Molecular Screening for MRSA: Impact on Patient Care

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Disclosures

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Goals for the presentation today

• Define the problem of MRSA in the US today
  » Include strategies which are used to prevent its spread
  » Discuss the current controversies surrounding admission screening for MRSA

• Discuss different techniques that have been applied for the detection of this organism when screening is done:
  » Molecular methods
    • PCR
  » Culture methods
    • Chromogenic agar
Resistance in S. aureus

- Methicillin/oxacillin resistance mechanism
  - Penicillin Binding Protein (PBP 2a)
    - Encoded by mecA
    - β-lactams bind to PBPs to inhibit cell wall synthesis and cause cell lysis
    - PBP 2a has a lower affinity for β-lactams than wild type PBPs which allows the organism to grow even in the presence of all β-lactams

Rybak MJ, LaPlante KL
Pharmacotherapy. 2005 Jan;25(1):77
Methods to distinguish/characterize MRSA

- **Antibiogram**--drug susceptibility profiles

HA-MRSA

- pen
- doxy
- cefox
- tmp-smz
- clinda
- gent
- vanc

CA-MRSA

- pen
- doxy
- cefox
- tmp-smz
- clinda
- gent
- vanc

UNC

- 93% are erythromycin resistant
- 16% clindamycin resistant

8/30/2010
# Episodes of Bloodstream Infections at UNC Hospitals 7-09 to 6-10

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>203</td>
</tr>
<tr>
<td>MRSA=88 (43%)</td>
<td></td>
</tr>
<tr>
<td>Coag neg staph</td>
<td>172</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>140</td>
</tr>
<tr>
<td><strong>Enterococcus spp</strong></td>
<td>85</td>
</tr>
<tr>
<td>viridans streptococci</td>
<td>79</td>
</tr>
<tr>
<td><strong>Klesiella pneumoniae</strong></td>
<td>73</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>51</td>
</tr>
<tr>
<td><strong>Candida albicans</strong></td>
<td>36</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>33</td>
</tr>
</tbody>
</table>
Clinical Significance of MRSA

20-30% mortality rate in MRSA BSIs

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>No. of deaths in 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA infection¹</td>
<td>18,650</td>
</tr>
<tr>
<td>AIDS</td>
<td>12,543</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>648</td>
</tr>
<tr>
<td>Meningococcal infection</td>
<td>123</td>
</tr>
<tr>
<td>Invasive GAS infection</td>
<td>118</td>
</tr>
</tbody>
</table>

Current MRSA Rates in the US

- 43 US medical centers
- June – December, 2009
- 4210 isolates of *S. aureus*
  - recovery in hospital laboratories
  - 54% IP, 44% OP, 2% ?
  - 48% SSTI, 26% BSI, 12% LRTI

53.4% *mecA* positive

(Richter and Doern et al, unpublished observations, 2010)
Economic Impact of MRSA

Median Hospital Charges:

- MRSA greater 90-day mortality vs. MSSA (adjusted odds ratio, 3.4; 95% CI: 1.5-7.2)
- MRSA greater LOS after infection (media additional days = 5, p<0.001)

The controversy surrounding active surveillance for MRSA

• Because MRSA infection is clearly a public health threat, states have passed laws (Illinois, PA, NJ) or are considering laws that would require active surveillance for MRSA. Admission screening of high risk patients would be considered an important component of high risk screening.

• The major infection control professional organizations (APIC and SHEA) are opposed to this in part because they believe that **active surveillance** is only **part of a program** that will be necessary to control MRSA spread as well as the spread of other multi-drug resistant organisms (MDRO). Further there is controversy about how important a role active surveillance has in the control of MRSA infections with at least one systematic review suggesting there are no good data to support it. ([Weber et al Am J Infect Control 2007; 35:73-85, McGinigle et al Clin Infect Dis 200846:1717-25](#))
The controversy surrounding active surveillance for MRSA

- A seminal paper in support of admissions screening of all patients was by Robicsek et al. *(Ann Intern Med 2008, 148:409-418)*
  - They used PCR as a screening tool
  - They recommended decolonized patients which was attempted in more than half of the patients
  - Showed a 70% reduction in MRSA infections

- This manuscript has been criticized because multiple interventions were taken and historical controls were used for comparison so it was difficult to ascertain the importance of active surveillance in the reduction in the number of cases *(Diekema JCM 2010, 48: 686-689)*
Methods for active MRSA surveillance

