Antibiotic Resistance: Trends and Emerging Organisms

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My apologies…

Disclosures

- Research support – bioMerieux, Becton Dickinson, BioFire, Nanosphere
- Consulting – ThermoFisher


PANEL 23

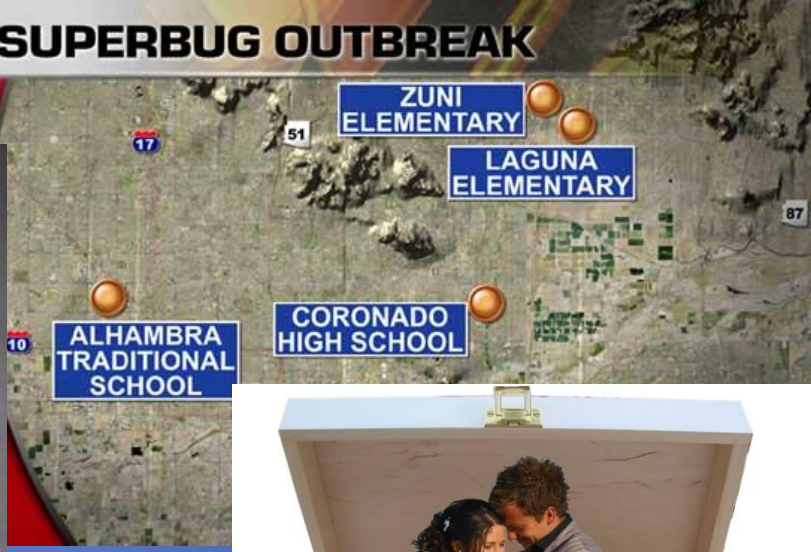
Drug-resistant 'superbug' traced to India

May Hit Medical Tourism, Fear Docs

Pushpa Narayan | TNN

Germ Threat

Chennai: Scientists have



Centers for Disease Control and Prevention
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A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Safe Healthcare

Hosted by CDC's Division of Healthcare Quality Promotion

Preventing Infections in Healthcare Settings > Safe Healthcare

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NDM-1: New Route, Same Destination - Untreatable Infections

Categories: Antimicrobial Resistance, Gram negatives, Healthcare-associated infections

September 17th, 2010 3:24 pm ET - .

Author – ***Brandi Limbago, PhD***
CDC's Division of Healthcare Quality Promotion


Brandi Limbago, PhD

You've likely seen the news over the last couple of weeks warning people about "The [so-called] New Superbug NDM-1," a newly discovered gene that makes bacteria resistant to last-resort antibiotics called beta-lactams or carbapenems. NDM stands for New Delhi Metallo-beta-lactamase, and in this case the NDM gene rendered antibiotics useless in three cases of infection with carbapenem-resistant *Enterobacteriaceae* (CRE). CDC discovered NDM-1 in the United States this year and reported it through the MMWR in June. Is it concerning? Absolutely; and we are working closely with healthcare providers and health departments to stop transmission of these bacteria.

That said, I'd like to point out that the story shouldn't be solely about these bacteria being new or imported from other countries; the story should be about the whole group of CRE and untreatable infections they cause. In reality, these are not the first CRE cases we've seen in the United States. Not even close. NDM-1 is actually just one type of CRE and represents a larger antibiotic resistance issue that we already have, right now, in this country. CDC has been working with partners to prevent a type of CRE known as KPCs (carbapenemase-


News

The rise of the superbug

SGH's Director of Infection Control clues us in on the importance of simple hygiene habits to combat the superbug

BY JACQUELINE DIA

Combating the deadly superbug is a responsibility everyone must share by practising good hygiene habits, the transmission of the bacteria, said Dr Ling Mei Lin (below), Director of Infection Control, Singapore General Hospital.

Running out of time

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Officials alarmed by increasing superbug reports

March 6, 2013 8:23 AM

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(AP Photo)

NEW YORK (AP) – Health officials are reporting an alarming increase in some dangerous superbugs at U.S. hospitals.

These superbugs from a common germ family have become extremely resistant to treatment with antibiotics. Only 10 years ago, such resistance was hardly ever seen in this group.

Infections from these superbugs are still uncommon. But in the first six months of last

Goals

- Things you will not hear about…
  - MRSA
  - VRE
- Things you will hear about…
  - Common Mechanisms of Gram negative resistance – ESBL's vs. AmpC's
    - And why you should care.
  - Vancomycin Resistant *Staphylococcus aureus*
    - And why you shouldn't care.
  - The Untreatable Gram negative Infection

Empiric Antibiotic Therapy

- When a patient is suspected of having infection and a physician must guess and treat according to the most likely etiologies.
  - Typically empiric therapy will cover for the most likely Gram positive and Gram negative agents.

Let's talk about some options for the empiric treatment of blood stream infection…

What are you covering and what aren't you covering?

1. Vancomycin?
2. Vancomycin and Ampicillin?
3. Vancomycin and 3rd generation cephalosporin?
4. Vancomycin and cefepime?
5. Vancomycin and carbapenem?

Gram positive empiric therapy is easy.
Gram negative empiric therapy is challenging and dependent on local epidemiology

Gram Negative Mechanisms of Resistance

The Big Three Beta-Lactamases

1. Carbapenemases
   - *Klebsiella pneumoniae* Carbapenemases (KPC)
   - New Delhi Metallo Beta-Lactamases (NDM-1)
2. Extended Spectrum Beta Lactamases (ESBL's)
3. Class C cephalosporinases (AmpC)

Beta-Lactamase Resistance Patterns

Beta-Lactamase	1st Gen. Cephs	2nd Gen. Cephs	Cephamycins	3rd Gen. Cephs	4th Gen. Cephs (Cefepime)	Carbapenems	Monobactams	Beta-Lactamase Inhibitor Effective?
KPC	Resistant	Resistant	Variable	Resistant	Resistant	Resistant	Resistant	Weakly
NDM-1	Resistant	Resistant	Resistant	Resistant	Resistant	Resistant	Susceptible	No
Low Level AmpC	Variable	Susceptible	Susceptible	Susceptible	Susceptible	Susceptible	Susceptible	No
Hyper-produced AmpC	Resistant	Resistant	Resistant	Resistant	Susceptible	Susceptible	Resistant	No
ESBL	Resistant	Resistant	Susceptible	Resistant	Variable	Susceptible	Resistant	Yes

Gram negative Beta-Lactam Resistance: In North Texas

What is the difference between an AmpC and an ESBL

ESBLs

- Class A
- BLI Inhibited - **YES**
- Plasmid – **YES**
- Chromosome - **NO**
- Inducible - **NO**

- Organisms
  - All *Enterobacteriace*

AmpC

- Class C
- BLI Inhibited - **NO**
- Plasmid - **YES**
- Chromosome - **YES**
- Inducible - **YES**
  - Only on Chromosome
  - Constitutively ON when plasmid borne
- Organisms
  - Chromosome – SPACE
  - Plasmid – Non-SPACE *Enterobacteriaceae*

CTX-M ESBLs

- MIC's to cefotaxime > ceftazidime
- Aztreonam variable
- Efficiently hydrolyze **cefepime**
  - In contrast to other ESBLs
- Tazobactam > clavulanic acid
- Currently rare but emerging in North America but most common world wide.
  - Associated with community acquisition

CTX-M Profiles from the US

TABLE 2. *IN VITRO* ACTIVITY OF SELECTED ANTIMICROBIAL AGENTS TESTED AGAINST 67 CTX-M-PRODUCING ENTEROBACTERIACEAE ISOLATES

	CTX-M producing isolates (number of strains)								
	All Enterobacteriaceae (67)[a]			Escherichia coli *(51)*			Klebsiella pneumoniae *(13)*		
Antimicrobial agent	MIC_{50}	MIC_{90}	*% susceptible/ resistant*[b]	MIC_{50}	MIC_{90}	*% susceptible/ resistant*[b]	MIC_{50}	MIC_{90}	*% susceptible/ resistant*[b]
Cefepime	>16	>16	28.4/56.7	>16	>16	33.3/52.9	>16	>16	7.7/76.9
Ceftazidime	16	>16	34.3/61.2	16	>16	35.3/58.8	>16	>16	15.4/84.6
Ceftriaxone	>32	>32	1.5/98.5	>32	>32	1.9/98.1	>32	>32	0.0/100.0
Piperacillin/tazobactam	16	>64	65.7/17.9	16	64	72.5/9.8	>64	>64	38.5/53.8
Imipenem	0.25	0.5	95.5/0.0	0.25	0.25	100.0/0.0	0.25	0.5	92.3/0.0
Meropenem	≤0.12	≤0.12	98.5/1.5	≤0.12	≤0.12	100.0/0.0	≤0.12	0.25	92.3/7.7
Gentamicin	≤4	>8	58.2/37.3	≤4	>8	64.7/31.4	>8	>8	38.5/61.5
Tobramycin	>8	>8	31.3/52.2	>8	>8	31.4/54.9	8	16	23.1/46.2
Ciprofloxacin	>2	>2	7.5/92.5	>2	>2	2.0/98.0	>2	>2	15.4/84.6
Levofloxacin	>4	>4	9.0/89.6	>4	>4	2.0/96.1	>4	>4	23.1/76.9
Tigecycline[c]	0.25	1	100.0/0.0	0.25	0.25	100.0/0.0	0.5	2	100.0/0.0

[a]Includes *E. coli* (51 strains), *K. pneumoniae* (13 strains), *K. oxytoca* (1 strain), *P. vulgaris* (1 strain), and *P. mirabilis* (1 strain).

[b]Breakpoint criteria as published by the CLSI [2010] (susceptibility/resistance in μg/ml): cefepime ≤8/≥32, ceftriaxone ≤1/≥4, ceftazidime ≤4/≥16, piperacillin/tazobactam ≤16/4/≥128/4, imipenem ≤1/≥4, meropenem ≤1/≥4, gentamicin ≤4/≥16, tobramycin ≤4/≥16, ciprofloxacin ≤1/≥4, and levofloxacin ≤2/≥8.

