Controlling endemic MRSA

Prof Christian Brun-Buisson
Director, Medical ICU
& Infection Control Unit
Univ. Hosp. Henri Mondor
Créteil, France
MRSA: Clearly an endemic MDR pathogen throughout Europe and elsewhere
*S. aureus* : Proportion of invasive isolates resistant to methicillin (MRSA) - Europe, 2006
S. aureus: Proportion of invasive isolates resistant to methicillin (MRSA) - Europe, 2012
The incidence of invasive MRSA infections such as bacteraemia, pneumonia, and cellulitis reached \(31.8/100\,000\) population in 2005. MRSA infection rate was higher than the combined rates of invasive pneumococcal disease (\(14.1/100\,000\)), invasive group A streptococcus (\(3.6/100\,000\)), invasive meningococcal disease (\(0.35/100\,000\)), and invasive \textit{Haemophilus influenzae} (\(1.4/100\,000\)).

MRSA was associated with an estimated \(18\,650\) hospital deaths in 2005. MRSA killed more US citizens that year than HIV.

\textit{JAMA} 2007;298:1763-71


source: NHS - Voluntary laboratory reporting to CDSC
MRSA: a commensal MDRB that adds on susceptible strains

Management of Multidrug-Resistant Organisms In Healthcare Settings, 2006

Jane D. Siegel, MD; Emily Rhinehart, RN MPH CIC; Marguerite Jackson, PhD; Linda Chiarello, RN MS; the Healthcare Infection Control Practices Advisory Committee (HICPAC)


Jane D. Siegel, MD; Emily Rhinehart, RN MPH CIC; Marguerite Jackson, PhD; Linda Chiarello, RN MS; the Healthcare Infection Control Practices Advisory Committee (HICPAC)

CDC – HICPAC, 2006
Gradation of preventive measures: Screening & Isolation

- Standard precautions (formerly « universal »)
- Contact isolation (CP) of patients « clinically » identified or known prior carriers
- Targeted screening of carriers on admission + (preemptive) CP
- Universal screening on admission + CP (+/- decontamination)
- Universal screening on admission + (2x) weekly (+/- discharge) & CP (+/- decontamination)
Persistent MRSA carriage and readmissions

- 146 previously known MRSA carriers
  - 78 readmitted after ≥3 mo.
- Variables associated with MRSA persistence after ≥3 mo:
  - Skin breaks: OR 4.34 [1.6 – 11.8]
  - Admission from nursing home or rehabilitation: OR 3.6 [0.95 – 12]

Median 8 months

Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature


- **Results** - 46 studies were analysed; 18 used isolation wards, 9 used nurse cohorting, and 19 used other isolation policies. Most were interrupted time series (ITS), with few planned formal prospective studies. All but one reported multiple interventions.

- Consideration of potential confounders, measures to prevent bias, and appropriate statistical analysis were mostly lacking.

- Six long ITS provided the strongest evidence: 4 provided evidence that intensive control measures including patient isolation were effective in controlling MRSA; in 2 others, isolation wards failed to prevent endemic MRSA.

- **Conclusion** - *No well designed studies exist that allow the role of isolation measures alone to be assessed. Nonetheless, there is evidence that concerted efforts that include isolation can reduce MRSA even in endemic settings. Current isolation measures recommended in national guidelines should continue to be applied until further research establishes otherwise.*

BMJ; 329, Sep 2004
Pros and Cons ASC & Isolation

- **Standard precautions (universal-horizontal):**
  - Effective for both S & MDR pathogens
  - Obviates the workload and costs of ASC
  - May not be sufficiently adhered to in routine ICU life to prevent transmission
  - May not be enough for some specific pathogens (eg, VRE, C.diff)

- **Contact precautions (targeted-vertical):**
  - Many unknown carriers (MRSA, VRE, HRE) & need for ASC
  - Increases awareness and emphasizes prevention of MDRB Various measures difficult to implement in routine practice
  - May incur adverse effects for the patient
Single-room Isolation and Cohorting:
Single to Scanty cases and to Outbreak setting

- Single-room isolation
- Cohorting patients
- Cohorting patients and personnel
- Dedicated isolation unit...
- ... Closure of unit
Nearly all studies reporting successful MDRO control employed a median of 7 to 8 different interventions concurrently or sequentially.

Several factors affect the ability to generalize the results of the various studies reviewed, including differences in definition, study design, endpoints and variables measured, and period of follow-up.

It has not been possible to determine the effectiveness of individual interventions, or a specific combination of interventions, that would be appropriate for all healthcare facilities to implement in order to control their target MDROs.

Randomized controlled trials are necessary to acquire this level of evidence and provide further insight into optimal control measures (eg, the NIH-sponsored, cRCT on the prevention of MRSA and VRE transmission in adult ICUs: education and SP vs. ASC + Contact Precautions).

