Bacterial Resistance in Haematology-ECIL 4
Study Groups & Participants

- Epidemiology & resistance
  - M Mikulska*, M Akova, D Averbuch, G Klyasova, DM Livermore, C Orasch, M Tumbarello
- Empirical & targeted antibacterial therapy
  - D Averbuch*, C Cordonnier, WV Kern, C Viscoli
- Duration of antibacterial therapy
  - C Orasch*, G Klyasova, P Munoz
- Antibiotic stewardship
  - IC Gyssens*, WV Kern, DM Livermore

Group leader: Murat AKOVA
Meeting: September 8-10th, 2011
Final version: Feb 14th, 2012

* Presenting authors
Epidemiology of Bacterial Infections & Antimicrobial Resistance in Haematological Cancer Patients

M Mikulska*, M Akova, D Averbuch, G Klyasova, DM Livermore, C Orasch, M Tumbarello
Background to the guidelines
Bacterial infections & resistance

• These slides summarise published data on the epidemiology and treatment of bloodstream infections in adults and children with haematological cancer
  – *These data support the guidelines due to be published*

• The published guidelines will also include results of a questionnaire on the major pathogens, resistance epidemiology and treatments in European centres
Empirical & Targeted Antibiotics in Haematological Cancer Patients

D Averbuch*, C Cordonnier, W Kern, C Viscoli
Why new recommendations for empirical therapy of fever during neutropenia-I?

- Resistance rates among Gram +ve cocci & Gram –ve rods are increasing in many haematology centres

  ...consequently

- Commonly used empirical monotherapy with a 3rd or 4th generation cephalosporin or piperacillin-tazobactam
  - May be inadequate
  - May lead to increased mortality
Why new recommendations for empirical therapy of fever during neutropenia-II?

Emergence of:

- Staphylococci with raised vancomycin MICs
- Vancomycin-resistant enterococci

may evade anti-Gram +ve coverage by glycopeptides
Challenges in building recommendations

• Resistance rates vary with hospital, unit, & latitude
• Antibiotic options are changing:
  – *New anti-Gram +ve drugs now exist*
  – *Tigecycline has some new anti-Gram –ve activity*
  – *Old and ‘revived’ antibiotics are being used in ICUs*
• …But little published experience with these antibiotics in neutropenic patients
• Methods to optimize drug exposure are not well studied in oncohaematological patients
Inappropriate initial therapy predicts increased mortality

Multiple studies show that failure to cover resistant pathogens, including ESBL-producers, significantly and independently impairs outcomes for haematology patients

Ariffin et al. Int J Infect Dis 1999
Trecarichi et al. J Infect 2009
Martinez et al. Antimicrob Agents Chemother 2010
Trecharichi et al. Haematologica 2011
Haematology patients with ESBL producers more often receive inappropriate initial antibiotics

<table>
<thead>
<tr>
<th>Study</th>
<th>% treatments inappropriate</th>
<th>No of episodes; causative bacteria; ESBL rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESBL +ve</td>
<td>ESBL -ve</td>
</tr>
<tr>
<td>Gudiol et al.</td>
<td>65%</td>
<td>6%</td>
</tr>
<tr>
<td><em>J Antimicrob Chemother 2010</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortega et al.</td>
<td>52%</td>
<td>5%</td>
</tr>
<tr>
<td><em>J Antimicrob Chemother 2009</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumbarello et al.</td>
<td>50%</td>
<td>2%</td>
</tr>
<tr>
<td><em>Antimicrob Agents Chemother 2006</em></td>
<td></td>
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</tr>
</tbody>
</table>
ECIL Recommendations
Questions to answer for febrile neutropenia

1. What are the key parameters in choosing empirical antibiotics in an era of increasing resistance?

2. Should we replace commonly used escalation therapy with de-escalation?

3. What should be done at 24-72h?
   a) In escalation approach
   b) In de-escalation approach

4. What are the best therapies for documented infections due to resistant bacteria?
Q1: Factors in choosing a regimen

• Local bacterial epidemiology and resistance patterns

• Patient’s prior colonization or infection by resistant pathogens, particularly:
  – MRSA and MRSE, especially with vancomycin MICs >2 mg/L
  – Vancomycin-resistant enterococci
  – ESBL- or carbapenemase- producing Enterobacteriaceae
  – A. baumannii, Pseudomonas spp. & S. maltophilia

