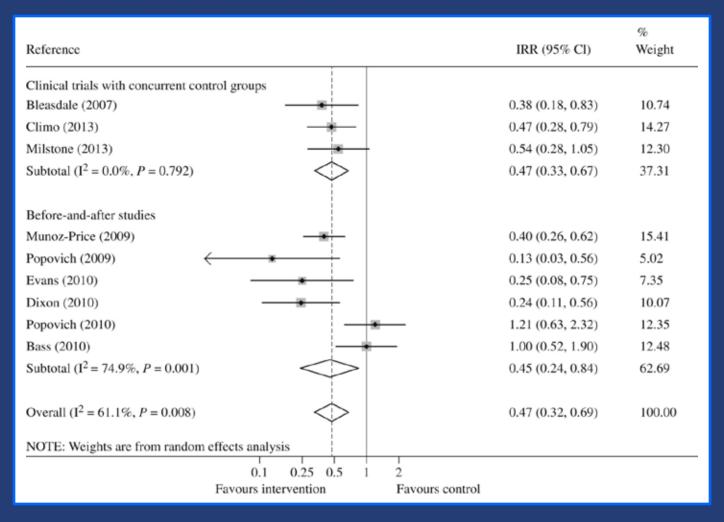
**Results:** Patients in the CHG intervention arm were significantly less likely to acquire a primary BSI (4.1 vs 10.4 infections per 1000 patient days; incidence difference, 6.3 [95% confidence interval, 1.2-11.0). The incidences of other infections, including clinical sepsis, were similar between the units. Protection against primary BSI by CHG cleansing was apparent after 5 or more days in the MICU.

**Conclusions:** Daily cleansing of MICU patients with CHG-impregnated cloths is a simple, effective strategy to decrease the rate of primary BSIs.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00130221

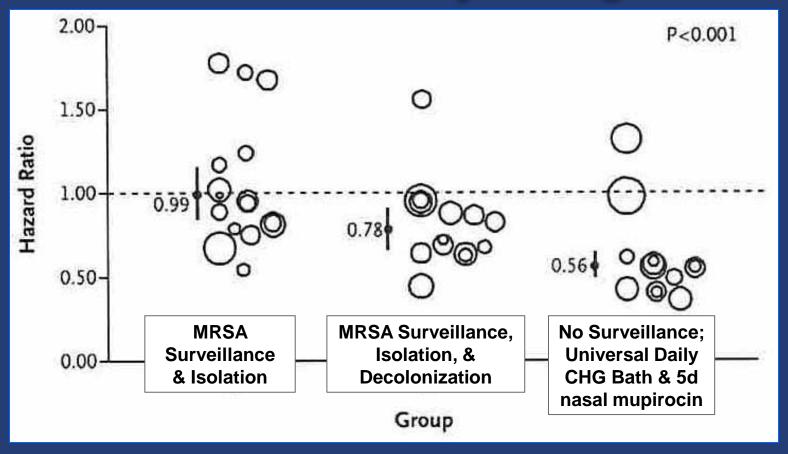
Arch Intern Med. 2007;167(19):2073-2079

# Effect of No-rinse 2% Chlorhexidine Washcloths on Reducing Incidence of Central-line Associated Bloodstream Infection



IRR, incidence rate ratio; CI, confidence interval

## Effect of Interventions on Bloodstream Infection from Any Pathogen



Shown are hazard ratios and 95% confidence intervals (vertical lines) for outcomes attributable to intensive care unit. Results based on unadjusted proportional-hazard models that accounted for clustering within hospitals. Bubble plots of hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to group effects are shown. Bubble size indicates relative number of patients contributing data to trial.

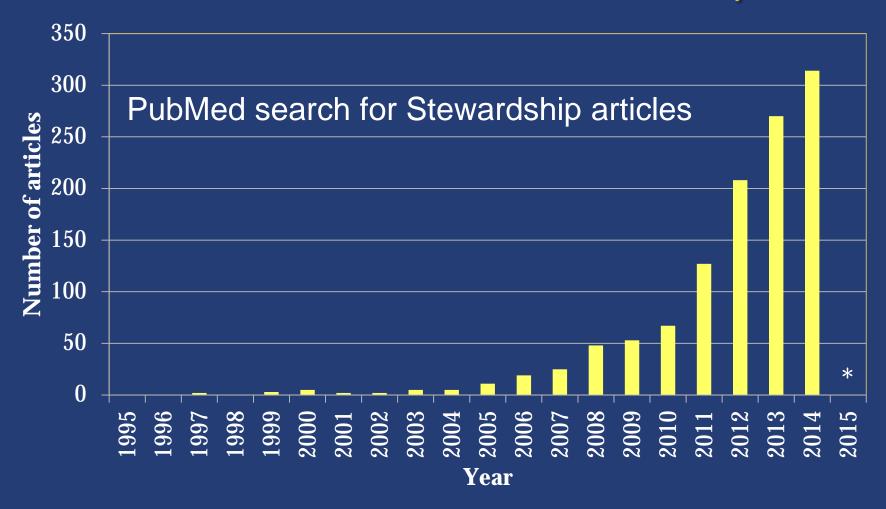
Huang et al, *N Engl J Med* 2013; 368(24):2255-65

### Screening Inpatients for MRSA — Case Closed

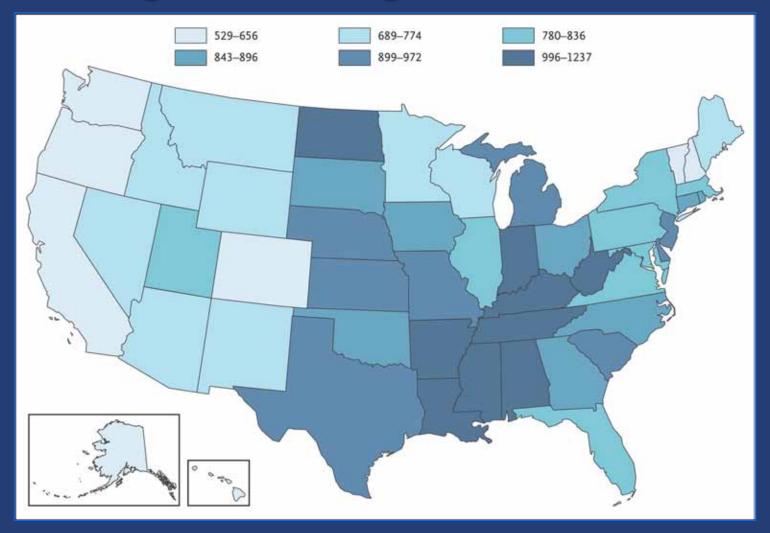
Michael B. Edmond, M.D., M.P.H., and Richard P. Wenzel, M.D.

