Discontinuation of empirical antibiotics in patients with fever and neutropenia. Is it possible?

Inge C Gyssens MD PhD
The pyramid of Infectious Diseases

- **Antibiotic**
  - Therapy
    - Activity
    - Resistence
- **Infection**
  - Host
    - Host resistance
    - Virulence
    - Colonization
    - Colonization resistance
- **Pathogens**
- **Commensals**

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Escherichia coli: multidrug-resistant (third-generation cephalosporins, fluoroquinolones and aminoglycosides) in 2017 (Data source: EARS-Net surveillance report 2017)
Haematological patients

BROAD SPECTRUM EMPIRICAL ANTIBIOTIC THERAPY
Collateral damage of broad-spectrum antimicrobial therapy

• *C. difficile* infections
  – Haematology patients with *C. difficile*-associated disease had received more different antibiotics than those without the infection (5.18 ± 1.99 vs. 2.54 ± 2.13)

  Apostolopoulou et al. Eur J Oncol Nurs 2010

• Risk factors
  – Larger number of antibiotics
  – Longer therapy: 7 vs. 4 days
  – Ceftazidime use

  Schalk et al. Ann Hematol 2009
Collateral damage of broad-spectrum antimicrobial therapy: fungal infections

- Chronic disseminated candidiasis
  - *Neutropenia for >15 days* (OR, 11.7; 95% CI, 3.04-45)
  - *Quinolone prophylaxis* (OR, 3.85; 95% CI, 1.11-13.4)

  Sallah *et al.* Cancer 2001

- Candidemia
  - *Use of broad-spectrum antibiotics* (92%),
  - *Presence of an intravascular device* (82%)

  Das *et al.* Int J Infect Dis 2011
## Changing Etiology in Bloodstream Infections in Neutropenic Patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>No. BSI episodes</td>
<td>272</td>
<td>283</td>
<td></td>
</tr>
<tr>
<td>FQ prophylaxis</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Gram (+) BSI</td>
<td>64%</td>
<td>41%</td>
<td>.001</td>
</tr>
<tr>
<td>Gram (-) BSI</td>
<td>28%</td>
<td>49%</td>
<td>.001</td>
</tr>
<tr>
<td>MDR Gram (-) BSI</td>
<td>1%</td>
<td>6%</td>
<td>.001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>3%</td>
<td>11%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2%</td>
<td>6%</td>
<td>.018</td>
</tr>
<tr>
<td>48h case fatality</td>
<td>2%</td>
<td>5%</td>
<td>.071</td>
</tr>
<tr>
<td>30d case fatality</td>
<td>19%</td>
<td>15</td>
<td>.25</td>
</tr>
</tbody>
</table>

Risk factors for infection with resistant bacteria

- Previous exposure to broad-spectrum antibiotics, especially 3rd generation cephalosporins
- Serious illness (e.g. end-stage disease, sepsis, pneumonia)
- Nosocomial infection
- Prolonged hospital stay and/or repeated hospitalizations
- Urinary catheters
- Older age
- Intensive care unit stay


4th European Conference on Infections in Leukemia
Guidelines

DISCONTINUATION OF EMPIRICAL THERAPY

ICG 2016
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, Eric J. Bow, Kent A. Sepkowitz, Michael J. Boeckh, James I. Ito, Craig A. Mullen, Issam I. Raad, Kenneth V. Rolston, Jo-Anne H. Young, and John R. Wingard
Early discontinuation of antibiotic therapy while fever and neutropenia both persist is strongly discouraged for high-risk patients.…

Therefore, patients with profound, persistent myelosuppression and no identifiable source of infection should continue antibiotic therapy until there is evidence of marrow recovery …


Duration of Empirical Therapy

- In all settings until recovery of neutropenia (>500/mm$^3$) (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
Box 1. Definitions of fever and neutropenia