• Other patient-related factors
  – Other risk factors for infection due to resistant pathogens
  – Clinical presentation
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

Factors predicting a complicated clinical course in febrile neutropenia

- Advanced age
- Inpatient status
- Prolonged and severe aplasia
- Co-morbidities (bleeding, dehydration, organ failure, chronic illness)
- Shock, haemodynamic instability, hypotension, sensory loss
- Localised infection (e.g. pneumonia, enteritis, catheter infection)

*The physician’s clinical judgement is pivotal in this evaluation*

Q2: Is antibiotic de-escalation better than escalation in febrile neutropenia?

Defining commonly used ‘escalation’

– Initial empirical therapy covers typical Enterobacteriaceae and \textit{P. aeruginosa}, but not ESBL or carbapenemase producers, nor multi-resistant non-fermenters

  • (e.g. ceftazidime, cefepime or piperacillin-tazobactam)

– If the patient deteriorates, or a resistant pathogen is isolated, therapy is ‘escalated’, e.g. to a carbapenem
Q2: Is antibiotic de-escalation better than escalation in febrile neutropenia?

**Defining de-escalation**

- Initial empirical regimen is very broad, with coverage of multi-resistant Gram +ve and –ve pathogens (e.g. ESBL-producers)
  
  • e.g. carbapenem + anti-MRSA agent

- Therapy is de-escalated to a simpler or narrower spectrum (‘targeted’) therapy once the microbiology lab does not report resistant pathogens
Examples of de-escalation or simplification

Discontinuation of empirically prescribed

- Aminoglycoside or quinolone, if given in combination
- Agents used against multi-resistant Gram –ves (e.g. colistin)
- Glycopeptides (i.e. vancomycin or teicoplanin) or other anti-Gram +ve agents (e.g. tigecycline, linezolid, daptomycin etc)

...............if relevant pathogen **NOT** isolated
Examples of de-escalation or simplification-II

Switch to a narrower-spectrum antibacterial

- e.g. cefepime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam or ticarcillin-clavulanate.

- More drastic changes could be envisaged, if a fully susceptible organism is isolated from blood cultures of a stable patient under hospital observation B III.

  - e.g. step down to an aminopenicillin (e.g., ampicillin or piperacillin) when an α-haemolytic streptococcus is isolated from blood cultures.
Escalation approach

**Pro:** Avoids early use of broadest-spectrum antibacterials, including carbapenems

- *Less toxicity and cost*
- *Less selection of carbapenem resistance*

**Con:** If initial empirical therapy fails to cover the pathogens in neutropenic patients, prognosis is significantly worsened

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Trecarichi et al. *J Infect* 2009
Ortega et al. *J Antimicrob Chemother* 2009
Martinez et al. *Antimicrob Agents Chemother* 2010
De-escalation approach

• **Pro**: More likely to achieve cover in the first 48h, before microbiology data become available

• **Con**: Leads to unnecessary use of broad-spectrum antibiotics in many patients
  
  – *Common failure to de-escalate when possible to do so*
  
  – *Consequent risk of selecting for resistance (especially for carbapenems)*
Rationale for combination therapy

• May cover bacteria resistant to one antibiotic
  – Aminoglycosides, if active, may be strongly bactericidal in the first 48h, whilst susceptibility test data are awaited

• *In-vitro* data suggest some benefit in combining two agents, even when pathogen is resistant to each alone

Safdar et al. Lancet Infect Dis 2004
Combinations increase the chance of empirical therapy covering resistant bacteria

Retrospective analysis:

- 4,863 Gram-negative bacteraemias, 710 (15%) patients with haematological malignancy or post-HSCT
  - 14% β-lactam monotherapy vs. 86% β-lactam + aminoglycoside