"....the folly of pursuing legislative mandates when evidence is lacking has been shown, and laws mandating MRSA screening should be repealed."

# The 800 lb Gorilla "Antimicrobial Stewardship"



## Profligate Antibacterial Use: Antibiotic Prescriptions per 1,000 Persons of All Ages According to State, 2010



### Antimicrobial Use and Risk of Resistance

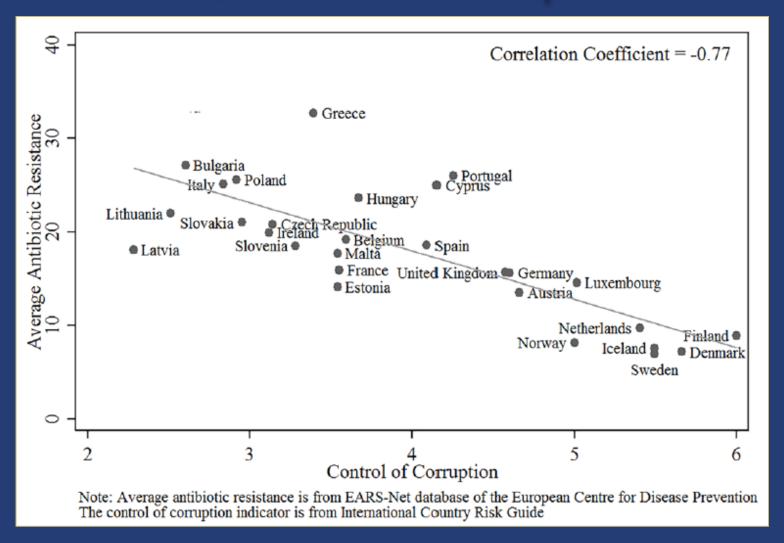
Fluoroquinolone Usage<sup>1</sup> and Resistance Rates in <u>P. aeruginosa</u> and Gram-negative Bacilli<sup>2</sup>



<sup>&</sup>lt;sup>2</sup>77 to 117/year in 43 states.

Neuhauser et al, *JAMA* 2003; 289(7):885-8.

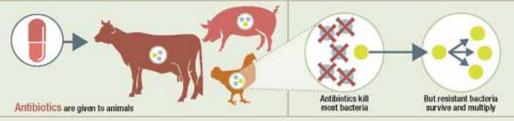
# Average Microbial Resistance vs Control of Corruption





from the farm to the table

RESISTANCE All animals carry bacteria in their intestines



### SPREAD Resistant bacteria can spread to...







produce through contaminated water or soil



prepared food through contaminated surfaces



the environment when animals poop

### EXPOSURE People can get sick with resistant infections from...



### IMPACT Some resistant infections cause...





Learn more about antibiotic resistance and food safety at www.cdc.gov/foodsafety/antibiotic-resistance.html



NARES

National Antimicrobial Resistance Monitoring System: Enteric Bacteria

**A2012** S

**Human Isolates Final Report** 

#### Important Resistance Trends in 2011

- Ceftriaxone resistance among E. coli isolates from retail chicken increased from 8% in 2002 to 13% in 2011; ground turkey isolates showed a larger increase in resistance during the same time period (from 1% to 10%). There was a similar trend in Salmonella isolates.
- Ceftriaxone resistance among isolates from slaughtered chicken increased from 6% in 2000 to 12% in 2010, and then dropped slightly to 9% in 2011. This was the first decline observed in the last 3 years







# Seven Core Elements Critical to the Success of Hospital Antibiotic Stewardship Programs

- Leadership commitment: Dedicating necessary human, financial, and information technology resources
- Accountability: Appointing a single leader responsible for program outcomes.
   Experience with successful programs has shown that a physician leader is effective
- Drug expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours)
- Tracking: Monitoring antibiotic prescribing and resistance patterns
- Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff members
- Education: Educating clinicians about resistance and optimal prescribing

Source: CDC. Core elements of hospital antibiotic stewardship programs. Atlanta, GA: US Department of Health and Human Services, 2014. Available at <a href="http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html">http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html</a>

### AS — A CMS Condition of Participation (CoP)?

### CMS

- In 2015 plans to propose AS as a CoP, with implementation in 2017
- Challenge Permit flexibility based on size/resources (<a href="http://www.modernhealthcare.com/article/20141220/magazine/312209980">http://www.modernhealthcare.com/article/20141220/magazine/312209980</a>)
- Making AS a CoP "A Transformative Effect"?