CDC – HICPAC, 2006
Recent studies of strategies to control MRSA
Moving MRSA-positive patients into single rooms or cohorted bays did not reduce cross-infection.

Because transfer and isolation of critically ill patients in single rooms carries potential risks, our findings suggest that re-evaluation of isolation policies is required in intensive-care units where MRSA is endemic.
Isolation and cohorting of MRSA patients?


OR = 0.73 [0.49-1.10]

Compliance with hand hygiene = 21%
Impact of screening & isolation of MRSA carriers in ICUs on hospital-acquired MRSA-BSI rates

S.Huang & al, CID 2006; 43: 971-78.
PCR–based nasal surveillance for MRSA followed by topical decolonization therapy and contact isolation of patients who tested positive for MRSA.

1. Baseline control period, no intervention
2. Intervention in ICUs only
3. Intervention extended Hospital-wide
Study design

<table>
<thead>
<tr>
<th></th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>None</td>
<td>ICU admission</td>
<td>Any admission; retesting on ICU admission</td>
</tr>
<tr>
<td>Admissions Tested (Intended), n (%)</td>
<td>0</td>
<td>3334 (75.9)</td>
<td>62,035 (84.4)</td>
</tr>
<tr>
<td>Positive Test Results (Total), n (%)</td>
<td>0</td>
<td>277 (8.3)</td>
<td>3926 (6.3)</td>
</tr>
<tr>
<td>Routine Therapy for Colonization</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Follow-up for MRSA Disease</td>
<td>180 days after discharge</td>
<td>180 days after discharge</td>
<td>180 days after discharge (less if discharged in final 180 days of period)</td>
</tr>
</tbody>
</table>

Segmented Poisson regression model: aggregate hospital-associated MRSA prevalence density throughout the study

Relative adjusted Prevalence density of HA MRSA infections:
- 0.64 [0.35-1.10]
- 0.48 [0.22-0.91]

Two simultaneous conflicting studies in ICUs

- 150 VA hospitals, 4 yrs
- Quasi-experimental study
- MRSA
  - Screening at admission, upon transfer and discharge
  - Hand hygiene, contact precautions
  - No decolonization

- 18 ICUs, 17 months
- Cluster RCT
- MRSA & VRE
  - Rapid screening (MRSA + VRE) at admission, weekly, at discharge
  - Preemptive isolation (“universal gloving”) and contact precautions
  - No decolonization

Jain R et al, NEJM 2011  Huskins WC et al, NEJM 2011
VA sytem (153 hospitals; 196 ICUs & 428 wards)

“MRSA bundle” implemented in 2007, including universal surveillance screening (nasal) for MRSA (PCR or Chromagar), contact precautions for patients colonized or infected with MRSA, hand hygiene, and a « change in the institutional culture » (‘positive deviance’).
Health Care–Associated Infections with MRSA in VA Facilities

Transmission rate of MRSA in ICUs reduced from 3.02 to 2.50 per 1,000 patient-days.

ICU: -62%, P<0.001

Non-ICUs: -45%, P<0.001

Health Care–Associated Infection with MRSA in VA Facilities, According to the Type of Infection

ICUs

VAP rates: 1.7 -> 0.33 per 1000 device-days
CVC-RBSI: 0.46 -> 0.31 per 1000 device-days

Questions about the VA study

- Reduction (Oct. 2007-June 2010) in MRSA-acquisitions events (p.1000 pt-d):
  - ICUs: 3.02 to 2.50 (-17%)
  - Non-ICUs: 2.54 to 2.00 (-21%)

- Reduction in MRSA Infection rates (p.1000 pt-d):
  - ICUs: 1.64 to 0.62 (-62%)
  - Non-ICUs: 0.47 to 0.26 (-45%)

- Modeling the risk of infection from reduced MRSA transmission and acquisition shows that transmission prevention can only account for as much as 6-15% in ICUs and 17-26% in non-ICUs areas of the reduction in infection rates (for a RR=10).

- Other interventions (decolonisation, antibiotic stewardship, prevention bundles, ...)?
Cluster-randomised trial (10 intervention and 8 control ICUs); 6 months

Intervention: Screening (MRSA, VRE) + contact precautions for colonised pts or universal gloving vs. ‘standard’ care without knowledge of screening.
Monthly Incidence of Colonization or Infection with MRSA or VRE among Patients in ICUs.

Intervention ICUs (median rates)
MRSA: 11.9 (range, 6.8 to 19.6),
VRE: 25.7 (range, 9.7 to 78.2)

Intervention ICUs (median rates)
MRSA: 14.6 (range, 6.8 to 21.8)
VRE: 36.8 (range, 6.6 to 87.0)

Overall Results of the STAR-ICU Trial

Prevalence at admission (%), incidence of acquisitions (/1000 pt-d.)