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>No./total no. (%) receiving:</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combination</td>
<td>β-Lactam</td>
<td></td>
</tr>
<tr>
<td>Non-ESBL E. coli</td>
<td>242/248 (98)</td>
<td>2,454/2,489 (99)</td>
<td>0.6 (0.2–1.7)</td>
</tr>
<tr>
<td>ESBL E. coli</td>
<td>21/28 (75)</td>
<td>62/122 (51)</td>
<td>2.9 (1.07–8.2)</td>
</tr>
<tr>
<td>Non-ESBL K. pneumoniae</td>
<td>62/63 (98)</td>
<td>393/420 (94)</td>
<td>4 (0.7–177)</td>
</tr>
<tr>
<td>ESBL K. pneumoniae</td>
<td>18/20 (90)</td>
<td>38/63 (60)</td>
<td>2 (1.2–4.2)</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>10/10 (100)</td>
<td>116/118 (98)</td>
<td>1</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>15/15 (100)</td>
<td>108/109 (99)</td>
<td>1</td>
</tr>
<tr>
<td>AmpC organisms</td>
<td>78/82 (95)</td>
<td>258/326 (79)</td>
<td>5.1 (1.8–20)</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>133/143 (93)</td>
<td>201/319 (63)</td>
<td>7.8 (3.8–16)</td>
</tr>
<tr>
<td>Other nonfermenters</td>
<td>24/51 (47)</td>
<td>53/105 (51)</td>
<td>0.9 (0.4–1.8)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>18/18 (100)</td>
<td>105/114 (92)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Martinez et al. Antimicrob Agents Chemother 2010
General strategy for the empirical treatment of febrile neutropenia-I

Initial regimen targeted on the most prevalent bacteria at the centre, unless the patient

- is seriously ill at presentation or
- is known to be colonized with resistant bacteria or
- has had an infection with resistant bacteria

If these risk factors apply, initial treatment may be modified
Modification of the initial regimen (escalation or de-escalation) should be considered at 24-72 h

Any changes depend upon:

- **Clinical course**
- **Microbiological results**
ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

Escalation Strategy

Escalation should be employed for patients with

- An uncomplicated presentation

- Without specific risk factors for resistant pathogens

- In centres where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia  \[BII\]
ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

De-escalation Strategy

De-escalation should be applied for patients

– *With complicated presentations*

– *With individual risk factors for resistant pathogens,*

– *In centres where resistant pathogens are regularly seen at the onset of febrile neutropenia BII*

• Review of infection control is mandatory
Suggested initial regimens in an escalation strategy

- Use non-carbapenem β-lactam
  - No coverage vs. resistant Gram +ve bacteria such as MRSA & vancomycin-resistant enterococci
  - No combination with aminoglycoside / quinolone
Suggested initial regimens in a de-escalation strategy

• Carbapenem monotherapy
• Combination of anti-pseudomonal β-lactam + aminoglycoside or quinolone
  – With carbapenem as the β-lactam in seriously ill-patients
• Colistin + β-lactam or rifampicin etc.
• Early coverage of resistant-Gram +ves with a glycopeptide or newer agent
  – If risk factors for Gram +ves present –see slide 35
Initial empirical therapy for febrile, high-risk patients with uncomplicated neutropenia

- Anti-pseudomonal ceph (cefepime*, ceftazidime*) AI
- Piperacillin-tazobactam AI
- Other possible options include:
  - Anti-pseudomonal carbapenem** AI
  - Ticarcillin-clavulanate, cefoperazone-sulbactam

  * Avoid if ESBLs are prevalent

  ** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients
First-line carbapenems should be reserved for situations where:

- Known colonization or previous infection with:
  - *ESBL*-producing *Enterobacteriaceae*
  - *Gram*-ves resistant to narrower-spectrum $\beta$-lactams BII
- Seriously-ill patients
  - *e.g. presentation with septic shock, pneumonia* BII
- Centres with a high prevalence of infections due to *ESBL*-producers at the onset of febrile neutropenia
  - *Should also prompt infection control review* BIII
Is there a ‘cut-off’ prevalence of resistance to prompt changing initial empirical therapy?