### States

Only California mandates AS programs in hospitals

### Do we need "An antibiotic prenuptial agreement"?

 Antibiotic prescribing licenses, consequences for prescriber nonadherence, antibiotic time-outs (and/or auto-stops), out-reach (to prescriber and public) (Lancet Infect Dis 2014; 14:1168-9)

#### AS, Antimicrobial Stewardship

# Seeking the Holy Grail of Treatment

Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review

Rajender Agarwal<sup>1</sup> and David N. Schwartz<sup>2,3</sup>

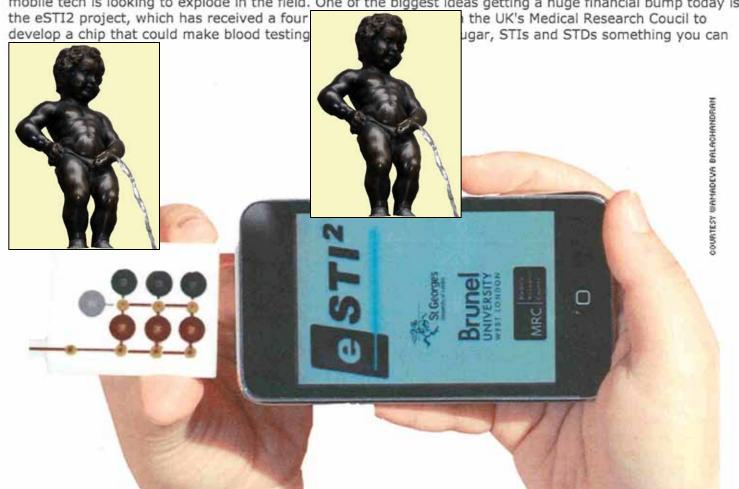
Procalcitonin guidance of antimicrobial duration appears to decrease antimicrobial use in the ICU safely and significantly and may also decrease the length of stay in the ICU.

of ICU stay was significantly decreased in 2 studies but was unchanged in the others. Neither infection relapse nor mortality varied significantly in any of the studies. Procalcitonin guidance of antimicrobial duration appears to decrease antimicrobial use in the ICU safely and significantly and may also decrease the length of stay in the ICU.

## NEEDED: Rapid Bedside Work-up — eDiagnosis

# eSTI2 project looks to develop blood testing chip for mobile devices

The mobile industry is making its way into a ton of fields and one area that it is becoming more and more influential is the medical field. From tablet implementation in hospitals to scheduling appointments online, mobile tech is looking to explode in the field. One of the biggest ideas getting a huge financial bump today is



# Bacterial Genetic Mechanism and Barriers for Resistance: **Traditional** Interventions

### **Mutations: Stewardship** (& Infection Control)

Imipenem-S P. aeruginosa — Imipenem — Imipen

### Gene Transfer: Infection control (& Stewardship)

Multi-S  $E.\ coli$  NDM-containing Klebsiella NDM-containing  $E.\ coli$ 

### Clonal Dissemination: Infection Control (& Stewardship)

MSSA — Methicillin "NEVER" MRSA

MRSA — Clonal Dissemination

### **High Barrier: Fate?**

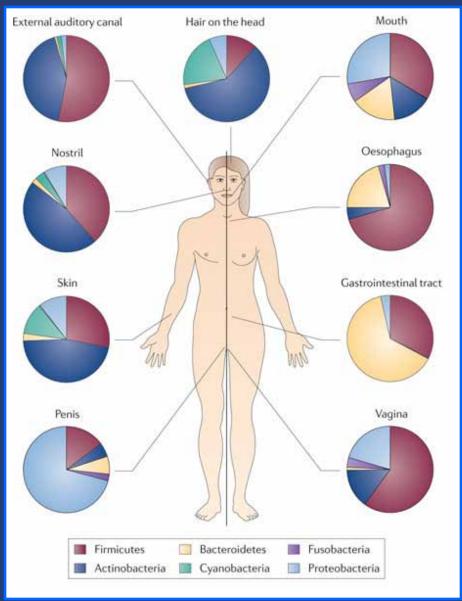
Grp A Strep 

→ Penicillin → No Pcn-R Grp A Strep (yet)

### Antibiotic Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae: Systematic Evaluation of the Available Evidence

- Twenty nonrandomized studies comprising 692 patients
- Almost all studies reported on *Klebsiella* spp. In 8 studies, majority of infections were bacteremias
- Clinical heterogeneity precluded meta-analysis
- Three studies (194 critically ill patients with bacteremia) showed lower mortality in the combination than in the monotherapy arms (mortality, ~50% to ~80%)
- Other studies showed no significant differences in mortality between the compared groups

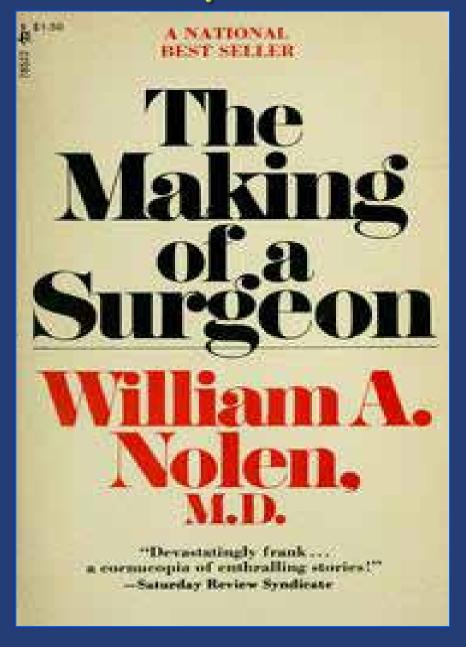
## NIH Human Microbiome Project



### WE ARE WHAT WE EAT?

- Gut Microbiomes of Malawian Twins Discordant for Kwashiorkor, *Science* 2013; 339:548-54
- Antibiotics Treat Malnutrition? N Engl J Med 2013; 368:425-35
- Intestinal Metabolism and Cardiac Risk, *N Engl J Med* 2013; 368:1575-84
- Gut Microbiota in Diabetes, *Nature* 2012; 490:55-60
- Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile, N Engl J Med 2013; 368:407-15

## Microbiome Manipulation — Not New



## Microbiome Manipulation to Control Resistance?

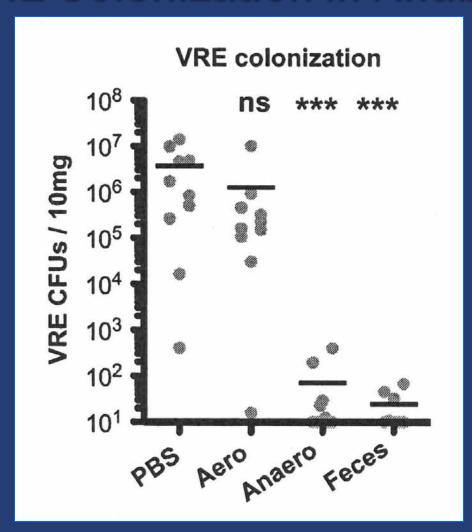
# Intestinal Microbiota Containing Barnesiella Species Cures Vancomycin-Resistant Enterococcus faecium Colonization

