IV to PO switch of Antibiotics

ABG Symposium
Nov 2019
Intravenous AB from an organisational point of view

- Resistance
- Cost of hospitalization / LOS
- Cost of OPAT
- Cost of antibiotics
- Microbiome
- Complications (indwelling catheter related infections)
- PROM & PREM
- Duration of therapy
- Available options for AB
- Habits & Beliefs
- …
ES/ED programs

**Early switch (ES) from intravenous to oral AB**

- improved patient comfort and mobility,
- reduced incidence of IV-line-related adverse effects,
- reduced IV antimicrobial preparation time,
- decreased hospital stays,
- reduced antimicrobial purchasing and administration costs,
- decreased patient deconditioning, and
- shortened recovery times.

It should be combined with an **early discharge (ED)** plan, protocol, or care pathway.
Evidence: MRSA cSSTI

- Difference in prescription attitudes
  - Treatment duration: 10.1 (UK) to 18.6 days (Poland)
  - Hospital stay duration: 15.2 (UK) to 25.0 days (Portugal)

- OPAT
  - is an option to reduce LOS when protracted treatment is needed
  - At discharge oral therapy is possible in many patients
  - Burden of OPAT is high for both the patient and health care.
  - Risk of IV-line-related infections

Efforts to implement (1)

Department of Health
Advisory Committee on Antimicrobial Resistance and
Healthcare Associated Infection (ARHAI)

Antimicrobial stewardship
Right Drug, Right Dose, Right Time, Right Duration...
..... Every patient

START SMART

THEN FOCUS

Do not start antibiotics in the absence of evidence of bacterial infection

• Take history of relevant allergies
• Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with life threatening infections
• Comply with local prescribing guidance
• Document clinical indication and dose on drug chart and in clinical notes
• Include review/stop date or duration
• Ensure relevant microbiological specimens taken

CLINICAL REVIEW & DECISION*
AT 48 HOURS

Clinical review, check microbiology, make and document decision*

1. STOP
2. IV/oral switch
3. Change: to narrow spectrum agent
4. Continue and review again after a further 24 hours
5. OPAT*

DOCUMENT DECISION

# Antimicrobial Prescribing Decision *Outpatient Parenteral Therapy

Efforts to implement (2)
Barriers to Implementation ES and/or ED

- Acceptance of nationally or centrally developed programs is slow
  - Prescribing appears to be influenced by
    - the cultural beliefs of the patient and the prescriber
    - patient demand
    - socio-economic factors
    - clinical autonomy

- Staffing time constraints, staffing changes and prescribing etiquette
  - Reassessant of antimicrobial therapy after 48–72 h of treatment is often neglected
  - Information on why the antimicrobial was started and the goal of therapy may not be communicated
  - Prescribing etiquette, or the reluctance of junior medical staff members to change the prescribing habits of more senior staff members

- Prescribers are often hesitant to modify an apparently efficacious empirical therapy
  - Time constraints, rapid rotation of physicians in charge of patients, and
  - The belief that IV therapy is superior to oral therapy
Perceived recommended duration of therapy

Violin Plot: Recommended (perceived) treatment duration

Recommended treatment duration according to pathogen

Median recommended durations of Australia and New Zealand respondents when asked about different pathogens causing central venous catheter-related bloodstream infection.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Median (IQR) duration recommended (days)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>10 (7–14)</td>
<td>Comparator</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>7 (7–10)</td>
<td>0.37</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>10 (7–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>10 (7–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>10 (7–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>14 (14–14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>7 (7–10)</td>
<td>0.001</td>
</tr>
<tr>
<td>CoNS</td>
<td>5 (3–7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*IQR, interquartile range; CoNS, coagulate-negative staphylococci. *Wilcoxon rank-sum test.

When is enough antibiotics enough? Shorter duration!

A. Oral step-down therapy group
- Blood cultures performed, in vitro active IV antibiotics initiated
- IV antibiotics changed to in vitro active oral step-down therapy
- Day 1: Source control
  - Pitt bacteremia score ≤1
  - Ability to consume and absorb enteral antibiotics
  - In vitro active oral antibiotic option available
- Day 7: Total duration of antibiotic therapy, 7-15 d
- Day 15

B. IV therapy group
- Blood cultures performed, in vitro active IV antibiotics initiated
- In vitro active antibiotics continued until discontinuation of antibiotics
- Day 1: Source control
  - Pitt bacteremia score ≤1
  - Ability to consume and absorb enteral antibiotics
  - In vitro active oral antibiotic option available
- Day 7: Total duration of antibiotic therapy, 7-15 d
- Day 15

All patients received at least 7 days of treatment, with a range of 7 to 15 days. IV indicated intravenous.

