Séminaire de pathologie infectieuse

Jeudi 25 novembre 2004 à 12h30
Cliniques Universitaires de l'UCL à Mont-Godinne
Auditoire J. Heremans, Yvoir

Prof. A. Voss
Medical Microbiology, University Medical Centre St Radboud, Nijmegen, Pays-Bas

Preventing the spread of MRSA: common sense and observational studies
The golden cocci …

MSSA

MRSA
Risk and outcome of nosocomial *Staphylococcus aureus* bacteraemia in nasal carriers versus non-carriers

Heiman F L Wertheim, Margreet C Vos, Atevijn Ott, Alex van Belkum, Andreas Voss, Jan AJ W Kluytmans, Peter HJ van Keulen, Christina MJE Vandemouwke-Grays, Marlene H M Meester, Henri A Verbrugh

*Staphylococcus aureus* is the second most frequent cause of nosocomial blood infections. We screened 14 008 non-bacteraemic, non-surgical patients for *S aureus* nasal carriage at admission, and monitored them for development of bacteraemia. Nosocomial *S aureus* bacteraemia was three times more frequent in *S aureus* carriers (40/3420, 1·2%) than in non-carriers (41/10 588, 0·4%; relative risk 3·0, 95% CI 2·0–4·7). However, in bacteraemic patients, all-cause mortality was significantly higher in non-carriers (19/41, 46%) than in carriers (seven/40, 18%, p=0·005). Additionally, *S aureus* bacteraemia-related death was significantly higher in non-carriers than in carriers (13/41 [32%] vs three/40 [8%], p=0·006). *S aureus* nasal carriers and non-carriers differ significantly in risk and outcome of nosocomial *S aureus* bacteraemia. Genotyping revealed that 80% of strains causing bacteraemia in carriers were endogenous.

Lancet 2004;364:703-05
## Nosocomial S. aureus bacteraemia

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carrier</strong></td>
<td>40</td>
<td>3388</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>(1.2%)</td>
<td>(98.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-carrier</strong></td>
<td>41</td>
<td>10547</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(0.4%)</td>
<td>(99.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Nasal and subsequent bloodstream isolate clonally related in 80% of patients

*Lancet 2004;364:703-05*
## Mortality of S. aureus bacteraemia

<table>
<thead>
<tr>
<th>%</th>
<th>Carrier</th>
<th>Non-carrier</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18</td>
<td>43</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Lancet 2004;364:703-05
Risc factors for developing MRSA infections
(prospective cohort study in 479 MRSA colonized pts)

- intensive care treatment*
- three or more antibiotics
- pressure ulcers *
- surgical wounds
- nasogastric or endotracheal tubes
- drains
- urinary or intravenous * catheterization

* independent risc factors

Coello et al, J Hosp Infect 1997;37:39-46
Why continue to fight MRSA

- Higher transmissibility ?*
- Problems with treatment
- Higher virulence (mortality) ?
- Increased incidence of infections!
- Higher costs
- New threats

* Vriens et al  ICHE 2002;23:491-494
## Nosocomial infections: Importance of cross-transmission

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates</th>
<th>Proportion of transmissions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>169</td>
<td>51</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>61</td>
<td>38</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>458</td>
<td>26</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>135</td>
<td>17</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>159</td>
<td>11</td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td><strong>1270</strong></td>
<td><strong>24</strong></td>
</tr>
</tbody>
</table>

1,828 German ICU patients  
4,962 isolates (18 months)  

Grundmann et al; Crit Care Med, in press
Problems with treatment

- Fewer effective antibiotics
- Vancomycin less active against *S. aureus*
- More side-effects of Rx
- Higher costs (drugs, extended stay, more diagnostic, TDM)
- Empiric treatment possibly insufficient
- Hardly new antibiotics
Higher virulence
Higher mortality

- Prospective study with 815 patients with nosocomial S. aureus BSI (CID 2003;37:1453-9)

<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aantal</td>
<td>433</td>
<td>382</td>
</tr>
<tr>
<td>Herstel</td>
<td>86,4%</td>
<td>70,4%</td>
</tr>
<tr>
<td>Overleden (niet infectie gerelateerd)</td>
<td>8,5%</td>
<td>17,8%</td>
</tr>
<tr>
<td>Overleden (infectie gerelateerd)</td>
<td>5,1%</td>
<td>11,8%</td>
</tr>
</tbody>
</table>

RR: 2,32  95% CI: 1,42 – 3,79
Higher mortality

  - 1980-2000
  - 31 studies with 3963 patients
  - 2603 MSSA and 1360 MRSA
  - 11 studies corrected for confounders using multivariate analysis
Increased incidence of infections

OR: 1.93, 95% CI: 1.54 - 2.42
Furthermore ....