Carles Ubeda, a,e,f Vanni Bucci, b Silvia Caballero, a,e Ana Djukovic,f Nora C. Toussaint, a,e Michele Equinda, a,e Lauren Lipuma, a,c,e Lilan Ling, a,e Asia Gobourne, a,c,e Daniel No, a,c,e Ying Taur, a,c Robert R. Jenq, Marcel R. M. van den Brink, Joao B. Xavier, b,c Eric G. Pamera,c,e

Infectious Diseases Service, Department of Medicine,<sup>a</sup> Computational Biology Center,<sup>b</sup> Lucille Castori Center for Microbes, Inflammation and Cancer,<sup>c</sup> and Bone Marrow Transplant Service, Department of Medicine,<sup>d</sup> Memorial Sloan-Kettering Cancer Center, New York, New York, USA; Immunology Program, Sloan-Kettering Institute, New York, New York, USA<sup>c</sup>; Department of Genómica y Salud, Centro Superior de Investigación en Salud Pública, Valencia, Spain<sup>f</sup>

Bacteria causing infections in hospitalized patients are increasingly antibiotic resistant. Classical infection control practices are only partially effective at preventing spread of antibiotic-resistant bacteria within hospitals. Because the density of intestinal colonization by the highly antibiotic-resistant bacterium vancomycin-resistant Enterococcus (VRE) can exceed 10° organisms per gram of feces, even optimally implemented hygiene protocols often fail. Decreasing the density of intestinal colonization, therefore, represents an important approach to limit VRE transmission. We demonstrate that reintroduction of a diverse intestinal microbiota to densely VRE-colonized mice eliminates VRE from the intestinal tract. While oxygen-tolerant members of the microbiota are ineffective at eliminating VRE, administration of obligate anaerobic commensal bacteria to mice results in a billionfold reduction in the density of intestinal VRE colonization. 16S rRNA gene sequence analysis of intestinal bacterial populations isolated from mice that cleared VRE following microbiota reconstitution revealed that recolonization with a microbiota that contains Barnesiella correlates with VRE elimination. Characterization of the fecal microbiota of patients undergoing allogeneic hematopoietic stem cell transplantation demonstrated that intestinal colonization with Barnesiella confers resistance to intestinal domination and bloodstream infection with VRE. Our studies indicate that obligate anaerobic bacteria belonging to the Barnesiella genus enable clearance of intestinal VRE colonization and may provide novel approaches to prevent the spread of highly antibiotic-resistant bacteria.

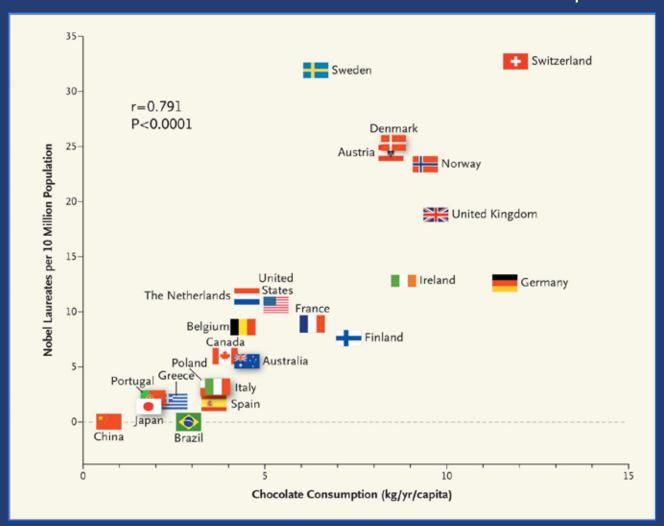
## Commensal Anaerobic Bacteria Suppress VRE Colonization in Antibiotic-treated Mice



Mice were infected with 108 VRE CFU after 1 week of ampicillin treatment. One day after infection, ampicillin treatment was stopped. Mice were orally gavaged for 3 consecutive days, starting 1 day after antibiotic cessation, with PBS, a suspension of fecal pellets from untreated mice (feces), or an aerobic (aero) or anaerobic (anaero) culture of fecal microbiota from untreated mice. Numbers of VRE CFU in the fecal pellets of infected mice were analyzed 5 weeks after infection (n 8 to 10). Limit of detection, 10 CFU/10 mg. \*\*\*, significantly different (*P*<0.001) from the PBS group; ns, not significant.

### Chocolate & Fecal Transplants – A "Ray Hogan Two-fer"

Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates Per 10 Million Population



