Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies

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Cytomegalovirus (CMV) remains the most important viral pathogen in patients after allogeneic haematopoietic cell transplantation (HCT), resulting in morbidity and mortality. The European Conference on Infections in Leukaemia (ECIL) brings together experts in several fields to produce evidence-based recommendations from comprehensive literature reviews. Management of CMV has been addressed twice before; the previous guideline update from the ECIL was published in 2019. The 10th ECIL meeting in 2024 addressed new developments in CMV management after allogeneic HCT, and recommendations are presented in this Review. Management recommendations include diagnostics, such as immune monitoring, antiviral prophylaxis with letermovir, management of resistant and refractory CMV infections, and paediatric aspects of CMV management. Furthermore, the 10th ECIL introduced recommendations for two new categories: patients treated with chimeric antigen receptor T cells or treated with bispecific T-cell-engaging antibodies.

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Introduction

Cytomegalovirus (CMV) remains the most important viral pathogen in patients after allogeneic haematopoietic cell transplantation (HCT). CMV replication is strongly associated with increased mortality early and in long-term survivors after allogeneic HCT, even in the modern era.[1,2] Substantial progress has been made in diagnostics for surveillance and prevention of CMV disease. Nevertheless, the outcome of established CMV end-organ disease remains poor.

Although CMV-associated morbidity is higher in adults, CMV infection also impacts the clinical outcome in children.[1,3] CMV affects up to 40% of paediatric recipients of haematopoietic cell transplants at a median of 20–40 days after transplantation. Some data suggest an even higher incidence of CMV reactivation in children than in adults and a higher risk of direct and indirect effects.[3,4]

New therapies for haematological malignancies are available, especially chimeric antigen receptor (CAR) T cells and bispecific T-cell-engaging antibodies, and their use is increasing rapidly. Both therapies can result in T-cell suppression and thereby be risk factors for CMV reactivation and possibly symptomatic CMV infection and disease.

The European Conference on Infections in Leukaemia (ECIL) develops management guidelines for different infections. Recommendations regarding the management of CMV were last published in 2019.[5] This current update reflects the developments in the field since the last published guidelines, including new patient groups, especially patients treated with CAR T cells and patients treated with T-cell-engaging antibodies.

Development of recommendations

The methodology for ECIL guidelines has been previously published.[5] A working group was convened and divided into teams who searched MEDLINE for papers published from July 1, 2017, to June 30, 2024, on several subtopics.

The relevant studies were analysed, with particular attention given to the study design, the population, and the endpoints. Recommendations were developed and graded on the amount of evidence and strength of the recommendation according to the European Society of Clinical Microbiology and Infectious Diseases grading system (appendix p 1).[6] The whole working group reviewed all provided materials and proposed recommendations. These suggested recommendations were presented in a plenary session of the ECIL 10 at Sophia Antipolis, France

Key messages

- Cytomegalovirus (CMV) serostatus should preferably be assessed both at diagnosis of the underlying disease and close to the planned allogeneic haematopoietic cell transplantation (HCT)
- Letermovir is recommended as the strategy of choice for CMV primary prophylaxis to prevent CMV reactivation for CMV-seropositive adult allogeneic HCT recipients
- Letermovir should be considered as CMV prophylaxis in children at high risk undergoing allogeneic HCT
- Maribavir is effective for treatment of resistant and refractory CMV infection and disease and is associated with lower risk for serious side-effects than previously used antiviral drugs, primarily ganciclovir and foscarnet
- CMV infection should be considered in the management of patients treated with chimeric antigen receptor T cells

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See Online for appendix

Panel 1: Proposed alternative terminology to CMV serological status

Pre-HCT CMV positive status is defined as:

- Patients with positive pre-transfusion serology (at diagnosis of the underlying disease or before receiving more intensive therapy)
- Patients who, before allogeneic HCT, had CMV detected from any site, including patients with CMV disease
- Patients without a pre-transfusion sample who are seropositive in the pre-HCT sample (as defined by the locally used assay)

Pre-HCT CMV negative status is defined as:

A patient in whom both pre-transfusion (if applicable) and pre-HCT samples were CMV seronegative and with no CMV detected before HCT.

Pre-HCT CMV uncertain status is defined as:

Patients who are CMV seronegative at diagnosis of the haematological disorder but have CMV indeterminate serology in the pre-HCT evaluation (as defined by the locally used assay) or patients without a pre-transfusion serology but who have a CMV indeterminate serology in the pre-HCT sample.

HCT=haematopoietic cell transplantation. CMV=cytomegalovirus.

(Sept 20–21, 2024) consisting of 54 experts from 19 countries representing infectious diseases, clinical microbiology, virology, paediatrics, and haemato-oncology. The recommendations were discussed until a consensus was reached and subsequently made available on the ECIL website from Oct 7 to Nov 8, 2024, for open consultation.

Results

Diagnostics and monitoring

Determination of CMV risk status in patients undergoing HCT

CMV serological status is one of the basic biological parameters that must be assessed before allogeneic HCT on all patients and their donors. Before transplantation, HCT recipient CMV serostatus remains the most important predictor of CMV reactivation after allogeneic HCT[7] and is one of the critical criteria used for donor selection as CMV serological status of patients and donors strongly influences the outcome of HCT.[5] More recently, CMV seropositivity in the recipient was found to be a negative risk factor for overall mortality in patients infected by SARS-CoV-2 who are undergoing allogeneic HCT.[8] In the pre-letermovir era, CMV-seropositive patients had poorer outcomes than seronegative patients,[9,10] presumably due to the adverse direct and indirect effects of CMV replication.[1] Different real-world studies have shown that letermovir could level the mortality disparity between patients who are CMV seropositive and seronegative[11,12] and reduce the incidence of resistant and refractory CMV infections.[13]

Standard practice is determining the presence or absence of CMV-specific antibodies before allogeneic HCT.[5,7] The interpretation of both positive and negative results has important limitations in situations where antibodies are passively administered, such as transfusion of plasma products, including immunoglobulins, or transfer of maternal antibodies in newborns, converting a patient without previous CMV exposure into CMV seropositive. In a patient previously infected with CMV, insufficient production of CMV-specific immunoglobulins, common in several haematological and immunodeficiency diseases, can give negative results, classifying the patient as CMV seronegative despite harbouring a latent virus. These two opposite situations might result in false CMV seropositivity or false CMV seronegativity, with implications on selecting the best donor and the appropriate CMV preventive strategy. CMV-specific T-cell assays can be used to help establish previous CMV exposure and, consequently, CMV latent infection status of patients and donors. However, according to the American Society for Transplantation and Cellular Therapy guidelines, insufficient data exist to recommend these immune-based assays for this purpose.[7]

Several retrospective studies in patients undergoing HCT[14–16] have analysed the problem of biologically false-positive serological cases, indicating that samples from close to the time of HCT are likely to overestimate the rate of seropositivity by approximately 12–25%. In populations with a high baseline rate of seropositivity, the overestimation risk is likely to be lower. Less published evidence is available for the risk of false seronegativity, but one study reported the risk to be approximately 2%.[16] We therefore propose to use the terminology outlined in panel 1 instead of CMV serological status.

CMV screening and monitoring

Measurement of CMV DNA load in peripheral blood by quantitative nucleic acid testing (QNAT) is the preferred technique for managing CMV infection in allogeneic HCT recipients. The pp65 antigenaemia assay is less sensitive but can be used if a QNAT test is unavailable. A wide array of commercial CMV QNAT assays validated for peripheral blood is available, most of which have been approved or CE-marked by regulatory agencies. Calibration to international units (IU) by use of the first WHO-approved standard is recommended that is integrated into automated platforms because it reduces the overall interassay and inter-laboratory differences in CMV DNA loads on average to less than 0·5 $\log_{10}$. However, some commercial assays deviate by 1·5 $\log_{10}$ IU/mL or more.[17,18]

Whole blood and plasma specimens are equally suitable for CMV DNAaemia screening and monitoring. Although CMV DNA loads measured in whole blood and plasma correlate well,[19–21] those in whole blood tend to be

higher than in plasma.[20,21] Ultimately, this correlation still depends on the starting volume, elution volume, and, importantly, on total DNA content and extraction capacity, which varies depending on the number of peripheral blood leukocytes.[19]

Kinetic analyses of plasma CMV DNA loads (eg, CMV DNA doubling time) can be a valuable parameter for guiding the start of pre-emptive antiviral treatment.[22–24] Specifically, a viral DNA load doubling time of less than 2 days predicts the eventual need for pre-emptive therapy.[22,23] In turn, timely initiation of pre-emptive antiviral therapy can reduce the overall days needed on antiviral therapy, the associated side-effects and costs, and progression to CMV disease (defining pre-emptive strategy failure).[23] Due to the centre-specific use of these parameters, no generalised recommendations on thresholds and kinetics can be made. Nevertheless, most experts agree that more than 0·5 $\log_{10}$ changes in CMV DNA loads are clinically significant if the same laboratory, matrix, and CE-marked and approved QNAT assay are used.

Use of CMV QNAT assays in samples other than blood for the diagnosis of CMV disease

CMV DNA might not be detected in blood from patients with CMV disease (especially in the gastrointestinal tract or in cases with retinitis). Most currently available commercial CMV QNAT assays have not been approved or CE-marked for clinical specimens other than blood, such as bronchoalveolar lavage fluid (BALF), cerebrospinal fluid (CSF), tissue (biopsies), vitreous or aqueous humours, or stools. The US Food and Drug Administration-approved or CE-marked multiplex PCR assays, including CMV as a target providing qualitative results, are available for CSF. Since studies that use commercial assays to define thresholds in non-blood specimens are not validated for the purpose of laboratory-developed tests, many experts consider a positive CMV DNA result informative for CSF, tissue samples, or vitreous or aqueous humour. By contrast, BALF and stool samples are difficult to interpret without normalisation; for example, normalising per millilitre of standardised diagnostic BALF volume (eg, 50 mL), per 150 000 diploid cell equivalents, or per microgram total DNA.[25]

Testing for antiviral resistance

The presence of antiviral resistance is established in clinical practices by genotypic assays. DNA sequencing by Sanger sequencing or next-generation sequencing can be used to screen for the most common resistance mutations on specific codons. The genotyping assay should include all the genes involved in the antiviral mechanism of action. Sequencing of full-length genes is necessary to detect all resistance mutations and new mutations. An updated list of known mutations and their impact can be retrieved in the international database available.[26,27] The level of resistance conferred by a new mutation is defined by recombinant phenotyping by transferring the mutation to a wild-type recombinant virus and measurement of the half maximal effective concentration (known as EC_{50}) increase conferred by the mutation compared with the parental wild-type strain. Specific laboratories with such expertise can perform such analyses. Recommendations for antiviral resistance testing are shown in panel 2.

Panel 2: Recommendations for antiviral resistance testing graded according to the European Society of Clinical Microbiology and Infectious Diseases grading system

- Resistance during primary letermovir prophylaxis in HCT recipients is uncommon. Since detection of mutations that might prevent further use of the drug is important, genotyping for resistance, if available, could be done when pre-emptive therapy is started due to increasing cytomegalovirus DNA viral load (grade BII).
- Genotyping should be done in any case of non-response to allow adjustment of further therapy (grade AII). In case of refractory infections, treatment should be adjusted without waiting for genotyping results (grade AII).
- Genotyping for resistance should include sequencing all target genes by either Sanger or next-generation sequencing (NGS) methods, although the emergence capacity of low-level mutations detected by NGS should be confirmed by repeated testing (grade BIIt).
- Repeated genotyping is recommended if the viral load does not improve within 2 weeks of appropriate therapy (grade BIII).
- Genotyping results should be combined with clinical interpretation to guide clinical decision (grade BIIt).

CMV immune monitoring

Immune responses protecting against high-level CMV viraemia and CMV end-organ disease in allogeneic HCT involve both innate and adaptive mechanisms. Functional CMV-specific T cells targeting a wide variety of viral proteins, among which pp65 and IE1 are immunodominant, are primed upon CMV replication.[28] Several ex-vivo immunoassays have been developed to assess CMV-specific cellular-mediated immunity (CMV-CMI). Flow cytometry-based assays enumerate CMV-specific $CD4^+$ and $CD8^+$ T cells in peripheral blood mononuclear cells or whole blood producing one (monofunctional) or more (polyfunctional) intracellular cytokines upon antigenic stimulation. These assays lack standardisation and external validation (laboratory-developed procedures). Other assays based on flow cytometry enumerate CMV-specific T cells (usually $CD8^+$ T cells) binding HLA-I multimers coupled with CMV immunogenic peptides.[29] CMV-CMI can also be measured by cytokine release assays based upon enzyme-linked immunospot technology (ELISpot) or cytokines quantitation in plasma

by ELISA.[30] Assays measuring interferon γ (IFN-γ) release, such as the IFN-γ release assay (IGRA), have been commercialised and are standardised, simple to perform, robust (within-assay variation <15%), and potentially automatable. Importantly, qualitative agreement and quantitative correlation between the results returned by commercial IGRAs are fairly good, although not entirely interchangeable.[31] Additional information is in the appendix (pp 1–2).

Several non-interventional studies have collected a large body of evidence using the aforementioned commercially available immunoassays. The studies suggest that peripheral blood concentrations of IFN-γ-producing T cells that are specific to CMV measured at early (within the first 100 days) or late stages (after 100 days) after allogeneic HCT act as a reasonably reliable marker of protection against clinically significant CMV infection (CS-CMVi), recurrent CMV DNAaemia, and CMV end-organ disease, most notably in the absence of severe acute graft-versus-host disease (GVHD) requiring high corticosteroid doses.[11–36]

Screening and monitoring of CMV-CMI might be useful in managing CMV infection in the allogeneic HCT setting, potentially allowing personalised or targeted strategies. However, possible interventions based on CMV-CMI assessments are not supported by randomised interventional clinical trials. Therefore, the use of these techniques with current evidence is seen as optional, and further controlled interventional trials are needed. Recommendations for diagnostics and monitoring are shown in table 1.

Prevention of CMV disease and complications

Antiviral prophylaxis

Letermovir prophylaxis has, since its introduction in 2018, become the standard for preventing CS-CMVi in adult seropositive allogeneic HCT recipients. The pivotal study showed not only reduced risk for CS-CMVi, but also reduced all-cause mortality.[37,38] Many real-life studies have been published and summarised in a systematic review and meta-analysis, confirming the reduction of CS-CMVi and of CMV reactivation and CMV disease.[39] Furthermore, the effect on all-cause mortality was confirmed, but there was also a decrease in non-relapse mortality and acute GVHD.[39] Although no randomised controlled trial has been performed regarding the best time to start letermovir, a delayed start has been shown to confer a risk for CMV reactivation occurring before initiation of prophylaxis.[40] In patients undergoing letermovir prophylaxis, non-encapsidated and fragmented CMV DNA can be detected in blood without evidence of bona fide CMV infection[41]—ie, letermovir blips. These blips has been partly attributed to the mechanism of action of letermovir, which interferes with the excision of linear genomes from concatemers generated by rolling circle replication of the circularised intranuclear CMV genome.[42] The CMV DNA loads in patients under primary letermovir prophylaxis that develop self-resolving CMV DNAaemia episodes usually do not exceed 1500 IU/mL in plasma or 10 000 IU/mL in whole blood.[41,43,44] This phenomenon is not a sign of a breakthrough infection or letermovir resistance, and pre-emptive therapy can be withheld.

One randomised, placebo-controlled trial studied the effects of prolonged letermovir prophylaxis for 200 days and reported an effective reduction in the risk for CS-CMVi during the duration of prophylaxis. However, reactivations occurred later in the letermovir-treated group, resulting in no difference at 48 weeks after allogeneic HCT.[45] Moreover, mortality did not differ. Some centres have given an even longer duration of letermovir prophylaxis for patients at high risk.[11,46] The side-effect profile with letermovir has remained favourable, and the drug-drug interactions are manageable with therapeutic drug monitoring performed according to recommendations.

No controlled study has been done in CMV-seronegative patients, and letermovir is not recommended regardless of donor CMV status. Based on the superior efficacy and low risk for severe side-effects of letermovir compared with other options for antiviral prophylaxis in adults, other alternatives can only be recommended in cases where letermovir cannot be used.

Secondary prophylaxis with letermovir after a treated CMV reactivation has not been prospectively studied in a controlled setting. However, uncontrolled and retrospective studies reported that it might also be effective.[47–49]

Letermovir resistance is uncommon during primary prophylaxis in HCT recipients, with a reported incidence below 2% in phase 3 trials.[50] It might be higher when used for secondary prophylaxis.[47] Treatment breakthrough (temporary suspension of treatment, malabsorption, or any other cause leading to low drug concentrations) was reported as a specific risk factor for the rapid emergence of letermovir resistance during both primary and secondary prophylaxis.[49–51] Recommendations for antiviral prophylaxis in adults are summarised in table 2.

High doses of acyclovir or valaciclovir have been shown to reduce the risk of CMV infection in randomised trials, including adults and children.[52–54] Furthermore, ganciclovir reduced the risk of CMV disease compared with placebo in a randomised trial including adults and children;[54] however, neither acyclovir nor ganciclovir exerted an effect on survival, and no difference was found when ganciclovir was used as prophylaxis or pre-emptive treatment.

Letermovir is also changing the paediatric landscape. Reported real-world data for letermovir as primary or secondary prophylaxis confirm its safety and efficacy in preventing CMV infection after HCT in the paediatric population at high risk. Incidence of CS-CMVi in CMV-seropositive patients receiving letermovir prophylaxis ranges up to 9·8% in the 6 months after HCT, and no

	ESCMID grade
CMV risk status determination	
All patients and donors should be tested for CMV IgG antibodies	AIIu
CMV serology in allogeneic HCT candidates should be done at two timepoints	
At diagnosis of an underlying disease, which might be an indication for an allogeneic HCT, and before any blood transfusion is administered	AIIu
If no CMV serology result is available at the time of diagnosis, any available stored pre-transfusion samples should be tested	BII
Before HCT, close to the transplant	AIIu
CMV PCR before HCT is recommended	BIIu
Clinical judgement should be used to decide on whether to administer anti-CMV prophylaxis in patients with unclear CMV status; these patients need to be monitored as patients who are CMV seropositive	BII
Screening and monitoring	
All CMV D+/R+, D−/R+, and D+/R− allogeneic HCT recipients should be monitored for CMV DNA load in plasma or whole blood by QNAT	AII
Monitoring for CMV DNAaemia is recommended for allogeneic HCT recipients receiving letermovir prophylaxis	AI
Less frequent monitoring can be considered, especially in CMV D−/R− allogeneic HCT recipients undergoing low or standard risk HCT because the risk of primary infection and the incidence of end-organ disease are low if the administration of CMV-safe blood products can be assured	CII
Monitoring of CMV DNAaemia should be done at least once a week for the first 100 days after the transplant	AIIu
Extended monitoring for CMV DNAaemia is recommended for at least another 3 months in patients at higher risk, such as those having undergone mismatched, cord blood, or haploidentical HCT, T-cell depleted patients, patients on steroids, patients with ongoing GVHD, and patients with previous episodes of CMV DNAaemia	BII
Monitoring should be extended in patients with chronic GVHD requiring more intensive systemic immunosuppression, or in those with persistent immunodeficiency according to the perceived clinical risk for CMV reactivation and disease	BII
Monitoring of CMV DNA load for a given patient should be done with the same specimen type (plasma or whole blood) and QNAT platform	AIItu
CMV DNA load values for initiating pre-emptive antiviral therapy should take into account the QNAT platform used, the matrix chosen for CMV DNA quantification, the associated risk of CMV-disease, and the presence or absence of antiviral prophylaxis	AIIu
For a given patient and transplant centre, screening and monitoring of CMV DNA loads should be done with the same QNAT platform and type of specimen unless there are specific reasons to suspect underperformance of a given matrix indicating comparison of both plasma and whole blood	AIIu
Changes in CMV DNA load in plasma or whole blood (>0·5 $\log_{10}$) can assist in making decisions as to when to initiate pre-emptive antiviral treatment	BIIt
CMV immune monitoring	
The main applications of these assays may include	
Extending or shortening the duration of primary letermovir prophylaxis	IIt
Withholding therapy for low-level viral loads	CII
To identify patients that might benefit from secondary letermovir prophylaxis	CII
For future non-interventional or randomised studies assessing the clinical value of monitoring CMV-specific T-cell responses that produce IFN-γ in the management of CMV infection, the use of commercially available CMV IGRA that were investigated in clinical settings is preferable over flow cytometry-based immunoassays developed in laboratories	CII

CMV=cytomegalovirus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. IgG=immunoglobulin G. HCT=haematopoietic cell transplant. D+/R+=donor seropositive, recipient seropositive. D−/R+=donor seronegative, recipient seropositive. D+/R−=donor seropositive, recipient seronegative. D−/R−=donor seronegative, recipient seronegative. QNAT=quantitative nucleic acid testing. GVHD=graft-versus-host disease. IFN-γ=interferon γ. IGRA=IFN γ release assay.

Table 1: **Recommendations regarding CMV status assessment, screening, and monitoring**

increased incidence of other viral reactivations has been recorded. An impact on survival of letermovir in standard risk patients still needs to be defined.[42,55–59] Although no randomised trial is available, one phase 2b study on prophylaxis with letermovir in children reported a similar incidence of CS-CMVi (24·0%) until week 24 after HCT in the adolescent population (aged 12–18 years) to the pivotal phase 3 study in adults (37·5%).[39,60] Preliminary results of this ongoing trial showed an incidence of CS-CMVi of 11% until week 24 in 63 seropositive paediatric patients receiving letermovir.[61] Additional recommendations regarding antiviral prophylaxis in children are summarised in table 2.

Treatment of CS-CMVi after allogeneic HCT

Since the last set of ECIL recommendations was published, the term CS-CMVi, defined as the use of pre-emptive antiviral therapy or the development of CMV disease, has been introduced. This endpoint was first used in the pivotal letermovir trial and has been included in the 2024 published definitions of CMV infection and disease.[62]

A viral load threshold cannot be defined for CS-CMVi at different centres because patient groups vary greatly. Such a threshold might be locally adapted according to well known risk factors and the analytical performance of the used assay. In a 2024 published systematic review of randomised and observational studies, pre-emptive

	ESCMID grade	
	Adults	Children
Letermovir is recommended as the strategy of choice for preventing CMV for CMV primary prophylaxis for CMV seropositive allogeneic HCT recipients	AI	BIIa
Letermovir prophylaxis should be started as early as feasible after allogeneic HCT to reduce the risk of early reactivations	BII	No data
Letermovir should be started no later than day 28 after transplantation	AI	No data
Prophylaxis should be continued for at least 100 days after HCT	AI	AIIu
Extended prophylaxis should be considered in patients at high risk for CMV disease and can continue to at least 200 days after transplantation	BI	CIII
For some individuals, prophylaxis for longer than 200 days after transplantation can be considered if the treating physician's judgement is that the benefit is stronger than the risk	CII	CIII
Drug-drug interactions should be considered when giving letermovir prophylaxis	BII	CIIt
Letermovir blips (single test low-level DNA positivity in plasma or whole blood samples occurring especially early during letermovir prophylaxis) are common; interruption of letermovir prophylaxis is not recommended unless there are repeated positive samples showing increased viral load	BII	CIIt
Primary letermovir prophylaxis in patients with CMV negative status, regardless of the donor serostatus, is not recommended	DII	DIII
After discontinuation of letermovir prophylaxis, secondary prophylaxis with letermovir can be considered		
After successful treatment (negative QNAT test) of a CMV reactivation in patients perceived to be at increased risk for CMV disease	BII	CIII
In patients who, for some reason, have not received primary prophylaxis and have reactivated CMV that has been successfully treated	BII	CIII
Prophylactic valaciclovir could be used if letermovir prophylaxis is not used as primary prophylaxis for CMV seropositive allogeneic HCT recipients	CI	CIIt
The use of valganciclovir, ganciclovir, intravenous immunoglobulin, or foscarnet as prophylaxis against CMV reactivation is generally not recommended	DII	CIIt (GCV), DIIt (FOS), DIII (IVIG)

ESCMID=European Society for Clinical Microbiology and Infectious Diseases. CMV=cytomegalovirus. HCT=haematopoietic cell transplant. QNAT=quantitative nucleic acid testing. GCV=ganciclovir. FOS=foscarnet. IVIG=intravenous immunoglobulin.

