De-escalation as a Critical Strategy in Acute Care

Prof Bojana Beović, MD, PhD
University Medical Centre Ljubljana
Faculty of Medicine, University of Ljubljana
Ljubljana, Slovenia
Disclosures

Speaker for Alkaloid, Astellas, AstraZeneca, Altamedics, Lek (Sandoz), MSD, Pfizer
Consultant: Lenis, Lek (Sandoz)
Research grants: MSD, Pfizer
De-escalation: Definition

De-escalation

from Latin „scala“, ladder or „scalae“ pl., stairs

*De-escalation is*

• *replacing the empirical antibiotic treatment with a narrower spectrum antibiotic*

• *discontinuing redundant antibiotic therapy*

• *(switching to oral therapy).*
The Theoretical Concept of De-escalation

Timely broad-spectrum antibiotic treatment → pathogen isolation (exclusion of a pathogen) → Narrower spectrum adapted to the isolate and its susceptibility

Successful control of infection (morbidity, mortality) → Limited antibiotic selection pressure (lower antibiotic cost)
The Theoretical Concept of De-escalation

Timely broad-spectrum antibiotic treatment → pathogen isolation (exclusion of a pathogen) → Narrower spectrum adapted to the isolate and its susceptibility

Successful control of infection (morbidity, mortality) → Limited antibiotic selection pressure (Lower antibiotic cost)

Individual patient benefit

Societal benefit: safeguarding the activity of empirical treatment
Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,1 Robert C. Owens,2 John E. McGowan, Jr.,2 Dale N. Gerding,4 Robert A. Weinstein,4 John P. Burke,4 W. Charles Huskins,7 David L. Paterson,8 Neil O. Fishman,9 Christopher F. Carpenter,9 P. J. Brennan,5 Marianne Billeter,11 and Thomas M. Hooton12

F. Streamlining or de-escalation of therapy. 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).

A: good evidence to support recommendation

II: evidence from 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies; from multiple time-series; or from dramatic results from uncontrolled experiments.
There is no separate recommendation for de-escalation, but:

Prospective audit and feedback can address de-escalation of antibiotics and duration of therapy.

Rapid diagnostics coupled with ASP involvement was also associated with more rapid appropriate de-escalation.

PCT as a tool for de-escalation.

Evidence based recommendation classified as relevant:

1. Provide rationale for antibiotic start
2. Perform appropriate microbiological sampling
3. Prescribe empirical therapy according to guidelines (day 1)
4. Review diagnosis
5. Evaluate de-escalation based on microbiological results (day 2 to 5)
6. Consider discontinuation of antibiotic treatment (day 3 to 5).
Skills of an ID Physician as the Antimicrobial Stewardship Programme Leader

- Alignment with public health needs
- Impact on prescribing behavior of others
- Clinical expertise
- Positive impacts:
  - Improved patient outcomes
  - Less antimicrobial use
  - Lower antimicrobial costs
  - Less resistance
  - Fewer adverse events
  - Fewer drug-drug interactions
  - Improved quality metrics:
    - Decreased CLABSI rate
    - Decreased *C. difficile* infection
    - Shorter length of stay
- Conversion to oral agents
- Understanding of resistance and mitigation strategies
- De-escalation to narrow-spectrum agents

De-escalation: a key pillar to antibiotic stewardship YES!! JF Timsit, F

De-escalation of antibiotic therapy „Much ado about nothing“ J Schouten NL
De-constructing De-escalation

by Huttner B, Pulcini C, and Schouten J.

Not enough evidence:

- the damage to microbiota: when and how long
- is sequential treatment beneficial or harmful
- the role of combination treatment
- the role of dosing and duration for resistance selection

At present de-escalation is more a woodoo than science!