[c]U.S. Food and Drug Administration breakpoints were applied.[13]

Just down

- CTX-M's are now the predominant ESBL

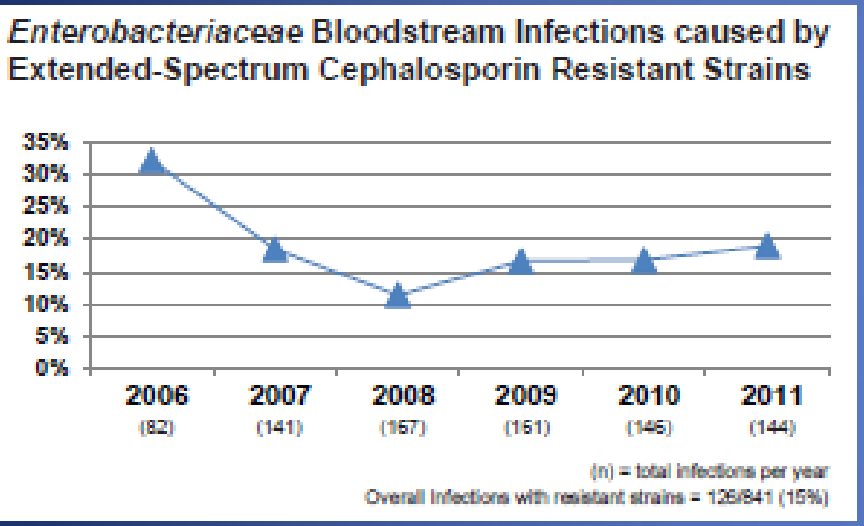
TABLE 3. Number of ESBL-producing isolates by year of isolation, organism, and type of enzyme

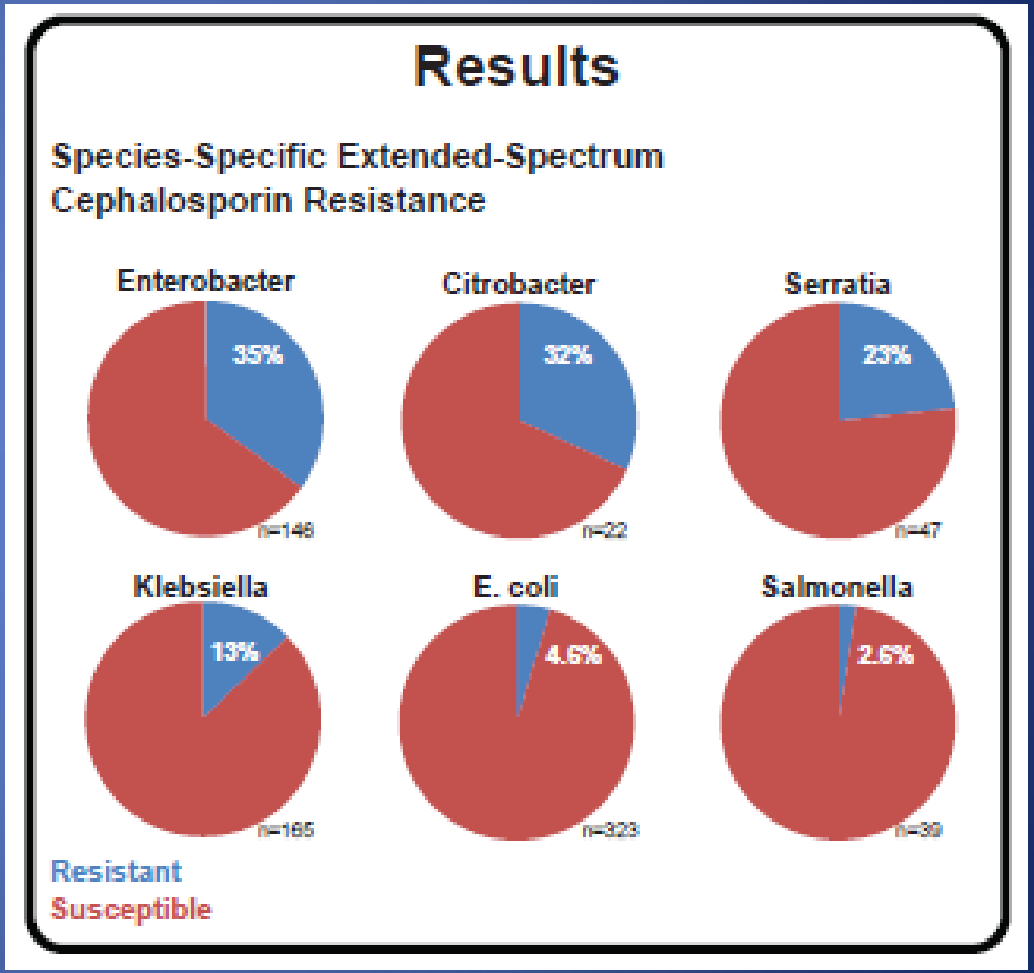
Yr and organism	No. of isolates producing:			
	CTX-M	TEM	SHV	CTX-M + SHV
2000				
E. coli	0	0	0	1
K. pneumoniae	0	0	1	0
K. oxytoca	0	1	1	0
2001				
E. coli	0	0	2	1
K. pneumoniae	0	0	4	0
K. oxytoca	0	0	3	0
2002				
E. coli	0	0	2	0
K. pneumoniae	0	0	3	0
E. cloacae	0	0	1	0
2003				
E. coli	3	1	0	0
K. pneumoniae	0	0	3	0
K. oxytoca	3	0	0	0
2004				
E. coli	8	0	2	0
K. pneumoniae	0	0	1	1
E. cloacae	0	0	1	0
2005				
E. coli	8	0	0	0
K. pneumoniae	1	0	1	0
K. oxytoca	4	0	1	1
Enterobacter spp.	2	0	0	0
2006 (first 6 mo)[a]				
E. coli	12	0	2	1
K. pneumoniae	1	0	6	2
K. oxytoca	1	0	0	0
M. morganii	1	0	0	0
P. mirabilis	1	0	0	0

[a] 27 isolates were recovered in this time.

Lewis et al. 2007. AAC

Breakdown of 3rd Generation Cephalosporin Resistance in BSI



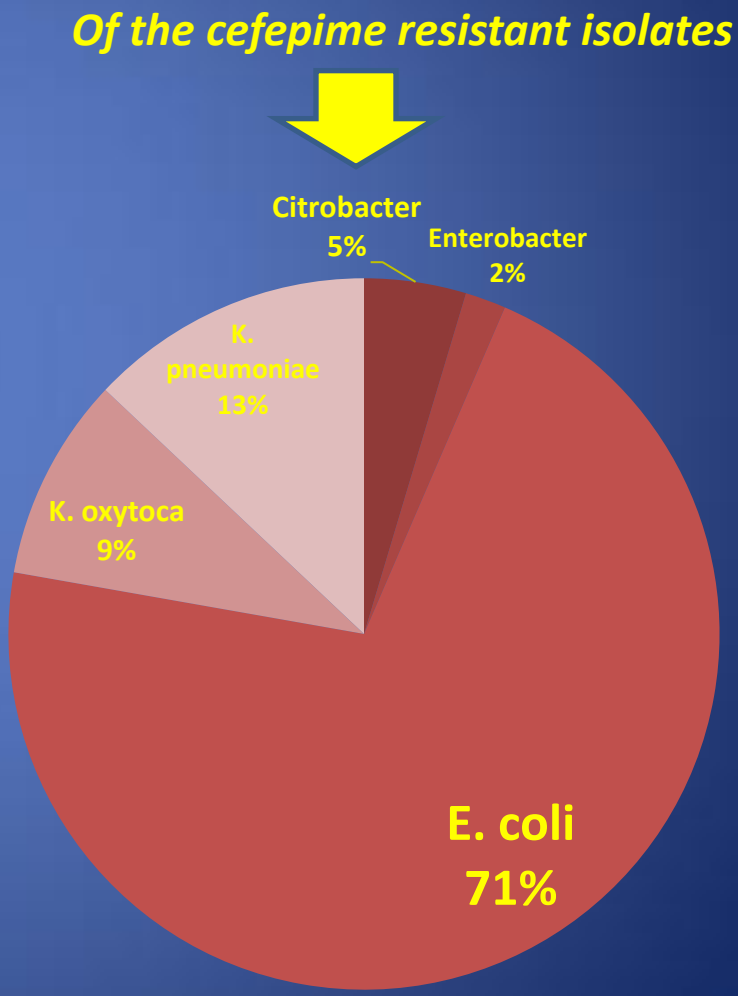


Data from Children's Medical Center

What types of infections do ESBL producing organisms cause at CMC?

1. IC – 33%
2. Urine – 51%
3. Blood – 9%
4. Respiratory – 3%

Other – Ear (2), Wound (4), Body fluid (3), CSF (1), Abscess (2)



Remember S.P.A.C.E. for inducible chromosomal *ampC* carriers

- S- *Serratia*
- P- *Pseudomonas aeruginosa* and *Proteus*-like organisms including *Providencia* and *Morganella.*
- A- *Aeromonas/Acinetobacter*
- C- *Citrobacter*
- E- *Enterobacter*

Conspicuous by their absence…

Notable *Enterobacteriaceae* that lack a chromosomal *ampC* gene

- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Proteus mirabilis*
- *Salmonella* spp.
- *Citrobacter koseri*
- *E. coli***

The catch: *ampC* genes also exist on transmissible plasmids

Epidemiology of *ampC*

Organism	Inducible *ampC* (%)	Constitutive *ampC* (%)	Total *ampC* (%)
P. aeruginosa	115/134 (85.5)	15/134 (11.2)	130/134 (97.0)
Citrobacter spp.	10/13 (76.9)	1/13 (7.7)	11/13 (84.6)
S. marcescens	12/13 (92.3)	0/13 (0)	12/13 (92.3)
Enterobacter spp.	34/40 (85)	6/40 (15)	40/40 (100)

- High percentage of SPACE organisms possess *ampC.*
- Reflexively make all SPACE organisms resistant to beta-lactam antibiotics up through 3rd generation cephelosporins

Dunne *et al*. 2005. *J. Clin. Microbio*.