Table 2: **Recommendations for antiviral prophylaxis in adults and children**

antiviral therapy started at CMV DNA load thresholds between 2 $\log_{10}$ IU/mL and 3 $\log_{10}$ IU/mL were associated with similar rates of CMV disease.[63] However, factors dependent on centres, assays, and patients, and the appropriate sample size needed, are acknowledged as limitations. No consensus exists on when to discontinue the pre-emptive antiviral therapy. Depending on the assay sensitivity, discontinuation after one CMV DNA result decreasing to below the limit of detection (LOD) for highly sensitive assays or two sequential CMV load results below the LOD 1 week apart have been reported. Each centre should have a working definition in its standard operating procedures to guide the start and end of pre-emptive therapy. This procedure should include patients on letermovir prophylaxis and those who have discontinued or never received it. Of note, even low viral loads affect outcomes in patients not given prophylaxis and after prophylaxis has been discontinued.[1,2]

Recommendations regarding drugs to use for pre-emptive therapy are mainly unchanged since ECIL 7,[5] except for the addition of maribavir as an alternative in some patients. Maribavir as first-line pre-emptive therapy was compared with valganciclovir in a randomised controlled non-inferiority trial. Both drugs were given for 8 weeks.[64] The study did not show non-inferiority (confirmed viraemia clearance: valganciclovir 77·4% *vs* maribavir 69·6%), although bone marrow toxicity was lower with maribavir. Of note, both drugs were given in a median of approximately 55 days (54 *vs* 56), which is longer than the usual duration of pre-emptive therapy with valganciclovir. ECIL 10, therefore, recommends that maribavir be considered for patients with neutropenia who cannot be treated with valganciclovir (BI) or patients with renal function impairment who foscarnet (BII) is not appropriate for.

Most available data come from uncontrolled studies involving both children and adults; therefore, recommendations for first-line CMV treatment in paediatric patients do not differ substantially from those previously published.[5]

Management of resistant or refractory CMV, including management of CMV disease

First-line treatment of CMV disease

The previous ECIL recommendations for the treatment of CMV disease have not been changed except for refractory CMV disease. The updated 2024 definitions of CMV disease should be used when studies on this topic are performed and reported.[62]

Management of resistant or refractory CMV

Resistance to the previously commonly used antiviral drugs remains infrequent in HCT recipients,[65,66] between 0% and 15%, and usually only emerges after several weeks of therapy and after treatment of several episodes

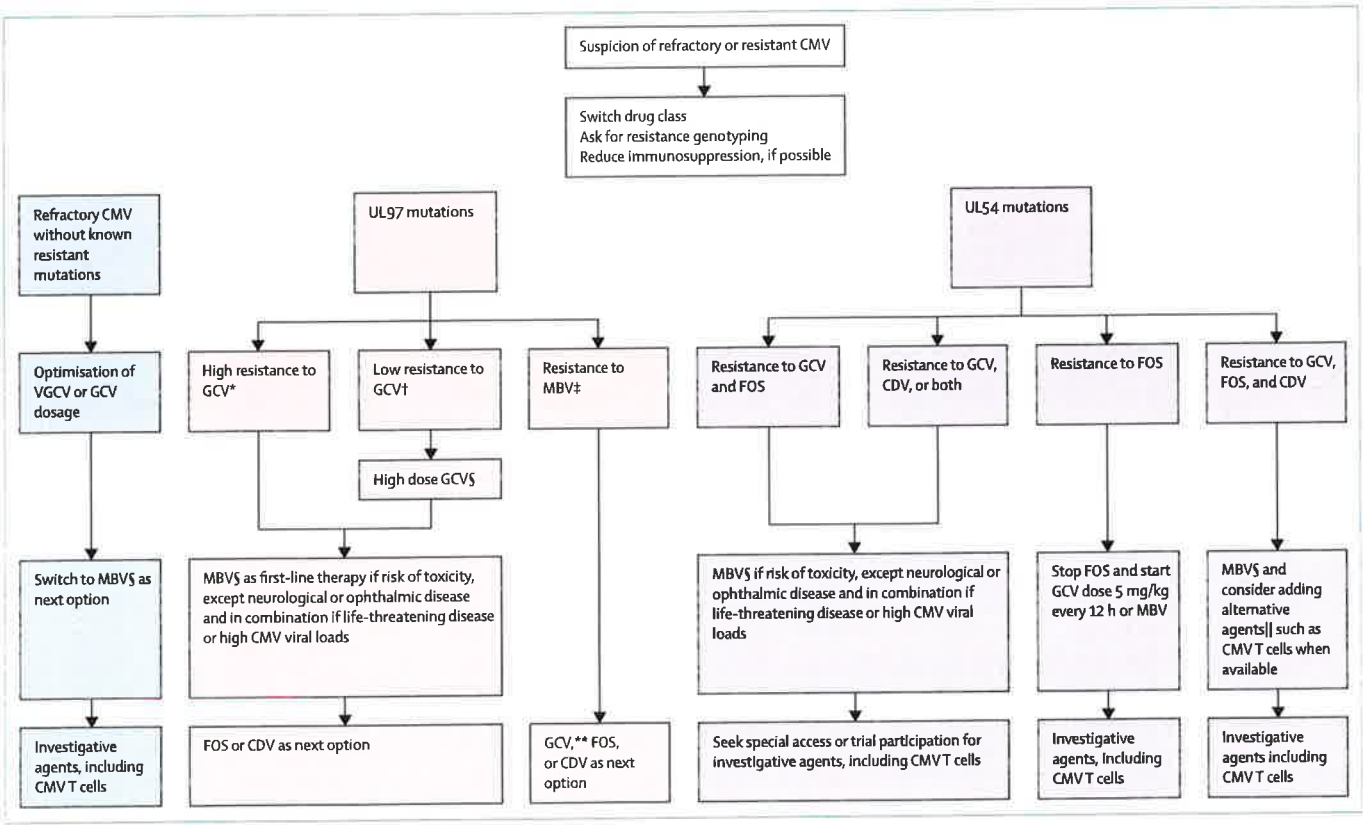

Figure: **Algorithm for management of refractory or resistant CMV infection**
CMV=cytomegalovirus. VGCV=valganciclovir. GCV=ganciclovir. MBV=maribavir. FOS=foscarnet. CDV=cidofovir. *High resistance is defined as mutations that increase IC_{50} more than 5-fold. †Low resistance is defined as mutations that increase IC_{50} more than 2-fold and less than 5-fold. §High dose GCV is 7·5–10·0 mg/kg every 12 h as tolerated, if CMV disease not present. ¶Check for pre-existing resistance mutations to MBV by resistance genotyping. Combination of MBV and VGCV or GCV is not recommended. ‡If MBV is given as first-line treatment. ||Alternative agents include leflunomide, artesunate, donor lymphocytes (under evaluation), or other CMV-activated T cells. **Check for infrequent but possible cross-resistance.

of CMV infections.[67] Rising cytomegalovirus DNA load or progression of cytomegalovirus disease might indicate clinical (refractory) resistance, viral resistance, or both.[68] Ljungman and colleagues updated the definitions in 2024.[62]

Host factors associated with refractory and resistant CMV are like those associated with the risk of infection, with some additional viral or drug factors.[7,69] Interestingly, the use of letermovir prophylaxis has decreased the incidence of CS-CMVi, including the emergence of resistant and refractory infections.[13]

Since the previous recommendations were published, maribavir has been shown in a pivotal trial to have a higher response rate and lower risk for clinically significant organ toxicity than the alternative, investigator-assigned therapy. Maribavir is therefore recommended for the treatment of resistant or refractory CMV infections after allogeneic HCT.[70] However, penetration to the CNS and the eyes is poor, so maribavir should not be used for CMV disease in these localisations.

The drug has a seemingly lower threshold for the development of resistance than do other agents used for CMV therapy. The rate of maribavir resistance in the pivotal trial for treatment of patients with resistant or refractory CMV infections was 26% in a population including solid organ transplant and HCT recipients,[70,71] substantially higher than documented during first-line pre-emptive therapy.[72] Maribavir resistance was associated with 17% of recurrences after completion of the 8 weeks of treatment, 48% of relapses while on therapy, and 86% of non-response cases with increased viral load; genotyping should be performed in these situations.[71]

Foscarnet is an alternative therapy for resistant or refractory CMV infections, especially those located in the CNS and eyes, but it is associated with clinically significant toxicity. Cidofovir is an option for the treatment of CMV retinitis. Combination therapy for resistant or refractory CMV infections has not been systematically studied but could be considered in patients with difficult-to-manage infection. However, the combination of maribavir with valganciclovir or ganciclovir should not be used due to their antagonistic mechanism of action.

No good data exist regarding letermovir, which is not indicated for the therapy of CMV infection, including resistant or refractory infections, or the treatment of

	ESCMID grade	
	Adults	Children
Maribavir is effective for treatment of resistant or refractory CMV infection and disease and is associated with lower risk for side-effects than the other alternatives	AI	BIIt*
Maribavir is not indicated for CMV disease involving the CNS and the eyes	DIIt	DIIt
If resistance is suspected, it should be documented by genotyping	AII	AII
Change of therapy is recommended before having results of resistance testing available	BII	BII
Foscarnet is an alternative therapy for resistant or refractory CMV infections, in particular in the CNS and eyes, but is associated with clinically significant toxicity	BII	AII
Cidofovir is an option for the treatment of CMV retinitis	BII	BII
CMV-specific T cells are an option for treatment of resistant or refractory CMV infection or disease, if available	BII	CIIu
Combination therapy for resistant or refractory CMV infections could be considered	BII	CII
The combination of maribavir with valganciclovir or ganciclovir should not be used	DIIt	CIII
Letermovir is not indicated for pre-emptive therapy of CMV infection or treatment of CMV end-organ disease including resistant or refractory infections	DIII	DIIt

CMV=cytomegalovirus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. *Can be considered when the patient is older than 12 years. However, it is not approved by the European Medical Association for individuals younger than 18 years.

Table 3: **Treatment of resistant or refractory CMV**

CMV end-organ disease. Several series of patients treated with CMV-specific T cells have shown good efficacy and a low risk for toxicity. This topic was covered in the last version of ECIL guidelines[5] and is therefore not discussed in detail in this Review.

Available options for children who have a second episode of CS-CMVi, drug toxicity, or develop a refractory infection include the alternate use of ganciclovir or valganciclovir, or foscarnet and maribavir as second-line therapy. Maribavir is currently approved by the US Food and Drug Administration (but not the European Medicines Agency) for second-line or third-line treatment for children aged 12 years or older. It is not approved for children younger than 12 years.

The figure shows an algorithm for treating resistant or refractory CMV infections and disease, and table 3 summarises the recommendations.

CMV in patients treated with CAR T cells

CMV was reported to be the most common viral infection in the first month after CAR T-cell therapy.[73] Analysis of six studies of 438 patients focused on CMV-associated complications showed an incidence of CMV infection of 17–56% (median 29%), including CMV high-level viraemia or CS-CMVi in 7–15% (median 11%). With the implementation of pre-emptive therapy, the occurrence of CMV end-organ disease was incidental.[73–79]

CMV reactivation occurs early after CAR T-cell therapy, with a median time to reactivation of 14–21 days.[73–78] This timing might be because cell-mediated immunity specific to CMV reaches a nadir 2 weeks after CAR T-cell infusion (possibly due to lymphodepleting therapy) and recovers to baseline levels by week 4.[74,75] The most common clinical manifestation is symptoms such as CMV syndrome after solid organ transplant.[74]

Patients receiving immunomodulating or immunosuppressive treatments, particularly corticosteroids and tocilizumab, for the management of CAR T-cell-related toxicities have an increased risk of CMV reactivation. Factors contributing to the high risk of any CMV reactivation include patients with CMV DNAaemia before CAR T-cell infusion, those developing grade 3–4 cytokine release syndrome (CRS), use of corticosteroids for more than 3 days, and persistent lymphocytopenia less than 200 cells per µL, or use of two or more immunosuppressants.[74,78,79] Other reported risk factors for CMV viraemia include being older than 50 years[77] and application of CAR T cells directed to BCMA.[75]

CMV in patients receiving T-cell-engaging antibodies

More data allowing risk assessment regarding CMV reactivation and CMV disease is necessary in this patient population. In general, the risk seems to be low. However, case reports exist regarding the development of CMV disease. Furthermore, prolonged use of T-cell-engaging antibodies might lead to T-cell exhaustion,[80–82] and there are reports of other infections characteristic for patients with severe T-cell suppression such as Epstein–Barr virus infection, symptomatic adenovirus infection, and even JC-virus-associated progressive multifocal leukoencephalopathy. The risk might also be increased in patients receiving consecutive therapies with bispecific antibodies and CAR T cells, as is increasingly used in patients with B-cell acute lymphoblastic leukaemia, B-cell non-Hodgkin lymphoma, and multiple myeloma. Risk factors for CMV reactivation after T-cell-engaging therapy seem similar to those reported to be of importance in patients treated with CAR T cells with the exception of lymphodepletion, including CRS grade of 2 or greater, receiving corticosteroids for more than 3 days, but also combination therapy with anti-CD38 antibodies,

	ESCMID grade
Patients treated with CAR T cells	
CMV monitoring is only required in patients who are CMV seropositive before CAR T-cell therapy	AIIu
In CMV-seropositive patients, a viral load determination should be done before lymphodepletion begins; if the tests show evidence of CMV replication, close monitoring is recommended	BIIu
Active monitoring for CMV DNAaemia testing should be considered between 2 weeks and 6 weeks after cell infusion in CAR-T-cell recipients at high risk	AIIu for high risk; BIIu for others
Pre-emptive antiviral treatment could be considered in cases of high level or rapidly increasing levels of CMV DNAaemia	BIIu
Whether CAR T cells directed against different antigens have the same risk for CMV reactivation is unclear, and therefore the same strategy should be used regardless of the target	BIII
Letermovir prophylaxis is not recommended	No recommendation grade can be given
Patients receiving bispecific T cell-engaging antibodies	
CMV testing is only required in patients who are CMV-seropositive before treatment with bispecific antibodies	AIIu
In CMV-seropositive patients, a viral load determination could be done before therapy with bispecific antibodies begins	CIII
If the tests show evidence of CMV replication, close monitoring is recommended	BIIt
Testing for CMV DNAaemia could be considered in febrile patients who have received bispecific antibodies for >4 weeks	BIII
Antiviral treatment could be considered in case of symptoms and high level or rapidly increasing levels of CMV DNAaemia	BIII

CAR=chimeric antigen receptor. CMV=cytomegalovirus. ESCMID=European Society for Clinical Microbiology and Infectious Diseases.

Table 4: **Recommendations for CMV management in patients who received CAR T cells or therapy with T-cell engaging-antibodies**

immunomodulatory drugs, and proteasome inhibitors. Whether T-cell-engaging antibodies directed against different antigens have the same risk for CMV reactivation is unclear; therefore, the same strategy should be used.

Therefore, the recommendations (table 4) should be seen as provisional and aimed at stimulating increased attention to the possibility of CMV as a pathogen in the patient group. Furthermore, further research and structured reporting of CMV reactivation and disease are of major importance.

Conclusions and future directions

Major advances have been made regarding CMV diagnostics and management, and antiviral prophylaxis is now the most essential part of CMV management after allogeneic HCT. However, further refinement regarding which patients need antiviral prophylaxis, including children, is necessary. Future studies are also needed to better separate letermovir blips from CMV reactivations for which interventions with pre-emptive therapy are needed. Other areas requiring additional development include how to implement immune monitoring into treatment strategies. For example, helping to establish the duration of prophylaxis and management of antiviral resistance, especially with the introduction of new drugs. Interesting work is ongoing with CMV vaccines, but no data are available to assess a possible introduction in a future CMV management framework. New treatment options have emerged but are associated with an increased rate of antiviral resistance. Patients with resistant or refractory infections represent an unmet medical need and require other therapeutic options. Combination therapies and future studies of adoptive virus-specific T-cell therapies are possible ways to address this gap. New patient groups are becoming of interest, but further research is needed to identify the importance of CMV in these groups.

Search strategy and selection criteria

A working group was convened and divided into teams addressing subtopics. Each team searched MEDLINE (including MEDLINE In Process) for papers published from July 1, 2017, to June 30, 2024, to identify potentially relevant English language studies related to cytomegalovirus (CMV) infection or disease in patients after allogeneic haematopoietic cell transplantation, patients treated with chimeric antigen receptor T cells, and in patients treated with bispecific T-cell-engaging antibodies. Each team used their own search terms based on their subtopic. Specifically addressed topics included diagnostics, antiviral prophylaxis, pre-emptive therapy, monitoring of CMV-specific cell-mediated immunity, paediatrics, and management of resistant and refractory CMV. References were also screened for other potentially relevant papers.

Contributors

The manuscript is based on the European Conference on Infections in Leukaemia (ECIL) guidelines update working group on cytomegalovirus (CMV) infections. The group was co-chaired by PL and RdlC. PL wrote the first draft of the paper. All authors participated equally in reviewing the literature, preparing the guidelines, and finalising the paper.

Declaration of interests

PL has served as a consultant and speaker for MSD, a consultant and speaker for Moderna, a speaker for Biotest, and a consultant for Anocca Pharmaceuticals and Takeda on CMV. RFC serves as a consultant, speaker, or scientific advisor related to CMV for Merck (USA), MSD (Europe), Takeda, Oxford Immunotec, Moderna, and Eurofins-Viracor. He received research grants related to CMV paid to his institution from Merck, Takeda, Oxford Immunotec, and Eurofins Viracor. JS served as a speaker, and a member of an advisory board for Merck (USA) and MSD

(Europe). DN reports grants from Pfizer, Roche Diagnostics, BioMerieux, and Abbott Diagnostic and consulting fees and honoraria from Pfizer, Roche Diagnostics, BioMerieux, Gilead, Takeda, and Abbott Diagnostic. HHH has received an honorarium for consulting for Allovir, AstraZeneca, Roche, Moderna, and VeraTx and as speaker for Eurofins-Viracor, Takeda, Biotest, VeraTx, and Gilead. AS-K has served as a speaker for Astellas. RdlC has served as a consultant and speaker for MSD and Moderna for CMV. SA reports research grants to her institution from Takeda, MSD, Hologic, and Elitech. FG and HE declare no competing interests.

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References

1 Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol* 2016; **3**: e119–27.

2 Sadowska-Klasa A, Özkök S, Xie H, et al. Late cytomegalovirus disease after hematopoietic cell transplantation: significance of novel transplantation techniques. *Blood Adv* 2024; **8**: 3639–51.

3 Camacho-Bydume C, Mauguen A, Rodriguez-Sanchez MI, et al. Time to initiation of pre-emptive therapy for cytomegalovirus impacts overall survival in pediatric hematopoietic stem cell transplant recipients. *Cytotherapy* 2022; **24**: 428–36.

4 Czyżewski K, Styczyński J, Giebel S, et al. Age-dependent determinants of infectious complications profile in children and adults after hematopoietic cell transplantation: lesson from the nationwide study. *Ann Hematol* 2019; **98**: 2197–211.

5 Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis* 2019; **19**: e260–72.

6 Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect* 2012; **18** (suppl 7): 53–67.

7 Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3-prevention of cytomegalovirus infection and disease after hematopoietic cell transplantation. *Transplant Cell Ther* 2021; **27**: 707–19.

8 Ljungman P, Tridello G, Piñana JL, et al. Improved outcomes over time and higher mortality in CMV seropositive allogeneic stem cell transplantation patients with COVID-19: an infectious disease working party study from the European Society for Blood and Marrow Transplantation registry. *Front Immunol* 2023; **14**: 1125824.

9 Boeckh M, Nichols WG. The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. *Blood* 2004; **103**: 2003–08.

10 Ince E, Galimard JE, Ifversen M, et al. Donor cytomegalovirus serology impacts overall survival in children receiving first unrelated hematopoietic stem cell transplant for acute leukemia: European Society of Bone Marrow Transplantation Pediatric Diseases Working Party Study. *Haematologica* 2024; published online Nov 24. https://doi.org/10.3324/haematol.2024.286082.

11 Su Y, Stern A, Karantoni E, et al. Impact of letermovir primary cytomegalovirus prophylaxis on 1-year mortality after allogeneic hematopoietic cell transplantation: a retrospective cohort study. *Clin Infect Dis* 2022; **75**: 795–804.

12 Febres-Aldana A, Khawaja F, Morado-Aramburo O, et al. Mortality in recipients of allogeneic haematopoietic cell transplantation in the era of cytomegalovirus primary prophylaxis: a single-centre retrospective experience. *Clin Microbiol Infect* 2024; **30**: 803–9.

13 Sassine J, Khawaja F, Shigle TL, et al. Refractory and resistant cytomegalovirus after hematopoietic cell transplant in the letermovir primary prophylaxis era. *Clin Infect Dis* 2021; **73**: 1346–54.

14 Morton S, Danby R, Rocha V, Peniket A, Murphy MF. Transfusion of CMV-unselected blood components may lead to inappropriate donor selection for patients subsequently undergoing allogeneic stem cell transplant. *Transfus Med* 2015; **25**: 411–13.

15 Portillo V, Masouridi-Levrat S, Royston L, et al. Revisiting cytomegalovirus serology in allogeneic hematopoietic cell transplant recipients. *Clin Infect Dis* 2024; **78**: 423–29.

16 Sayyed A, Wilson L, Stavi V, et al. Impact of cytomegalovirus (CMV) seroconversion pre-allogeneic hematopoietic cell transplantation on posttransplant outcomes. *Eur J Haematol* 2024; **113**: 441–53.

17 Preiksaitis JK, Hayden RT, Tong Y, et al. Are we there yet? Impact of the first International Standard for cytomegalovirus DNA on the harmonization of results reported on plasma samples. *Clin Infect Dis* 2016; **63**: 583–89.

18 Hayden RT, Sun Y, Tang L, et al. Progress in quantitative viral load testing: variability and impact of the WHO Quantitative International Standards. *J Clin Microbiol* 2017; **55**: 423–30.

19 Vinuesa V, Giménez E, Solano C, et al. Factors influencing cytomegalovirus DNA load measurements in whole blood and plasma specimens from allogeneic hematopoietic stem cell transplant recipients. *Diagn Microbiol Infect Dis* 2019; **94**: 22–27.

20 Lazzarotto T, Chiereghin A, Piralla A, et al. Cytomegalovirus and Epstein-Barr virus DNA kinetics in whole blood and plasma of allogeneic hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant* 2018; **24**: 1699–706.

21 Babady NE, Cheng C, Cumberbatch E, Stiles J, Papanicolaou G, Tang YW. Monitoring of cytomegalovirus viral loads by two molecular assays in whole-blood and plasma samples from hematopoietic stem cell transplant recipients. *J Clin Microbiol* 2015; **53**: 1252–57.

22 Giménez E, Muñoz-Cobo B, Solano C, Amat P, Navarro D. Early kinetics of plasma cytomegalovirus DNA load in allogeneic stem cell transplant recipients in the era of highly sensitive real-time PCR assays: does it have any clinical value? *J Clin Microbiol* 2014; **52**: 654–56.

23 Solano C, Giménez E, Piñana JL, et al. Preemptive antiviral therapy for CMV infection in allogeneic stem cell transplant recipients guided by the viral doubling time in the blood. *Bone Marrow Transplant* 2016; **51**: 718–21.

24 Funk GA, Gosert R, Hirsch HH. Viral dynamics in transplant patients: implications for disease. *Lancet Infect Dis* 2007; **7**: 460–72.

25 Leuzinger K, Stolz D, Gosert R, et al. Comparing cytomegalovirus diagnostics by cell culture and quantitative nucleic acid testing in broncho-alveolar lavage fluids. *J Med Virol* 2021; **93**: 3804–12.

26 Tilloy V, Díaz-González D, Laplace L, et al. Comprehensive herpesviruses antiviral drug resistance mutation database (CHARMD). *Antiviral Res* 2024; **231**: 106016.