Huskins WC et al, *NEJM* 2011
Gloving practices according to personnel category and care area

<table>
<thead>
<tr>
<th>Gloving practices</th>
<th>Gloves worn during contact</th>
<th>Gloves not worn when indicated</th>
<th>HH after removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICUs (n=95)</td>
<td>95.2 [91.7 – 98.7]</td>
<td>6.4 [2.3 – 10.5]</td>
<td>53.3 [43.2 – 63.3]</td>
</tr>
<tr>
<td>Medical wards (n=25)</td>
<td>87.3 [77.2 – 95.3]</td>
<td>14 [1.4 – 26.7]</td>
<td>44.6 [23.0 – 66.2]</td>
</tr>
<tr>
<td>P value</td>
<td>0.10</td>
<td>0.14</td>
<td>0.43</td>
</tr>
<tr>
<td>Nurses (n=72)</td>
<td>92.5 [87.7 – 97.3]</td>
<td>9.9 [4.2 – 15.6]</td>
<td>46.8 [35.6 - 58.1]</td>
</tr>
<tr>
<td>Assistant Nurses (n=40)</td>
<td>99.1 [97.7 – 100]</td>
<td>1.3 [0 – 3.1]</td>
<td>56.3 [39.2 – 73.3]</td>
</tr>
<tr>
<td>P value</td>
<td>0.04</td>
<td>0.03</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Correct indication: 58%

Universal Glove and Gown Use and acquisition of MRSA or VRE in the ICU – A randomised trial

- cRCT 20 matched ICUs randomised to « universal gloving » or « standard care »
- Baseline 3-mo. Period, followed by 9-mo. intervention period
- Intervention ICUs: decrease in MRSA / VRE acquisitions
  - from 21.3 (95%CI, 17.6 to 25.9) / 1000 pt-d at baseline to 16.9 / 1000 patient-days (95%CI, 14.1 to 20.3)
- control ICUs: decrease in MRSA or VRE acquisitions
  - from 19.0 (95%CI, 14.2 to 25.5) / 1000 at baseline to 16.3 (95%CI, 13.48 to 19.68) / 1000 pt-days
- difference in changes, −1.71 acquisitions per 1000 pt-days, 95%CI, −6.15 to 2.73; \( P = .57 \).

AD.Harris et al, JAMA Oct 2013
## Universal gloving

### Table 2. Rates at Risk of Acquisition of Antibiotic-Resistant Bacteria per 1000 Patient-Days

<table>
<thead>
<tr>
<th>Drug-Resistant Bacteria</th>
<th>Intensive Care Units</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Acquisitions</td>
<td>Patient-Days at Risk</td>
</tr>
<tr>
<td><strong>VRE or MRSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study period</td>
<td>577</td>
<td>32 693.0</td>
</tr>
<tr>
<td>Baseline</td>
<td>178</td>
<td>8684.0</td>
</tr>
<tr>
<td>Change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−4.47 (−9.34 to 0.45)</td>
<td></td>
</tr>
<tr>
<td><strong>VRE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study period</td>
<td>411</td>
<td>27 765.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>108</td>
<td>7691.5</td>
</tr>
<tr>
<td>Change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−1.60 (−7.18 to 3.98)</td>
<td></td>
</tr>
<tr>
<td><strong>MRSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study period</td>
<td>199</td>
<td>30 454.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>77</td>
<td>7841.0</td>
</tr>
<tr>
<td>Change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−4.03 (−6.50 to −1.56)</td>
<td></td>
</tr>
</tbody>
</table>

AD. Harris & al, JAMA Oct 2013
The two recent trials of decolonisation strategies
Multicenter (8 ICUs+1BMT, 6 hospitals), nonblinded, cluster-randomized, crossover trial

Bathing patients either with no-rinse 2% CHX–impregnated washcloths or with nonantimicrobial washcloths for a 6-mo. period; alternate product during the subsequent 6 months.

MDRO acquisition decreased 23% (6.60 vs. 5.10 1000 pt-d) with CHX bathing vs. nonantimicrobial washcloths (P = 0.03).

