CRE: The good, the (mostly) bad and the ugly

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No conflicts


THE GOOD
THE BAD
AND
THE UGLY
ART (C) ZACH ELLISSIMO 2008

What…

- Kinds of patients get CRE colonization?
- Determines invasive disease?
- Treatment is most effective?
- Can I do to prevent the disease?
- TF?

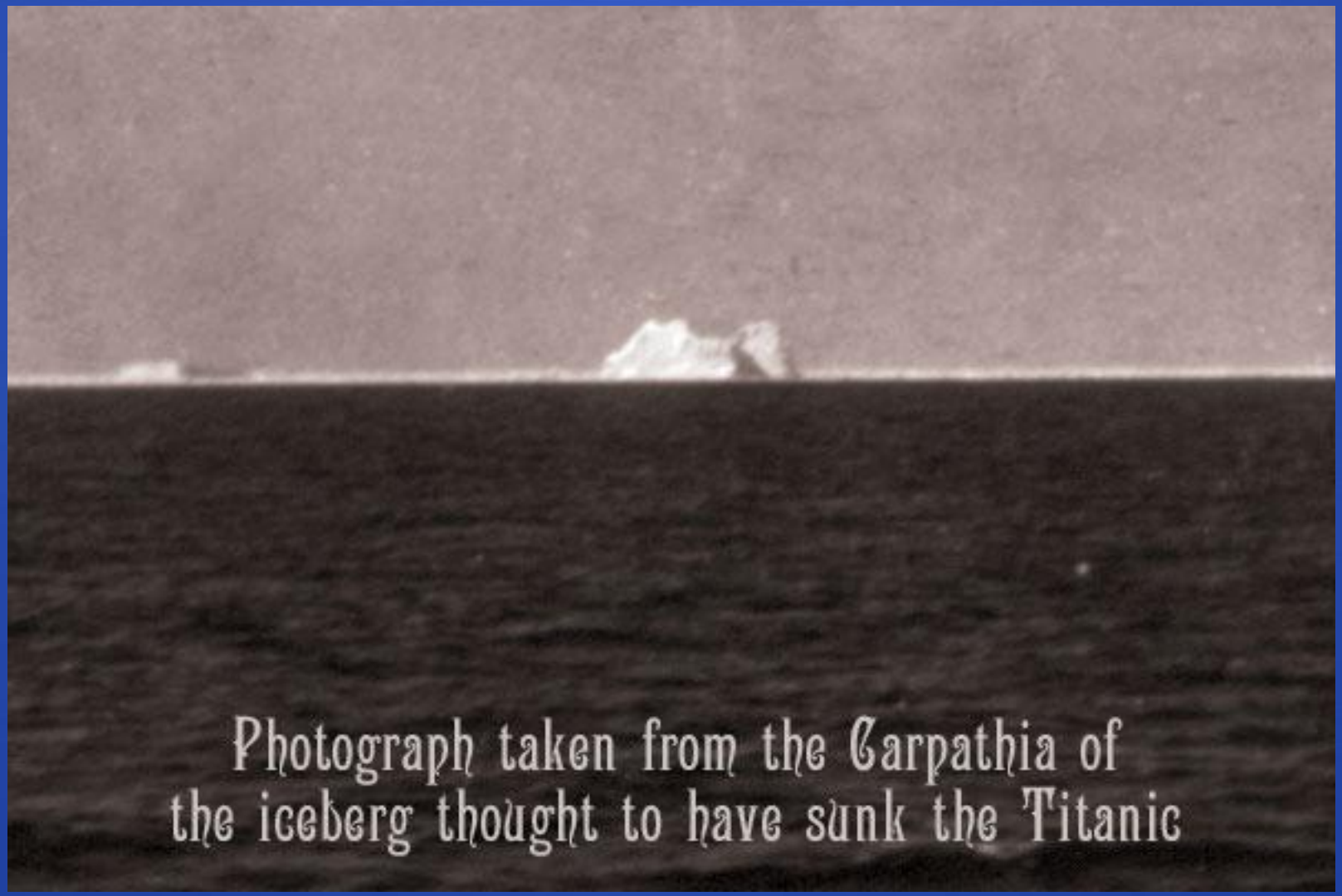
The problem


CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS
CARBAPENEM-RESISTANT *KLEBSIELLA* SPP. 7,900
1,400 CARBAPENEM-RESISTANT *E. COLI*
CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

1912 Growler

$19.12

1912 Growler



CRE is an iceberg

- Hidden unless you look for it
- Slips past quietly; problems when not expected
- Other icebergs around
  - Avoiding one doesn't mean you're out of danger