27 Centre National de Référence des Herpèsvirus. Comprehensive herpesviruses antiviral drug resistance mutation database (CHARMD). https://www.unilim.fr/cnr-herpesvirus/outils/codexmv/database/all_references (accessed Jan 20, 2025)

28 Sylwester AW, Mitchell BL, Edgar JB, et al. Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects. *J Exp Med* 2005; **202**: 673–85.

29 Gratama JW, Boeckh M, Nakamura R, et al. Immune monitoring with iTAg MHC Tetramers for prediction of recurrent or persistent cytomegalovirus infection or disease in allogeneic hematopoietic stem cell transplant recipients: a prospective multicenter study. *Blood* 2010; **116**: 1655–62.

30 Hall VG, Humar A, Kumar D. Utility of cytomegalovirus cell-mediated immunity assays in solid organ transplantation. *J Clin Microbiol* 2022; **60**: e01716–21.

31 Callens R, Colman S, Delie A, et al. Immunologic monitoring after allogeneic stem cell transplantation: T-SPOT.CMV and QuantiFERON-CMV, are they the same? *Transplant Cell Ther* 2023; **29**: 392e1–7.

32 Chemaly RF, El Haddad L, Winston DJ, et al. Cytomegalovirus (CMV) cell-mediated immunity and CMV infection after allogeneic hematopoietic cell transplantation: the REACT study. *Clin Infect Dis* 2020; **71**: 2365–74.

33 El Haddad L, Ariza-Heredia E, Shah DP, et al. The ability of a cytomegalovirus ELISPOT assay to predict outcome of low-level CMV reactivation in hematopoietic cell transplant recipients. *J Infect Dis* 2019; **219**: 898–907.

34 Nesher L, Shah DP, Ariza-Heredia EJ, et al. Utility of the enzyme-linked Immunospot interferon-γ-release assay to predict the risk of cytomegalovirus infection in hematopoietic cell transplant recipients. *J Infect Dis* 2016; **213**: 1701–07.

35 Yong MK, Cameron PU, Slavin M, et al. Identifying cytomegalovirus complications using the quantiferon-CMV assay after allogeneic hematopoietic stem cell transplantation. *J Infect Dis* 2017; **215**: 1684–94.

36 Wagner-Drouet E, Teschner D, Wolschke C, et al. Standardized monitoring of cytomegalovirus-specific immunity can improve risk stratification of recurrent cytomegalovirus reactivation after hematopoietic stem cell transplantation. *Haematologica* 2021; **106**: 363–74.

37 Ljungman P, Schmitt M, Marty FM, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis* 2020; **70**: 1525–33.

38 Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* 2017; **377**: 2433–44.

39 Vyas A, Raval AD, Kamat S, LaPlante K, Tang Y, Chemaly RF. Real-world outcomes associated with letermovir use for cytomegalovirus primary prophylaxis in allogeneic hematopoietic cell transplant recipients: a systematic review and meta-analysis of observational studies. *Open Forum Infect Dis* 2022; **10**: ofac687.

40 Marty FM, Ljungman PT, Chemaly RF, et al. Outcomes of patients with detectable CMV DNA at randomization in the phase III trial of letermovir for the prevention of CMV infection in allogeneic hematopoietic cell transplantation. *Am J Transplant* 2020; **20**: 1703–11.

41 Cassaniti I, Colombo AA, Bernasconi P, et al. Positive HCMV DNAemia in stem cell recipients undergoing letermovir prophylaxis is expression of abortive infection. *Am J Transplant* 2021; **21**: 1622–28.

42 Yan B, Sun G, Wu Y, et al. Letermovir prophylaxis reduced cytomegalovirus reactivation and resistance post umbilical cord blood transplantation. *Br J Haematol* 2024; **204**: 2378–89.

43 Gimenez E, Guerreiro M, Torres I, et al. Features of cytomegalovirus DNAemia and virus-specific T-cell responses in allogeneic hematopoietic stem-cell transplant recipients during prophylaxis with letermovir. *Transpl Infect Disease* 2023; **25**: e14021.

44 Studer U, Khanna N, Leuzinger K, et al. Incidence of CMV replication and the role of letermovir primary/secondary prophylaxis in the early phase after allogeneic hematopoietic stem cell transplantation—a single centre study. *Anticancer Res* 2020; **40**: 5909–17.

45 Russo D, Schmitt M, Pilorge S, et al. Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol* 2024; **11**: e127–35.

46 Politikos I, Lau C, Devlin SM, et al. Extended-duration letermovir prophylaxis for cytomegalovirus infection after cord blood transplantation in adults. *Blood Adv* 2022; **6**: 6291–300.

47 Robin C, Thiebaut A, Alain S, et al. Letermovir for secondary prophylaxis of cytomegalovirus infection and disease after allogeneic hematopoietic cell transplantation: results from the French Compassionate Program. *Biol Blood Marrow Transplant* 2020; **26**: 978–84.

48 Styczyński J, Tridello G, Xhaard A, et al. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. *Bone Marrow Transplant* 2021; **56**: 1171–79.

49 Lin A, Maloy M, Su Y, et al. Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: real-world experience. *Transpl Infect Disease* 2019; **21**: e13187.

50 Douglas CM, Barnard R, Holder D, et al. Letermovir resistance analysis in a clinical trial of cytomegalovirus prophylaxis for hematopoietic stem cell transplant recipients. *J Infect Dis* 2020; **221**: 1117–26.

51 Alain S, Feghoul L, Girault S, et al. Letermovir breakthroughs during the French Named Patient Programme: interest of monitoring blood concentration in clinical practice. *J Antimicrob Chemother* 2020; **75**: 2253–57.

52 Prentice HG, Gluckman E, Powles RL, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. *Lancet* 1994; **343**: 749–53.

53 Ljungman P, de La Camara R, Milpied N, et al. Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. *Blood* 2002; **99**: 3050–56.

54 Burns LJ, Miller W, Kandaswamy C, et al. Randomized clinical trial of ganciclovir vs acyclovir for prevention of cytomegalovirus antigenemia after allogeneic transplantation. *Bone Marrow Transplant* 2002; **30**: 945–51.

55 Galaverna F, Baccelli F, Zama D, et al. Letermovir for cytomegalovirus infection in pediatric patients undergoing allogenic hematopoietic stem cell transplantation: a real-life study by the Infectious Diseases Working Group of Italian Association of Pediatric Hematology-Oncology (AIEOP). *Bone Marrow Transplant* 2024; **59**: 505–12.

56 Styczynski J. Comment on: Letermovir for cytomegalovirus prophylaxis in pediatric hematopoietic cell transplantation. *Pediatr Blood Cancer* 2023; **70**: e30692.

57 Körholz KF, Füller MA, Hennies M, et al. Letermovir for prophylaxis and pre-emptive therapy of cytomegalovirus infection in paediatric allogeneic haematopoietic cell transplant patients. *Paediatr Drugs* 2023; **25**: 225–32.

58 Chen TT, David AP, Barthelmess EK, MacBrayne CE. Letermovir for cytomegalovirus prophylaxis in pediatric hematopoietic stem cell transplantation. *Pediatr Blood Cancer* 2023; **70**: e30608.

59 César T, Le MP, Klifa R, et al. Letermovir for CMV prophylaxis in very high-risk pediatric hematopoietic stem cell transplantation recipients for inborn errors of immunity. *J Clin Immunol* 2023; **44**: 6.

60 Groll AH, Schulte JH, Antmen AB, et al. Pharmacokinetics, safety, and efficacy of letermovir for cytomegalovirus prophylaxis in adolescent hematopoietic cell transplantation recipients. *Pediatr Infect Dis J* 2024; **43**: 203–08.

61 Schulte JH, Gefen A, Groll AH, et al. Cytomegalovirus (CMV) prophylaxis with letermovir (LET) in pediatric (birth to < 18 years of age) allogeneic hematopoietic cell transplant (HCT) recipients: pharmacokinetics (PK), safety and efficacy results of a phase 2b study. *Open Forum Infect Dis* 2023; **10**: 0fad500.2180.

62 Ljungman P, Chemaly RF, Khawaya F, et al. Consensus definitions of cytomegalovirus (CMV) infection and disease in transplant patients including resistant and refractory CMV for use in clinical trials: 2024 update from the Transplant Associated Virus Infections Forum. *Clin Infect Dis* 2024; **79**: 787–94.

63 Sadowska-Klasa A, Leisenring WM, Limaye AP, Boeckh M. Cytomegalovirus viral load threshold to guide preemptive therapy in hematopoietic cell transplant recipients: correlation with cytomegalovirus disease. *J Infect Dis* 2024; **229**: 1435–39.

64 Papanicolaou GA, Avery RK, Cordonnier C, et al. Treatment for first cytomegalovirus infection post-hematopoietic cell transplant in the AURORA Trial: a multicenter, double-blind, randomized, phase 3 trial comparing maribavir with valganciclovir. *Clin Infect Dis* 2024; **78**: 562–72.

65 Shmueli E, Or R, Shapira MY, et al. High rate of cytomegalovirus drug resistance among patients receiving preemptive antiviral treatment after haploidentical stem cell transplantation. *J Infect Dis* 2014; **209**: 557–61.

66 Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. *Ann Intern Med* 2015; **162**: 1–10.

67 Allice T, Busca A, Locatelli F, Falda M, Pittaluga F, Ghisetti V. Valganciclovir as pre-emptive therapy for cytomegalovirus infection post-allogenic stem cell transplantation: implications for the emergence of drug-resistant cytomegalovirus. *J Antimicrob Chemother* 2009; **63**: 600–08.

68 Chemaly RF, Chou S, Einsele H, et al. Definitions of resistant and refractory cytomegalovirus infection and disease in transplant recipients for use in clinical trials. *Clin Infect Dis* 2019; **68**: 1420–26.

69 Yong MK, Shigle TL, Kim YJ, Carpenter PA, Chemaly RF, Papanicolaou GA. American Society for Transplantation and Cellular Therapy Series: #4—cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation. *Transplant Cell Ther* 2021; **27**: 957–67.

70 Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. *Clin Infect Dis* 2022; **75**: 690–701.

71 Chou S, Alain S, Cervera C, et al. Drug resistance assessed in a phase 3 clinical trial of maribavir therapy for refractory or resistant cytomegalovirus infection in transplant recipients. *J Infect Dis* 2024; **229**: 413–21.

72 Chou S, Winston DJ, Avery RK, et al. Comparative emergence of maribavir and ganciclovir resistance in a randomized phase 3 clinical trial for treatment of cytomegalovirus infection. *J Infect Dis* 2024; published online Sept 24. https://doi.org/10.1093/infdis/jiae469.

73 Beyar-Katz O, Kikozashvili N, Bar On Y, et al. Characteristics and recognition of early infections in patients treated with commercial anti-CD19 CAR-T cells. *Eur J Haematol* 2022; **108**: 52–60.

74 Lin RY, Anderson AD, Natori Y, et al. Incidence and outcomes of cytomegalovirus reactivation after chimeric antigen receptor T-cell therapy. *Blood Adv* 2024; **8**: 3813–22.

75 Kampouri E, Ibrahimi SS, Xie H, et al. Cytomegalovirus (CMV) reactivation and CMV-specific cell-mediated immunity after chimeric antigen receptor T-Cell therapy. *Clin Infect Dis* 2024; **78**: 1022–32.

76 Solano de la Asuncion C, Hernani R, Albert E, et al. Cytomegalovirus DNAemia in haematological patients undergoing CD19-directed chimeric antigen receptor T-cell therapy: should it be systematically monitored? *Clin Microbiol Infect* 2023; **29**: 1093–95.

77 Chen G, Herr M, Nowak J, et al. Cytomegalovirus reactivation after CD19 CAR T-cell therapy is clinically significant. *Haematologica* 2023; **108**: 615–20.

78 Márquez-Algaba E, Iacoboni G, Pernas B, et al. Impact of cytomegalovirus replication in patients with aggressive B cell lymphoma treated with chimeric antigen receptor T cell therapy. *Transplant Cell Ther* 2022; **28**: 851 e1–8.

79 Khawaja F, Ahmed S, Iyer SP, et al. Cytomegaloviral infections in recipients of chimeric antigen receptor T-cell therapy: an observational study with focus on oncologic outcomes. *Open Forum Infect Dis* 2024; **11**: ofae422.

80 Philipp N, Kazerani M, Nicholls A, et al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. *Blood* 2022; **140**: 1104–18.

81 van de Donk NWCJ, Chari A, Mateos MV. Mechanisms of resistance against T-cell engaging bispecific antibodies in multiple myeloma: implications for novel treatment strategies. *Lancet Haematol* 2024; **11**: e693–707.

82 Verkleij CPM, O'Neill CA, Broekmans MEC, et al. T-cell characteristics impact response and resistance to T-cell-redirecting bispecific antibodies in multiple myeloma. *Clin Cancer Res* 2024; **30**: 3006–22.

J Antimicrob Chemother 2016; **71**: 2405–2413
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ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients

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The initiation of systemic antimicrobial treatment of *Pneumocystis jirovecii* pneumonia (PCP) is triggered by clinical signs and symptoms, typical radiological and occasionally laboratory findings in patients at risk of this infection. Diagnostic proof by bronchoalveolar lavage should not delay the start of treatment. Most patients with haematological malignancies present with a severe PCP; therefore, antimicrobial therapy should be started intravenously. High-dose trimethoprim/sulfamethoxazole is the treatment of choice. In patients with documented intolerance to this regimen, the preferred alternative is the combination of primaquine plus clindamycin. Treatment success should be first evaluated after 1 week, and in case of clinical non-response, pulmonary CT scan and bronchoalveolar lavage should be repeated to look for secondary or co-infections. Treatment duration typically is 3 weeks and secondary anti-PCP prophylaxis is indicated in all patients thereafter. In patients with critical respiratory failure, non-invasive ventilation is not significantly superior to intubation and mechanical ventilation. The administration of glucocorticoids must be decided on a case-by-case basis.

Introduction

The impact of *Pneumocystis jirovecii* pneumonia (PCP) on morbidity and mortality of immunocompromised patients is substantial. Up to 40% of patients with acute lymphoblastic leukaemia or lymphoproliferative diseases are affected, unless systemic prophylaxis is given.[1] Patients with PCP have an almost 50% incidence of acute lung injury,[2] while survivors have a higher risk of long-term deterioration of lung function (chronic lung injury) than survivors of bacterial pneumonia.[3] In HIV-positive patients, outcome has been improved over the past few decades by early diagnosis, refined intensive care management (low tidal volume, conservative fluid management), identification and effective treatment of co-infections, adjunctive glucocorticosteroids (GCS; in patients with an oxygen partial pressure PaO_2 <9.3 kPa), secondary PCP prophylaxis and early combination antiretroviral therapy.[4] We aimed to provide an updated, evidence-based guideline for the treatment and secondary prevention of PCP in patients with haematological diseases. Separate guidelines by ECIL expert groups focus on epidemiology, risk factors, diagnosis and prevention of PCP.[5–7]

Methodology

Search criteria

A systematic literature review was performed using the PubMed database for publications up to September 2015 for the following MeSH terms: 'pneumocystis OR *Pneumocystis carinii* OR *Pneumocystis jirovecii* AND pneumonia'; 'pneumonia AND neutropenia OR treatment OR haematological malignancies OR stem cell transplantation'. The group co-authoring this manuscript reviewed the 195 publications identified and prepared a slide set comprising evidence-based statements and recommendations presented to the plenary session at the ECIL-6 meeting, 11–12 September 2015, Nice, France. After revision according to the results of the plenary discussion, a summarizing slide set was made available at www.kobe.fr/ecil in November 2015. The final manuscript has been written and revised by all co-authors. Recommendations were graded according to the ECIL-6 evidence-based medicine (EBM) grading system, compatible with the EBM grading system of ESCMID.[6,8]

Symptoms of PCP in haematology patients

Among 55 patients with haematological malignancies who had PCP during the period 1990–99, the characteristic clinical presentation was acute onset with fever (86%), dyspnoea (78%), non-productive cough (71%) and severe hypoxaemia (71%), while thoracic pain (14%) and chills (5%) were less commonly observed.[9] In another retrospective analysis of 56 patients, of whom 44 (78.6%) had haematological malignancies, 18 had undergone HSCT and 12 patients had solid tumours, the main symptoms were fever (85.7%), dyspnoea (78.6%) and cough (57.1%). Their clinical course was rather acute with a median time from symptom onset of 7 (3–14) days. PCP presented as severe pneumonia [PaO_2, 58 mmHg/Torr (range 50–70)] with bilateral interstitial infiltrates (80.4%) and bilateral ground-glass attenuation (89.3%) on CT scans. Twenty-four patients (42.9%) required referral to an ICU, 11 (19.6%) underwent mechanical ventilation, and 11 patients died.[10]

Importantly, a wide range of co-infections, particularly pulmonary, are present in 28%–71% of patients, with multiple potentially involved pathogens such as *Staphylococcus aureus*, Gram-negative bacteria, *Aspergillus* species or cytomegalovirus (CMV).

In allogeneic HSCT recipients, PCP is associated with CMV pneumonia in ∼50% of cases.[11–14]

Criteria for initiation of PCP treatment

As delay of treatment increases the need for mechanical ventilation and mortality, prompt initiation of PCP-specific treatment is of critical importance.[15–18] Initiation of treatment should not be deferred by diagnostic procedures, such as bronchoalveolar lavage (BAL), since *P. jirovecii* remains detectable in bronchial secretions for many days after the start of systemic treatment.[19] PCP is highly likely in patients at risk who present with clinical symptoms mentioned above.[20] Prompt diagnostic procedures and antimicrobial treatment against *P. jirovecii* should be triggered by composite criteria (**A-III**) (Figure 1), as single clinical diagnostic criteria are insufficient to prove the diagnosis.

Grading of PCP severity and prognostic factors

For the decision on the planned duration and the route of administration of systemic antimicrobial treatment, PCP in HIV-positive patients has been categorized as mild, moderate or severe (Table 1).[21] For moderate and severe PCP, treatment recommendations do not differ substantially. In non-HIV patients, differentiation of PCP severity has not been specifically addressed in prospective clinical studies. However, recommendations regarding first-line antimicrobial treatment refer to a grading of PCP severity also in non-HIV patients, while in clinical practice most non-HIV patients do have severe disease at the time of diagnosis. It appears therefore appropriate to grade the severity of PCP in non-HIV patients into mild versus moderate-to-severe (**B-III**). For assessment of PCP severity, the use of conventional grading systems used for community-acquired pneumonia (such as A-DROP, CURB-65 or Pneumonia Severity Index) has been shown to underestimate the severity of PCP in non-HIV patients;[22] therefore, their use in this setting is not recommended (**D-II*u*; formerly B-II against use**). The grading system of Miller[21] appears to provide the most useful criteria for PCP severity assessment in non-HIV patients (**B-III**). Importantly, not only oxygen saturation should be used, but also clinical criteria such as respiratory rate, age, co-morbidities or additional organ dysfunction must be taken into account (**A-II*u*, formerly A-II**).

For prediction of poor clinical outcome in non-HIV patients with PCP, both factors present at treatment onset and factors presenting later during antimicrobial therapy have been identified (Table 2).

First-line treatment

Selection of drugs

In haematological patients, prospective randomized clinical trials on the optimal selection of antimicrobial agents for the treatment of PCP have not been conducted. Therefore, therapeutic recommendations are based on those in HIV-associated PCP and observational studies on treatment including haematological patients (Table 3). In a comprehensive literature review, we have assessed the outcome of different treatment regimens among non-HIV patients with PCP. Published reports on treatment results in this patient cohort included ∼800 patients treated first-line with trimethoprim/sulfamethoxazole[23–27] and <40 patients who received this regimen in combination with other antimicrobials or other drugs including pentamidine, atovaquone or primaquine/clindamycin.[9,13,28–31] For first-line treatment (Table 4),

- Patient at risk

  with
- Clinical signs and symptoms
  - Dyspnoea and/or cough
  - Fever (may rarely be absent)
  - Hypoxaemia (may not yet be present)
  - Chest pain (rare; from pneumothorax)

  with
- Suggestive radiology finding compatible with PCP (preferably thoracic CT scan)

  with or without
- Unexplained serum lactate dehydrogenase (LDH) elevation

Figure 1. Indication for starting systemic antimicrobial treatment against *P. jirovecii* in patients with haematological diseases.

Table 1. Grading of severity of *Pneumocystis* pneumonia[21]

Variable	Severity grading		
	mild	moderate	severe
Symptoms and signs	increasing exertional dyspnoea with or without cough and sweats	dyspnoea on minimal exertion, occasional dyspnoea at rest, fever with or without sweats	dyspnoea at rest, tachypnoea at rest, persistent fever, cough
Arterial oxygen tension (PaO_2) at rest, room air	>11.0 kPa (>82.5 mmHg)	8.1–11.0 kPa (60.75–82.5 mmHg)	<8.0 kPa (<60 mmHg)
Arterial oxygen saturation (SaO_2) at rest, room air	>96%	91%–96%	<91%
Chest radiograph	normal or minor perihilar shadowing	diffuse interstitial shadowing	extensive interstitial shadowing with or without diffuse alveolar shadowing ('white out') sparing costophrenic angles and apices

Table 2. Poor prognostic factors for outcome in non-HIV patients with PCP[13,20,23,25,28,31,40,56,75]

Poor prognostic factors at onset
Poor control of underlying disease
ECOG PS >2
Long-term glucocorticosteroids
Delayed onset of PCP treatment
Hypoalbuminaemia
Co-infection with HSV or CMV
High neutrophil count in BAL
High APACHE-II or SAPS-II score
Poor prognostic factors during PCP treatment
Vasopressor use/shock
Need for high-dose glucocorticosteroid treatment
Respiratory failure/high oxygen support
Need for mechanical ventilation
ARDS
Clinical worsening at day 8

ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; ECOG, Eastern Cooperative Oncology Group; HSV, herpes simplex virus; PS, performance score; SAPS, simplified acute physiology score.

trimethoprim/sulfamethoxazole at a dosage of 15–20 mg/kg (trimethoprim) and 75–100 mg/kg (sulfamethoxazole) for ≥14 days is recommended as primary choice (**A-II*r*, formerly A-II**). Co-medication with methotrexate should be avoided because of potentially serious adverse drug effects. For very obese patients, no specific dose limits have been defined. While not routinely available, therapeutic drug monitoring may be recommended in individual patients[32,33] with target peak concentration for sulfamethoxazole of 100–200 mg/L.[34] Alternative treatment regimens for patients with contraindications to trimethoprim/sulfamethoxazole include intravenous pentamidine (4 mg/kg/day),[29] primaquine/clindamycin (30 mg/day + 600 mg every 8 h daily)[30] and atovaquone (750 mg every 8–12 h daily)[30,31] (**C-II*t*, formerly C-II**, for each regimen). Prior to the use of primaquine, patients should be checked for glucose-6-phosphate dehydrogenase deficiency.