HA-BSI decreased 28% (6.6 vs. 4.8 cases / 1000 pt-d) with CHX bathing vs. with nonantimicrobial washcloths (P = 0.007)

### Table 1. Characteristics of the Participating Study Units.*

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Unit</th>
<th>Mean No. of Monthly Admissions</th>
<th>Mean No. of Monthly Patient-Days</th>
<th>Mean Length of Stay</th>
<th>MRSA Prevalence</th>
<th>VRE Prevalence</th>
<th>Baseline Rate of Primary Bloodstream Infections†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>number (range)</td>
<td>days (range)</td>
<td>percent of admissions</td>
<td>no./1000 patient-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>MICU</td>
<td>123.8 (114–142)</td>
<td>692.3 (504–773)</td>
<td>5.6</td>
<td>11.0</td>
<td>21.0</td>
<td>8.1</td>
</tr>
<tr>
<td>C</td>
<td>SICU</td>
<td>46.3 (31–59)</td>
<td>285.7 (251–314)</td>
<td>6.2</td>
<td>11.4</td>
<td>4.3</td>
<td>9.6</td>
</tr>
<tr>
<td>D</td>
<td>SICU 2</td>
<td>51.6 (32–71)</td>
<td>285.7 (227–338)</td>
<td>5.5</td>
<td>4.4</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>CSICU</td>
<td>85.3 (80–100)</td>
<td>425.9 (375–486)</td>
<td>5.0</td>
<td>6.6</td>
<td>8.3</td>
<td>0.4</td>
</tr>
<tr>
<td>F</td>
<td>BMT</td>
<td>41.8 (32–58)</td>
<td>786.3 (725–858)</td>
<td>18.8</td>
<td>2.4</td>
<td>21.6</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>MICU</td>
<td>111.6 (98–126)</td>
<td>598.8 (449–641)</td>
<td>5.4</td>
<td>21.8</td>
<td>21.0</td>
<td>3.1</td>
</tr>
<tr>
<td>C</td>
<td>MICU–CCU</td>
<td>55.8 (43–73)</td>
<td>299.1 (211–345)</td>
<td>5.4</td>
<td>16.1</td>
<td>9.7</td>
<td>8.5</td>
</tr>
<tr>
<td>D</td>
<td>SICU 1</td>
<td>62.3 (47–76)</td>
<td>316.3 (266–356)</td>
<td>5.1</td>
<td>10.8</td>
<td>8.2</td>
<td>2.2</td>
</tr>
<tr>
<td>E</td>
<td>MICU</td>
<td>72.7 (56–88)</td>
<td>467.1 (404–525)</td>
<td>6.4</td>
<td>23.3</td>
<td>27.9</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Effect of Daily Chlorhexidine Bathing on Hospital-Acquired Infection

Cumulative probability of primary BSI

Climo MW & al, NEJM 2012
Baseline rates and impact of interventions

Table 2. Incidence of Hospital-Acquired Bloodstream Infections and Acquisition of Multidrug Resistant Organisms (MDROs), MRSA, and VRE.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Period</th>
<th>Control Period</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>3970</td>
<td>3842</td>
<td>0.32</td>
</tr>
<tr>
<td>Total days of care</td>
<td>24,902</td>
<td>24,983</td>
<td>0.85</td>
</tr>
<tr>
<td>Central-catheter use (days)</td>
<td>13,425</td>
<td>13,049</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean length of stay (days)</td>
<td>6.4</td>
<td>6.4</td>
<td>0.53</td>
</tr>
<tr>
<td>MRSA prevalence (%)</td>
<td>13.8</td>
<td>12.8</td>
<td>0.14</td>
</tr>
<tr>
<td>VRE prevalence (%)</td>
<td>16.3</td>
<td>15.1</td>
<td>0.24</td>
</tr>
<tr>
<td>VRE acquisition (p. 1000 pt-days)</td>
<td>3.21</td>
<td>4.28</td>
<td>0.05</td>
</tr>
<tr>
<td>MRSA acquisition (p. 1000 pt-days)</td>
<td>1.89</td>
<td>2.32</td>
<td>0.29</td>
</tr>
<tr>
<td>HA-BSI rate (p. 1000 pt-days)</td>
<td>4.78</td>
<td>6.60</td>
<td>0.007</td>
</tr>
<tr>
<td>Primary BSI (no./ 1000 pt-days)</td>
<td>3.61</td>
<td>5.24</td>
<td>0.006</td>
</tr>
<tr>
<td>CR-BSI (no. / 1000 catheter-days)</td>
<td>1.55</td>
<td>3.30</td>
<td>0.004</td>
</tr>
</tbody>
</table>

# Microorganisms causing primary BSI

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Intervention</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Incidence*</td>
<td>N</td>
</tr>
<tr>
<td>S. aureus</td>
<td>9</td>
<td>0.36</td>
<td>8</td>
</tr>
<tr>
<td>CNS</td>
<td>15</td>
<td>0.60</td>
<td>34</td>
</tr>
<tr>
<td>Enterococci</td>
<td>19</td>
<td>0.76</td>
<td>26</td>
</tr>
<tr>
<td>E. faecium</td>
<td>6</td>
<td>0.24</td>
<td>6</td>
</tr>
<tr>
<td>GNB</td>
<td>23</td>
<td>0.92</td>
<td>27</td>
</tr>
<tr>
<td>Candida</td>
<td>7</td>
<td>0.28</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>90</td>
<td>3.61</td>
<td>131</td>
</tr>
</tbody>
</table>

