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8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation

Thomas Lehrnbecher, Dina Averbuch, Elio Castagnola, Simone Cesaro, Roland A Ammann, Carolina Garcia-Vidal, Jukka Kanerva, Fanny Lanternier, Alessio Mesini, Malgorzata Mikulska, Dorothea Pana, Nicole Ritz, Monica Slavin, Jan Styczynski, Adilia Warris, Andreas H Groll, on behalf of the 8th European Conference on Infections in Leukaemia

Paediatric patients with cancer and those undergoing haematopoietic cell transplantation are at high risk of bacterial infections. The 8th European Conference on Infections in Leukaemia (ECIL-8) convened a Paediatric Group to review the literature and to formulate recommendations for the use of antibiotics according to the European Society of Clinical Microbiology and Infectious Diseases grading system. The evaluation of antibacterial prophylaxis included mortality, bloodstream infection, febrile neutropenia, emergence of resistance, and adverse effects as endpoints. Initial antibacterial therapy and antibiotic de-escalation or discontinuation focused on patients with a clinically stable condition and without previous infection or colonisation by resistant bacteria, and on patients with a clinically unstable condition or with previous infection or colonisation by resistant bacteria. The final considerations and recommendations of the ECIL-8 Paediatric Group on antibacterial prophylaxis, initial therapy, and de-escalation strategies are summarised in this Policy Review.

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For the full scientific faculty of the 8th European Conference on Infections in Leukaemia meeting see **Online** for appendix p 6

Pediatric Hematology and Oncology, Hospital for Children and Adolescents, Johann Wolfgang Goethe University, Frankfurt, Germany (Prof T Lehrnbecher MD); **Department of Pediatrics, Hadassah Hebrew University Medical Center, Jerusalem, Israel** (Prof D Averbuch MD); **Infectious Diseases Unit, Department of Pediatrics, IRCCS Istituto Giannina Gaslini, Genoa, Italy** (Prof E Castagnola MD, A Mesini MD); **Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata, Verona, Italy** (Prof S Cesaro MD); **Pediatric Hematology and Oncology, Department of Pediatrics, Inselspital, Bern University Hospital, Bern, Switzerland** (Prof R A Ammann MD); **Department of Infectious Diseases, Hospital Clinic of Barcelona** (Prof C Garcia-Vidal MD), **IDIBAPS** (Prof C Garcia-Vidal), **University of Barcelona, Barcelona, Spain; Division of Hematology-Oncology and Stem Cell Transplantation, New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland** (Prof J Kanerva MD); **Infectious Diseases Unit, Necker-Enfants Malades Hospital, Assistance Publique—Hôpitaux de Paris, University of Paris, Paris, France** (Prof F Lanternier MD);

Introduction

Paediatric patients with leukaemia or lymphoma and those undergoing haematopoietic cell transplantation (HCT) are at high risk of bacterial infections, which can be associated with high morbidity and mortality. The incidence of these infections depends on various factors, such as the underlying disease (eg, the incidence of bacterial infections is higher in patients with acute myeloid leukaemia than in patients with acute lymphoblastic leukaemia) or the phase of treatment (eg, the incidence of bacterial infections is higher in the induction therapy phase than in the consolidation phase).[1,2] Depending on the study, the incidence of bloodstream infections in these patient populations can exceed 50%, with an overall mortality of 6% and higher.[2,3] Similarly to what happens with adults, resistance to antibacterial agents in paediatric patients is increasing, but varies widely across institutions and countries.[4,5] Data from 39 European haematology centres showed infection incidence rates of 15–24% for extended-spectrum β-lactamase-producing Enterobacteriaceae, 5–14% for aminoglycoside-resistant Gram-negative bacteria, and 5–14% for carbapenem-resistant *Pseudomonas aeruginosa* in adult and paediatric patients.[6] Importantly, antibiotic resistance adversely affects the overall survival of patients with haematological malignancies and after HCT.[7]

The high incidence of bacterial infections in patients with neutropenia and the emergence of antibiotic resistance has led to an increased use of broad-spectrum antibiotics, including carbapenems, either as monotherapy or as combination therapy.[8] To optimise the use of antibiotics, evidence-based guidelines (which need a regular update) have been developed for patients with cancer who are immunocompromised or have undergone HCT.[8–10] Unfortunately, these guidelines are not specific for children and adolescents, who can differ from adult patients in several aspects. For example, children have a different spectrum of cancer diagnoses compared with adults, and are consequently treated with different treatment protocols, which mostly have higher dose intensity.[11] Moreover, children usually have fewer comorbidities than adults, and the haematopoietic and immunological recovery also differs between children and adults.[11] Finally, safety and pharmacokinetic data for paediatric patients is not always available for many antibiotics. All these factors have important implications for the choice and use of antibiotics for prophylaxis and treatment. Several paediatric-specific guidelines that cover some aspects of antibacterial drug administration to children with neutropenia have been published.[12,13] Importantly, these guidelines used a different methodological approach for development because they are solely based on the results of randomised trials and do not consider information such as approval status by the European Medicines Agency or the US Food and Drug Association.

In this Policy Review, we provide the recommendations for the use of antibiotics in children and adolescents with cancer and those undergoing HCT that were developed at the 8th European Conference on Infections in Leukaemia (ECIL-8) meeting, and we summarise the background and considerations on which these recommendations are based.