- MRSA surveillance is typically done on a nasal swabs although culture of wounds may also be included
  » Additional sampling of axilla, groin and throat may increased yield but only minimally so it is not routinely done
- Broth enrichment
  » Reference method used in most research studies
  » Done by inoculating a broth containing selective agent for staphylococci (high salt) and/or oxacillin or cefoxitin and then plating on a selective or non-selective medium
- Molecular methods
  » Three FDA approved real time PCR kits in US
- Chromogenic agar
  » Used for direct plating of nasal swabs
  » Five available
Summary of what we know about MRSA PCR

- Three real time PCR tests are FDA approved
  - Xpert MRSA Cepheid
  - GeneOhm MRSA Becton-Dickinson
  - LightCycler MRSA Roche
- PCR tests are in general more sensitive than directly plated screening cultures but also 5 to 15 times more expensive
- PCR tests have a turn around time of approximately 1 to 2 hours
- The Cepheid test has the advantage over the over two tests of much simpler specimen processing and as a result shorter turn-around-time
Summary of what we know about MRSA PCR

• All the three tests have a sensitivity of 90-95% compared to broth culture and in clinical evaluations were found to be more sensitive than direct plating on chromogenic agar; the Roche test (Lightcycler) appears to be more specific (Peterson et al JCM 2010, 48:1661-6, Wolk et al, JCM 2009, 47:758-64, Lucke et al JCM 2010, 48:981-4, Snyder et al JCM 2010, 48:1305-9)

• Both GeneOhm and Cepheid have a problem with false positive especially with MSSA strains that have excision of the SCCmec. The prevalence of this strain may vary depending upon the geographic locale (Marlowe and Wolk Clin Micro Newsl 2008, 30:183-188, Snyder et al. JCM 2010 48:1305-9, Miller, MB, unpublished data)
Unintended consequences of false positive MRSA PCRs

- In two recent studies, approximately 30% of PCR positives were identified as being false positives using one of the PCR systems (GeneOHM) (Peterson et al JCM 2010 48:1661-6, Snyder et al JCM 2010, 48 1305-9)
- Individuals with false positive PCR will be placed on contact isolation
- Consequences of isolation (Diekema JCM 2010 48:686-9)
  - Patient feeling anxious or depressed
  - Receives fewer caregiver visits
  - May miss having vital signs taken or medication doses
  - Increased numbers of falls, pressure ulcers, electrolyte disorders
  - Lower satisfaction with their care
Why would people do culture?

- Direct culture is more specific than PCR although less sensitive
  - Fewer instances of false positives and thus fewer unintended consequences
- With PCR being done once a day in most settings, turn-around-time is not that much better for PCR than screening culture on chromogenic agar which are typically plated in real time
- Significantly less expensive
- Much less complex especially compared with PCR tests that require nucleic acid extraction
MRSA chromogenic agar

- Currently 5 on the market
- Sensitivity of these media are approximately 90-95% so only slightly less than PCR but may take up to 48 hr to become positive
- Cultures giving specific chromogenic reaction at 24 hours are more likely to be MRSA (higher specificity) but more isolates with appropriate chromogenic reaction will be found at 48 hours (higher sensitivity) but fewer will be MRSA (lower specificity)
- Malhorta-Kumar et al. 2010 48:1040-6
Active surveillance at UNC

• After the publication of Robicsek article and other information obtained from experience at ECU SOM teaching hospital, we undertook active surveillance for all ICU admissions and other selected high risk situations
• Used Xpert MRSA PCR screening of nasal swab
• Testing was offered twice daily Monday-Friday and once/day on weekends
• Patients were maintained on contact precautions until MRSA results were known
Outcome of UNC ICU admission screening

- UNC 18 month outcome
  - Screen ICU admissions
  - Other targeted surveillance

Courtesy: Emily Sickbert-Bennett, PhD
Why did we fail?

• No evidence of other parts of the successful MRSA elimination program discussed by Robicsek et al..
  » importantly MRSA decolonization using mucpirocin and chlorohexidine wash was not attempted in our setting

• This suggests that a multi-disciplinary team of which laboratorians are contributing members needs to be in place for successful interventions such as the one described by Robicsek et al. to take place.
Conclusions

- MRSA is a major health problem in the US
- The use of active surveillance for control of MRSA is controversial but is being mandated by a number of states
- PCR is a highly sensitive and rapid method for detection of MRSA; however false positive results may have significant unintended consequences
- Our attempt to use active surveillance on MICU patients using PCR was unsuccessful pointing out the need for multi-disciplinary approach to be in place before offering this testing
- New technologies such as loop-mediated isothermal PCR (LAMP) and helicase dependent amplification (HAD) are low cost alternative to PCR that may put price pressure on this technology
Thanks for Gary Doern, Emily Sickert-Bennett, Melissa Miller, and Alan Kerr for providing data for this presentation