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

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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 overuse, and the further selection of resistance.

Introduction

Hematology patients and hematopoietic stem cell transplant (HSCT) recipients undergoing intensive myelosuppressive or immunosuppressive treatment are at high risk for severe, life-threatening, bacterial infections. Thirteen to 60% of HSCT recipients develop bloodstream infection (BSI), which are associated with 12-42% mortality.[1-6] Although the prevalence and pattern of resistance varies among centers and countries, there is a growing problem of resistance to antibiotics worldwide, including in onco-hematologic and HSCT patients (*M. Mikulska et al., 2013, submitted for publication*).

Growing resistance to standard antibiotics leads to increased use of broad-spectrum regimens, including carbapenems and combinations, with consequent collateral damage, including the selection of carbapenem- and multidrug resistant (MDR) pathogens, predisposition to fungal infections and *Clostridium difficile*- associated diarrhea.

Building recommendations for empirical therapy in this era of growing resistance is challenging. Of special concern is the emergence of carbapenem-resistant Gram-negative bacteria, against which there are very few treatment alternatives, often just tigecycline, colistin, gentamicin and fosfomycin,[7] which all have efficacy, resistance and/or toxicity issues. Emerging resistance in Gram-positive pathogens is also worrying, although there are more new antimicrobial agents active against them, including daptomycin and linezolid.[8,9]

Experience with novel and 'resurrected' antibiotics in neutropenic patients is limited and is discussed in another paper on the European Conference on Infections in Leukemia (ECIL) series in this issue of the Journal.[10]

In order to minimize the empirical use of carbapenems and combination therapies, it is vital to optimize antibiotic choice, the application of pharmacokinetic (PK) and pharmacodynamic (PD) principles, and infection control. The ECIL has, therefore, developed its recommendations for the management of bacterial infections in hematology patients,11 particularly febrile neutropenic patients, in the light of

 doi:10.3324/haematol.2013.091025.
DE and MA contributed equally to this manuscript.
Manuscript received on May 24, 2013. Manuscript accepted on September 17, 2013.
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increasing resistance.

The draft of these guidelines was discussed by the Expert Group at the ECIL-4 meeting in September 2011 and considers: i) bacterial epidemiology in neutropenic patients; ii) risk factors for resistance; iii) escalation and de-escalation approaches; iv) the appropriate duration of empirical therapy; iv) non-conventional therapies against multi-resistant pathogens; and v) other issues on the management of bacterial infections in these patients. Up-dated slide sets from ECIL-4 covering these aspects are available on the websites of the four organizations involved in ECIL: the European Group for Blood and Marrow Transplantation, the European Organisation for Research and Treatment of Cancer, the Immunocompromised Host Society (ECIL), and the European Leukaemia Net.[12,13] This article summarizes the main ECIL recommendations on the initial empirical therapy of bacterial infections, but will also be valuable for the management of the many non-neutropenic but severely-immunosuppressed hematology patients.

Methods

The methodology of the ECIL conferences has been described previously.[11]

A working group of experts in the field of infectious diseases, microbiology or hematology was constituted, and reviewed the published literature in order to prepare proposals covering the following aspects:

1) empirical antibiotic therapy for febrile neutropenia in an era of resistance, and the influence of appropriate initial therapy on outcome. The main search terms used in these searches were: "antibiotic therapy" AND "bacterial resistance or resistant bacteria" AND "stem cell transplantation or bone marrow transplantation or hematological malignancy or cancer" AND "febrile neutropenia".

2) risk factors for resistant bacterial infections. The main search terms used were: "resistance" AND "bloodstream infection or bacteremia or bacterial infection" AND "stem cell transplantation or bone marrow transplantation or hematological malignancy or cancer".

3) duration of empirical therapy. The main search terms used were "antibiotic therapy" AND "stem cell transplantation or bone marrow transplantation or hematological malignancy or cancer" AND "febrile neutropenia" AND "duration therapy" AND "discontinuation antibiotics".