Selecting for Stably Derepressed AmpC's

Table 7. Mutant selection

Good selectors	Poor selectors
Second- and third-generation cephalosporins	Carbapenems
Aztreonam	Cephamycins
	First- and fourth-generation cephalosporins
	Penicillins

TABLE 4. Emergence of resistance during therapy

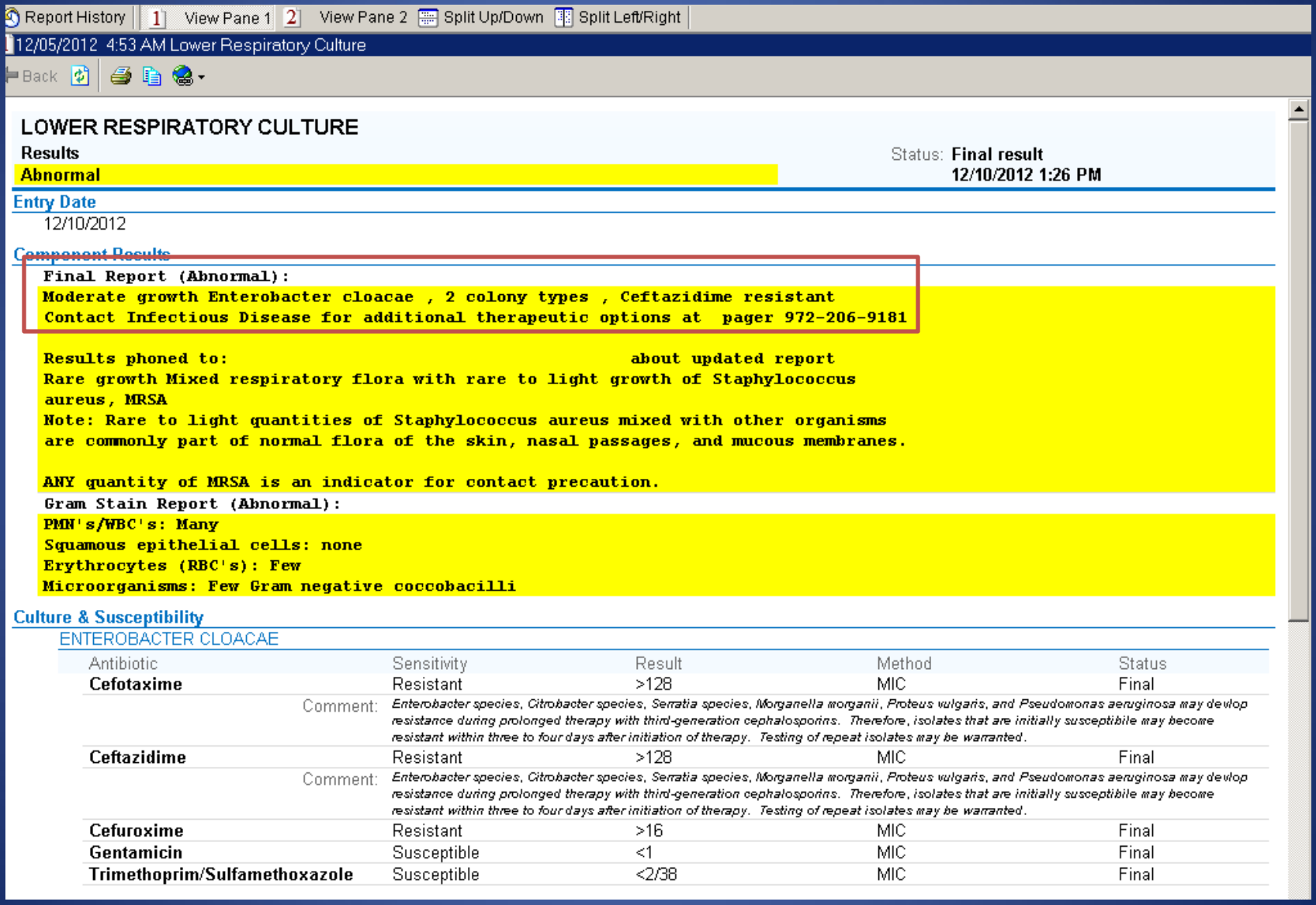
Characteristic	No. of patients with emergence of resistance to the therapy/total no. of patients in the group (%)	
	All patients	Patients with bacteremia
Overall	14/732 (1.9)	5/202 (2.5)
Antimicrobial agent		
Broad-spectrum cephalosporin	11/218 (5.0)	4/54 (7.4)
Cefepime	0/20 (0)	0/6 (0)
Extended-spectrum penicillin	2/100 (2.0)	1/18 (5.6)
Carbapenem	0/226 (0)	0/98 (0)
Ciprofloxacin	0/153 (0)	0/27 (0)
Aminoglycoside	1/89 (1.1)	0/22 (0)
Organism		
Enterobacter spp.	13/443 (2.9)	5/125 (4.0)
E. cloacae	10/287 (3.5)	2/88 (2.3)
E. aerogenes	3/143 (2.1)	3/32 (9.4)
E. agglomerans	0/11 (0)	0/4 (0)
E. asburiae	0/2 (0)	0/1 (0)
C. freundii	1/130 (0.8)	0/34 (0)
S. marcescens	0/113 (0)	0/33 (0)
M. morganii	0/46 (0)	0/10 (0)

- Extended spectrum **cephalosporins** but NOT **cefepime** nor **carbapenems** selected for resistance.
- *Enterobacter* most likely to develop resistance
- **5%** of patients treated with broad spectrum cephalosporin developed resistance
- Treatment time to resistance = AVG 7 days (range 3-28 days)

Moland *et al*. Clin. Micro. Newsletter. 2008

Choi *et al*. AAC. 2008

A recent example from CMC



Report History | 1 View Pane 1 | 2 View Pane 2 | Split Up/Down | Split Left/Right

12/05/2012 4:53 AM Lower Respiratory Culture

Back

LOWER RESPIRATORY CULTURE

Results

Abnormal

Status: **Final result**
12/10/2012 1:26 PM

Entry Date

12/10/2012

Component Results

Final Report (Abnormal):
Moderate growth Enterobacter cloacae , 2 colony types , Ceftazidime resistant
Contact Infectious Disease for additional therapeutic options at pager 972-206-9181

Results phoned to: about updated report
Rare growth Mixed respiratory flora with rare to light growth of Staphylococcus aureus, MRSA
Note: Rare to light quantities of Staphylococcus aureus mixed with other organisms are commonly part of normal flora of the skin, nasal passages, and mucous membranes.

ANY quantity of MRSA is an indicator for contact precaution.

Gram Stain Report (Abnormal):
PMN's/WBC's: Many
Squamous epithelial cells: none
Erythrocytes (RBC's): Few
Microorganisms: Few Gram negative coccobacilli

Culture & Susceptibility

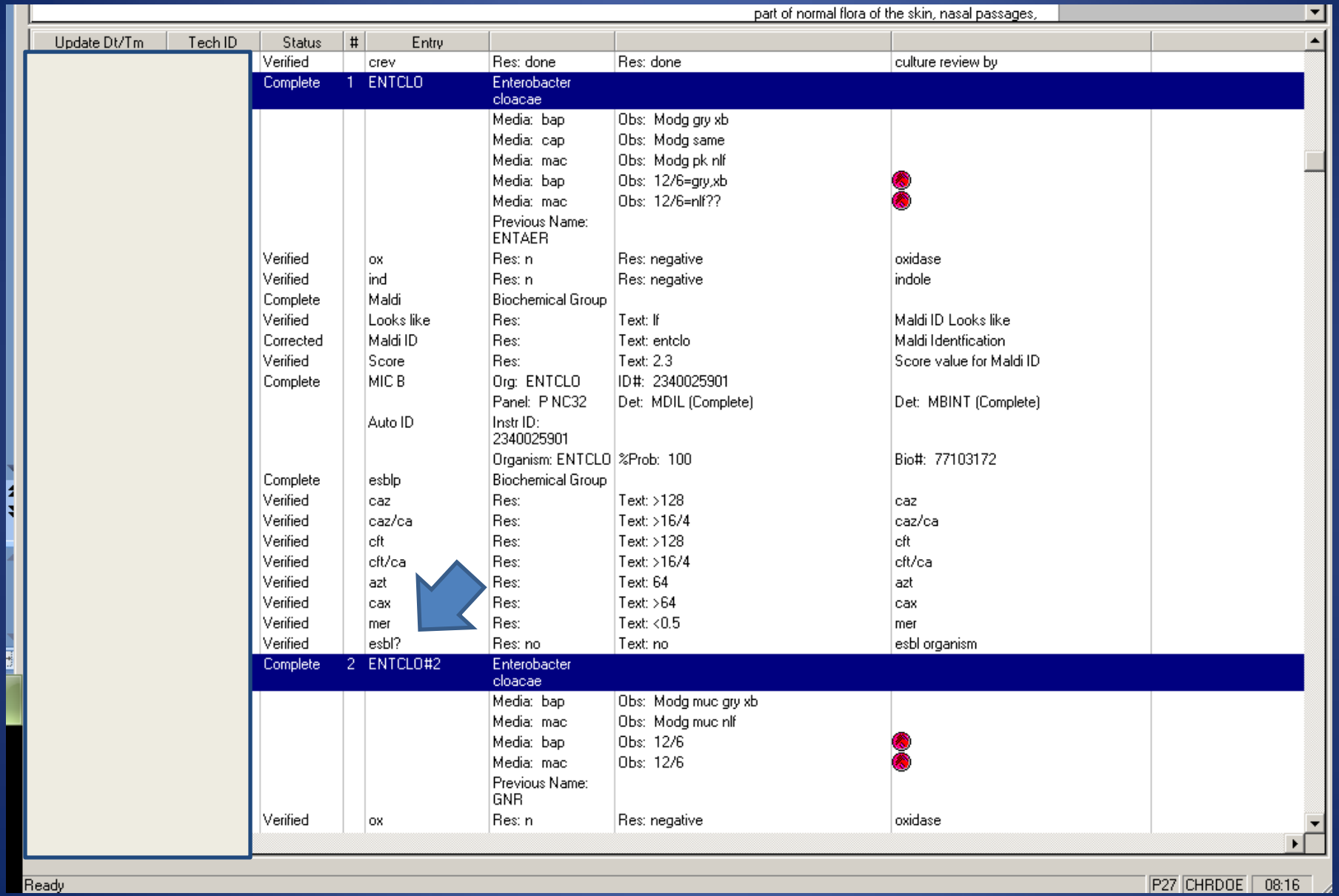
ENTEROBACTER CLOACAE

Antibiotic	Sensitivity	Result	Method	Status
Cefotaxime	Resistant	>128	MIC	Final
Comment:	*Enterobacter species, Citrobacter species, Serratia species, Morganella morganii, Proteus vulgaris, and Pseudomonas aeruginosa may develop resistance during prolonged therapy with third-generation cephalosporins. Therefore, isolates that are initially susceptibile may become resistant within three to four days after initiation of therapy. Testing of repeat isolates may be warranted.*			
Ceftazidime	Resistant	>128	MIC	Final
Comment:	*Enterobacter species, Citrobacter species, Serratia species, Morganella morganii, Proteus vulgaris, and Pseudomonas aeruginosa may develop resistance during prolonged therapy with third-generation cephalosporins. Therefore, isolates that are initially susceptibile may become resistant within three to four days after initiation of therapy. Testing of repeat isolates may be warranted.*			
Cefuroxime	Resistant	>16	MIC	Final
Gentamicin	Susceptible	<1	MIC	Final
Trimethoprim/Sulfamethoxazole	Susceptible	<2/38	MIC	Final