- Lack of literature data precludes any recommendation
- Several ways to measure the burden of resistance
  - % Resistance rate in \( \geq 1 \) key species
  - Incidence of infections due to resistant bacteria
  - Attributable morbidity and mortality due to these infections

% resistance may be high, but incidence of infections low ....
Initial therapy in patients colonised or previously infected by resistant Enterobacteriaceae

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL</td>
<td><em>Carbapenem</em> + BII</td>
</tr>
<tr>
<td>Carbapenemase</td>
<td><em>Colistin</em> CIII + β-Lactam</td>
</tr>
<tr>
<td></td>
<td>+/- one of:</td>
</tr>
<tr>
<td></td>
<td><em>Tigecycline</em> CIII or</td>
</tr>
<tr>
<td></td>
<td><em>Aminoglycoside CIII or Fosfomycin</em> CIII</td>
</tr>
</tbody>
</table>

*Freifeld et al. Clin Infect Dis 2011*
Initial therapy in patients colonised or previously infected by resistant non-fermenters **BIII**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactam</strong> resistant <em>P. aeruginosa</em></td>
<td>Colistin + β-lactam +/− fosfomycin</td>
</tr>
<tr>
<td><strong>β-lactam</strong> resistant <em>Acinetobacter</em></td>
<td>Colistin + β-lactam +/− tigecycline</td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td>Co-trimoxazole + β-lactam (preferable ticarcillin-clavulanate) +/− moxifloxacin</td>
</tr>
</tbody>
</table>

Falagas et al. J Antimicrob Chemother 2008
When is combination with an aminoglycoside indicated? BIII

- In seriously-ill patients
  - e.g. septic shock, pneumonia

- If resistant non-fermenters likely, based upon
  - Local epidemiology
  - Previous colonization or infection with these pathogens,
  - Previous use – during the last month – of carbapenems

- If piperacillin or ticarcillin (without β-lactamase inhibitors) is used as initial empirical therapy
When to add antibiotics vs. resistant-Gram +ve bacteria to the initial empiric therapy CIII

- Haemodynamic instability, or other evidence of severe sepsis, septic shock or pneumonia
- Colonisation with MRSA, vancomycin-resistant enterococci, or penicillin-resistant S. pneumoniae
- Suspicion of serious catheter-related infection
  - e.g. chills or rigours with infusion through catheter and cellulitis around the catheter exit site
- Skin or soft-tissue infection at any site

Freifeld et al. CID 2011
Q 3a: Actions at 24-72h in neutropenic patients in an escalation approach

Where the bacteria are identified: treat based on susceptibility tests, ideally with MIC determinations AI

- Note drugs with specific activities (e.g., trimethoprim-sulfamethoxazole for S. maltophilia)
- Prefer narrower-spectrum agents with good activity against the pathogen
  - Prefer penicillins and penicillin/β-lactamase inhibitor over cephalosporins and carbapenems, if similarly active in vitro BII
- Consult an ID expert / microbiologist, if available
No bacteria documented BII

– If the patient is afebrile and stable: no change

  Consider discontinuing antibiotics at >72h if patient has been afebrile for ≥ 48 h

– If the patient is febrile but stable: no change + diagnostic work-up (at 72h)

  Fever alone is not a criterion to escalate antibiotics
Actions at 24-72 h in neutropenic patients in an escalation approach-III

No bacteria isolated, patient deteriorating BII

- Diagnostic work-up (e.g., repeat cultures, galactomannan, imaging); also consider fungi and other aetiologies

- Consider resistant Gram-ve bacteria & if likely, switch to a carbapenem possibly +aminoglycoside, quinolone or colistin

- Consider resistant Gram +ve bacteria and if likely, (e.g. if using a 3rd generation ceph) add appropriate agent

- **In all cases**, choices should reflect patient history, colonisation and other risk factors
Q 3b: Actions at 24-72h in neutropenic patients in a de-escalation approach I

When causative bacteria are identified: treat based on susceptibility tests, ideally with MIC determinations AI

- Note drugs with specific activities (e.g., trimethoprim-sulfamethoxazole for S. maltophilia)

- Prefer narrower-spectrum agents with good activity against the pathogen
  - Prefer penicillins and penicillin/β-lactamase inhibitor over cephalosporins and carbapenems, if similarly active in vitro BII