Route of administration

In patients with mild PCP (which are rarely seen in haematology), an oral strategy is possible from the beginning for compliant patients in whom enteral absorption is not compromised (**B-II*t*, formerly B-II**).[35] The dosage of drugs should be identical for oral and intravenous administration (**A-II*t*, formerly A-II**). In patients with moderate-to-severe PCP, treatment should be started intravenously (**A-II*u*, formerly A-II**). A switch to oral therapy can be considered, once clinical improvement is achieved in compliant patients in whom enteral absorption is not compromised (**A-II*u*, formerly A-II**).[36,37]

Assessment of treatment response

The efficacy of systemic antimicrobial treatment should be assessed on a daily basis. While early clinical deterioration (within the first 3–5 days after treatment initiation) is common, re-evaluation should not be done before 8 days of full-dose treatment (**A-III**). In a study on non-HIV patients with PCP, radiologic improvement by repeated thoracic CT scan during treatment was seen in 57% of patients at a median of 13 days after initiation of therapy.[38]

In patients without clinical improvement and/or with worsening of respiratory function documented by arterial blood gases after 8 days of adequate anti-PCP treatment, clinical failure should be suspected. β-D-Glucan monitoring is not recommended for response assessment (**D-II*u***), as there are conflicting data for serum β-D-glucan during the course of PCP; elevated levels may indicate treatment failure or another fungal co-infection, whereas decreasing levels are not clearly predictive of treatment success.[29,39]

In patients with clinically documented treatment failure at day 8, a repeat bronchoscopy and BAL to look for co-infections should be ordered (**A-III**). Co-infections are present in 20% of patients at time of admission to an ICU, while another 22% of patients with PCP acquire relevant second infections during ICU treatment.[40]

Table 3. Studies on first-line and salvage antimicrobial treatment of PCP

Population	Intention	Intervention	References	Comment
First-line treatment				
HM, SOT, cancer, autoimmune/inflammatory diseases	cure	TMP/SMX 15–20 mg/kg (TMP) 75–100 mg/kg (SMX) per day for ≥14 days	9,24,26–29,31,45	no randomized trials; high number of cases; low toxicity
		pentamidine iv 4 mg/kg/day	29	retrospective; 5 non-HIV patients
		primaquine + clindamycin 30 mg/day + 600 mg×3/day	30	retrospective; 5 non-HIV patients
		atovaquone 750 mg×2 (or 3)/day	30,31	retrospective; 3 non-HIV patients
Second-line (salvage) treatment				
HM, SOT, cancer, autoimmune diseases	cure	primaquine (30 mg) + clindamycin (600 mg×3) per day	23,44,45	few cases
		pentamidine iv 4 mg/kg/day	9,28,44,45	few cases
		TMP/SMX (15–20 mg/kg) + caspofungin (70–50 mg/day)	47–49	few cases, no haematological patients
		echinocandin alone	76,77	only case reports

HM, haematological malignancies; iv, intravenously; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 4. Recommended first-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune/inflammatory diseases	to cure	TMP/SMX 15–20 mg/kg (TMP) 75–100 mg/kg (SMX) per day for ≥14 days	**A**	**IIr**
		pentamidine iv 4 mg/kg/day	**C**	**IIt**
		primaquine + clindamycin 30 mg/day oral + 600 mg×3/day iv or oral	**C**	**IIt**
		atovaquone 750 mg×2(or 3)/day oral	**C**	**IIt**

HM, haematological malignancies; iv, intravenously; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

For evaluation of BAL findings, the persistence of a positive *P. jirovecii* PCR should not be interpreted as treatment failure (**D-IIt, formerly A-II against use**), as *P. jirovecii* will remain detectable for days or even weeks under systemic anti-PCP treatment.[19] With respect to BAL *P. jirovecii* load using quantitative PCR, there are currently no data on the kinetics under treatment. For β-D-glucan in follow-up BAL, no data from clinical studies have been reported so far.

In addition, a new thoracic CT scan should be ordered to monitor the course of PCP-related lung infiltrates and to check for PCP complications such as spontaneous pneumothorax or pleural effusion (**A-III**).[13]

An unnecessary switch to second-line PCP treatment in patients receiving high-dose trimethoprim/sulfamethoxazole should be avoided (**A-IIt, formerly A-II**), as the efficacy of second-line treatment is less well documented than that of front-line trimethoprim/sulfamethoxazole. A switch to second-line treatment should therefore only be considered after exclusion of a co-infection or another cause of (clinical and/or radiologic) deterioration.

Dihydropteroate synthase gene mutations, while associated with failure of sulfa-based PCP prophylaxis,[41] are not associated with failure of high-dose trimethoprim/sulfamethoxazole treatment in HIV-positive or -negative patients.[42,43]

Salvage treatment (second-line treatment)

In patients with intolerance to or treatment failure under high-dose trimethoprim/sulfamethoxazole treatment, second-line (or 'salvage') therapy is required (Table 5). While clinical trials on this indication in non-HIV patients have not been reported, reports from the literature[23,44,45] suggest that first choice of drugs in this setting is the combination of primaquine and clindamycin (**B-IIt, formerly B-II**). In the setting of HIV-positive patients with PCP, Helweg-Larsen *et al.*[46] reported the results of a large observational study, in which second-line treatment with primaquine/clindamycin was superior to pentamidine, translating into reduced mortality. Prior to the use of primaquine, patients should be checked for glucose-6-phosphate dehydrogenase deficiency. Alternatives are intravenous pentamidine (4 mg/kg/day) (**B-III**)[9,28,44,45] or the combination of high-dose trimethoprim/sulfamethoxazole with caspofungin (70–50 mg per day) (**C-IIu, formerly C-II**); however, the possible efficacy of this combination

Table 5. Options for second-line treatment in non-HIV patients with PCP

Population	Intention	Intervention	SoR	QoE
HM, SOT, cancer, autoimmune diseases	cure	primaquine (30 mg) + clindamycin (600 mg × 3) per day	**B**	**IIt**
		pentamidine iv 4 mg/kg/day	**B**	**III**
		TMP/SMX (15–20 mg/kg/day) + caspofungin (70–50 mg/day)	**C**	**IIu**
		echinocandin alone	**D**	**IIu**

HM, haematological malignancies; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 6. PCP treatment: main drug-related adverse events

TMP/SMX	Clindamycin/primaquine	Pentamidine iv
• rash and fever • nephrotoxicity • electrolyte disorders • bone marrow depression • hepatotoxicity	• nausea and vomiting • neutropenia • *Clostridium difficile*-associated diarrhoea • haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency	• bone marrow suppression • nephrotoxicity • electrolyte disorders • dysglycaemia, insulin-dependent diabetes mellitus • pancreatitis • Q-T prolongation

TMP/SMX, trimethoprim/sulfamethoxazole.

has only been reported in individual patients.[47–49] An echinocandin alone should not be considered (**D-II*u*, formerly A-II against use**), because a sufficient anti-PCP efficacy has not been demonstrated,[45,50] and reports of breakthrough PCP in patients being treated with an echinocandin for other purposes have been published.[51]

Drug-related side effects and drug–drug interactions

Most of the drugs recommended for PCP treatment are associated with a substantial rate of drug-related adverse events (AEs). While a detailed discussion of these potential AE exceeds the scope of this guideline, an overview of the main side effects is given in Table 6.

Clinically important drug–drug interactions may be relevant in patients being treated for PCP. Atovaquone interacts with rifampicin and rifabutin, clindamycin with macrolide antibiotics, dapsone with rifampicin, trimethoprim and probenecid, pentamidine with foscarnet, and trimethoprim/sulfamethoxazole with dapsone and rifampicin. It is of utmost importance to check all co-medications for drug–drug interactions in patients treated for PCP.

Treatment duration

Standard duration of drug treatment in PCP is 3 weeks (**B-IIt**). In mild cases, it should be at least 2 weeks (**A-IIt, formerly A-II**). In case of slow clinical improvement, the unmodified treatment should be continued for at least 3 weeks (**A-II*u*, formerly A-II**).[13,30]

ICU management

Short- and long-term survival rates of ICU patients with haematological malignancies have improved markedly in recent years,[52,53] and haematological outcomes may not be affected by temporary organ dysfunction(s).[52,54,55] Therefore, evidence-based expert consensus recommends full ICU support for a growing number of patients.[53]

Almost every second patient with haematological malignancy and PCP develops acute respiratory failure (ARF) requiring ICU admission.[9,10,56] While mortality rates of non-HIV patients with PCP-associated ARF are generally higher than in HIV-positive patients,[57–59] the prognosis of haematological patients with PCP-associated ARF may not be different from ARF due to other aetiologies.[60] In patients with haematological malignancies, any signs or symptoms of respiratory deterioration (dyspnoea, cough, sputum, chest pain, rales, haemoptysis, increasing pulmonary infiltrates, demand for O_2 >1 L/min) are associated with the development of ARF, ICU admission and adverse outcome.[61,62] Timely recognition of such situations in patients with PCP is crucial, since late ICU transfers are associated with increased mortality rates (**A-II*h*, formerly A-II**).[63,64]

Historical data suggested that non-invasive ventilation (NIV) was associated with reduced intubation rates and improved mortality in immunosuppressed patients with hypoxic ARF, when compared with standard oxygen.[65] In accordance, a current meta-analysis of earlier, mainly observational data showed a survival benefit with NIV used as an initial ventilatory strategy when compared with invasive mechanical ventilation in patients with haematological malignancies.[66] However, a recently published large propensity score matched analysis in haematological patients[67] and a large interventional trial in immunosuppressed (mainly haematological) patients with hypoxic ARF did not show any harm or benefit of early NIV when compared with standard oxygen.[68] The discussion of these study results prompted a revision of the provisional preference (**B-I**) of the group for NIV, as stated in the original ECIL-6 slide set. While survival rates of primarily intubated haematological patients with ARF have improved steadily over the last two decades,[60] NIV failure with secondary intubation may be associated with excess mortality in (at least subgroups of) haematological patients.[66,69–71] In general, NIV failure rates in haematological patients with severe hypoxic ARF (acute respiratory distress syndrome)[60] and specifically in those with PCP are particularly high (~70%).[58] If clinicians decide to

Table 7. Adjunctive GCS in non-HIV patients with PCP

First author (year)	Number (haematological malignancy)	Years	*n* (%); mortality (%)		Mortality, total (%)
			with GCS	without GCS	
Bollée[a] (2007)[10]	56 (44)	2001–06	21 (38); 10	35 (62); 26	20
Burke (1973)[78]	46 (20)	1959–71	—	—	80
Delclaux (1999)[79]	31 (24)	1988–96	23 (74); 39	8 (26); 50	42
Overgaard[b] (2007)[80]	44 (33)	2002–04	33 (77); 12	11 (23); 20	14 (PCP)
Kofteridis (2014)[26]	62 (31)	2004–13	50 (81); 30	12 (19); 25	29 (PCP)
Lemiale[a] (2013)[40]	139 (55)	1988–2011	107 (77); 26	32 (23); 25	26 (ICU)
Moon (2011)[27]	88 (26)	2007–10	59 (67); 31	29 (33); 34	32 (3 months)
Pagano (2002)[9]	55 (55)	1990–99	22 (37); 36	33 (63); 36	29 (PCP)
Pareja[a] (1998)[81]	30 (8)	1989–95	16 (53); 44	14 (47); 36	40
Roblot (2002)[31]	103 (60)	1995–99	58 (56); ND	42 (51); ND	38 (1 month)
Zahar[a] (2002)[82]	39 (28)	1989–99	33 (79); 68	6 (15); 20	33 (3 months)

GCS, glucorticosteroids; ND, no difference.
[a]Substantial overlap of patients.
[b]Data reanalysed in 2015 by J. H.-L.

use NIV as primary ventilation strategy, the development of incipient NIV failure must be monitored closely: poor tolerance of NIV, no clinical improvement within 6 h, no improvement of arterial blood gases within 6 h, respiratory rate remaining >30/min, NIV dependency >3 days, clinical or respiratory deterioration, unknown aetiology of ARF (**A-II*h*, formerly A-II**).[72] If NIV failure becomes imminent, patients must be evaluated for prompt intubation and invasive mechanical ventilation (**A-III**).

Glucocorticosteroids as adjunctive therapy in non-HIV patients with PCP

In HIV-positive patients with moderate-to-severe PCP, evidence derived from a meta-analysis on six randomized controlled trials suggests a survival benefit of adjunctive GCS therapy.[73] Accordingly, in these patients, adjunctive GCS are strongly recommended by current guidelines.[74] However, there are no interventional trials in non-HIV patients with PCP and the results of several retrospective observations are conflicting. All reports have typical limitations of retrospective observational analyses with a substantial risk of confounding by indication: most report on small patient numbers, different doses and (often non-reported) timing of GCS treatment, different definitions regarding PCP severity, as well as considerably heterogeneous cohorts with respect to underlying diseases and proportions of haematological malignancies. No detailed data on patients with leukaemia (or subgroup analyses) are available. Furthermore, there may be considerable patient overlap between some studies (Table 7). The most recent investigation with the largest number of patients performed a pooled analysis of 139 non-HIV ICU patients with severe PCP by first employing multi-variable statistics. High-dose GCS treatment (>1 mg/kg bodyweight per day) was an independent predictor of ICU mortality but not associated with the rate of ICU-acquired infections.[40]

The routine adjunctive use of GCS in non-HIV patients with PCP and respiratory failure is not recommended. The decision to add GCS in a non-HIV patient with PCP and respiratory failure has to be made on an individual basis (**B-II*h*, formerly B-II**). A significant proportion of non-HIV patients with PCP have been treated with GCS prior to PCP onset. It remains unclear how to treat these patients (maintaining the dose versus escalation versus tapering). Investigational trials on the use of GCS accounting for previous GCS treatment and PCP severity are needed in haematology patients with PCP.

Secondary anti-PCP prophylaxis

All non-HIV patients who have been successfully treated for PCP, should be given secondary anti-PCP prophylaxis (**A-II*h*, formerly A-II**). Preferred and alternative regimens for secondary PCP prophylaxis should be chosen as for primary prophylaxis.[7] Co-medication with methotrexate may cause substantial toxicity.

A stopping rule for secondary PCP prophylaxis in patients whose immune system is recovering has not yet been defined; therefore, the decision to discontinue secondary PCP prophylaxis has to be made on an individual basis.

Conclusions

Early treatment of PCP through intravenous antimicrobial therapy is of high importance in patients with haematological malignancies, and high-dose trimethoprim/sulfamethoxazole is currently the treatment of choice. Recent recommendations from ECIL-6 provide updated, evidence-based guidelines for the treatment of PCP in this patient population, including guidance on first-line and salvage treatment, therapy duration, assessment of the treatment response and ICU management in non-HIV patients with PCP.

High-dose trimethoprim/sulfamethoxazole for over 2 weeks remains the recommended treatment in non-HIV patients with PCP (**A-II**), with primaquine plus clindamycin the preferred second-line therapy (**B-II**). The routine adjunctive use of GCS in non-HIV patients with PCP and respiratory failure is not recommended but may be used on an individual patient basis (**B-II*h***).

These recommendations should assist healthcare professionals in making timely and effective decisions in regards to treatment of PCP in this patient population.

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References

1 Hughes WT, Feldman S, Aur RJ *et al*. Intensity of immunosuppressive therapy and the incidence of *Pneumocystis carinii* pneumonitis. *Cancer* 1975; **36**: 2004–9.

2 Kojicic M, Li G, Hanson AC, Lee KM *et al*. Risk factors for the development of acute lung injury in patients with infectious pneumonia. *Crit Care* 2012; **16**: R46.

3 Morris AM, Huang L, Bacchetti P *et al*. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 2000; **162**: 612–6.

4 Zolopa A, Andersen J, Powderly W *et al*. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One* 2009; **4**: e5575.

5 Alanio A, Hauser PM, Lagrou K *et al*. ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; **71**: 2386–96.

6 Cordonnier C, Cesaro S, Maschmeyer G *et al*. *Pneumocystis jirovecii* pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; **71**: 2379–85.

7 Maertens J, Cesaro S, Maschmeyer G *et al*. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; **71**: 2397–404.

8 Ullmann AJ, Akova M, Herbrecht R *et al*. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect* 2012; **18** Suppl 7: 53–67.

9 Pagano L, Fianchi L, Mele L *et al*. *Pneumocystis carinii* pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. *Br J Haematol* 2002; **117**: 379–86.

10 Bollée G, Sarfati C, Thiéry G *et al*. Clinical picture of *Pneumocystis jiroveci* pneumonia in cancer patients. *Chest* 2007; **132**: 1305–10.

11 Ewig S, Bauer T, Schneider C *et al*. Clinical characteristics and outcome of *Pneumocystis carinii* pneumonia in HIV-infected and otherwise immunosuppressed patients. *Eur Respir J* 1995; **8**: 1548–53.

12 Toper C, Rivaud E, Daniel C *et al*. [*Pneumocystis jirovecii* pneumonia in non-HIV infected patients: a study of 41 cases]. *Rev Pneumol Clin* 2011; **67**: 191–8.

13 Torres HA, Chemaly RF, Storey R *et al*. Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of *Pneumocystis jiroveci* pneumonia in cancer patients. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 382–8.

14 Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 1996; **71**: 5–13.

15 Asai N, Motojima S, Ohkuni Y *et al*. Early diagnosis and treatment are crucial for the survival of *Pneumocystis* pneumonia patients without human immunodeficiency virus infection. *J Infect Chemother* 2012; **18**: 898–905.

16 Guo F, Chen Y, Yang SL *et al*. *Pneumocystis* pneumonia in HIV-infected and immunocompromised non-HIV infected patients: a retrospective study of two centers in China. *PLoS One* 2014; **9**: e101943.

17 Li MC, Lee NY, Lee CC *et al*. *Pneumocystis jiroveci* pneumonia in immunocompromised patients: delayed diagnosis and poor outcomes in non-HIV-infected individuals. *J Microbiol Immunol Infect* 2014; **47**: 42–7.

18 Roux A, Canet E, Valade S *et al*. *Pneumocystis jirovecii* pneumonia in patients with or without AIDS, France. *Emerg Infect Dis* 2014; **20**: 1490–7.

19 Roger PM, Vandenbos F, Pugliese P *et al*. Persistence of *Pneumocystis carinii* after effective treatment of *P. carinii* pneumonia is not related to relapse or survival among patients infected with human immunodeficiency virus. *Clin Infect Dis* 1998; **26**: 509–10.

20 Roux A, Gonzalez F, Roux M *et al*. Update on pulmonary *Pneumocystis jirovecii* infection in non-HIV patients. *Med Mal Infect* 2014; **44**: 185–98.

21 Miller RF, Le Noury J, Corbett EL *et al*. *Pneumocystis carinii* infection: current treatment and prevention. *J Antimicrob Chemother* 1996; **37** Suppl B: 33–53.

22 Asai N, Motojima S, Ohkuni Y *et al*. Non-HIV *Pneumocystis* pneumonia: do conventional community-acquired pneumonia guidelines under estimate its severity? *Multidiscip Respir Med* 2012; **7**: 2.

23 Boonsarngsuk V, Sirilak S, Kiatboonsri S. Acute respiratory failure due to *Pneumocystis* pneumonia: outcome and prognostic factors. *Int J Infect Dis* 2009; **13**: 59–66.

24 Cerón I, Rabagliati R, Langhaus J *et al*. [*Pneumocystis jiroveci* pneumonia: comparative study of cases in HIV-infected patients and immunocompromised non-HIV-infected patients]. *Rev Chilena Infectol* 2014; **31**: 417–24.

25 Kim SJ, Lee J, Cho YJ *et al*. Prognostic factors of *Pneumocystis jirovecii* pneumonia in patients without HIV infection. *J Infect* 2014; **69**: 88–95.

26 Kofteridis DP, Valachis A, Velegraki M *et al*. Predisposing factors, clinical characteristics and outcome of *Pneumocystis jirovecii* pneumonia in HIV-negative patients. *J Infect Chemother* 2014; **20**: 412–6.

27 Moon SM, Kim T, Sung H *et al*. Outcomes of moderate-to-severe *Pneumocystis* pneumonia treated with adjunctive steroid in non-HIV-infected patients. *Antimicrob Agents Chemother* 2011; **55**: 4613–8.

28 Ko Y, Jeong BH, Park HY *et al*. Outcomes of *Pneumocystis* pneumonia with respiratory failure in HIV-negative patients. *J Crit Care* 2014; **29**: 356–61.

29 Matsumura Y, Shindo Y, Iinuma Y *et al*. Clinical characteristics of *Pneumocystis* pneumonia in non-HIV patients and prognostic factors including microbiological genotypes. *BMC Infect Dis* 2011; **11**: 76.

30 McKinnell JA, Cannella AP, Kunz DF *et al*. *Pneumocystis* pneumonia in hospitalized patients: a detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (HIV)-infected and HIV-uninfected persons. *Transpl Infect Dis* 2012; **14**: 510–8.

31 Roblot F, Godet C, Le Moal G *et al*. Analysis of underlying diseases and prognosis factors associated with *Pneumocystis carinii* pneumonia in immunocompromised HIV-negative patients. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 523–31.

32 Brown GR. Cotrimoxazole—optimal dosing in the critically ill. *Ann Intensive Care* 2014; **4**: 13.

33 Dao BD, Barreto JN, Wolf RC *et al*. Serum peak sulfamethoxazole concentrations demonstrate difficulty in achieving a target range: a retrospective cohort study. *Curr Ther Res Clin Exp* 2014; **76**: 104–9.

34 Chin TW, Vandenbroucke A, Fong IW. Pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients. *Antimicrob Agents Chemother* 1995; **39**: 28–33.

35 Safrin S, Finkelstein DM, Feinberg J *et al*. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med* 1996; **124**: 792–802.

36 Carmona EM, Limper AH. Update on the diagnosis and treatment of *Pneumocystis* pneumonia. *Ther Adv Respir Dis* 2011; **5**: 41–59.

37 Cooley L, Dendle C, Wolf J *et al*. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. *Intern Med J* 2014; **44**: 1350–63.

38 Vogel MN, Vatlach M, Weissgerber P *et al*. HRCT-features of *Pneumocystis jiroveci* pneumonia and their evolution before and after treatment in non-HIV immunocompromised patients. *Eur J Radiol* 2012; **81**: 1315–20.

39 Held J, Wagner D. β-D-Glucan kinetics for the assessment of treatment response in *Pneumocystis jirovecii* pneumonia. *Clin Microbiol Infect* 2011; **17**: 1118–22.

40 Lemiale V, Debrumetz A, Delannoy A *et al*. Adjunctive steroid in HIV-negative patients with severe *Pneumocystis* pneumonia. *Respir Res* 2013; **14**: 87.

41 Nahimana A, Rabodonirina M, Zanetti G *et al*. Association between a specific *Pneumocystis jiroveci* dihydropteroate synthase mutation and failure of pyrimethamine/sulfadoxine prophylaxis in human immunodeficiency virus-positive and -negative patients. *J Infect Dis* 2003; **188**: 1017–23.

42 Navin TR, Beard CB, Huang L *et al*. Effect of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of *P. carinii* pneumonia in patients with HIV-1: a prospective study. *Lancet* 2001; **358**: 545–9.

43 Yoon C, Subramanian A, Chi A *et al*. Dihydropteroate synthase mutations in *Pneumocystis* pneumonia: impact of applying different definitions of prophylaxis, mortality endpoints and mutant in a single cohort. *Med Mycol* 2013; **51**: 568–75.

44 Kim T, Kim SH, Park KH *et al*. Clindamycin-primaquine versus pentamidine for the second-line treatment of *pneumocystis* pneumonia. *J Infect Chemother* 2009; **15**: 343–6.

45 Kim T, Hong HL, Lee YM *et al*. Is caspofungin really an effective treatment for *Pneumocystis jirovecii* pneumonia in immunocompromised patients without human immunodeficiency virus infection? Experiences at a single center and a literature review. *Scand J Infect Dis* 2013; **45**: 484–8.

46 Helweg-Larsen J, Benfield T, Atzori C *et al*. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J Antimicrob Chemother* 2009; **64**: 1282–90.

47 Armstrong-James D, Stebbing J, John L *et al*. A trial of caspofungin salvage treatment in PCP pneumonia. *Thorax* 2011; **66**: 537–8.

48 Tu GW, Ju MJ, Xu M *et al*. Combination of caspofungin and low-dose trimethoprim/sulfamethoxazole for the treatment of severe *Pneumocystis jirovecii* pneumonia in renal transplant recipients. *Nephrology (Carlton)* 2013; **18**: 736–42.

49 Utili R, Durante-Mangoni E, Basilico C *et al*. Efficacy of caspofungin addition to trimethoprim-sulfamethoxazole treatment for severe *Pneumocystis* pneumonia in solid organ transplant recipients. *Transplantation* 2007; **84**: 685–8.

50 Lobo ML, Esteves F, de Sousa B *et al*. Therapeutic potential of caspofungin combined with trimethoprim-sulfamethoxazole for *pneumocystis* pneumonia: a pilot study in mice. *PLoS One* 2013; **8**: e70619.

51 Kamboj M, Weinstock D, Sepkowitz KA. Progression of *Pneumocystis jiroveci* pneumonia in patients receiving echinocandin therapy. *Clin Infect Dis* 2006; **43**: e92–4.