Lessons of the NIH

- June, 2011: Patient with KPC producing K. pneumoniae transferred from New York to ICU at NIH in Bethesda
- Precautions taken from day 1
- Patient discharged one month later
- No further cases of KPC producing K. pneumoniae seen during this month-long stay

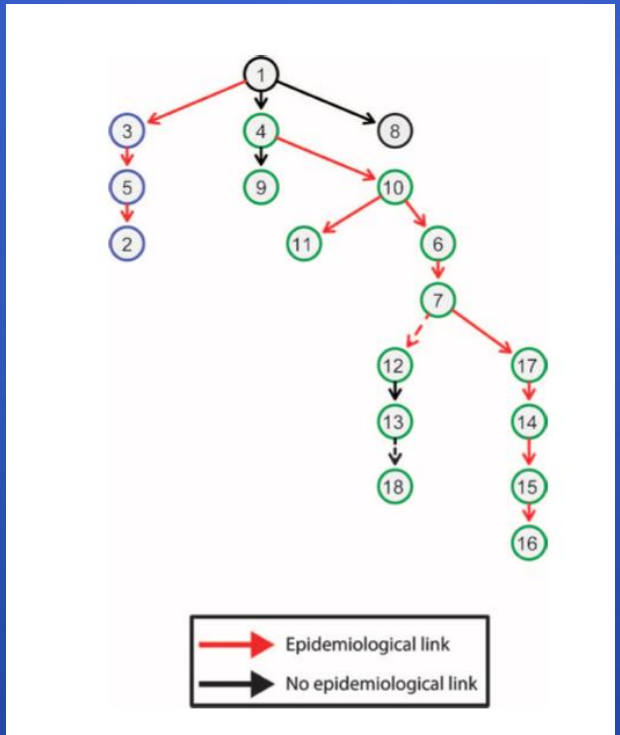
Snitkin, et al. Sci Transl Med. 2012

But then…

- August 5: KPC producing K. pneumoniae isolated from tracheal secretions of patient who never shared a hospital unit with index patient
- Eventually 17 patients were colonized/infected with KPC producing K. pneumoniae
  - 10/17 died: 6 attributable to KPC producing K. pneumoniae
- Strict cohorting, aggressive isolation, enhanced equipment sterilization stopped epidemic

Were these isolates related?

- Complete genome analysis of 18 strains (all were ST 258)
- 41 single nucleotide variation loci in 6,000,000 bases



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What's more chilling…

- Initial strain was susceptible to gent, tigecycline, colistin
- Subsequent strains developed resistance to all 3
- Multiple acquisitions of resistance to colistin
- The 41 SNV were not random: many of them led to resistance

To become carbapenem resistant

- Bacteria have to earn it
  - They have a PhD in resistance before their post-doc CRE work
- Origin of CRE phenotype is mostly enzymatic
- Several families of beta-lactamase have CRE members (KPC, NDM, IMI, OXA)
- Additionally, permeability reduction can contribute when less specific beta-lactamases (ESBL) are present

"Swimming in resistance"

- Patients infected/colonized with CRE often harbor other resistant bacteria
- 86 Detroit patients with CRE: 40% also had carbapenem resistant Pseudomonas aeruginosa or Acinetobacter
- As compared to CRE alone, co-colonized patients: more
  - Sick
  - ICU / LTACH exposure
  - Procedures
  - MRSA Rx

Marchaim D, et al. Am J Infect Contr. 2012; 40:830

Antibiotics for CRE

- Tigecycline (and tetracyclines)
- Colistin and polymyxin
- Aminoglycosides
- Surprise: carbapenems

- How about some dark horses?

So crazy it just might work?

- Temocillin
- Chloramphenicol
- Mecillinam/Amdinocillin (with or without BLI)
- Fosfomycin

- Really not sufficient clinical experience to support – in vitro variable

Table 1
Minimum inhibitory concentrations (MICs) of antibiotics in relation to carbapenemase type[a].