- Consult with an ID expert/microbiologist, if available
Actions at 24-72 h in neutropenic patients in a de-escalation approach-II

No bacteria documented (FUO) patient afebrile BIII

- If the patient was seriously ill (e.g. septic shock, pneumonia) at presentation, keep on the initial regimen

- If the patient was stable at presentation
  - Switch to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin/tazobactam, cefoperazone/sulbactam or ticarcillin/clavulanate
  - Stop any aminoglycoside, quinolone or colistin or anti-Gram +ve agent, if given in combination
  - Consider stopping antibacterial treatment at 72 h if patient has been afebrile ≥48 h and is stable BII
Actions at 24-72 h in neutropenic patients in a de-escalation approach-III

No bacteria isolated (FUO); patient febrile but stable **BIII**

If the patient was seriously-ill (e.g. septic shock, pneumonia) at presentation, keep on the initial regimen

If the patient was stable at presentation

- *Keep on the same therapy or switch to a narrower-spectrum regimen*

- *Stop any aminoglycoside, quinolone, colistin or anti-Gram-positive agent, if given in combination*

- *Re-try to obtain a diagnosis (e.g., repeat cultures, galactomannan); also consider fungi and other aetiologies*
Actions at 24-72 h in neutropenic patients in a de-escalation approach-IV

No bacteria documented; patient deteriorating BIII

- Try to obtain a diagnosis
  - (e.g. repeat cultures, imaging, galactomannan)
- Consider resistant Gram -ve bacteria
  - possibly add colistin or other anti-Gram -ve agent depending on history, colonisation and other risk factors
- Consider fungal/viral and other aetiologies, and treat accordingly
Actions at 24-72h in neutropenic patients with clinically documented infection BIII

If the patient is febrile, but stable

- Assess appropriateness of antibiotics given

If the patient is deteriorating

- Try to obtain a diagnosis (e.g., repeat cultures, imaging, galactomannan)

- Consider resistant-Gram -ve bacteria and adding colistin or other anti-agents depending on history, colonization and other risk factors

- Consider fungal/viral infection and other aetiologies, and treat accordingly
Q 4: Suggested therapy for documented infections due to resistant bacteria

- When the causative bacteria are identified: treat based on susceptibility tests, ideally with MIC determinations
  - Note drugs with specific activities (e.g., trimethoprim-sulfamethoxazole for *S. maltophilia*)
  - Prefer narrower-spectrum agents with good activity against the pathogen found
    - Prefer penicillins and penicillin/β-lactamase inhibitor over cephalosporins and carbapenems, if similarly active in vitro
  - Consult with an ID expert/microbiologist, if available
Options for infections due to glycopeptide non-susceptible Gram-positive pathogens

Oxazolidinone (linezolid) **AII**
- May delay marrow recovery

Cyclic lipopeptide (daptomycin) **BII**
- Not if pneumonia present

Streptogramin (quinupristin/dalfopristin) **BIII**

Glycylcycline (tigecycline) **BIII**
- Low blood levels
- Limited experience with VRE
- FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia
- Few data with febrile neutropenia
Options for infections due to carbapenem-resistant Enterobacteriaceae

The following antibiotics should be combined with other antibiotics active in vitro, unless they are the only active agents

– Colistin +… BII
  • A loading dose and high maintenance dose may be required

– Tigecycline +… BIII
  • Low blood levels; ineffective in ventilator-associated pneumonia; FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia

– Aminoglycosides + … BIII

– Fosfomycin +… CIII

For colistin, tigecycline, aminoglycoside and fosfomycin resistant pathogens consult ID / microbiologist CIII
Options for infections due to beta-lactam resistant *P. aeruginosa*

- Colistin +…* All
- Fosfomycin +…* CIII
- For *P. aeruginosa* resistant to colistin, β-lactams, quinolone, aminoglycoside and fosfomycin – consult ID/microbiologist CIII

* Use combined with other agents active *in vitro*; if these are the only active antibiotics - consult ID/microbiologist
Options for infections due to beta-lactam resistant *Acinetobacter spp.*