## Social Network Analysis & Regional Control

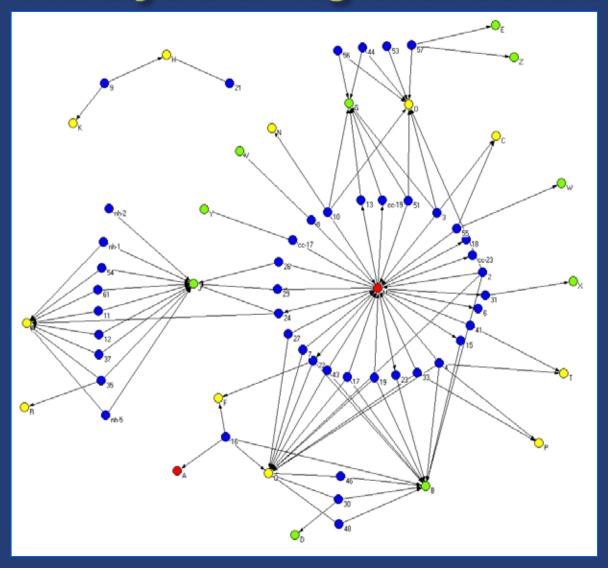
#### **Social Network**

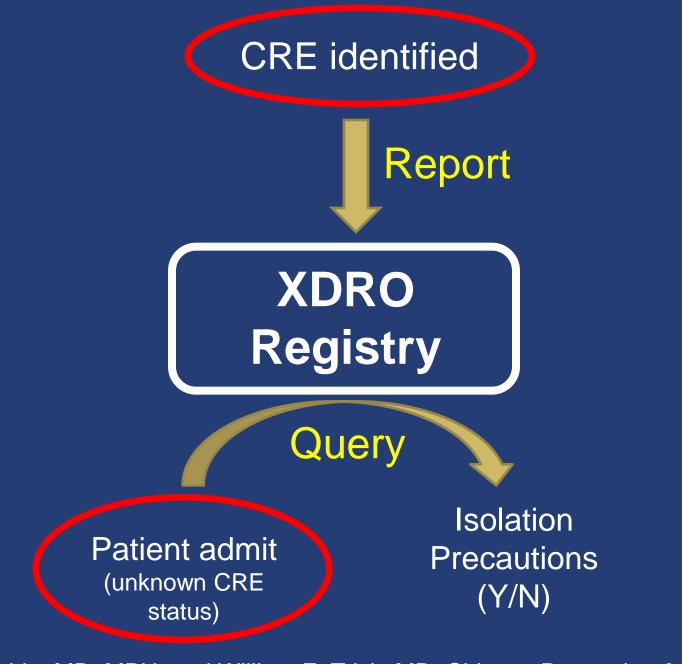
depiction of LTACH, Nursing Home, & Hospital spread of KPC (Carbapenem-resistant Klebsiella pneumoniae)

### Legend

- LTACH
- Nursing Home
- Acute Hospital
- Patient

LTACH, Long term acute care hospital; MDRO, Multi-drug resistant organism.

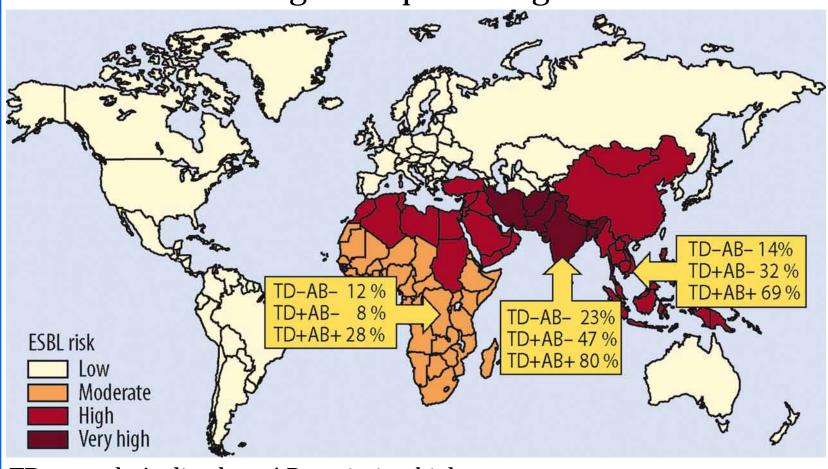




Michael Y. Lin, MD, MPH, and William E. Trick, MD, Chicago Prevention & Intervention Epicenter & IL Dept of Public Health

#### Antimicrobials Increase Travelers' Risk of

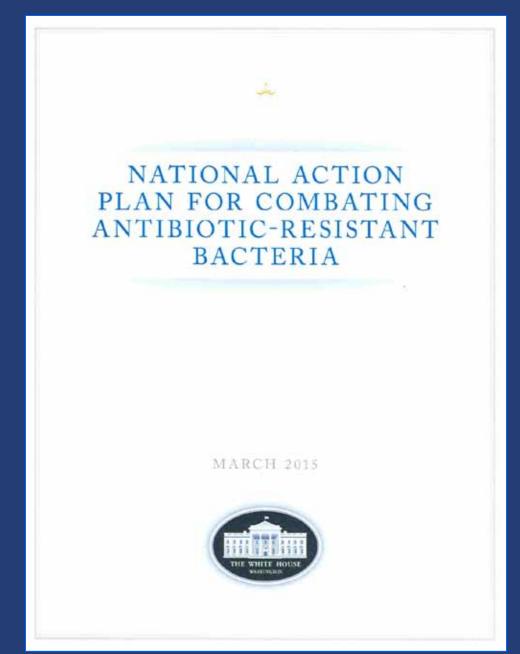




TD, traveler's diarrhea; AB, antimicrobials

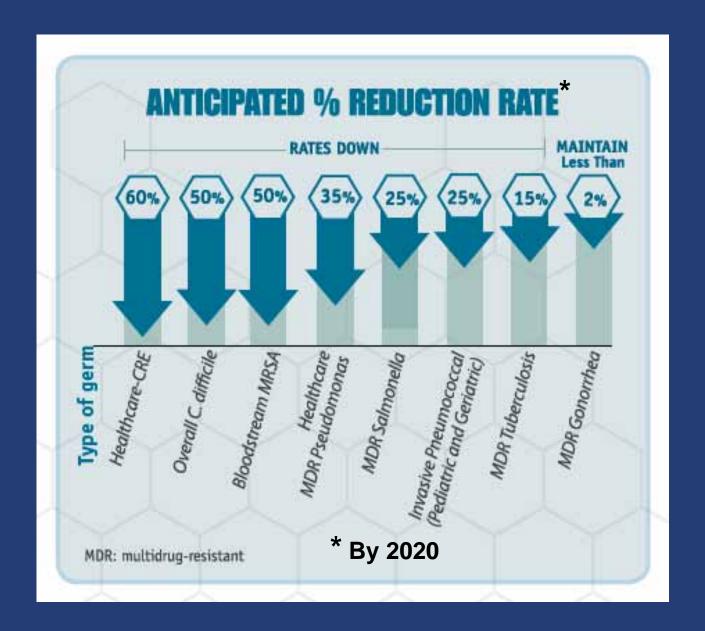
## Way Forward & Take Home Messages

- Epidemiology of resistance and control Much is known
- Problems
  - Motivating healthcare workers
  - Promoting judicious antibiotic use
  - Insuring regional and wider use of control measures
- Solutions
  - Continue to promote/monitor traditional and newer hospital control measures — And act Regionally
  - Federal mandates/support for in- and out-patient Antimicrobial Stewardship
  - Public Reporting; P4P & DRA/(carrot & stick)?
  - Better understanding and control of our microbiomes?
  - New National Action Plan



#### The National Strategy Identifies Five Core Actions:

- Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections
- Strengthen National One-Health Surveillance Efforts to Combat Resistance
- Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
- Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development



# Thank You (and Ray Hogan)

## Outbreak Management

it takes a village....