English language papers were selected from the PubMed database. These were analyzed, and recommendations were graded according to the criteria of the Infectious Disease Society of America (IDSA) (Table 1).[14]

Table 1. Infectious Diseases Society of America grading system for ranking recommendations.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥ 1 properly-randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Definitions of resistant bacteria

A bacterial isolate is considered non-susceptible if it tested resistant, intermediate or non-susceptible using the clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), Clinical and Laboratory Standards Institute (CLSI) or the US Food and Drug Administration (FDA). Definitions of "MDR" vary among authors and although no uniform definition was used, it usually presumed resistance to at least two antibiotics used in empirical therapy (3rd or 4th generation cephalosporins, carbapenems or piperacillin/tazobactam) or resistance to at least three of the following antibiotic classes: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones.[3,15-18]

Literature review

Importance of appropriate initial antibiotic therapy in febrile neutropenia

In a world of increasing resistance, standard empirical monotherapy with a 3rd or 4th generation cephalosporin or piperacillin-tazobactam may prove 'inappropriate' against an increasing proportion of Gram-negative pathogens. Inappropriate therapy is defined, in context, as not including at least one antibiotic active *in vitro* against the infecting microorganism(s).

Several studies demonstrate that onco-hematologic patients infected with extended-spectrum β–lactamase (ESBL)- or AmpC-β–lactamase-producing Enterobacteriaceae, MDR *Pseudomonas aeruginosa*, *Acinetobacter spp.* or *Stenotrophomonas spp.* are significantly more likely to receive an inadequate initial empirical antibiotic therapy than those with a susceptible strain (31-69% *vs.* 2-9%).[6,19-22] These studies also show that the time to appropriate therapy is much longer where the pathogen is resistant. Furthermore, many of these studies show that failure to cover Gram-negative pathogens, particularly ESBL producers and MDR *P. aeruginosa*, significantly and independently impairs outcomes in onco-hematology patients, increasing mortality and prolonging hospitalization.[6,21-26] Resistance to colistin has been independently associated with worse outcomes against carbapenem-resistant *Klebsiella pneumoniae*.[27] Nevertheless, there is no universal agreement on these associations, and some studies do not find statistically significant differences in outcome in relation to inappropriate therapy, including for infections due to carbapenem-resistant Enterobacteriaceae and non-fermenters.[20,28,29] There are also conflicting results regarding the influence of adequate initial appropriate therapy on the outcome of bacteremias due to vancomycin-resistant enterococci (VRE);[30-32] perhaps because these are not very pathogenic organisms, except maybe in a small subset of the most vulnerable neutropenic patients.[5,8,9,30,31,33-35]

Factors associated with bacterial resistance and/or a complicated clinical course that should influence empiric antibiotic choice

The most important risk factor for infection with resistant pathogens is prior colonization or infection by resistant organisms (Table 2). This applies for ESBL- and carbapenemase-producing Enterobacteriaceae; *A. baumannii, P. aeruginosa, S. maltophilia*; methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE[8,9,31,35-43] with recent reports also in the case of colistin-resistant *K. pneumoniae*. Administration of broad-spectrum antibiotics for prophylaxis and management of fever and neutropenia within months, especially within the last month, before current infectious episode, may be associated with subsequent infection with resistant bacteria.[19-22,44-47] Especially important in this context is the potential role of fluoroquinolone prophylaxis in selecting for, e.g. MRSA, *Clostridium difficile*, ESBL-producing and fluoroquinolone-resistant *Enterobacteriaceae*.[6,21,48-52] Other risk factors for infection with resistant bacteria are listed in Table 2.[6,9,18-22,26,31,35,37-43,51,53,54] In addition, and, independently of the risk of bacterial resistance, the patient's clinical presentation may also predict a severe clinical course or further deterioration.[24,55-57]

The physician's clinical judgment is pivotal in this evaluation, and in any modification to be made in the antimicrobial regimen.