Guideline development

The major goal of the ECIL is to develop evidence-based guidelines for the management of infectious complications in patients with a haematological malignancy

Division of Infectious Diseases, Department of Health Sciences, University of Genoa, Genoa, Italy (Prof M Mikulska MD); **IRCCS Ospedale Policlinico San Martino, Genoa, Italy** (Prof M Mikulska); **Department of Medicine, European University of Cyprus, Nicosia, Cyprus** (D Pana MD); **Pediatric Infectious Diseases and Vaccinology, University of Basel Children's Hospital, Basel, Switzerland** (N Ritz MD); **Department of Infectious Diseases and National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia** (Prof M Slavin MD); **Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland** (Prof J Styczynski MD); **MRC Centre for Medical Mycology, University of Exeter, Exeter, UK** (Prof A Warris MD); **Infectious Disease Research Program, Center for Bone Marrow Transplantation, Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany** (Prof A H Groll MD)

Correspondence to: Prof Thomas Lehrnbecher, Pediatric Hematology and Oncology, Hospital for Children and Adolescents, Johann Wolfgang Goethe University, Frankfurt D-60590, Germany **thomas.lehrnbecher@kgu.de**

See Online for appendix

For the **ECIL-8 website** see http://www.ecil-leukaemia.com/

Panel 1: **European Society of Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology grading system for ranking recommendations**

Grade of recommendation

Grade A

The guideline group strongly supports a recommendation for use.

Grade B

The guideline group moderately supports a recommendation for use.

Grade C

The guideline group marginally supports a recommendation for use.

Grade D

The guideline group supports a recommendation against use.

Level of evidence

Level I

Evidence from at least one properly designed randomised, controlled trial

Level II

Evidence from at least one properly designed clinical trial without randomisation, from cohort or case-controlled analytical studies (preferably from more than one centre), from multiple time series, or from striking results of uncontrolled experiments. Added index for source of level II evidence:

- r: meta-analysis or systematic review of a randomised controlled trial
- t: transferred evidence (ie, results from different patient cohorts, or similar immune status situation
- h*: historical control as comparator group
- u: uncontrolled trials
- a*: published abstract presented at an international symposium or meeting

Level III

Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*Not used in this Policy Review because not applicable to any recommendation of this guideline.

or undergoing HCT. The guideline development methodological approach has been previously described.[14] A group of 16 experts, including paediatric haematologists and oncologists, transplantation experts, and infectious disease specialists, were identified by the two designated group leaders (TL and AHG) from publications on bacterial infections and antibiotic use in paediatric patients with cancer. Methodological expertise and geographical location were also considered for the selection of experts. This group of experts convened at the 8th ECIL conference (Sept 19–21, 2019) to develop guidelines on antibiotic use in children with neutropenia, covering antibiotic prophylaxis in the era of increasing antibiotic resistance, and guidance on empirical antibiotic therapy and de-escalation and discontinuation.[12,13]

Recommendations were elaborated on the basis of the retrieved data and graded according to the European Society of Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology grading system (panel 1).[15] A strong recommendation implies that it can be adapted as a policy in most situations, whereas in weaker recommendations, different choices are likely to be appropriate for different patients, and the strategy should be tailored to the individual patient.[16] All 56 participants of the 8th ECIL conference (54 from Europe, and one each from the USA and Australia; appendix p 6) received the literature analysis and proposed recommendations ahead of the meeting. In a consensus development conference, moderated by two members of the ECIL-8 group (MM and MS) the proposed guidelines were discussed and revised until a consensus, which was defined as simple majority (>50%), was reached. However, all group members had to find the resolution acceptable. The final version was approved on Oct 11, 2019, and the slide set was made available without restriction on the ECIL website on Dec 2, 2019. To include the most up-to-date information on novel antibiotics in the paediatric setting, an additional literature search was done on May 15, 2020.

Prophylaxis of bacterial infections

One approach to reduce bacterial infections and their negative consequences is to use antibiotics as prophylaxis. Of note, the use of these agents is potentially associated with drug toxicity and with the emergence of antibiotic resistance. Therefore, antibiotic efficacy, measured by the reduction of overall and infection-related mortality, bacterial bloodstream infections, and febrile neutropenia, should be weighed against the potential negative consequences of antibiotic use.

The ECIL-8 group does not recommend routine antibacterial prophylaxis for paediatric patients with lymphoma, acute leukaemia, relapsed acute leukaemia, or patients with neutropenia during the pre-engraftment stage of HCT (recommendation 1; grade D, level of evidence III). Of the 292 references on antibacterial prophylaxis retrieved by the literature search, four randomised studies analysed the efficacy of antibacterial prophylaxis in children undergoing therapy for haematological malignancies or solid tumours.[17–20] The strategies used were: levofloxacin given for two chemotherapy cycles;[20] ciprofloxacin during induction therapy, or from start of chemotherapy until an absolute neutrophil count of 1000/μL was reached;[18,19] or amoxicillin–clavulanate during a period of neutropenia.[17] For patients undergoing HCT, levofloxacin was given from day –2 until engraftment.[20] In these studies, antibacterial prophylaxis did not significantly reduce

mortality in children with acute leukaemia and those undergoing HCT (0–6% in the control groups). Two studies with a low rate of bacteraemia in the control groups (6–10%) did not find a significant reduction in bloodstream infection,[17,19] whereas one study reported that levofloxacin prophylaxis reduced the rate of bacteraemia in relapsed acute lymphoblastic leukaemia (19% with prophylaxis *vs* 50% without prophylaxis; p=0·007) and acute myeloid leukaemia (23% with prophylaxis *vs* 40% without prophylaxis; p=0·05).[20] Levofloxacin prophylaxis did not have a significant effect on the occurrence of blood stream infections in patients after HCT (11% with prophylaxis *vs* 17% without prophylaxis, p=0·06). In two of the four studies, antibacterial prophylaxis significantly reduced the risk of febrile neutropenia.[19,20]

The efficacy data from these four randomised trials of antibacterial prophylaxis in children are supported by five meta-analyses in paediatric and adult patients published after 2000.[21–25] The analyses differed regarding the timeframe of the inclusion of older studies, with the inclusion of studies since 1966 in one meta-analysis.[21] Four of the five meta-analyses, including the most recent one,[24] which included studies published up to 2018, did not find a significant effect of fluoroquinolone prophylaxis on mortality.[24] A fifth study that included studies before the 1970s, however, showed a reduction in mortality with fluoroquinolone.[21] All five meta-analyses noted that antibiotic prophylaxis reduced the rate of bloodstream infections and febrile neutropenia. One analysis described this reduction with the prophylactic use of levofloxacin, but not of ciprofloxacin.[24]