Antibiotic/carbapenemase	No. isolates with indicated MIC (mg/L):												
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Chloramphenicol													
IMP								3	2		4		4
NDM							2	1	3	1	1	1	8
VIM							1			1		3	
KPC								1	1	2	4		3
SME-1											1		
OXA-48							5	3				4	7
Impermeability + ESBL							2	1		2	1		3
Impermeability + AmpC								2	3	1			
Ciprofloxacin													
IMP	2		1	1	1	1	3			3	1		
NDM	1[b]							2	1	1	4	4	4
VIM					2				1	1			1
KPC										2	3	5	1
SME-1	1[b]												
OXA-48	2[b]	1		1		7	1			1	1	2	3
Impermeability + ESBL						1	1	1		3	3		
Impermeability + AmpC	4[b]						1		1				
Colistin													
IMP				10[b]	3								
NDM				13[b]	2			1			1[c]		
VIM				4[b]	1								
KPC				9[b]	1					1			
SME-1											1[c]		
OXA-48				11[b]	7					1			
Impermeability + ESBL				7[b]	1					1			
Impermeability + AmpC				5[b]	1								
Fosfomycin													
IMP						1[b]	3	4	1	1			3
NDM						6[b]	1	3	1	2	2	1	1
VIM								1	1	1	1		1
KPC								1	4	1	4		1
SME-1									1				
OXA-48						2[b]	1	2	1	5	3	5	
Impermeability + ESBL										2	1	1	5
Impermeability + AmpC						1			1	1	2	1	

Nitrofurantoin											
IMP					1[b]		2	1	1	5	3
NDM							3		3	4	7
VIM									1	1	3
KPC											11
SME-1											1
OXA-48										3	16
Impermeability + ESBL											9
Impermeability + AmpC									1	2	3
Temocillin											
IMP								1	6	5	1
NDM						1	1		4	1	10
VIM										1	4
KPC							2	4	4	1	
SME-1						1					
OXA-48						1					18
Impermeability + ESBL						1	1	7			
Impermeability + AmpC							5	1			
Minocycline											
IMP					2	6	3	1	1[c]		
NDM			1	3	1	5	3	2	2[c]		
VIM					1	3	1				
KPC						6	1	1	3[c]		
SME-1						1					
OXA-48				2	3	8	2	3	1[c]		
Impermeability + ESBL					4	2	2	1			
Impermeability + AmpC					4		1		1[c]		
Tigecycline											
IMP		1	4	4	4						
NDM	1[b]	5	4	3	3	1					
VIM			3	1	1						
KPC			2	6	2	1					
SME-1					1						
OXA-48		3	6	9	1						
Impermeability + ESBL		1	3	3	2						
Impermeability + AmpC			5	1							

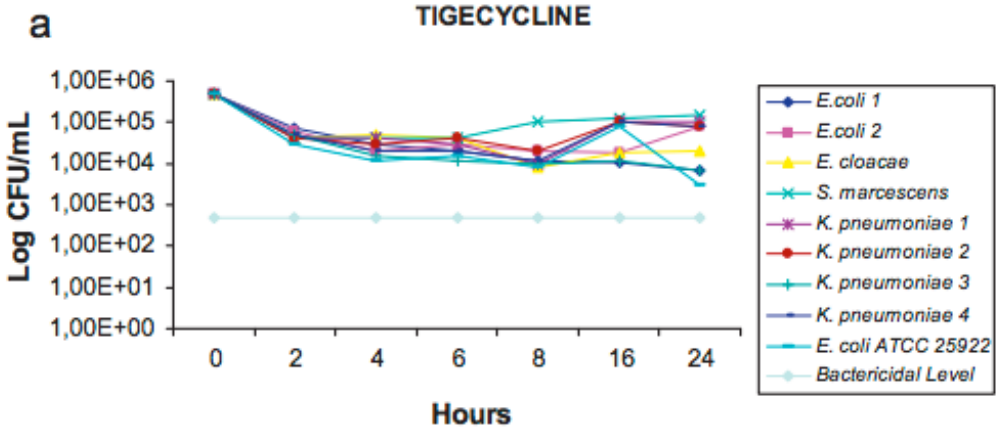
Bottom line

- As expected, colistin and tigecycline are attractive *in vitro*
- Only other "surprise" is fosfomycin
  - Currently only available as single 3 g oral dose
  - Can IV fosfomycin be developed as an "orphan" drug?