- Colistin +…* BIII
- Tigecycline +…* BIII
  - Low blood levels
  - Not effective in ventilator-associated pneumonia
  - FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia
  - Use combined with other agents active *in vitro*, if they are the only active antibiotics - consult ID/microbiologist
Options for infections due to *S. maltophilia*

- Trimethoprim-sulfamethoxazole **AI**
- Fluoroquinolone (ciprofloxacin or moxifloxacin based on in-vitro susceptibility) **BII**
- Ticarcillin-clavulanate **BII**
- In seriously-ill or neutropenic patients, combination therapy can be considered (e.g. trim-sulpha + ceftazidime or ticarcillin-clavulanate) **CIII**
Duration of Antibacterial Therapy in Neutropenic Patients

C Orasch*, G Klyasova, P Munoz
Challenges in establishing recommendations

• Different clinical situations:
  − *Empirical treatment (FUO)*
  − *Documented infection*
  − *Low- vs. high- risk patients for severe infections*
  − *Short vs. long duration of neutropenia (≤7d vs. >7d)*

• Different outcomes after antibiotics stopped
  − *Recovery, relapse of fever, bacterial infection, death*

• Evolution of diagnostic and therapeutic tools
Duration of empiric antibiotic therapy in neutropenic patients with cancer

- **33 High-risk neutropenic patients with FUO** who become afebrile on empirical cefazolin + gentamicin + carbenicillin
- **After 7 days** (with persisting neutropenia) *randomised between stopping vs. continuing these antibiotics*

<table>
<thead>
<tr>
<th>Patients (n=33)</th>
<th>Relapse of fever</th>
<th>Infection</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped therapy (n=17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median 13d (8-24)</td>
<td>7 (41%)</td>
<td>5 (29%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cellulitis</td>
<td>2 <em>E. coli</em> bacteraemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 <em>E. coli</em> bacteraemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cervical adenitis</td>
<td></td>
</tr>
<tr>
<td>Continued therapy (n=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of neutropenia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>median 11d (8-25)</td>
<td></td>
<td>pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

*Pizzo et al., Am J Med 1979*
3-Day imipenem for FUO during prolonged neutropenia in haematology patients on fluoroquinolone + fluconazole prophylaxis

- Prospective observational study in high-risk patients
- **Discontinuation** of imipenem after $\leq 3$ days for FUO: $n=169$
- Prophylaxis (continued): ciprofloxacin ($\pm$ colistin po $\pm$ penicillin)

<table>
<thead>
<tr>
<th>Patients ($n=169$)</th>
<th>Relapse of fever</th>
<th>Infection</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia $\geq 10$ days (mean 20.5 days)</td>
<td>0</td>
<td>0</td>
<td>3 (2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 aspergillosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 severe typhlitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 progressive AML</td>
</tr>
</tbody>
</table>

Slobbe et al., Eur J Cancer 2009
Cefepime & imipenem in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies

- Randomised study; 207 patients; 89 (43%) with FUO
- High- and low- risk patients (mean duration of neutropenia 6.2 ±5.1d)
- Afebrile for 48 h: stop AB in neutropenia (n=49) vs. N > 500/mm³ (n=11)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Relapse of fever</th>
<th>Infection</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still neutropenic (n=49)</td>
<td>9 (18%)</td>
<td>-</td>
<td>2 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 progressive lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 invasive fungal infection</td>
</tr>
<tr>
<td>Neutrophils recovered (n=11)</td>
<td>2 (18%)</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Cherif et al., Scand J Infect Dis 2004
Discontinuation of antimicrobial therapy for febrile neutropenic children with cancer

- Prospective: neutropenic (mostly high-risk) patients with FUO (n=75)
- **Day 3**: randomised between **stop** vs. **continue** empirical therapy

<table>
<thead>
<tr>
<th>Patients (n=75)</th>
<th>Relapse of fever</th>
<th>Infection</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stop</strong> antibiotics (n=36, 7 febrile)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia mean 8.3 ± 5.4d</td>
<td></td>
<td><strong>E. aerogenes</strong> bacteraemia</td>
<td></td>
</tr>
<tr>
<td><strong>Continue</strong> antibiotics (n=39)</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia mean 9 ± 5.8 d</td>
<td></td>
<td>2 catheter-related bacteraemia (coag-neg staph)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 periodontal abscess</td>
<td></td>
</tr>
</tbody>
</table>