Regarding the emergence of resistance, the four aforementioned clinical trials reported inconclusive data on fluoroquinolone resistance evaluated by stool surveillance. Two studies found significantly increasing rates of resistance from baseline to 3 weeks.[19,26] The same increase was not seen in the most recent randomised study,[20] which did, however, report a higher rate of fluoroquinolone-resistant blood stream isolates in the levofloxacin group, although the number of isolates was too small for a statistical analysis.[20] Similarly, inconsistent findings on fluoroquinolone resistance were reported by the five meta-analyses. Although one analysis that included studies published between 1966 and 2011 did not find an increase in the proportion of fluoroquinolone resistance among isolates causing bloodstream infections,[21] a significant increase was reported by another analysis that included studies published between 1980 and 2018.[24] Importantly, none of the studies assessed the long-term consequences of prophylaxis on the local resistance pattern.

One meta-analysis evaluated whether or not fluoroquinolones increased the risk of musculoskeletal toxicity, but did not find a significant effect.[24] In contrast to previous reports,[27] one randomised study found that fluoroquinolone prophylaxis did not increase the incidence of *Clostridioides difficile*-associated diarrhoea. In this study, fluoroquinolone prophylaxis was associated with a 6·2% (p=0·02) lower likelihood of having a positive test for *C difficile*, and the authors speculated that this lower risk was due to less therapeutic antimicrobial exposure in the prophylaxis group.[20]

The recommendation of the ECIL-8 group against routine antibacterial prophylaxis (panel 2) was based on several considerations (grade D recommendation, evidence level III). First, antibacterial prophylaxis did not significantly decrease overall mortality, considered by the group as the most important endpoint (although the ECIL-8 group also recognised that it is unlikely that a study will be sufficiently powered to show a reduction in mortality if the baseline risk of mortality is low). Second, the decrease in bloodstream infections in the study by Alexander and colleagues was shown in the two patient populations, of which the control group (no prophylaxis) had an unusually high incidence of bacteraemia compared with the intervention group; by contrast, prophylaxis did not result in a significant reduction in bacteraemia in HCT recipients.[20] Because studies have reported that the incidence of bloodstream infections in acute leukaemia is approximately 20% (also seen in special patient populations, such as children with Down syndrome with acute myeloid leukaemia[28–30]), the ECIL-8 group concluded that antibacterial prophylaxis would not reduce the incidence of bacteraemia in these patients. The ECIL-8 group acknowledged that bloodstream infections are not only associated with adverse outcomes but can also be considered a proxy for other complications, such as admission to the intensive care unit. However, these considerations have to be weighed against the increased resistance rates in centres using fluoroquinolone prophylaxis, and against the fact that bloodstream infections caused by resistant Gram-negative pathogens have a poor outcome.[7] Finally, in contrast with other guidelines,[13] the ECIL-8 group included also non-randomised studies in the decision process, because the panel recognised that randomised trials (and meta-analyses based on these randomised trials) cannot be used for epidemiological purposes, on the grounds that a randomised, controlled trial generally does not collect data on infections occurring after the end of the study and in patients excluded from the trial itself. In this regard, an observational study by the Paul-Ehrlich Society in Germany found that the ciprofloxacin resistance of *Escherichia coli* increased from 0%, in 1984 (when the drug started to be used in Germany), to 5·2% in 1995, 14·5% in 2001, and 22% in 2004,[31] which shows that the follow-up time of randomised studies is too short to detect the emergence of resistance to fluoroquinolone. Resistance to β-lactam antibiotics in isolates from blood and surface cultures has not been observed in paediatric studies.[19,20] However, studies in adults have reported a correlation between fluoroquinolone exposure and increased infections with

Panel 2: **Recommendations for antibacterial prophylaxis and for antibacterial therapy in paediatric patients with leukaemia or after haematopoietic cell transplantation (HCT)**

Prophylaxis of bacterial infections

Recommendation 1: the ECIL-8 group does not recommend routine antibacterial prophylaxis for paediatric patients with lymphoma, acute leukaemia, relapsed acute leukaemia, or patients with neutropenia during the pre-engraftment stage of HCT (grade D recommendation, level of evidence III). This recommendation is based on data from randomised trials and meta-analyses, information from long-term observational studies on resistance, and European Medicines Agency recommendations.

Antibacterial therapy in patients with febrile neutropenia

Initial empirical antibacterial therapy

Recommendation 2: the ECIL-8 group recommends that initial empirical antibacterial therapy should be administered according to these escalation and de-escalation principles:

- Monotherapy with an antipseudomonal non-carbapenem β-lactam and β-lactamase inhibitor combination, or with fourth-generation cephalosporin, is recommended for clinically stable patients at low risk of resistant infections (grade A recommendation, level of evidence IIr)
  - This group includes patients without colonisation or previous infections with resistant bacteria, or patients treated in institutions with a low rate of resistant pathogens; for these patients, carbapenems are not recommended due to the risk of collateral damage and resistance development
- Carbapenem, with or without a second anti-Gram-negative agent, with or without a glycopeptide, is recommended for clinically unstable patients, even when at low risk of resistant infections (grade A recommendation, level of evidence IIt)
- Empirical treatment should be adjusted on the basis of the results of resistance testing for patients who are colonised or were previously infected with resistant Gram-negative bacteria, or in centres with a high rate of resistant pathogens (grade A recommendation, level of evidence IItu)

Antibiotic strategy beyond the initial empirical therapy

Recommendation 3: the ECIL-8 group recommends that, on the basis of the parameters identified in the validated risk prediction rules, each centre should define risk groups for the decision to discontinue or de-escalate antibiotic therapy and for the duration of inpatient follow-up (grade A recommendation, level of evidence IIu). This strategy requires an analysis of the local epidemiology and a definition of patients at low risk of invasive infection and adverse outcome during febrile neutropenia, and depends on local infrastructure and ability to follow-up and on patient return to hospital.

