MRSA in Humans: 
Epidemiology, Resistance, and Treatment

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Durham, North Carolina
## Disclosures

<table>
<thead>
<tr>
<th>Nature of Relevant Financial Relationship</th>
<th>Commercial Interest</th>
</tr>
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<tbody>
<tr>
<td>Grant or research support</td>
<td>Merck, Theravance, Cerexa, Pfizer, Novartis, MedImmune, Advanced Liquid Logics, National Institutes of Health</td>
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<tr>
<td>Paid consultant</td>
<td>Cerexa, Durata, Novartis, Merck, Pfizer, NovaDigm, The Medicines Company, MedImmune</td>
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<tr>
<td>Speaker’s Bureau</td>
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<td>Employment</td>
<td>Duke University</td>
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<td>Honoraria</td>
<td>Arpida, Astellas, Cubist, Inhibitex, Merck, Pfizer, Targanta, Theravance, Wyeth, Ortho-McNeil, Novartis, Vertex Pharmaceuticals</td>
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<tr>
<td>Membership on advisory committees or review panels, board membership, etc.</td>
<td>Merck Co-Chair V710 Vaccine</td>
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<td>Ownership Interest (e.g., stocks, stock options or other interests)</td>
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<td>Other relevant financial interests</td>
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</table>
Lessons Learned:

Epidemiology: Dynamic & Dramatic

Resistance: Growing Problem

Treatment: Success, Setback, & Confusion
Lessons Learned:

Epidemiology: Dynamic & Dramatic

Resistance: Growing Problem

Treatment: Success, Setback, & Confusion
Intrafamilial Transmission of *S. aureus* is a Recent Phenomenon


**Netherlands:** Mollema *J Clin Microbiol* 2010; 48: 202–7.


**Staphylococcus aureus** Colonization Among Household Contacts of Patients With Skin Infections: Risk Factors, Strain Discordance, and Complex Ecology

- Patients with STI & their household contacts in LA, Chicago
- Nares, Oropharynx, Inguinal Region cultured
- Colonization: Index patients: 40% (137/350)  
  Household contacts: 53% (405/812)
- Nares only culture would have missed 48% of *S. aureus*
- Most common infecting and colonizing strain USA300
- 65% households had >1 *S. aureus* genotype

**CONCLUSIONS**

USA300 MRSA associated with household transmission
Decolonization may need to address extra-nasal sites
Human-Animal MRSA Transmission

MRSA Transmission between Cows and Humans

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 2, February 2007

Don't Mess with the Pig

Methicillin-resistant \textit{Staphylococcus aureus} in Horses and Horse Personnel, 2000–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 3, March 2005

Transmission of a Panton-Valentine Leucocidin-Positive, Methicillin-Resistant \textit{Staphylococcus aureus} Strain between Humans and a Dog


Methicillin-Resistant \textit{Staphylococcus aureus} in a Family and Its Pet Cat

• NT-MRSA - distinct clone (ST398) in Dutch Pigs

• Unknown Prior to 2002

• Now > 20% human MRSA in Netherlands

MRSA ST398 in Midwestern US Swine & Swine Workers

- Cultured nares of 299 swine and 20 workers from 2 hog farms
- Overall MRSA Prevalence:
  - Swine 49% (147/299)
  - Workers 45% (9/20)
- ST398 was only strain present
CC398 MRSA is Present in Hog Workers from Industrial, but not Antibiotic-Free Facilities in North Carolina

• Similar *S. aureus* carriage in both groups
  Industrial: 41%
  Antibiotic-Free: 40%

• CC398 Carriage
  Industrial Workers: 41% (17/41)
  Antibiotic Free Workers 7% (3/42)
Livestock-Asstd MRSA in US Patients: Where’s the Beef?

NEWS FOCUS

INFECTION DISEASE

From Pigs to People: The Emergence of a New Superbug

The discovery of a novel strain of MRSA able to jump from livestock to humans has sparked a multicountry effort to see how dangerous it might be.