* p. 1000 pt-d

Climo MW & al, NEJM 2013
Targeted versus Universal Decolonization to Prevent ICU Infection


Box:

- « Pragmatic » cRCT, 43 Hospitals (73 ICUs) randomly assigned to one of 3 interventions, with all adult ICUs in a given hospital assigned to the same strategy for 18 mo., after a 12-mo. Baseline period. All groups used contact precautions as in Group 1.
- Group 1 (23 ICUs), standard MRSA screening and isolation (+ known carriers);
- group 2 (20 ICUs), targeted decolonization (i.e., screening, isolation, and decolonization of MRSA carriers with nasal mupirocin and CHX bathings);
- group 3 (29 ICUs), universal decolonization (i.e., no screening, and decolonization of all patients for the ICU stay).

Primary outcome: ICU-attributable, MRSA positive clinical cultures; study powered on MRSA BSI.
Targeted vs. Universal Decolonization

HR for MRSA clinical isolates (P = 0.01):
- Gr1 screening and isolation: 0.92 [0.77-1.10] (crude rate, 3.2 vs. 3.4 per 1000 days),
- Gr 2: targeted decolonization 0.75 [0.63-0.89] (3.2 vs. 4.3 per 1000 days),
- Gr 3: universal decolonization 0.63 [0.52-0.75] (2.1 vs. 3.4 per 1000 days)

HR for BSI with any pathogen (P<0.001):
- Gr1: 0.99 [0.84 - 1.16] (crude rate, 4.1 vs. 4.2 per 1000 pt-days),
- Gr 2: 0.78 [0.66 - 0.91] (3.7 vs. 4.8 per 1000 pt-days),
- Gr 3: 0.56 [0.49 – 0.65] (3.6 vs. 6.1 per 1000 pt-days)

Huang & al, N Engl J Med 2013
Targeted vs. Universal Decolonization

Huang & al, N Engl J Med 2013
## Targeted vs. Universal Decolonization

<table>
<thead>
<tr>
<th></th>
<th>Gr.1 Baseline</th>
<th>Gr.1 Interv</th>
<th>Gr.2 Baseline</th>
<th>Gr.2 Interv</th>
<th>Gr.3 Baseline</th>
<th>Gr.3 Interv</th>
</tr>
</thead>
<tbody>
<tr>
<td>History MRSA</td>
<td>10.2</td>
<td>9.7</td>
<td>11.5</td>
<td>11.1</td>
<td>10.6</td>
<td>3.9</td>
</tr>
<tr>
<td>MRSA clin cult+*</td>
<td>3.4</td>
<td>3.2</td>
<td>4.3</td>
<td>3.2</td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td>MRSA BSI</td>
<td>0.6</td>
<td>0.7</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>All BSI *</td>
<td>4.2</td>
<td>4.1</td>
<td>4.8</td>
<td>3.7</td>
<td>6.1</td>
<td>3.6</td>
</tr>
<tr>
<td>GPC BSI</td>
<td>2.6</td>
<td>2.6</td>
<td>2.8</td>
<td>2.2</td>
<td>3.7</td>
<td>1.9</td>
</tr>
<tr>
<td>GNB BSI</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
<td>0.8</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Candida</td>
<td>0.6</td>
<td>0.6</td>
<td>1.0</td>
<td>0.7</td>
<td>0.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Huang & al, N Engl J Med 2013
Take home messages from the Huang’s Study

- Active detection and isolation without decolonization did not reduce rates of MRSA-positive clinical cultures, MRSA bloodstream infections, or bloodstream infections from any pathogen;
- Targeted and universal decolonization resulted in significant reductions in MRSA-positive clinical cultures and bloodstream infections from any pathogen, but not of MRSA bloodstream infections;
- The effect of universal decolonization was greater than the effect of targeted decolonization.
« The lack of effectiveness of active detection and isolation should prompt hospitals to discontinue the practice for control of endemic MRSA. »
The debate: Limitations of the Huang’ study

- The study provides **no information about the absolute effect of screening and isolation**, as this strategy was already in place before starting the trial;

- Impact on NBSI linked to reduced CNS BSI, with **no significant reduction in MRSA BSI**; a **reduction in the contamination rate of blood cultures with CNS** rather than in the rate of true bacteremia cannot be ruled out.