Panel: (All) Organism: ENTCLO

	P NC32	F	M	A	D	MDIL	Status	M	A	D	MBINT	Status
	A Generic					**NR**	Verified				**N/R**	Verified
	A Isolate						Pending					Pending
	A A/S					**>16/8**	Verified				**R**	Verified
	A Ak					**<4**	Verified				**S**	Verified
	A Am	f				**>16**	Verified				**R**	Verified
	A Azt					**>16**	Verified					Pending
	A Cax	f				**>64**	Verified				**R**	Verified
	A Caz	f				>128	Verified		@		R	Verified
	A Cft	f				>128	Verified				R	Verified
	A Cfz	f					Pending					Pending
	A Cp					**<1**	Verified				**S**	Verified
	A Cpe					**4**	Verified				**S**	Verified
	A Crm	f				>16	Verified				R	Verified
	A Ctn					**>32**	Verified				**R**	Verified
	A Gm					<1	Verified				S	Verified
	A Imp					**<4**	Verified				**S**	Verified
	A Lvx					**<2**	Verified				**S**	Verified
	A Mer					**<4**	Verified				**S**	Verified
	A Mxf					**<2**	Verified				**S**	Verified
	A Pi					**>64**	Verified				**R**	Verified
	A P/T					**>64**	Verified				**R**	Verified
	A T/S					<2/38	Verified				S	Verified
	A Tim					**>64**	Verified				**R**	Verified
	A To					**<1**	Verified				**S**	Verified
	A Esbl-a						Pending					Pending
	A Esbl-b						Pending					Pending

Behind the scenes



part of normal flora of the skin, nasal passages,

Update Dt/Tm	Tech ID	Status	#	Entry			
		Verified		crev	Res: done	Res: done	culture review by
		Complete	1	ENTCLO	Enterobacter cloacae		
					Media: bap	Obs: Modg gry xb	
					Media: cap	Obs: Modg same	
					Media: mac	Obs: Modg pk nlf	
					Media: bap	Obs: 12/6=gry,xb	
					Media: mac	Obs: 12/6=nlf??	
					Previous Name: ENTAER		
		Verified		ox	Res: n	Res: negative	oxidase
		Verified		ind	Res: n	Res: negative	indole
		Complete		Maldi	Biochemical Group		
		Verified		Looks like	Res:	Text: lf	Maldi ID Looks like
		Corrected		Maldi ID	Res:	Text: entclo	Maldi Identfication
		Verified		Score	Res:	Text: 2.3	Score value for Maldi ID
		Complete		MIC B	Org: ENTCLO	ID#: 2340025901	
					Panel: P NC32	Det: MDIL (Complete)	Det: MBINT (Complete)
				Auto ID	Instr ID: 2340025901		
					Organism: ENTCLO	%Prob: 100	Bio#: 77103172
		Complete		esblp	Biochemical Group		
		Verified		caz	Res:	Text: >128	caz
		Verified		caz/ca	Res:	Text: >16/4	caz/ca
		Verified		cft	Res:	Text: >128	cft
		Verified		cft/ca	Res:	Text: >16/4	cft/ca
		Verified		azt	Res:	Text: 64	azt
		Verified		cax	Res:	Text: >64	cax
		Verified		mer	Res:	Text: <0.5	mer
		Verified		esbl?	Res: no	Text: no	esbl organism
		Complete	2	ENTCLO#2	Enterobacter cloacae		
					Media: bap	Obs: Modg muc gry xb	
					Media: mac	Obs: Modg muc nlf	
					Media: bap	Obs: 12/6	
					Media: mac	Obs: 12/6	
					Previous Name: GNR		
		Verified		ox	Res: negative	Res: negative	oxidase

Ready P27 CHRDOE 08:16

Major CLSI Updates in 2010-- *Enterobacteriaceae*

- Revised MIC and disk diffusion breakpoints for some cephalosporins and aztreonam
- ESBL confirmatory testing no longer "required"
  - "Not needed for patient management in light of revised breakpoints"
- No reflexive change in interpretation for cephalosporins required in ESBL producing organisms

Here's why they did it…

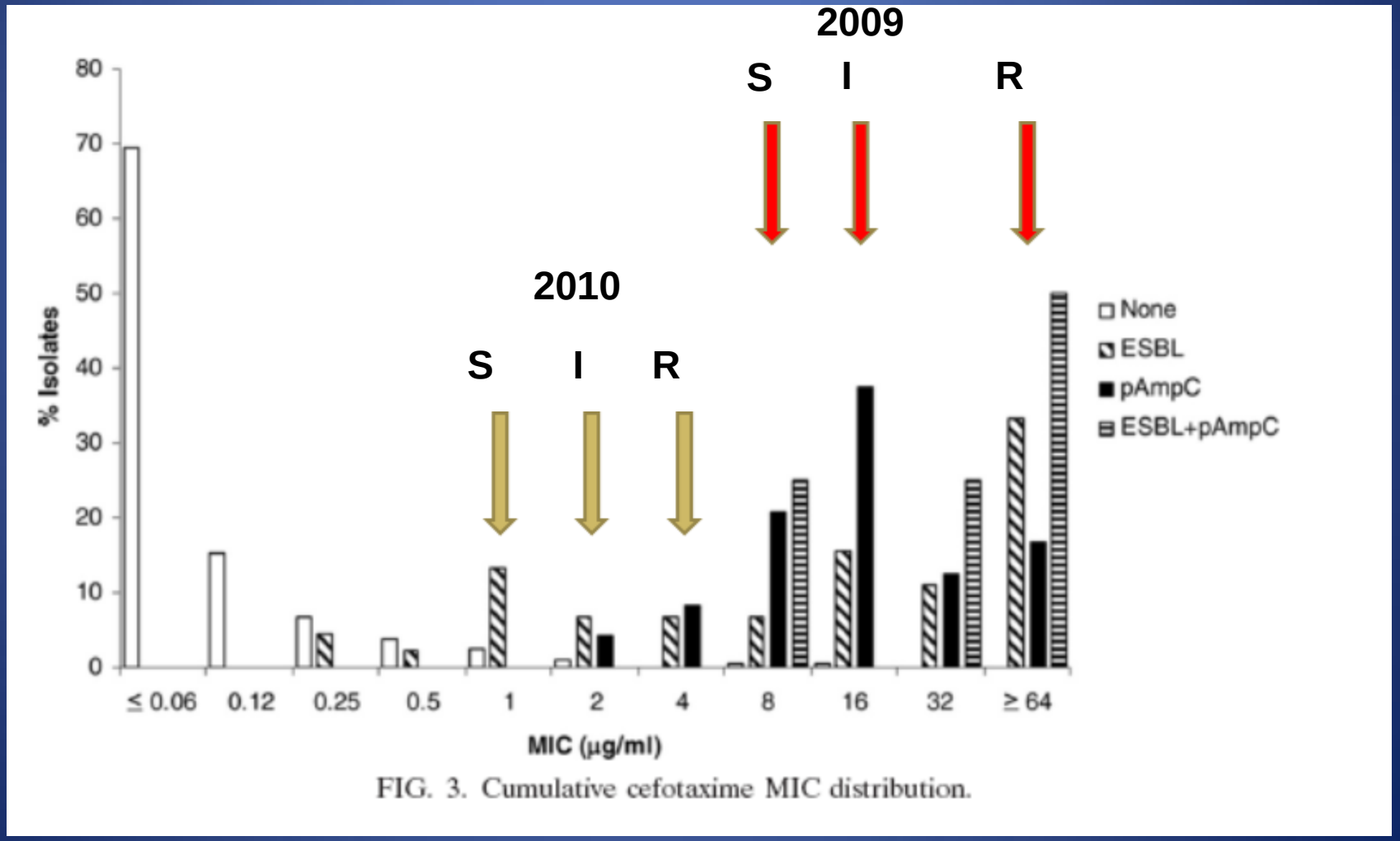


FIG. 3. Cumulative cefotaxime MIC distribution.

Why the CLSI Changes were Controversial

The Argument…

- For the change
  - Phenotypic detection (i.e. non-molecular methods) aren't very good at detecting ESBL's
  - Simplifies testing (sort of)
- Against the change
  - Mechanism NOT MIC predicts outcome
  - NO cephalosporin should be used to treat an ESBL producing organism

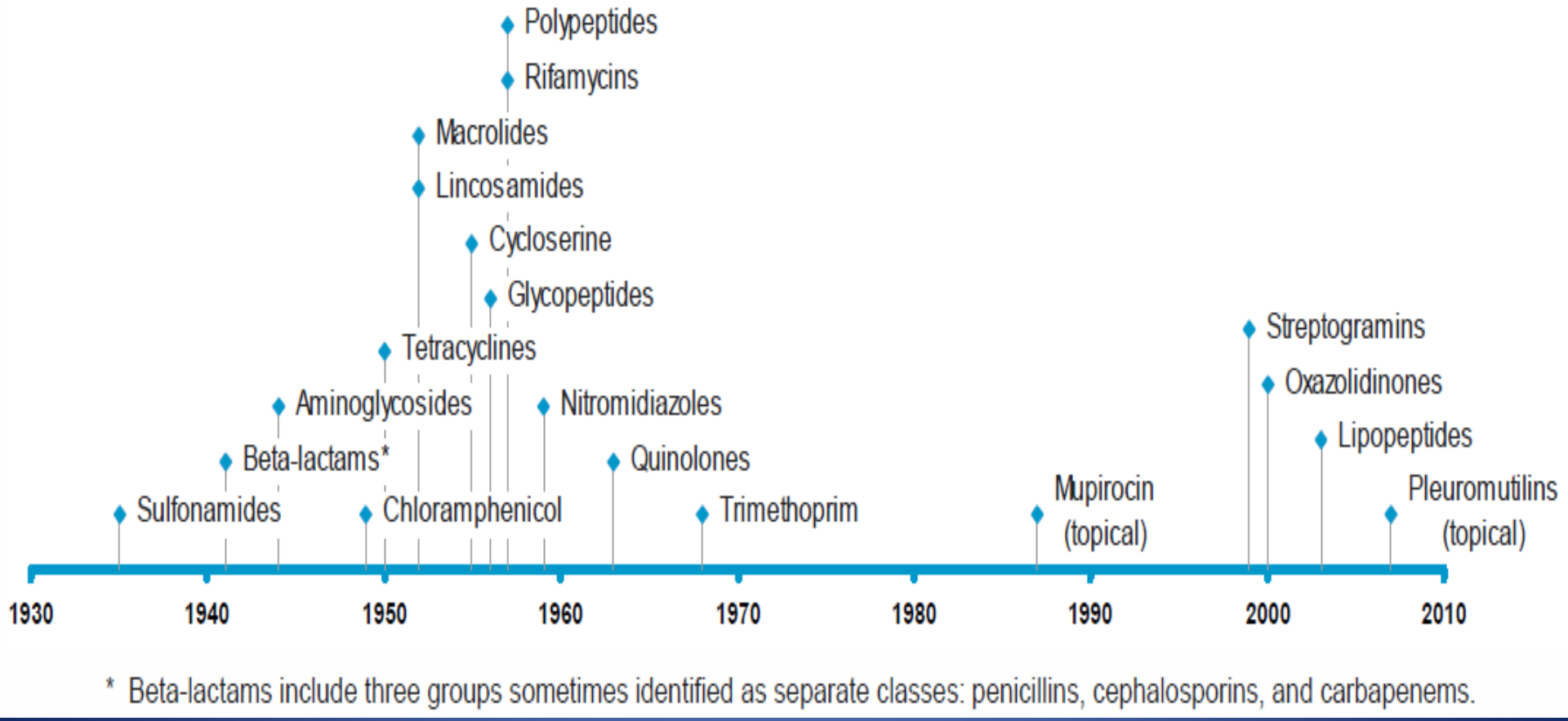
Why it matters to you…

- Labs no longer required to routinely test for these mechanism
  - Infection prevention implications
- Antibiograms may change for the worse…
- Lower break points may drive usage of broader spectrum antibiotics