- MRSA infections increase the incidence of nosocomial S. aureus infections
S. aureus bacteremia in England & Wales

S. aureus bacteremia in England & Wales
Higher costs

- Patients with SSI, corrected for type of surgery (CID 2003;36:592-8)

<table>
<thead>
<tr>
<th></th>
<th>Geen infectie</th>
<th>MSSA</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aantal</td>
<td>193</td>
<td>165</td>
<td>25</td>
</tr>
<tr>
<td>Mediane opnameduur na OK</td>
<td>5</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Mediane opnameduur na infectie</td>
<td>0</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Kosten (mediaan in K $)</td>
<td>29</td>
<td>53</td>
<td>92</td>
</tr>
</tbody>
</table>
Extra-costs linked to *S. aureus* infections in ICU patients

<table>
<thead>
<tr>
<th>Costs</th>
<th>MRSA (N = 24)</th>
<th>MSSA (N = 64)</th>
<th>No infection (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>37,278 €</td>
<td>27,755 €</td>
<td>9,745 €</td>
</tr>
<tr>
<td>Medical procedures</td>
<td>12,345 €</td>
<td>10,632 €</td>
<td>5,791 €</td>
</tr>
</tbody>
</table>

Methicillin + Vancomycin resistente S. aureus

VRSA

- mecA gen
- vanA gen

MRSA
VRE

June 2002 first patient in the USA

MMWR juli 2002 (26);565-567
Some say that they look for MRSA

... but do they use the right methods?
Diagnosis, surveillance and control of MRSA

- 90 HCFs in 30 countries
- 9% wrong microbiological methods

Richet et al  ICHE 2003;24:334-341
• use enhancing media <A-I>
  (without 45% false-negative)
• one set of cultures enough <A-II> *
• when looking for a new strain do not use
  selective media <A-I>
• create selective media for screening of
  known strains <B-I>

• *S. aureus*: latex-agglutination (CF, prot A,
  surface antigens) <A-II>
• confirmation by tube-coagulase, DNase,
  AccuProbe <A-II>

* still two in Nijmegen
Sometimes they try to hide …

mecA positive

OXA 1-2 mg/l
Susceptibility

- Cave: heteroresistent MRSA strains with an MIC around the breakpoint <A>
- Use a dilution method plus oxa-1 disc or oxa-screen agar <A-I>
- In MRSA always test vancomycin en mupirocine <C-I>
- In oxacillin susceptible strains resistant to: quinolones, aminoglycosides, macrolides, clinda, or tetracyclin → PBP2a or het mec-A gen <C-II>
- Any strain suspicious for MR needs to be tested for PBP2a or mecA-gen. <I>
• Glycopeptide Intermediate Staphylococcus aureus

• Problem: to separate susceptible strains (MIC 0.5–2 µg/ml) from intermediate strains (MIC 4–8 µg/ml) by disc-diffusion

• NCCLS = vancomycin agar screen test (low sensitivity)

**Screening op verminderde gevoeligheid voor glycopeptiden met Etest**

Antibiotica: vancomycin en teicoplanine
Medium: Brain Heart Infusion agar
Inoculum: 2 McFarland
Incubatietijd: 48 uur
Temperatuur: 35°C
Interpretatie: R = vanco & teico ≥ 8, or teico ≥ 12
Incidence of Nosocomial and Imported MRSA cases per 1,000 admission detected by clinical cultures
Erasme hospital, 1990-2002

Courtesy: M. Struelens
Hospitals

Policy for Methicillin-resistant *Staphylococcus aureus*
MRSA guidelines

Is this evidence based??

Don’t you mean eminence based?
In the lack of science, empiric results are evidence. Cooper et al (BMJ September 2004)…

...some proof that concerted interventions, including isolation measures, can reduce MRSA transmission...
Controlling of multi-resistant m.o.’s

- Block their way into your hospital
  - Search & destroy strategy

- Immediate reaction when first detected
  - Screening, isolation and decolonization

- Controlling epidemic spread
  - Maximum measurements: isolation, screening, flagging, closing wards, …
“In the battle to control staphylococci and particularly to prevent staphylococcal infections, I have chosen three military titles for our changing strategies”

- Scutari
- S. aureus limitation technique (SALT)
- Search & Destroy

John Spicer, J Hosp Infect 1984;5:45-49 (Suppl. A)
Scutari Strategy

- Scant resources
- Staff shortages
- Scant knowledge
- Soap & water

Sounds like healthcare in 2004, but meant was Florence Nightingale’s hospital in the Crimean war more than 150 years ago.

What else is new?