May 12, 2015

Linda Stein Marge Gribogiannis



## Objectives

Describe the steps in a CRE investigation.

 Explain the decision-making process for ERCP re-processing using a risk assessment/CDC/FDA guidelines

 Provide examples of CRE prevention strategies.



## Disclosures

Financial- No relevant financial relationship exists.

 Non financial- No relevant non-financial relationship exists.

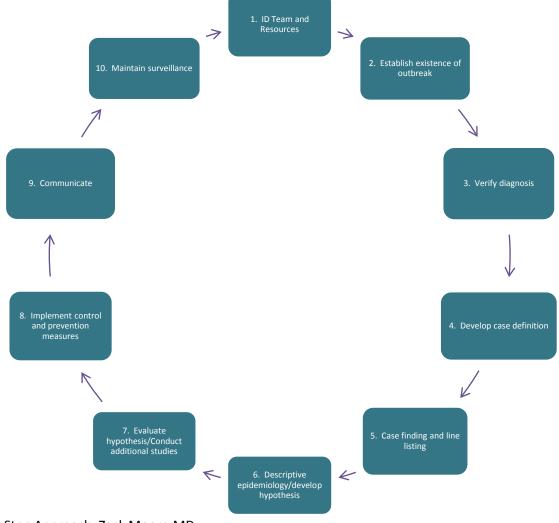
## Outbreak Investigation

#### **Principles**

- Be systematic
- Re-assess
- Coordinate with partners



## Outbreak Management Cycle





## Establish existence of outbreak

#### What made this an outbreak?

Over the course of one month:

- 3 readmissions with clinical CRE cultures
- Specimen source varied
- Organism metallo beta-lactamase positive
- Confirmed strain as NDM-1(Epidemiologically important pathogen)
- Eventually PFGE same



## Verify the Diagnosis

- Background
  - Diagnosis
  - Not lab error
  - Commonality
    - Possible cause
    - Source spread of disease

## Develop case definition

- Person, place & time
- Clinical information: characteristics, location, time

#### Case finding:

Any patient identified with specimens positive for Enterobacteriaceae metallo beta lactamase and/or a readmission history of GI procedure.



## Case finding & line listing

- Identification, clinical info, time, demographics, location, risk factors, possible causes
  - Patient
  - Sex
  - Age
  - Admit diagnosis
  - Admit date
  - Patient location
  - Previous admissions and room locations
  - Medical history (surgery, immuno-compromised)
  - Risk Factors (e.g. prior nursing home stay, roommate of other CRE patient, procedure, equipment)
  - Culture and date of collection
  - Treatment
  - Discharge status



## Descriptive epidemiology/ develop hypothesis

- Three patients were identified with specimens (e.g., urine, sputum,) positive for *E. coli*, New Delhi metallo beta-lactamase and history of GI lab procedure.
- Could this be related to specific procedure?
- ERCP/EUS?



## Evaluating the hypothesis

#### Infection prevention measures:

- Review department policy & procedure
- Observation practice
  - ERCP procedure (pre & post)
  - High level disinfection
- Bring in equipment manufacturers
- Review & observe Environmental Services procedure
- Environmental surveillance (transmission source)
- Education
- Epi-linked surveillance (unit-based surveillance)



## Epi-linked Active Surveillance Testing

- Develop "detect and protect" screening protocol
  - Engage your IP partners.(i.e. Nursing, IS, Physicians)-
  - Conduct bed-trace of patients
  - Provide education on CRE to both physicians and healthcare associates including specimen collection.
  - Provide patient education (SHEA MDRO FAQ)
  - Connect with Laboratory about testing
  - Follow up for any positive CRE screen results
  - Performed on various nursing units, & Epi-link ECF

## Unit based AST

- Informing the patients/families/physicians
- Conducted over various time frames of the investigation:
  - March , April, May, July
  - All hospital epi-linked cultures were reported as negative for CRE.

## Laboratory-Clinical Microbiology

Follow Clinical and Laboratory
Standards Institute guidelines
for susceptibility testing.



- Establish a protocol for detection of carbapenemase production (e.g. modified Hodge test)
- Use e-swab for collection. Lab will place swab in TSB broth with ertapenem and plate onto chromagar with meropenem. This will identify any CRE. Additional identification required to determine if CRE isolates are NDM-1 strain.
- Establish system to ensure prompt notification of IP staff of all CREs.

## Evaluate hypothesis & conduct additional studies

- Environmental culture found positive for *E.coli*, NDM-1 (ERCP Scope, specifically at the elevator platform)
- Epi-linked AST negative (No unit based transmission)
- Additional studies identified "rugged" surface inside ERCP scope elevator platform.

## Our initial Hypothesis

**Situation:** (4) NDM and (3) KPC patient cases were identified from varied specimens (e.g. blood, urine, sputum, wound) and readmission history of GI lab procedure, specifically same ERCP scope.

\*Elevator section with possible platform defect.



## Additional studies

Inside elevator platform (Magnified 100X)

#### **Actions taken:**

- √Scope A removed from service
- ✓ ALGH filed complaint with the FDA (SMDA)
- ✓ CCDPH/IDPH initiated EPI-AID from the CDC arrival-August 2013
- √Scope manufacturer notified of potential "defect"
- √ Scope A sent to CDC for investigation
- ✓ CDC partnering with (FDA) for guidance &recommendation
- ✓ Complete high level disinfection process reviewed.

