Study of efficacy of octenidine against antibiotic resistant *Staphylococcus aureus* strains

Marta Aires-de-Sousa

Escola Superior de Saúde da Cruz Vermelha Portuguesa
Lisboa, Portugal

6\textsuperscript{th} International Congress of Hospitals – November 2016
- Gram+ cocci
- One of the major human pathogens
**S. aureus** can colonize healthy people

- **Skin**
  - Nose (~30%)

- **Mucosa**

Wertheim et al. 2005. JCM. 5:751
**S. aureus** responsible for a wide range of infections

- **Superficial lesions**
  (wound infections, skin abscesses,..)

- **Life-threatening conditions**
  (bacteremia, pneumonia, osteomyelitis, endocarditis, meningitis,..)

- **Toxinoses**
  (food poisoning, toxic shock syndrome, scalded skin syndrome)

Wertheim et al. 2005. JCM. 5:751
S. aureus evolution – new challenges

Pre-antibiotic era

1941
Penicillin

1944
Penicillinases

1960
Methicillin

1961
MRSA

1960s Europe

1970s USA

1996
VISA

1993
CA-MRSA

1996
VISA

2002
VRSA

2003
LA-MRSA

Penicillinases

90%

S. aureus infections

Late 1980s-90s

Worldwide spread

Quinopristin/dalfopristin
Daptomycin
Linezolid
Tigecycline
Telavancin

Multidrug Resistant S. aureus
MRSA prevalence - Worldwide

Canada  5%
USA  48%
Latin America  47%
Europe  17%
Africa  40%
Australia  34%
South Korea, Japan, Taiwan, Thailand >57%
China  47%
Russia Federation  34%

MRSA prevalence - Europe

2014
17.4%

Portugal
47.4%

http://www.ecdc.europa.eu
The **European Centre for Disease Prevention and Control (ECDC)** estimated that:

171,200 **nosocomial MRSA infections** are acquired **annually** in the EU, and in Iceland and Norway

Resulting in:

- **5,400** attributable **excess deaths**
- **> 1 million** **excess days of hospitalization**
- **EUR 380 million** **excess in-hospital costs**

EMEA doc. ref. EMEA/576176/2009
The burden of MRSA

In the US, MRSA is responsible for more deaths annually than many other serious infectious diseases.

Surgical site infections

- MRSA prevalence

S. aureus

CoNS

Enterococcus spp.

E. coli

P. aeruginosa

Enterobacter spp.

K. pneumoniae

Candida spp.

A. baumannii

The burden of MRSA

- >80% of health care-associated *S. aureus* infections are endogenous (= originating within a patient)

- *S. aureus* nasal carriage has been identified as a risk factor for the development of nosocomial infections, namely in:
  - General hospital populations
  - Surgical patients
  - Patients on hemodialysis or continuous peritoneal dialysis
  - Patients with liver cirrhosis and after liver transplantation
  - HIV-infected patients
  - Patients admitted to ICU

Presurgical decolonization

• Randomized, double blinded, placebo controlled multicentric study

6771 patients screened on admission for S. aureus

917 (MSSA+)

504 Antiseptic wash lotion (CHG) & mupirocin; 5 days

413 placebo

Rate of S. aureus SSI

3.4%

7.7%

The number of SSI caused by S. aureus can be reduced by rapid screening and decolonization on admission
### Presurgical decolonization (MRSA)

**US hospital**
(10,000 orthopedic, vascular, cardiac, or neurosurgical procedures/year)

Mupirocin & 2% CHG cloth bath (5 days)

**Results**
- MRSA prevalence
- Presurgical decolonization (MRSA)

**Thompson & Houston. 2013. J Infect Control. 41:629**

<table>
<thead>
<tr>
<th>2002</th>
<th>Jan 06</th>
<th>Mar 06</th>
<th>Sep 06</th>
<th>Dec 06</th>
<th>Jan 07</th>
<th>Dec 08</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 MRSA SSI Rate: 0.39/100 procedures (pre-intervention)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007 MRSA SSI Rate: 0.20/100 procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008 MRSA SSI Rate: 0.13/100 procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- MRSA active screening began: Much higher incidence in community than previously documented
- MRSA SSI rates calculated for historical baseline
- Education completed on policy on use of intranasal Bactroban and CHG baths
- Retrospective chart review conducted; MRSA SSI rates in this surgical population analyzed
- Intervention protocol implemented
Presurgical decolonization (MRSA)

Decolonization significantly reduced the number of SSI caused by MRSA

Mupirocin & 2% CHG cloth bath (5 days)

MRSA SSI rate (pre/post intervention)

2006: 0.39/100 procedures

2008: 0.13/100 procedures (P = 0.003)

Thompson & Houston. 2013. J Infect Control. 41:629
One of the most successful strategies:

- Mupirocin nasal ointment + chlorhexidine-based skin disinfectants

BUT....