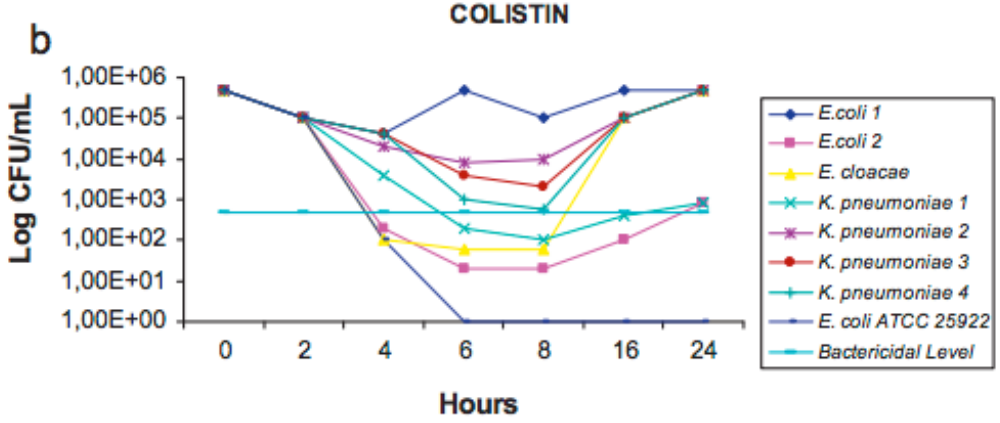
		Overall cultures		Urinary cultures	
		Number tested	Fosfomycin, number susceptible (%)	Number tested	Fosfomycin, number susceptible (%)
Carbapenem-resistant *Enterobacteriaceae*	*Klebsiella* species	79	67 (85%)	29	23 (57%)
	Enterobacter species	13	11 (72%)	5	4 (80%)
	Escherichia coli	1	1 (100%)	1	1 (100%)

Pogue JM, et al. J Antibiot 2013; doi: 10.1038/ja.2013.56

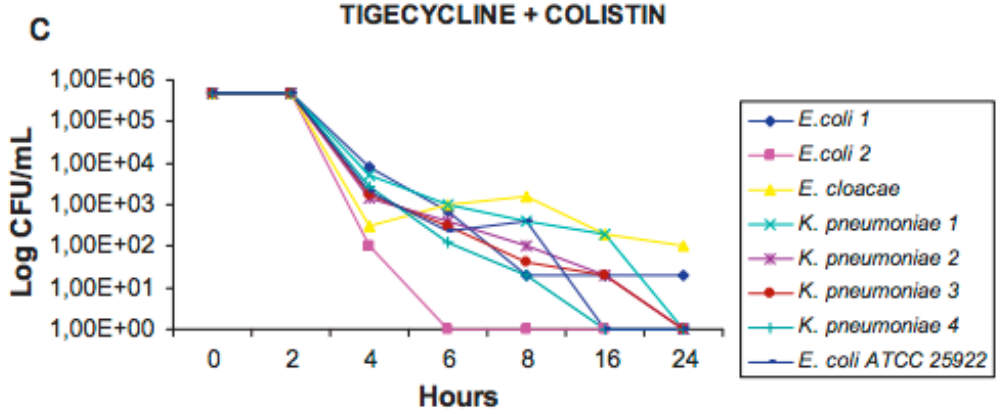
a


TIGECYCLINE
Log CFU/mL
1,00E+06
1,00E+05
1,00E+04
1,00E+03
1,00E+02
1,00E+01
1,00E+00
0
2
4
6
8
16
24
Hours
E.coli 1
E.coli 2
E. cloacae
S. marcescens
K. pneumoniae 1
K. pneumoniae 2
K. pneumoniae 3
K. pneumoniae 4
E. coli ATCC 25922
Bactericidal Level

b


COLISTIN
Log CFU/mL
1,00E+06
1,00E+05
1,00E+04
1,00E+03
1,00E+02
1,00E+01
1,00E+00
0
2
4
6
8
16
24
Hours
E.coli 1
E.coli 2
E. cloacae
K. pneumoniae 1
K. pneumoniae 2
K. pneumoniae 3
K. pneumoniae 4
E. coli ATCC 25922
Bactericidal Level

c


TIGECYCLINE + COLISTIN
Log CFU/mL
1,00E+06
1,00E+05
1,00E+04
1,00E+03
1,00E+02
1,00E+01
1,00E+00
0
2
4
6
8
16
24
Hours
E.coli 1
E.coli 2
E. cloacae
K. pneumoniae 1
K. pneumoniae 2
K. pneumoniae 3
K. pneumoniae 4
E. coli ATCC 25922

What is the clinical experience?

- Cleveland experience
  - 60 patients with KPC bacteremia
  - 14d mortality 42%
    - Only 31% in people who were diagnosed ante-mortem
    - All non-survivors were on "active" treatment at time of death
  - This was a sick cohort but non-survivors were even sicker
- Underlying conditions might predispose to CRE or determine eventual fate of patient

Neuner , et al. Diagn Microbiol Infect Dis 2011; 69:357

Role of specific Rx agent

- All the data are from case reports and case series
- No RCT data available
- Cohort studies are available but their data might be hard to generalize
- Case control studies are hard to interpret
  - Who is really a good control?