Duration of antibiotic therapy in febrile neutropenia

Continuation of empirical broad-spectrum antibiotics until neutrophil recovery has been the standard approach, especially for high-risk patients with neutropenia persisting for more than seven days. This is based on a study by Pizzo *et al*. from 1979 which included very few patients and showed that stopping antibiotics on Day 7 of neutropenia resulted in significantly more infections and higher mortality (2 of 17 *vs.* 0 of 16 when antibiotics were administered until neutrophil recovery).[58] A later report maintained the empirical therapy for at least two afebrile days in patients with increasing neutrophil count or seven days in patients with persistent neutropenia.[59] Two more recent prospective studies in children found that discontinuation of antibiotics before marrow recovery did not increase fatality due to bacterial infections. In the first study, children considered to be at low risk for bacterial infections (no identifiable focus, hemodynamic stability, negative admission cultures, and serum C-reactive protein (CRP) < 40 mg/L on Days 1 and 2; normal <10) were randomized on Day 3 of empirical antibiotic therapy to stop antibiotic therapy (n=36) or to continue (n=39) until the resolution of fever and neutropenia. The recurrence of fever was similar in both groups (6-8%) and all survived.[60] In the second study, which was double blind and placebo-controlled, children at low risk for bacterial infection were randomized after 48-120 h of empirical therapy to placebo or to step-down to oral cefixime plus cloxacillin for up to 14 days or until neutrophil recovery. There was no significant difference in frequency of recurrence of fever between the two groups (6% in placebo *vs.* 14% in the antibiotic group), and all the children survived.[61] Once again, only children at low risk for bacterial infection were included, defined as being afebrile for more than 24 h, having negative blood cultures and lacking signs of clinical sepsis. Those with fever for over 96 h after starting intravenous (i.v.) antibiotics, underlying cancer not in remission, or co-morbid conditions necessitating continued inpatient stay were excluded. In another randomized prospective study, designed to compare cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia, antibiotic treatment was safely stopped 48 h after defervescence irrespective of the neutrophil count in a subgroup of 31 patients, of whom 23 remained neutropenic.[62]

Several further prospective and retrospective observa-

Table 2. **Major factors to consider when choosing empirical therapy for febrile neutropenic patients, based on the literature review (6, 8, 9, 18-24, 26, 31, 35-43, 51, 53, 54).**

Risk factors for infection with resistant bacteria	Risk factors for a complicated clinical course
1. Patient's prior colonization or infection by resistant pathogens, particularly:	1. Shock, hemodynamic instability, hypotension, sensory loss
- ESBL or carbapenemase- producing Enterobacteriaceae	2. Localized infection (e.g. pneumonia, enteritis, central venous catheter infection)
- Resistant non-fermenters: *Acinetobacter baumannii, Pseudomonas aeruginosa and Stenotrophomonas maltophilia*	3. Inpatient status
- MRSA, especially with vancomycin MICs ≥2 mg/L	4. Prolonged and severe aplasia
- Vancomycin-resistant enterococci	5. Co-morbidities (bleeding, dehydration, organ failure, chronic illness)
2. Previous exposure to broad-spectrum antibiotics, especially but not limited to 3rd generation cephalosporins*	6. Advanced age (over 60 years)
3. Serious illness (e.g. end-stage disease, sepsis, pneumonia)	
4. Nosocomial infection	
5. Prolonged hospital stay and/or repeated hospitalizations	
6. Urinary catheters	
7. Older age	
8. Intensive care unit stay	

*ESBL: extended-spectrum –lactamase; MRSA: methicillin-resistant Staphylococcus aureus. *Administration of broad-spectrum antibiotics for prophylaxis and management of fever and neutropenia within months, especially within the last month, before current infectious episode, may be associated with subsequent infection with resistant bacteria (18-21, 43-46). Especially important in this context is the potential role of fluoroquinolone prophylaxis in selecting for e.g. MRSA, Clostridium difficile, ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae.[6,21,48-52]*

tional studies in children and adults also show that, although the discontinuation of antibiotics is associated with relapse of fever in a few neutropenic patients, there is no increase in mortality, providing the antibacterials are re-started immediately if fever recurs.[63-71] These studies included patients with prolonged neutropenia, and, therefore, classically judged to be at high risk of bacterial infection.[63-65,67-75] Evidence of bone marrow recovery was required before stopping antibiotics in only a minority of these studies.[63-65,67,70] In two observational studies, empirical therapy was even stopped in neutropenic patients regardless of continued fever.[71,75]

We may also gain insight into the optimal duration of empirical antibiotic therapy from trials comparing different antibiotic combinations. Most studies report that treatment in patients for fever of unknown origin (FUO) or clinically (CDI) and/or microbiologically (MDI) documented infections was continued for at least seven days, with at least 4-5 afebrile days.[62,76-83] although, in one study, empirical therapy for FUO was continued for only 48 h after defervescence.[62] These studies excluded severely-ill patients, such as those with severe renal or hepatic impairment, septic shock, central nervous system infection, lung infiltrates, high probability of death in 48 h and blast crisis of chronic myeloid leukemia.[76-81]

ECIL-4 guidelines

ECIL-4 advocates implementation of the principles of escalation and de-escalation for management of febrile neutropenia.

