What Should be the Duration of Empirical Antibiotic Treatment?

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Causes of Fever in Neutropenic Patients

- Bacteremia: 20%
- Microbiol. infection: 20%
- Clinical infection: 20%
- FUO: 20%
- Noninfectious: 20%
Sources of Opportunistic Pathogens

- Endogenous flora (%80)
- Exogenous (%20)

Endogenous flora (%80)
Source of Infection in Neutropenic Patients
Response to Empirical Antimicrobial Therapy

Efficacy of Combinations in Bacteremic Patients

Proportion without failure

Time (days)

Ceftazidime + Amikacin
9 days

Ceftazidim + Amikacin
3 days

Azlocillin + Amikacin

Monotherapy

**Advantages**
- Decreased toxicity
- Decreased cost
- Effective as combination therapy for the initial treatment
- May be the treatment of choice for “low-risk” patients

**Disadvantages**
- Frequent modification required
- Selection of resistance
- Lack of activity against *S. epidermidis*, MRSA, some other gram-positives
Meta-analysis of Beta-Lactam Monotherapy vs Aminoglycosides Combinations

- 47 trials, 7807 patients
  - 9 trials compared the same beta-lactam
- No significant difference in all cause fatality (RR 0.85, 95% CI 0.72-1.02)
- Monotherapy was significantly succesful (RR 0.92, 95% CI 0.85-0.99)
  - In trials comparing different beta-lactams
- Superinfection rates were similar
- Adverse events were more common with combination regimens

Drug Combinations and the Development of Resistance

- A study of synergistic and antagonistic antibiotic combinations against *E. coli*

- Synergistic combinations facilitated development of resistance to both agents

- A high correlation between synergy and the rate of resistance adaptation was found

Problems of Prolonged Hospitalization in Patients with Neutropenia and Fever

- A large percentage have negative blood cultures & exhibit prompt defervescence
- Toxicities of antimicrobials
- High cost
- Exposure to nosocomial pathogens
- Increased risk of fungal infection
- Suboptimal quality of life
- Continued absence from work, school, home
Antibiotic Stewardship
A British Example

Use of iv-im Cephalosporins & Quinolones ↑↑↑↑

↑↑↑↑↑ C. difficile
100s to >50,000

From 1990s to 2007-2008

↓↓↓↓↓ use of Cephalosporins >80%
↑↑↑↑↑ use of Pip-tazo

2004-2009

↓↓↓↓ C. difficile
>50,000 to 14,689

2012-2013

Additional Results…

• Expected
  – Cephalosporin and quinolone R stabilized in *E. coli* and decreased in *Klebsiella* and *Enterobacter* spp.

• Somewhat expected
  – No increase in pip-tazo resistance

• Unexpected
  – Increase in carbapenamase-producing *Enterobacteriaceae*
    • Highly-R to pip-tazo, MIC >128 mg/L
    • Less R to carbapenems

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,¹ Eric J. Bow,⁵ Kent A. Sepkowitz,² Michael J. Boeckh,⁴ James I. Ito,⁵ Craig A. Mullen,³ Issam I. Raad,⁵ Kenneth V. Rolston,⁶ Jo-Anne H. Young,⁷ and John R. Wingard⁸

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Duration of Empirical Therapy

- In all settings until recovery of neutropenia (>500/mm³) (B-II)
  - In documented settings, longer if necessary (B-III)
  - If signs and symptoms of a documented infection resolve with appropriate duration of therapy, neutropenic patients may switch to oral quinolone prophylaxis until recovery

Introduction to ECIL

from ECIL1 to ECIL 4

4th European Conference on Infections in Leukemia
Duration of antibacterial treatment in FUO: Key points

- Relapse of fever and bacterial infection are independent of discontinuing antibiotic therapy during neutropenia or after its resolution.
- With appropriate antibiotic therapy, FUO has low mortality, unless patient is in septic shock.
Duration of antibiotics in FUO: Evidence & Recommendations

- Discontinue iv empirical antibacterials after ≥ 72h
  - If patient has been afebrile ≥ 48h and is stable
  - Irrespective of neutrophil count or expected duration of neutropenia BII

Joshi et al., Am J Med 1984
Jones et al., J Pediatr 1994
Cornelissen et al., Clin Infect Dis 1995
Horowitz et al., Leuk Lymphoma 1996
Santolaya et al., Clin Infect Dis 1997
Lehmbecher et al., Infection 2002
Cherif et al., Scand J Infect Dis 2004
Slobbe et al., Eur J Cancer 2009

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4th European Conference on Infections in Leukemia

With few Precautions...

