De-escalation of antibiotic therapy

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Istanbul, Oct 7th 2016
De-escalation: concept

- Increase MDR pathogens
- Severe ill patient with infection
- Link antibiotic use and development of resistance
- No new antibiotics in pipeline
- Rapid, adequate therapy
- Broad Spectrum empirical R/
- Narrow spectrum, reduce AB use

**De-escalation**

*figure: Liesbeth de Bus*
De-escalation: concept

Streamlining or de-escalation of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in decreased antimicrobial exposure and substantial cost savings.

A-II → good evidence, but no RCT’s (2007)
Antimicrobial regimen should be reassessed daily for potential de-escalation

Grade 1B → strong recommendation, but no RCT’s (2012)
Authors conclusions (2012)

• “We did not include any study”

• There is no adequate evidence that de-escalation of antimicrobial agents is effective and safe in patients with sepsis, severe sepsis and septic shock
De-escalation: definitions

- Narrow the spectrum
- Reduce the amount of antibiotics
- Stop ‘safety’ antibiotics (MRSA)
- Stop if infection is unlikely
- Therapy aimed at ‘causative pathogen’
- ‘Switching’
The de-escalation paradigm

Hit hard with appropriate antibiotic(s)
administered adequately - early, IV,
high dose, PK/PD

De-escalate when possible:
change to NARROWER SPECTRUM

This is not exactly right!
Elaboration of a **consensual definition of de-escalation** allowing a ranking of β-lactams


- **It is not just about the spectrum!** but also on the impact on bystander microbiota and on colonisation resistance: both have to be considered (84% agreement)

- potential ecological effects = not only spectrum but also route, PK/PD, and *in vivo* inactivation
Elaboration of a **consensual definition of de-escalation** allowed


- **no consensus was reached** on the delay within which DE should be performed and on whether or not the shortening of antibiotic therapy duration should be included in DE definition

- **work also underlines the difficulties of reaching a consensus** on the relative ecological impact of each individual drug and on the timing of DE
De-escalation: goals?

- Reduce selection of MDR bacteria
- Reduce colonisation with MDR bacteria
- Reduce infection with MDR bacteria
- Reduce Antibiotic use (DDD)
- Reduce costs
- Reduce time to recovery LOS, mortality
De-escalation in pneumococcal bacteremia

Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James WT Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins

Fig. 2 Effect on mortality of de-escalation of therapy based on culture results
Goal

• Which are the definitions used for de-escalation in the literature?

• What is the effect of de-escalation on outcomes of care in ICU patients?
What evidence exists to support antimicrobial de-escalation in the intensive care unit? 

_A systematic review_

**Results: 14 studies**

- **two randomised clinical trials (unblinded) Cochrane Risk of Bias tool**
- **12 cohort studies Newcastle–Ottawa Quality Assessment Scale**

A. Tabah, J.F. Timsit, J. Schouten, J. Dewaele _CID 2016_
What evidence exists to support antimicrobial de-escalation in the intensive care unit? 

A systematic review

Which definitions are used for de-escalation in the literature?

- Always described as “narrowing” or “streamlining” therapy, considerable variability
- Ranking “broadness of spectrum” in 4/14 studies
- Concept of the “pivotal” antibiotic (Leone)
What evidence exists to support antimicrobial de-escalation in the intensive care unit?

_A systematic review_

Outcomes after de-escalation:

- Lower or improving severity scores associated with DE (p=0.04 to <0.001)
- Pooled effect of DE on mortality protective (RR 0.68, 95% CI 0.52-0.88)
- Limited quality of cohort studies
  - Adjustment and multivariable analysis on the effect of DE on outcome only in 4/12 cohort studies
  - Two studies accounted for severity of illness at the moment where DE was considered
What evidence exists to support antimicrobial de-escalation in the intensive care unit?  

*A systematic review*

Secondary outcomes after de-escalation:

- Non-inferiority length of stay in DE group
- More superinfections and longer AB use in DE
- No (measurable) effect on ecology
De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial
De-escalation: Leone et al. 2014

- Multicenter (9) ICU study in France
- Randomised: continue vs. de-escalate
- Unblinded
- 120 patients
- Primary outcome: LOS (non-inferiority de-escalation)
- Secondary outcomes: 90 day M; AB free days; superinfections; *Clostridium difficile* infections

Leone et al. 2014
De-escalation: Leone et al. 2014

- Inclusion severe sepsis / septic shock
- Randomisation as soon as positive cultures available
- Adequate empirical therapy acc. guidelines