De-escalation of antibiotics in patients with neutropenia and a microbiologically documented infection

Recommendation 4: the ECIL-8 group recommends that, if a causative pathogen is identified, the patient should be treated with narrower-spectrum antibiotics, according to the causative organism identified (assuming it is a plausible pathogen). Treatment should be guided by in-vitro susceptibility tests, including minimum inhibitory concentrations when available (grade A recommendation, level of evidence IItu).

De-escalation of antibiotics in patients with neutropenia and fever of unknown origin with clinically unstable condition or previous colonisation or infection with resistant pathogens

Recommendation 5:

- If a patient was clinically unstable at presentation (eg, signs of sepsis or septic shock) and has stabilised with empirical therapy, no change in initial therapy is recommended, even if blood or other cultures remain negative (grade B recommendation, level of evidence III)
- If a patient was clinically stable at presentation but empirical therapy was chosen on the basis of known colonisation or previous infection with resistant bacteria, de-escalation of the initial therapy should be considered after 72–96 h, including
  - Discontinuation of any aminoglycoside, fluoroquinolone, colistin, or any antibiotic directed against resistant Gram-positive pathogens, if given in combination (grade A recommendation, level of evidence IItu [for patients at high risk] or I [for patients at low risk])
  - Change to a narrower-spectrum antibiotic (eg, an antipseudomonal non-carbapenem β-lactam and β-lactamase inhibitor combination) in patients initially treated with a carbapenem (grade A recommendation, level of evidence IItu)

De-escalation of antibiotics in patients with fever of unknown origin with clinically stable condition and no previous colonisation or infection with resistant pathogens

Recommendation 6: Consider a de-escalation strategy in patients with fever of unknown origin (ie, without clinically or microbiologically documented infection) after ≥72 h of intravenous antibiotics if patients have been haemodynamically stable since presentation and have been afebrile for 24–48 h, even before signs of haematological recovery, provided careful patient monitoring is available.

- Follow-up can be done on an inpatient or an outpatient basis according to local infrastructure and ability of the patient to return quickly to the hospital (since heterogeneity among centres can limit the implementation of some de-escalation strategies)
- For patients with fever of unknown origin, consider:
  - Switching patients at low risk (grade B recommendation, level of evidence II) or some patients at high risk (grade C recommendation, level of evidence IItu) to oral antibiotics
  - Discontinuing all empirical antibiotics in patients at low risk (grade B recommendation, level of evidence II) or some patients at high risk (grade C recommendation, level of evidence IIt)

extended-spectrum β-lactamase-producing, carbapenem-resistant (including *P aeruginosa*), and multidrug-resistant Gram-negative bacteria.[32–35] This correlation might be of relevance to paediatric patients presenting with febrile neutropenia while taking prophylactic fluoroquinolones, since especially resistant Gram-negative pathogens represent the major threat for patients with neutropenia and are associated with a poor prognosis in case of invasive disease.[7] In addition to the risk of increasing resistance, the panel recognised that fluoroquinolones are associated with an increased risk of adverse effects. Musculoskeletal problems occur in up to 4% of paediatric patients treated with fluoroquinolones, and a systematic review and meta-analysis found that CNS-related adverse events occur three times more often in patients receiving fluoroquinolones than in those receiving any other antimicrobial drug,[36] all of which led to a warning against the use of fluoroquinolones issued by the European Medicines Agency on March 11, 2019.[36–38] Although the ECIL-8 group does not recommend routine antibacterial prophylaxis for patients at high risk, which contrasts with a previous international paediatric specific guideline ("consider systemic antibacterial prophylaxis administration in children with acute myeloid leukaemia and relapsed acute lymphoblastic leukaemia receiving intensive chemotherapy expected to result in severe neutropenia [absolute neutrophil count <500/μL] for at least 7 days"; weak recommendation, high quality of evidence),[13] the group agrees that a careful risk–benefit evaluation might favour antibacterial prophylaxis in individual patients, depending on their circumstances.

Antibacterial therapy in patients with febrile neutropenia

Empirical antibacterial therapy is a long-standing standard of care for children and adults with neutropenia at the onset of fever or at any other sign or symptom of a possible infection,[8,12,39] although antibiotic use can be withheld, with no clinical detriment, in selected patients with cancer and febrile neutropenia.[40] There are several considerations regarding the choice of antibiotics, both for initial empirical treatment and for de-escalation strategies and discontinuation (panel 2). For example, the increasing risk of resistance to standard antibiotics has a major influence on the initial choice of empirical antibacterial therapy. Studies in adults have shown that, compared with patients without multidrug-resistant Gram-negative bacteria, patients with cancer and infected with multidrug-resistant Gram-negative bacteria more frequently received inadequate empirical antibacterial therapy, which was associated with poorer outcome.[41] Patient-specific factors, such as the clinical presentation (eg, clinical instability or hypotension), comorbidities, and previous infections, must also be considered before deciding which empirical antibacterial therapy to prescribe, since all these factors can be associated with poor outcomes.[8,39]

