Bacterial Resistance in Haematology-ECIL 4 Study Groups & Participants

- **Epidemiology & resistance**
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- **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

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Epidemiology of Bacterial Infections & Antimicrobial Resistance in Haematological Cancer Patients

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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 haemato-oncology patients

Elting *et al. Clin Infect Dis* 1997
Ariffin *et al. Int J Infect Dis* 1999
Tumbarello *et al. Antimicrob Agents Chemother* 2006
Ortega *et al. J Antimicrob Chemother* 2009
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

Study	% treatments inappropriate		No of episodes; causative bacteria; ESBL rate
	ESBL +ve	ESBL -ve	
Gudiol et al. *J Antimicrob Chemother* 2010	65%	6%	135; *E. coli*;12.6%
Ortega et al. *J Antimicrob Chemother* 2009	52%	5%	4758; *E. coli*; 4%
Tumbarello et al. *Antimicrob Agents Chemother* 2006	50%	2%	147; *K. pneumoniae*; 30%

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

Cohen *et al. J Infect Dis* 1983, Tancrede *et al. J Infect Dis* 1985, Wingard *et al. Antimicrob Agents Chemother* 1986, Henning *et al. Pediatr Infect Dis J* 1996, El Amari *et al. Clin Infect Dis* 2001, Tsiatis *et al. Bone Marrow Transpl* 2004, Donskey *et al. Clin Infect Dis* 2006, Dubberke *et al. Bone Marrow Transpl* 2006, Martinez *et al. J Antimicrob Chemother* 2006, Salgado *et al. Bone Marrow Transpl* 2006, Tumbarello *et al. Antimicrob Agents Chemother* 2006, Narimatsu *et al. Bone Marrow Transpl* 2007, Oliviera *et al. Bone Marrow Transpl* 2007, Rolston *et al. Bone Marrow Transpl* 2007, Weinstock *et al. Biol Blood Marrow Transpl* 2007, Zirakzadeh *et al. Bone Marrow Transpl* 2008, Garnica *et al. Braz J Med Biol Res* 2009, Lopez-Dupla *et al. Am J Infect Control* 2009, Ortega *et al. J Antimicrob Chemother* 2009, Trecharichi *et al. J Infect* 2009, Gudiol *et al. J Antimicrob Chemother* 2010, Gudiol *et al. J Antimicrob Chemother* 2011, Tumbarello *et al. Antimicrob Agents Chemother* 2011

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

Viscoli *et al. Eur J Cancer* 1994, Elting *et al. Clin Infect Dis* 1997, Klastersky *et al. J Clin Oncol* 2000, Gonzalez-Barca *et al. Eur J Clin Microbiol Infect Dis* 2009

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

Defining commonly used 'escalation'

- Initial empirical therapy covers typical Enterobacteriaceae and *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-I

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

Tumbarello *et al. Antimicrob Agents Chemother* 2006
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*

Microorganism	No./total no. (%) receiving:		OR (95% CI)	*P*
	Combination	β-Lactam		
Non-ESBL *E. coli*	242/248 (98)	2,454/2,489 (99)	0.6 (0.2–1.7)	0.3
ESBL *E. coli*	21/28 (75)	62/122 (51)	2.9 (1.07–8.2)	0.02
Non-ESBL *K. pneumoniae*	62/63 (98)	393/420 (94)	4 (0.7–177)	0.2
ESBL *K. pneumoniae*	18/20 (90)	38/63 (60)	2 (1.2–4.2)	0.01
P. mirabilis	10/10 (100)	116/118 (98)		1
Salmonella spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8–20)	0.001
P. aeruginosa	133/143 (93)	201/319 (63)	7.8 (3.8–16)	<0.0001
Other nonfermenters	24/51 (47)	53/105 (51)	0.9 (0.4–1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

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

General strategy for the empirical treatment of febrile neutropenia-II

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 were 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 β-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 ≥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

Resistance type	Treatment
ESBL	*Carbapenem** ***BII***
Carbapenemase	*Colistin** ***CIII*** + β-Lactam +/- one of : *Tigecycline** ***CIII*** *or* *Aminoglycoside* ***CIII*** *or Fosfomycin* ***CIII***