ESBL/AmpC Wrap Up

- Most common mechanism you'll encounter
- Plasmid transmissible = rapid inter-species spread
- Changing test requirements have and are leading to great diversity in lab practices

Introduction of New Antibiotimicrobial Classes



* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

Source: Policy Responses to The Growing Threat of Antibiotic Resistance, *Extending The Cure*, May 2008

Courtesy of Dr. Gary Doern

Vancomycin and *S. aureus*

Definitions

- VSSA – Vancomycin susceptible *S. aureus*
- VISA – Vancomycin intermediate *S. aureus*
- hVISA – heterogeneous Vancomycin intermediate *S. aureus*
- VRSA – Vancomycin resistant *S. aureus*

Origins of reduced glycopeptide susceptibility

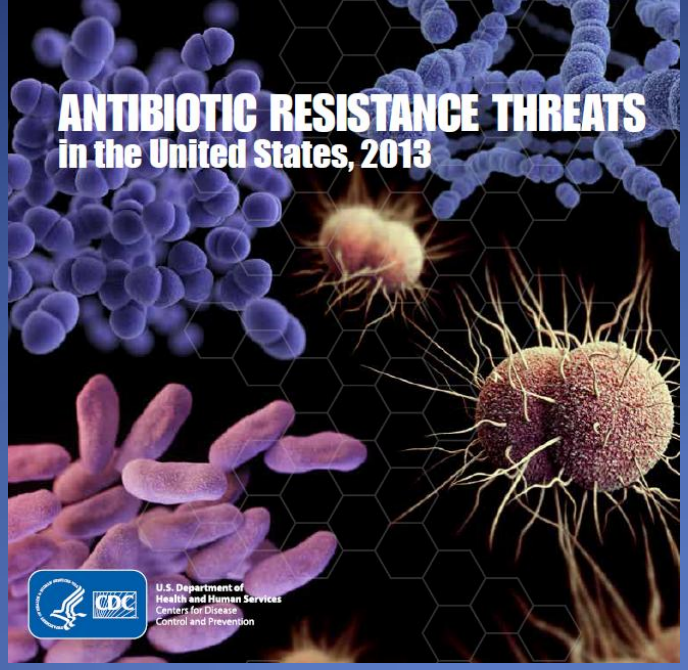
- Indications for vancomycin
  - prophylaxis (35%)
  - empirical therapy (32%)
  - directed treatment (33%)
- Use in animal husbandry
  - Denmark in 1994:
    - 24 kg vancomycin for human therapy
    - 24,000 kg of avoparcin were in animal feed.
  - Australia 1992-1996:
    - 582 kg of vancomycin per year for medical purposes
    - 62,642 kg of avoparcin per year for animals
  - United States
    - 25 million pounds of antibiotics are used yearly

Ena et al JAMA 1993
Ena et al J Chemother 1993
Witte et al Science 1998
www.pewhealth.org

Is there a link between animal antibiotic use and human resistance?

- 70% of antibiotics sold are given to healthy animals.
  - Used without the consultation of a veterinarian.

- July 2010 – The FDA and the US Dept. of Agriculture and the CDC testifies before congress that there was a definitive link between animal use and the crisis of antibiotic resistance in humans.



VANCOMYCIN-RESISTANT STAPHYLOCOCCUS AUREUS

13 CASES

IN **4** STATES SINCE 2002

SOME STAPHYLOCOCCUS STRAINS ARE RESISTANT TO VANCOMYCIN

LEAVING FEW OR NO TREATMENT OPTIONS

THREAT LEVEL

CONCERNING

This bacteria is concerning, and careful monitoring and prevention action are needed.

VRSA: What's the big deal?

- Discovered in 1953.
- Over 50+ years of Vancomycin usage and we have had 13 (As of early 2011) reports of VRSA… TOTAL!!
- 8 of 13 have been in Michigan
- Never been a case of VRSA transmitted from patient to patient
  - Fitness cost too great to maintain resistance?

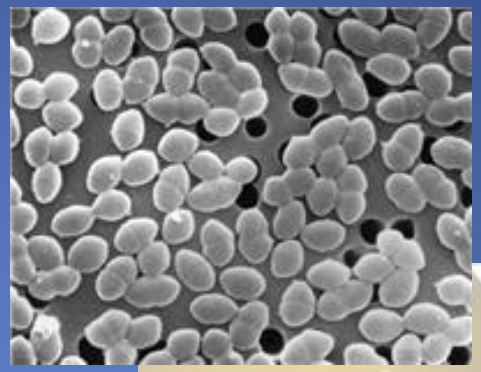
VRSA: Is it untreatable? Treatment Options (n = 13)

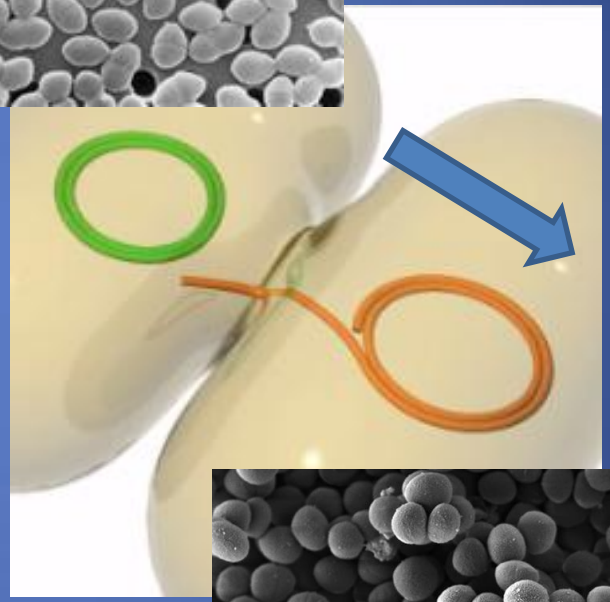
Antibiotic	MIC Range	% Susceptible
Ceftaroline	0.12-1	100
Daptomycin	0.25-1	100
Linezolid	0.5-4	100
Minocycline	0.03-2	100
Trim/Sulfa	0.06/1.2-2/38	100
Tigecycline	<0.03-1	92
Clindamycin	>64	0
Telavancin	2-6	0
Vancomycin	32->64	0

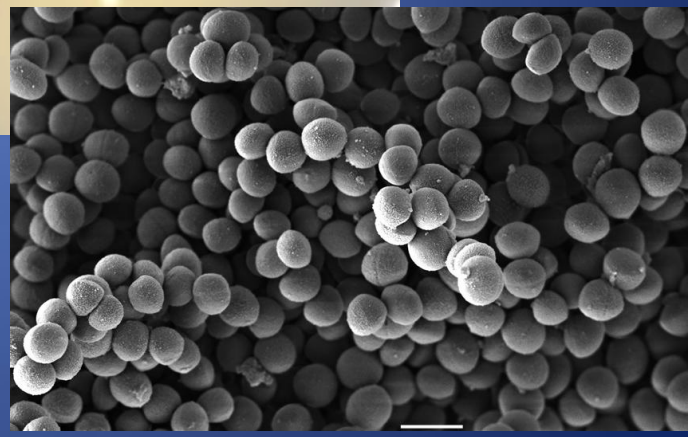
Saravolatz et al. CID. 2012. 55(4)

VRSA: How does it happen?

- *vanA*-mediated vancomycin resistance
  - Mechanism that confers vancomycin resistance in Enterococci
- Of the first 7 VRSA… 6 of those patients were co-colonized/infected with VRE
- VRSA 4-7 were all different *S. aureus* strains but contained the same plasmid type.







http://www.nature.com/scitable/definition/conjugation-prokaryotes-290

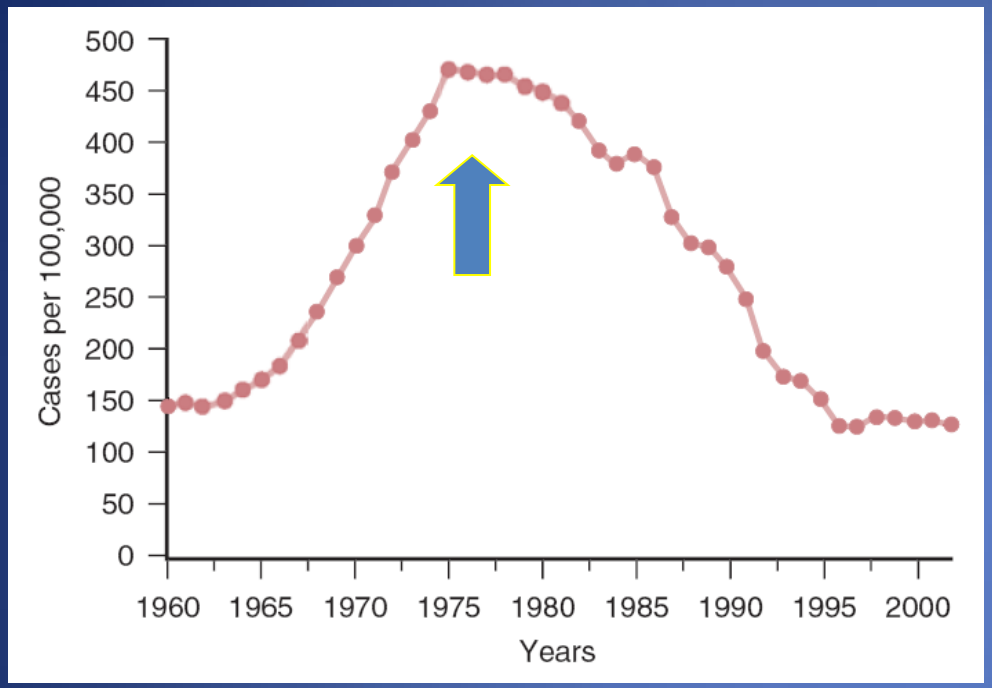
VRSA Summary

- Vancomycin is an important drug for treating MRSA, thus VRSA is a concern
- So far VRSA is EXTREMELY rare and does not appear to be stable.
- VRSA can be susceptible to other drugs like daptomycin, linezolid, bactrim and ceftaroline.
- Laboratory detection is not difficult if using MIC method.