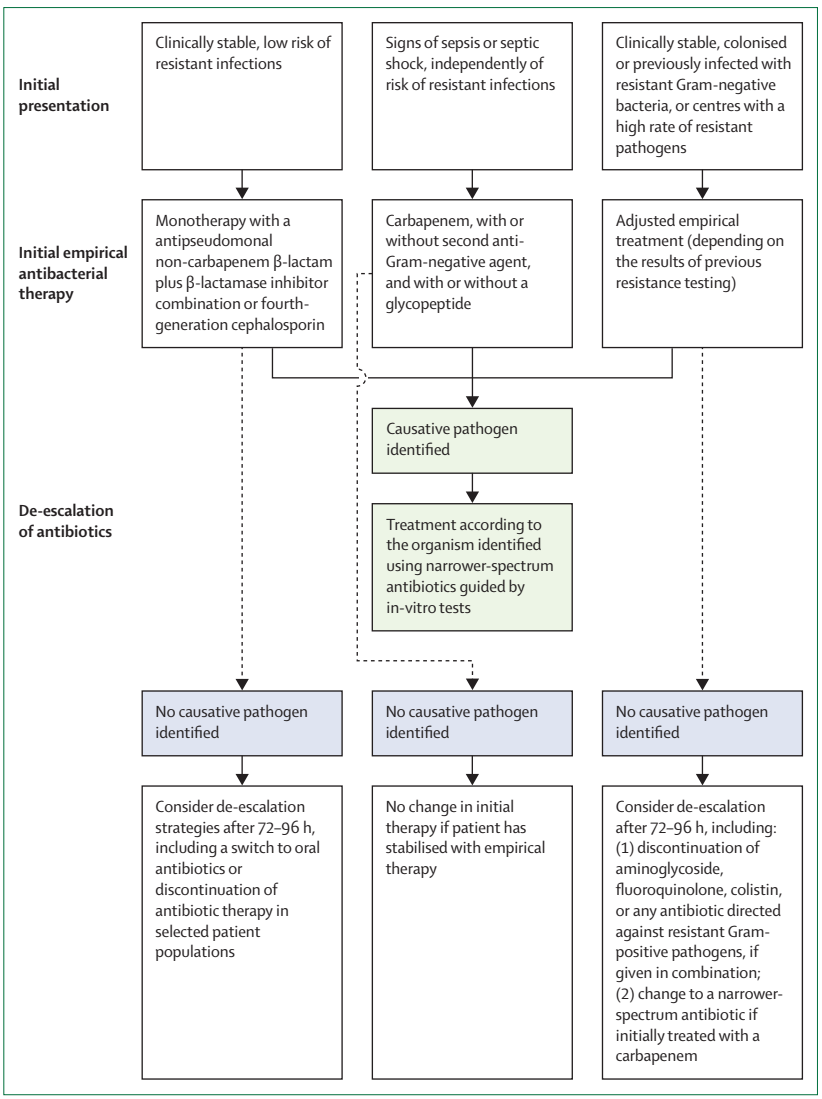

Figure: **Algorithm for initial empirical antibacterial therapy depending on initial presentation**
De-escalation of antibiotics depends on both the initial presentation and whether (solid arrow) or not (dotted arrow) a causative pathogen has been identified.

Initial empirical antibacterial therapy

The ECIL-8 group recommends that initial empirical antibacterial therapy should be administered according to the following escalation and de-escalation principles (recommendation 2; figure). For clinically stable patients at low risk of resistant infections, monotherapy with an antipseudomonal non-carbapenem β-lactam plus β-lactamase inhibitor combination or fourth-generation cephalosporin is recommended (grade A recommendation, level of evidence IIr). For clinically unstable patients (eg, those with clear signs of severe sepsis), even when at low risk of resistant infections, carbapenem with or without a second anti-Gram-negative agent and with or without a glycopeptide is recommended (grade A recommendation, level of evidence IIt). For patients who are colonised or were previously infected with resistant

Gram-negative bacteria, or are in centres with a high rate of resistant pathogens, empirical treatment should be adjusted on the basis of the results of resistance testing (grade A recommendation, level of evidence IItu).

A systematic review of empirical management of paediatric patients with cancer and HCT recipients with fever and neutropenia found that aminoglycoside-containing combination therapy did not reduce treatment failures and mortality compared with guideline-consistent monotherapy.[42] Additionally, antipseudomonal penicillin plus β-lactamase inhibitor and fourth-generation cephalosporin monotherapy were associated with similar results.[42] Therefore, the ECIL-8 panel strongly recommends an escalation strategy with monotherapy with an antipseudomonal non-carbapenem β-lactam plus β-lactamase inhibitor combination (such as piperacillin–tazobactam), or fourth-generation cephalosporin for clinically stable patients at low risk of resistant infections (eg, no colonisation or previous infections with resistant bacteria, and low rate of local resistant pathogens; grade A recommendation, level of evidence IIr). Because of the risk of adverse events (eg, pseudomembranous colitis) and resistance development associated with carbapenem use (eg, the emergence of carbapenem-resistant Gram-negative bacteria with few treatment alternatives), the panel does not recommend carbapenems as empirical therapy for clinically stable patients.[8,43] Novel β-lactam plus β-lactamase combinations, such as ceftazidime–avibactam or ceftolozane–tazobactam, should not be routinely used as empirical antibacterial therapy because there are currently no paediatric safety and efficacy data. For clinically unstable patients, even when at low risk of infection with resistant pathogens, the ECIL-8 panel recommends a de-escalation strategy (eg, start with broad-spectrum antibiotics and switch to narrow-spectrum antibiotics when safe), which is in line with paediatric-specific guidelines.[12] These patients should initially be treated with a carbapenem, which can be combined with a second anti-Gram-negative agent, a glycopeptide, or both (grade A recommendation, level of evidence level IIt). Although no evidence suggests that outcomes with carbapenem-based therapy are superior to outcomes with other antibiotic combinations that have a high chance of covering probable pathogens, the ECIL-8 group based their recommendation on the following facts. First, a systematic review reported an increasing prevalence of Gram-negative bacteria producing broad-spectrum β-lactamases.[44] Second, a multinational study found that 49·4% of Gram-negative bacteria isolated in children after allogeneic HCT and 36·4% of those isolated in children after autologous HCT were resistant to non-carbapenem β-lactams.[45] Third, delays in the administration of appropriate therapy in patients with a haematological malignancy and extended-spectrum β-lactamase bacteraemia are associated with increased mortality.[46] Finally, presentation in septic shock is associated with high mortality rates in patients with febrile neutropenia.[47] However, the ECIL-8 group agreed that local epidemiology has to be included in the choice of antibacterial agents. In addition to resistant Gram-negative pathogens, the possibility of resistant Gram-positive cocci, in particular viridans streptococci, must be considered.