KPC Enterobacteriaceae infections

- Systemic review in 2011 (66 articles, 61 abstracts)
  - 38 articles (105 cases) analyzed
  - Choice of Rx was varied (single/combo/different classes)
  - K. pneumoniae, E. coli, Enterobacter cloacae and others
  - Mostly ICU patients with mean APACHE II of 21
  - Duration of hospital stay before infection, mean of 18 d
    - For reference, 4-6d LOS is typical for acute care hospital pts

Lee GC, Burgess DS. Ann Clin Microbiol Antimicrob 2012; 11:32

KPC Enterobacteriaceae infections

- Which treatment is best?
  - Impossible to control for all variables
  - Some success with almost every regimen

	Monotherapy (%)	Combination (%)	*P*
Overall treatment failure	24/49(49)	14/56(25)	0.01
Source:			
Blood	12/24 (50)	9/32(28)	0.09
Pulmonary	10/15(67)	5/17(29)	0.03
Urine	1/8(13)	0/3(0)	0.4
Polymyxin treatment failure	8/11(73)	10/34(29)	0.02
Carbapenem treatment failure	12/20(60)	5/19(26)	0.03
Tigecycline treatment failure	2/7(29)	7/19(37)	0.4
Aminoglycoside treatment failure	0/6(0)	4/24(17)	0.6

Lee GC, Burgess DS. Ann Clin Microbiol Antimicrob 2012; 11:32

Tigecycline plus…

- Trauma UCI in Italy
  - Outbreak of ST512 KPC K. pneumoniae
  - Overall good outcomes (24/26 patients completed Rx alive)
  - This is despite high level of resistance to colistin and tigecycline
  - Patients did not get carbapenems but almost all got tigecycline combination Rx (tigecycline plus…, colistin, gentamicin, fosfomycin)

Sbrana et al., Clin Infect Dis. 2013; 56:697

Tigecycline resistance

- Initial resistance (MIC >2) varies but usually less than 10%
- Emergence of resistance on or after therapy is recognized
- Unsurprisingly, receipt of tigecycline for CRE Rx has a large selection effect on subsequent resistance (OR = 6 with $p < .001$)

Nigo M, et al. Antimicriob Agents Chemother. 2013; 57:5743

SICU outbreak Italy

- 30 cases of KPC K. pneumo (ST258) with mortality 40%
- Best outcomes: double dose (200 mg loading, 100 Q12h) tigecycline + 5 mg/kg/d colistin

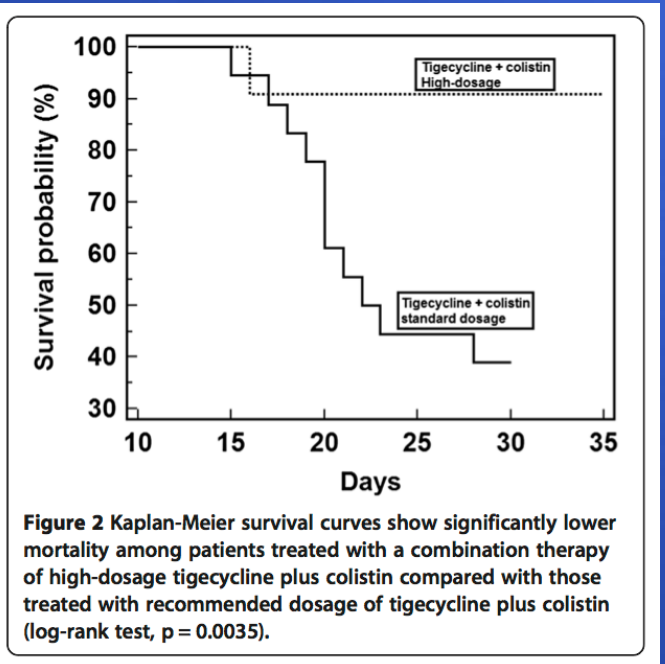


Figure 2 Kaplan-Meier survival curves show significantly lower mortality among patients treated with a combination therapy of high-dosage tigecycline plus colistin compared with those treated with recommended dosage of tigecycline plus colistin (log-rank test, p = 0.0035).

Di Carlo et al. BMC Anesthesiology 2013, 13:13

Rx conclusions

- Sketchy and uncertain data
- Extensive variation makes interpretation hard!
  - Significant patient variability
  - Species (Klebsiella, E. coli, Enterobacter, others)
  - Enzymes (KPC variants, NDM, IMI, OXA as well as ESBL)
  - Intrinsic/baseline resistance makes some choices moot
  - Combination using agents that have little in vitro activity is counter-intuitive but sometimes successful

It’s the Wild West out there!