The first infection was puzzling, almost inexplicable. In July 2004, Andreas Voss of Radboud University Nijmegen Medical Center in the Netherlands admitted a 6-month-old girl for surgery to repair a congenital heart defect. Because an infection with the common bacterium Staphylococcus aureus would pose a grave risk following heart surgery, Voss and his colleagues screened the baby girl for the microbe. They found not just S. aureus but also a menacing drug-resistant form known as methicillin-resistant S. aureus (MRSA). The physicians were flummoxed. Although MRSA has reached epidemic proportions in much of the developed world, MRSA infections are rare in the Netherlands, thanks to an aggressive “search and destroy” policy the country launched in the mid-1990s to screen or other livestock harbored MRSA, and no MRSA strain had ever been known to jump from livestock to humans. If the Dutch doctors’ fears were correct, a novel strain had just gained that ability, opening up a new route for a potentially dangerous superbug to spread among humans. “Initially, we were very much afraid that this would be a major problem that could spread to the entire population,” says Jan Kluytmans, a microbiologist at VU University Medical Center in Amsterdam whom Voss recruited early on to help investigate.

In recent months, the dangers of livestock-associated MRSA...
Multi-Drug Resistant *S. aureus*, but Not MRSA, is Common in Meat Products

Transmission of MRSA between Companion Animals and Infected Human Patients Presenting to Outpatient Medical Care Facilities

Jorge Pinto Ferreira¹,², Kevin L. Anderson¹, Maria T. Correa¹, Roberta Lyman¹, Felicia Ruffin², L. Barth Reller², Vance G. Fowler Jr.²

- 6% of MRSA-infected outpatients lived with an animal colonized with identical MRSA strain

- no MRSA found in the control population (human and animal)
Nares/oropharyngeal cultures of Chimpanzees and sanctuary workers in Uganda and Zambia

Carriage: 58% chimpanzees
33% humans

45% of all Chimp isolates were human-associated lineages

Higher antibiotic resistance than wild chimps

Concern: release of sanctuary-raised chimps risks transmission to wild chimps

CONCLUSION: Plans to reintroduce sanctuary apes should be reevaluated in light of the high risk of introducing human-adapted S. aureus into wild ape populations where treatment is impossible.
Soft Tissue Infection
Epidemiology of *Staphylococcus aureus* Blood and Skin and Soft Tissue Infections in the US Military Health System, 2005-2010

- DOD TRICARE recipients (56 million person-years)
- Unadjusted: Bacteremia: \(4.7/100\,000\) person-years
  - STI: \(142.8\) per \(100\,000\) person-years
- Bacteremia: All forms Decreased Significantly
  - Community \(↓\) MRSA \(\text{to } 1.2/100,000\) \(p=0.005\)
  - Community \(↓\) MSSA \(\text{to } 1.7/100,000; \ p=0.005\)
  - Hospital \(↓\) MRSA \(\text{to } 0.4/100,000\) \(p=0.005\)
  - Hospital \(↓\) MSSA \(\text{to } 0.3/100,000; \ p=0.05\)
- SSTI: No significant overall trend in frequency
  - Prevalence of Community MRSA \(↓\) to 52% (\(p < 0.001\))

**CONCLUSIONS:** All forms of *S. aureus* bacteremia and proportion of Community SSTI due to MRSA declined
Endocarditis
Nationwide Inpatient Sample (NIS) Dataset
78.2 Million Patients from 1999-2008

P<0.001
Compared to 1999, *S. aureus* increased, while *Streptococci* decreased.

Primary risk factor: Healthcare contact.

Associations of Bacterial Genotype & Endocarditis

Methicillin-Susceptible *Staphylococcus aureus* Endocarditis Isolates Are Associated With Clonal Complex 30 Genotype and a Distinct Repertoire of Enterotoxins and Adhesins

Juhsien J.C. Nienaber,¹ Batu K. Sharma Kuinkel,¹ Michael Clarke-Pearson,¹ Supaporn Lamlertthon,¹ Lawrence Park,¹² Thomas H. Rude,¹ Steve Barrière,³ Christopher W. Woods,¹,⁴ Vivian H. Chu,¹,² Mercedes Marín,⁵ Suzana Bukovski,⁶ Patricia Garcia,⁷ G.Ralph Corey,¹,² Tony Korman,⁸ Thanh Doco-Lecompte,⁹ David R. Murdoch,¹⁰ L. Barth Reller,¹ and Vance G. Fowler Jr,¹,² for the International Collaboration on Endocarditis-Microbiology Investigators⁶

*The Journal of Infectious Diseases* 2011;204:704–13

An Association Between Bacterial Genotype Combined With a High-Vancomycin Minimum Inhibitory Concentration and Risk of Endocarditis in Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection

Clare E. Miller,¹ Rahul Batra,¹,² Ben S. Cooper,³,⁴ Amita K. Patel,² John Klein,² Jonathan A. Otter,¹ Theodore Kypraios,⁵ Gary L. French,¹ Olga Tosas,² and Jonathan D. Edgeworth¹,²