Santoloya et al., Clin Infect Dis 1997
Short course empirical iv antibiotics in febrile neutropenic children with cancer

• Retrospective: 56 children, 106 fever episodes (84 FUO, 16 MDI, 6 CDI)
• Neutropenic (high & low risk) children: leukaemia/lymphoma (n=17); solid tumours (n=29)
• 47/84 FUO: afebrile within 72h ⇒ stop AB and discharge
• Prophylaxis: trimethoprim/sulfamethoxazole (3x/week)

<table>
<thead>
<tr>
<th>Patients (n=47)</th>
<th>Relapse of fever</th>
<th>Re-hospitalisation</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia, median 10 d (2-39)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Lehrnbecher et al., Infection 2002
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
Santoloya et al., Clin Infect Dis 1997
Lehrnbecher et al., Infection 2002
Cherif et al., Scand J Infect Dis 2004
Slobbe et al., Eur J Cancer 2009
Duration of therapy in documented infections

Continue targeted antibiotics for clinically- or microbiologically-documented infection

- Until infection is microbiologically eradicated &
- Until all clinical signs of infection are resolved
- At least 7 days, of which at least 4 days afebrile

Eggimann et al., J Antimicrob Chemother 1993
Cometta et al., Antimicrob Agents Chemother 1995
Cordonnier et al., Clin Infect Dis 1997
Biron et al., J Antimicrob Chemother 1998
Elting et al., J Clin Oncol 2000
Feld et al., J Clin Oncol 2000

Giamarello et al., Antimicrob Agents Chemother 2000
Viscoli et al., Clin Microbiol Infect. 2002
Sanz et al., J Antimicrob Chemother 2002
Tamura et al., Am J Hematol 2002
Cometta et al., Clin Infect Dis 2003
Raad et al., Cancer 2003
The Role of Antibiotic Stewardship in Limiting Antibacterial Resistance for Haematology Patients

IC Gyssens*, W Kern, DM Livermore
Collateral damage of broad-spectrum antimicrobial therapy

- Emerging resistance
- *C. difficile* infections
- Fungal infections
Collateral damage of broad-spectrum antimicrobial therapy

• Selection of important resistance types
  – MRSA, VISA, VRE
  – Enterobacteriaceae and P. aeruginosa resistant to 3rd generation cephalosporins or carbapenems

• Increased multi-resistant Gram-vees, by risk factor
  – Intensive care unit (ICU) admission (14% vs. 5%; P=0.023)
  – Mechanical ventilation (14% vs. 3%; P=0.005)
  – Higher overall case-fatality rate (41% vs. 21%; P=0.003)
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)*

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

Apostolopoulou et al. Eur J Oncol Nurs 2010

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

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

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

Sallah et al. Cancer 2001

Das et al. Int J Infect Dis 2011
Basic Antimicrobial Stewardship Principles for Haematological Cancer Patients

• Aim: to limit the (unnecessary) use of broad-spectrum antibiotics
Basic infection control principles for haematological cancer patients: CDC & Other Guidelines

Aim: to prevent spread of resistant organisms in the unit

- Isolation guidelines enforced
- Hand hygiene, gowns enforced
- Isolation criteria enforced vs. MRSA, ESBL ...
- Cohorting
- Ventilation of rooms

http://www.cdc.gov/hicpac/pubs.html
http://www.wip.nl/UK/document.htm
How might antimicrobial stewardship be implemented for haematological cancer patients-I?

Collaboration and support from microbiology lab, pharmacy, ID consultation service

– Surveillance and monitoring reports (6-monthly)

– Multidisciplinary protocols and algorithms on diagnosis, prevention and treatment

– Frequent multidisciplinary grand rounds

– Active rapid reporting of positive cultures

– Changing regimens

Local surveillance & monitoring in haematology centres

• What? How?
  – Antibiotic consumption
  – Resistance patterns of blood isolates of indicator organisms or top10 pathogens
  – Outcome of bacteraemias (ICU stay, total stay, mortality)

• Surveillance data guide empiric therapy for future patients with neutropenia and fever
How might antimicrobial stewardship be implemented in haematological cancer patients-II?

