Antibiotic stewardship programs – How do they promote a “safer” environment

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Hannover, Germany
Disclosures

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OVERUSE

“The desire to ingest medicines is one of the principal features which distinguish man from the animals.”

Osler W: Aecquanimitas, 1920
What is antibiotic stewardship?

- An activity that optimizes antimicrobial management and includes selection, dosing, route and duration of antimicrobial therapy and prophylaxis
- A marriage of infection control and antimicrobial management
- Mandatory infection control compliance
- Selection of antimicrobials that do the least collateral damage, e.g., MRSA, ESBLs, *Clostridium difficile*

ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*


Antibiotic stewardship in Europe:
European survey to investigate antibiotic policy criteria in 170 hospitals from 32 countries

- Only 57% of European hospitals surveyed have a written antibiotic policy; one-fifth of teaching hospitals do not
- Hospitals in northern and western Europe are most likely to convene antibiotic committees
- No differences in overall antibiotic use
- Policies and practices relating to antibiotic stewardship vary considerably across Europe
- New stewardship initiatives are necessary to achieve harmonization of recommended practices

ABS – Local aspects:
Foundation doctors, staff induction, pharmacist training packs, guidelines

ABS, antibiotic stewardship.
With courtesy of Prof. Dilip Nathwani, OBE

ABS – General aspects

• Source control – necessary or unnecessary?
• Initiation of therapy – early vs. delayed?
• Diversity – first line vs. multiple substances?
• De-escalation – broad vs. narrow spectrum?
• Duration of therapy – how long to treat?
• Discontinuation of therapy – any markers?
• What are the early switch and early discharge strategies?

ABS, antibiotic stewardship.
Prognosis of intra-abdominal infections: Importance of source control


Treatment of peritonitis 1925

- “Very inconsistent therapy”
- Collective: n=25
- Mortality: 80% (!)
- “Improvement necessary”
Effect of early vs. delayed antimicrobial therapy in septic shock

“Aggressive” vs. “Conservative” approach to antibiotic therapy in hemodynamically stable surgical ICU patients

The early antibiotic therapy in septic patients - milestone or sticking point?

Michael Bernhard¹, Christoph Lichtenstem², Christian Eckmann³ and Markus A Wegand⁴
“Aggressive” vs. “Conservative” approach to antibiotic therapy in hemodynamically stable surgical ICU patients

<table>
<thead>
<tr>
<th></th>
<th>Aggressive</th>
<th>Conservative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>762</td>
<td>721</td>
<td></td>
</tr>
<tr>
<td>Infected, n (%)</td>
<td>101 (13)</td>
<td>100 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>Appropriate</td>
<td>144/231 [62%]</td>
<td>158/214 [74%]</td>
<td>0.0095</td>
</tr>
<tr>
<td>Duration</td>
<td>17.7</td>
<td>12.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>27</td>
<td>13</td>
<td>0.015</td>
</tr>
<tr>
<td>Adjusted mortality</td>
<td>OR 2.5 (95% CI 1.5-4.0)</td>
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</tr>
</tbody>
</table>

CI, confidence interval; ICU, intensive care unit; ns, non-significant; OR, odds ratio.


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Antibiotic diversity

Pre-establishment and reparation period

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<tr>
<th></th>
<th>PAMS</th>
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</thead>
</table>
Antibiotic diversity

Pre-establishment and reparation period

PAMS

All changes significant at p<0.001

4GC, fourth generation cephalosporin; GNR, gram-negative rods; PAMS, periodic antimicrobial monitoring and supervision; P/T, piperacillin/tazobactam.


save the Carbapenems!

love the earth
Treatment options for cIAI caused by ESBL-producing bacteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>• High clinical success rates</td>
<td>• “Overuse” results in increased carbapenem resistance</td>
</tr>
<tr>
<td>Imipenem/Cilastatin</td>
<td>• High clinical success rates</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>• High clinical success rates</td>
<td>• Limited activity against <em>Pseudomonas</em> spp.</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>• Favorable clinical response in recent trials</td>
<td>• Varying susceptibility rates (around 70%)</td>
</tr>
<tr>
<td></td>
<td>• Well known and well tolerated</td>
<td>• Varying clinical success rates</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>• Favorable clinical results in recent trials with severely ill patients</td>
<td>• Increased mortality discussion</td>
</tr>
<tr>
<td></td>
<td>• Broad range of activity against resistant rods</td>
<td>• Lack of activity against <em>Pseudomonas</em> and <em>Proteus</em> spp.</td>
</tr>
<tr>
<td>Ceftolozane/Tazobactam</td>
<td>• High clinical success in cIAI due to ESBL producers</td>
<td>• Not yet licensed</td>
</tr>
<tr>
<td></td>
<td>• Broad range of activity</td>
<td>• Information on pricing yet to be confirmed</td>
</tr>
</tbody>
</table>

cIAI, complicated intra-abdominal infection; ESBL, extended spectrum β-lactamase.

What is your view on de-escalation of antibiotics?

1. I ♡ de-escalation! I always do it when I receive the microbiological report.
2. I never do it because it is not proven to be safe!
3. It is not safe for polymicrobial infections.
4. I don’t trust culture results to give definitive proof of the absence of additional microorganisms, e.g., MDR.
De-escalation: The “evidence”

Main results

- 436 references.
- No randomized controlled trials testing de-escalation could be included in this review.