52 Azoulay E, Mokart D, Pene F *et al*. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. *J Clin Oncol* 2013; **31**: 2810–8.

53 Azoulay E, Pène F, Darmon M *et al*. Managing critically ill hematology patients: Time to think differently. *Blood Rev* 2015; **29**: 359–67.

54 Schellongowski P, Staudinger T, Kundi M *et al*. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with *de novo* acute myeloid leukemia: a single center experience. *Haematologica* 2011; **96**: 231–7.

55 Wohlfarth P, Carlström A, Staudinger T *et al*. Incidence of intensive care unit admission, outcome, and post intensive care survival in patients with diffuse large B-cell lymphoma. *Leuk Lymphoma* 2016 Jan 13 [Epub ahead of print].

56 Roblot F, Le Moal G, Godet C *et al*. *Pneumocystis carinii* pneumonia in patients with hematologic malignancies: a descriptive study. *J Infect* 2003; **47**: 19–27.

57 Mikaelsson L, Jacobsson G, Andersson R. *Pneumocystis* pneumonia—a retrospective study 1991–2001 in Gothenburg, Sweden. *J Infect* 2006; **53**: 260–5.

58 Monnet X, Vidal-Petiot E, Osman D *et al*. Care management and outcome of severe *Pneumocystis* pneumonia in patients with and without HIV infection. *Crit Care* 2008; **12**: R28.

59 Nüesch R, Bellini C, Zimmerli W. *Pneumocystis carinii* pneumonia in human immunodeficiency virus (HIV)-positive and HIV-negative immunocompromised patients. *Clin Infect Dis* 1999; **29**: 1519–23.

60 Azoulay E, Lemiale V, Mokart D *et al*. Acute respiratory distress syndrome in patients with malignancies. *Intensive Care Med* 2014; **40**: 1106–14.

61 Chaoui D, Legrand O, Roche N *et al*. Incidence and prognostic value of respiratory events in acute leukemia. *Leukemia* 2004; **18**: 670–5.

62 Gruson D, Vargas F, Hilbert G *et al*. Predictive factors of intensive care unit admission in patients with haematological malignancies and pneumonia. *Intensive Care Med* 2004; **30**: 965–71.

63 Lengliné E, Raffoux E, Lemiale V *et al*. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure. *Leuk Lymphoma* 2012; **53**: 1352–9.

64 Mokart D, Lambert J, Schnell D *et al*. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. *Leuk Lymphoma* 2013; **54**: 1724–9.

65 Hilbert G, Gruson D, Vargas F *et al*. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001; **344**: 481–7.

66 Amado-Rodríguez L, Bernal T, López-Alonso I *et al*. Impact of initial ventilatory strategy in hematological patients with acute respiratory failure: a systematic review and meta-analysis. *Crit Care Med* 2016 Feb 23 [Epub ahead of print].

67 Lemiale V, Resche-Rigon M, Mokart D *et al*. Acute respiratory failure in patients with hematological malignancies: outcomes according to initial ventilation strategy. A groupe de recherche respiratoire en réanimation onco-hématologique (Grrr-OH) study. *Ann Intensive Care* 2015; **5**: 28.

68 Lemiale V, Mokart D, Resche-Rigon M *et al*. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. *JAMA* 2015; **314**: 1711–9.

69 Adda M, Coquet I, Darmon M *et al*. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med* 2008; **36**: 2766–72.

70 Depuydt PO, Benoit DD, Vandewoude KH *et al*. Outcome in noninvasively and invasively ventilated hematologic patients with acute respiratory failure. *Chest* 2004; **126**: 1299–306.

71 Molina R, Bernal T, Borges M *et al*. Ventilatory support in critically ill hematology patients with respiratory failure. *Crit Care* 2012; **16**: R133.

72 Soares M, Salluh JI, Azoulay E. Noninvasive ventilation in patients with malignancies and hypoxemic acute respiratory failure: a still pending question. *J Crit Care* 2010; **25**: 37–8.

73 Ewald H, Raatz H, Boscacci R *et al*. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection. *Cochrane Database Syst Rev* 2015; **4**: CD006150.

74 Limper AH, Knox KS, Sarosi GA *et al*. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med* 2011; **183**: 96–128.

75 Roembke F, Heinzow HS, Gosseling T *et al*. Clinical outcome and predictors of survival in patients with *Pneumocystis jirovecii* pneumonia—results of a tertiary referral centre. *Clin Respir J* 2014; **8**: 86–92.

76 Annaloro C, Della Volpe A, Usardi P *et al*. Caspofungin treatment of *Pneumocystis* pneumonia during conditioning for bone marrow transplantation. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 52–4.

77 Hof H, Schnülle P. *Pneumocystis jiroveci* pneumonia in a patient with Wegener's granulomatosis treated efficiently with caspofungin. *Mycoses* 2008; **51** Suppl 1: 65–7.

78 Burke BA, Good RA. *Pneumocystis carinii* infection. *Medicine (Baltimore)* 1973; **52**: 23–51.

79 Delclaux C, Zahar JR, Amraoui G *et al*. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in non-human immunodeficiency virus-infected patients: retrospective study of 31 patients. *Clin Infect Dis* 1999; **29**: 670–2.

80 Overgaard UM, Helweg-Larsen J. *Pneumocystis jiroveci* pneumonia (PCP) in HIV-1-negative patients: a retrospective study 2002–2004. *Scand J Infect Dis* 2007; **39**: 589–95.

81 Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. *Chest* 1998; **113**: 1215–24.

82 Zahar JR, Robin M, Azoulay E *et al*. *Pneumocystis carinii* pneumonia in critically ill patients with malignancy: a descriptive study. *Clin Infect Dis* 2002; **35**: 929–34.

Empirical and targeted antimicrobial therapy in patients with febrile neutropenia and haematological malignancy or after haematopoietic cell transplantation: recommendations from the 10th European Conference on Infections in Leukaemia

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Febrile neutropenia can lead to life-threatening infections in patients with haematological malignancies or after hematopoietic cell transplantation. Infection management is challenged by rising antibiotic resistance and regional differences in bacterial epidemiology. The 10th European Conference on Infections in Leukaemia panel recommends a personalised approach guided by local resistance patterns and individual risk factors. For patients who are haemodynamically stable without colonisation or infection by resistant Gram-negative bacteria in low-resistance prevalence settings, empirical monotherapy sparing carbapenems or novel β-lactams with or without β-lactamase inhibitors (BLI) is recommended. For patients who are critically ill or haemodynamically unstable, those with previous resistant Gram-negative bacteria colonisation or infection, or in high-resistance prevalence settings, broader-spectrum therapy is indicated. Treatment options include β-lactam plus aminoglycoside combinations, carbapenem with or without BLI, anti-pseudomonal cephalosporin and BLI combinations, or cefiderocol, individualised by local epidemiology and patient factors. Antimicrobial stewardship is recommended, including antimicrobial de-escalation once resistant Gram-negative bacteria infection is excluded; and antibiotic discontinuation regardless of neutrophil count, in patients who are afebrile and stable after completing the intended course. We provide treatment strategies for resistant Gram-negative bacteria infections.

Introduction

Patients with haematological malignancies with chemotherapy-induced neutropenia or after haematopoietic cell transplantation (HCT) are at high risk for severe, life-threatening infections. Fever in patients with neutropenia is often the first and sometimes the only sign of infection justifying the immediate initiation of empirical antibiotic therapy (EAT) before microbiological results become available.[1] Approximately half the patients with febrile neutropenia have clinically or microbiologically documented infections, while others present with unexplained fever or non-infectious fever.[2] Bacterial infections are the most common cause of fever during neutropenia, complicated by bloodstream infection in approximately 20–30% of patients.[3–6] The proportion of Gram-negative bacteria (30–67%) and Gram-positive bacteria (32–68%) varies across centres and geographical locations.[1,3–9] Infections due to Gram-negative bacteria are associated with high mortality, especially when appropriate therapy is delayed.[10–13] The increasing prevalence of antibiotic resistance among Gram-negative bacteria complicates the choice of EAT and is associated with long-term hospitalisation and increased mortality.[14] Resistance rates vary substantially between centres, with 30–50% of Gram-negative bacteria producing extended-spectrum β-lactamases (ESBL) or showing resistance to third generation cephalosporins, while 9–32% exhibit carbapenem resistance. Among *Pseudomonas aeruginosa* isolates, 20–37% are reported as multidrug resistant.[7,10,11,15,16]

Given the growing concern of antibacterial resistance and geographical variations in bacterial epidemiology and resistance patterns, the previous European Conference on Infections in Leukaemia (ECIL) recommendations introduced a personalised approach for EAT in 2011.[17,18] However, epidemiological challenges posed by the rise of multidrug resistance continue to evolve[19] and new antibiotic treatments were recently licensed to counter the development of resistance. Therefore, recommendations for fever in patients with neutropenia published over a decade ago by ECIL and Infectious Diseases Society of America might no longer reflect current best practices.[17,18,20] Due to this urgent need, we updated the ECIL recommendations based on review of literature in haematology and patients with HCT (adults and children) published after 2011. These revised recommendations, based on the antimicrobial stewardship principles, provide guidance on treatment options for patients with neutropenia due to chemotherapy or conditioning for HCT and with suspected or confirmed infections due to resistant Gram-negative bacteria.

Development of recommendations

ECIL is a collaborative initiative of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation, the European Organization for Research and Treatment of Cancer, the International Immunocompromised Host Society and the European LeukemiaNet. The standardised

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Key messages

- Empirical antibiotic therapy selection: base empirical therapy on local epidemiology, previous colonisation or infection with resistant bacteria, and the patient's clinical presentation.
- Monotherapy versus combination therapy: empirical monotherapy is appropriate for most patients with febrile neutropenia. Consider combination therapy in patients who are haemodynamically unstable or when resistant bacteria are likely.
- Coverage for resistant bacteria: choose empirical β-lactam therapy targeting known resistant Gram-negative colonisers or previously infecting pathogens. De-escalate therapy to narrower spectrum antibiotics once the patient is clinically stable or when microbiologically documented infection with resistant organisms is not documented. Reserve empirical coverage against resistant Gram-positive bacteria for patients who are haemodynamically unstable, have suspected catheter-related or skin and soft-tissue infections, or have known colonisation with methicillin-resistant *Staphylococcus aureus*.
- Persistent fever management: in clinically stable patients with persistent fever during neutropenia, continue diagnostic evaluation and consider non-bacterial causes rather than broaden empirical antibiotic therapy.
- Discontinuation of empirical therapy: consider stopping antibiotics in the following scenarios: after at least 72 h of treatment in patients with fever of unknown origin who remain stable and afebrile for at least 48 h; after completing the intended therapy course in patients with documented infections who are clinically stable and afebrile for at least 72 h, regardless of neutrophil count or duration of neutropenia.
- Targeted therapy for multidrug-resistant Gram-negative infections: use an active β-lactam as backbone therapy. Consider combination therapy when clinically appropriate or supported by susceptibility testing.

methodology used by ECIL recommendations has been previously reported.[18] The grading system previously used by ECIL with strength of recommendation and level of evidence is shown in the appendix (p 23).[18]

Group leaders (DA and TC) invited international experts in haematology, infectious diseases, and clinical microbiology to join the working group, who identified topics and clinical questions for review by team members. Topics included empirical therapy for fever in patients with neutropenia, optimal duration of therapy, and targeted treatments of resistant Gram-negative bacteria. Resistant Gram-negative bacteria compromised carbapenemase-producing Enterobacterales (CPE) stratified by the type of carbapenemase produced (eg, *Klebsiella pneumoniae* carbapenemase [KPC], OXA-48-like β-lactamases, and metallo-β-lactamase [MBL]-producing Gram-negative bacteria), difficult-to-treat resistant *P aeruginosa*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*.

Recommendations were prepared and discussed in an iterative process involving subgroup teams and the entire working group, and were later presented and interactively discussed by a forum of 54 experts in haematology, infectious diseases, HCT, and clinical microbiology from 19 countries at the plenary session of the 10th ECIL (ECIL-10) meeting held on Sept 20–21, 2024, in Sophia Antipolis, France. After refinement and approval by the ECIL-10, consensus recommendations were made available for public consultation and comments on the ECIL website from Oct 7 to Nov 8, 2024.

Results

Empirical antibiotic therapy in patients with febrile neutropenia

General recommendations

The ECIL-10 recommendations advocate for a risk-stratified personalised approach to EAT in patients with febrile neutropenia. Key factors guiding the choice of empirical antibiotic therapy include the local microbial ecology, the history of colonisation or previous infections with resistant Gram-negative bacteria, the suspected primary site of infection, and the severity of the clinical presentation.

Low-risk clinical settings

Low-risk settings are characterised by a low local prevalence of resistant Gram-negative bacteria, absence of colonisation or previous infection with resistant Gram-negative bacteria, and patients with neutropenia who are hemodynamically stable with fever and presenting with an uncomplicated clinical condition. In these favourable clinical contexts, the ECIL-10 panel recommends implementing carbapenem-sparing empirical monotherapy with piperacillin–tazobactam, ceftazidime, cefepime, or cefoperazone–sulbactam (table 1).

The evidence supporting these recommendations draws from a large body of literature, including seven meta-analyses, four randomised controlled trials (RCT; three single-centre and one multicentre), four retrospective studies (two single-centre and two multicentre), and one post-hoc analysis of a multicentre prospective study.[11,21–35] These studies failed to show reduced all-cause and infection-related mortality when combination therapy was used (appendix pp 11–12, 24–28).

High-risk clinical settings

High-risk settings are characterised by a high local prevalence of resistant Gram-negative bacteria, previous colonisation, or infection with resistant Gram-negative bacteria, or in patients who are critically ill or haemodynamically unstable presenting with sepsis or septic shock. In these challenging clinical contexts, the risk–benefit balance shifts considerably, favouring broader spectrum coverage with either single-agent or combination

	Recommendations	ECIL-10 grade
Low-risk clinical settings		
(1) Low local prevalence of resistant bacteria, and (2) no known colonisation or previous infection with resistant bacteria, and (3) haemodynamic stability	Carbapenem-sparing monotherapy with extended-spectrum penicillins or third-generation or fourth-generation cephalosporin (eg, piperacillin-tazobactam, cefepime, ceftazidime, or cefoperazone-sulbactam)	AI
High-risk clinical settings (any of the following)		
High local prevalence, colonisation, or previous infection with ESBL-producing *Enterobacterales* or Gram-negative bacteria resistant to first-line agents (but susceptible to carbapenems)*	Carbapenem	AIIu
Colonisation or previous infection with carbapenem resistant Gram-negative bacteria	Refer to table 2 for specific recommendations by bacterial resistance type	..
Patient who is critically ill (eg, haemodynamic instability, sepsis, septic shock, or pneumonia): (1) without colonisation or previous infection with carbapenem-resistant Gram-negative bacteria, or (2) with colonisation or previous infection with resistant Gram-negative bacteria	Carbapenem with or without β-lactamase inhibitor; β-lactam plus aminoglycoside combination therapy (refer to table 2 for specific recommendations by bacterial resistance type)	AIIu
Coverage of resistant Gram-positive bacteria†	Consider coverage for streptococcal infections when using agents with limited Gram-positive activity (eg, ceftazidime with or without avibactam or cefiderocol), particularly in patients with severe mucositis	CIII
Coverage of resistant Gram-positive bacteria†	Include anti-resistant Gram-positive coverage in patients with: (1) suspicion of catheter-related infection or skin and soft-tissue infection, or (2) sepsis, septic shock, or pneumonia (regardless of colonisation status)	(1) BIII, (2) CIII
Coverage of resistant Gram-positive bacteria†	Include methicillin-resistant *Staphylococcus aureus* coverage in colonised patients with: (1) haemodynamic instability (eg, sepsis or septic shock) or pneumonia, or (2) haemodynamic stability	(1) AIIt, (2) BIIrt
Coverage of resistant Gram-positive bacteria†	In all other clinical conditions, the routine empirical use of agents targeting resistant Gram-positive bacteria is not recommended	DIIru
Persistent fever	In patients who are hemodynamically stable with persistent fever without source, ECIL-10 panel recommends against addition of antibiotics targeting (1) resistant Gram-positive bacteria and (2) resistant Gram-negative bacteria	(1) DI, (2) DIIu

For the ECIL-10 grades, see the appendix (p 23). ECIL-10=10th European Conference on Infections in Leukaemia. ESBL=extended-spectrum β-lactamase. *First-line agents include piperacillin–tazobactam, cefepime, ceftazidime, or cefoperazone–sulbactam. †For example, vancomycin, linezolid, or daptomycin (daptomycin should not be used in patients with pneumonia).

Table 1: **Recommendations for empirical antibiotic therapy in patients with febrile neutropenia**

therapy. The ECIL-10 panel recommends EAT with one of several options: a carbapenem with or without β-lactamase inhibitors (BLI), an anti-pseudomonal cephalosporin with a BLI, cefiderocol, or a β-lactam plus aminoglycoside combination. Detailed specifications for each therapeutic option are provided in tables 1 and 2.

Among these recommended regimens, the β-lactam plus aminoglycoside combination represents the only true combination therapy approach. Several retrospective studies, primarily conducted in high-resistance settings (eg, Spain, Türkiye, and Italy), suggest potential survival benefits in selected subgroups, particularly patients with septic shock, Gram-negative bacteria (including *P aeruginosa*) bloodstream infection, or *P aeruginosa* pneumonia, who received combination therapy with a β-lactam and an aminoglycoside for at least 2 or 3 days (appendix pp 26–28).[7,15,36–38] The combination empirical therapy should be maintained throughout the initial management period until bloodstream infection can be definitely ruled out. Current recommendations for cephalosporins–BLI or carbapenem–BLI combinations are primarily based on clinical experience with targeted use in resistant Gram-negative bacteria infections, as evidence supporting their empirical use for fever in patients with neutropenia remains scarce (table 2 and appendix p 13).

Considerations for resistant organism history and screening

Recommendation on EAT should consider recent colonisation or previous infection with resistant Gram-negative bacteria. This consideration is supported by evidence from a large number of studies showing an increased risk of invasive infections with colonising resistant bacteria in patients with haematological malignancies or HCT (appendix pp 12, 29) and higher mortality when appropriate therapy is delayed (appendix p 13).[8,11,12,34,37,39–48] The median interval from colonisation detection to the bloodstream infection with the same resistant Gram-negative bacteria was 5–48·5 days (range 0–180 days) across multiple studies,[4,44,49–53] including three studies where patients were followed for 180–365 days after colonisation detection, indicating that recent colonisation might be associated with increased risk of bloodstream infection. In the most recent publication, the median time since colonisation detection to concordant bloodstream infection in patients with haematological malignancies ranged from 10 days for third-generation cephalosporin-resistant *Escherichia coli* to 58·5 days for difficult-to-treat resistant *P aeruginosa*.[53] Therefore, screening for colonisation with resistant Gram-negative bacteria, including ESBL-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales* (CRE), and difficult-to-treat resistant *Pseudomonas*, based

or

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See Online for appendix

	ECIL-10 grade	
	Empirical therapy	Targeted therapy
CPE: KPC (ambler class A)		
Ceftazidime–avibactam	AIIu	AIItu
Meropenem–vaborbactam	BIItu	BIItu
Imipenem–cilastatin–relebactam	CIIt	CIIt
Cefiderocol	CIII	CIIt
CPE: OXA-48-like (ambler class D)		
Ceftazidime–avibactam	AIItu	AIItu
Cefiderocol	CIII	CIIt
CPE: MBL (eg, NDM, VIM, and IMP; ambler class B)		
Ceftazidime–avibactam plus aztreonam	AIItu	AIItu
Cefiderocol	CIII	BIIt
Combination therapy with a non-β-lactam agent is generally not recommended but it might be considered in the following clinical conditions: (1) patients who are critically ill with sepsis or septic shock until clinical improvement, or (2) difficult-to-treat infections (eg, pneumonia or uncontrolled infection source), or (3) infections due to CPE with MIC values near the resistance breakpoint (MIC can vary by one dilution)	..	CIII
Treatment of difficult-to-treat resistant *Pseudomonas aeruginosa*		
Ceftolozane–tazobactam (high dose of 9 grams per day)	AIItu	AIItur
Ceftazidime–avibactam	AIItu	AIItu
Imipenem–cilastatin–relebactam	BIIt	BIIt
Cefiderocol	CIII	BIItur
Addition of an active non-β-lactam antibiotic (eg, aminoglycoside, fluoroquinolone, or fosfomycin) can be considered in: patients who are critically ill (eg, sepsis, septic shock, or pneumonia) until clinical improvement, or *P aeruginosa* infections with MIC values near the resistance breakpoint (MIC can vary by one dilution), or uncontrolled infection source in combination with (1) ceftolozane–tazobactam, (2) ceftazidime–avibactam, (3) imipenem–cilastatin–relebactam, or (4) cefiderocol	..	(1) BIIr, (2) BIII, (3) BIII, (4) BIII
Treatment of carbapenem-resistant *Acinetobacter baumannii*		
Sulbactam–durlobactam† plus high-dose imipenem	..	AIIt
High dose sulbactam (≥9 grams per day) plus other drug[1,2]	..	BIIt
Other combinations[3]	..	BIIt
Treatment of *Stenotrophomonas maltophilia*		
First-line therapy (whenever feasible), TMP–SMX in combination with levofloxacin‡, or high dose tetracycline derivatives (eg, minocycline or tigecycline) or cefiderocol	..	BIItu
If TMP–SMX not feasible (eg, resistance or intolerance) use one of the following two options§: (1) two-drug combination of levofloxacin (if susceptible), high dose tetracycline derivatives (eg, minocycline or tigecycline), or cefiderocol, or (2) triple combination of ceftazidime–avibactam plus aztreonam and one of levofloxacin (if susceptible) or high dose tetracycline derivatives (eg, minocycline or tigecycline)	..	(1) BIIu, (2) CIII
Duration of therapy for Gram-negative bacteraemia		
Antibiotics can be discontinued after at least 7 days of treatment when all symptoms and clinical signs of infection are resolved and infection is microbiologically eradicated: (1) with neutrophil recovery, or (2) without neutrophil recovery	..	(1) AIIu, (2) BIIu

For the ECIL-10 grades, see the appendix (p 23). CPE=carbapenemase-producing *Enterobacterales*. ECIL-10=10th European Conference on Infections in Leukaemia. IMP=metallo-β-lactamase active on imipenem. KPC=*Klebsiella pneumoniae* carbapenemase. MIC=minimal inhibitory concentration. MBL=metallo-β-lactamase. NDM=New Delhi metallo-β-lactamase. OXA-48-like=oxacillin-type 48 β-lactamase. TMP–SMX=trimethoprim–sulfamethoxazole. VIM=Verona integron-encoded metallo-β-lactamase. *Empirical therapy in patients colonised or previously infected with these Gram-negative bacteria. †Durlobactam is currently not approved for use in Europe by the European Medicines Agency. (1) In case sulbactam–durlobactam is not available; (2) in combination with any of the following agents: colistin (preferred agent whenever possible), cefiderocol, tigecycline, minocycline, and fosfomycin; or (3) combination of two of the following agents—preferably colistin and cefiderocol—if not possible or not available use tigecycline, minocycline, or fosfomycin. ‡Levofloxacin is likely not reliable empirical coverage for *Stenotrophomonas* in centres where levofloxacin is used for neutropenic prophylaxis. §Step down to monotherapy might be considered after clinical (and microbiological, if applicable) response is obtained and susceptibility to the single agent is confirmed.

Table 2: **Recommendations for empirical* and targeted therapy for resistant Gram-negative bacteria**

on the local prevalence of these bacteria, should be considered in patients with haematological malignancies or after HCT. This screening should start upon hospital admission and continue regularly thereafter to guide timely adjustment in empirical therapy. While the optimal frequency of screening remains undefined in the literature, the ECIL-10 panel suggests weekly screenings, as has been done in several studies.[4,49,53–55] Additional research is needed to establish a correlation between screening for resistant bacteria, especially using diagnostic platforms enabling rapid diagnosis of resistance determinants and survival.