*Clinical Infectious Diseases* 2012;54(5):591–600
“Team Science” Approach to *S. aureus*: A Case Study

Polymorphisms in fibronectin binding protein A of *Staphylococcus aureus* are associated with infection of cardiovascular devices

Steven K. Lower\textsuperscript{a,1,2}, Supaporn Lamlerthton\textsuperscript{b,3,4}, Nadia N. Casillas-Ituarte\textsuperscript{a,1,2}, Roberto D. Lins\textsuperscript{d,1}, Ruchirej Yongsunthon\textsuperscript{a,5}, Eric S. Taylor\textsuperscript{a}, Alex C. DiBartola\textsuperscript{a}, Catherine Edmonson\textsuperscript{e}, Lauren M. McIntyre\textsuperscript{e}, L. Barth Reller\textsuperscript{b}, Yok-Ai Que\textsuperscript{f}, Robert Ros\textsuperscript{g}, Brian H. Lower\textsuperscript{a}, and Vance G. Fowler, Jr.\textsuperscript{b,2,3}

\textsuperscript{a}Ohio State University, Columbus, OH 43210; \textsuperscript{b}Duke University Medical Center, Durham, NC 27705; \textsuperscript{c}Naresuan University, Phitsanulok, Thailand 65000; \textsuperscript{d}Universidade Federal de Pernambuco, Recife, PE 50570-901, Brazil; \textsuperscript{e}University of Florida, Gainesville, FL 32611; \textsuperscript{f}University of Lausanne, Lausanne, 1011 Switzerland; and \textsuperscript{g}Arizona State University, Tempe, AZ 85287

Edited by Richard P. Novick, New York University School of Medicine, New York, NY, and approved October 5, 2011 (received for review June 8, 2011)
Fibronectin-FnBP binding

- FnBP is a bacterial surface protein
- FnBP binds to human fibronectin
CLINICAL RESEARCH AND BACTERIOLOGY
Clinical Groups:

• Cardiac Device Infection (CDI):
  
  *Pacemaker + SAB + Device Infection*

• Cardiac Device Uninfected (CDU):
  
  *Pacemaker + SAB + Device Uninfected*
3 SNPs are More Common in CDI

<table>
<thead>
<tr>
<th>synonymous SNP</th>
<th>non-binding region</th>
<th>amino acid change*</th>
<th>occurrence of non-synonymous SNP</th>
<th>P-value</th>
<th>relative risk (RR)</th>
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<tbody>
<tr>
<td>GAG to GAT</td>
<td>FnBPA-5</td>
<td>E652D</td>
<td>CDI: 12 (46)</td>
<td>CDU: 1 (5)</td>
<td>0.003</td>
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<tr>
<td>CAT to CAA</td>
<td>FnBPA-9</td>
<td>H782Q</td>
<td>CDI: 14 (54)</td>
<td>CDU: 1 (5)</td>
<td>0.0004</td>
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<tr>
<td>AAA to AAT</td>
<td>FnBPA-9</td>
<td>K786N</td>
<td>CDI: 14 (54)</td>
<td>CDU: 3 (15)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* E = Glutamic acid, D = Aspartic acid, H = Histidine, K = Lysine, N = Asparagine, Q = Glutamine, S = Serine and T = Threonine

Having > 1 of these SNPs increased the risk of CDI 11.5 times

ATOMIC FORCE MICROSCOPY
Atomic Force Microscope (AFM)

- measuring binding forces between fibronectin and a single cell of *S. aureus*
CDI Isolates Associated With Increased Strength & Binding Frequency

SNP Number and Binding Energy Are Directly Associated

<table>
<thead>
<tr>
<th>Occurrence of SNPs in FnBPA</th>
<th>Binding energy</th>
<th>Low (&lt;74 aJ)</th>
<th>High (&gt;74 aJ)</th>
<th>P value</th>
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<tr>
<td>CDI and CDU</td>
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<tr>
<td>≤1 SNP at 652, 782, 786</td>
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<td>20</td>
<td>10</td>
<td>&lt;0.01</td>
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<tr>
<td>&gt;1 SNP at 652, 782, 786</td>
<td></td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

MOLECULAR DYNAMIC SIMULATIONS OF FN-FNBPA BOND
MD Simulation

• Chinook Supercomputer (Dept. of Energy, Richland, Washington)
  - 160 trillion calculations/second
  - $21 million to build in 2009
• Calculations: 4 d (24h/d) (=2.8 core years on desktop)
• > 72,000 atoms in each Fn-FnBPA simulation
• $10^9$ atomic interactions calculated 10 million times for each simulation
782Q and 786N form extra hydrogen bonds with fibronectin

