MDR Acinetobacter baumannii

Has the post antibiotic era arrived?

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The Armageddon recipe

- Transmissible organism with prolonged environmental survival
- Significant mortality & morbidity
- Rapid development of resistance
- Increasing global epidemiology
- Challenges in instituting effective treatment
  - extensive multi-resistance
  - toxicity of therapeutic options
Survival of *Acinetobacter baumannii* on Dry Surfaces: Comparison of Outbreak and Sporadic Isolates

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<table>
<thead>
<tr>
<th>Strain no.</th>
<th>Site of isolation</th>
<th>Outbreaka</th>
<th>Mean survival time (days) ± SDb</th>
</tr>
</thead>
<tbody>
<tr>
<td>St-284</td>
<td>Blood</td>
<td>G-III</td>
<td>22 ± 4.42</td>
</tr>
<tr>
<td>St-14733</td>
<td>Blood</td>
<td>G-III</td>
<td>31 ± 0.71</td>
</tr>
<tr>
<td>St-1650</td>
<td>Blood</td>
<td>G-X</td>
<td>25 ± 1.14</td>
</tr>
<tr>
<td>St-1954</td>
<td>Blood</td>
<td>G-X</td>
<td>27 ± 0.71</td>
</tr>
<tr>
<td>St-2312</td>
<td>Blood</td>
<td>G-VIII</td>
<td>27 ± 1.14</td>
</tr>
<tr>
<td>St-8195</td>
<td>Catheter</td>
<td>G-VIII</td>
<td>21 ± 3.53</td>
</tr>
<tr>
<td>St-11681</td>
<td>Blood</td>
<td>G-VIII</td>
<td>21 ± 1.14</td>
</tr>
<tr>
<td>St-7961</td>
<td>Blood</td>
<td>G-VIII</td>
<td>23 ± 4.42</td>
</tr>
<tr>
<td>St-14970</td>
<td>Catheter</td>
<td>G-V</td>
<td>28 ± 4.42</td>
</tr>
<tr>
<td>St-15598</td>
<td>Catheter</td>
<td>G-V</td>
<td>26 ± 2.12</td>
</tr>
<tr>
<td>St-16706</td>
<td>Blood</td>
<td>G-IV</td>
<td>26 ± 1.14</td>
</tr>
<tr>
<td>St-20820</td>
<td>Blood</td>
<td>G-IV</td>
<td>30 ± 2.82</td>
</tr>
<tr>
<td>St-21359</td>
<td>Catheter</td>
<td>G-IV</td>
<td>32 ± 1.14</td>
</tr>
<tr>
<td>St-17093</td>
<td>Blood</td>
<td>G-VI</td>
<td>27 ± 2.12</td>
</tr>
<tr>
<td>V-7459</td>
<td>Tracheal aspirate</td>
<td>G-VI</td>
<td>26 ± 0.71</td>
</tr>
</tbody>
</table>
Does AB increase mortality? YES

- Pairwise matched 1:1 case-control study in a medical-surgical ICU
- Eighty-seven patients were included, with 75 pairs successfully matched.

<table>
<thead>
<tr>
<th></th>
<th>Colonisation</th>
<th>Infection</th>
<th>Respiratory infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable mortality</td>
<td>30%</td>
<td>43%</td>
<td>53%</td>
</tr>
<tr>
<td>Estimated risk of death</td>
<td><strong>2.6</strong> p&lt;0.001</td>
<td><strong>4.0</strong> p&lt;0.001</td>
<td><strong>4.0</strong> p&lt;0.01</td>
</tr>
<tr>
<td>Excess LOS</td>
<td>13 days p&lt;0.001</td>
<td>13 days p&lt;0.001</td>
<td>13 days p&lt;0.01</td>
</tr>
</tbody>
</table>

Garcia-Garmendia et al  Crit Care Med 1999
Does AB increase mortality? NO

• Disease-matched controls to determine the clinical and financial impacts of treating colonization.

• 102 patients in each group
  – Mortality correlated with APACHE II scores - **not colonisation or infection**.
    • Mean ICU stay of 27.35 days vs 5.53 days for controls.
    • Required significantly more use of ventilators.
    • Significantly longer hospital stay, more bed transfers, greater duration and number of antibiotics.

  – Unnecessary treatment for colonization with either imipenem or amikacin resulted in a substantial decrease of *P. aeruginosa* susceptibility.

Weingarten CM et al. *Pharmacotherapy* 1999
Does AB increase mortality? Probably

- Systematic review of matched case-control and cohort studies.
- Six matched case-control studies included.
- **Attributable mortality** of patients with AB infection ranged:
  - from **7.8% to 23%** in hospital wards
  - from **10% to 43%**, in intensive care.
- In addition, a statistically **significantly higher mortality** was reported for patients with **AB acquisition**
- “Although definitive statements about the mortality attributable to the acquisition of *A. baumannii* cannot be made from the available studies because of their methodological heterogeneity, the reviewed data suggest that **infection with or acquisition of A. baumannii seems to be associated with increased mortality**”

