Antimicrobial de-escalation in the ICU
A FOCUS ON EVIDENCE-BASED STRATEGIES

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Antimicrobials and Painting

Escalated Therapy

Empiric Therapy

De-escalated Therapy
Where do we start?

Philosophy/ Definitions
Empiric Therapy

- Observational studies
- Side effects
- Cost
- Bacterial resistance
- Superinfection

- Cefazolin better for MSSA than vanco, 3rd gen ceph, or pip/tazo
  - Vanco worse for E. faecalis
- Pseudomonas and Acinetobacter – dual therapy for directed treatment not helpful

Appropriate

- Randomized trials

Keep it!

Randomized trials

Modify it!

De-escalation: Guidelines on board

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

2b. Antimicrobial regimen should be reassessed daily for potential deesaclation (grade 1B).


American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

3. The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible on the basis of culture data (Level II) (205).

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

XXIII. Should Antibiotic Therapy Be De-escalated or Fixed in Patients With HAP/VAP? Recommendation

1. For patients with HAP/VAP, we suggest that antibiotic therapy be de-escalated rather than fixed (weak recommendation, very low-quality evidence).
De-escalation generally refers to reduction in the spectrum of administered antibiotics through

1. Discontinuation of antibiotics
   - providing activity against nonpathogenic organisms
   - with similar activity
2. Switching to an agent with narrower spectrum
3. Intravenous to oral route?

De-escalation is mostly accomplished by a reduction in the number of antibiotics prescribed
Where do we start?
How do I promote a “culture” of de-escalation?

1. Cultures
2. Appropriate and adequate empiric therapy
3. Streamline therapy per microbiological results
4. IV to Enteral?

Side note: 2016 HAP/VAP IDSA Guidelines have re-emphasized attaining a culture
Tip: prompt inducing sputum on ordersets, if needed

Culture negative – Steps?

Don’t continue antibiotics beyond 72 hours in hospitalized patients unless patient has clear evidence of infection.

Antibiotics are often started when a patient is possibly infected. After three days, laboratory and radiology information is available and antibiotics should either be deescalated to a narrow-spectrum antibiotic based on culture results or discontinued if evidence of infection is no longer present. Lessening antibiotic use decreases risk of infections with Clostridium difficile (C. difficile) or antibiotic-resistant bacteria.

Where do we start?

- Rapid identification methods
- Cultures
- Philosophy/Definitions
Rapid Identification

- **PCR (polymerase chain reaction)**
  - Cepheid Xpert-MRSA/SA and C difficile, BD GeneOhm
  - Can differentiate MSSA, MRSA, and CoNS within 1 hr

- **PNA FISH (peptide nucleic acid fluorescence in situ hybridization)**
  - AdvanDx QuickFish
  - Results in 20 minutes for gram+, 1.5 hrs for *Candida* spp.

- **Nucleic Acid/PCR**
  - Nanosphere Verigene, BioFire
  - For blood culture
  - Detects 13 bacterial targets (gram + and -), 3 resistance determinants
  - Results within 2.5 hr

- **MALDI-TOF (also known as mass spectrometry)**
  - Matrix-assisted laser desorption ionization-time of flight
  - Can be used to identify bacteria or fungal organism from blood, respiratory, urine, wound, and more
  - Results within 6 min

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Rapid Identification - Limitations

- Need a positive culture available molecular tests
- No clear way to rule out infection
- Does not replace traditional culture (need susceptibility)

Validation and technical skills

Benefit not realized unless combined with other mechanisms (ASP support or rapid notification of results)

was a consistent feature of the studies that found statistically significant associations between rapid testing and outcomes.

RADICAL Trial

- Observational study of critically ill patients in Europe
- PCR/ESI-MS (polymerase chain reaction/electrospray ionization-mass spectrometry)
  - 800 pathogens (incl. Candida spp.)
  - 6 hour turnaround
- Negative predictive value:
  - Bloodstream infection - 97%
  - Lower resp tract - 81%
- Does not rely on positive cultures!

“The ability to rule out infection within 6 hours has potential clinical and economic benefits”

What is the ballpark cost and what am I getting??