- Impact on emergence of resistance to mupirocin and chlorhexidine not evaluated /reported.
The debate

- « Edmond and Wenzel question the wisdom of targeted detection and isolation of carbapenem-resistant Enterobacteriaceae (CRE). We disagree.
- Targeted interventions to prevent the spread of a *sporadic MDRO* have been shown to be effective.
- The decision to pursue “vertical” or “horizontal” interventions versus multidrug-resistant organisms (MDROs) should be made while considering the pathogens, their prevalence, and the resources available to implement control measures. »

Mitchell J. Schwaber, M.D.
Bina Rubinovitch, M.D.
Yehuda Carmeli, M.D., M.P.H.
*National Center for Infection Control, Tel Aviv, Israel*
A further key question

- Vertical infection-control interventions, such as active detection and isolation, are useful in outbreak settings.
- However, for control of endemic pathogens, we conclude that horizontal interventions should be the cornerstone of prevention.
- Horizontal and vertical interventions are not mutually exclusive.
- However, the key question remains: given an optimally functioning horizontal program (i.e., near perfect compliance with hand hygiene and chlorhexidine bathing), what is the incremental benefit of a superimposed vertical strategy? »

Michael B. Edmond, M.D., M.P.H.
Richard P. Wenzel, M.D.
*Virginia Commonwealth University, Richmond, VA*
Platform II (WP 3-4-5):
Team leaders:
Marc Bonten, Yehuda Carmeli, Stephan Harbarth,
L. Derde, A. Lee

The Interventional Clinical Trials

WP3: ICU-acquired colonization with (all) AMRB

Coordinator: C. Brun-Buisson

Mastering hospital antimicrobial resistance in Europe
Design of the MOSAR-ICU trial

6 mo. baseline
HHIP + CBW

6 mo.

12 mo. cRCT
HHIP + CBW

cRCT Rapid vs. Conventional testing
Screening + feedback & isolation

Screening, no feedback

Incremental effect from baseline of (HH + CBW) ->+ (screening & isolation)

“CA”
A - Chromagar MRSA, VRE
No feedback of screening HRE

“RA”
B - PCR MRSA, VRE
Chromagar HRE
WP3 Participating centers

>14000 eligibles pts -> 8976 at risk -> 8519 (95%) analysed

- Fondation Hop St Joseph
- CHU Henri Mondor
- CHU R. Poincaré
- Hosp S. Camillo
- Hosp Villa Real
- Hosp Clinic, Barcelona
- Clinic Resp Allergic Dis.
- UMC Ljubljana
- Attikon Gal Hosp.
- Laikon Gal Hosp.

Rapid testing
Chromogenic testing
## Flowchart of the Mosar ICU trial

### Assessed for eligibility

- **n=14390**

### Phases

- **Phase 1**
  - **n=3215**

- **Phase 2**
  - **n=3345**

- **Phase 3**
  - **n=7830**

### Inclusions

- **Phase 1**
  - **n=3215**

- **Phase 2**
  - **n=3345**

- **Phase 3**
  - **n=7830**

### Randomization

- **CA**
  - **n=3710**
  - **n=2043**

- **RA**
  - **n=4120**
  - **n=2513**

### LS patients only

- **Phase 1**
  - **n=2043**

- **Phase 2**
  - **n=2072**

- **Phase 3**
  - **n=2348**

### Excluding incomplete data

- **Phase 1**
  - **n=1962**

- **Phase 2**
  - **n=1926**

- **Phase 3**
  - **n=2280**

### LS not colonized on admission

- **Phase 1**
  - **n=1709**

- **Phase 2**
  - **n=1699**

- **Phase 3**
  - **n=2045**

- **Phase 4**
  - **n=2020**
Interventions and implementation rates

- Following implementation of the HHIP with auditing & feedback, hand hygiene compliance improved from 52% in phase 1 to 69% and 77%, in phases 2 and 3.

Hand Hygiene Improvement

**MOSAR-ICU trial**

**MOSAR – ESICM Lives**
Interventions

- Hand Hygiene compliance improved from 52% to 69% to 77% from phase 1 to 3
- Median proportions of patients receiving CBW were 0%, 100% and 100% in phase 1, 2 and 3, respectively

CHX body washing
## Interventions

- **Hand Hygiene compliance** improved from 52% to 69% to 77% from phase 1 to 3.
- Median proportions of patients receiving **CBW** were 0%, 100% and 100% in phase 1, 2 and 3, respectively.
- Median **turn-around-times** of chromagar and molecular screening were 24 and 2.5 hours, respectively.