Definitions of escalation and de-escalation approaches for the management of febrile neutropenia

Escalation

An escalation strategy is defined, in context, as giving an initial empirical monotherapy regimen (e.g. ceftazidime, cefepime or piperacillin-tazobactam) that covers most *Enterobacteriaceae* and *P. aeruginosa* except those that produce ESBLs or carbapenemases, or which are otherwise MDR. Notably, ceftazidime has limited coverage for Gram-positive organisms (methicillin-susceptible staphylococci, viridans group streptococci, *Streptococcus pneumoniae*). If the patient deteriorates, or a resistant pathogen is isolated, therapy is 'escalated' to an antibiotic or a combination with a broader spectrum: e.g. a carbapenem plus an aminoglycoside.

De-escalation

A de-escalation strategy is defined as giving a very broad initial empirical regimen, aiming to cover even highly resistant pathogens, e.g. ESBL-producing *Enterobacteriaceae* and MDR *P. aeruginosa*. Examples include the early use of carbapenems (imipenem or meropenem), or colistin in combination with a β–lactam, or an aminoglycoside with a β–lactam, with or without a further agent against MDR Gram-positive cocci. Other examples are noted below. Therapy is then de-escalated to a narrower-spectrum therapy once the microbiology laboratory does not report on resistant pathogens or identifies a pathogen and defines its susceptibility profile.

Escalation and de-escalation approaches are well-established in intensive care units for the treatment of hospital-acquired pneumonia (especially ventilator-associated pneumonia) and severe sepsis, and de-escalation is preferred for patients at high risk of having MDR pathogens.[84-86] There are very few data on de-escalation strategies in neutropenic patients after identification of a clinically relevant pathogen, but no data on de-escalation when no pathogen has been identified.[87]

Key criteria in choosing an escalation or de-escalation approach

The choice of empirical antibiotic therapy should depend, first, upon the local bacterial epidemiology and prevalent resistance patterns, which varies hugely around Europe (*M. Mikulska, et al., 2013, submitted for publication*), and, secondly, on patient-related factors, which may indicate the need for broader-spectrum coverage than for the generality of patients (Table 3). Although, in terms of efficacy, carbapenems are graded AI,[14] they should be avoided as empirical agents in uncomplicated patients without risk factors for resistant bacteria, so as to preserve their activity for seriously-ill patients.

Situations in which specific de-escalation protocols should be used as an initial approach are summarized in Table 4. As colonization with resistant bacteria is a major predictive factor for infection with such bacteria, initial (at admission) and regular screening, once or twice weekly, for gastrointestinal colonization with these organisms should be considered in centers with a high prevalence of resistance.[9,35,39,42,43,88] Nevertheless blood cultures should always be taken in cases of fever, aiming to identify the pathogen and its resistances. Previous resistant colonizing pathogens should not be presumed to be a current cause of infection without microbiological confirmation.

Determining a cut-off prevalence of resistance at which a unit should adopt a de-escalation approach is very difficult, and the lack of literature data precludes any recommendation along these lines. Moreover: i) the percentage of resistance rate in a particular pathogen may be high, but the incidence of infections with this pathogen in the ward may be low; ii) the risk of resistant pathogens varies with the patient and their treatment history; and iii) the attributable morbidity due to infection with resistant bacteria should be taken into consideration while deciding upon the approach for initial therapy. Centers where infections due to resistant pathogens are frequently seen at the onset of febrile neutropenia should review their antibiotic stewardship program and infection control measures: de-escalation should never be used as an alternative to infection control in settings where resistance is prevalent. If multiple patients have infections with similarly resistant bacteria, the likelihood of cross-infection should be investigated, with microbiological typing if possible. If cross-infection is confirmed, appropriate control measures (isolation, cohorting, reinforcement of hygienic precautions, staff education, surveillance cultures and use of alert systems) should be deployed.

Patients must be examined daily for clinical condition and possible infectious focus, and microbiological exams must be reviewed with the laboratory daily. In case no microbiological documentation is found, initial empirical treatment should be reviewed at 72-96 h regardless of whether an escalation or de-escalation approach is being employed, unless the patient deteriorated earlier or the microbiological results justify an earlier modification, as discussed below.

Table 3. ECIL-4 recommendation for initial empirical treatment in high-risk patients (anticipated to have neutropenia for more than 7 days), by indication and escalation or de-escalation approach.