- Verigene Nanosphere – $30-40K USD
  - Choose either nucleic acid/PCR or protein, blood cultures
- BioFire – $60K USD
  - Nucleic acid/PCR only, blood cultures
- MALDI-TOF - $250K USD
  - Mass spectrometry, any culture
- T2 Bio Test – $400K **for candida spp**
  - 1 CFU/mL, uses MRI!
  - Blood cultures
- Abbot PCR/ESI-MS - $1 million
  - Essentially PCR and MALDI-TOF combined
  - Any culture + lowest level of detection available + ability to r/o infection
Where do we start?

- Philosophy/Definitions
- Attaining cultures
- Rapid identification methods
- Electronic notification
How to get the word out
SANFORD HEALTH--:
e11232 respiratory
culture positive for E.
COLI by mass spec. EW
room 112.

01:e11232 blood
culture positive for
S. aureus by
Verigene - EW Room
Where do we start?

- Rapid identification methods
- Electronic notification
- Attaining cultures
- Philosophy/Definitions
- Biomarkers
Biomarkers

- Conversation becomes limited to procalcitonin and C-reactive protein (PCT and CRP)
- Only PCT got a graded recommendation for discontinuation in HAP/VAP/ASP/Sepsis guidelines
- Meta-analyses have demonstrated
  - PCT performs statistically better to CRP
  - Q value for procalcitonin 0.78 [95% CI 0.71–0.84] vs. Q value for CRP 0.71 [95% CI 0.64–0.76], corrected p=0.02
- PCT algorithm might reduce antibiotic exposure in septic, critically ill patients without compromising clinical outcomes
SAPS Trial

- Largest RCT with PCT to date (>750 in each group)
- Advised to stop the prescribed antibiotics if:
  1. ↓ by =/> 80% or more of peak value (relative stopping threshold)
  2. Any value of =/<0.5 μg/L (absolute stopping threshold)
- Compliance with stopping criterion within 24 hrs of result – 44%

de Jong et al. Lancet Infectious Disease. 2015.
SAPS Trial

- Defined daily doses: Procalcitonin 7.5, Standard of care 9.3, P < 0.01
- Duration of treatment (days): Procalcitonin 5, Standard of care 7, P < 0.01
- 28-d mortality (%): Procalcitonin 19.6, Standard of care 25, P = 0.01

de Jong et al. Lancet Infectious Disease. 2015.
Where do we start?

- Rapid identification methods
- Attaining cultures
- Philosophy/Definitions
- Electronic notification
- Biomarkers
- Durations
Pneumonia

Conclusions: Among patients who had received appropriate initial empirical therapy, with the possible exception of those developing nonfermenting gram-negative bacillus infections, comparable clinical effectiveness against VAP was obtained with the 8- and 15-day treatment regimens. The 8-day group had less antibiotic use.
Pneumonia

“For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration (strong recommendation, moderate-quality evidence).”

“The panel agreed that a different recommendation was not indicated because, even if there is a small increased recurrence rate, mortality and clinical cure do not appear to be affected; in addition, the evidence for recurrence is from subgroup analyses with important limitations.”

Remarks: There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection


Intra-abdominal – STOP-IT Trial

- RCT of >500 patients in US and Canada
  - 1/3 colon/rectal origin
  - 4 days versus “up to 10 days” (~8 days) after source control
- The adequacy of source control was confirmed by the local investigator and the principal investigator of the study
- However, ICU specific data not reported
  - % in ICU, % requiring pressors, % requiring MV

Intra-abdominal – STOP-IT Trial

Duration of therapy

- Longer course: 8
- Shorter course: 4

Composite primary outcome*

- Longer course: 22.3
- Shorter course: 21.8

P < 0.01

* Surgical-site infection, recurrent intraabdominal infection, or death

Where do we start?

1. Philosophy/Definitions
2. Rapid identification methods
3. Attaining cultures
4. Electronic notification
5. Biomarkers
6. Durations
7. Clinical scores
Clinical Pulmonary Infection Score (CPIS)

"...it may be harmful if it does not reliably discriminate patients who can safely have their antibiotics discontinued from patients who should have their antibiotics continued..."