<table>
<thead>
<tr>
<th>Time to result</th>
<th>Median</th>
<th>Percentile 25</th>
<th>Percentile 75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>02:00</td>
<td>01:50</td>
<td>03:32</td>
</tr>
<tr>
<td>VRE</td>
<td>01:55</td>
<td>01:14</td>
<td>03:11</td>
</tr>
<tr>
<td><strong>chromagar</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>24:00</td>
<td>23:00</td>
<td>26:00</td>
</tr>
<tr>
<td>VRE</td>
<td>24:30</td>
<td>23:00</td>
<td>26:00</td>
</tr>
<tr>
<td>HRE</td>
<td>24:00</td>
<td>23:00</td>
<td>26:40</td>
</tr>
</tbody>
</table>
AMRB colonisation rate on ICU admission

<table>
<thead>
<tr>
<th></th>
<th>Phase 1 (n=1962)</th>
<th>Phase 2 (n=1926)</th>
<th>Phase 3 (n=5631)</th>
<th>Phase 3 CA (n=2280)</th>
<th>Phase 3 RA (n=2351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA (%)</td>
<td>4.9</td>
<td>4.8</td>
<td>4.1</td>
<td>4.1</td>
<td>3.3</td>
</tr>
<tr>
<td>VRE (%)</td>
<td>3.8</td>
<td>2.8</td>
<td>3.7</td>
<td>1.1</td>
<td>5.8</td>
</tr>
<tr>
<td>HRE total (%)</td>
<td>7.4</td>
<td>6.6</td>
<td>7.1</td>
<td>6.0</td>
<td>7.7</td>
</tr>
<tr>
<td>E.coli (%)</td>
<td>4.0</td>
<td>2.8</td>
<td>3.7</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>KESC (%)</td>
<td>3.4</td>
<td>4.8</td>
<td>3.6</td>
<td>2.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Any AMRB</td>
<td>12.9</td>
<td>11.8</td>
<td>12.2</td>
<td>10.3</td>
<td>14.1</td>
</tr>
</tbody>
</table>
# Contact Isolation Precautions

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CA</td>
<td>RA</td>
<td>CA</td>
</tr>
<tr>
<td>Patients isolated for MRSA</td>
<td>4.06</td>
<td>3.20</td>
<td>2.15</td>
</tr>
<tr>
<td>Patients isolated for VRE</td>
<td>.00</td>
<td>.64</td>
<td>.24</td>
</tr>
<tr>
<td>Patients isolated for HRE</td>
<td>2.67</td>
<td>5.66</td>
<td>2.51</td>
</tr>
<tr>
<td>Patients isolated for non-AMRB reasons</td>
<td>6.81</td>
<td>4.06</td>
<td>9.61*</td>
</tr>
</tbody>
</table>

* Non-AMRB isolation rates increased because of the flu pandemic
Interventions

- **Hand Hygiene compliance** improved from 52 % to 69% to 77% from phase 1 to 3
- Median proportions of patients receiving **CBW** were 0%, 100% and 100% in phase 1, 2 and 3, respectively
- Median **turn-around-times** of chromagar and molecular screening were 24 and 2.5 hours, respectively
- In P3, there was an increase in **contact isolation precautions** for VRE, and for MRSA in both screening arms
  - For HRE, contact precautions increased in RA arm

*MOSAR-ICU trial*
Change in risk of weekly acquisition of AMRB
(multi-level Poisson regression model)

<table>
<thead>
<tr>
<th>AMRB</th>
<th>IRR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trend P1</td>
<td>1.01 (1.00, 1.03)</td>
</tr>
<tr>
<td>Step P2</td>
<td>0.95 (0.68, 1.35)</td>
</tr>
<tr>
<td><strong>Trend P2</strong></td>
<td><strong>0.98 (0.95, 1.00)</strong> *</td>
</tr>
<tr>
<td>Step P3, CA</td>
<td>0.63 (0.35, 1.15)</td>
</tr>
<tr>
<td>Trend P3, CA</td>
<td>1.015 (1.00, 1.03)</td>
</tr>
<tr>
<td>Step P3, RA</td>
<td>1.07 (0.62, 1.85)</td>
</tr>
<tr>
<td>Trend P3, RA</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
</tbody>
</table>
Main results – All AMRB

- **AMRB acquisition** increased by 1.4% per week (CI -0.4%, 3.1%) in baseline.
- Following P2 there was a **reduction in trend** (*weekly IRR 0.98 [CI 0.95, 1.00]*).
- In P3, **neither CA nor RA was associated with further changes in trend**
- **No difference** in acquisition rates between CA and RA (p=.06, likelihood ratio test)
## Change in risk of weekly acquisition of AMRB (multi-level Poisson regression regression model)

<table>
<thead>
<tr>
<th></th>
<th>IRR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMRB</td>
</tr>
<tr>
<td>Trend P1</td>
<td>1.014 (0.996, 1.031)</td>
</tr>
<tr>
<td>Step P2</td>
<td>0.95 (0.68, 1.35)</td>
</tr>
<tr>
<td>Trend P2</td>
<td>0.98 (0.95, 1.00) *</td>
</tr>
<tr>
<td>Step P3, CA</td>
<td>0.63 (0.35, 1.15)</td>
</tr>
<tr>
<td>Trend P3, CA</td>
<td>1.01 (1.00, 1.03)</td>
</tr>
<tr>
<td>Step P3, RA</td>
<td>1.07 (0.62, 1.85)</td>
</tr>
<tr>
<td>Trend P3, RA</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
</tbody>
</table>