Prevention

- Think hand-to-hand combat
- Think ahead
- Think globally, act locally

Hands

- Infection prevention starts with hand hygiene
- Relevant to community and hospital settings
- How do we know it works?

Pittet D., et al. Lancet ID 2006; 6:641

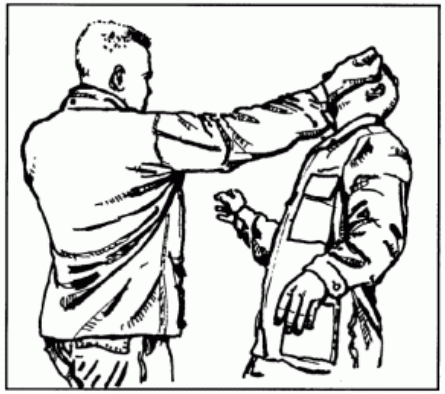


Figure 4-5. Hammer-fist strike to face.

Reference	Hospital setting	Results	Duration of follow-up
Casewell and Phillips (1977)[31]	Adult ICU	Significant reduction (p<0·001) in the percentage of patients colonised or infected by *Klebsiella* spp	2 years
Conly et al (1989)[95]	Adult ICU	Significant reduction (p=0·02) in health-care-associated infection rates immediately after hand hygiene promotion (from 33% to 12% and from 33% to 9%)	6 years
Simmons et al (1990)[96]	Adult ICU	No effect on health-care-associated infection rates (no significant [p<0·05] improvement of hand hygiene adherence)	11 months
Doebbeling et al (1992)[90]	Adult ICUs	Significant (p<0·02) difference between rates of health-care-associated infection using two different hand hygiene agents	8 months
Webster et al (1994)[91]	NICU	Elimination of MRSA, when combined with multiple other infection control measures. Reduction of vancomycin use. Significant p<0·02 reduction of nosocomial bacteraemia (from 2·6% to 1·1%) using triclosan compared with chlorhexidine for handwashing	9 months
Zafar et al (1995)[92]	Newborn nursery	Control of a MRSA outbreak using a triclosan preparation for handwashing, in addition to other infection control measures	3·5 years
Larson et al (2000)[94]	MICU/NICU	Significant (85%, p=0·02) relative reduction of VRE rate in the intervention hospital; insignificant (44%) relative reduction in control hospital; no significant change in MRSA	8 months
Pittet et al (2000)[93]	Hospital-wide	Significant (p=0·04 and p<0·001) reduction in the annual overall prevalence of health-care-associated infections (41·5%) and MRSA cross-transmission rates (87%). Active surveillance cultures and contact precautions were implemented during same time period	5 years
Hilburn et al (2003)[99]	Orthopaedic surgical unit	36·1% decrease in infection rates (from 8·2% to 5·3%)	10 months
MacDonald et al (2004)[97]	Hospital-wide	Significant (p=0·03) reduction in hospital-acquired MRSA cases (from 1·9% to 0·9%)	1 year
Swoboda et al (2004)[98]	Adult intermediate care unit	Reduction in health care-associated infection rates (not significant, p value not reported)	2·5 months
Lam et al (2004)[100]	NICU	Reduction (not significant, p=0·14) in health-care-associated infection rates (from 11·3 per 1000 patient-days to 6·2 per 1000 patient-days)	6 months
Won et al (2004)[101]	NICU	Significant reduction (p=0·003) in health care-associated infection rates (from 15·1 per 1000 patient-days to 10·7 per 1000 patient-days), in particular of respiratory infections	2 years
Zerr et al (2005)[102]	Hospital-wide	Significant (p=0·01) reduction in hospital-associated rotavirus infections	4 years
Rosenthal et al (2005)[103]	Adult ICUs	Significant (p<0·001) reduction in health-care-associated infection rates (from 47·5 per 1000 patient-days to 27·9 per 1000 patient-days)	21 months
Johnson et al (2005)[104]	Hospital-wide	Significant (p=0·01) reduction (57%) in MRSA bacteraemia	36 months

ICU=intensive care unit, NICU=neonatal ICU, MRSA=meticillin-resistant *Staphylococcus aureus*, MICU=medical ICU, VRE= vancomycin-resistant enterococci.

Table: **Association between adherence with hand hygiene practice and health-care-associated infection rates: hospital-based studies, 1975–2005**

Is antibiotic exposure relevant?