Where do we start?

- Rapid identification methods
- Attaining cultures
- Philosophy/Definitions
- Data tracking
- Clinical scores
- Electronic notification
- Biomarkers
- Durations
Antimicrobial stewardship program interventions – Sanford-Fargo

**Total Intervention Count July 2015 - June 2016**

- Total Interventions Documented: 2259

**Intervention Provider Response July 2015 - June 2016**

- 1508, 73%: ACCEPT
- 301, 15%: MODIFIED
- 186, 9%: REJECT
- 73, 3%: UNRESOLVED

**Intervention Outcomes July 2015 - June 2016**

- **De-escalation**: 684
- **Discontinuation**: 501
- **Escalation**: 101
- **Change dose or frequency**: 66
- **Cultures**: 24
- **ID consult recommended**: 23
- **Initiation**: 7
- **Other**: 274

Includes Accepted or Modified Interventions

- **Avg ASP interventions/day**: 8.6
- **Avg ASP accepted/day**: 6.3
- **Avg ASP accepted with modification/day**: 0.8
Antimicrobial Use and Costs
FY04 – FY16

ASP Initiation

Abx $ Per Pt-Day

DDD Per 1000 Pt-Days
Sanford Fargo Medical Center
Antimicrobial Utilization and Hospital Mortality

DOT/1000 Patient Days

Lung Infection: % Hospital Mortality
Sepsis: % Hospital Mortality
“To-Consider” List

- Orderset-driven culture orders
- Discuss negative culture practice at dept meeting
- Find out if/what rapid testing is available
- Meet with pharmacy, micro, IT etc to help with result alerting mechanisms
- If using procalcitonin, formulate algorithm
- Discuss and disseminate abx duration best practices
- Automatic IV to enteral policy or protocol
Conclusions

- The conversation of de-escalation has changed from “IF” to “HOW”
- There are various methods to help facilitate de-escalation in the ICU
  - Focus on what we CAN do
- More research is needed regarding how various strategies are best combined
Antimicrobial de-escalation in the ICU

A FOCUS ON EVIDENCE-BASED STRATEGIES

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Antibiogram?

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified Antibiotics, Compared With Nonstratified Antibiotics?

Recommendation

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy (weak recommendation, low-quality evidence).

Comment: Although there is limited evidence at this time that stratified antibiograms (e.g., by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.
“We suggest that patients with suspected HAP (non-VAP) be treated according to the results of microbiologic studies performed on respiratory samples obtained noninvasively, rather than being treated empirically.”
VII. Should Computerized Clinical Decision Support Systems Integrated Into the Electronic Health Record at the Time of Prescribing be Incorporated as Part of ASPs to Improve Antibiotic Prescribing?

Recommendation

7. We suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs (weak recommendation, moderate-quality evidence).
## Decision support

### Antibiotics: Source of Infection: Unknown

- Healthcare-Associated Pneumonia (HCAP) OR Hospital Acquired Pneumonia
- Intra-Abdominal or Biliary
- Urinary Tract
- Wound Infection / Diabetic Ulcer / Skin and Soft Tissue
- IV Access Related
- Febrile Neutropenia
- Bacterial Meningitis
- Clostridium Difficile Infection

### Antibiotics: Source of Infection: Intra-Abdominal or Biliary

- Initial therapy (Preferred): ceTRIAXone (ROCEPHIN) and metronIDAZOLE (FLAGYL) IV
- Initial therapy with penicillin allergy (non-anaphylaxis): ceftime (MAXIPIME) and metronIDAZOLE (FLAGYL) IV
- Initial therapy with penicillin allergy (anaphylaxis): meropenem (MERREM)
- Alternative therapy: levofloxacin (LEVAQUIN) and metronIDAZOLE (FLAGYL) IV
# IV to enteral

