The Evolution of MRSA: Does it Matter for Infection Control?

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Disclosures

• Salary and benefits from Cepheid a molecular diagnostics company
Staphylococcus aureus – What comes to mind?
The Continuing Diversification of MRSA Leads to Several Challenges

- Strains not detected by molecular methods
- Phenotypically susceptible MRSA (stealth MRSA)
- Emergence of virulent clones
- All of which are challenges for infection prevention
spa Typing Indicates Increasing S. aureus Diversity

Spa-types: 18,613

Gives you a sense of the constant evolution that this organism undergoes, including acquisition of virulence factors and antimicrobial resistance genes.

Sequence data curated by SeqNet.org

https://www.spaserver.ridom.de/
Accessed on 3/8/2019
Staphylococcus aureus is a genetically dynamic organism that can harbor a wide variety of mobile genetic elements including resistance genes.

S. aureus isolates are continually under selective pressure from antibiotic use, immune responses, and environmental factors that often lead to genetic changes in the organism in order to survive. Not every strain responds in the same way.

The sequence changes that the organism undergoes may occur in regions targeted by molecular diagnostics and may impact the accuracy of those tests.

Antimicrobial resistance genes are among the genetic elements often acquired by S. aureus.
Characterization of the staphylococcal cassette chromosome mec insertion site in 108 isolates lacking the mecA gene and identified as methicillin-resistant Staphylococcus aureus by the Xpert MRSA assay

M. Stojanov, D. S. Blanc

Analysis of Staphylococcal Cassette Chromosome mec in BD GeneOhm MRSA Assay-Negative Strains

Meng Zhang, a Teruyo Ito, a,b Shanshuang Li, a Shigeki Misawa, c Shigemi Kondo, d Takashi Miida, d Akimichi Ohsaka, e Keiichi Hiramatsu a,b

Antimicrobial Agents and Chemotherapy p. 2890–2891

Failure of the BD GeneOhm StaphSR Assay for Direct Detection of Methicillin-Resistant and Methicillin-Susceptible Staphylococcus aureus Isolates in Positive Blood Cultures Collected in the United States

James W. Snyder, 1* Gina K. Munier, 2 Stacy A. Heckman, 2 Pamela Camp, 3 and Timothy L. Overman 3,4

Molecular methods called these strains MRSA, but colonies were phenotypically oxacillin-susceptible.

However, when exposed to cefoxitin, colonies became oxacillin resistant.

Resistance may emerge on therapy.

*Journal of Global Antimicrobial Resistance 1 (2013) 79–83*
Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections — United States


MRSA decreasing

MSSA increasing

Isaac See, Yi M, Valerie Albrecht, Maria Karlsson, Ghinwa Dumyati

New strains have increased virulence factors and ability to spread, that makes them an infection issue. Most of the decline in MRSA BSIs was from decreases in USA100 BSI incidence. **Prevention of USA300 MRSA BSIs in the community will be needed to further reduce burden from MRSA BSIs.**
MRSA Healthcare-associated bloodstream infections 2011-2016 in Canada
Historical View of Strain Evolution

Community MRSA: the Story of USA300
Four Pediatric Deaths from Community-acquired Methicillin-Resistant *S. aureus* -- Minnesota and North Dakota, 1997-1999 (MMWR 48:707; 1999)

- **Background:** Children with severe staphylococcal disease treated seemingly appropriately with cephalosporins, failed therapy due to resistance and died.

- **Key finding:** MRSA infections were emerging in community settings among patients without established risk factors (e.g., recent hospitalization, recent surgery, residence in a long-term-care facility, or injecting-drug use) and antimicrobial therapy needed to be modified.

- **Strain type:** USA400 (MW2) ST1: SCC*mec*IV, PVL+

- **Beginning of a major change in MRSA epidemiology**
Change from USA400 to USA300 in Pediatric CA-MRSA Isolates, Dallas Texas, 1999-2002

Annual rates of visits for skin and soft-tissue infections (SSTIs) in the United States (1997-2005)

Increase in SSTIs from 32.1 to 48.1/1000 population
a 50% increase (p=0.003)

Increase in visits for abscess/cellulitis increased from 4.6 to 9.6 million;
a 109% increase (p=0.001)

Other SSTI visits (like impetigo) remained steady

ARCH INTERN MED/VOL 168 (NO. 14), JULY 28, 2008
Since ST8-MRSA-IVa/USA300 has proved to be a successful clone capable of epidemic spread, the emergence of a *cfr*-positive variant of this strain is cause for significant concern and warrants close surveillance.
USA300 with Reduced Susceptibility to Critical Antimicrobial Agents

We describe a case of treatment failure caused by a strain of USA300 CA-MRSA with intermediate susceptibility to vancomycin and reduced susceptibility to daptomycin. 56-year-old man with lumbar osteomyelitis after a 6-weeks of vancomycin for catheter-associated septic thrombophlebitis.