Evidence behind IDSA Guidelines (January 1994 to May 2010)

„A“ recommendations (good evidence for support):

23% were level I (≥ 1 randomized controlled trial),

37% were level III (based on expert opinion only)

Re-con structing De-escalation (a practice oriented approach)

Efficacy of de-escalation:

Decrease of antimicrobial resistance
Less infections with resistant pathogens
Less adverse events related to antibiotic therapy incl. *C. difficile* infections
Lower cost of treatment

Safety of de-escalation:

Morbidity, length of hospital stay
Mortality
Re-con structing De-escalation
(a practice oriented approach)

Efficacy of de-escalation:

✓ Decrease of antimicrobial resistance
✓ Less infections with resistant pathogens
✓ Less adverse events related to antibiotic therapy incl. *C. difficile* infections
  Lower cost of treatment

Safety of de-escalation:

Morbidity, length of hospital stay
✓ Mortality
### Efficacy of De-escalation: Antibiotic Resistance

**(Systematic Reviews)**

<table>
<thead>
<tr>
<th>The author, year of publication</th>
<th>Inclusion criteria</th>
<th>Definition of de-escalation</th>
<th>Number and type of studies included</th>
<th>Assessment of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gutiérrez-Pizarraya, 2017</td>
<td>Randomized or prospective, adult immunocompetent patients with sepsis/septic shock in ICU</td>
<td>- withdrawal of at least one antibiotic - switch to narrower spectrum - both</td>
<td>1 RTC 1 prospective</td>
<td>ND</td>
</tr>
<tr>
<td>Guo, 2016</td>
<td>Adult patients with sepsis/septic shock</td>
<td>withdrawal of at least one antibiotic - switch to narrower spectrum</td>
<td>1 RTC 4 prospective 4 retrospective</td>
<td>ND</td>
</tr>
<tr>
<td>Paul, 2016</td>
<td>Adult patients with microbiologically documented infection</td>
<td>- withdrawal of an antibiotic in combination treatment - switch to narrower spectrum</td>
<td>3 RTCs 16 observational</td>
<td>Contradictory results or no effect</td>
</tr>
<tr>
<td>Ohji, 2016</td>
<td>Any comparative studies that assessed the de-escalation therapy</td>
<td>- withdrawal of at least one antibiotic - switch to narrower spectrum - both</td>
<td>23 studies</td>
<td>ND</td>
</tr>
<tr>
<td>Tabah, 2016</td>
<td>ICU, studies assessing the effects or determinants of de-escalation</td>
<td>variable</td>
<td>2 RTC 4 prospective observational 8 retrospective</td>
<td>No effect on antimicrobial resistance found in two studies,</td>
</tr>
</tbody>
</table>
## The Efficacy of De-escalation: Antibiotic Resistance

### (recent studies)

<table>
<thead>
<tr>
<th>Author/year of publication</th>
<th>Type of study</th>
<th>Type of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee/2017</td>
<td>retrospective</td>
<td>Community-onset bacteremia</td>
<td>More blood-stream infections with MDR Gram-negative bacteria in non-de-escalated group, NS.</td>
</tr>
<tr>
<td>Weiss/2016</td>
<td>retrospective</td>
<td>VAP</td>
<td>Less ESBL acquisition in the de-escalation group, NS.</td>
</tr>
<tr>
<td>De Bus/2016</td>
<td>prospective observational</td>
<td>ICU</td>
<td>Higher cumulative incidence of bacteria resistant to initial beta-lactam antibiotic or MDR in de-escalated group, NS, no difference when only documented infections or only therapies &gt; 5 days were compared.</td>
</tr>
<tr>
<td>Rattanaumpawan/2017</td>
<td>RCT</td>
<td>ESBL infections</td>
<td>No difference in stool colonisation with MDR bacteria.</td>
</tr>
</tbody>
</table>

VAP, ventilator associated pneumonia, RCT, randomized controlled trial, ICU, intensive care unit, HAP, hospital acquired pneumonia, MDR, multidrug resistant