Identifying an exact resistance prevalence threshold that warrants broader spectrum antibiotic therapy proves challenging, as no specific cutoffs are established in the current literature. Therefore, empirical choices should be guided by comprehensive assessment incorporating local epidemiology, patient-specific factors (eg, previous antibiotic exposure and origin from high-resistance regions), and results from colonisation screening programmes.

Empirical addition of antibiotics against resistant Gram-positive bacteria

Although Gram-positive bacteria cause a substantial amount of bloodstream infection in patients with febrile neutropenia, most infections are due to low-virulence pathogens, such as coagulase-negative *staphylococci*, and mortality is generally low in Gram-positive bacteria bloodstream infection.[3–5,13,56,57] Bloodstream infection caused by *Staphylococcus aureus* is uncommon in patients with neutropenia (0–3%),[3–5,13,14,56,58] although methicillin resistance rates are substantial when it does occur.[13,58] This pattern mirrors *S aureus* resistance rates in the general population, which varies considerably across European countries (15–51%), with rates greater than 20% in southern Europe (eg, Portugal, Spain, Italy, Croatia, Romania, Greece, and Cyprus).[59] Typical mucosal injury-associated infections due to streptococci and enterococci are also uncommon, accounting for less than 15% of bloodstream infection in most studies; and β-lactam-susceptible strains are covered by some empirical protocols, such as piperacillin–tazobactam.[4–6,13,58] Routine empirical addition of antibiotics targeting resistant Gram-positive bacteria is not recommended for patients with neutropenia and fever as this approach has not been shown to decrease mortality when added for all these patients upfront, or for these patients with persistent fever.[7,60] Even empirical addition of antibiotics active against vancomycin-resistant *Enterococci* infections and penicillin-non-susceptible viridans-group streptococcal infections did not decrease mortality in patients who eventually had bloodstream infection caused by these pathogens (appendix p 13). However, there are specific situations where the addition of empirical anti-Gram-positive bacterial agents should be considered—for example, adding anti-streptococcal coverage for patients receiving β-lactams with limited activity against Gram-positive bacteria (eg, ceftazidime, ceftazidime–avibactam, and cefiderocol), especially in case of severe mucositis. The benefits of empirical addition of the anti-Gram-positive bacterial agent cannot be ruled out in patients with septic shock, as data in this specific situation are limited; therefore, antibiotics active against resistant Gram-positive bacteria should be added in patients who are haemodynamically unstable.

Data from the general population, including some patients who are immunocompromised, revealed that inappropriate EAT was associated with mortality in patients with methicillin-resistant *S aureus* (MRSA) bloodstream infection.[61] Therefore, agents targeting resistant Gram-positive bacteria should be added empirically during the first few days of management in patients colonised with MRSA, or when there is a suspicion of clinical infections caused by Gram-positive bacteria, such as skin and soft tissue infections (table 1). Data on MRSA screening at admission for haematological malignancy or HCT and its association with subsequent infection are scarce (appendix p 29). Therefore, the panel could not make specific recommendations regarding routine MRSA screening.

Recommendations for clinical management after 72–96 h from the onset of fever in patients with neutropenia

ECIL-10 panel recommendations imply antimicrobial stewardship as a crucial component in the management of febrile neutropenic cancer. After 72–96 h, physicians have to reassess the need for continuation, escalation, de-escalation, or discontinuation of empirically started antibiotic therapy based on the patient clinical condition, documentation of infection, and microbiological results (appendix pp 13–16; figures 1 and 2). The goals are to minimise unnecessary antibiotic exposure, reduce the risk of resistance development, and prevent the occurrence of adverse events.

Clinical algorithms (figures 1 and 2) and recommendations with grading and levels of evidence guide patient management after 72–96 h of empirical therapy. Figure 1 addresses patients started on empirical monotherapy with piperacillin–tazobactam, ceftazidime, cefepime, or cefoperazone–sulbactam, while figure 2 focuses on patients who presented with one of the following: critical illness, haemodynamic instability, previous colonisation or infection with resistant Gram-negative bacteria, or treatment in high prevalence resistance settings. Regardless of the initial treatment regimen, deterioration of a patient's condition should prompt a thorough diagnostic workup and reassessment of antimicrobial coverage with antibiotic escalation based on the patient's history, colonisation, and risk factors (figures 1 and 2). Conversely, persistent fever in a stable patient calls also for a comprehensive diagnostic workup looking for other infectious and non-infectious aetiologies, including opportunistic pathogens, but does not impose an immediate change in antibiotic therapy.

In patients with microbiologically documented infections, treatment should be based on susceptibility tests. Consider de-escalating therapy to narrower spectrum, regardless of the initial approach (figures 1 and 2). The safety of this approach has been shown in several non-RCTs (appendix pp 13–14). When a patient presents with a bloodstream infection secondary to other infection focus (eg, abdominal), antibiotics should target the main potential pathogens of the primary infectious site. Specific therapy for resistant Gram-negative bacteria is addressed in the section on targeted

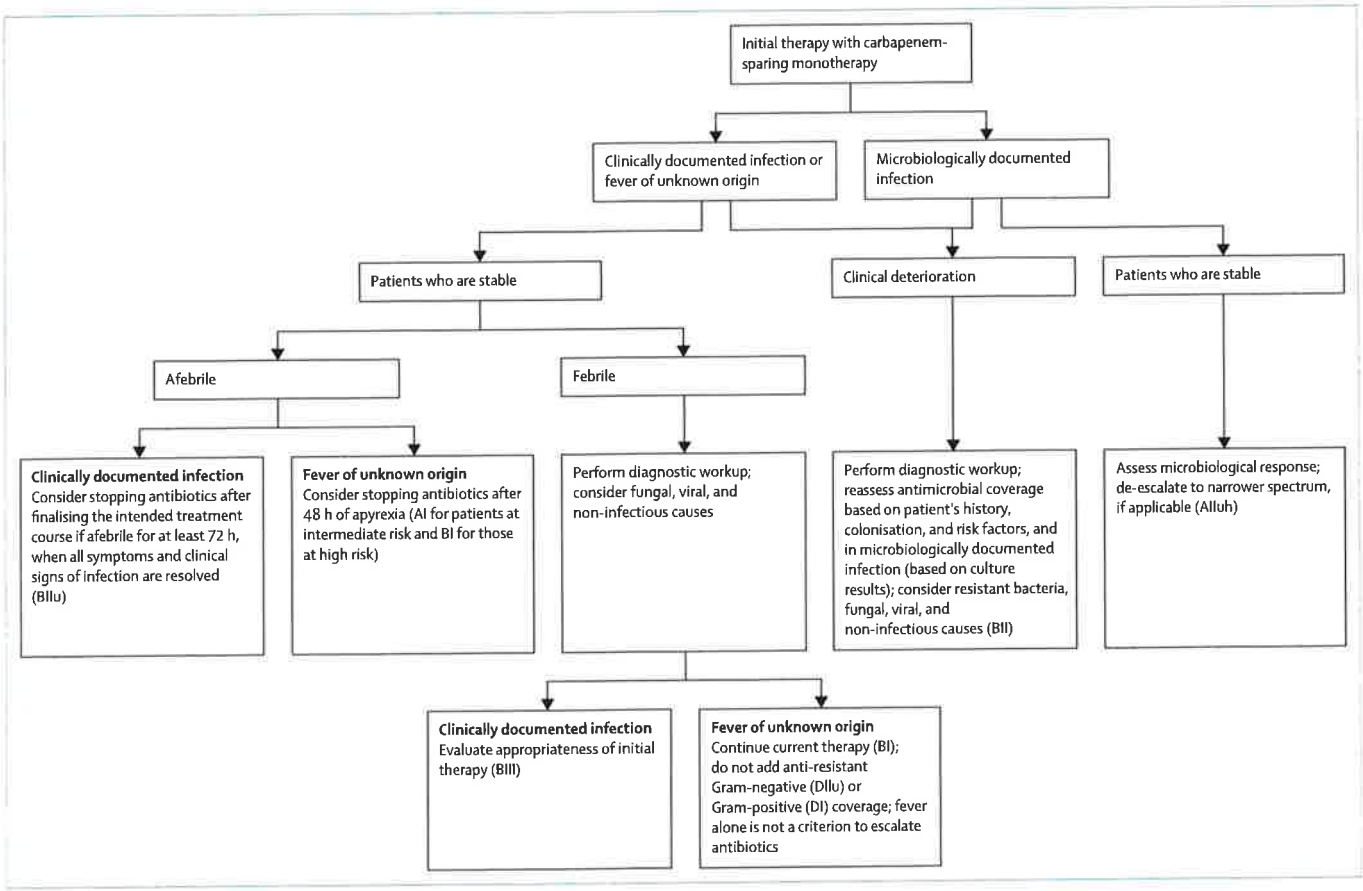

Figure 1: **Initial therapy with carbapenem-sparing monotherapy**
For the ECIL-10 grades, see the appendix (p 23).

therapy. In a patient who is deteriorating with microbiologically documented infection, appropriate supportive care should be initiated and transfer to the intensive care unit (ICU) should be considered. Source control, including central venous catheter (CVC) removal, is crucial in patients with sepsis when the CVC is the suspected source of infection. CVC removal is indicated for complicated CVC-related bloodstream infection (ie, sepsis, suppurative thrombophlebitis, endocarditis, or possible metastatic seeding); for short-term CVC-related uncomplicated bloodstream infection due to coagulase-negative *staphylococci*, *S aureus*, *Enterococcus*, Gram-negative bacilli, *Candida*, and mycobacterium; for long-term CVC-related uncomplicated bloodstream infection that continues despite longer than 72 h of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S aureus*, *P aeruginosa*, fungi, or mycobacteria.[62]

Microbiological data should be reviewed considering the identified pathogen and potential induced resistances, and the likelihood of co-pathogens based on the clinical presentation and source of infection. Antimicrobial coverage should be broadened as needed until the diagnostic workup is complete. Also, antimicrobials should be dosed appropriately based on their pharmacokinetic and pharmacodynamic properties, with therapeutic drug monitoring performed if available. Other infections (eg, viral, fungal, and parasitic) and the non-infectious causes of deterioration should be considered.

In patients with clinically documented infections, the appropriateness of the antibiotic regimen should be evaluated (figures 1 and 2). In patients who are afebrile, consider discontinuation of aminoglycosides or of anti-resistant Gram-positive bacteria antibiotics if these agents were part of the initial empirical regimen (figure 2; appendix pp 13–14).

In patients with fever of unknown origin who were started with carbapenem-sparing monotherapy, continue this therapy and consider stopping antibiotics after 48 h of apyrexia. Persistence of fever in patients who are haemodynamically stable with fever of unknown origin should not automatically warrant escalation of antibiotic therapy (figure 1). Consider discontinuation of aminoglycosides or anti-Gram-positive bacteria antibiotics if these agents were part of the initial empirical antibiotic

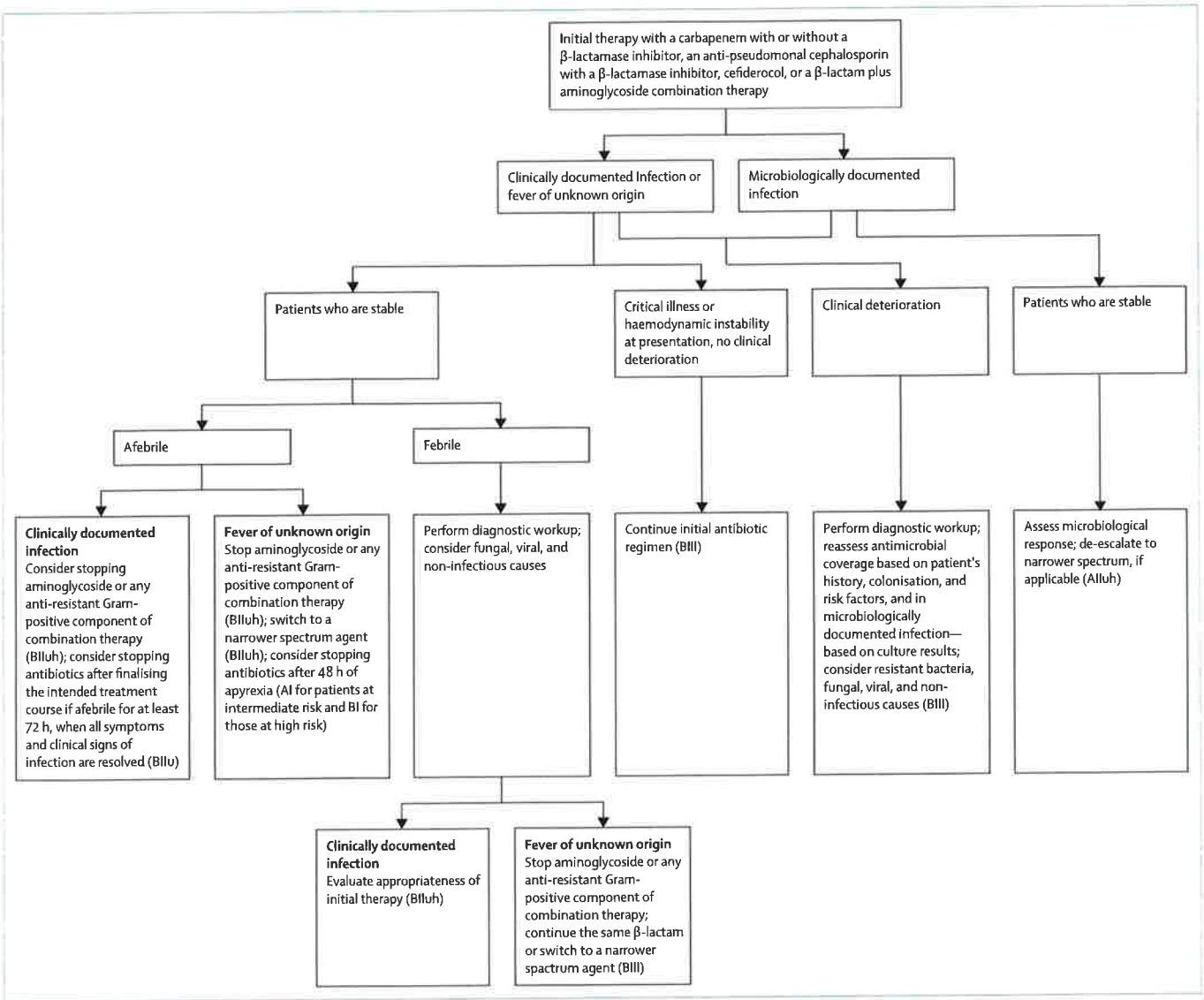

Figure 2: **Initial therapy with a carbapenem with or without a β-lactamase inhibitor, an anti-pseudomonal cephalosporin with a β-lactamase inhibitor, cefiderocol, or a β-lactam plus aminoglycoside combination therapy**
For the ECIL-10 grades, see the appendix (p 23).

regimen; de-escalation to narrower spectrum; and stopping antibiotics after 48 h of apyrexia (figure 2; appendix pp 13–16).

Discontinuation of antibiotic therapy

Five RCTs, 29 non-RCTs, and three meta-analyses have examined early antibiotic discontinuation before neutrophil recovery in patients with fever of unknown origin, clinically documented infections, and microbiologically documented infection (appendix pp 14–16, 30).[63–91] In patients who are afebrile, short duration of EAT was associated with decreased antibiotic exposure in most studies without increasing the risks of sepsis, septic shock, ICU admission, or mortality when compared with long-term treatment duration. However, one RCT reported increased overall and infection-related mortality in patients who discontinued EAT while still febrile.[67] This study also found increased treatment failure risk with short versus long EAT duration in patients with an initial Multinational Association of Supportive Care in Cancer (MASCC) score less than 21 (ie, patients with more severe illness) while no difference occurred in the patients with less severe illness with a MASCC score equal or greater than 21.[67] Mortality was not increased following early antibiotic discontinuation in two meta-analyses.[64,65] Another meta-analysis reported that early EAT de-escalation and discontinuation were

associated with decreased mortality.[63] Yet, these studies combined outcomes from patients at high risk (eg, allo-HCT recipients or patients with acute leukaemia with anticipated neutropenia lasting more than 10 days), together with patients at intermediate-risk (eg, auto-HCT or lymphoma with an expected profound neutropenia of 7–10 days), with patients at intermediate-risk representing most patients included in the RCT.[92] The limitations of these data are presented in the appendix (pp 15–16).

Based on these data, ECIL-10 recommends considering EAT discontinuation before neutrophil recovery in patients who are afebrile and haemodynamically stable with fever of unknown origin, clinically documented infections, or microbiologically documented infection. For patients with fever of unknown origin, discontinuation after confirming negative blood cultures is strongly recommended for patients at intermediate risk and moderately recommended for patients at high risk (table 3). For patients with clinically documented infections or microbiologically documented infections, discontinuation can be considered after completing the intended treatment course with confirmed clinical and, if appropriate, microbiological resolution, if the patient is afebrile for at least 72 h (table 3).

Universal follow-up blood cultures to document clearance of bloodstream infection should be considered selectively based on the specific pathogen involved and clinical circumstances, such as bloodstream infection caused by *S aureus*, *enterococci*, resistant Gram-negative bacteria, *Candida* spp, suspected or proven infective endocarditis, and endovascular infections.[93–95] In other clinical scenarios, follow-up blood cultures are typically unnecessary in patients with febrile neutropenia, particularly in those who have defervesced and show clinical improvement. The yield of follow-up blood culture is very low in patients who are persistently febrile, except when evaluating for breakthrough pathogens resistant to current antibiotic therapy or in the setting of new clinical instability.[96–99]

As patients with neutropenia remain at risk for severe infections, close monitoring and prompt reinitiation of antibiotics at the first sign of a new infection are essential. Centres using antibiotic prophylaxis should consider restarting prophylaxis upon discontinuation of empirical therapy if neutropenia persists according to individual centre policy.

Targeted therapy for Gram-negative infections

National and international recommendations have established clinical management protocols for infections caused by resistant Gram-negative bacteria in patients who are not immunocompromised.[100,101] In the current document, the ECIL-10 panel provides treatment recommendations for patients with febrile neutropenia for four key resistant bacterial types: CPE categorised by specific enzyme type, difficult-to-treat resistant *P aeruginosa*, CRAB, and *Stenotrophomonas maltophilia* (table 2).

21 indication-based RCTs (and two sub-analyses) have shown the non-inferiority of the cephalosporins with BLI, carbapenems with BLI, and cefiderocol compared with other treatments for nosocomial pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections (appendix pp 16, 18, 31–36). However, few patients with CRE or CPE, multidrug-resistant or carbapenem-resistant *P aeruginosa* (CRPA), CRAB, and *S maltophilia* were included in these trials, and outcomes of patients with resistant Gram-negative bacteria were rarely reported. All but one trial excluded patients who are immunocompromised.[102] The new antibiotics were predominantly used as monotherapy (except when metronidazole was added for complicated intra-abdominal infections).

Six pathogen-based RCT and eight follow-up analyses specifically examined treatment of resistant Gram-negative bacteria. Eight studies covered multidrug-resistant Gram-negative bacteria, three carbapenem-resistant Gram-negative bacteria, one CRE, one CRAB, and one CRPA. Three of these studies included patients who are immunocompromised (appendix pp 31–36). Observational data for patients who are immunocompromised (including those with haematological malignancy or HCT) remain scarce. Most available information focused on ceftazidime–avibactam treatment for KPC-producing CPE, with there being limited data on OXA-48-like CPE and difficult-to-treat resistant *P aeruginosa*, and minimal data on MBL-producers (appendix pp 16–19, 37–49). Studies often failed to clearly report on patient numbers and on the specific underlying immunocompromising conditions, and few compared different treatment options. Among studies of patients with haematological malignancies and HCT, very few specified how many patients had neutropenia. For example, observational studies on ceftolozane–tazobactam treatment of *P aeruginosa* included 136 patients with neutropenia across studies.[39,103] Eight studies reported 547 neutropenic patients with CPE treated with ceftazidime–avibactam, while one study included just eight patients with neutropenia treated with meropenem–vaborbactam.[104–112] Notably, neutropenia was associated with greater mortality in five of these studies.[104–108] Multiple studies have documented the development of antibiotic resistance during treatment with these newer antibiotics (appendix pp 37–49).[38,103,105,106,112–116]

Treatment of carbapenemase-producing Enterobacterales infections

Observational studies including patients who are immunocompromised have reported higher clinical cure and survival rates in patients with CRE (including CPE) treated with ceftazidime–avibactam (combined with aztreonam for MBL-producing CPE) compared with older best available treatments (appendix pp 37–49). These findings align with those in the general population (appendix pp 50–53). Recommendations for imipenem–cilastatin–relebactam, meropenem–vaborbactam, and

	Recommendations	ECIL-10 Grade
Fever of unknown origin		
Patients who are afebrile for at least 48 hours and remained haemodynamically stable since presentation	Discontinue empirical antibiotic therapy after at least 72 h, regardless of the neutrophil count or the anticipated duration of neutropenia	BI for patients at high risk* and AI for patients at intermediate risk*
Patients who are afebrile whose antibiotics were discontinued, particularly if neutropenia persists	Close inpatient or outpatient clinical observation is recommended	AIIu
Patients who are afebrile with antibiotics discontinued before neutrophil recovery in centres where prophylactic antibiotics are routinely used for neutropenia	Consider resuming antibiotic prophylaxis	CIII
Patients who develop recurrent fever after stopping antibiotics (after initial defervescence)	Antibiotics should be promptly restarted after clinical evaluation and appropriate microbiological workup	AIIu
Patients with persistent fever and haemodynamic stability (patients at high risk or intermediate risk)	(1) Continue empirical antibiotic therapy; or (2) continue diagnostic efforts to identify occult infections or alternative explanation of fever; discontinuation of empirical therapy can be considered at a later stage, once a bacterial source has been reasonably ruled out	(1) BI, (2) CIII
Microbiologically documented infections, clinically documented infections		
Patients who have completed the intended treatment course, are haemodynamically stable, afebrile for at least 72 h, have resolution of all symptoms and clinical signs of infection, and have microbiological eradication of infection (when re-sampling is feasible)	Consider discontinuing antibiotic therapy before neutrophil recovery	BIIu
Patients who are afebrile whose antibiotics were discontinued, particularly if neutropenia persists	Close inpatient or outpatient clinical observation is recommended	AIIu
Patients who are afebrile with antibiotics discontinued before neutrophil recovery in centres where prophylactic antibiotics are routinely used for neutropenia	Consider resuming antibiotic prophylaxis	CIII
Patients who develop recurrent fever after stopping antibiotics (after initial defervescence)	Antibiotics should be promptly restarted after clinical evaluation and appropriate microbiological workup	AIIu

For the ECIL-10 grades, see the appendix (p 23). *For patients at high risk: allogeneic haematopoietic stem cell transplantation recipients or patients with acute leukaemia with anticipated neutropenia of more than 10 days. For patients at intermediate risk: autologous haematopoietic stem cell transplantation recipients or other patients (eg, with lymphoma) with an expected profound neutropenia of 7–10 days.[92]

Table 3: **Recommendations for the duration of antibiotic therapy and management following antibiotic discontinuation**

cefiderocol are based on scarce evidence, including pathogen-targeted RCT with few patients with CRE and CPE and few non-comparative studies in patients who are immunocompromised (appendix pp 16–18). No data on aztreonam–avibactam in patients who are immunocompromised were available at the time these recommendations were developed. A recent RCT in a general population included only a few patients with MBL-producing CPE.[117] Due to insufficient evidence, no recommendation could be made for this antibiotic combination.

Current evidence does not support routine use of combinations of β-lactam antibiotics with non-β-lactam agents for treating CPE infections. This conclusion is supported by RCTs in the general population, meta-analyses, and observational studies, including patients who are immunocompromised (appendix pp 37–49, 54–55).[105,107,109,112,113,118–126] However, these studies have notable limitations: they are low quality observational studies, they often used cephalosporins–BLI or carbapenem–BLI combinations or cefiderocol in combination without analysing specific drug combinations separately, they did not stratify results by individual antibiotics, and they did not separately analyse patients who are immunocompromised. Selection bias was possible as combination therapy was often reserved for patients who are critically ill. Given these limitations, combination therapy involving active β-lactam and a non-β-lactam antibiotic (mostly aminoglycoside) might still be considered for patients who are critically ill or those with difficult-to-treat CPE infections (table 2).