	Escalation approach	De-escalation approach
Indication B-II for all		
	1) Uncomplicated presentation; 2) No known colonization with resistant bacteria; 3) No previous infection with resistant bacteria; 4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia;	1) Complicated presentations; 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy		
	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include†: - Ticarcillin-clavulanate‡ - Cefoperazone-sulbactam‡ - Piperacillin + gentamicin§	1) Carbapenem monotherapy **BII**¶ 2) Combination of anti-pseudomonal β–lactam + aminoglycoside or quinolone‖ (with carbapenem as the β–lactam in seriously ill patients) **BIII** 3) Colistin + β–lactam ± rifampicin **BIII**¶ 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII

In a setting of high ESBL prevalence, ceftazidime, and cefepime should not be used as empirical therapy for febrile neutropenia* ***BII**. †Carbapenems should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients although in terms of efficacy in first-line treatment of febrile neutropenia they are graded AI. ‡Are not available in many European countries. §A combination of piperacillin + gentamicin has been successfully used in some centers in an escalation approach, although it evidently does not meet the definition of monotherapy. ¶In terms of efficacy as first-line treatment of febrile neutropenia carbapenems are graded AI. ‖Fluoroquinolones are recommended as possible part of a combination therapy only in patients who are not receiving fluoroquinolones prophylaxis. [88] for Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia; CIII for carbapenem-resistant Enterobacteriaceae. Notably, a randomized, open-label clinical trial published very recently, which enrolled 210 patients with life-threatening infections due to extensively drug resistant A. baumannii (being sensitive to colistin only) showed that 30-day mortality was not reduced by addition of rifampicin to colistin.[88]*

Recommended strategies at 72-96 hours in various circumstances when using an escalation or de-escalation approach unless the patient deteriorated earlier or the microbiological results justify an earlier modification

The further management of febrile neutropenic patients should be based on their clinical course and microbiological results.

a) If a pathogen is identified

Whatever the initial approach was (escalation or de-escalation) the patient should be treated according to the organism identified (assuming it is a plausible pathogen) using narrower-spectrum agents, guided by *in vitro* susceptibility tests, including minimum inhibitory concentrations (MIC) when available, and based on knowledge on drugs with specific activities **AI**.

Consultation with an infectious diseases expert/clinical microbiologist is recommended, if available.

b) Escalation approach, no bacteria documented (Figure 1)

Broadening of initial antibiotic regimen is recommended only for a deteriorating patient. The appropriateness of the antibiotic choice for CDI should be assessed. It is important to emphasize that continuing fever in a stable patient is not a criterion to escalate antibiotics, but diagnostic efforts should be continued, including repeated blood and other cultures (sampling any focus repeatedly at the discretion of the physician), and possibly including seeking fungal or viral infections, serum fungal diagnostic tests (galactomannan or β-(1-3)-D glucan assays), chest X-rays and eventually computed tomography (CT) scans of the lungs, abdomen, sinuses and brain. The number of blood cultures and amount of blood that should be obtained were not discussed in ECIL, but is addressed in the IDSA detailed recommendation. Briefly, two sets of blood cultures (via periphery and catheter, if present; or via two separate venipunctures if no central catheter is present) should be obtained. Blood culture volumes should be limited to less than 1% of total blood volume.[14]

c) De-escalation approach, no bacteria documented (Figure 2)

If a de-escalation approach was chosen based on severe illness at presentation (e.g. septic shock) and the patient has stabilized on treatment, no change in initial therapy is recommended, even if blood or other cultures remain negative.

If a de-escalation approach was chosen based on known colonization or previous infection with resistant bacteria and the patient was stable at presentation, streamlining of initial therapy should be considered (Figure 2) including: i) discontinuation of any aminoglycoside, quinolone, colistin or any antibiotic directed against resistant Gram-positive pathogens, if given in combination; or ii) for patients with FUO initially treated with a carbapenem, change to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam or ticarcillin-clavulanate (the last two agents are not available in many European countries). Diagnostic efforts should be continued, including repeated cultures (sampling any focus repeatedly at the discretion of the physician) and possibly including seeking fungal or viral infections, serum fungal diagnostic tests (galactomannan or β-(1-3)-D glucan assays), chest X-rays and eventually a CT scan of the lungs, abdomen, sinuses and brain.

Duration of antibacterial treatment

Empirical antibiotics can be discontinued after 72 h or more of intravenous administration in patients who have been hemodynamically stable since presentation and have been afebrile for 48 h or more, irrespective of their neutrophil count or expected duration of neutropenia **BII**. The patient should be kept hospitalized under close observation for at least a further 24-48 h if the patient is still neutropenic when antibiotic therapy is stopped. If fever recurs, antibiotics should be re-started urgently, after obtaining blood cultures and clinical evaluation. Centers that give prophylactic antibacterial agents should consider renewing this regimen upon discontinuation of the empirical therapy if the patient is still neutropenic **CIII**.