The Untreatable Infection

Let’s start in an unusual place

Neisseria gonorrhoeae - Epidemiology



…as long as people are still having promiscuous sex with many anonymous partners without protection while at the same time experimenting with mind-expanding drugs in a consequence-free environment, I'll be sound as a pound!

- CDC implementation of GC control program in the mid 70's.
- Decreased incidence of GC in the US by 74%

Sexually Transmitted Diseases (STDs)

Sexually Transmitted Diseases
Diseases & Related Conditions
Pregnancy & Infertility
Publications & Products
Program Tools
Projects & Initiatives
Gonococcal Isolate Surveillance Project (GISP)
Infertility Prevention Project (IPP)
STD Awareness Month
Syphilis Elimination Effort (SEE)
Data & Statistics
Training
Treatment
About the Division of STD Prevention

Gonococcal Isolate Surveillance Project (GISP)

The Gonococcal Isolate Surveillance Project (GISP) was established in 1986 to monitor trends in antimicrobial susceptibilities of strains of *N. gonorrhoeae* in the United States in order to establish a rational basis for the selection of gonococcal therapies. GISP is a collaborative project among selected sexually transmitted diseases (STD) clinics, five regional laboratories, and the Centers for Disease Control and Prevention (CDC).

On this Page
- Protocol
- Annual Report
- Sentinel Sites and Regional Laboratories
- Forms & Coding Guide

In GISP, *N. gonorrhoeae* isolates are collected from the first 25 men with urethral gonorrhea attending STD clinics each month in approximately 28 cities in the United States. At regional laboratories, the susceptibilities of these isolates to penicillin, tetracycline, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, and azithromycin are determined by agar dilution. Minimum inhibitory concentrations (MICs) are measured, and values are interpreted according to criteria recommended by the National Committee for Clinical Laboratory Standards (NCCLS).

Protocol

- GISP Protocol

Annual Reports and Profiles

- 2009 GISP Profiles
- GISP Profiles (2008-2009) and Annual Reports (1998-2007)

Sentinel Sites and Regional Laboratories

Click thumbnail for larger map

* indicates Regional Laboratories

Albuquerque, NM	Miami, FL
Atlanta, GA *	Minneapolis, MN

Text size: S M L XL
Email page
Print page
Bookmark and share

Contact Us:
Centers for Disease Control and Prevention
1600 Clifton Rd
Atlanta, GA 30333
800-CDC-INFO
(800-232-4636)
TTY: (888) 232-6348
24 Hours/Every Day
cdcinfo@cdc.gov

Current Neisseria gonorrhoeae
Treatment recommendations

Infection	Primary	Alternative
Urethritis, cervicitis and proctitis	Ceftriaxone or cefixime PLUS doxycycline or azithromycin	
Conjunctivitis	Ceftriaxone IM	
Disseminated gonococcal infection (DGI)	IM or IV Ceftriaxone	IV Cefotaxime or IV ceftizoxime
Pharyngitis	Ceftriaxone IM PLUS doxycycline or azithromycin	

As of 2007, fluoroquinolones no longer recommended due to widespread emergence of resistance.

MMWR 2010 – Dec 17, 2010 – STD Treatment Guidelines

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 26
July 8, 2011

Morbidity and Mortality Weekly Report

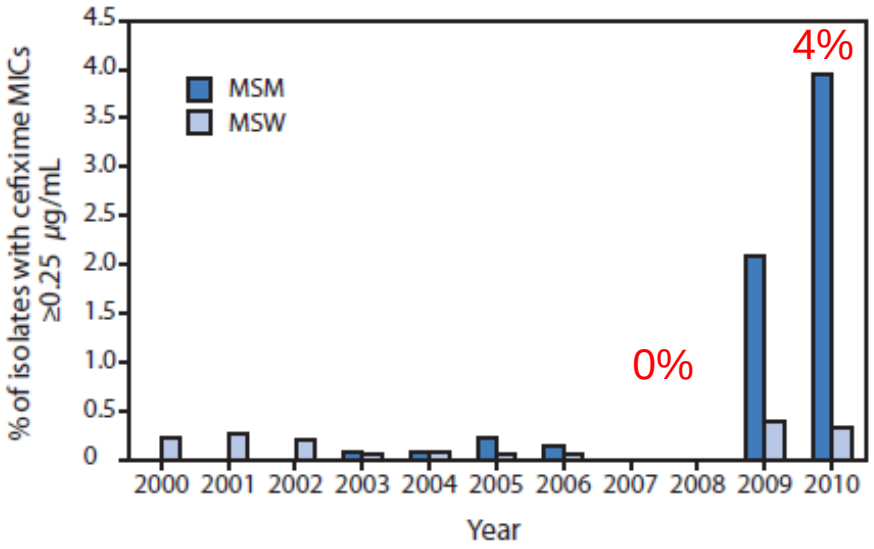
Cephalosporin Susceptibility Among *Neisseria gonorrhoeae* Isolates — United States, 2000–2010

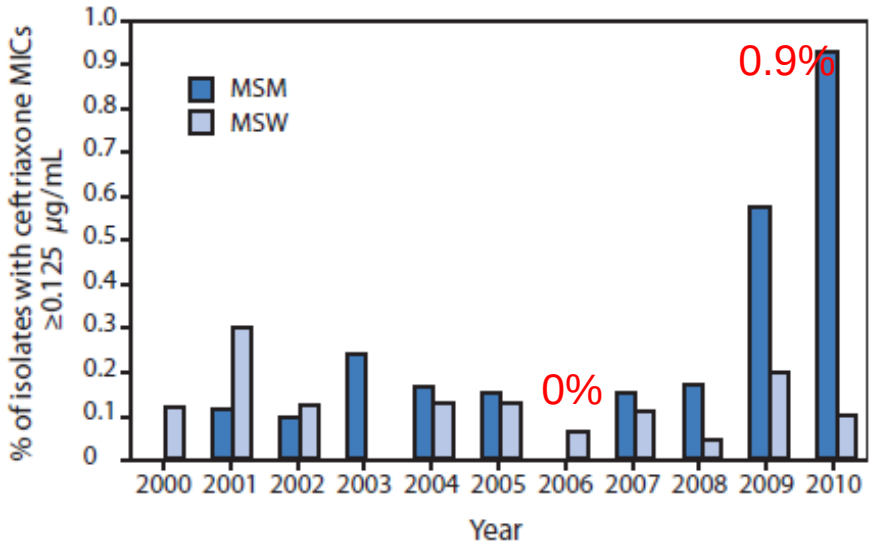
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 18
May 13, 2011

Morbidity and Mortality Weekly Report

Neisseria gonorrhoeae with Reduced Susceptibility to Azithromycin — San Diego County, California, 2009

FIGURE 2. Percentage of gonorrhea isolates with cefixime MICs ≥0.25 µg/mL and ceftriaxone MICs ≥0.125 µg/mL, by sex of sex partner — Gonococcal Isolate Surveillance Project, United States, 2000–2010





Abbreviations: MICs = minimum inhibitory concentrations; MSM = men who have sex with men; MSW = men who have sex exclusively with women.

Drug	Susceptible (MIC (µg/mL))	Susceptible (Disk (mm))
Cefotaxime	<= 0.5	>= 31
Ceftriaxone	<= 0.25	>= 35
Cefixime	<= 0.25	>= 29
Azithromycin	Eucast <=0.25 GISP <=1	No interpretation

EUCAST Version 1.1, April 2010 CLSI – M100-S21 MMWR 2011 – July 8, 2011

Neisseria gonorrhoeae: Regional Treatment

Oklahoma City, OK

Figure E. Drugs used to treat *Chlamydia trachomatis* infection among GISP participants, 2009

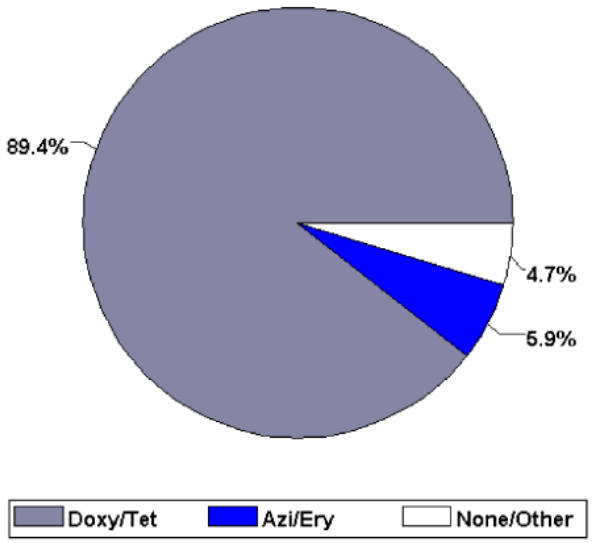
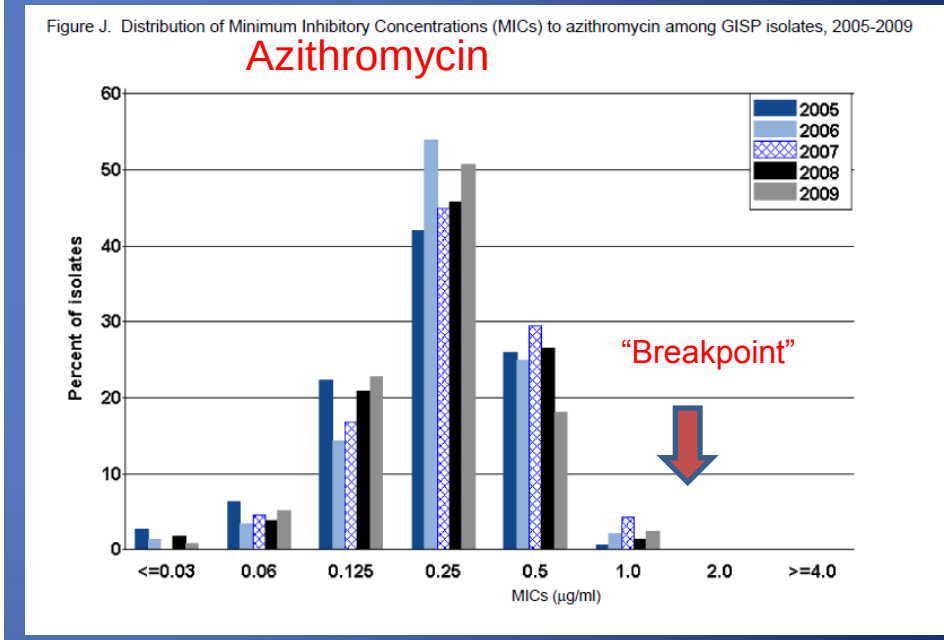