* (p<.05), ** (p<.01) or *** (p<.001). 95% CI interval including 1.00 can be significant due to rounding.
Cox regression results of daily hazard of acquisition of AMRB colonisation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRSA</th>
<th>VRE</th>
<th>HRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>P1 trend (days since P1 start)</td>
<td>1.00</td>
<td>(1.00, 1.01)</td>
<td>0.15</td>
</tr>
<tr>
<td>P2 Step change</td>
<td>1.25</td>
<td>(0.70, 2.23)</td>
<td>0.46</td>
</tr>
<tr>
<td>P2 trend</td>
<td>0.99</td>
<td>(0.99, 1.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>P3 CA Step change</td>
<td>1.17</td>
<td>(0.39, 3.49)</td>
<td>0.78</td>
</tr>
<tr>
<td>P3 CA trend</td>
<td>1.01</td>
<td>(1.00, 1.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>P3 RA Step change</td>
<td>1.78</td>
<td>(0.69, 4.61)</td>
<td>0.24</td>
</tr>
<tr>
<td>P3 RA trend</td>
<td>1.01</td>
<td>(1.00, 1.01)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Secondary outcomes - bacteremia

- ICU-acquired AMRB bacteremias during the trial
  - 83 HRE-
  - 28 MRSA
  - 9 VRE-bacteremias in total

- For AMRB, no significant decrease between phases or between the intervention arms in P3 (LRT; p=.09)
  - For HRE, significant decrease during baseline, no effects demonstrated in P2 or P3, and no difference between the intervention arms (LRT; p=.57)
  - For MRSA and VRE, numbers were too low to perform statistical analyses
Secondary outcomes – LOS

- In P2, **LOS decreased by 1.2% per week, to give a net reduction of 26% (CI 16%, 48%) at the end of P2**

- At the end of P3, **LOS increased by 18% (CI 1%, 39%) in RA, but not in CA (8% [CI -8%, 27%])**
  - Difference in trend between the arms highly significant
  - Rapid arm was associated with a stepwise increase in LOS at the start of P3

- Mortality unaffected by any of the interventions
Conclusions

- Hand hygiene can be improved to a large extent in ICUs, despite the often high workload, using repeated auditing and feedback.
- Improved hand hygiene (+CBW) results in a significant reduction in acquisition of MDRB, mostly because of a reduction in MRSA acquisition.
- In this context of high hand hygiene compliance, there is no incremental effect of screening and isolation, whether using conventional or rapid screening.
- ESBL rates were unaffected by any of the interventions.
- ICU LOS was lower in phase 2, and increased in phase 3, suggesting an adverse effect of isolation.
Interventions for colonisation and transmission of antibiotic resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial

Lennie P G Derde, Ben S Cooper, Herman Goossens, Surbhi Malhotra-Kumar, Rob J L Willems, Marek Gniadkowski, Waleria Hyrniewicz, Joanna Eempel, Mirjam J D Dautzenberg, Djillali Annane, Irene Aragão, Annie Chalfine, Ugo Dumps, Francisco Esteves, Helen Giamarelou, Igor Muzlovic, Giuseppe Nardi, George L Petrikkos, Viktorija Tomic, Antonio Torres Marti, Pascal Stammet, Christian Brin-Buisson*, and Marc J M Bonten*, on behalf of the MOSAR WP3 Study Team

Interpretation Improved hand hygiene plus unit-wide chlorhexidine body-washing reduced acquisition of antimicrobial-resistant bacteria, particularly MRSA. In the context of a sustained high level of compliance to hand hygiene and chlorhexidine bathings, screening and isolation of carriers do not reduce acquisition rates of multidrug-resistant bacteria, whether or not screening is done with rapid testing or conventional testing.

Funding European Commission.
Curbing Methicillin-Resistant Staphylococcus aureus in 38 French Hospitals Through a 15-Year Institutional Control Program

Vincent Jarlier, MD, PhD; David Trystram, MD; Christian Brun-Buisson, MD, PhD; Sandra Fournier, MD; et al

Arch Intern Med. 2010;170(6):552-559
Interventions to control MRSA
Implementation of AHR solutions

Jarlier et al, Arch Intern Med 2010
MRSA control: Focus on ICUs and High-risk Surgery

Hand Hygiene Improvement Campaign and MRSA rates within the NHS

Quarterly use of HH consumables

Quarterly IRR MRSA BSI rate

Stone HH & al, BMJ May 2012
How much improvement in HH is needed to control MRSA?

8 « before-after » studies

Sroka S et al, J Hosp Infect 2010