Duration of antibacterial-targeted treatment in MDI with or without bacteremia is described in the companion manuscript in this issue of the Journal.[10]

Conclusions

Our recommendations for empirical antibacterial agents focus on the first days of the febrile neutropenia episodes and do not deal with FUO later during hospitalizations, nor with antifungal and antiviral therapy.

Owing to increasing resistance and the very limited arsenal of new agents, especially against Gram-negative pathogens, carefully designed antibiotic regimens are obligatory for febrile neutropenic patients. Initial empirical antibiotic treatment should reflect; i) the department/unit epidemiology; ii) the patient's risk factors for resistant bacteria; and iii) the patient's risk factors for a complicated clinical course. Epidemiological data should be obtained through continuous and up-dated monitoring of local pathogens and their resistances.

The standard approach for febrile neutropenia without a severe presentation should be escalation. The main con-

Table 4. De-escalation approach: ECIL-4 guidelines for indications of initial specific regimens.

Situations for which carbapenems are indicated as the first-line regimen
1. Seriously-ill patients e.g. *presentation with septic shock* **BII**
or
2. Known colonization or previous infection with **BII**:
a. *ESBL-producing Enterobacteriaceae*
b. *Gram-negatives resistant to narrower-spectrum β–lactams*
or
3. Centers with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia BIII
Should also prompt infection control review

Situations in which combination with an aminoglycoside is indicated as the first-line regimen BIII for all
1. Seriously-ill patients e.g. *severe sepsis, septic shock or*
2. If resistant non-fermenters (*Pseudomonas aeruginosa or Acinetobacter* spp.) are likely, based upon:
a. *Local epidemiology*
b. *Previous colonization or infection with these pathogens*
c. *Previous use – during the last month – of carbapenems*

Situations in which antibiotics *vs.* resistant Gram-positive bacteria is indicated to combine in the first-line regimen CIII for all
1. Hemodynamic instability or other evidence of severe sepsis, septic shock or pneumonia *or*
2. Colonization with MRSA or VRE *or*
3. Suspicion of serious catheter-related infection *e.g. chills or rigors with infusion through catheter and cellulitis around the catheter exit site or*
4. Skin or soft-tissue infection at any site

ESBL: extended spectrum β–lactamase; MRSA: methicillin-resistant Staphylococcus aureus; VRE: vancomycin-resistant enterococci.