Figure J. Distribution of Minimum Inhibitory Concentrations (MICs) to azithromycin among GISP isolates, 2005-2009

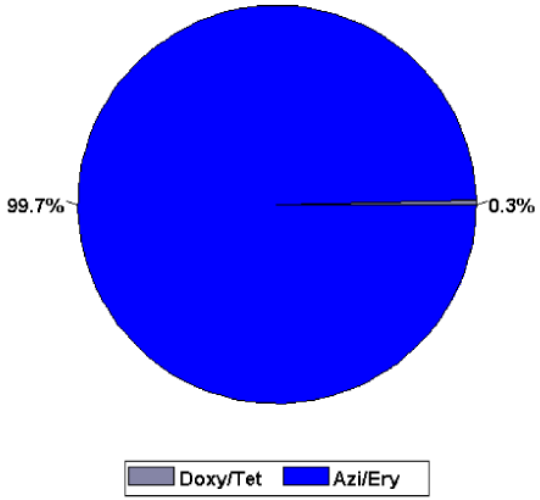


http://www.cdc.gov/std/gisp2009/okc-2009.pdf

Neisseria gonorrhoeae: APIC DFW Region

Different in Dallas…

Figure E. Drugs used to treat *Chlamydia trachomatis* infection among GISP participants, 2009



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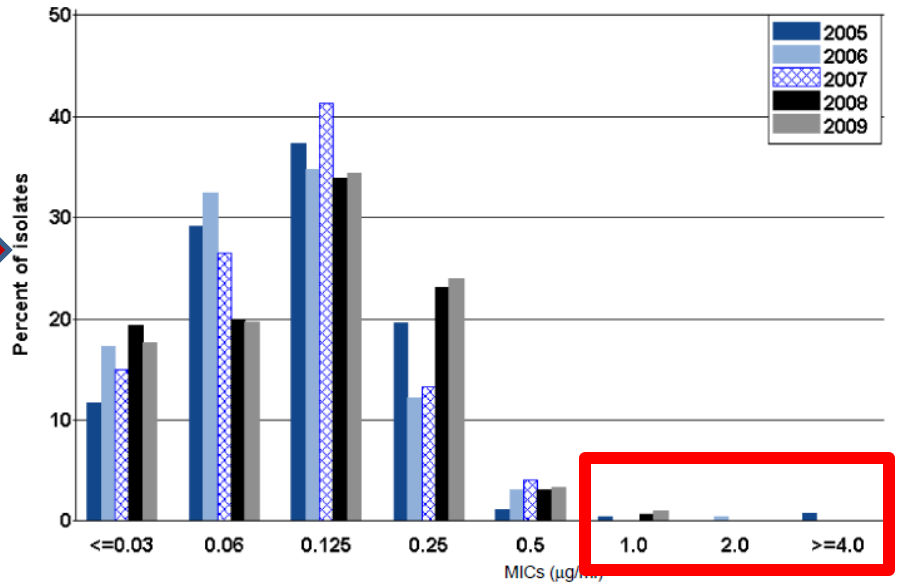
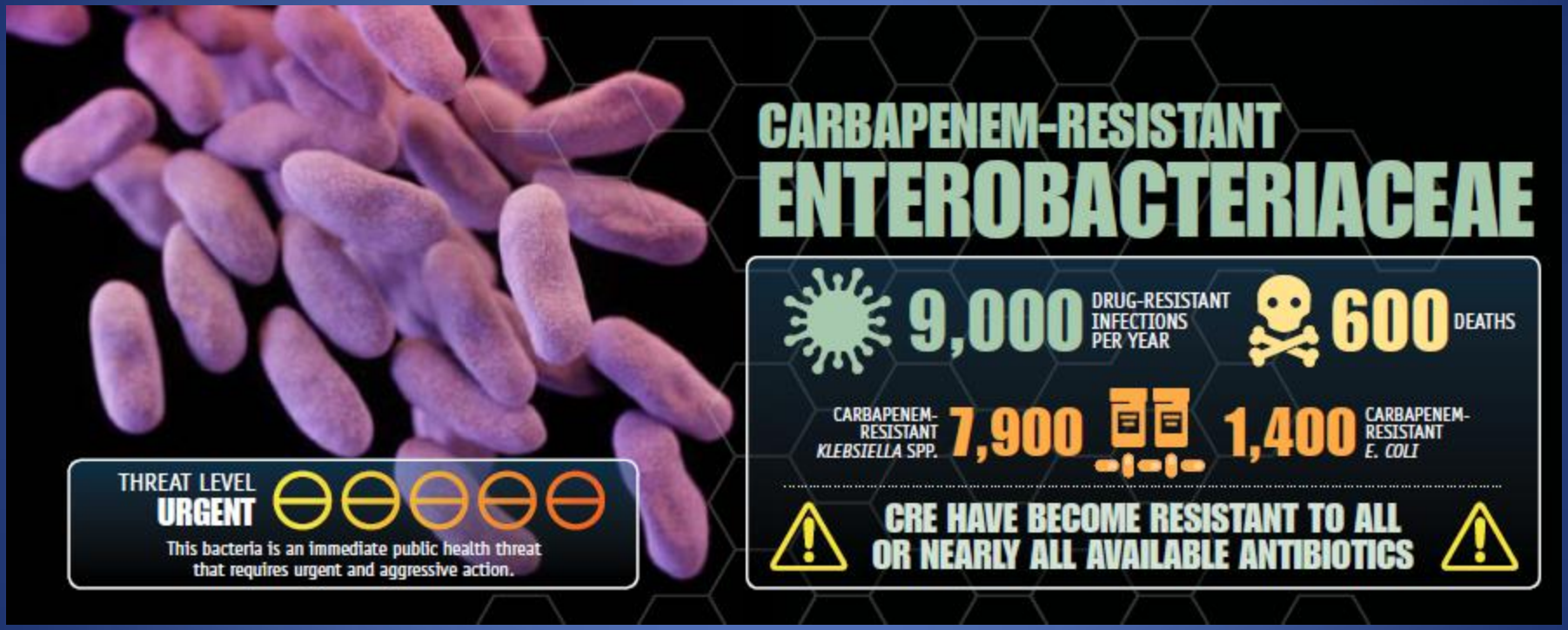


Same treatment pattern in MO and LA but with AZT susceptibility patterns resembling that of OKC

http://www.cdc.gov/std/gisp2009/default.htm

Why is this a HUGE problem?

CRE's: And you thought you didn't want Gonorrhoeae?!?!



KPC (*Klebsiella pneumoniae* carbapenemase)

- Plasmid-encoded molecular Ambler class A enzyme
  - Weakly inhibited by beta-lactamase inhibitors - unlike other class A enzymes
  - Hydrolyses all beta-lactam molecules
- Predominantly found in *K. pneumoniae* but has also been identified in *K. oxytoca*, *Enterobacter* spp., *E. coli*, *C. freundii*, *Salmonella enterica*, *Proteus mirabilis* and *P. aeruginosa*.

TABLE 4. Substrate and inhibition profiles of the carbapenemases

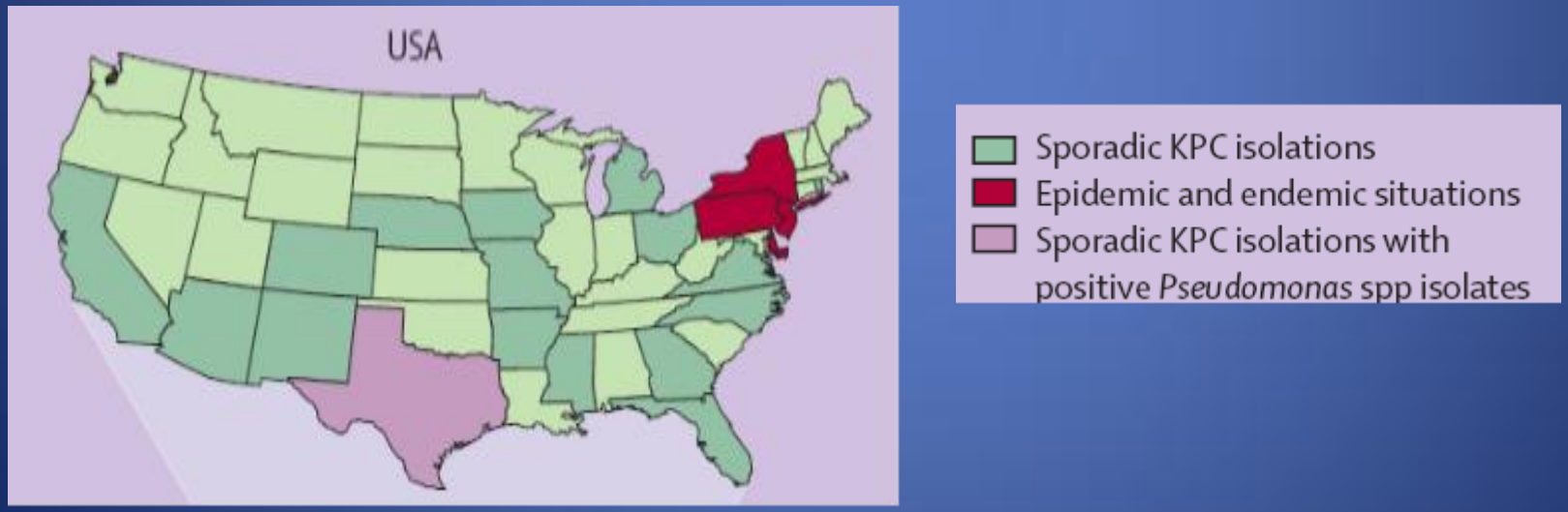
Molecular class	Functional group	Enzyme	Hydrolysis profile[a]					Inhibition profile[b]		Reference(s)
			Penicillins	Early cephalosporins	Extended-spectrum cephalosporins	Aztreonam	Carbapenems	EDTA	Clavulanic acid	
A	2f	NMC	+	+	+	+	+	−	+	124
		IMI	+	+	+	+	+	−	+	183
		SME	+	+	±	+	+		+	179
		KPC	+	+	+	+	+	−	+	4
		GES	+	+	+	−	±	−	+	174, 219
B1	3	IMP	+	+	+	−	+	+	−	224
		VIM	+	+	+	−	+	+	−	224
		GIM	+	+	+	−	+	+	−	224
		SPM	+	+	+	−	+	+	−	224
D	2d	OXA	+	+	±	−	±	−	±	225

[a] Symbols: +, strong hydrolysis (generally, k_{cat} of >2 s^{-1}); ±, weak hydrolysis (generally, k_{cat} of 0.5 to 2 s^{-1}); −, no measurable hydrolysis reported (generally, k_{cat} of <0.5 s^{-1}).
[b] Symbols: +, reported inhibition; ±, variable inhibition among β-lactamase family members; −, no inhibition reported.