- Different studies come to different conclusions
  - In some settings, carbapenems appear to play a strong role
  - Other studies focus on fluoroquinolones, advanced cephalosporins and BLI combinations
- Less surprising than on face value
  - Hospitals have heavy antibiotic pressure
  - CRE arises from acquisition of plasmids: usually with multiple resistance genes

From a case/control trial

- … multivariable analysis showed that exposure to fluoroquinolones [odds ratio (OR) 4.54, 95% confidence intervals (CIs) 1.78–11.54, *P* = 0.001] and exposure to antipseudomonal penicillins (OR 2.57, 95% CI 1.00–6.71, *P* = 0.04) were independent risk factors for CRKp infections.

Falagas ME., et al. J Antimicrob Chemo 2007; 60:1124

Avoid selection pressure

- Temptation for broad therapy
- Fear of "missing" something
- Why do other classes of Abx select for CRE?
  - These are almost always multi-drug resistant
  - Healthy flora likely suppresses these highly resistant strains

De-escalation

- Studies of de-escalation therapy are limited
  - Poor uptake of de-escalation recommendations
  - Study groups not always comparable
  - Hard to prove a negative
- Good news: no evidence of harm
- Bad news: hard to prove ecological benefit
- Unsurprising news: ID docs are more comfortable with de-escalation than other clinicians