*Freifeld *et al. Clin Infect Dis* 2011

Initial therapy in patients colonised or previously infected by resistant non-fermenters BIII

Bacteria	Treatment
β-lactam resistant *P. aeruginosa*	Colistin + *β-lactam* +\- fosfomycin
β-lactam resistant *Acinetobacter*	Colistin + *β-lactam* +/- tigecycline
S. maltophilia	Co-trimoxazole + *β-lactam* (preferable ticarcillin-clavulanate) +\- moxifloxacin

Hachem *et al. Antimicrob Agents Chemother* 2007
Falagas *et al. J Antimicrob Chemother* 2008
Peleg *et al. Clin Microbiol Rev* 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

Cometta *et al. Eur J Cancer* 2007
Freifeld *et al. CID* 2011

Q 3a: Actions at 24-72h in neutropenic patients in an escalation approach-I

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

Actions at 24-72h in neutropenic patients in an escalation approach-II

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 All

- **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 +…* **AII**
- 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**

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

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 ≤ **3d** for **FUO:** n=169
- Prophylaxis (continued): ciprofloxacin (±colistin po ± penicillin)

Patients (n=169)	Relapse of fever	Infection	Death
Neutropenia ≥ 10 d (mean 20.5 d)	**0**	**0**	**3 (2%)** 1 aspergillosis 1 severe typhlitis 1 progressive AML

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/mm^3 (n=11)

Patients	Relapse of fever	Infection	Death
Still neutropenic (n=49)	**9 (18%)**	-	**2 (4%)** 1 progressive lymphoma 1 invasive fungal infection
Neutrophils recovered (n=11)	**2 (18%)**	-	**0**

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

Patients (n=75)	**Relapse of fever**	**Infection**	**Death**
Stop antibiotics (n=36, 7 febrile) neutropenia mean 8.3 ± 5.4d	**2 (6%)**	**1 (3%)** *E. aerogenes* bacteraemia	**0**
Continue antibiotics (n=39) Neutropenia mean 9 ± 5.8 d	**3 (8%)**	**3 (8%)** 2 catheter-related bacteraemia (coag-neg staph) 1 periodontal abscess	**0**

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)

Patients (n=47)	Relapse of fever	Re-hospitalisation	Death
Neutropenia, median 10 d (2-39)	0	0	0

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 <u>all</u> clinical signs of infection are resolved*
- *At least 7 days, of which at least 4 days afebrile*

BIII

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

Giamarellou *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-ves, 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*)

Gudiol J *et al. Antimicrob Chemother* 2011

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 N*urs 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)*
- Candidemia

Sallah *et al. Cancer* 2001

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

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*

Kerremans *et al. J Antimicrob Chemother* 2008
Vos *et al. J Clin Microbiol* 2006

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

Clinical Practice Guidelines of IDSA, Freifeld *et al. Clin Infect Dis* 2011

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*

Cornelissen *et al. Clin Infect Dis* 1995
Slobbe *et al. Eur J Cancer* 2009
Clinical Practice Guidelines of IDSA Freifeld *et al. Clin Infect Dis* 2011

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)*

Gudiol J *et al. Antimicrob Chemother* 2011

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*

Scaglione & Paraboni. *Expert Rev Anti Infect Ther* 2006
van Zanten *et al. J Crit Care* 2008
Roberts *et al. Br J Clin Pharmacol* 2011

Individualising aminoglycoside dosing

- Concentration-dependent drugs
- Best efficacy correlates: C_{max}/MIC or AUC/MIC ratios
- Dosing optimised by large (once-daily) doses, aiming for a C_{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)

Robertset *et al. Int J Antimicrob Agents* 2010
Blondiaux *et al. Int J Antimicrob Agents* 2010

Individualising glycopeptide dosing

- Best correlate of efficacy … debated!
- $AUC_{0\text{-}24}$/MIC ratio >400 correlates with outcome, as do trough levels >15 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

Del Mar *et al. Intensive Care Med* 2007
Rybak *et al. Clin Infect Dis* 2009

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!*