Author’s conclusions

- No adequate, direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock.
- Not possible to either recommend or not recommend the de-escalation of antimicrobial agents in clinical practice for septic patients.
- This uncertainty warrants further research via randomized controlled trials or cohort studies.

De-escalation in ICU?

- Design: Multicenter, prospective, randomized, non-blinded, non-inferiority trial
- Collective: 59 patients de-escalation (DE), 57 continued (CON)
- Endpoints: Days on ICU (non-inferiority margin 2 days); days with antibiotics; 90-day mortality
- Results I: Days on ICU not significantly different
- Results II: More superinfections in DE group (27% DE vs. 11% CON, p=0.03)
- Results III: More antibiotic days in DE group (9 vs. 7.5 days, p=0.03)


Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): A multicenter, randomized, controlled trial

- Collective: n=621 patients, prospectively
- Mortality day 28: 21% PCT, 20% control
- Mortality day 60: 30% PCT, 27% control
- Days without AB: 14.3 vs. 11.6 days (p<0.0001)

Exception: Surgical cohort!!!

Conclusion: A PCT-guided strategy to treat suspected bacterial infections in non-surgical patients in ICU could reduce antibiotic exposure and selective pressure.

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Procalcitonin: Kinetics fails to predict treatment response in secondary peritonitis with septic shock

- Collective: n = 101 patients
- Design: PCT on days 0,1,3,5 correlated with treatment success and outcome
- Results: 50% of patients with treatment success still had elevated PCT-values
  40% of patients with an 80% PCT reduction had treatment failure
Procalcitonin: Kinetics fails to predict treatment response in secondary peritonitis with septic shock


Monitoring treatment response in abdominal sepsis with procalcitonin - if only!

Christian Eckmann and Miguel Sanchez-Garcia

Is the “Low-Hanging Fruit” Worth Picking for Antimicrobial Stewardship Programs?

Debra A. Goff, Karri A. Bauer, Erica E. Reed, Kurt B. Stevenson, Jeremy J. Taylor, and Jessica E. West

A new antimicrobial stewardship program can be overwhelmed at the breadth of interventions and education required to conduct a successful program. The expression “low-hanging fruit,” in reference to stewardship, refers to selecting the most obtainable targets, rather than confronting more complicated management issues. These targets include intravenous-to-oral conversions, batching of intravenous antimicrobials, therapeutic substitutions, and formulary restriction. These strategies require fewer resources and less effort than other stewardship activities; however, they are applicable to a variety of healthcare settings, including limited-resource hospitals, and have demonstrated significant financial savings. Our stewardship program found that staged and systematic interventions that focus on obvious areas of need, that is, low hanging fruit, provided early successes in our expanded program with a substantial cumulative cost savings of $432,590.
Do you have an intravenous to oral switch protocol in your hospital?

1. Yes
2. No
3. Don’t know
4. Don’t care

ES/ED criteria

- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study; inclusive of Desai\(^1\) and Parodi\(^2\) criteria
- The key (essential) criteria were selected by KOLs and used to estimate ES/ED hypothetical opportunities

<table>
<thead>
<tr>
<th>ES</th>
<th>ED</th>
</tr>
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<tbody>
<tr>
<td>Stable clinical infection(^2)</td>
<td>WBC count normalizing (WBC 4-12 × 10(^9)/L)(^{1,2})</td>
</tr>
<tr>
<td>No unexplained tachycardia(^1)</td>
<td>Systolic BP ≥100 mmHg(^3)</td>
</tr>
<tr>
<td>Afebrile / temperature &lt;38°C for 24 hours(^{1,2})</td>
<td>Patient tolerates oral fluids / diet(^{1,2})</td>
</tr>
<tr>
<td>No other reason to stay in hospital except infection management(^2)</td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; ED, early discharge; ES, early switch; WBC, white blood cell; KOL, key opinion leader

Key results: Country level
ES/ED opportunities

Per-country % ES/ED eligible

ED, early discharge; ES, early switch.

Early switch and early discharge potential days saved

ES Eligible: Patient met literature-based criteria for early switch ≥1 day before their IV antibiotic treatment was discontinued.
ED Eligible: Patient met literature-based criteria for early discharge ≥1 day before they were discharged.
Antibiotic stewardship: Conclusion

- Don’t forget possible source control!
- Early initiation is indicated in severely ill patients
- Diversity might be a useful tool against selective pressure
- The value of de-escalation still needs to be determined
- Procalcitonin does not always help for discontinuation of therapy (mostly, 7 days of therapy is enough)
- Early switch and early discharge strategies can be beneficial for patients and for the hospital
- Overcome barriers for implementation of antibiotic stewardship

Implementation of antibiotic stewardship:
Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00</td>
<td>Chairman’s welcome and introduction</td>
<td>Jonathan Cooke</td>
<td>Manchester, UK</td>
</tr>
<tr>
<td>12:20</td>
<td>Antibiotic stewardship programs – How do they promote a “safer” environment</td>
<td>Christian Eckmann</td>
<td>Hannover, Germany</td>
</tr>
<tr>
<td>12:40</td>
<td>Intravenous to oral switching, OPAT, and early discharge</td>
<td>Mark Gilchrist</td>
<td>London, UK</td>
</tr>
<tr>
<td>13:00</td>
<td>The role of new antibiotics in the treatment of severe infections – Safety and efficacy features</td>
<td>Christian Eckmann</td>
<td>Hannover, Germany</td>
</tr>
<tr>
<td>13:15</td>
<td>Q&amp;A with panel discussion</td>
<td>All</td>
<td></td>
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