FnBPA-5: E652D

X-ray crystal structure model

Wild type E652

Variant 652D

Fibronectin Binding Protein A & Cardiac Device Infection

- Three SNPS (E652D, H782Q and K786N) were significantly more common in CDI

- Fibronectin adherence:

  higher in CDI

  in isolates multiple SNPs

- Potential Mechanism: Increased hydrogen bonds between human fibronectin and S. aureus fibronectin binding protein A
Community Acquired Pneumonia
Prevalence of Methicillin-Resistant Staphylococcus aureus as an Etiology of Community-Acquired Pneumonia

- 627 Prospectively enrolled patients from 12 University ED in Winter-Spring 2006-7
- 2.4% Culture confirmed MRSA
- MRSA USA300 in all genotyped isolates
- Risk factors for MRSA CAP:
  - Presentation: Shock, Pressors, Comatose, Intubation
  - History: Prior MRSA, Contact with STI Patient, Nursing Home
  - Radiograph: Cavitation, Multiple Infiltrates

CONCLUSIONS:
- MRSA CAP: uncommon, severe, often USA300
• 100 Community Onset Pneumonia & 236 CLA-BSI MRSA Isolates from unique patients from 6 Metropolitan centers

• USA100 vs. USA300

• USA300 was Associated with Early Complications in Pneumonia (admission - 48h)

• USA300 not associated with mortality in either Pneumonia or BSI
Negative Studies for PVL

Panton-Valentine Leukocidin Is Not the Primary Determinant of Outcome for Staphylococcus aureus Skin Infections: Evaluation from the CANVAS Studies

Amy Tong¹, Steven Y. C. Tong¹,⁴, Yurong Zhang¹, Supaporn Lamlerthton¹,³, Batu K. Sharma-Kuinkel¹, Thomas Rude¹, Sun Hee Ahn¹, Felicia Ruffin¹, Lily Llorens⁵, Ganesh Tamarana⁵, Donald Biek⁵, Ian Critchley⁵, Vance G. Fowler Jr.¹,² *

Presence of Genes Encoding the Panton-Valentine Leukocidin Exotoxin Is Not the Primary Determinant of Outcome in Patients with Complicated Skin and Skin Structure Infections Due to Meticillin-Resistant Staphylococcus aureus: Results of a Multinational Trial

In-Gyu Bae¹,²,³ Giang T. Tonthat,² Martin E. Stryjewski,¹,⁴ Thomas H. Rude,² Lindsay F. Reilly,² Steven L. Barriere,⁵ Fredric C. Genter,⁵ G. Ralph Corey,¹,² and Vance G. Fowler, Jr.¹,² *

Genotypic Characteristics of Staphylococcus aureus Isolates from a Multinational Trial of Complicated Skin and Skin Structure Infections

Steven J. Campbell¹, Hitesh S. Deshmukh,¹ Charlotte L. Nelson,² In-Gyu Bae,¹,⁴ Martin E. Stryjewski,² Jerome J. Federspiel,¹ Giang T. Tonthat,¹ Thomas H. Rude,¹ Steven L. Barriere,³ Ralph Corey,¹,² and Vance G. Fowler, Jr.¹,² *
Lessons Learned: The Epidemiology of *S. aureus* is Dynamic

- Interfamilial transmission: Often USA300
  Often beyond the nose

- Prevalence of *S. aureus* in infections is syndrome specific

- Zoonotic Transmission of MRSA happens

- New clones of *S. aureus* will continue to emerge

- Genetic techniques will increasingly help us understand the Epidemiology and Pathogenesis of *S. aureus*
Lessons Learned:

Epidemiology: Dynamic & Dramatic

Resistance: Growing Problem

Treatment: Success, Setback, & Confusion
“False Negative” MRSA by PCR-based Diagnostics

- *S. aureus* LG251: methicillin resistant but tested neg for *mecA* by PCR
- *mecA* homologue (*mecA*$_{LG251}$) in novel type XI SCCmec
- 3 difft MLST in cows
- Identified in human isolates in Scotland, England, Denmark
- *spa* type 843 predominant in cows & humans