Several studies in adults have clearly shown that the most important risk factor for infection with a resistant pathogen is previous colonisation or infection with a resistant pathogen, in particular Gram-negative bacteria.[8] According to the ECIL-8 panel, the initial empirical antibacterial treatment in these patients should be adjusted on the basis of the resistance profile of the pathogen detected earlier. Furthermore, in centres with a high rate of resistant pathogens, the panel recommended that initial empirical antibacterial treatment should be tailored to the local epidemiology (grade A recommendation, evidence level IItu). However, the panel also recognised that thresholds for rates of resistance mandating this strategy are not established.

Irrespective of the choice of empirical antibiotic therapy, the panel underlined that rigorous local epidemiological surveillance is essential, and that empirical antibiotic regimens should be reviewed regularly in light of evolving institutional microbial resistance patterns.

Antibiotic strategy beyond initial empirical therapy

In stable patients without evidence of infection with resistant pathogens, the antibiotic strategy beyond initial empirical therapy includes several scenarios, such as switching to narrower-spectrum antibiotics in a de-escalation strategy (eg, for patients with a documented infection), switching to oral antibiotics, discharging the patient to outpatient management, or discontinuing antibiotics. These strategies have been evaluated in various patient populations, such as in patients with neutropenia with or without signs of haematological recovery, in patients with neutropenia with or without fever, and in patients with different risk profiles. Although there are various proposed risk stratification strategies,[39] the risk prediction rules use different criteria and have been validated in different paediatric populations, but none was universally predictive.[48,49]

The ECIL-8 group recommends that, on the basis of the identified variables in the validated risk prediction rules, each centre should define risk groups for the decision to discontinue or de-escalate antibiotic therapy and for the duration of inpatient follow-up (recommendation 3, grade A, level of evidence IIu). This strategy requires an analysis of the local epidemiology and a definition of patients at low risk of invasive infection and adverse outcomes during febrile neutropenia, and depends on local infrastructure and ability to follow-up and on the patient's return to hospital. The development and evaluation of new biomarkers for risk stratification and de-escalation strategies was identified as a research gap.

De-escalation of antibiotics in patients with neutropenia with a microbiologically documented infection

The ECIL-8 group recommends that patients with an identified causative pathogen are treated with narrower-spectrum antibiotics according to the organism identified (assuming it is a plausible pathogen), the choice of which should be guided by in-vitro susceptibility tests, including minimum inhibitory concentrations when available (recommendation 4, grade A, level of evidence IItu; figure). Although a de-escalation strategy for patients with ventilator-associated pneumonia and severe sepsis is well established in intensive care units, little data exist on de-escalating antibiotics in paediatric and adult patients with cancer with a documented bloodstream infection.[50–53] Of the 207 references retrieved by the search on de-escalation strategies, one retrospective chart review analysed 194 episodes of febrile neutropenia in 67 paediatric patients with leukaemia.[53] A total of 19 episodes met the de-escalation criteria for children with bloodstream infection, such as clinical stability, defervescence, and clearance of the pathogen. In nine of these 19 episodes, de-escalation of antibiotic therapy did not result in recurrent fever or bacteraemia or any deaths, results that corroborate the data of observational studies in adult patients. The ECIL-8 group gave its recommendation on the basis of these observations, but it is important to note that paediatric safety and efficacy data are scarce, especially regarding the use of novel antibiotics (appendix pp 1–5).

De-escalation of antibiotics in patients with neutropenia with fever of unknown origin

Patients presenting in an unstable clinical presentation or with previous colonisation or infection with resistant pathogens

For patients with neutropenia and fever of unknown origin (ie, without clinically or microbiologically documented infection) presenting with a clinically unstable condition or with previous colonisation or infection with resistant pathogens, the ECIL-8 group makes the following recommendations (recommendation 5; figure). If a patient was clinically unstable at presentation (eg, had signs of sepsis or septic shock), blood or other cultures remain negative, and the patient has stabilised with empirical therapy, there should be no change in initial therapy (grade B recommendation, level of evidence III). If a patient was clinically stable at presentation, but empirical therapy was chosen based on known colonisation or previous infection with resistant bacteria, de-escalation of initial therapy should be considered after 72–96 h. This includes discontinuation of any aminoglycoside, fluoroquinolone, colistin, or any antibiotic directed against resistant Gram-positive pathogens, if given in combination (grade A recommendation, level of evidence IItu, for patients at high risk, and I, for patients at low risk), or a change to a narrower-spectrum antibiotic (eg, an anti-pseudomonal non-carbapenem β-lactam plus β-lactamase inhibitor combination) for patients who presented in a clinically stable condition, were colonised or had a previous infection with resistant pathogens, and were initially treated with a carbapenem (grade A recommendation, level of evidence IItu).

Very few data exist on the feasibility of antibacterial de-escalation therapy in patients with neutropenia who present with signs of sepsis or septic shock, and there are no studies in children. In a small prospective observational study in adult patients with cancer with severe sepsis, the 44 patients for whom antibacterial therapy was de-escalated did not have a worse outcome than the 57 patients who did not have de-escalation of antibacterial therapy.[54] The 4th ECIL group has already discussed this problem extensively in adults, and gave a grade B, level of evidence III recommendation at the time (2011).[8] No major study has been done since, and the ECIL-8 group decided to keep this moderate recommendation not to de-escalate antibacterial therapy in patients who presented in a clinically unstable condition (grade B recommendation, level of evidence III). Notably, according to the European Society of Clinical Microbiology and Infectious Diseases grading system, a moderate recommendation can go along with weak evidence.