Retrospective review and direct observation of endoscope reprocessing did not identify lapses in protocol.

Prevention steps taken: New scope purchased to replace scope A Next steps: Continue investigation- how & why related to the scope





## Implement control & prevention measures

- Re-reviewed department policies
  - -ERCP procedure
  - High level disinfection
- Re-review manufacturer recommendations.
- Repeat audit of Environmental Services cleaning process
- Engage manufacturers to audit associates performing process.
- Additional environment culture (Clean room & Storage unit)
- Epi-linked AST
- Education



### **CDC Partners**

#### Initial CDC findings:

- PFGE results of Cluster: genetically related.
- Suggesting that Hospital 1 was the source of transmission for many of the patients, with subsequent transmission at ECF between two roommates.
- CDC to conduct further analysis of Scope A (Confirmed positive isolate for NDM)



## **ERCP Specimen Collection**

#### NON-DESTRUCTIVE RECOVERY OF ENTERIC BACTERIA FROM DUODENOSCOPE

#### **Equipment**

#### **Materials and Reagents**

ERCP scope, post ETO sterilization Sterile gloves

E-swab (green top)

Plastic specimen transport bag

#### **Procedure:**

Note: Due to the length of the device, it is recommended that this sampling procedure be performed by two persons, with one holding the endoscope steady while the other manipulates it.

- Don sterile gloves.
- Using the endoscope controls, manipulate the last 1.5-2 inches of the tip several times.
- Swab the endoscope channel tip, and the elevator channel repeatedly with the E-swab, moving back and forth 15 times.
- Place swab in E-swab container. Label container accordingly.
- Complete lab requisition.
- Transport in plastic bag to laboratory. Hand-off to Microbiology Tech.



## Elevator mechanism - distal tip



### Communication

- Patient Notification of all who had ERCP procedures with Scope A
- IP Resources: Administration, Risk Management, Public Relations, CCDPH,IDPH, CDC
  - Weekly conference calls
- Deliver consistent message to public
- Ensure any patients screened positive are informed, verbally and in writing.



## Community Outreach

- Transparency
- Contacting patients/outreach to patients in ECFs
- IP resources included Post Acute Network, CCDPH to follow up on screening patients discharged to LTCFs.
- Additional mailings to patients who did not respond with first letter sent by certified mail.



## Evaluate hypothesis\*

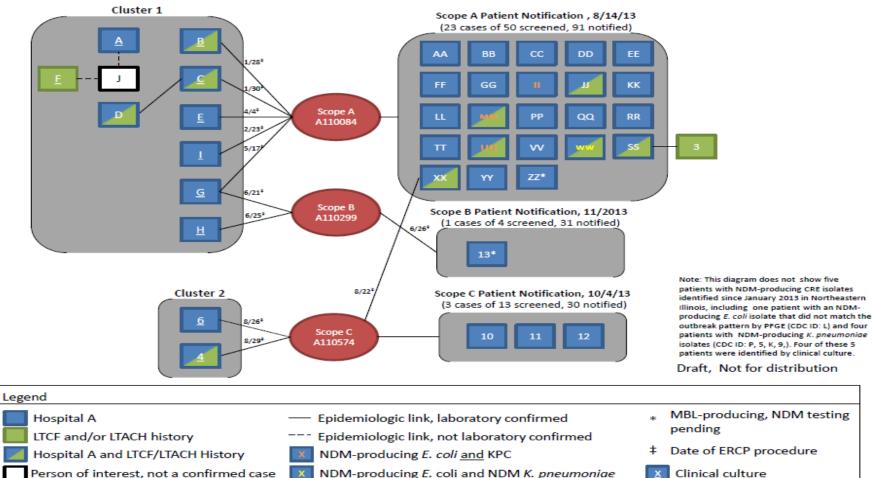
- A patient who had an ERCP with scope "C" had a positive culture for *E.coli MBL* (metallo beta lactamase). This was the second case identified with the same source scope.
- There was a one month period of no discernible transmission between cluster 1 associated with scope "A" and cluster 2 associated with scope "B".

#### \* New Hypothesis:

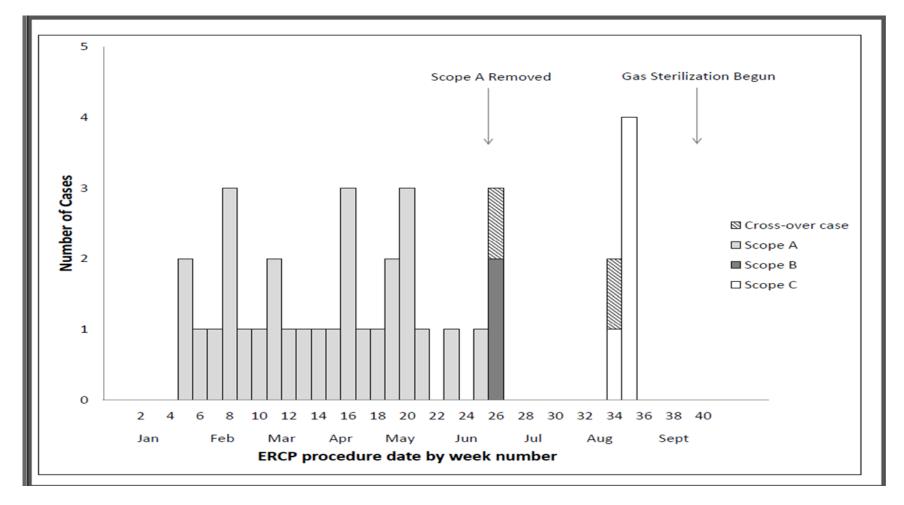
We have a repeated instance of another new scope associated with *E.coli MBL*, this would imply the source of the biofilm may be located within the integral components of the AER (automated endoscope reprocessor) which functions to wash and disinfect the scopes.