The Efficacy of De-escalation: *Clostridium difficile* Infections

<table>
<thead>
<tr>
<th>Author/year of publ.</th>
<th>Type of study</th>
<th>Type of patients</th>
<th>Clostridium difficile Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder/2017</td>
<td>retrospective</td>
<td>Patients after HSCT</td>
<td>no difference</td>
</tr>
<tr>
<td>Viasus/2017</td>
<td>prospective observational</td>
<td>Community-acquired pneumonia</td>
<td>no difference</td>
</tr>
<tr>
<td>Leon/2014</td>
<td>RCT</td>
<td>Severe sepsis in ICU</td>
<td>no difference</td>
</tr>
<tr>
<td>Bohan/2016</td>
<td>retrospective</td>
<td>Health-care associated pneumonia</td>
<td>de-escalation <strong>not associated</strong> with <em>C. difficile</em> infection in 30 days.</td>
</tr>
</tbody>
</table>

The Efficacy/Safety of De-escalation: Superinfections

- **No difference** in superinfection rate in de-escalated and not de-escalated arm in a secondary analysis of a large VAP study.

- **No difference** in recurrent pneumonia rate in VAP patients in a retrospective study.

- **Non-significantly lower** superinfection rate in de-escalation arm in a randomized controlled study investigating de-escalation from 2nd generation carbapenems to ertapenem in ESBL infections.

- **Significantly higher** superinfection rate in de-escalation arm in a randomized controlled study in severe sepsis in ICU ($p=0.03$).

- In febrile neutropenia patients, there were significantly less confirmed infections in de-escalation arm in a retrospective study ($p=0.01$).

- **Non-significantly higher** hospital infection rate in de-escalation arm in patients with ICU stay > 5 days in a prospective observational study in patients with severe sepsis/septic shock.

- **More** secondary blood-stream infections with resistant micro-organisms in not de-escalated arm in a retrospective study on community acquired bacteremia, no statistical analysis.

Benefits and Un-intended Harms of De-escalation: a Mathematical Model

De-escalation reduces the use of high-value drugs and preserves the effectiveness of empiric therapy, while also selecting for multidrug-resistant strains and leaving patients vulnerable to colonization and superinfection.
Safety of De-escalation: Mortality (1)

Systematic review of 16 observational and 3 RTCs with microbiologically documented infections, published until September 2015: adjusted all-cause mortality

## Safety of De-escalation: Mortality (2)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of Studies</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review and meta-analysis of studies on de-escalation in patients with severe sepsis/septic shock</td>
<td>9 studies (1 RCT)</td>
<td>All-cause mortality lower in the de-escalation group, the difference is not significant.</td>
</tr>
<tr>
<td>Systematic review of studies on de-escalation in ICU</td>
<td>13 studies (1 RCT)</td>
<td>De-escalation is related to decreased all-cause mortality (OR =0.68, CI 0.52-0.88)</td>
</tr>
<tr>
<td>Any comparative studies that assessed the de-escalation therapy, analysis per infection</td>
<td>23 studies (2 RCT)</td>
<td>De-escalation associated with lower mortality in most infections.</td>
</tr>
</tbody>
</table>

De-escalation Associated Mortality: Randomized Controlled Studies

HAP, hospital-acquired pneumonia, ICU, intensive care unit, CAP, community acquired pneumonia, ESBL, extended-spectrum beta-lactamases, COPD, chronic obstructive lung diseases

De-escalation Associated Mortality: Conclusions

• Lower unadjusted mortality in observational studies may be caused by the fact that de-escalation is performed in less severely ill patients.

• Adjustments in statistical analyses compensated for the known differences between the de-escalated and not de-escalated groups, but there might be other differences that stimulate physicians in observational studies to de-escalate.

• RCT are very heterogeneous, not controlled for confounding factors, in two studies the empirical regimen was different, small number of patients.