Queenan and Bush. 2007. *Clin. Microbiol. Rev.*

Epidemiology of KPCs

- Most prevalent in Pennsylvania, New York and New Jersey
  - More than 1/3 of *K. pneumoniae* in New York City are KPC positive
- No KPCs have been identified @ CMC
- Parkland identifies occasional KPCs



Nordmann et al. 2009. *Lancet. Infect. Dis.*

KPC's in Texas

- No KPC's identified in Texas before 2009
  - 3 index patients (in Houston)
    - Patient 1 – KPC producing *Klebsiella* – BSI - survived
      - Resistant to all antibiotics except colistin and amikacin
    - Patient 2 – KPC producing *Klebsiella* – BSI - died
      - Resistant to all antibiotics except gentamicin, tigecycline and colistin
    - Patient 3 – KPC producing *Klebsiella* – BSI - survived
      - Resistant to all antibiotics except amikacin, tigecycline and colistin

Hirsch et al. DMID. 2011. 69(2)

KPC's in Texas

- Since the first 3 KPC's in Houston…
- At least 18 more have been identified in Texas (that we know of)
- True scope of the spread is not appreciated.
- Hospitals in the DFW area are starting to isolate CRE's.
  - CMC has never had a "true" CRE.

The New Delhi Metallo Beta-Lactamase (NDM-1)

- Metallo-beta lactamase
- Had not been identified in the United States prior to 2010

The story in the UK

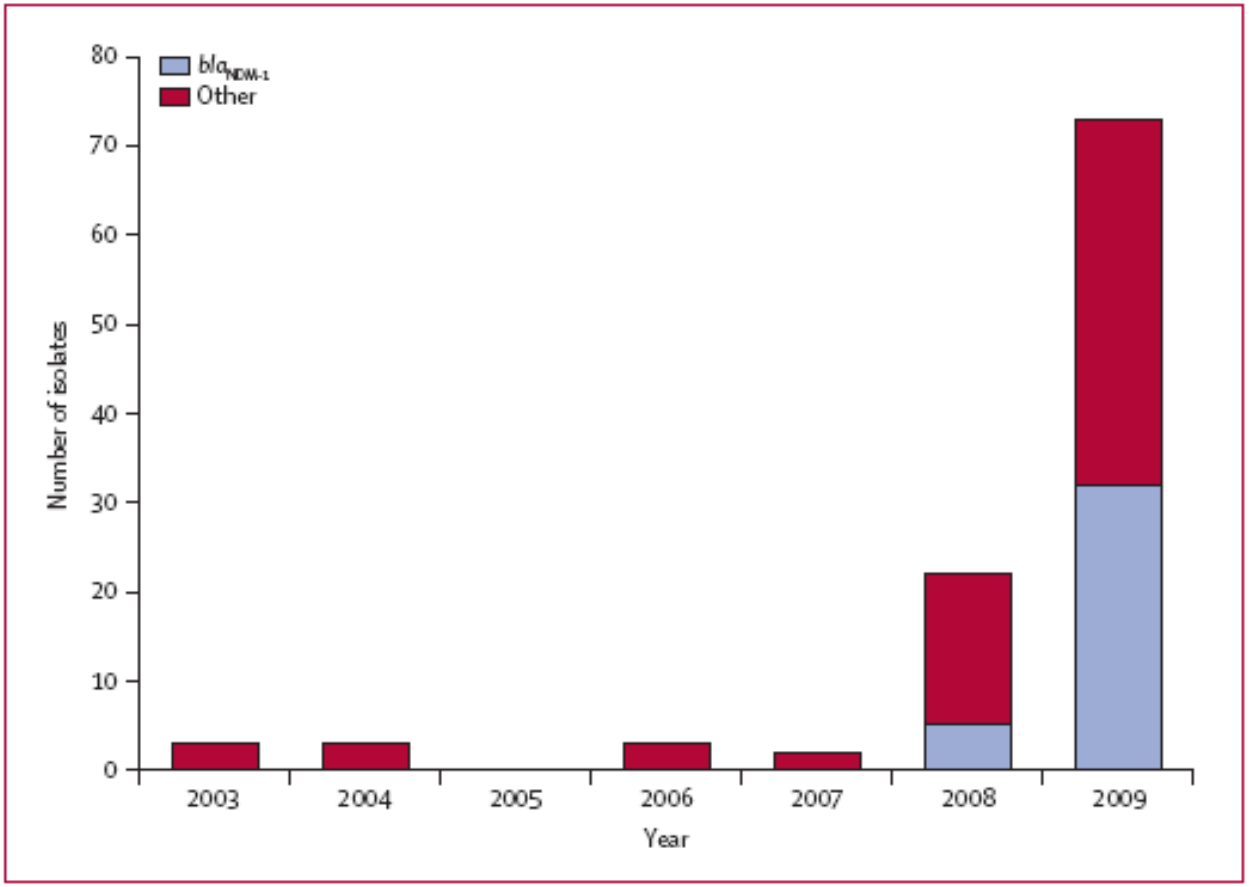


Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009

The predominant gene is bla_{NDM-1}, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

NDM – New Delhi Metallo Beta Lactamase

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	0%	>8; >8	0%	>8; >8	0%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: **Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)**

All NDM isolates were multi-drug resistant

Kumarasamy et al. 2010. Lancet

NDM in the United States

Table 3. Antimicrobial drug susceptibility profiles of NDM-producing isolates collected and *Escherichia coli* transformants, United States, April 2009–March 2011*

Isolate no.	Organism	MIC, µg/mL									Broth microdilution MBL screen result			Modified Hodge test result
		TGC	SXT	CTX	FEP	ATM	DOR	ETP	MER	IMP	IMP+EP†	Ratio	MBL	ETP/MER
US-506	*Klebsiella pneumoniae*	≤0.5	>8	>64	>32	>64	>8	>4	>8	>32	1	≥64	+	–/–
1100770	*K. pneumoniae*	2	>8	>64	>32	>64	>8	>4	>8	32	0.5	64	+	+/–
1100975	*K. pneumoniae*	2	>8	>64	>32	>64	>8	>4	>8	32	1	32	+	+/+
1100192	*K. pneumoniae*	1	>8	>64	>32	>64	>8	>4	>8	8	≤0.5	≥16	+	+/–
1000527	*K. pneumoniae*	>4	>8	>64	>32	>64	>8	>4	>8	>32	≤0.5	>64	+	+/+
1101459	*K. pneumoniae*	2	>8	>64	>32	>64	>8	>4	8	16	≤0.5	≥32	+	+/+
1101168	*Salmonella enterica* serovar Senftenberg	1	0.5	>64	>32	>64	8	>4	8	4	≤0.5	≥8	+	+/+
1100101	*E. coli*	≤0.5	>8	>64	>32	>64	>8	>4	>8	16	1	16	+	+/–
1001728	*E. coli*	≤0.5	>8	>64	>32	16	>8	>4	>8	8	≤0.5	≥16	+	+/+
1000654	*Enterobacter cloacae*	>4	>8	>64	>32	>64	>8	>4	>8	>32	4	>8	+	+/+

Rasheed et al. EID. 2013. 19(6)

How did it spread so quickly to the UK?

INDEPENDENT BLOGS

THE INDEPENDENT HEALTH & FAMILIES

NHS 'could save millions' by flying patients to India

Experts urge Department of Health to consider using hospitals outside Europe

By Nina Lakhani

Sunday, 17 January 2010

Tens of millions of pounds would be saved and waiting lists slashed if some NHS patients were treated abroad, according to figures seen by The Independent on Sunday.

Thousands of patients waiting for operations such as hip replacements and hernia repairs could be treated more cheaply and quickly if the Government set up formal agreements with countries such as India.

The NHS can currently pay for patients who meet strict criteria to receive treatment in Europe, but only if the flight is under three hours. This means patients are denied access to scores of internationally renowned hospitals outside the continent.

JASON ALDEN

Harish Raithatha, 47, a mechanic from London, went to India last year for a knee replacement

- Several of the UK source patients had elective surgery in India or Pakistan.

The bad news….

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 59 / No. 24
June 25, 2010

Detection of *Enterobacteriaceae* Isolates Carrying Metallo-Beta-Lactamase — United States, 2010

During January–June 2010, three *Enterobacteriaceae* isolates carrying a newly described resistance mechanism, the New Delhi metallo-beta-lactamase (NDM-1) (*1*), were identified from three U.S. states at the CDC antimicrobial susceptibility laboratory. This is the first report of NDM-1 in the United States, and the first report of metallo-beta-lactamase carriage among *Enterobacteriaceae* in the United States. These isolates, which include an *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, carry bla_{NDM-1}, which confers resistance to all beta-lactam agents except aztreonam (a monobactam antimicrobial) (*1*); all three isolates were aztreonam resistant, presumably by a different mechanism. In the United Kingdom, where these organisms are increasingly common, carriage of *Enterobacteriaceae* containing bla_{NDM-1} has been closely linked to receipt of medical care in India and Pakistan (*2*). All three U.S. isolates were from patients who received recent medical care in India.

Clinicians should be aware of the possibility of NDM-1–producing *Enterobacteriaceae* in patients who have received medical care in India and Pakistan, and should specifically inquire about this risk factor when carbapenem-resistant *Enterobacteriaceae* are identified. CDC asks that carbapenem-resistant isolates from patients who have received medical care within 6 months in India or Pakistan be forwarded through state public health laboratories to CDC for further characterization. Infection control interventions aimed at preventing transmission, as outlined in current guidance (*5*), should be implemented when NDM-1–producing isolates are identified, even in areas where other carbapenem-resistance mechanisms are common among *Enterobacteriaceae*. Additional information is available by contacting Brandi Limbago or Alex Kallen at search@cdc.gov.

References

I'll leave you with "The Vicious Cycle" Something to think about

Usage drives resistance…

- Objective:
  - To determine if restriction of cephalosporin would reduce incidence of ESBL producing Klebsiella spp.
- Results
  - Cephalosporin restriction led to 44% decline in 1 year of ESBL isolates
    - 70.9% reduction in the ICU
  - Imipenem use increased by 140%
    - Concomitant 69% increase in imipenem resistant *P.aeruginosa*

Rahal etl al. 1998. JAMA

Thank you for your attention!

UT SOUTHWESTERN MEDICAL CENTER

children's MEDICAL CENTER