Falagas ME, Bliziotis IA, Siempos II. *Crit Care*. 2006
• Genome sequencing of the French epidemic strain AYE
• Identified 52 genes associated with resistance,
  – including 17 genes not previously described in A. baumannii.
• 86% of resistance genes were clustered in a “resistance island”
  – Built through the insertion of broad host-range mobile genetic elements originating from Pseudomonas, Salmonella, and Escherichia.
  – Similar structure in the genome of susceptible strain SDF, exhibiting mobility-associated genes but no resistance markers.
  – Specific hotspot of genomic instability in the A. baumannii genome
• Identification of several putative resistance genes despite not exhibiting the associated phenotype
  – maintenance of spare copies of “ready-to-optimize” resistance genes, perhaps selected by exposure to sub-inhibitory levels of the drug in the environment,
• Ability to “switch” its genomic structure when under antibacterial pressure,
  – such as in hospital intensive care units.
Figure

Percentage of participants who reported having treated patients with infections due to selected antibiotic-resistant bacteria during the past six months, 2009 (n=95 participants)

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococcus* spp. (VRE)
- Penicillin-resistant *Streptococcus pneumoniae* (PRSP)
- Vancomycin-resistant/intermediate *S. aureus* (VRSA/VISA)
- Third-generation cephalosporin-resistant *Enterobacteriaceae*
- Carbapenem-resistant *Pseudomonas aeruginosa*
- Carbapenem-resistant *Acinetobacter spp.*
- Bacteria totally or almost totally resistant to available antibiotics

% respondents

- >10 patients
- 3-10 patients
- 1-2 patients
- 0
- Do not know
- Missing
Carbapenem resistance
(MYSTIC study 2004)

2007;51:3471-3484
An increasing challenge

Highlighted countries have reported CRAB > 50%
Malta isolates: resistance profiles

- 92% TZP CAZ IPM GEN TOB CIP
- 5% TZP CAZ IPM AMK GEN TOB CIP
- TZP CAZ IPM CIP
- TZP CAZ IPM GEN CIP
- TZP TOB
Therapeutic options

• Colistin
  – Often the only realistic therapeutic option
  – Highly active against *A. baumannii*
    • including carbapenem resistant strains.
  – However, heteroresistance has been described and has been associated with clinical failure.
    • Patients who had prior receipt of colistin were more likely to have heteroresistant strains.
  – Biggest limitation is nephrotoxicity
• 43% patients developed nephrotoxicity
  – RIFLE criteria: Risk (13%), Injury (17%), or Failure (13%)
• Patients who developed nephrotoxicity received significantly higher mean doses
  – toxicity occurred in a dose-dependent fashion.
• Independent predictors for nephrotoxicity
  – colistin dose of ≥5.0 mg/kg per day of IBW (OR = 23.41)
  – receipt of concomitant rifampin (OR = 3.81)
  – coadministration of ≥3 concomitant nephrotoxins (OR = 6.80)
Colistin nephrotoxicity

• Narrow therapeutic window
  – questions whether PK/PD optimization is even possible patients who are
    • Obese
    • Have relatively high creatinine clearances,
    • infections due to pathogens with MIC at the upper end of the susceptibility range.
Prevention of MDR-AB

ENDEMIC SETTINGS:
• Implementation of hand hygiene programme and contact precaution;
• Implementation of education programme and antibiotic stewardship should be added in a multifaceted approach.

EPIDEMIC SETTINGS:
• Implementation of hand hygiene programme, contact precaution, and isolation room;
• Implementation of environmental cleaning should be added in a multifaceted approach.
Acinetobacter baumanii cases:
ICU St. Luke’s Hospital (2000 – 12)
November 2007 →

St. Luke’s Hospital

Mater Dei Hospital
Acinetobacter baumanii ICU cases: (2000 – 12)

Hospital migration

Antibiotic pharmacist

Others
Urine
SST
Blood
Sputum
Carbapenem consumption
DDD/100BD
Acinetobacter baumanii & MRSA bacteremia epidemiology (ICU MDH)
CRAB & MRSA bacteraemia epidemiology (ICU MDH)

CRAB bacteraemia

MRSA bacteraemia initiatives

- MRSA screening & decolonisation
- Chlorhexidine daily baths for all ICU patients

MRSA bacteraemia
Possible confounders

Hand hygiene compliance (%)

BSI rate per 1000 pt-days (>48hrs)
Impact of 4% chlorhexidine whole-body washing on multidrug-resistant *Acinetobacter baumannii* skin colonisation among patients in a medical intensive care unit

A. Borer, J. Gilad, N. Porat, R. Megrelesvilli, L. Saidel-Odes, N. Peled, S. Eskira, F. Schlaeffer, Y. Almog

- Prevalence of ACBA-BSIs decreased from 4.6% to 0.6% (P<0.001; OR: 7.6)
- Incidence of ACBA-BSIs decreased from 7.8 to 1.25 per 100 admissions (85% reduction)
Conclusions

• MDR Acinetobacter baumanii offer a significant post-antibiotic era threat
• Increasing prevalence in many countries
• Genetic propensity for rapid resistance development
• Therapeutic limitations
  – Limited antimicrobial options
  – Toxicity of colistin
• Infection prevention and control is the key
  – Multimodal interventions most likely to succeed
WE ARE THE BORG
RESISTANCE IS FUTILE

THANK YOU