Masterton RG. Crit Care Clin 2011; 27:149

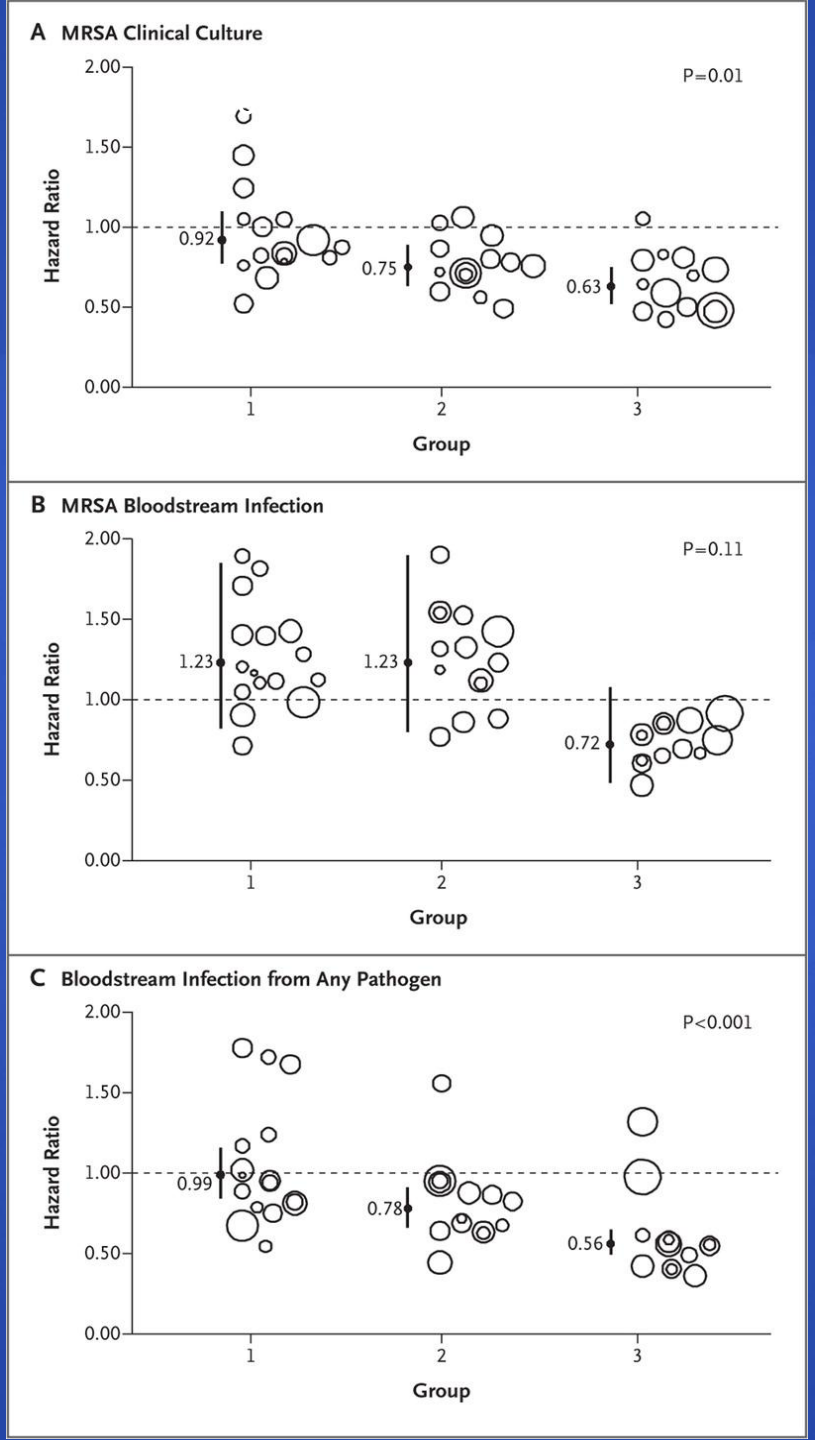
The Universe

- Universal decontamination… really works in the ICU
- Standard "hospital contact isolation" was not successful in the NIH CRE outbreak
  - Even equipment decontamination was challenging
- Targeted strategies (e.g. MRSA) are cumbersome
- What if something simpler were available?

Trial of target vs. general

- A large cluster randomized trial was done to test various MRSA strategies
- Screening and isolation plus/minus decolonization were less effective than decolonization efforts for all ICU patients

Huang SS et al. N Engl J Med 2013;368:2255-2265.



Grp 1: screen/isolate

Grp 2: screen/isolate decolonize

Grp 3: decolonize

Interventions for Reducing Antibiotic Exposure in Hospitals.

Interventions for Reducing Antibiotic Exposure in Hospitals.

Intervention	Comments
Promote clear, accessible decision support for appropriate duration of antibiotic therapy	Target common diagnoses and provide links to evidence
Use standardized order sets	Clearly define the appropriate antimicrobial agent, dose, and duration of treatment
Make the antibiotic indication visible at the point of care	Potential strategies include requiring the indication to be specified at the time the order is written and highlighting the indication on the medication administration record
Include start day, day of treatment, and expected duration in documentation of patient care	Provide visible reminders of the amount of antibiotic received and expected, facilitating awareness and daily decision making
Implement an antibiotic "time out" after 72 hours of treatment	Promotes timely, team-based assessment of whether antibiotic therapy can be discontinued or de escalated
Send appropriate cultures before starting antibiotics	Positive cultures help to tailor regimens to the narrowest spectrum appropriate; negative cultures reduce clinicians' anxiety about discontinuing unnecessary therapy
Implement prospective-audit with feedback strategies and build an organizational culture in which feedback is viewed as valuable input toward enhancing safety and quality of care	Engages frontline clinicians and tracks progress

Sandora TJ, Goldmann DA. N Engl J Med 2012;367:2168-2170.

The NEW ENGLAND JOURNAL of MEDICINE

Does CRE colonization exist?

- Colonization is a prelude to infection
- Not all colonized patients will proceed to infection
- Rx of colonized patients not likely to be effective
  - In a study of 42 patients, nearly ½ had only colonization
  - Of these about ½ were treated with antibiotics
  - Only 1 went on to show infection (29 days later)

Rihani DS, et al. Scand J Infect Dis 2012; 44:325.

How to screen

- First, determine WHOM to screen
- Culture?
  - Chromogenic agar can be helpful in environmental screening
- PCR
  - If you know which KPC genotype you are looking for

Lerner A, et al. J Clin Microbiol. 2013; 51:177
Lerner A. Antimicrob Agents Chemother. 2013; 57:1474

Consider LTACH

- Long term acute care hospitals (LTACH) are a source of CRE
- In Chicago study, > 30% of patients in 7 LTACHs colonized/infected by KPC strains
  - Compared to 3.3% in acute care hospitals
- Smart to screen patients entering acute care
- Possible role of health workers going back and forth?

Lin MY, et al. Clin Infect Dis 2013; 57:1246

Where does this leave us?

- Plenty of suggestions, little data
- Where to go from here?

The good

- We have techniques to screen for and distinguish among highly resistant Enterobacteriaceae
- Molecular techniques enhance understanding of spread
- Getting better at universal decontamination, etc.
- Not all colonization leads to infection (but a lot does)
  - Some strain not exceptionally virulent
- Treatments work reasonably in patients with clinical reserve

The bad and the ugly

- Hospitals, LTACHs nursing homes are not ready for CRE
- Screening, arbitrary; treatment inconsistent (chaotic?)
- Optimal infection prevention strategy still not clear
  - Role of equipment sterilization, environment, etc.
- CRE getting more resistant… and maybe more virulent
- Coming soon, ambulatory CRE infection
  - NDM epidemic
  - ESBL Enterobacteriaceae

So, it's that time

If you're going to shoot, shoot. Don't talk