When is enough antibiotics enough? Shorter duration!

Table 2. Antibiotic Therapy Administered to Patients Transitioned to Oral Antibiotic Therapy for Enterobacteriaceae Bacteremia

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Common Regimen</th>
<th>Bioavailability</th>
<th>Patients Receiving Treatment, No. (%) (n = 739)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>500-1000 mg orally every 8-12 h</td>
<td>Low</td>
<td>38 (5.1)</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>300 mg orally every 12 h</td>
<td>Low</td>
<td>30 (4.1)</td>
</tr>
<tr>
<td>Ceftixime</td>
<td>200-400 mg orally every 12-24 h</td>
<td>Low</td>
<td>21 (2.8)</td>
</tr>
<tr>
<td>Cephalexin hydrochloride</td>
<td>500 mg orally every 6 h</td>
<td>Low</td>
<td>16 (2.2)</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>200-400 mg orally every 12 h</td>
<td>Low</td>
<td>17 (2.3)</td>
</tr>
<tr>
<td>Ciprofloxacin hydrochloride</td>
<td>500-750 mg orally every 12 h</td>
<td>High</td>
<td>337 (45.6)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500-750 mg orally every 24 h</td>
<td>High</td>
<td>171 (23.1)</td>
</tr>
<tr>
<td>Moxifloxacin hydrochloride</td>
<td>400 mg orally every 24 h</td>
<td>High</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>160-320 mg orally every 6-12 h</td>
<td>High</td>
<td>99 (13.4)</td>
</tr>
</tbody>
</table>

Shorter AB period for gram negative bacteria

- In low risk, stable, patients → **7 days of antibiotic therapy was noninferior to 14 days.**
- Seven days of antibiotic therapy had the advantage of **fewer cumulative antibiotic days within 3 months** and **more rapid regain of baseline functional capacity.**

In selected low-risk patients with an early oral switch to linezolid between days 3 and 9 of treatment until completion is not associated with an increased risk of mortality or relapse.
Staph aureus: IV to PO switch

No significant differences in the treatment failure rates and crude mortalities between short-course and intermediate-course therapy.

However, less than 14 days of therapy was significantly associated with relapse.

High Charlson comorbidity score was an independent risk factor for treatment failure.

### TABLE 2 Outcomes 12 weeks after S. aureus bacteremia in 111 patients according to the duration of parenteral antibiotic therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) with outcome</th>
<th>P value</th>
</tr>
</thead>
</table>
|                       | Total (n = 111) | Group I (<14)
| (n = 38) | Group II (≥14)
| (n = 73) |
| Recurrence            | 4 (3.6) | 3 (7.9) | 1 (1.4) | 0.12 |
| Relapse               | 3 (2.7) | 3 (7.9) | NA | | |
| Bacteremia            |          |          |       |       |
| Deep-seated infection |          |          |       |       |
| Reinfection           | 1 (1)   | 1 (1.4) | >0.99 |       |
| Bacteremia            |          |          |       |       |
| Deep-seated infection |          |          |       |       |
| All-cause death       | 23 (20.7)| 7 (18.4)| 16 (21.9)| 0.67 |
| Treatment failure     | 27 (24.3)| 10 (26.3)| 16 (21.9)| 0.64 |

*Duration of parenteral antibiotic therapy (days).

NA, not applicable.
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Design
- Multicenter, open-label non-inferiority trial
- N=400 patients
  - PO treatment (n=201)
  - IV treatment (n=199)
- Setting: Danish patients referred to a cardiac center for suspected IE
- Enrollment: 2011-2017
- Mean follow-up: 6 months after ABx completed
- Analysis: Intention-to-treat
- Primary outcome: All-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen

Intervention
- Participants were randomized to a group:
  - PO treatment - With initial IV antibiotics
    - Completion of antibiotic therapy with a regimen of 2 antibiotics of different classes, based on sensitivities and MIC’s of cultured organisms. Serum levels of antibiotics in this arm were checked at Day 1 and 5 of therapy.
    - Most common regimens: Dicloxacillin and Rifampicin (RIF), Amoxicillin (AMX) and Moxifloxacin, AMX + RIF, AMX + Linezolid.
    - Specifics about the PO regimens appear in table S2 (page 17) of the supplementary appendix.
    - At patients' preference and with attending physician's discretion, patients in the oral group were discharged to follow-up in outpatient clinics 2-3 times a week until completion of therapy.
  - IV treatment
    - Completion of antibiotic therapy with continued IV antibiotics.
    - Transesophageal echocardiogram (TEE) was done in all patients 1 week prior to completion of treatment. After completion of therapy, all patients were seen in clinic follow-up at 1 week, 1, 3, and 6-months.

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Inclusion criteria

- ≥18 years old
- Left-sided endocarditis fulfilling the modified Duke criteria (native or prosthetic valve)
- 1 of these specific microorganism:
  - Streptococcus
  - Enterococcus faecalis
  - Staphylococcus aureus
  - Coagulase-negative staphylococci (CoNS)
- ≥ 10 days of appropriate IV antibiotic treatment overall
- If valve surgery, ≥7 days of appropriate parenteral treatment after procedure
- T < 38.0°C for >2 days
- A C-reactive protein (CRP) decrease to less than 25% of peak value OR < 20 mg/L, and WBC count < 15 x 10⁹/L during antibiotic treatment
- TTE and TEE performed within 48 hours of randomization

Exclusion criteria

- Abscess formation demonstrated with transesophageal echocardiography
- BMI > 40 kg/m²
- Concomitant infection requiring intravenous antibiotic therapy
- Inability to give informed consent to participation
- Suspicions of reduced absorption of oral treatment due to abdominal disorder
- Reduced compliance

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

- **Demographics**: Age 68 years, female sex 21%
- **Comorbidities**: DM 15%, renal failure 10% (HD 8%), COPD 4%, liver disease 3%, cancer 9%, IVDU 1%
- **Lab results at randomization**:  
  - WBC: 7.2  
  - C-reactive Protein: 19.9 mg/L  
  - Creatinine: 141 micromol/L
- **Pathogen**:  
  - Streptococcus: 46%  
  - *E. faecalis*: 25%  
  - Methicillin-Sensitive *S. Aureus* (MSSA): 23%  
  - Coag negative staph: 6%  
  - Methicillin-Resistant *S. Aureus* (MRSA): 0%
- **Prosthesis/Implants**:  
  - Prosthetic heart valve: 27%  
  - Pacemaker: 10%  
    - Pacemaker endocarditis: 4.0% of entire group
- **Valves involved**:  
  - Mitral-valve endocarditis: 35%  
  - Aortic-valve endocarditis: 54%  
  - Mitral + aortic-valve endocarditis: 10%
- **Valve surgery during current disease course**: 38%

Outcomes

- **Primary Outcomes**
  - All-cause mortality, unplanned cardiac surgery, clinically evident embolism, and relapse of bacteremia
    - 9.0% vs. 12.1% (OR 0.72, 95% CI, 0.37 to 1.36)
    - 3.1% difference (95% CI, -3.4 to 9.6, P non-inferiority=0.40)

- **Component Analysis**
  - No difference in:
    - All cause mortality
    - Unplanned cardiac surgery
    - Embolic event
    - Relapse of positive blood culture
    - AE
    - Subgroup analysis

- **Shorter LOS in oral AB group**

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**Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.**

The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment. The inset shows the same data on an enlarged y axis.
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis: Limitations

- Only patients with left-sided IE
- 25-30% of patients with IE were excluded → other bacteria
- Few patients with IV drug use (n=5/400)
- Patients were referred into the study by other physicians → referral bias
- Outpatients were seen frequently (2-3x a week) (not real world situation)
- No patients with MRSA IE
- Only 20% of the screened population was randomized

Osteomyelitis: OVIVI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection


Osteomyelitis

Design

- Multi-center, parallel group, randomized, open label, non-inferiority trial
- N=1,054
  - Intravenous antibiotics (n=527)
  - Oral antibiotics (n=527)
- Setting: 26 centers in the UK
- Enrollment: 2010-2015
- Follow-up: 1 year
- Analysis: Intention-to-treat
- Primary Outcome: Definite treatment failure within 1 year after randomization