**Definition** de-escalation:

- Change “Pivotal antibiotic” to AB with narrowest possible spectrum
- Stop combination therapy (quinolone, amino-glycoside or macrolide) at day 3
- Stop Vancomycin if no rationale for MRSA
De-escalation: Leone et al. 2014

• Definition continue:

  • Continue “Pivotal antibiotic”

  • Stop combination therapy (quinolone, amino-glycoside or macrolide) between day 3 and 5

  • Stop Vancomycin if no rationale for MRSA

  • Therapy duration acc. to international guidelines
$p = 0.35$
De-escalation: Leone et al. 2014

<table>
<thead>
<tr>
<th>Duration</th>
<th>De-escalation group (n = 59)</th>
<th>Continuation group (n = 57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of ICU stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From inclusion to discharge</td>
<td>15.2 ± 15.0</td>
<td>11.8 ± 12.6</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>9 [1–79]</td>
<td>8 [1–60]</td>
<td></td>
</tr>
<tr>
<td>From admission to discharge</td>
<td>29.1 ± 50.0</td>
<td>18.1 ± 15.7</td>
<td>0.11</td>
</tr>
</tbody>
</table>
De-escalation: Leone et al. 2014

![Graph showing comparison of de-escalation and continuation]

- aantal dagen combinatie therapie
- carbapenem vrij dagen
- anti-MRSA ab vrij dagen
- anti-pseudomonas ab vrij dagen
- antibiotic days

Legend:
- De-escalatie
- Continuatie
De-escalation: Leone et al. 2014

Number of secondary infections

- De-escalatie: 25%
- Continuatie: 10%

P = 0.03
De-escalation: goals?

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Retrospective study comparing de-escalation vs. escalation vs. continuation for betalactam use

Outcomes:

- Duration of antibiotic course, Antibiotic consumption
- Cumulative incidence of MDR resistant pathogens to the initial betalactam antibiotic using systematically collected surveillance cultures (!)
<table>
<thead>
<tr>
<th>Patient outcome</th>
<th>Treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 344)</td>
<td>Continuation (n = 221; 64%)</td>
<td>De-escalation (n = 85; 25%)</td>
<td>Escalation (n = 38; 11%)</td>
<td>p value</td>
<td>De-escalation vs. continuation</td>
<td>Escalation vs. continuation</td>
<td></td>
</tr>
<tr>
<td>Antibiotic treatment duration in the ICU for the infection under study (days)</td>
<td>6 (5–9)</td>
<td>5 (4–7)</td>
<td>8 (6–10)</td>
<td>11 (8–19)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total antibiotic consumption in the ICU (days)</td>
<td>10 (5–20)</td>
<td>7 (4–15)</td>
<td>12 (7–22)</td>
<td>24 (13–39)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic-free days (14 days after onset of infection)³ (n = 116)</td>
<td>1 (0–4)</td>
<td>2 (0–6)</td>
<td>1 (0–3)</td>
<td>0 (0–1)</td>
<td>0.04</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2 a Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of pathogens resistant to the initial anti-pseudomonal betalactam antibiotic. b Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of MDR pathogens.
### Table 2: Multivariate analysis on determinants of de-escalation and escalation of anti-pseudomonal beta-lactam antibiotic therapy

<table>
<thead>
<tr>
<th>Factors associated with de-escalation or escalation</th>
<th>De-escalation versus continuation</th>
<th>Escalation versus continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)(^a)</td>
<td>(p) value</td>
</tr>
<tr>
<td>ICU department (medical/surgical ICU)</td>
<td>0.81 (0.5–1.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hospitalization duration prior to initiation of BL therapy (days)</td>
<td>0.99 (0.98–1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Antibiotic exposure during ICU stay prior to initiation of BL therapy</td>
<td>0.68 (0.41–1.15)</td>
<td>0.15</td>
</tr>
<tr>
<td>Type of initial BL therapy</td>
<td>0.98 (0.75–1.28)</td>
<td>0.88</td>
</tr>
<tr>
<td>Focus of infection</td>
<td>0.98 (0.86–1.12)</td>
<td>0.76</td>
</tr>
<tr>
<td>Severe sepsis/septic shock</td>
<td>1.1 (0.65–1.85)</td>
<td>0.72</td>
</tr>
<tr>
<td>ΔSOFA(^c)</td>
<td>1.01 (0.94–1.08)</td>
<td>0.83</td>
</tr>
<tr>
<td>Microbiologically documented infection</td>
<td>3.96 (2.4–6.55)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Presence of (non-etiologic) Isolates resistant to the Initial BL therapy</td>
<td>1.46 (0.87–2.48)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for ICU department, hospitalization duration, antibiotic exposure, type of initial BL therapy, focus of infection, and severe sepsis/septic shock.