## Antimicrobials

<table>
<thead>
<tr>
<th>Intravenous</th>
<th>Oral or Per Feeding Tube (FT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 500 mg IV</td>
<td>Azithromycin tablet 500 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Azithromycin 250 mg IV</td>
<td>Azithromycin tablet 250 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Ciprofloxacin 400 mg IV</td>
<td>Ciprofloxacin tablet 500 mg PO, <strong>Do not change if FT</strong></td>
</tr>
<tr>
<td>Ciprofloxacin 200 mg IV</td>
<td>Ciprofloxacin tablet 250 mg PO, <strong>Do not change if FT</strong></td>
</tr>
<tr>
<td>Doxycycline 100 mg IV</td>
<td>Doxycycline tablet 100 mg PO, <strong>Do not change if FT</strong></td>
</tr>
<tr>
<td>Fluconazole 800 mg IV</td>
<td>Fluconazole tablet 800 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Fluconazole 400 mg IV</td>
<td>Fluconazole tablet 400 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Fluconazole 200 mg IV</td>
<td>Fluconazole tablet 200 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Fluconazole 100 mg IV</td>
<td>Fluconazole tablet 100 mg PO or FT (crush)</td>
</tr>
<tr>
<td>Levofloxacin 750 mg IV</td>
<td>Levofloxacin tablet 750 mg PO, <strong>Do not change if FT</strong></td>
</tr>
<tr>
<td>Levofloxacin 500 mg IV</td>
<td>Levofloxacin tablet 500 mg PO, <strong>Do not change if FT</strong></td>
</tr>
<tr>
<td>Levofloxacin 250 mg IV</td>
<td>Levofloxacin tablet 250 mg PO, <strong>Do not change if FT</strong></td>
</tr>
</tbody>
</table>

Need inclusion and exclusion criteria!
**Outcome Type** | **Description/Examples for Use**
--- | ---
**Allergy addressed** | When antimicrobials modified d/t your allergy-related assessment—other outcomes are N/A. Also includes recommendations related to skin testing and desensitization. Note there is an iVent Type "Allergy detection" in same queue as "Antimicrobial Stewardship". In general, use this "allergy addressed" outcome under "Antimicrobial Stewardship" when allergy intervention pertains to antimicrobial therapy.

**Change dose or frequency** | For adjustment d/t renal (or other organ) function.

**Change route or dosage form** | For non-IV to PO changes. (E.g., Patient lost PO access/absorption concerns and change to IV needed. Liquid used in place of non-crushable med. Ordered drug IV but meant rectal—i.e. vancomycin for C. diff.)

**Cultures** | When you recommended cultures be taken/discontinued/changed. (If therapy is changed based on a culture result, use an applicable outcome from this list.)

**De-escalation** | When therapy is modified to narrow coverage. It can be in response to culture data or clinical scenario. This can be done with more, less, or the same number of agents.

**Discontinuation** | Use when all antimicrobial therapy is recommended to be discontinued. Use when stop date(s) are recommended. This pertains to duration of therapy and duplicative therapy. If individual drug(s) are discontinued to narrow coverage (vancomycin d/c'd to stop MRSA coverage, but ceftriaxone continued), use de-escalate.

**Drug information provided** | When information provided on antimicrobial therapy (e.g., to provider, nurse, or patient) and other outcome picks are N/A.

**ID consult recommended** | As stated.

**Escalation** | When therapy is modified to broaden coverage (e.g., in response to culture data or clinical scenario). This can be done with more, less, or the same number of agents.

**Formulary substitution** | Eg., caspofungin to micafungin.

**Formulary restriction** | Eg., an ID-restricted antimicrobial was ordered by hospitalist, you called to clarify OK w/ID. Whether drug is OK'd or alternative selected, you are fine entering this outcome.

**Initiation** | No antimicrobial therapy was present but recommended to initiate (e.g., culture result, S&S of infection).

**IV to PO** | IV drug changed to SAME PO drug (eg, ciprofloxacin, amoxicillin, doxycycline) or PO drug w/similar coverage (i.e., unasyn to augmentin, ceftriaxone to cefuroxime).

**Monitoring/Pharmacokinetics** | When these activities are performed or recommended to guide therapy (ordering levels for vancomycin, sub; other drug levels for efficacy/toxicity assessment; CK for daptomycin, platelets/WBC for drugs that could influence). If another outcome results, enter a subsequent intervention.