Intervention

- Initiated within 7 days of definitive therapy (e.g., following surgical intervention and after microbiological sensitivities available), participants were randomized to a group:
  - **IV antibiotics** - Continued for 6 weeks
  - **PO antibiotics** - Continued for 6 weeks
- Limited (up to 5 days) IV or oral adjunctive therapy was allowed based on local practice patterns
- Adjunctive rifampin was allowed at investigator discretion
- Therapy beyond 6 weeks was allowed at investigator discretion

Osteomyelitis

Inclusion criteria

- Age ≥18 years
- Bone or joint infection requiring 6 weeks of antibiotics
  - Specific infections include one of the following:
    - Osteomyelitis of the extraaxial native skeleton
    - Native joint infection requiring excision arthroplasty
    - Prosthetic joint infection
    - Orthopedic fixation-device infection
    - Vertebral osteomyelitis +/- associated discitis or soft-tissue infection
- Received ≤7 days of IV therapy from the date of definitive surgery or the start of planned curative treatment in patients managed non-operatively
- Life expectancy >1 year

Exclusion criteria

- Staphylococcus aureus bacteraemia or any bacterial endocarditis on presentation or within prior month
- Mild osteomyelitis not requiring 6 weeks of therapy per clinician judgement
- Septic shock
- Infection where no oral option is a viable option
- Non-bacterial infection

Osteomyelitis

Baseline characteristics

- Demographics: median age 60 years, 64.3% male
- Baseline surgical procedure:
  - No prosthetic present and underwent debridement 31%,
  - No prosthetic and no debridement 5%,
  - Debridement and implant retention 23%,
  - Orthopedic device removal 16%,
  - Prosthetic joint removal 13%,
  - Prosthetic joint revision 8%,
  - Spinal debridement 1%,
  - Spinal surgery 2%
- Deep tissue histology: Infected 52%, equivocal 3%, Uninfected 6%, not available or missing 40%
- Microbiological diagnostic sample: ≥2 samples of same organism 66%, 1 of 2 samples positive for likely organism causing infection 5%, no sample positive 15%, not available or missing 5%
- Organism: Staphylococcus aureus 38%, Coagulase-negative staphylococcus (CoNS) 27%, Streptococcus species 15%, Pseudomonas species 5%, Other gram-negative organisms 17%, culture negative 16%
- Antimicrobials: Glycopeptides IV (e.g., vancomycin) 23%, Penicillins IV 5%, Cephalosporins IV 17%, Carbapenems IV 4%, Penicillins PO 9%, Quinolones PO 22%, Macrolides PO 8%
  - Rifampin: None 51%, <2 weeks 5%, 2-6 weeks 16%, >6 weeks 27%

Outcomes: IV vs Oral

- Primary Outcomes
  - Definite treatment failure within 1 year after randomization
    - 14.6% vs. 13.2% (risk difference oral vs. IV -1.4%; 95% CI -5.6 to 2.9)
- Secondary Outcomes
  - Probable or possible treatment failure 1.2% vs. 2.0%
  - Early discontinuation of therapy 18.9% vs. 12.8% (ARR 6.1, P = 0.006) NNT 16
  - Median hospital length of stay 14 days vs. 11 days, P < 0.001
- Subgroup Analysis
  - Events
    - Complications from the IV catheter 9.4% vs. 1.0% (ARR 8.4%, P < 0.001) NNT 12
    - C. difficile-associated diarrhea 1.7% vs. 1.0%, P = 0.30
  - At least one serious adverse event 27.7% vs. 26.2%, P = 0.58

Limitations

- Incidence of serious adverse events was very high
- Open-label design, while improved practicality of conducting the trial complicates the potential for bias
- Depending on the delivery of the IV therapy, the oral group may have had significantly less monitoring
- No comparison of antimicrobial regimens was made and bias may have been present
- Rifampin was more commonly utilized in the oral group
- Antibiotic regimens were not prespecified in the protocol
Conclusions

- IV/PO ES programs should be accompanied by a complete set of interventions:
  - Appropriate AB
  - Narrow spectrum AB
  - Indication for prescription
  - Shorter duration
  - OPAT

- Early trials and recent publications are encouraging for PO switch
  - But trials will always suffer methodological problems
  - When is enough data enough data

- Change of culture in AB use must be comprehensive
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