Intermediate Vancomycin Susceptibility in a Community-associated MRSA Clone

Christopher J. Graber,* Margaret K. Wong,* Heather A. Carleton,* Françoise Perdreau-Remington,* Barbara L. Haller,* and Henry F. Chambers*
Comparing PFGE to spa types for Blood and Nasal MRSA Isolates

USA300 contains at least 13 spa types which can harbor several different SCCmec types

<table>
<thead>
<tr>
<th>TABLE 1: spa, SCCmec, and pulsed-field gel electrophoresis types of study isolates</th>
<th>Blood</th>
<th>Total no. of isolates (194)</th>
<th>Nares</th>
<th>Total no. of isolates (299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFGE type</td>
<td>spa type-SCCmec (n)</td>
<td>(n)</td>
<td>Total no. of isolates</td>
<td>(n)</td>
</tr>
<tr>
<td>USA100</td>
<td>t002-II (43), t002-NT (1), t045-II (4), t062-II (1), t062-IV (1), t067-II (1), t068-II (1), t214-II (1), t242-II (9), t242-NT (1), t688-II (1), t985-II (1), t1062-II (1), t2358-II (1), t2666-II (1), t6778-II (1)</td>
<td>69</td>
<td>t002-II (110), t002-NT (5), t010-II (1), t045-II (5), t062-II (1), t067-II (4), t071-II (1), t088-II (3), t105-II (3), t105-NT (4), t242-II (15), t242-NT (5), t509-II (2), t535-II (1), t539-II (2), t548-II (1), t548-NT (1), t570-II (1), t586-II (1), t587-II (1), t895-II (1), t1220-II (1), t1567-II (1), t2666-II (1), t3357-II (1), t3558-II (1), t4571-II (1), t4916-II (1), t4963-II (1), t5081-II (1), t6778-II (1)</td>
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<tr>
<td>USA200</td>
<td>None observed</td>
<td>0</td>
<td>93</td>
<td>t021-IV (1)</td>
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<td>USA300</td>
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<td>0</td>
<td>0</td>
<td>t008-IV (76), t008-NT (2), t024-IV (1), t051-IV (1), t304-IV (2), t334-IV (1), t622-IV (1), t648-IV (1), t6167-IV (1), t2743-IV (2), t3908-IV (1), t0069-IV (2), t4229-IV (1), t6774-IV (1)</td>
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<tr>
<td>USA400</td>
<td></td>
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<td>t178-IV (1)</td>
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<td>USA500</td>
<td>t604-IV (8)</td>
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<tr>
<td>USA700</td>
<td>None observed</td>
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<tr>
<td>USA800</td>
<td>t002-IV (3), t062-IV (1), t1265-IV (1)</td>
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<td>USA1000</td>
<td>t216-IV (1)</td>
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<td>CMRSA9</td>
<td>t008-VIII (1), t197-VIII (1)</td>
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<td>EMRSA15</td>
<td>t020-IV (1)</td>
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<td>ST239-associated pattern</td>
<td>t037-III (2)</td>
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<tr>
<td>Unnamed</td>
<td>Unnamed-II (1), unnamed-IV (1), t189-IV (1), t668-II (5), t6770-II (2), t6771-IV (1), t6771-II (1)</td>
<td>12</td>
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</table>
Origins of USA300- One of the Many Descendants of Clonal Complex 8

Progenitor ST 8 MSSA

USA500

USA300

Brazilian clone

Iberian clone

Li et al PNAS 2009
Strain diversity is also about the methicillin-Resistance elements
These have both stable regions (mec and ccr) and variable regions. Some include additional antimicrobial resistance genes. Note the inversion of mec and ccr in types VII and IX.
Novel Types of Staphylococcal Cassette Chromosome mec Elements Identified in Clonal Complex 398 Methicillin-Resistant Staphylococcus aureus Strains

Shanshuang Li, Robert Leo Skov, Xiao Han, Anders Rhod Larsen, Jesper Larsen, Marit Sørum, Mireille Wulf, Andreas Voss, Keiichi Hiramatsu, and Teruyo Ito
What does this mean for Infection Prevention?

- Be aware of the fact that epidemic clones continue to emerge and disseminate.
- USA300 is a remarkably successful clone, but others, like ST398, the livestock clone, are emerging in humans and causing outbreaks in the Netherlands and elsewhere.
- Be aware that some oxacillin-susceptible *S. aureus* especially from multidrug-resistant strains from blood cultures, may be MRSA.
Conclusions

- *Staphylococcus aureus* is a genetically dynamic organism that continually acquires new virulence mechanisms and antimicrobial resistance genes.
- Some of these virulence genes can lead to increased chance for outbreaks.
- Some mutations mask methicillin resistance, which is readily recovered when the strain is exposed to antibiotics.
- Infection preventionists need to be vigilant for potential outbreaks as new strain types are introduced into hospitals.
- Nonetheless, remember that infection control works and rates are dropping globally.
Thank You.

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