• Overall, at present, de-escalation does not seem to be associated with higher mortality, but caution is warranted!
Apparently Poor/Unclear Performance of De-escalations: the Reasons Behind

- Pathogen?
- Antibiotic?
- Infection?
- Setting?
- Prescriber?
The role of the Pathogen

A 70-years old patient with relaps of rectal carcinoma and a fistula to urinary bladder became febrile, he was put on piperacillin/tazobactam, the next day *Streptococcus intermedius* grew from urine culture: would you de-escalate?

A 40-years old patient with sudden onset of lobar pneumonia, co-amoxiclav started, many Gram-positive diplococci and leucocytes in sputum: would you de-escalate?

- De-escalation was performed in 61% of patients with VAP documented by BAL and 21% of patents with VAP documented by tracheal aspirate.

The role of the Pathogen

De-escalation can have poorer outcome if the isolates are not the causative agents of infections or not the only causative agents.

Situations related to lower de-escalation rate in observational studies:

• Infections with MDR bacteria
• High risk of un-diagnosed pathogen (abdominal infections)

The Role of Antibiotics

• No standard protocol for de-escalation in the studies: decreasing the number of antibiotics, change to narrow spectrum, discontinuation.

• The time to de-escalation in the studies varies from 2 to 7 days.

• Various definitions of narrow and broad spectrum antibiotics.

Ranking of Antibiotics According to Their Antimicrobial Spectrum: a Tool to Guide/Assess the De-escalation


Method: National VA susceptibility data and the Delphi process.

Criterium for scoring: susceptibility.

Scoring of beta-lactam antibiotics for Gram-negative bacteria (simplified):

<table>
<thead>
<tr>
<th>Score</th>
<th>E. coli</th>
<th>K. pneumoniae</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>p/t, carba, all cephalo</td>
<td>p/t, carba, all cephalo, amino-peni/ bl-inh</td>
<td>p/t, anti-Ps carba, anti Ps cephalo</td>
</tr>
<tr>
<td>3</td>
<td>amino-peni/ bl-inh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>amino-peni</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Method: Delphi process.

Criteria for ranking: susceptibility and ecological impact.

Ranking of beta-lactam antibiotics for Gram-negative bacteria (simplified):

<table>
<thead>
<tr>
<th>Rank</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>amino-peni</td>
</tr>
<tr>
<td>2</td>
<td>amino-peni/ bl-inh</td>
</tr>
<tr>
<td>3</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; cephalo</td>
</tr>
<tr>
<td>4</td>
<td>p/t, 4&lt;sup&gt;th&lt;/sup&gt; cephalo, anti-Ps cephalo</td>
</tr>
<tr>
<td>5</td>
<td>ertapenem</td>
</tr>
<tr>
<td>6</td>
<td>Imipenem, meropenem, doripenem</td>
</tr>
</tbody>
</table>

p/t, piperacillin/tazobactam, amino-peni, aminopenicillins, bl-inh, beta-lactamase inhibitor, carba, carbapenem, cephalo, cephalosporin, anti-Ps, anti-pseudomonal
**PRE-DEFINED ANTIBIOTIC RANKING**

<table>
<thead>
<tr>
<th>Step</th>
<th>Antibiotics</th>
</tr>
</thead>
</table>
| **Step 1** | - Non-anti-pseudomonal penicillins  
- Second generation or third generation non-anti-pseudomonal cephalosporins  
- Fluoroquinolones: levofloxacin (500mg q12h), moxifloxacin (500mg q24h)  
- Trimethoprim/sulfamethoxazole (160mg/800mg q12h) |
| **Step 2** | - Anti-pseudomonal penicillins: piperacillin-tazobactam (16g over 24h)  
- Third generation anti-pseudomonal cephalosporins: ceftazidime (6g over 24h)  
- Fluoroquinolones: ciprofloxacin (400mg q8h) |
| **Step 3** | - Anti-pseudomonal carbapenems: meropenem (3g over 24h) |
| **Step 4** | - Anti-pseudomonal carbapenems (meropenem) + other antibiotic with Gram-negative coverage |
Other Antibiotic/Bacterium Issues Related to De-escalation

• Various resistance selection potential of antibiotics.