## **CRE Network Diagram**

Network diagram of NDM-producing E. coli cases and person of interest, January 1 – December 11, 2013 — Northeastern Illinois



## **Epi Curve- Scopes**



## Infection Control Measures

- Manufacturer product evaluation of our AER equipment.
- Review manufactures recommendation of products (detergent, disinfectant)
- AER bay, detergent and alcohol lines bleached.
- Performed environmental surveillance cultures of AER reservoir holding tanks and filters.
- Patient notification
- Moved from HLD to sterilization with ETO (ethylene oxide).
- ERCP scopes post sterilization were cultured.
- Repeat audit of ERCP patient procedure (pre, during and post)
- Repeat audit of Environmental Services protocol.
- Prior to ERCP procedure, conduct AST CRE screening.

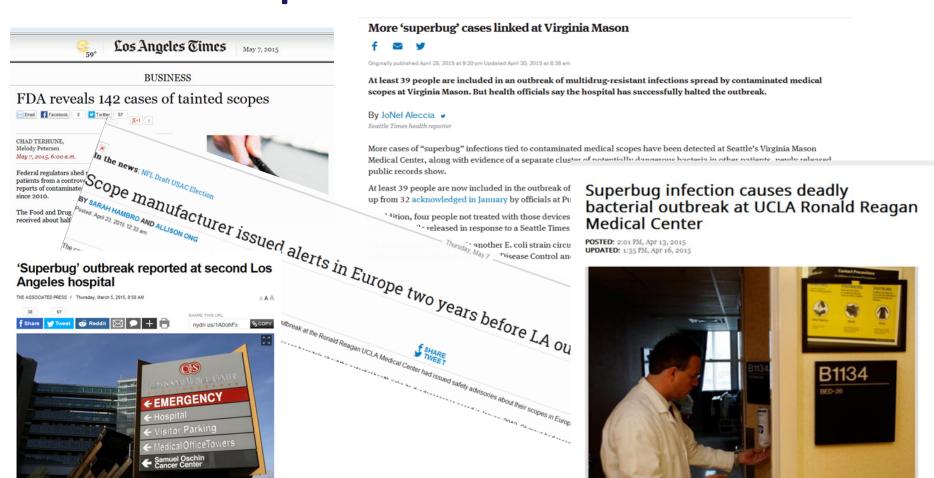


## Final Hypothesis\*

- Inability to effectively High Level Disinfect ERCP scopes.
- Challenges related to equipment design, impacting the cleaning and disinfection process. (i.e.) Service, maintenance, length of time device kept in service.
- Options for alternative methodologies to ensure equipment is safe for patients.



## Over the past 6 months...



The Bacteria Will See You Now: How Little Bugs Create Big Problems in Hospitals

Healthline News



## Searching for a solution...

- FDA Safety Communication ... Feb 19, 2015
  - Design of Endoscopic Retrograde cholangiopancreatography (ERCP) duodenoscopes may impede effective cleaning.
- ECRI Institute: High Priority Hazard Report March 3 #8 on ECRI's Top 10 Patient Safety Concerns for Healthcare Organizations 2015
- American Gastroenterological Association (AGA),
   FDA,CDC, ECRI and endoscope manufacturers meet on March 30, 2015



### To test or not to test.....

#### CDC Interim Duodenoscope surveillance protocol, March 11, 2015

 Routine culturing of endoscopes is not part of current U.S. guidelines, recent outbreaks associated with duodenoscopes have led some facilities to <u>consider regular monitoring</u> to assess the adequacy of duodenoscope reprocessing

## ASM, The Question of Culturing of Duodenoscopes, April 2015

- little to no data that document the performance of this culture method for either routine practice, or periodic validation of duodenoscope reprocessing practices
- At this time, it <u>seems clinical microbiology labs should not perform</u>
   <u>routine cultures</u> of reprocessed duodenoscopes due to lack of data on
   utility of such culturing.
- If culturing is deemed necessary as part of an outbreak investigation, consider sending to an appropriate reference lab.

  Advocate Health Care

## Ongoing CRE Prevention Strategies

- Surveillance: CRE alert using data mining system
- Reporting: XDRO registry
- Develop a comprehensive QC Program
  - Visual inspection
  - Cleaning verification (ATP, Protein, bioburden)
  - On a monthly basis, each ERCP/EUS endoscope will be cultured specifically for CRE
  - Follow the method described in obtaining samples for culture using the E-swab.(1) swabs from each ERCP & EUS scope
    - Elevator up & down position
- Patient Education & Consent



## CRE prevention strategies

#### Competency (Pre-cleaning, manual cleaning & HLD)

- Written standardize competency upon hire, change in process and annually.
- Observed competency(demonstration) upon hire, change in process and bi-annually.

#### **Traceability**

- Able to identify scope to patient for every procedure
- One hour time frame from end of procedure to reprocessing. If this cannot be met then scope should be flushed with enzymatic and soaked for one hour
- Ability to identify who cleaned & reprocessed scopes
- Infection Prevention will trace all new +CRE clinical cultures to determine if ERCP/EUS performed.



## CRE prevention strategies

- Notification of positive culture
  - Notify site IP (Outbreak management plan)
  - Sequester scope Notify Risk Management
  - Positive culture will result in sequester scope (should not be returned to service until 2 negative cultures are obtained-this is a minimum of 4-6 days)
  - Complete SMDA (Safe Medical Devise Act)
  - Notify Manufacturer
  - Begin outbreak management process
- GI lab to maintain record of culture results
- Resource: <a href="http://www.cdc.gov/hai/outbreaks/index.html">http://www.cdc.gov/hai/outbreaks/index.html</a>



## Lessons Learned

- Keep a log/diary of investigation (timeline)
- Senior leadership is essential (resource allocation)
- Developing & performing a risk assessment is key
  - Standardization of products
  - Competency/education
  - Maintenance/inspection
  - Prevention strategies
- Renewed respect for associates dedicated to doing this job, every day.
- It truly does take a village......



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   &zidType=CH&zid=9379886&zsubscriberId=93268278&zbdom=http://www.informz.net