Treatment of difficult-to-treat resistant Pseudomonas aeruginosa infections

P aeruginosa can develop resistance to multiple antibiotic classes, primarily via non-enzymatic mechanisms. These recommendations focus on difficult-to-treat resistant *P aeruginosa* infections.[127] Observational studies in patients with haematological malignancies or undergoing HCT have shown improved outcomes in *P aeruginosa* infections, particularly multidrug-resistant, extensively-drug-resistant *P aeruginosa* and CRPA, treated with ceftolozane–tazobactam (often with high doses of 9 g per day) or ceftazidime–avibactam, compared with the best available therapies (appendix pp 18–19, 37–49, 54–55).[39,128,129] Both agents were frequently used in combination with other antibiotics—ie, in 42–75% of cases. No data are available for imipenem–cilastatin–relebactam in patients who are immunocompromised. Data on cefiderocol treatment in patients with haematological

malignancies or undergoing HCT with *P aeruginosa* infection are restricted to small case series and individual case reports, with some showing resistance development during treatment.[116]

Mixed results were obtained from combination therapy for *P aeruginosa* infections (appendix pp 37–49, 54–55). In observational studies in patients with haematological malignancies or undergoing HCT, newer antibiotics were often used in combination. One meta-analysis of eight non-RCTs, which included 238 (60·9%) of 391 patients with *P aeruginosa* infections, found a significant reduction of mortality when ceftolozane–tazobactam was used in combination versus monotherapy.[130] However, two other meta-analyses found no significant outcome difference when ceftazidime–avibactam was used alone versus in combination.[119,122] Yet, while patients who are immunocompromised were included in these analyses, they were not analysed separately.

Given the available data, reports of resistance developing during treatment, and the particularly poor prognosis of patients with neutropenia and *P aeruginosa* infections, the ECIL-10 panel recommends a different approach than standard international guidelines for the general population.[100,101] In recognition of the unique challenges and higher risks faced by patients with neutropenia, the panel supports the use of combination therapy for selected infections caused by difficult-to-treat resistant *P aeruginosa*, as specified in table 2.

Treatment of carbapenem-resistant Acinetobacter baumannii infections

Sulbactam remains a cornerstone in the treatment of CRAB, particularly when administered in high dosages (≥9 g daily) and combined with other agents (table 2; appendix pp 19–20, 37–61).[101,131–134] The preferred regimen is sulbactam–durlobactam combined with imipenem.[135] In settings where durlobactam is unavailable, the panel recommends combining high-dose sulbactam with colistin, which has historically been widely used for the treatment of CRAB.[101,131–134] While cefiderocol monotherapy has been associated with higher mortality in RCTs, cefiderocol-based combination therapies have shown improved clinical outcomes in meta-analyses and retrospective studies.[136–140] Therefore, these combinations are considered a favourable option in cases of sulbactam resistance and when colistin cannot be used.

Evidence supporting the use of other agents, such as fosfomycin, minocycline, and tigecycline, which are often used in combination for CRAB infections, is scarce and primarily derived from retrospective studies with variable outcomes. High-dose tigecycline can be used if tolerated but should be avoided when the minimum inhibitory concentration (MIC) exceeds 2 mg per L, and is not recommended for bacteraemia, pneumonia, or urinary tract infections. High-dose tigecycline use should be limited to intra-abdominal infections and skin and soft tissue infections. High-dose minocycline can serve as an alternative to tigecycline. In case of sulbactam resistance (MIC >16 mg per L), combination therapy should be considered. Colistin is preferred as one of the components, with other options including cefiderocol, tigecycline, or minocycline and fosfomycin.

Combination therapy is recommended as first-line therapy in patients who are immunocompromised and have CRAB infections, particularly until antibiotic susceptibilities are available (table 2). This strategy is justified by the high risk of these patients, the risk of poor clinical outcomes with inadequately therapy, the high prevalence of resistance, and the potential for selection of multidrug-resistant isolates.

Treatment of Stenotrophomonas maltophilia infections

Trimethoprim–sulfamethoxazole has been the cornerstone of therapy for *S maltophilia* infections. However, several observational studies and meta-analyses, primarily involving patients with pneumonia in ICU, have shown similar or even superior outcomes with fluoroquinolones, and similar outcomes with tetracycline derivatives (appendix pp 20–22).[141–145] One study showed improved outcome with minocycline therapy.[146] Cefiderocol and the combination of ceftazidime–avibactam plus aztreonam are newer agents with in vitro activity against *S maltophilia*. However, clinical data supporting their use, particularly in patients with haematological malignancies, remain scarce (appendix pp 62–66).

Given the high mortality rates, exceeding 50% in adult and paediatric HCT recipients, emerging resistance, and some data showing benefit of combination therapy, ECIL-10 recommends using trimethoprim–sulfamethoxazole (8–12 mg per kg daily of trimethoprim component) and ceftazidime–avibactam plus aztreonam or cefiderocol in combination with another active agent.[147–149] Options include levofloxacin (especially for pneumonia) or high-dose tetracycline derivatives (minocycline or tigecycline) or cefiderocol in addition to trimethoprim–sulfamethoxazole (table 2). For patients who have received levofloxacin prophylaxis, levofloxacin can be a less reliable treatment option due to the potential risk for developing resistance from prolonged exposure. In all cases, de-escalation to monotherapy can be considered once a favourable clinical response is observed and, if applicable, microbiological clearance is achieved, provided that susceptibility to the monotherapy agent has been confirmed.

Duration of treatment of Gram-negative bacteraemia

Four non-RCT studies compared short versus long (11–21 days) durations of antibiotics in 432 versus 482 adult patients with haematological malignancies or HCT with Gram-negative bacteria bacteraemia.[150–153] Short duration was defined as 7–11 days,[150] 7 days,[151,152] or 8 days (IQR 7–10).[153] Two studies included patients with *P aeruginosa* bacteraemia, while the third one focused

exclusively on patients with *P aeruginosa* bacteraemia.[150,151,153] All studies included bacteraemia caused by resistant Gram-negative bacteria (including ESBL-producers, CRE, and multidrug-resistant *P aeruginosa*). Among the four non-RCTs, resistant organisms were identified in 73 (16·9%) of 432 patients in the short-duration groups and 105 (21·8%) of 482 patients in the long-duration groups. The source of bacteraemia, primarily abdominal or CVC-related, was identified in 45–70% of cases. Source control (including CVC removal) was observed in most patients (69·2–100%). In three studies, 11–72 patients discontinued antibiotics while still having neutropenia.[150–152] Importantly, short-course antibiotic therapy was not associated with increased mortality, ICU admission, septic shock, or infection relapse, even among patients with neutropenia and those with *P aeruginosa* bacteraemia.[150–153]

Based on these findings, the ECIL-10 panel recommends discontinuation of antibiotic therapy after completing the intended treatment course (at least 7 days) in patients who are afebrile and clinically stable, regardless of neutrophil count and expected duration of neutropenia (table 2). Evidence for this recommendation is limited (only four non-RCTs) and short course was not consistently defined, sometimes including up to 11 days of therapy. Duration of therapy should be individualised. A shorter course might be reasonable for patients with Gram-negative bacteraemia who improve rapidly and have no clear focus of infection. In contrast, patients with Gram-negative bacteraemia who have a slower clinical response or a clear focus of infection (eg, typhlitis or pneumonia or perirectal phlegmon) might require a longer treatment course.

Conclusion

The ECIL-10 consensus provides strategies for the management of febrile neutropenia in patients with haematological malignancies and HCT, with major emphasis on antimicrobial stewardship in the era of escalating antimicrobial resistance, particularly among Gram-negative pathogens. The recommendations highlight the need for an individualised approach driven by illness severity and local epidemiology, with clinical management algorithms that extend beyond the consideration of initial empirical treatment alone. Antimicrobial stewardship strategies are essential to preserve antibiotic efficacy and mitigate emerging resistance. These strategies include using combination regimens only when clearly warranted, de-escalating to narrower-spectrum agents, implementing shorter treatment durations, and discontinuing therapy for all types of infection documentation regardless of neutrophil count. However, considerable gaps remain in our treatment strategies and there are still important limitations of the existing literature (addressed in the appendix pp 11–16). Future research should focus on refining the assessment of infectious and non-infectious fevers of unknown origin, including those due to the immunomodulatory therapies, and defining optimal treatments for multidrug-resistant Gram-negative bacteria. The lack of RCTs in patients with haematological malignancies and HCT limits definitive guidance on the use of newer therapeutic agents, including combinations of β-lactam and BLI or cefiderocol, and addressing specific scenarios and subgroups of patients with febrile neutropenia.

Search strategy and selection criteria

The working group was divided into subgroups to address selected subtopics. Each subgroup searched PubMed for potentially relevant articles published in English from Jan 1, 2011 to Sept 1, 2024, and analysed relevant articles for study design, population, endpoints, and main findings (search terms are in the appendix pp 3–11). For empirical therapy, the group specifically addressed monotherapy versus combination therapy, the use of new β-lactam antibiotics and the continuation, escalation, de-escalation, discontinuation, and duration of therapy as essential elements of antimicrobial stewardship. Original studies performed in high-income and middle-income countries, in children and in adults, and meta-analyses were included. Articles identified from these searches and relevant references cited within them were reviewed. For targeted treatment of resistant Gram-negative bacteria, the group analysed data from randomised controlled trials and meta-analyses in the general population and observational studies in patients with haematological malignancies or following haematopoietic cell transplantation, when available. In the absence of published data, observational studies in the general population or case reports were reviewed. Each topic search was performed by two group members and approved by the others.

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Contributors
DA and TC coordinated the project, guided the development of the recommendations, drafted the initial manuscript, revised the manuscript, and prepared the point-by-point response to the editor and reviewers' comments. DA, YV, FB, MM, DN, CG-V, MA-G, PM, and CC conducted the literature search. All authors contributed to the literature review, data compilation and interpretation, and the formulation of recommendations. All authors reviewed and revised the manuscript and approved the final version.

Declaration of interests
DA served as speaker for Merck Sharp & Dohme. MM received lecture, board meeting, and advisory board fees from AstraZeneca, Gilead, Janssen, Moderna, Mundipharma, Pfizer, and Shionogi; and received a research grant from Gilead paid to her institution. CG-V received honoraria for talks on behalf of Pfizer, Merck Sharp & Dohme, Gilead, Shionogi, Basilea, Sanofi, Advanz Pharma, Janssen, Mundipharma, AbbVie, and Avir Pharma; is an advisory board membership for Gilead, Shionogi, Merck Sharp & Dohme, Mundipharma, Advanz Pharma, and Pfizer; and received grant support from Gilead Science and Mundipharma. MA-G received honoraria as a speaker from Pfizer. PM reports participation in meetings and advisory boards for Advanz Pharma, Gilead, Pfizer, Mundipharma, Pharmamar, Roche, and Shionogi; and received funding from Fondo de Investigación Sanitaria, Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Red Española de Investigación en Patología Infecciosa, Mutua Madrileña, European Community funds, Fundación Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica and Grupo de Estudio de Sida, Fundación Código sepsis, UMP, and Fundación de Ciencias de la Salud, Fundación Ramón Areces. MA reports funding from Horizon 2020 of the European Commission and Pfizer (both paid to institution). TC received funding from the Swiss Personalized Health Network of the Swiss Academy of Medical Sciences and Horizon 2020 of the European Commission (paid to institution); and received compensation for advisory boards for Basilea, Gilead Sciences, Merck Sharp & Dohme, Moderna, Pfizer, and Shionogi (paid to institution). All other authors declare no competing interests.

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References

1 Pizzo PA. Management of patients with fever and neutropenia through the arc of time: a narrative review. *Ann Intern Med* 2019; **170**: 389–97.
2 Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. *J Oncol Pract* 2019; **15**: 19–24.
3 Bilinski J, Robak K, Peric Z, et al. Impact of gut colonization by antibiotic-resistant bacteria on the outcomes of allogeneic hematopoietic stem cell transplantation: a retrospective, single-center study. *Biol Blood Marrow Transplant* 2016; **22**: 1087–93.
4 de la Court JR, Heijmans J, Huynh J, et al. Guidance of empirical antimicrobial therapy by surveillance cultures in high-risk neutropenic patients: a retrospective cohort study. *Antimicrob Resist Infect Control* 2022; **11**: 160.
5 Mikulska M, Raiola AM, Galaverna F, et al. Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: impact of T cell-replete transplantation from a haploidentical donor. *Biol Blood Marrow Transplant* 2018; **24**: 109–18.
6 Ram R, Farbman L, Leibovici L, et al. Characteristics of initial compared with subsequent bacterial infections among hospitalised haemato-oncological patients. *Int J Antimicrob Agents* 2012; **40**: 123–26.
7 Chumbita M, Puerta-Alcalde P, Gudiol C, et al. Impact of empirical antibiotic regimens on mortality in neutropenic patients with bloodstream infection presenting with septic shock. *Antimicrob Agents Chemother* 2022; **66**: e0174421.
8 Puerta-Alcalde P, Chumbita M, Charry P, et al. Risk factors for mortality in hematopoietic stem cell transplantation recipients with bloodstream infection: points to be addressed by future guidelines. *Transplant Cell Ther* 2021; **27**: 501.e1–6.
9 Baccelli F, Aguilar-Guisado M, Vidal CG, et al. Epidemiology of resistant bacterial infections in patients with hematological malignancies or undergoing hematopoietic cell transplantation in Europe: a systematic review by the European Conference on Infections in Leukemia (ECIL). *J Infect* 2025; **91**: 106571.
10 Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in Gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis* 2017; **65**: 1819–28.
11 Chumbita M, Puerta-Alcalde P, Yáñez L, et al. High rate of inappropriate antibiotics in patients with hematologic malignancies and *Pseudomonas aeruginosa* bacteremia following international guideline recommendations. *Microbiol Spectr* 2023; **11**: e0067423.
12 Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, et al. Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance. *Clin Infect Dis* 2020; **70**: 1068–74.
13 Puerta-Alcalde P, Cardozo C, Marco F, et al. Changing epidemiology of bloodstream infection in a 25-years hematopoietic stem cell transplant program: current challenges and pitfalls on empiric antibiotic treatment impacting outcomes. *Bone Marrow Transplant* 2020; **55**: 603–12.
14 Sallah YH, Bratti VF, Rafinejad-Farahani B, et al. Antimicrobial resistance in patients with haematological malignancies: a scoping review. *Lancet Oncol* 2025; **26**: e242–52.
15 Albasanz-Puig A, Gudiol C, Puerta-Alcalde P, et al. Impact of the inclusion of an aminoglycoside to the initial empirical antibiotic therapy for Gram-negative bloodstream infections in hematological neutropenic patients: a propensity-matched cohort study (AMINOLACTAM study). *Antimicrob Agents Chemother* 2021; **65**: e0004521.
16 Girmenia C, Bertaina A, Piciocchi A, et al. Incidence, risk factors and outcome of pre-engraftment Gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. *Clin Infect Dis* 2017; **65**: 1884–96.
17 Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). *Haematologica* 2013; **98**: 1836–47.
18 Averbuch D, Orasch C, Cordonnier C, et al. 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. *Haematologica* 2013; **98**: 1826–35.
19 Sati H, Carrara E, Savoldi A, et al. The WHO Bacterial Priority Pathogens List 2024: a prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. *Lancet Infect Dis* 2025; **25**: 1033–43.
20 Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2011; **52**: e56–93.
21 Ishikawa K, Nakamura T, Kawai F, Ota E, Mori N. Systematic review of beta-lactam vs. beta-lactam plus aminoglycoside combination therapy in neutropenic cancer patients. *Cancers* 2024; **16**: 1934.
22 Manji A, Lehrnbecher T, Dupuis LL, Beyene J, Sung L. A systematic review and meta-analysis of anti-pseudomonal penicillins and carbapenems in pediatric febrile neutropenia. *Support Care Cancer* 2012; **20**: 2295–304.
23 Marcus R, Paul M, Elphick H, Leibovici L. Clinical implications of β-lactam-aminoglycoside synergism: systematic review of randomised trials. *Int J Antimicrob Agents* 2011; **37**: 491–503.
24 Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database Syst Rev* 2013; **2013**: CD003038.
25 Robinson PD, Lehrnbecher T, Phillips R, Dupuis LL, Sung L. Strategies for empiric management of pediatric fever and neutropenia in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review of randomized trials. *J Clin Oncol* 2016; **34**: 2054–60.
26 Tang X, Chen L, Li Y, Jiang J, Li X, Liang X. Carbapenems versus alternative β-lactams monotherapy or in combination for febrile neutropenia: systematic review and meta-analysis of randomized controlled trial. *Medicine* 2020; **99**: e22725.

27 Wang Y, Du Z, Chen Y, Liu Y, Yang Z. Meta-analysis: combination of meropenem vs ceftazidime and amikacin for empirical treatment of cancer patients with febrile neutropenia. *Medicine* 2021; **100**: e24883.

28 Bucaneve G, Micozzi A, Picardi M, et al. Results of a multicenter, controlled, randomized clinical trial evaluating the combination of piperacillin/tazobactam and tigecycline in high-risk hematologic patients with cancer with febrile neutropenia. *J Clin Oncol* 2014; **32**: 1463–71.

29 Kamonrattana R, Sathitsamitphong L, Choeyprasert W, Charoenkwan P, Natesirinilkul R, Fanhchaksai K. A randomized, open-labeled, prospective controlled study to assess the efficacy of frontline empirical intravenous piperacillin/tazobactam monotherapy in comparison with ceftazidime plus amikacin for febrile neutropenia in pediatric oncology patients. *Asian Pac J Cancer Prev* 2019; **20**: 2733–37.

30 Zengin E, Sarper N, Kılıç SC. Piperacillin/tazobactam monotherapy versus piperacillin/tazobactam plus amikacin as initial empirical therapy for febrile neutropenia in children with acute leukemia. *Pediatr Hematol Oncol* 2011; **28**: 311–20.

31 Lee NH, Kang JM, Lee JW, et al. Cefepime versus cefepime plus amikacin as an initial antibiotic choice for pediatric cancer patients with febrile neutropenia in an era of increasing cefepime resistance. *Pediatr Infect Dis J* 2020; **39**: 931–36.

32 Lopez R, Rello J, Taccone FS, et al. Aminoglycosides in immunocompromised critically ill patients with bacterial pneumonia and septic shock: a post-hoc analysis of a prospective multicenter multinational cohort. *Shock* 2020; **54**: 731–37.

33 Oliver AC, Riva E, Mosquera R, et al. Comparison of two different anti-infectious approaches after high-dose chemotherapy and autologous stem cell transplantation for hematologic malignancies in a 12-year period in British Hospital, Uruguay. *Ann Hematol* 2020; **99**: 877–84.

34 Royo-Cebrecos C, Laporte-Amargós J, Peña M, et al. *Pseudomonas aeruginosa* bloodstream infections presenting with septic shock in neutropenic cancer patients: impact of empirical antibiotic therapy. *Microorganisms* 2024; **12**: 705.

35 Anoshirvani AA, Zarinfar N, Rafiee M, Zamani Z. Effect of combination therapy of ceftazidime/amikacin and monotherapy with imipenem on the treatment of fever and neutropenia in patients with cancers. *Open Access Maced J Med Sci* 2018; **6**: 1423–30.

36 Albasanz-Puig A, Durà-Miralles X, Laporte-Amargós J, et al. Effect of combination antibiotic empirical therapy on mortality in neutropenic cancer patients with *Pseudomonas aeruginosa* pneumonia. *Microorganisms* 2022; **10**: 733.

37 de Souza ILA, Cappellano P, Ferreira DB, et al. Carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in haematological malignances and hematopoietic stem cell transplantation: clinical impact of combination therapy in a 10-year Brazilian cohort. *PLoS One* 2024; **19**: e0297161.

38 Vena A, Schenone M, Corcione S, et al. Impact of adequate empirical combination therapy on mortality in septic shock due to Pseudomonas aeruginosa bloodstream infections: a multicentre retrospective cohort study. *J Antimicrob Chemother* 2024; **79**: 2846–53.

39 Bergas A, Albasanz-Puig A, Fernández-Cruz A, et al. Real-life use of ceftolozane/tazobactam for the treatment of bloodstream infection due to *Pseudomonas aeruginosa* in neutropenic hematologic patients: a matched control study (ZENITH study). *Microbiol Spectr* 2022; **10**: e0229221.

40 Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant* 2015; **50**: 282–88.

41 Kim HS, Park BK, Kim SK, et al. Clinical characteristics and outcomes of *Pseudomonas aeruginosa* bacteremia in febrile neutropenic children and adolescents with the impact of antibiotic resistance: a retrospective study. *BMC Infect Dis* 2017; **17**: 500.

42 Kleinhendler E, Cohen MJ, Moses AE, Paltiel O, Strahilevitz J, Cahan A. Empiric antibiotic protocols for cancer patients with neutropenia: a single-center study of treatment efficacy and mortality in patients with bacteremia. *Int J Antimicrob Agents* 2018; **51**: 71–76.

43 Li J, Feng X, Wang J, et al. *Acinetobacter* spp. bloodstream infection in hematological patients: a 10-year single-center study. *BMC Infect Dis* 2023; **23**: 796.

44 Micozzi A, Gentile G, Minotti C, et al. Carbapenem-resistant *Klebsiella pneumoniae* in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant Klebsiella pneumoniae bacteremias. *BMC Infect Dis* 2017; **17**: 203.

45 Micozzi A, Gentile G, Santilli S, et al. Reduced mortality from KPC-*K.pneumoniae* bloodstream infection in high-risk patients with hematological malignancies colonized by KPC-*K.pneumoniae*. *BMC Infect Dis* 2021; **21**: 1079.

46 Shargian-Alon L, Gafter-Gvili A, Ben-Zvi H, et al. Risk factors for mortality due to *Acinetobacter baumannii* bacteremia in patients with hematological malignancies – a retrospective study. *Leuk Lymphoma* 2019; **60**: 2787–92.

47 Tang Y, Wu X, Cheng Q, Li X. Inappropriate initial antimicrobial therapy for hematological malignancies patients with Gram-negative bloodstream infections. *Infection* 2020; **48**: 109–16.

48 Wang X, Zhang L, Sun A, et al. *Acinetobacter baumannii* bacteraemia in patients with haematological malignancy: a multicentre retrospective study from the Infection Working Party of Jiangsu Society of Hematology. *Eur J Clin Microbiol Infect Dis* 2017; **36**: 1073–81.

49 Averbuch D, Moshkovitz L, Ilan S, Abu Ahmad W, Temper V, Strahilevitz J. Bacteremia with carbapenemase-producing *Enterobacterales* in immunocompromised patients colonized with these bacteria. *Microb Drug Resist* 2022; **28**: 593–600.

50 Cattaneo C, Di Blasi R, Skert C, et al. Bloodstream infections in haematological cancer patients colonized by multidrug-resistant bacteria. *Ann Hematol* 2018; **97**: 1717–26.

51 Liu LP, Lin QS, Yang WY, et al. High risk of bloodstream infection of carbapenem-resistant *enterobacteriaceae* carriers in neutropenic children with hematological diseases. *Antimicrob Resist Infect Control* 2023; **12**: 66.

52 Micozzi A, Minotti C, Capria S, et al. Benefits and safety of empiric antibiotic treatment active against KPC-*K. pneumoniae* in febrile neutropenic patients with acute leukemia who are colonized with KPC-*K. pneumoniae*. A 7-years retrospective observational cohort study. *Infect Drug Resist* 2023; **16**: 695–704.

53 Gallardo-Pizarro A, Lopera C, Peyrony O, et al. Rectal colonization by multidrug-resistant Gram-negative bacteria and subsequent bacteraemia in haematological patients. *Clin Microbiol Infect* 2025; **31**: 1579–83.