Fever in neutropenic patients is defined as a single oral temperature of $\geq 38.3^\circ\text{C}$ ($101^\circ\text{F}$) or a temperature of $\geq 38.0^\circ\text{C}$ ($100.4^\circ\text{F}$) sustained over a 1-hour period. Neutropenia is defined as an absolute neutrophil count $< 1,000/\mu\text{L}$ (equivalent to $< 1.0 \times 10^9/\text{L}$), severe neutropenia as absolute neutrophil count $< 500/\mu\text{L}$ (equivalent to $< 0.5 \times 10^9/\text{L}$), and profound neutropenia as $< 100/\mu\text{L}$ (equivalent to $< 0.1 \times 10^9/\text{L}$). The period of neutropenia is considered protracted if it lasts for $\geq 7$ days.
European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

Diana Averbuch,¹ Christina Orasch,² Catherine Cordonnier,² David M. Livermore,¹ Małgorzata Mikulska,⁵ Claudio Viscoli,⁵ Inge C. Gyssens,⁶,⁷ Winfried V. Kern,⁹ Galina Klyasova,¹⁰ Oscar Marchetti,² Dan Engelhard,¹ and Murat Akova,¹¹ on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

¹Pediatric Infectious Diseases Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; ²Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, Switzerland; ³APHP-Henri Mondor Hospital, Hematology Department and Université Paris Est - Créteil, France; ⁴Norwich Medical School, University of East Anglia, Norwich, UK; ⁵Division of Infectious Diseases, University of Genova, IRCCS San Martino-IST, Genoa, Italy; ⁶Department of Medicine and Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ⁷Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; ⁸Hasselt University, Diepenbeek, Belgium; ⁹Center for Infectious Diseases and Travel Medicine, Department of Medicine, University Hospital, Albert-Ludwigs University, Freiburg, Germany; ¹⁰National Research Center for Hematology, Moscow, Russia; and ¹¹Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

ABSTRACT

Owing to increasing resistance and the limited arsenal of new antibiotics, especially against Gram-negative pathogens, carefully designed antibiotic regimens are obligatory for febrile neutropenic patients, along with effective infection control. The Expert Group of the 4th European Conference on Infections in Leukemia has developed guidelines for initial empirical therapy in febrile neutropenic patients, based on: i) the local resistance epidemiology; and ii) the patient’s risk factors for resistant bacteria and for a complicated clinical course. An ‘escalation’ approach, avoiding empirical carbapenems and combinations, should be employed in patients without particular risk factors. A ‘de-escalation’ approach, with initial broad-spectrum antibiotics or combinations, should be used only in those patients with: i) known prior colonization or infection with resistant pathogens; or ii) complicated presentation; or iii) in centers where resistant pathogens are prevalent at the onset of febrile neutropenia. In the latter case, infection control and antibiotic stewardship also need urgent review. Modification of the initial regimen at 72-96 h should be based on the patient’s clinical course and the microbiological results. Discontinuation of antibiotics after 72 h or later should be considered in neutropenic patients with fever of unknown origin who are hemodynamically stable since presentation and afebrile for at least 48 h, irrespective of neutrophil count and expected duration of neutropenia. This strategy aims to minimize the collateral damage associated with antibiotic overdose, and the further selection of resistance.
Evidence before ECIL-4

DISCONTINUATION OF EMPIRICAL THERAPY

ICG 2016
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
Santoloya et al., Clin Infect Dis 1997
Lehmbecher et al., Infection 2002
Chenf et al., Scand J Infect Dis 2004
Slobbe et al., Eur J Cancer 2009
Haematological patients with neutropenia and fever