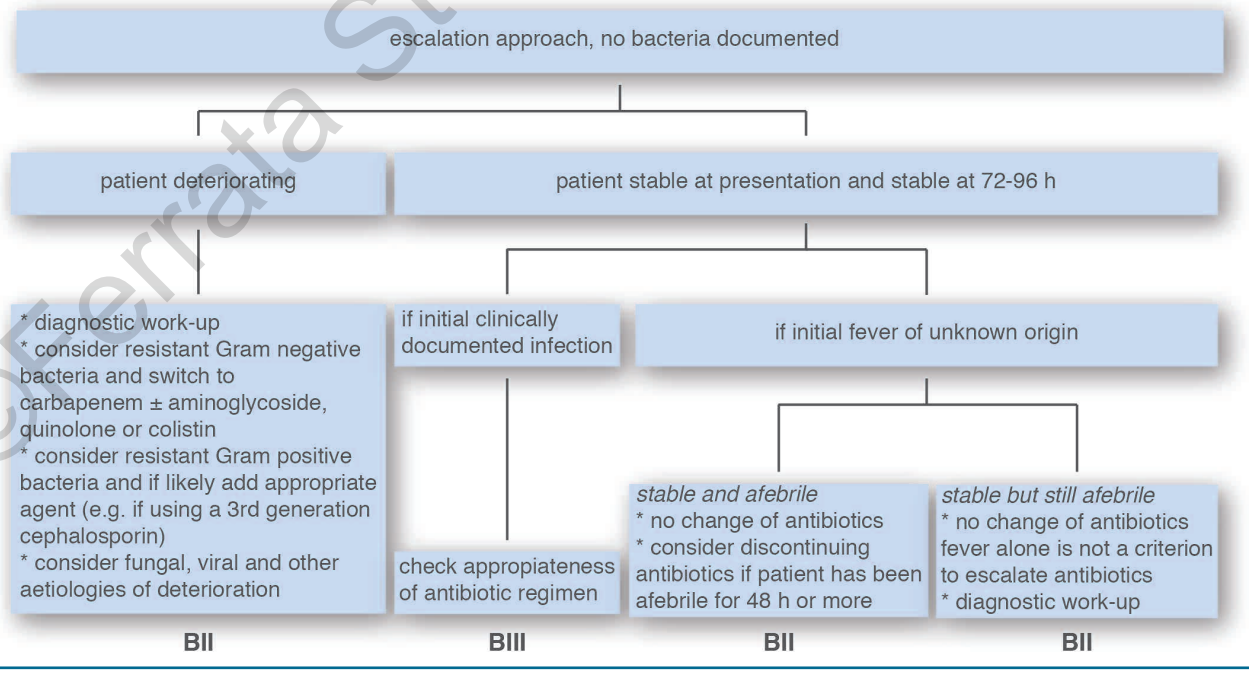

Figure 1. Recommended strategies in various circumstances when using an escalation approach.

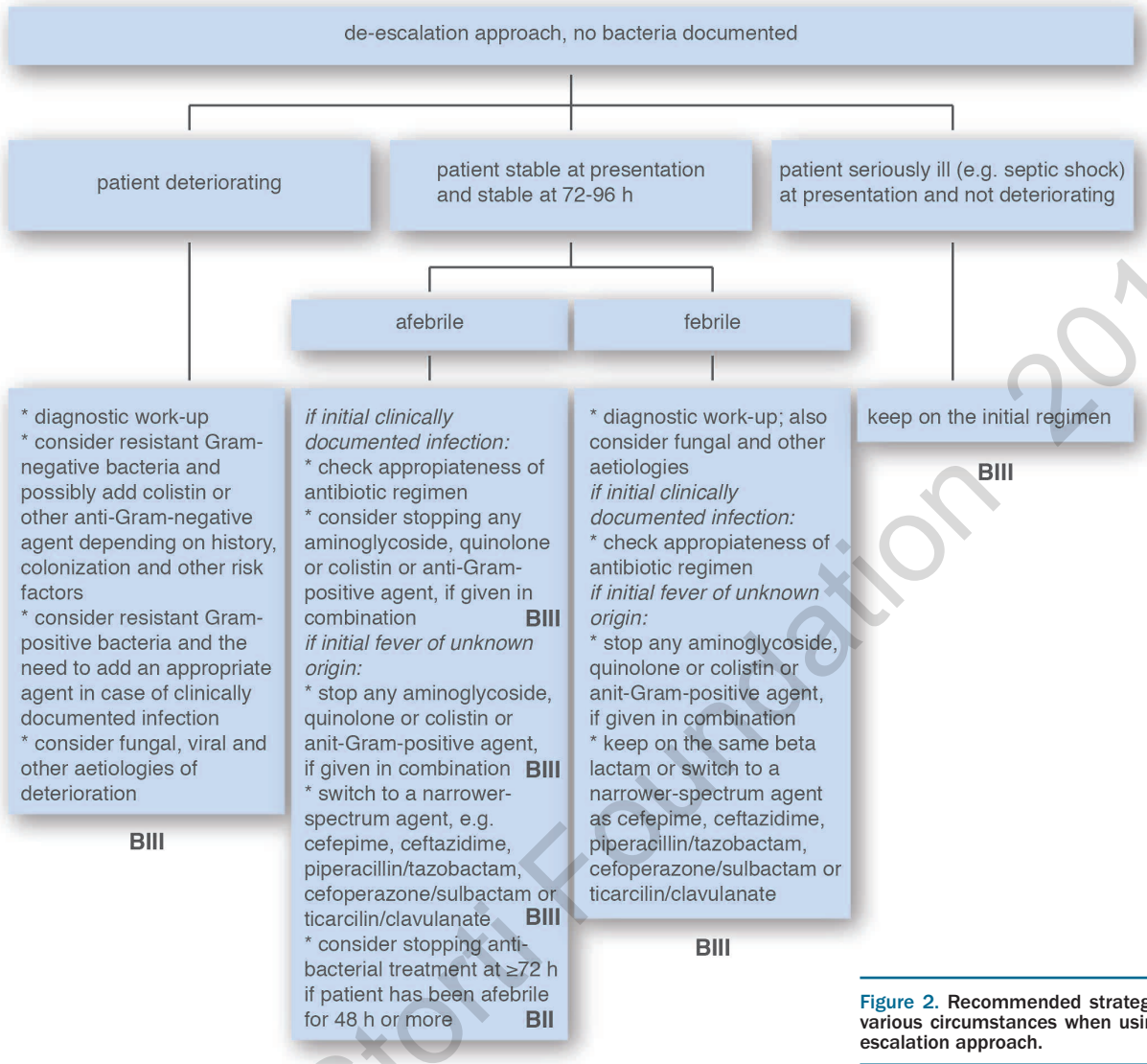

Figure 2. Recommended strategies in various circumstances when using de-escalation approach.