John Spicer, J Hosp Infect 1984;5:45-49 (Suppl. A)
SALT (S. aureus limitation technique)

- Selective with regard to infection vs colonization
- Aseptic techniques in patient care
- “smooth” limited number of isolation = limited stress for HCW and patients
- Saving money, time and staff

John Spicer, J Hosp Infect 1984;5:45-49 (Suppl. A)
Think bronchial suction!
Seen the high prevalence of MRSA in countries who use SALT and the missing logic of only isolating infected patients,

I conclude …

SALT harms (your patient’s) health
Search & Destroy

- MRSA patients

Strict isolation & screening of patients with risk of MRSA carriage on admission
Search & destroy strategy

A patient transferred from a hospital or nursing home where MRSA is present, or from a foreign hospital who:

- has been operated on
- has drains or catheters
- is intubated
- has been admitted more than 24 hrs
- has open wounds
- has possible sources of infection, like abscesses

www.wip.nl
Search & destroy strategy

- **Strict isolation**
  - in single isolation room (!)
  - nose-face mask, gown, gloves (and caps)

- **MRSA screening (x 2)**
  - nares and throat (one swab), plus perineum, or wounds, urine (if catheter present)

- **List of contacts**

- **Interventions postponed if possible**

www.wip.nl
Isolation and MRSA

- Setting: outbreak in ICU
- 16 of 331 admissions became MRSA positive
- None of 144 HCWs after contact with colonized patients became positive \(\Rightarrow\) patients = source
- Rate of transmission:
  - contact isolation \(\Rightarrow 0.009\) per day
  - no isolation \(\Rightarrow 0.14\) per day \((RR 15.6)\)

Jernigan et al, Am J Epidemiol 1996;143:496-504
## Diagnosis, surveillance and control of MRSA

<table>
<thead>
<tr>
<th>Routine use of (%)</th>
<th>Africa</th>
<th>East-Europe</th>
<th>West-Europe</th>
<th>South America</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private room</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glove use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gown use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand hygiene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Isolation sign</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.0%</td>
<td></td>
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</tbody>
</table>

Richet et al. ICHE 2003;24:334-341
When is S&D justified?

- depending on local situation
- not working when epidemic

- efforts & costs
- high
- low
- poor
- good

Success S&D
Should we still control MRSA?

1. Yes, hospital-wide
2. Yes, on certain wards/specialties
3. Only when causing clinical infections
4. No, doesn’t work
5. No, let MRSA go and concentrate efforts on other pathogens (VRE, ..)
Winning the battle but losing the war

- 1000-bed teaching hospital
- Screening high-risk patients, isolation, closure of wards and screening during outbreaks, epidemiology

Eradication policy

- about 1 MRSA patient/mo
- largest outbreak 11 patients, despite intro of EMRSA-16
- increasing workload HCWs
- interference clinical service

→ costs policy versus “costs” endemicity

Winning the battle but losing the war

- Main problem: increasing amount of positive patients admitted to the hospital

Implement policy in the whole region instead of a single centre!
... a “typical” Friday afternoon

❌ everyone (who could be of help) is gone
❌ you have an urgent appointment at home
   (in-laws visit)

beep-beep
... Professor Dr. B.I.G. Boss calls

Help!
MRSA spreads through your modern ICU

Catch me if you can!
MRSA outbreak control

Screening HCWs & patients

MRSA +

Isolation & cohorting

Remove source

MRSA +

Screening HCWs & patients

Isolation & cohorting

HCWs & patients MRSA -
What to do when out of control

- Cohort patients and HCWs
- No discharge (unless in isolation)
- Follow up possible former contacts (ex-patients)
- Screen all HCWs in the unit (not only those with “known” contact with index patient)
- Screen out-of-unit consultants
- Admission stop?
What is next?

- **Isolation and cohorting**
  - Index case(s) – possible – negative
  - Cohort patients and HCWs (if necessary close beds)
Be consequent!

- Transmission will continue as long as a permanent carrier among patients or HCWs is still in the outbreak unit.
No control $\rightarrow$ admission stop

typical infection control guy

typical administrator or clinician (dislikes IC measures)
Achieve the impossible
What to do

- Implement or re-enforce existing S&D strategy
- Decolonize and follow-up patients with epidemic strains
- Extend surveillance and improve communication between health-care institutions
- Define “risk-groups” (including new ones)
- Improve infection control outside hospitals...
Furthermore …

- Fast & reliable diagnostic
  - RT-PCR
  - IDI-MRSA

- Diagnostic guidelines
  - NVMM

- Infection Control guidelines
  - Implementation
  - Behavior of HCWs
Furthermore …

- Fast & reliable diagnostic
  - RT-PCR
  - IDI-MRSA
- Diagnostic guidelines
  - NVMM
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  - Implementation
  - Behavior of HCWs
ICU-acquired MRSA infections
(Geneva MICU 2003-04)

Masuet et al – ICAAC 2004: #D57