**Patient discharged before resolved** | Use if patient discharged before resolution.
XVII. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?

Recommendation

18. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation (weak recommendation, moderate-quality evidence).

Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.
Rapid testing

Figure 1. Mortality according to the implementation of ASP.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rapid diagnostic test</th>
<th>Conventional cultures</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.2.1 Combined with ASP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauer et al 2010 [15]</td>
<td>18</td>
<td>74</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>Forrest et al 2008 [37]</td>
<td>17</td>
<td>95</td>
<td>37</td>
<td>129</td>
</tr>
<tr>
<td>Huang et al 2013 [35]</td>
<td>31</td>
<td>245</td>
<td>52</td>
<td>256</td>
</tr>
<tr>
<td>Perez et al 2013 [33]</td>
<td>6</td>
<td>107</td>
<td>12</td>
<td>112</td>
</tr>
<tr>
<td>Perez et al 2014 [32]</td>
<td>10</td>
<td>112</td>
<td>33</td>
<td>157</td>
</tr>
<tr>
<td>Sango et al 2013 [31]</td>
<td>11</td>
<td>28</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>1.2.2 Rapid test alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez et al 2012 [38]</td>
<td>14</td>
<td>48</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>Frye et al 2012 [39]</td>
<td>14</td>
<td>110</td>
<td>17</td>
<td>134</td>
</tr>
</tbody>
</table>
XXIV. Should Discontinuation of Antibiotic Therapy Be Based Upon PCT Levels Plus Clinical Criteria or Clinical Criteria Alone in Patients With HAP/VAP?

Recommendation

1. For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone (weak recommendation, low-quality evidence).

Remarks: It is not known if the benefits of using PCT levels to determine whether or not to discontinue antibiotic therapy exist in settings where standard antimicrobial therapy for VAP is already 7 days or less.

XVIII. In Adults in Intensive Care Units (ICUs) With Suspected Infection, Should ASPs Advocate Procalcitonin (PCT) Testing as an Intervention to Decrease Antibiotic Use?

Recommendation

19. In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate-quality evidence).

Comment: Although randomized trials, primarily in Europe, have shown reduction in antibiotic use through implementation of PCT algorithms in the ICU, similar data are lacking for other regions including the United States where the patterns of antibiotic prescribing and approach to stewardship may differ. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.
Current evidence suggests that antibiotic de-escalation is a well tolerated strategy that may be even associated with a better outcome.

- The conversation of de-escalation has changed from “IF” to “HOW”.
- There are various methods to help facilitate de-escalation in the ICU.
  - Focus on what we CAN do.
- All initiatives to improve antibiotic prescriptions in critically ill septic patients are completely warranted and should include the streamlining of empirical antibiotics.
- More research is needed regarding how various strategies are best combined.
Conclusions

- Current evidence suggests that antibiotic de-escalation is a well tolerated strategy that may be even associated with a better outcome
- The conversation of de-escalation has changed from “IF” to “HOW”
- There are various methods to help facilitate de-escalation in the ICU
  - Focus on what we CAN do
- All initiatives to improve antibiotic prescriptions in critically ill septic patients are completely warranted and should include the streamlining of empirical antibiotics.
- More research is needed regarding how various strategies are best combined
## Duration of Therapy

**It May Be Shorter Than You Think!**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD exacerbation</td>
<td>5 days</td>
</tr>
<tr>
<td>CAP</td>
<td>5-7 days</td>
</tr>
<tr>
<td>HCAP, HAP</td>
<td>8 days</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5-10 days</td>
</tr>
<tr>
<td>UTI – Cystitis</td>
<td>5 days (macrodantin)</td>
</tr>
<tr>
<td></td>
<td>3 days (TMP-SMX, quinolones)</td>
</tr>
<tr>
<td>UTI – Pyelonephritis</td>
<td>5 days (quinolones)</td>
</tr>
<tr>
<td></td>
<td>14 days (TMP – SMX, or B-lactam)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4-7 days after source control</td>
</tr>
</tbody>
</table>