In adult patients who had allogeneic HCT and who are at high risk of infection, two retrospective observational studies showed the safety of de-escalating empirical antibacterial therapy (eg, discontinuing aminoglycosides, fluoroquinolones, colistin, or any antibiotic directed against resistant Gram-positive pathogens, or changing to a narrower-spectrum agent).[51,55] Both studies included, but were not restricted to, patients with known colonisation with resistant bacteria. An analysis in 66 adult patients at high risk (eg, with acute lymphoblastic leukaemia, acute myeloid leukaemia, and in the pre-engraftment period of allogeneic HCT with and without known colonisation with resistant bacteria) showed that this strategy reduced carbapenem use, but did not increase the risk of bacteraemia, intensive care unit admission, or mortality.[52] Several randomised, controlled trials reported similar results in paediatric patients at low risk.[56–58] Of note, depending on the study, the following were excluded because they were not defined as patients at low risk: children with expected neutropenia for more than 10 days or who had allogeneic HCT; with severe clinical presentation or comorbidity (such as liver or renal dysfunction), enteritis, or severe mucositis; unable to take or allergic to oral antibiotics; with uncontrolled local infection or respiratory failure; with bloodstream infection; or with infection with ceftriaxone-resistant or ciprofloxacin-resistant bacteria.[56–58] Although the paediatric trials included (but were not limited to) patients with known colonisation with resistant bacteria, this strategy seems safe and reduces the exposure to second-line antibiotics.

Patients presenting in a clinically stable condition and with no previous colonisation or infection with resistant pathogens

For patients with neutropenia and fever of unknown origin presenting in a clinically stable condition and with

Search strategy and selection criteria

Publications from Jan 1, 2000, to June 30, 2019, in English language exclusively, were retrieved from the MEDLINE (including MEDLINE In-Process) database. Additionally, abstract books from conferences between 2017 and 2019, including those from European Society of Clinical Microbiology and Infectious Diseases meetings and IDweek, were searched and used as preliminary and supporting data. The searches included a combination of indexed terms and free-text terms ("paediatric", "child", "children", "haematology", "cancer", "leukaemia", "stem cell transplantation", "antibacterial", "antibiotic", "prophylaxis", "levofloxacin prophylaxis", "fluoroquinolone prophylaxis", "fever", "febrile", "neutropenia", "neutropenic", "blood stream infection", "risk", "prediction", "empirical antibiotic therapy", "de-escalation", "discontinuation", "outpatient", "oral", "step-down", "withholding", "discharge", "continuation", "resistance", and "adverse effect"). Retrieved publications were manually screened for additional references. The guidelines were developed on the basis of the results of randomised, controlled trials in children and of data from meta-analyses and systematic reviews. However, important observational paediatric studies (with ≥90% patients up to 18 years of age) or mixed paediatric–adult studies with separately retrievable paediatric data, data from adult studies (in particular if no paediatric study was available), and approval status of antibiotics by the US Food and Drug Administration and the European Medicines Agency were included in the decision process, in contrast with previous paediatric specific guidelines, which were developed solely on the basis of data from randomised trials.

no previous colonisation or infection with resistant pathogens, the ECIL-8 group makes the following recommendations (recommendation 6; figure). After at least 72 h of intravenous antibiotics, and if a patient has been haemodynamically stable since presentation and afebrile for 24–48 h, consider a de-escalation strategy, even before signs of haematological recovery (provided careful patient monitoring is available). Follow-up can be done on an inpatient or an outpatient basis according to the local infrastructure and the patient's ability to quickly return to the hospital. De-escalation strategies in patients with fever of unknown origin can include a switch to oral antibiotics for patients at low risk (grade B recommendation, level of evidence II) or selected patients at high risk (grade C recommendation, level of evidence IItu); or discontinuation of all empirical antibiotics in patients at low risk (grade B recommendation, level of evidence II) or selected patients at high risk (grade C recommendation, level of evidence IIu).

Several randomised, controlled clinical trials evaluated, in the paediatric setting, the safety of an early switch from intravenous to oral antibiotics with or without discharging the patient from the hospital.[56–61] Patients were randomly assigned to receive intravenous antibiotics versus oral antibiotics as inpatients (one trial)[59] or as outpatients (three trials),[56–58] and two trials randomised intravenous antibiotics in inpatients versus oral antibiotics in outpatients.[60,61] Time from initial presentation of the patient to the switch from intravenous to oral antibiotics varied between 1 day and 4 days. Younger children (usually defined as those aged <1 year), patients at high risk (eg, children undergoing HCT, with acute myeloid leukaemia or relapsed acute lymphoblastic leukaemia), patients with severe comorbidity, and patients who presented in an unstable condition or with organ (eg, kidney or liver) dysfunction were excluded from most studies. In some trials, patients with profound neutropenia or in whom neutropenia was predicted to last for more than 1 week were also excluded. Overall, data on mortality, breakthrough bacteraemia, recurrence of fever, and re-hospitalisation did not differ between de-escalation strategies and control groups. Similar results were reported by six meta-analyses, four of which exclusively included studies in children,[42,62–64] and two of which included both paediatric and adult patients.[65,66] Two randomised trials also compared inpatient and outpatient settings for children receiving intravenous antibiotics.[67,68] No significant differences in treatment failure were seen between the two settings.