ETHICS REGARDING DISCONTINUATION OF EAT
LETTER TO THE EDITOR

Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical

In conclusion, after careful assessment of the interesting, but small and single-center, observations of Micol et al., the ECIL-4 panel confirms its recommendation for antibiotic discontinuation despite persistent neutropenia after resolution of FUO. This approach is effective, safe and ethical, provided that appropriate empirical antibacterial therapy is immediately initiated if fever relapses. The strategy reduces antibiotic usage and selection pressure for resistance at both the individual and unit levels. This is critical to maintaining our ability to treat infections in haematology patients.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Days neutropenic</th>
<th>AB prophylaxis</th>
<th>Continuation of antibiotics</th>
<th>Discontinuation during neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relapsing NF</td>
<td>Death due to bacterial infection</td>
</tr>
<tr>
<td>Pizzo</td>
<td>1979</td>
<td>Open random</td>
<td>12 (median)</td>
<td>none</td>
<td>1/16 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Joshi</td>
<td>1984</td>
<td>Observational</td>
<td>20.5 (mean)</td>
<td>genta+vanco, cotrimoxazole</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Pizzo</td>
<td>1987</td>
<td>Observational</td>
<td>&gt;14</td>
<td>cotrimoxazole</td>
<td>35/9 (3%)</td>
<td>No discontinuation</td>
</tr>
<tr>
<td>Cornelissen</td>
<td>1995</td>
<td>Observational</td>
<td>7 *(median) &lt;100 after response</td>
<td>cotrimoxazole</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Horowitz</td>
<td>1996</td>
<td>Observational</td>
<td>17 (mean)</td>
<td>Stepdown FQ</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Santolaya children</td>
<td>1997</td>
<td>Open random</td>
<td>9 (mean)</td>
<td>none</td>
<td>3/39 (8%)</td>
<td>0</td>
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<tr>
<td>Cherif</td>
<td>2004</td>
<td>Observational</td>
<td>NA</td>
<td>FQ+ oral colistin/tobra</td>
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<td>NA</td>
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<tr>
<td>Slobbe</td>
<td>2009</td>
<td>Observational</td>
<td>20.5 (mean)</td>
<td></td>
<td>NA</td>
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</tbody>
</table>

*Studies on discontinuation of empirical antibiotic treatment in neutropenia with fever before ECIL-4*
High-risk neutropenic patients

ANTIBACTERIAL PROPHYLAXIS
Recommendations

Antibacterial ... prophylaxis is recommended for patients who are at high risk of infection, including patients who are expected to have profound, protracted neutropenia, which is defined as < 100 neutrophils/µl for >7 days or other risk factors
Conclusions

HSCT recipients who are colonized with levofloxacin resistant ESBL-E pre-transplant (10%) and receive levofloxacin prophylaxis have high rates of bacteremia from their colonizing strain (32%) during neutropenia.

Assessing for ESBL-E colonization in neutropenic patients could lead to optimization of empirical antibacterial therapy.

Single center 312 patients including 212 allogeneic and 100 autologous HSCT recipients
Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

Malgorzata Mikulska a,*, Diana Averbuch 1,b, Frederic Tissot 1,c, Catherine Cordonnier d, Murat Akova e, Thierry Calandra f, Marcello Ceppi g, Paolo Bruzzi g, Claudio Viscoli a on behalf of the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHIS) and the European Leukemia Net (ELN)

Conclusions

The possible benefits of FQ prophylaxis on BSI rate, but not on overall mortality should be weighed against its impact in terms of toxicity and changes in local ecology in single centers.

In few studies an increased colonisation or infection with FQ or multi-drug resistant strains

Evidence after ECIL-4

DISCONTINUATION OF EMPIRICAL THERAPY

ICG 2016
Studies on discontinuation of empirical antibiotic treatment in neutropenia with fever after ECIL-4

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Days neutropenic</th>
<th>AB prophylaxis</th>
<th>Continuation of antibiotics</th>
<th>Discontinuation during neutropenia</th>
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<tbody>
<tr>
<td>LaMartire</td>
<td>2018</td>
<td>ITS intervention</td>
<td>19 (median)</td>
<td>oral colistin/genta</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td>Relapsing NF</td>
<td>Death due to bacterial infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0/52</td>
<td>0</td>
</tr>
<tr>
<td>LeClech</td>
<td>2018</td>
<td>Observational</td>
<td>16 (median)</td>
<td>amoxicillin</td>
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<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relapsing NF</td>
<td>Death due to bacterial infection</td>
</tr>
<tr>
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<td>17/82</td>
<td>0</td>
</tr>
<tr>
<td>Aguilar Guisado</td>
<td>2017</td>
<td>RCT</td>
<td>2.5 ** (median)</td>
<td>cotrimoxazole</td>
<td>ITT 14/79</td>
<td>ITT 11/78</td>
</tr>
</tbody>
</table>

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De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption

Giulia la Marti
Mathieu Lecler
Catherine Cor

Antibiotic consumption (DDD/1000d) for Carbapenems

Time (months)


Raw data
Fitted values
Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study

