The REDUCE MRSA Trial

Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA
Trial Rationale

• MRSA important in healthcare associated infections
• Many quality improvement strategies
  — Screen and isolate
  — Screen, isolate, decolonize
  — Universal decolonization
• No head-to-head comparisons
• Debate of high risk pathogen vs high risk populations
Targeted versus Universal Decolonization to Prevent ICU Infection

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and the AHRQ DECIDE Network and Healthcare-Associated Infections Program*

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- Harvard Pilgrim Healthcare Institute/Harvard Medical School
- University of California Irvine
- Rush University
- CDC Prevention Epicenters Steering Committee

Huang SS et al. NEJM Jun 2013:368:2255-2265
Cluster Randomized Trial

Randomized hospitals and all their adult ICUs to:

- **Arm 1: Routine Care**
  - Screened all patients; isolated known MRSA+

- **Arm 2: Targeted Decolonization**
  - Screened all patients; isolated if known MRSA+
  - Decolonized if MRSA+

- **Arm 3: Universal Decolonization**
  - No screening; isolated if known MRSA+
  - Decolonized all
Decolonization in Community ICUs

- 74 adult ICUs
- 43 hospitals, 16 states
  - 1 academic center, 42 community hospitals
  - 3-arm cluster randomized trial of hospitals

<table>
<thead>
<tr>
<th>Baseline 12 month</th>
<th>Phase In</th>
<th>Intervention 18 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2010</td>
<td>Apr 2010</td>
<td>Sep 2011</td>
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</tbody>
</table>
Decolonization Regimens

• **Arm 2: Targeted Decolonization**
  – Nasal mupirocin twice daily for 5 days
  – Chlorhexidine baths daily for 5 days

• **Arm 3: Universal Decolonization**
  – Nasal mupirocin twice daily for 5 days
  – Chlorhexidine baths daily for ICU duration
Outcomes

• **Primary**
  – Any MRSA clinical isolate attributed to ICU

• **Secondary**
  – MRSA bloodstream isolate attributed to ICU
  – Any bloodstream isolate attributed to ICU

• **Outcome Definitions**
  – Microbiology results alone
  – > 2d after ICU admit → 2d after ICU discharge
Intervention Period

Intervention: 74,256 patients
282,803 ICU patient days

<table>
<thead>
<tr>
<th>Arm</th>
<th>As Randomized</th>
<th>As Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1</td>
<td>Arm 2</td>
</tr>
<tr>
<td></td>
<td>16 Hospitals (23 ICUs)</td>
<td>14 Hospitals (22 ICUs)</td>
</tr>
<tr>
<td></td>
<td>N = 23,480</td>
<td>N = 24,752</td>
</tr>
</tbody>
</table>

1 Hospital (2 ICUs) withdraws
## Select Population Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm 1 Routine</th>
<th>Arm 2 Targeted</th>
<th>Arm 3 Universal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Stay in Days (median)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age (median)</td>
<td>65</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.3</td>
<td>33.0</td>
<td>30.7</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>20.0</td>
<td>20.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>10.4</td>
<td>10.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>3.4</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>History of MRSA (%)</td>
<td>10.2</td>
<td>11.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Surgery During Admission (%)</td>
<td>40.5</td>
<td>38.6</td>
<td>47.5</td>
</tr>
</tbody>
</table>

No important differences between Baseline, Intervention Periods
MRSA Clinical Cultures

Overall  \( P=0.01 \)
Arm 2 vs 1  \( P=0.09 \)
Arm 3 vs 1  \( P<0.003 \)
Arm 3 vs 2  \( P=0.16 \)
MRSA Bloodstream Infection

Overall P=0.11
All Pathogen Bloodstream Infection

Overall P<0.0001
Arm 2 vs 1 P=0.04
Arm 3 vs 1 P<0.0001
Arm 3 vs 2 P=0.003
BSI Reduction by Pathogen Type

Elevated baseline bloodstream rate in Arm 3 maybe related to higher acuity. Arm 3 had 2 of 3 BMT units in the trial, and 3 of 4 solid organ transplant units.
Protocol Compliance

- Compliance monitoring
  - Once a week point prevalence checks
  - Quarterly direct observation of bathing with checklist

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2 (among MRSA+)</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>98%</td>
<td>99%</td>
<td>1%</td>
</tr>
<tr>
<td>CHG bathing</td>
<td>&lt; 1%</td>
<td>89%</td>
<td>81%</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>&lt; 1%</td>
<td>91%</td>
<td>86%</td>
</tr>
</tbody>
</table>

- Reasons for non-compliance
  - < 1 day stay, discharge before scheduled activity, decline, moribund
Implementation – Key Features

• Usual quality improvement personnel
• No on-site investigators
• Rapid response email/phone
• Bi-weekly coaching calls
• Educational material provided
  – Protocols
  – Binders
  – Computer based training modules
  – FAQs
  – Bathing video, podcast
• Site visits for bathing training and as requested
• CDC Prevention Epicenters Steering Committee
Electronic Solutions

• Electronic nursing queries for compliance
• Coaching calls
  – Attendance tracked
  – Presentations recorded and posted
• Educational materials
  – Computer based training module and tracking
  – Bathing video
  – Podcast
• Analytic datasets
  – Descriptive variables and adjustors
  – Outcomes
Education Materials

REDUCE MRSA Trial
Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA
Targeted Decolonization ICU Toolkit Binder

1. What is the REDUCE MRSA Trial? A cluster-randomized trial of adult ICUs comparing 3 strategies to reduce MRSA. Approximately 120 ICU hospitals are participating. The hospital’s adult ICU has been randomized to Targeted MRSA Decolonization.