Linezolid
Mechanisms of Linezolid Resistance:
Methylation of 23S rRNA

Horizontal Acquisition of Mobile Element: cfr

- 1st Description in Man from Colombia: (Toh Mol Microbiol 2007, 64:1506-14)
- Product hypermethylates A2503 in 23S rRNA & affects Binding
- cfr associated with mobile genetic elements, suggests transferable
- 12 ICU patients from April-June 2008 with LRSA - 4 clones

Point Mutation of Chromosomal Gene: rlmN

- RlmN: Conserved RNA Methyltransferase
- Mutation leads to increased methylation of 23S rRNA at A2503
- Linezolid Resistance acquired in patient with Persistent MRSA

Summary: Linezolid Resistance
Two Paths, Single Destination

• **Treatment emergent**: Several mutations, uncommon
• **Plasmid-mediated**: *cfr* is the problem

Horizontal acquisition

• **Affects Binding**
  - Mutation of 23S rRNA subunit
  - Methylation of A2503 in 23S rRNA

• **Concern**: Increased use = increased resistance
  - *ZEPHYR trial*
  - *Patent Expiry in 2015*
Lessons Learned:

Epidemiology: *Dynamic & Dramatic*

Resistance:  *Growing Problem*

Treatment:  *Success, Setback, & Confusion*
Confusion
### MRSA Infection with Vanco MIC ≥1.5ug/mL Associated with Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High MIC≥1.5μg/mL</th>
<th>Low MIC&lt;1.5μg/mL</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<td>Bae et al (12)</td>
<td>13</td>
<td>37</td>
<td>11</td>
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<td>Choi et al (15)</td>
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<td>36</td>
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<td>Haque et al (19)</td>
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<td>Hidayat et al (21)</td>
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<td>51</td>
<td>4</td>
<td>44</td>
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<td>Holmes et al (23)</td>
<td>28</td>
<td>94</td>
<td>16</td>
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<td>Lalueza et al (32)</td>
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<td>Liao et al (34)</td>
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<td>Lodise et al (36)</td>
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<td>66</td>
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<td>Musta et al (43)</td>
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<td>Neuner et al (45)</td>
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<td>Schweizer et al (50)</td>
<td>46</td>
<td>341</td>
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<td>Soriano et al (52)</td>
<td>37</td>
<td>130</td>
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<td>Takesue et al (53)</td>
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<td>97</td>
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<td>662</td>
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<td>van Hal et al (54)</td>
<td>38</td>
<td>117</td>
<td>73</td>
<td>236</td>
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<td>Wang et al (55)</td>
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<td>27</td>
<td>97</td>
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**Total (95% CI)**

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<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>289</td>
<td>1.64 [1.14, 2.37]</td>
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Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

Test for overall effect: Z = 2.65 (P = .008)
Vancomycin MIC Associated with 30 Day Mortality in MSSA Bacteremia

Is all Vancomycin Created Equal?

No

Generic Vancomycin Products Fail In Vivo despite Being Pharmaceutical Equivalents of the Innovator

Omar Vesga,1,2* Maria Agudelo,1,3 Beatriz E. Salazar,1,4 Carlos A. Rodriguez,1,5 and Andres F. Zuluaga1,5

Antimicrobial Agents and Chemotherapy, Aug. 2010, p. 3271–3279

Generic Vancomycin Enriches Resistant Subpopulations of Staphylococcus aureus after Exposure in a Neutropenic Mouse Thigh Infection Model

Carlos A. Rodriguez,a,b Maria Agudelo,a,b Andres F. Zuluaga,a,b and Omar Vesga


Yes

Product Quality of Parenteral Vancomycin Products in the United States


Quality Assessment of U.S. Marketplace Vancomycin for Injection Products Using High-Resolution Liquid Chromatography-Mass Spectrometry and Potency Assays

Michael E. Hadwiger,a Cynthia D. Sommers,a Daniel J. Mans,a Vikram Patel,b and Michael T. Boyne IIa


• Similar in Rabbit Endocarditis Model

(Tattevin #B-645 ICAAC 2012)
Based on these study results, an AUC/MIC ratio of \( \geq 400 \) has been advocated as a target to achieve clinical effectiveness with vancomycin.
## Data for AUC/MIC and Clinical Outcome