• If still neutropenic, the patient should be kept hospitalized
  – Close observation further 24-48 h
• If fever recurs antibiotics should be re-started urgently
• Centers using prophylactic antibiotics should consider renewing this regimen after stopping therapy
### Relaps and Death After Discontinuation of Antibiotic Therapy During Persistent Neutropenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Duration of neutropenia</th>
<th>Relapsing neutropenic fever</th>
<th>Death due to bacterial infection</th>
<th>Discontinuation of antibacterial therapy</th>
<th>Discontinuation of antibacterial therapy during persistent neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzo et al.</td>
<td>1979</td>
<td>Open randomization continue vs. stop antibiotics</td>
<td>12 days (median)</td>
<td>1/16 (6%)</td>
<td>0 (0%)</td>
<td>7/17 (41%)</td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td>Joshi et al.</td>
<td>1984</td>
<td>Observational</td>
<td>20.5 days (mean)</td>
<td>NA</td>
<td>NA</td>
<td>8/16 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pizzo et al.</td>
<td>1987</td>
<td>Observational</td>
<td>&gt;14 days</td>
<td>35/93 (38%)</td>
<td>3/95 (3%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cornelissen et al.</td>
<td>1995</td>
<td>Observational</td>
<td>7 days (median)</td>
<td>NA</td>
<td>NA</td>
<td>7/85 (8%)</td>
<td>2/85 (2%)</td>
</tr>
<tr>
<td>Horowitz et al.</td>
<td>1996</td>
<td>Observational</td>
<td>17 days (median)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3/10 (33%)</td>
</tr>
<tr>
<td>Santolaya et al.</td>
<td>1997</td>
<td>Open randomization continue vs. stop antibiotics</td>
<td>9 days (mean)</td>
<td>3/39 (8%)</td>
<td>0 (0%)</td>
<td>2/36 (6%)</td>
<td>0 (0%)</td>
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<tr>
<td>IDG-EORTC—Cometta et al.</td>
<td>2003</td>
<td>Post hoc observational analysis</td>
<td>17.5 days (median)</td>
<td>49/114 (43%)</td>
<td>1/114 (1%)</td>
<td>NA</td>
<td>NA</td>
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<td>Cherif et al.</td>
<td>2004</td>
<td>Observational</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9/49 (18%)</td>
</tr>
<tr>
<td>Slobbe et al.</td>
<td>2009</td>
<td>Observational</td>
<td>20.5 days (mean)</td>
<td>NA</td>
<td>NA</td>
<td>1/169 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>FUO, fever of unknown origin; NA, not analysed or not applicable.</td>
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</tbody>
</table>

*Secondary ciprofloxacin prophylaxis.*

Early Cessation of Empirical Therapy in Patients with Neutropenia and FUO

January 2010-June 2014
283 neutropenia episodes (214 pts)

80 (28%) Inf. documented

203 (72%) FUO

8 (4%) Died under tx
4 remained neutropenic

163 (%80) Defervesced & survived up to 10 months

10 (6%) Died after 23d-10m

32 (16%) Fever reappeared in median 5 days (1-23)

Korucu B & Akova M. ECCMID 2015, Copenhagen
Outcome in 32 Episodes with Relapsed Fever

32 episodes
6 d median tx (5-22 d)
5 d median after defervesced (1-23 d)

20 (63%) relapsed as FUO
No mortality

12 (37%) relapsed as documented infection
2 died (6%)
- CR-Kp bacteremia
- Inv. aspergillosis
10 (94%) survived up to a year

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Conclusions

• Short duration of empirical therapy in patients with neutropenia and FUO is safe and effective

• Unnecessarily long duration of treatment may cause
  – Emerging resistance
  – Increased toxicity
  – High cost
Thank you...