Lenaïg Le Clech, Jean-Philippe Talarmin, Marie-Anne Couturier, Jean-Christophe Ianotto, Christophe Nicol, Ronan Le Calloch, Stéphanie Dos Santos, Pascal Hutin, Didier Tandé, Virginie Cogulet, Christian Berthou and Gaëlle Guillerm

Department of Haematology, Brest Teaching Hospital, Brest, France; Department of Internal Medicine, Infectious Diseases and Haematology, Comouaille Hospital Quimper, Quimper, France; Laboratory of Bacteriology, Brest Teaching Hospital, Brest, France; Department of Pharmacy, Brest Teaching Hospital, Brest, France

Methods: In the first phase of the study, empirical antibiotic therapy in FUO patients was stopped after 48 h of apyrexia, in accordance with European Conference on Infections in Leukaemia guidelines (n = 45). In the second phase of the study, antibiotics were stopped no later than day 5 for all FUO patients, regardless of body temperature or leukocyte count (n = 37).
Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

Manuela Aguilar-Guisado, Ildefonso Espigado, Almudena Martín-Peña, Carlota Gudiol, Cristina Royo-Cebrecos, José Falantes, Lourdes Vázquez-López, María Isabel Montero, Clara Rosso-Fernández, María de la Luz Martino, Rocío Parody, José González-Campos, Sebastián Garzón-López, Cristina Calderón-Cabrera, Pere Barba, Nancy Rodríguez, Montserrat Rovira, Enrique Montero-Mateos, Jordi Carratalá, José Antonio Pérez-Simón, José Miguel Cisneros

Lancet Haematol 2017; 4: e573–583
### Table 3: Efficacy and safety endpoints

<table>
<thead>
<tr>
<th></th>
<th>Experimental group (n=78)</th>
<th>Control group (n=79)</th>
<th>Between-group absolute difference (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Intention-to-treat population</strong></td>
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<td></td>
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<tr>
<td>Number of patients (%)</td>
<td>78 (100%)</td>
<td>79 (100%)</td>
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<tr>
<td>Efficacy variable</td>
<td></td>
<td></td>
<td></td>
<td>..</td>
</tr>
<tr>
<td>EAT-free days</td>
<td>16·1 (6·3)</td>
<td>13·6 (7·2)</td>
<td>-2·4 (-4·6 to -0·3)</td>
<td>0·026</td>
</tr>
<tr>
<td>Safety variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude mortality</td>
<td>1 (1·3)</td>
<td>3 (3·8)</td>
<td>NA</td>
<td>0·62</td>
</tr>
<tr>
<td>Days of fever</td>
<td>5·7 (5·0)</td>
<td>6·3 (5·9)</td>
<td>0·5 (-1·2 to 2·3)</td>
<td>0·53</td>
</tr>
<tr>
<td><strong>Per-protocol population</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>66 (85%)</td>
<td>66 (84%)</td>
<td></td>
<td>..</td>
</tr>
<tr>
<td>Efficacy variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAT-free days</td>
<td>16·9 (5·8)</td>
<td>13·0 (7·2)</td>
<td>-3·8 (-6·1 to -1·6)</td>
<td>0·0010</td>
</tr>
<tr>
<td>Safety variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude mortality</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>NA</td>
<td>0·49</td>
</tr>
<tr>
<td>Days of fever</td>
<td>5·9 (5·1)</td>
<td>6·7 (6·1)</td>
<td>0·86 (-1·1 to 2·8)</td>
<td>0·38</td>
</tr>
</tbody>
</table>
CONCLUSIONS of recent studies

The implementation of an AS intervention based on the discontinuation and de-escalation ECIL guidelines in high-risk neutropenic patients is safe and feasible and led to a significant reduction in carbapenem use and antibacterial expense. These preliminary results should encourage hematologists to change their practices and follow the ECIL guidelines.

Conclusions: These results suggest that early discontinuation of empirical antibiotics in FUO is safe for afebrile neutropenic patients.

Lancet Haematol 2017; 4: e573-583

Interpretation In high-risk patients with haematological malignancies and febrile neutropenia, EAT can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. This clinical approach reduces unnecessary exposure to antimicrobials and it is safe.