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

Thomas Fekete, MD
Temple University School of Medicine

No conflicts
THE GOOD
THE BAD
AND THE UGLY
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

THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
1912 Growler

$19.12
Photograph taken from the Carpathia of the iceberg thought to have sunk the Titanic.
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

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
But then...

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- 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 sterilization stopped epidemic?
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

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
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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?

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<td><strong>Number tested</strong></td>
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<td><em>Escherichia coli</em></td>
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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

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

KPC Enterobacteriaceae infections

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

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<td>Urine</td>
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<td>0/6(0)</td>
<td>4/24(17)</td>
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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)

SICU outbreak Italy

- 30 cases of KPC K. pneumoniae (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
Infection prevention starts with hand hygiene

Relevant to community and hospital settings

How do we know it works?

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<th>Reference</th>
<th>Hospital setting</th>
<th>Results</th>
<th>Duration of follow-up</th>
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<td>Caswell and Phillips (1977)</td>
<td>Adult ICU</td>
<td>Significant reduction (p=0.001) in the percentage of patients colonised or infected by <em>Klebsiella</em> spp</td>
<td>2 years</td>
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<td>Conly et al (1989)</td>
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<td>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%)</td>
<td>6 years</td>
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<tr>
<td>Simmons et al (1990)</td>
<td>Adult ICU</td>
<td>No effect on health-care-associated infection rates (no significant [p&lt;0.05] improvement of hand hygiene adherence)</td>
<td>11 months</td>
</tr>
<tr>
<td>Doebbeling et al (1992)</td>
<td>Adult ICUs</td>
<td>Significant (p&lt;0.02) difference between rates of health-care-associated infection using two different hand hygiene agents</td>
<td>8 months</td>
</tr>
<tr>
<td>Webster et al (1994)</td>
<td>NICU</td>
<td>Elimination of MRSA, when combined with multiple other infection control measures. Reduction of vancomycin use. Significant p&lt;0.02 reduction of nosocomial bacteraemia (from 2.6% to 1.1%) using triclosan compared with chlorhexidine for handwashing</td>
<td>9 months</td>
</tr>
<tr>
<td>Zafar et al (1995)</td>
<td>Newborn nursery</td>
<td>Control of a MRSA outbreak using a triclosan preparation for handwashing, in addition to other infection control measures</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Larson et al (2000)</td>
<td>MICU/NICU</td>
<td>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</td>
<td>8 months</td>
</tr>
<tr>
<td>Pittet et al (2000)</td>
<td>Hospital-wide</td>
<td>Significant (p=0.04 and p&lt;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</td>
<td>5 years</td>
</tr>
<tr>
<td>Hilburn et al (2003)</td>
<td>Orthopaedic surgical unit</td>
<td>36.1% decrease in infection rates (from 8.2% to 5.3%)</td>
<td>10 months</td>
</tr>
<tr>
<td>MacDonald et al (2004)</td>
<td>Hospital-wide</td>
<td>Significant (p=0.03) reduction in hospital-acquired MRSA cases (from 1.9% to 0.9%)</td>
<td>1 year</td>
</tr>
<tr>
<td>Swoboda et al (2004)</td>
<td>Adult intermediate care unit</td>
<td>Reduction in health care-associated infection rates (not significant, p value not reported)</td>
<td>2.5 months</td>
</tr>
<tr>
<td>Lam et al (2004)</td>
<td>NICU</td>
<td>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)</td>
<td>6 months</td>
</tr>
<tr>
<td>Won et al (2004)</td>
<td>NICU</td>
<td>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</td>
<td>2 years</td>
</tr>
<tr>
<td>Zerr et al (2005)</td>
<td>Hospital-wide</td>
<td>Significant (p=0.01) reduction in hospital-associated rotavirus infections</td>
<td>4 years</td>
</tr>
<tr>
<td>Rosenthal et al (2005)</td>
<td>Adult ICUs</td>
<td>Significant (p&lt;0.001) reduction in health-care-associated infection rates (from 47.5 per 1000 patient-days to 27.9 per 1000 patient-days)</td>
<td>21 months</td>
</tr>
<tr>
<td>Johnson et al (2005)</td>
<td>Hospital-wide</td>
<td>Significant (p=0.01) reduction (57%) in MRSA bacteraemia</td>
<td>36 months</td>
</tr>
</tbody>
</table>

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

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
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?
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

Grp 1: screen/isolate

Grp 2: screen/isolate decolonize

Grp 3: decolonize
## Interventions for Reducing Antibiotic Exposure in Hospitals.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote clear, accessible decision support for appropriate duration of antibiotic therapy</td>
<td>Target common diagnoses and provide links to evidence</td>
</tr>
<tr>
<td>Use standardized order sets</td>
<td>Clearly define the appropriate antimicrobial agent, dose, and duration of treatment</td>
</tr>
<tr>
<td>Make the antibiotic indication visible at the point of care</td>
<td>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</td>
</tr>
<tr>
<td>Include start day, day of treatment, and expected duration in documentation of patient care</td>
<td>Provide visible reminders of the amount of antibiotic received and expected, facilitating awareness and daily decision making</td>
</tr>
<tr>
<td>Implement an antibiotic “time out” after 72 hours of treatment</td>
<td>Promotes timely, team-based assessment of whether antibiotic therapy can be discontinued or de escalated</td>
</tr>
<tr>
<td>Send appropriate cultures before starting antibiotics</td>
<td>Positive cultures help to tailor regimens to the narrowest spectrum appropriate; negative cultures reduce clinicians’ anxiety about discontinuing unnecessary therapy</td>
</tr>
<tr>
<td>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</td>
<td>Engages frontline clinicians and tracks progress</td>
</tr>
</tbody>
</table>
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)

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

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?

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