cern is that, if the regimen fails to cover the pathogen present, the prognosis is significantly worsened. Nevertheless, this approach avoids early (and usually unnecessary) use of the broadest-spectrum antibacterials, including carbapenems and combinations, and consequently minimizes collateral damage, e.g. selection of carbapenem resistance, as well as reduced toxicity and lower cost.

The current recommendations define the situations in which a de-escalation approach seemed to be justified to the expert panel. De-escalation should provide a better chance to achieve appropriate cover in the first 48 h, before microbiology data become available, especially where resistance is prevalent. The main concern is that the increased use of hitherto "reserved" broad-spectrum antibiotics will select for more resistance, including to carbapenems. Moreover, physicians frequently hesitate to change a regimen that has already achieved clinical improvement. Discontinuation after two days of vancomycin or other coverage for Gram-positive organisms is also recommended in the IDSA guidelines when there is no evidence for a Gram-positive infection.[14] Current IDSA guidelines recommend that the initial empirical regimen in FUO should continue until there are clear signs of marrow recovery, defined as a neutrophil count more than 0.5×10^9/L.[14] Based on the literature, the ECIL-4 panel suggests discontinuation of antibiotics in FUO after 72 h, under certain conditions, irrespective of neutrophil count and expected duration of neutropenia. This must be managed with caution, but it is recommended to minimize antibiotic use and its contingent collateral damage.

Acknowledgments

The authors would like to thank the participants of the ECIL4 meeting:

Hamdi Akan, Murat Akova, Turkey; Diana Averbuch, Israel; Rose-Mary Barnes, United Kingdom; Nicole Blijlevens, The Netherlands; Thierry Calandra, Switzerland; Elio Castagnola, Simone Cesaro, Italy; Catherine Cordonnier, France; Oliver Cornely, Germany; Jean-Hughes Dalle, France; Rafael de la Camara, Spain; Emma Dellow (Gilead Sciences) United Kingdom; Peter Donnelly, The Netherlands; Lubos Dgrona, Slovakia; Hermann Einsele, Germany; Dan Engelhard, Israel; Bertrand Gachot, France; Corrado Girmenia, Italy; Andreas

Groll, Germany; Ingeborg Gyssens, The Netherlands; Werner Heinz, Germany; Raoul Herbrecht, France; Hans Hirsch, Switzerland; William Hope, United Kingdom; Petr Hubacek, Czech Republic; Chris Kibbler, United Kingdom; Galina Klyasova, Russia; Sean Knox (Astellas Pharma), United Kingdom; Michal Kouba, Czech Republic; Catherine Lagrou, Belgium; Thomas Lernbecher, Germany; Per Ljungman, Sweden; Johan Maertens, Belgium; Oscar Marchetti, Switzerland; Rodrigo Martino, Spain; Georg Maschmeyer, Germany; Tamas Masszi, Hungary; Suzanne Matthes-Martin, Austria; Małgorzata Mikulska, Alessandra Micozzi, Italy; Bilal Mohty, Switzerland; Patricia Munoz, Spain; David Nadal, Christina Orasch, Switzerland; Zdenek Racil, Czech Republic; Patricia Ribaud, France; Valérie Rizzi-Puechal (Pfizer), France; Emmanouil Roilidis, Greece; Janos Sinko, Hungary; Jan Styzynski, Poland; Alina Tanase, Hungary; Mario Tumbarello, Italy; Paul Verweij, The Netherlands; Claudio Viscoli, Italy; Kate-Nora Ward, United Kingdom; Aafje Warris, The Netherlands; Craig Wood (Merck), USA.

The authors would like to thank Jean-Michel Gosset and the staff of KOBE, group GL Events, Lyon, France, for the organization of the meeting.

Funding

The ECIL-4 meeting has been supported by unrestricted educational grants from Astellas Pharma, Gilead Sciences, Merck, Novartis, and Pfizer.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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