Increased prevalence of resistant strains against both compounds
Mupirocin resistance: increasing issue

- In literature 5%-79% of MRSA strains are reported as mupirocin-resistant (geographical variation)

1) Chlorhexidine and mupirocin susceptibilities of methicillin-resistant *Staphylococcus aureus* from colonized nursing home residents (Mc Danel, 2013)
2) Community-genotype strains of methicillin-resistant *Staphylococcus aureus* with high-level mupirocin resistance in a neonatal intensive care unit (Park, 2013)
3) Update: Methicillin-resistant *Staphylococcus aureus* screening and decolonization in cardiac surgery (Tom, 2009)
4) The prevalence of methicillin *Staphylococcus aureus* (MRSA) isolates with high-level mupirocin resistance from patients and personnel in a burn center (Abbasi-Montazeri, 2013)
5) Prevalence of high and low level mupirocin resistance among staphylococcal isolates from skin infection in a tertiary care hospital (Jayakumar, 2013)
6) Prevalence of mupirocin resistance among invasive coagulase-negative staphylococci and methicillin-resistant *Staphylococcus aureus* (MRSA) in France: emergence of a mupirocin-resistant MRSA clone harbouring mupA (Desroches, 2013)
7) Molecular epidemiology of plasmid-mediated high-level mupirocin resistance in methicillin-resistant *Staphylococcus aureus* in four Spanish healthcare settings (Perez-Roth, 2013)
8) Coexistence of mupirocin and antiseptic resistance in methicillin-resistant *Staphylococcus aureus* isolates from Korea (Lee, 2013)
Mupirocin resistance: increasing issue

- Mupirocin resistance is more and more reported in literature:
  - low-level mupirocin resistance (LL-MR)
    
    MIC 8-256 mg/L
  
  - high-level mupirocin resistance (HL-MR)
    
    MIC ≥ 512 mg/L
Mupirocin resistance: increasing issue

- MRSA decolonization achieved on day 3 after mupirocin (MUP) treatment
- However, after 4 weeks only 25% of both HL-MR and LL-MR MRSA groups were culture negative

Even LL-MUP resistance is sufficient to lead to MUP treatment failure
Also **resistance to Chlorhexidine** is described more often in *S. aureus*


2. McDanelet al., Chlorhexidine and Mupirocin Susceptibilities of Methicillin-Resistant *Staphylococcus aureus* from Colonized Nursing Home Residents, Antimicrobial Agents and Chemotherapy p. 552–558 January 2013 Volume 57 Number 1

3. Lee et al., Coexistence of mupirocin and antiseptic resistance in methicillin-resistant *Staphylococcus aureus* isolates from Korea, Diagnostic Microbiology and Infectious Disease 75 (2013) 308–312
Chlorhexidine resistance: increasing issue

Introduction of a daily chlorhexidine bath in SICU

- There was a significant trend for increasing \( qacA/B+ \) (\( P=0.02 \))

Implementation 2006: \( n=4; \) 6.3%
Post-implementation 2006/12: \( n=32; \) 7.2%

- \( qacA/B+ \) MRSA isolates were more likely to be mupirocin resistant

(9 of 36 [25%] \( qacA/B+ \) vs 26 of 468 [5.6%] \( qacA/B- \); \( P=.003 \)).
Increased prevalence of resistant strains against mupirocin and chlorhexidine

Need of alternative strategies
Results

Of 2590 patients screened, 146 patients (group I, 71; group P, 75) were randomized between January 2011 and July 2014. Primary outcome was missing for 11

Conclusion

This study suggests that under real-life conditions a single polyhexanide decolonization course is marginally effective in eradicating MRSA carriage.

Inhibition of the Anti-staphylococcal Activity of the Antiseptic Polihexanide by Mucin

Rainer Ansorg, Peter-Michael Rath, and Werner Fabry

Institute of Medical Microbiology, University Essen, Essen (Germany)


Mucin concentrations of 0.5% and 1%, that are even lower than the mucin concentrations in healthy nasal secretions, abolished the activity of the therapeutic concentrations of polihexanide
J Antimicrob Chemother
doi:10.1093/jac/dkw241

Efficacy of octenidine against antibiotic-resistant
*Staphylococcus aureus* epidemic clones

Teresa Conceição¹, Hermínia de Lencastre¹,²
and Marta Aires-de-Sousa³*
Efficacy of octenidine against antibiotic resistant S. aureus epidemic clones

**Study aim**

Investigation of the **bactericidal activity of octenidine** among international **epidemic clones of S. aureus** (MSSA, MRSA) including **mupirocin-resistant isolates**

**clinically relevant test conditions:**

- presence of organic load (albumin)
- short incubation time (30 sec)

Performed using the official European Norm for testing antiseptics (EN13727)
### Efficacy of octenidine against antibiotic resistant *S. aureus* epidemic clones

<table>
<thead>
<tr>
<th><em>S. aureus</em> test isolates</th>
<th>log$_{10}$ reduction factor (30 sec contact time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.001% octenidine w/o albumin</td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
</tr>
<tr>
<td>HL Mup</td>
<td>HP002</td>
</tr>
<tr>
<td></td>
<td>HP037</td>
</tr>
<tr>
<td>LL Mup</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>4A</td>
</tr>
<tr>
<td>Mup S</td>
<td>HDES57</td>
</tr>
<tr>
<td></td>
<td>HU245</td>
</tr>
<tr>
<td>MSSA</td>
<td>Mup S</td>
</tr>
<tr>
<td></td>
<td>IPOP37</td>
</tr>
<tr>
<td></td>
<td>HSA9</td>
</tr>
</tbody>
</table>

Albumin 0.6% used to simulate human nasal mucosa

(Lorin et al. J Lab Clin Med 1972; 80: 275)
Efficacy of octenidine against antibiotic resistant S. aureus epidemic clones

- Octenidine is a promising alternative for S. aureus eradication, including mupirocin resistant strains belonging to different epidemic clones.

- Octenidine is highly effective at significantly lower concentrations than those currently used in the clinical setting (0.05% to 0.1%).
Acknowledgments

ITQB – Lab. Molecular Genetics

Teresa Conceição
Hermínia de Lencastré