• Collaboration and support from microbiology lab, pharmacy, ID consultation service

• Policy choices to be made
  – *Antibiotic or antifungal prophylaxis or not?*
  – *Colonization cultures or not?*
    – In prophylaxis: probably yes!
    – Without prophylaxis: look for specific resistant pathogens

How might antimicrobial stewardship be implemented in haematological cancer patients-III?

- Collaboration and support from microbiology lab, pharmacy, ID consultation service
  - Selecting the empirical agent(s) for therapy
  - Reassessing empirical antibiotic therapy after 3 days
  - Strategies of de-escalation
  - Advising when to stop if prophylaxis is given & when to step down to oral prophylaxis

Slobbe et al. Eur J Cancer 2009
On empirical antibiotic therapy…

• What? How?
  – *Initiation of treatment prompted by:* fever, signs of (severe) sepsis; *not* CRP or other biomarkers
  – *Risk stratification* (low/high risk for infection, with *empirical therapy algorithm in place*)
  – *Individualisation of empirical therapy by risk assessment for multiresistant bacteria*
  – *No routine empirical glycopeptides*
  – *Algorithm for treatment duration should be present*

Clinical Practice Guidelines of IDSA, Freifeld et al., Clin Infect Dis 2011
Individualising drug selection by risk assessment for Gram –ve bacteria

- Independent risk factors for multi-resistant Gram-negative bacteria
  - *Previous antibiotics* (OR 3.57; 95% CI 1.63–7.80)
  - *Urinary catheter* (OR 2.41; 95% CI 1.01–5.74)

Individualising dosing regimens

- Haematology /critically-ill patients have large volumes of distribution/capillary leak syndrome

- Three patterns of activity among antibiotics
  - Concentration-dependent killing: aminoglycosides, fluoroquinolones and daptomycin
  - Time-dependent killing; little persistent effect: β-lactams
  - Time-dependent killing; prolonged persistent effect: azithromycin, tetracyclines (inc tigecycline) & clindamycin

Individualising aminoglycoside dosing

- Concentration-dependent drugs
- Best efficacy correlates: $C_{\text{max}}$/MIC or AUC/MIC ratios
- Dosing optimised by large (once-daily) doses, aiming for a $C_{\text{max}}$/MIC ratio of 8-12
- Nephrotoxicity is reduced by once-daily dosing
- Active therapeutic drug monitoring

Van Lent-Evers et al. Ther Drug Monit 1999
Buijk et al. Intensive Care Med 2002
Individualising β-lactam dosing

- Time-dependent drugs
- Best correlate for efficacy: time that serum level exceeds MIC (T>MIC),
  - Seek dose giving T>MIC of 40 to 70% of dose interval
- Optimise by continuous/prolonged infusion, if substance chemically stable at room temperature
  - e.g. piperacillin/tazobactam in extended infusion (4-5 h)
- Monitor PK variability (use individual MIC or local data)

Individualising glycopeptide dosing

- Best correlate of efficacy … debated!
- $\text{AUC}_{0-24}/\text{MIC}$ ratio $>400$ correlates with outcome, as do trough levels $>15 \text{ mg/L}$
- Use loading dose (up to 35 mg/kg) then dose q12h or by continuous infusion
- Nephrotoxic if combined with other nephrotoxic drugs
- Monitoring: ensure optimal trough levels

Summary of Recommendations for Haematological Centres

• Produce epidemiological data on blood isolates and colonization cultures (if prophylaxis is used) regularly

• Record infection-related outcome data (bacteraemia, candidaemias, attributable mortality)

• Discuss above data with ID / microbiologists / haematologists

• Develop multidisciplinary protocols and algorithms on diagnosis, treatment and prophylaxis for FUO
  – Provide ID training for haematologists and
  – Clinical haematology training for ID / microbiologists
  – Try to understand each other!