• Co-selection.

• Resistance may develop early during the antibiotic course but is more pronounced in prolonged treatment.

• Discontinuation of redundant antibiotics is probably the most sensible de-escalation strategy (the patient is not exposed to another antibiotic).

Insufficient PK/PD Target Attainment in De-escalated Antibiotic Regimens in Critically Ill:

*In silico* model based on PK in critically ill patients and EUCAST MIC distribution

The probability of the target attainment

![Bar chart showing target attainment probabilities for different antibiotics and pathogens.]

- **S. aureus**
- **E. coli**
- **K. pneumoniae**

**PK/PD targets:**
- 40% time > MIC for carbapenems
- 50% time > MIC for penicillins
- 65% time > MIC for cephalosporins

EI, extended infusion, I, infusion

Other Pharmacokinetic Considerations

Example:

Penetration of Antibiotics into Pancreatic Tissue:

- Aminoglycosides: poor penetration
- Ureidopenicillins, higher cephalosporin generations: moderate penetration, good spectrum
- Carbapenems, fluoroquinolones, metronidazole: good penetration

Less Effective Antibiotics?

• *Vancomycin less effective than anti-staphylococcal penicillins in Staphylococcus aureus bacteremia.*
• *Tigecycline less effective than beta-lactam antibiotics in severe infections.*
• *Aminoglycosides as monotherapy less effective than beta-lactam with the exception of urinary tract infection.*

• Little information on superiority (or inferiority) of new agents because of non-inferiority design of registration studies.

Infectious Syndromes/Patients

The studies on de-escalation included patients with:

- HAP
- VAP
- Sepsis/septic shock
- Community-acquired bacteremia
- CAP
- COPD
- UTI
- Intraabdominal infections
- Pneumococcal bacteremia
- Infections with ESBL producing bacteria
- Neutropenic patients
- Patients with cancer
- Patients with fungal infections
- ...

Open questions and controversies in de-escalation related to infections/syndromes:

The role of clinical certainty.

Less de-escalation in possible multiple concurrent infections (pneumonia or/and UTI in ICU patient or in elderly).

Do we need to expand de-escalation to out-patients?
The Setting

• Differences in definition of narrow/broad spectrum reflect the resistance patterns and the perceived ecological impact in a given setting.

  A change from a carbapenem to 3rd generation cephalosporin is not de-escalation in high ESBL setting.

• De-escalation is difficult (and less often) performed) in settings with high resistance rates.

De-escalation: The Role of Prescriber

Wide range of de-escalation rate described in observational (ICU: 10 to 60%, outside ICU: 5 to 55%).

Different attitudes towards de-escalation in young doctors in training internationally and among specialties.

Several studies described the increase in de-escalation rates by the use of various stewardship interventions incl. electronic alerts.

Some authors report on escalations based on susceptibility results that should lead to de-escalation.

Practical Tips for Safe (and Effective) De-escalation

- Consider de-escalation when there is high impact of empirical treatment and high need to preserve its efficacy.

- Consider de-escalation when second antibiotic therapy with lower resistance selection potential with respect to the setting is available.

- Make proper clinical diagnosis of infection.

- Assure relevant microbiological diagnostics.

- Use rapid diagnostics to accelerate the de-escalation and shorten the exposure to first antibiotic.

- Second antibiotic therapy should be given in a dose that attains the PK/PD target and the therapeutic concentration in the tissue.

- If possible: discontinuation of an antibiotic is more effective than de-escalation.
Conclusions

• The main objective of de-escalation is the control of antimicrobial resistance.

• According to the current level of evidence de-escalation is a complex procedure that requires support of an experienced antimicrobial steward.

• The resistance rates in many settings world-wide urgently call for lower use of critically important antibiotics and proper de-escalation is one of the methods that may help us to achieve this goal.