\(^b\)Adjusted for ICU department, hospitalization duration, antibiotic exposure, type of initial BL therapy, focus of infection, severe sepsis/septic shock, ΔSOFA, and microbiologically documented infection.

\(^c\)ΔSOFA = SOFA at admission - SOFA at day 2.
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De-escalation: future?

- Severely ill patient in ICU
- Increase MDR
- Rapid, adequate therapy
- Broad Spectrum empirical R/
  Narrow Spectrum
- Link antibiotic use and development of resistance
  Narrow spectrum, reduced AB
  Cost reduction

Rapid, adequate therapy for narrow spectrum antibiotics to reduce antibiotic use and development of resistance.
De-escalation?  
-no uniform definition  
-no reduction of AB duration, costs or length of stay  
-no effects on AMR  
-protective of mortality? bias!  

large cluster-RCT required
De-escalation: future

De-escalation?

rather focus on early stop!
Even short courses of antibiotics cause selection of resistant bacteria

- we need to move to more rapid culture-independent micro identification methods
- we need swift communication between micro lab and ICU:
  - leading to faster achievement of appropriate therapy
  - duration of empirical therapy may be limited

Harbarth Circulation 2000
Taconelli AAC 2010
Lefevre AAC 2013
Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients.

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial


Figure 2: Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population
<table>
<thead>
<tr>
<th>Antibiotic consumption (days)</th>
<th>Procalcitonin-guided group (n=761)</th>
<th>Standard-of-care group (n=785)</th>
<th>Between-group absolute difference in means (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily defined doses in first 28 days</td>
<td>7.5 (4.0 to 12.8)</td>
<td>9.3 (5.0 to 16.5)</td>
<td>2.69 (1.26 to 4.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>5.0 (3.0 to 9.0)</td>
<td>7.0 (4.0 to 11.0)</td>
<td>1.22 (0.65 to 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic-free days in first 28 days</td>
<td>7.0 (0.0 to 14.5)</td>
<td>5.0 (0.0 to 13.0)</td>
<td>1.31 (0.52 to 2.09)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>149 (19.6%)</td>
<td>196 (25.0%)</td>
<td>5.4% (1.2 to 9.5)</td>
<td>0.0122</td>
</tr>
<tr>
<td>1-year mortality</td>
<td>265 (34.8%)</td>
<td>321 (40.9%)</td>
<td>6.1% (1.2 to 10.9)</td>
<td>0.0158</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinfection</td>
<td>38 (5.0)</td>
<td>23 (2.9)</td>
<td>−2.1% (−4.1 to 0.1)</td>
<td>0.0492</td>
</tr>
<tr>
<td>Repeated course of antibiotics</td>
<td>175 (23.0)</td>
<td>173 (22.0)</td>
<td>−1.0% (−5.1 to 3.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Time (days) between stop and reinstitution of antibiotics</td>
<td>4.0 (2.0 to 8.0)</td>
<td>4.0 (2.0 to 8.0)</td>
<td>−0.22 (−1.31 to 0.88)</td>
<td>0.96</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cumulative costs of antibiotics</td>
<td>€150 082</td>
<td>€181 263</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median cumulative costs antibiotics per patient</td>
<td>€107 (51 to 229)</td>
<td>€129 (66 to 273)</td>
<td>€33.6 (2.5 to 64.8)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On the intensive care unit</td>
<td>8.5 (5.0 to 17.0)</td>
<td>9.0 (4.0 to 17.0)</td>
<td>−0.21 (−0.92 to 1.60)</td>
<td>0.56</td>
</tr>
<tr>
<td>In hospital</td>
<td>22.0 (13.0 to 39.3)</td>
<td>22.0 (12.0 to 40.0)</td>
<td>0.39 (−2.69 to 3.46)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

Table 2: Primary and secondary outcome measures

E de Jong, Lancet Infect Dis march 2016
De-escalation needs a more solid evidence base

• How quickly is the damage to the microbiota done and how long does it last?

• Does sequential therapy with two different antimicrobials increase damage or is it beneficial? What about combination therapy?

• What is the impact of dosing and duration of therapy on AMR selection?
De-escalation: a revised view

- Broad Spectrum empirical R/
  - Reevaluation d 2-3
    - Discontinue unnecessary and companion AB
      - short course (<5d) continue initial therapy
      - long course (7-10d) narrow monitor (PCT)

figure adapted with permission Jan Dewaele