2. What is Targeted MRSA Decolonization? MRSA screening using nasal swabs and then applying nasal mupirocin twice daily for 5 days every 7 days.

3. How should nasopharyngeal and oropharyngeal cultures be performed? Nasopharyngeal and oropharyngeal cultures are obtained at baseline and during follow-up. Nasopharyngeal cultures are obtained using a nasopharyngeal swab, and oropharyngeal cultures are obtained using a oral pharyngeal swab.

4. What about MRSA-negative patients? MRSA-negative patients should not receive mupirocin or chlorhexidine. Post-ICU follow-up is determined by admission date or if patient with MRSA is still in contact with patient care. For any questions, contact the Protocol Director at 303-534-0857.

5. How do I report a study-related event? Complete the Study Related Event Form in the REDUCE MRSA ICU Toolkit Binder. For the completed form to be submitted, contact 800-598-1403. REDUCE MRSA study staff will make daily visits to each hospital to review follow-up.

Challenges and Lessons Learned

- State legislation
  - 5 hospitals randomized separately to only Arms 1 or 2
  - Sensitivity analysis

- Coaching call structure and accountability
  - Roll call
  - Required questions each call

- Compatibility issues

- Tracking competing interventions
  - 69 interventions proposed
  - 36 not pursued due to trial conflict
REDUCE MRSA Trial Summary

- Effective pragmatic trial
  - Trial cost: $40/patient

- Universal decolonization: CHG and mupirocin
  - Reduces MRSA and all BSI
  - Saves effort and cost of screening
  - May reduce need for contact precautions
  - Minimal adverse events

- Horizontal vs Vertical Approaches
  - Universal better than targeted
## Evidence Summary

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Year</th>
<th>Study Type</th>
<th>Hospital</th>
<th>ICU</th>
<th>N</th>
<th>Findings</th>
<th>Publication</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernon</td>
<td>10/02-12/03</td>
<td>Observational</td>
<td>1</td>
<td>1</td>
<td>1,787</td>
<td>65% less VRE acquisition</td>
<td>Arch Intern Med 2006; 166:306-312</td>
<td>CDC, Sage</td>
</tr>
<tr>
<td>Climo</td>
<td>12/04-12/06</td>
<td>Observational</td>
<td>4</td>
<td>6</td>
<td>5,293</td>
<td>66% less VRE BSI</td>
<td>Crit Care Med 2009; 37:1858–1865</td>
<td>CDC</td>
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<tr>
<td>Bleasdale</td>
<td>12/05-6/06</td>
<td>Observational</td>
<td>1</td>
<td>2</td>
<td>836</td>
<td>61% less primary BSI</td>
<td>Arch Intern Med 2007; 167(19):2073-2079</td>
<td>CDC, Sage</td>
</tr>
<tr>
<td>Popovich</td>
<td>9/04-10/06</td>
<td>Observational</td>
<td>1</td>
<td>1</td>
<td>3,816</td>
<td>87% less CLABSI, 41% less blood contaminants</td>
<td>ICHE 2009; 30(10):959-63</td>
<td>CDC</td>
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<tr>
<td>Milstone</td>
<td>2/08-9/10</td>
<td>Cluster RCT</td>
<td>5</td>
<td>10</td>
<td>4,947</td>
<td>36% less total BSI (as treated)</td>
<td>Lancet. 2013; 381(9872):1099-106</td>
<td>Sage, NIH</td>
</tr>
<tr>
<td>Huang</td>
<td>1/09-9/11</td>
<td>Cluster RCT</td>
<td>43</td>
<td>74</td>
<td>122,646</td>
<td>37% less MRSA clinical cultures, 44% less all-cause BSI</td>
<td>N Engl J Med 2013 368:2255-2265</td>
<td>AHRQ, CDC, HCA</td>
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</tbody>
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Questions?
Decision for Universal Mupirocin

• Pro
  — S. aureus #1 HAI
  — Screening not comprehensive
  — Decolonization: CHG alone less effective than combination
  — Highly effective in REDUCE MRSA trial vs proactive control
  — Will not lose systemic agent
  — Alternatives in pipeline

• Con
  — Potential for resistance
  — Requires risk:benefit

1 Sievert et al. ICHE 2013;34(1):1-14
2 Harbarth et al. AACT 1999;43(6):1412-6