Early antibiotic discontinuation (eg, before haematological recovery) has been addressed in several paediatric trials.[69–74] Four studies were observational[69,72–74] and two had a randomised design.[70,71] Inclusion criteria and conditions to stop antibiotics varied widely. In almost all the studies evaluating de-escalation strategies, patients at high risk (eg, HCT recipients, those with acute myeloid leukaemia or relapsed acute lymphoblastic leukaemia, or patients with clinical sepsis) were excluded. Depending on the study, antibiotics were discontinued when patients were afebrile for 24–72 h. In the two randomised paediatric trials, no deaths occurred, and there was no difference between groups regarding breakthrough bacteraemia, recurrence of fever, antibiotic re-initiation, and readmission to hospital.[70,71] Similar results were reported in a meta-analysis that included a total of eight randomised studies, three of which were paediatric studies.[75] However, because of various factors, such as variable and inconsistent definitions of clinical failure across the studies, possible selection bias, and wide confidence intervals, the findings had a low certainty of evidence. Little information is available on early antibiotic discontinuation in patients with neutropenia at high risk of bacterial infection. A randomised paediatric trial that reported that early discontinuation of antibiotic therapy is safe for children with febrile neutropenia with documented respiratory viral infection included few patients at high risk (eg, children with leukaemia relapse).[70] These data corroborate the results of a study in adults that evaluated the safety of stopping antibacterial therapy in patients with neutropenia with haematological malignancies or HCT recipients after being afebrile for 72 h.[76] However, the number of patients at high risk was too small to draw a firm conclusion, especially in the paediatric setting.

The ECIL-8 panel recommended considering a de-escalation of antibacterial therapy strategy before signs of haematological recovery in patients at low risk with fever of unknown origin, which, per definition, excludes patients with clinically or microbiologically documented infection. The ECIL-8 group underlined the importance

of careful clinical monitoring and ability to quickly return to the hospital for patients with neutropenia and fever of unknown origin presenting in a clinically stable condition and with no previous colonisation or infection with resistant pathogens. As the panel realised that hospital and patient characteristics vary widely in their local organisational structure, no preference was given to either inpatient or outpatient settings.

Conclusions and future directions

In this Policy Review, we present the first paediatric-specific ECIL guidelines for the use of antibiotics in children with leukaemia or lymphoma or undergoing HCT. Compared with a recent guideline on antibacterial prophylaxis in the paediatric setting, the difference in this recommendation can be explained by the different methods used in the development of the guideline.[13] Harmonisation of the methods and, as an ultimate goal, harmonisation of the guidelines would facilitate their implementation and improve anti-infective supportive care for children with cancer. Although the guidelines were primarily generated for European countries, they can also be used in other settings, such as centres in low-income countries, but each centre will need to adapt the recommendations to their local infrastructure and local epidemiology.

The ECIL-8 panel identified research gaps that need to be addressed in future studies. The worldwide emerging resistance of bacterial pathogens is of major concern, and new antibiotics and concepts for treatment are urgently needed. Fortunately, antibiotic stewardship has entered paediatric oncology, with benefits already shown in targeted and untargeted antimicrobial therapy.[77] Clinical trials are needed to define risk groups in which the benefits of antibacterial prophylaxis outweigh the potential adverse effects, and to characterise patients at low risk with febrile neutropenia for whom initial outpatient management and initial oral antibacterial therapy is feasible and safe. In this respect, further development and evaluation of serum biomarkers as diagnostic and monitoring tools would be helpful. The different de-escalation strategies (eg, switching to oral antibiotics or discontinuing antibiotic therapy) need to be compared, and the optimal choice and length of oral antibiotic therapy need to be evaluated. Finally, the safety and efficacy of early de-escalation strategies must also be assessed in patients at high risk of bacterial infection.

Contributors

TL and AHG (group leaders) recruited the experts and compiled the recommendations. MM and MS moderated the consensus development conference. All authors were involved in the literature search, development of recommendations, and conception of the manuscript. All authors revised the manuscript and gave final approval for submission.

Declaration of interests

TL reports unrestricted research support from Gilead Sciences; is a consultant for Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas, and Roche; and serves at the speakers' bureau of Gilead Sciences, Merck Sharp and Dohme, Astellas, Pfizer, and GlaxoSmithKline. DA reports research support from Merck Sharp and Dohme; was a consultant for Pfizer; and served at the speakers' bureau of GlaxoSmithKline. EC is a consultant for Angelini and Ferrer. CG-V reports research grants from Gilead Sciences and Merck Sharp and Dohme; research grants from the Spanish Ministerio de Sanidad, Consumo y Bienestar Social, the Instituto de Salud Carlos III in Madrid, Spain, the European Regional Development Fund, and the European Institute of Innovation and Technology; and served at the speakers' bureau of Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer, Janssen, and Lilly. JK is a consultant for Bayer. FL served at the speakers' bureau of Gilead Sciences and Basilea. MM is a consultant for and served at the speakers' bureau of Pfizer, Gilead Sciences, Merck Sharp and Dohme, Janssen, and Biotest. MS reports research support from Gilead Sciences, Merck Sharp and Dohme, and F2G; and served on the speakers' bureau of Merck Sharp and Dohme and Gilead Sciences. JS reports support from Gilead Sciences, Merck Sharp and Dohme, Astellas, Roche, Jazz Pharmaceuticals, and Pfizer; is a consultant for Gilead Sciences, Novartis, Pfizer, Merck Sharp and Dohme; and served at the speakers' bureau of Gilead Sciences, Merck Sharp and Dohme, Fresenius, and Astellas. AW is supported by the MRC Centre for Medical Mycology at the University of Exeter (grant MR/N006364/2); reports research support from Gilead Sciences; and served at the speakers' bureau of Gilead Sciences. AHG reports research support from Gilead Sciences, Merck Sharp and Dohme, and Pfizer; is a consultant for Amplyx, Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp and Dohme, and Pfizer; and served at the speakers' bureau of Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp and Dohme, and Pfizer. All other authors declare no competing interests.

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