### Summary of Studies comparing AUC/MIC to Clinical Outcome in Patients with *S. aureus* Infection

<table>
<thead>
<tr>
<th>Design</th>
<th>Infection type</th>
<th>MIC</th>
<th>Outcome</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Association between Outcome and AUC/MIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moise-Broder(^1)</td>
<td>Retrospective n=50 (Van Rx)</td>
<td>HAP/VAP MR/MSSA</td>
<td>BMD</td>
<td>Clinical &amp; Microbiological Success</td>
</tr>
<tr>
<td>Kullar(^2)</td>
<td>Retrospective n=320</td>
<td>MRSA Bacteremia</td>
<td>BMD</td>
<td>Composite: - 30-d death, - SAB&gt;7d Symptoms</td>
</tr>
<tr>
<td>Brown(^3)</td>
<td>Retrospective n=50</td>
<td>MRSA IE/ Bacteremia</td>
<td>Etest</td>
<td>Attributable Mortality (n=8)</td>
</tr>
<tr>
<td><strong>No Association between Outcome and AUC/MIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuner(^4)</td>
<td>Retrospective n=222</td>
<td>MRSA Bacteremia</td>
<td>Etest</td>
<td>Persistent MRSAB (n=19)</td>
</tr>
<tr>
<td>Holmes(^5)</td>
<td>Prospective N=182</td>
<td><em>S. aureus</em> Bacteremia</td>
<td>BMD</td>
<td>30d Mortality (n=38)</td>
</tr>
</tbody>
</table>

\(^1\) Clin Pharmacok 2004; 43:925; \(^2\) CID 2011; 52:975; \(^3\) AAC 2012; 56: 634; \(^4\) DMID 2010; 67:228; \(^5\) ICAAC 2011 #A1681
NEGATIVE IN VIVO DATA

Vancomycin Dosed to Achieve AUC/MIC ≥400 Did Not Improve Outcome of MRSA Endocarditis Caused by Strains With Different VAN MICs

- 3 MRSA isolates with MIC 0.5, 1, and 2ug/mL each used to infect rabbits at control, regular dose, and high dose vanco (n=45 rabbits/isolate)

- After 2 days of VAN neither sterilization rate nor reduction in bacterial density in vegetations improved with Cmin levels of 15-20 mg/L or with AUC/MIC index ≥400.
Setback
Efficacy and Safety of an Investigational S. aureus Vaccine in Preventing Bacteremia and Deep Sternal Wound Infections After Cardiothoracic Surgery

VG Fowler Jr, KB Allen, ED Moreira, M Moustafa, F Isgro, HW Boucher, GR Corey, Y Carmeli, R Betts, JS Hartzel, NA Kartsonis, D Guris, S Smugar, B Turnbull, MJ DiNubile, MT Onorato, and A Sobanjo-ter Meulen

Analysis of Mortality and Multi-Organ Failure (MOF) in Subjects with Any *S. aureus* Infections

<table>
<thead>
<tr>
<th>Any <em>S. aureus</em> Infection</th>
<th>Deaths</th>
<th>Follow-Up Time (yrs)</th>
<th>Rate (per 100 person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V710</td>
<td>15</td>
<td>65.2</td>
<td>23.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
<td>94.4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

**Mortality**

**Mortality due to MOF**

Difference = V710 - Placebo
Bars = Unadjusted 95% CI

<table>
<thead>
<tr>
<th>MOFs</th>
<th>Follow-Up Time (yrs)</th>
<th>Rate (per 100 person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>65.9</td>
<td>7.6</td>
</tr>
<tr>
<td>0</td>
<td>94.5</td>
<td>0.0</td>
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</table>
Success
Randomized, Double-Blind Controlled Multicenter trial of Linezolid IV or Vanco for MRSA HCAP/HAP/VAP

Design: Hierarchical Non-inferiority-superiority$^1$

1° Endpoint: Clinical Cure at End of Study in evaluable Per Protocol patients

Cure rates in PP and mITT patients with MRSA HAP were higher in LNZ vs. VAN (58% v. 47%; p=0.042)

Significance lost in HCAP, HAP, & VAP subgroups$^2$

Nephrotox higher in VAN (18.2%) vs. LNZ (8.4%)

No difference in mortality

Conclusion: LNZ Superior to VAN in MRSA HAP/VAP

Lots of letters to editor

Treatment Summary

- **Confusion:** We need a definitive trial to characterize clinical role of Vanco AUC/MIC

- **Setback:** Vaccine studies should proceed with caution (but proceed nonetheless)

- **Success:** ZEPHYR:
  - showed LNZ superior to VAN in clinical cures
  - Hierarchical non-inferiority superiority design
Lessons Learned:

Epidemiology: Dynamic & Dramatic

Resistance: Growing Problem

Treatment: Success, Setback, & Confusion