54 Arnan M, Gudiol C, Calatayud L, et al. Risk factors for, and clinical relevance of, faecal extended-spectrum β-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies. *Eur J Clin Microbiol Infect Dis* 2011; **30**: 355–60.

55 Satlin MJ, Chavda KD, Baker TM, et al. Colonization with levofloxacin-resistant extended-spectrum β-lactamase-producing *Enterobacteriaceae* and risk of bacteremia in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2018; **67**: 1720–28.

56 Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. *Transpl Infect Dis* 2014; **16**: 106–14.

57 Fayard A, Daguenet E, Blaise D, et al. Evaluation of infectious complications after haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning: a study on behalf of the Francophone Society of Stem Cell Transplantation and Cellular Therapy (SFGM-TC). *Bone Marrow Transplant* 2019; **54**: 1586–94.

58 Cattaneo C, Zappasodi P, Mancini V, et al. Emerging resistant bacteria strains in bloodstream infections of acute leukaemia patients: results of a prospective study by the Rete Ematologica Lombarda (Rel). *Ann Hematol* 2016; **95**: 1955–63.

59 European Centre for Disease Prevention and Control. Surveillance atlas of infectious diseases. April 28, 2023. https://www.ecdc.europa.eu/en/surveillance-atlas-infectious-diseases (accessed Aug 30, 2025).

60 Beyar-Katz O, Dickstein Y, Borok S, Vidal L, Leibovici L, Paul M. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. *Cochrane Database Syst Rev* 2017; **6**: CD003914.

61 Ju M, Huang Y, Xu X, et al. Predictors of mortality in adult patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: a meta-analysis and systematic review. *Ann Palliat Med* 2021; **10**: 8617–27.

62 Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1–45.

63 Chen YH, Sun AY-E, Narain K, et al. Efficacy and safety of early antibiotic de-escalation in febrile neutropenia for patients with hematologic malignancy: a systematic review and meta-analysis. *Antimicrob Agents Chemother* 2025; **69**: e0159724.

64 Ishikawa K, Masaki T, Kawai F, Ota E, Mori N. Systematic review of the short-term versus long-term duration of antibiotic management for neutropenic fever in patients with cancer. *Cancers* 2023; **15**: 1611.

65 Stern A, Carrara E, Bitterman R, Yahav D, Leibovici L, Paul M. Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer. *Cochrane Database Syst Rev* 2019; **1**: CD012184.

66 Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol* 2017; **4**: e573–83.

67 de Jonge NA, Sikkens JJ, Zweegman S, et al. Short versus extended treatment with a carbapenem in patients with high-risk fever of unknown origin during neutropenia: a non-inferiority, open-label, multicentre, randomised trial. *Lancet Haematol* 2022; **9**: e563–72.

68 Ram R, Amit O, Adler A, et al. Early antibiotic deescalation and discontinuation in patients with febrile neutropenia after cellular therapy: a single-center prospective unblinded randomized trial. *Transplant Cell Ther* 2023; **29**: 708.e1–8.

69 Santolaya ME, Alvarez AM, Acuña M, et al. Efficacy and safety of withholding antimicrobial treatment in children with cancer, fever and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial. *Clin Microbiol Infect* 2017; **23**: 173–78.

70 Torres JP, Ibañez C, Valenzuela R, et al. Efficacy and safety of withholding antimicrobial therapy in children with cancer, fever, and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial. *Clin Microbiol Infect* 2024; **30**: 1029–34.

71 Chow V, Dorcy KS, Sandhu R, et al. Evaluation of early discharge after hospital treatment of neutropenic fever in acute myeloid leukemia (AML). *Leuk Res Rep* 2013; **2**: 26–28.

72 Kroll AL, Corrigan PA, Patel S, Hawks KG. Evaluation of empiric antibiotic de-escalation in febrile neutropenia. *J Oncol Pharm Pract* 2016; **22**: 696–701.

73 la Martire G, Robin C, Oubaya N, et al. De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome. *Eur J Clin Microbiol Infect Dis* 2018; **37**: 1931–40.

74 Paret R, Le Bourgeois A, Guillerm G, et al. Safety and risk of febrile recurrence after early antibiotic discontinuation in high-risk neutropenic patients with haematological malignancies: a multicentre observational study. *J Antimicrob Chemother* 2022; **77**: 2546–56.

75 Patel PA, Teherani MF, Xiang Y, et al. Short-course empiric antibiotics in children undergoing allogeneic hematopoietic cell transplantation. *Transplant Cell Ther* 2023; **29**: 778. e1–6.

76 Petteys MM, Kachur E, Pillinger KE, He J, Copelan EA, Shahid Z. Antimicrobial de-escalation in adult hematopoietic cell transplantation recipients with febrile neutropenia of unknown origin. *J Oncol Pharm Pract* 2020; **26**: 632–40.

77 Snyder M, Pasikhova Y, Baluch A. Evaluating initial empiric therapy for neutropenic fever in vancomycin-resistant *Enterococcus*-colonized patients. *Cancer Control* 2021; **28**: 10732748211045593.

78 Van de Wyngaert Z, Berthon C, Debarri H, et al. Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: a prospective cohort. *Int J Antimicrob Agents* 2019; **53**: 781–88.

79 Rearigh L, Stohs E, Freifeld A, Zimmer A. De-escalation of empiric broad spectrum antibiotics in hematopoietic stem cell transplant recipients with febrile neutropenia. *Ann Hematol* 2020; **99**: 1917–24.

80 Winget MD, Gatwood K, Jayani R, et al. Evaluating antibiotic de-escalation for autologous stem cell transplant patients with febrile neutropenia in a real-world clinical setting. *Transplant Cell Ther* 2024; **30**: 1031.e1–9.

81 Alali M, Prather C, Danziger-Isakov LA, et al. Absolute monocyte count as early and safe marker for antibiotic cessation in febrile neutropenia without etiology in pediatric oncology patients. *J Pediatr Hematol Oncol* 2023; **45**: e702–09.

82 Campbell ME, Friedman DL, Dulek DE, Zhao Z, Huang Y, Esbenshade AJ. Safety of discharge for children with cancer and febrile neutropenia off antibiotics using absolute neutrophil count threshold values as a surrogate marker for adequate bone marrow recovery. *Pediatr Blood Cancer* 2018; **65**: e26875.

83 Olson J, Mehra S, Hersh AL, et al. Oral step-down therapy with levofloxacin for febrile neutropenia in children with cancer. *J Pediatric Infect Dis Soc* 2021; **10**: 27–33.

84 Alegria W, Marini BL, Gregg KS, Bixby DL, Perissinotti A, Nagel J. Early antibiotic discontinuation or de-escalation in high-risk patients with AML with febrile neutropenia and prolonged neutropenia. *J Natl Compr Canc Netw* 2022; **20**: 245–52.

85 Clément L, Hélène D, Maud M, et al. Safety of empirical antibiotic therapy discontinuing for fever of unknown origin during high-risk neutropenia in children. *J Infect* 2024; **88**: 106171.

86 Contejean A, Abbara S, Chentouh R, et al. Antimicrobial stewardship in high-risk febrile neutropenia patients. *Antimicrob Resist Infect Control* 2022; **11**: 52.

87 Durand C, Risso K, Loschi M, et al. Efficacy of an antimicrobial stewardship intervention for early adaptation of antibiotic therapy in high-risk neutropenic patients. *Antimicrob Resist Infect Control* 2024; **13**: 5.

88 Fuller R, Moshier E, Jacobs SE, et al. Practicing antimicrobial stewardship: de-escalating antibiotics in patients with acute myeloid leukemia and neutropenic fever. *Open Forum Infect Dis* 2020; **7**: ofaa138.

89 Lucena M, Gaffney KJ, Urban T, et al. Early de-escalation of antibiotic therapy in hospitalized cellular therapy adult patients with febrile neutropenia. *Clin Hematol Int* 2024; **6**: 59–66.

90 Ly WJ, Brown EE, Pedretti Z, Auten J, Wilson WS. Evaluation of early de-escalation of empiric antimicrobial therapy in acute leukemia patients with febrile neutropenia at a large academic medical center. *J Oncol Pharm Pract* 2023; **29**: 305–10.

91 Verlinden A, Jansens H, Goossens H, et al. Safety and efficacy of antibiotic de-escalation and discontinuation in high-risk hematological patients with febrile neutropenia: a single-center experience. *Open Forum Infect Dis* 2021; **9**: ofab624.

92 Baden LR, Swaminathan S, Almyroudis NG, et al. Prevention and treatment of cancer-related infections, version 3.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2024; **22**: 617–44.

93 Ranganath N, Yetmar ZA, Saleh OA, Tande AJ, Shah AS. Risk factors for positive follow-up blood cultures in Gram-negative bacteremia among immunocompromised patients with neutropenia. *Transpl Infect Dis* 2024; **26**: e14203.

94 Sathya Kumar AM, George MM, Bhanuprasad K, et al. Persistent bacteremia predicts poor outcomes among neutropenic patients with carbapenem-resistant Gram-negative bloodstream infections receiving appropriate therapy. *Ann Clin Microbiol Antimicrob* 2023; **22**: 12.

95 Wattier RL, Dvorak CC, Auerbach AD, Weintrub PS. Repeat blood cultures in children with persistent fever and neutropenia: diagnostic and clinical implications. *Pediatr Blood Cancer* 2015; **62**: 1421–26.

96 Sheu M, Molina Garcia S, Shrivastava G, et al. Yield of repeat blood cultures in acute myeloid leukemia patients with febrile neutropenia and bacteremia following allogeneic hematopoietic stem cell transplant. *Transpl Infect Dis* 2024; **26**: e14345.

97 Robinson ED, Keng MK, Thomas TD, Cox HL, Park SC, Mathers AJ. Reducing repeat blood cultures in febrile neutropenia: a single-center experience. *Open Forum Infect Dis* 2022; **9**: ofac521.

98 Jafri F, Knoll BM. Low diagnostic yield of repeat blood cultures in adult haematologic malignancy patients with persistent neutropenic fever. *J Intern Med* 2021; **289**: 584–87.

99 Kimura SI, Gomyo A, Hayakawa J, et al. Clinical significance of repeat blood cultures during febrile neutropenia in adult acute myeloid leukaemia patients undergoing intensive chemotherapy. *Infect Dis* 2017; **49**: 748–57.

100 Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect* 2022; **28**: 521–47.

101 Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. *Clin Infect Dis* 2024; published online Aug 7. https://doi.org/10.1093/cid/ciae403 (preprint).

102 Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2018; **18**: 1319–28.

103 Hakki M, Lewis JS 2nd. Ceftolozane-tazobactam therapy for multidrug-resistant *Pseudomonas aeruginosa* infections in patients with hematologic malignancies and hematopoietic-cell transplant recipients. *Infection* 2018; **46**: 431–34.

104 Castón JJ, Lacort-Peralta I, Martín-Dávila P, et al. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing *Enterobacteriaceae* in hematologic patients. *Int J Infect Dis* 2017; **59**: 118–23.

105 Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-avibactam use for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* infections: a retrospective observational multicenter study. *Clin Infect Dis* 2021; **73**: 1664–76.

106 Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with Infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. *Clin Infect Dis* 2019; **68**: 355–64.

107 Zhen S, Lin Q, Chen Z, et al. Ceftazidime-avibactam in the treatment of bacteremia due to carbapenem-resistant gram-negative bacteria in hematological patients: experience in a single center. *J Infect Chemother* 2024; **30**: 608–15.

108 Meng H, Han L, Niu M, et al. Risk factors for mortality and outcomes in hematological malignancy patients with carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. *Infect Drug Resist* 2022; **15**: 4241–51.

109 Soriano A, Montravers P, Bassetti M, et al. The use and effectiveness of ceftazidime-avibactam in real-world clinical practice: EZTEAM study. *Infect Dis Ther* 2023; **12**: 891–917.

110 Zhang L, Zhen S, Shen Y, et al. Bloodstream infections due to carbapenem-resistant *Enterobacteriaceae* in hematological patients: assessment of risk factors for mortality and treatment options. *Ann Clin Microbiol Antimicrob* 2023; **22**: 41.

111 Herrera F, Torres D, Laborde A, et al. Ceftazidime-avibactam improves outcomes in high-risk neutropenic patients with *Klebsiella pneumoniae* carbapenemase-producing *Enterobacterales* bacteremia. *Microorganisms* 2024; **12**: 195.

112 Tumbarello M, Raffaelli F, Giannella M, et al. Outcomes and predictors of mortality in patients with KPC-Kp infections treated with meropenem vaborbactam: an observational multicenter study. *Open Forum Infect Dis* 2024; 11: ofae273.

113 Ackley R, Roshdy D, Meredith J, et al. Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* infections. *Antimicrob Agents Chemother* 2020; **64**: e02313–19.

114 Kirkegaard-Biosca C, Del Barrio-Tofiño E, Villamarín M, et al. Cefiderocol for the treatment of infections by VIM-type-producing Gram-negative bacteria. *Antibiotics* 2024; **13**: 874.

115 Larcher R, Laffont-Lozes P, Roger C, et al. Last resort beta-lactam antibiotics for treatment of New-Delhi metallo-beta-lactamase producing *Enterobacterales* and other difficult-to-treat resistance in Gram-negative bacteria: a real-life study. *Front Cell Infect Microbiol* 2022; **12**: 1048633.

116 Shields RK, Abbo LM, Ackley R, et al. Effectiveness of ceftazidime-avibactam versus ceftolozane-tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections in the USA (CACTUS): a multicentre, retrospective, observational study. *Lancet Infect Dis* 2024; **25**: 574–84.

117 Carmeli Y, Cisneros JM, Paul M, et al. Aztreonam-avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial. *Lancet Infect Dis* 2025; **25**: 218–30.

118 Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021; **21**: 226–40.

119 Onorato L, Di Caprio G, Signoriello S, Coppola N. Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis. *Int J Antimicrob Agents* 2019; **54**: 735–40.

120 Fiore M, Alfieri A, Di Franco S, et al. Ceftazidime-avibactam combination therapy compared to ceftazidime-avibactam monotherapy for the treatment of severe infections due to carbapenem-resistant pathogens: a systematic review and network meta-analysis. *Antibiotics* 2020; **9**: 388.

121 Li D, Fei F, Yu H, et al. Ceftazidime-avibactam therapy versus ceftazidime-avibactam-based combination therapy in patients with carbapenem-resistant Gram-negative pathogens: a meta-analysis. *Front Pharmacol* 2021; **12**: 707499.

122 Aslan AT, Ezure Y, Horcajada JP, Harris PNA, Paterson DL. In vitro, in vivo and clinical studies comparing the efficacy of ceftazidime-avibactam monotherapy with ceftazidime-avibactam-containing combination regimens against carbapenem-resistant *Enterobacterales* and multidrug-resistant *Pseudomonas aeruginosa* isolates or infections: a scoping review. *Front Med* 2023; **10**: 1249030.

123 El Ghali A, Kunz Coyne AJ, Lucas K, et al. Cefiderocol: early clinical experience for multi-drug resistant gram-negative infections. *Microbiol Spectr* 2024; **12**: e0310823.

124 Giacobbe DR, Labate L, Russo Artimagnella C, et al. Use of cefiderocol in adult patients: descriptive analysis from a prospective, multicenter, cohort study. *Infect Dis Ther* 2024; **13**: 1929–48.

125 Piccica M, Spinicci M, Botta A, et al. Cefiderocol use for the treatment of infections by carbapenem-resistant Gram-negative bacteria: an Italian multicentre real-life experience. *J Antimicrob Chemother* 2023; **78**: 2752–61.

126 Temkin E, Torre-Cisneros J, Beovic B, et al. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. *Antimicrob Agents Chemother* 2017; **61**: e01964-16.

127 Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 2018; **67**: 1803–14.

128 Fernández-Cruz A, Alba N, Semiglia-Chong MA, et al. A case-control study of real-life experience with ceftolozane-tazobactam in patients with hematologic malignancy and *Pseudomonas aeruginosa* Infection. *Antimicrob Agents Chemother* 2019; **63**: e02340-18.

129 Zhen S, Zhao Y, Chen Z, et al. Assessment of mortality-related risk factors and effective antimicrobial regimens for treatment of bloodstream infections caused by carbapenem-resistant *Pseudomonas aeruginosa* in patients with hematological diseases. *Front Cell Infect Microbiol* 2023; **13**: 1156651.

130 Fiore M, Corrente A, Pace MC, et al. Ceftolozane-tazobactam combination therapy compared to ceftolozane-tazobactam monotherapy for the treatment of severe infections: a systematic review and meta-analysis. *Antibiotics* 2021; **10**: 79.

131 Jung SY, Lee SH, Lee SY, et al. Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis. *Crit Care* 2017; **21**: 319.

132 Liu J, Shu Y, Zhu F, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. *J Glob Antimicrob Resist* 2021; **24**: 136–47.

133 Noguchi JK, Gill MA. Sulbactam: a beta-lactamase inhibitor. *Clin Pharm* 1988; **7**: 37–51.

134 Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2015; **59**: 1680–89.

135 Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii-calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *Lancet Infect Dis* 2023; **23**: 1072–84.

136 Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol- compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2022; **66**: e0214221.

137 Giannella M, Verardi S, Karas A, et al. Carbapenem-resistant *Acinetobacter* spp infection in critically ill patients with limited treatment options: a descriptive study of cefiderocol therapy during the COVID-19 pandemic. *Open Forum Infect Dis* 2023; **10**: ofad329.

138 Pascale R, Pasquini Z, Bartoletti M, et al. Cefiderocol treatment for carbapenem-resistant *Acinetobacter baumannii* infection in the ICU during the COVID-19 pandemic: a multicentre cohort study. *JAC Antimicrob Resist* 2021; **3**: dlab174.

139 Russo A, Bruni A, Gullì S, et al. Efficacy of cefiderocol- vs colistin-containing regimen for treatment of bacteraemic ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* in patients with COVID-19. *Int J Antimicrob Agents* 2023; **62**: 106825.

140 Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 2021; **21**: 213–25.

141 Maraolo AE, Licciardi F, Gentile I, Saracino A, Belati A, Bavaro DF. *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis of comparative efficacy of available treatments, with critical assessment of novel therapeutic options. *Antibiotics* 2023; **12**: 910.

142 Ko JH, Kang CI, Cornejo-Juárez P, et al. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. *Clin Microbiol Infect* 2019; **25**: 546–54.

143 Almangour TA, Alkherb Z, Alruwaite S, et al. Trimethoprim-sulfamethoxazole versus levofloxacin for the treatment of *Stenotrophomonas maltophilia* infections: a multicentre cohort study. *J Glob Antimicrob Resist* 2024; **38**: 42–48.

144 Hevia EC, Wooten L, Carr AL. Trimethoprim/sulfamethoxazole vs minocycline for the treatment of nonurinary monomicrobial *Stenotrophomonas maltophilia* infections in hospitalized patients. *Ann Pharmacother* 2024; **58**: 698–704.

145 Alhayani T, Philpott CD, Liao S, Gentene AJ, Mueller EW. Comparison of doxycycline or minocycline to sulfamethoxazole-trimethoprim for treatment of *Stenotrophomonas maltophilia* pneumonia. *Ann Pharmacother* 2024; **58**: 21–27.

146 Junco SJ, Bowman MC, Turner RB. Clinical outcomes of *Stenotrophomonas maltophilia* infection treated with trimethoprim/sulfamethoxazole, minocycline, or fluoroquinolone monotherapy. *Int J Antimicrob Agents* 2021; **58**: 106367.

147 Saburi M, Oshima K, Takano K, et al. Risk factors and outcome of *Stenotrophomonas maltophilia* infection after allogeneic hematopoietic stem cell transplantation: JSTCT, transplant complications working group. *Ann Hematol* 2023; **102**: 2507–16.

148 Richert-Przygonska M, Czyzewski K, Dziedzic M, et al. Infections with *Stenotrophomonas maltophilia* in children undergoing anticancer therapy or hematopoietic cell transplantation: a multicenter nationwide study. *Pediatr Infect Dis J* 2022; **41**: 846–50.

149 Dadashi M, Hajikhani B, Nazarinejad N, et al. Global prevalence and distribution of antibiotic resistance among clinical isolates of *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. *J Glob Antimicrob Resist* 2023; **34**: 253–67.

150 Feng X, Qian C, Fan Y, et al. Is short-course antibiotic therapy suitable for *Pseudomonas aeruginosa* bloodstream infections in onco-hematology patients with febrile neutropenia? Results of a multi-institutional analysis. *Clin Infect Dis* 2024; **78**: 518–25.

151 Herrera F, Torres D, Carena A, et al. Short course of antibiotic therapy for Gram-negative *Bacilli* bacteremia in patients with cancer and hematopoietic stem cell transplantation: less is possible. *Microorganisms* 2023; **11**: 511.

152 Herrera F, Torres D, Laborde A, et al. Seven-day antibiotic therapy for *Enterobacterales* bacteremia in high-risk neutropenic patients: toward a new paradigm. *Eur J Clin Microbiol Infect Dis* 2024; **43**: 1741–51.

153 Ranganath N, Yetmar ZA, McCandless AR, et al. Evaluating antimicrobial duration for Gram-negative bacteremia in patients with neutropenia due to hematologic malignancy or hematopoietic stem cell transplantation. *Transpl Infect Dis* 2023; **25**: e14085.

REVIEW ARTICLE OPEN

Check for updates

Primary antifungal prophylaxis in hematological malignancies. Updated clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL)

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At the 10th European Conference on Infections in Leukaemia (ECIL), the guidelines for antifungal prophylaxis in pediatric and adult patients with hematological malignancies (HM) were updated and some changes introduced. Regarding acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) patients undergoing remission induction chemotherapy, a B-II grading has been assigned to isavuconazole, micafungin, and caspofungin, based on non-randomized studies that have shown efficacy in preventing invasive fungal diseases (IFD). Regarding high-risk MDS patients treated with azacytidine, prophylaxis with posaconazole during the first four cycles of treatment is supported in the literature. Prophylaxis is not indicated in patients treated for myeloproliferative neoplasms (NPM), acute lymphoid leukemia (ALL), and Hodgkin lymphoma (HL). For patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), prophylaxis is not generally indicated. For patients with multiple myeloma (MM), prophylaxis is not indicated and the limited epidemiological data available do not support the use of prophylaxis in subjects treated with bispecific antibodies. For patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), no substantial changes were made, apart from the addition of isavuconazole with grading B-II in the post-engraftment period. In patients undergoing auto-HSCT, antifungal prophylaxis is not indicated. Previous ECIL guidelines did not include CAR-T cells. The expert panel proposes to endorse the use of anti-mold prophylaxis in high-risk patients during pre-infusion and post-infusion, while in low-risk patients, anti-yeast prophylaxis can be recommended (B-II). For pediatric hematology patients, based on newly published data, caspofungin received a B-I grading as mold-active prophylaxis. Moreover, patients with ALL with insufficient treatment response during induction therapy, and children older than 12 y.o are now considered at high risk for IFD and are recommended to receive antifungal prophylaxis.

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INTRODUCTION

In 2005, the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the European Leukemia Net (ELN), and the International Immunocompromised Host Society (ICHS) inaugurated the European Conference on Infections in Leukemia (ECIL). Its main goal was to establish guidelines or recommendations for the management of infections due to bacteria, viruses, parasites, and fungi in patients with leukemia and in patients undergoing hematopoietic stem cell transplantation (HSCT) [1]. The prevention of invasive fungal disease (IFD) has been one of the key topics from the beginning [1, 2].

The ECIL committee aims to update their guidelines regularly based on current available evidence. During the fifth and sixth meetings (2013 and 2015), guidelines on antifungal prophylaxis for adults were extensively revised, and during the ninth meeting (2021) recommendations for antifungal prophylaxis in pediatrics were developed [1, 3].

An update of previous recommendations was already done in 2018 [4], but over the last few years, several new antineoplastic drugs have been introduced into clinical practice for all hematological malignancies (i.e. BCL-2 inhibitors, FLT-3 inhibitors in acute myeloid leukemias, Bruton Tyrosine Kinase inhibitors (BTKIs) other new tyrosine kinase inhibitors (TKIs), bispecific

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Table 1. Evidence-based medicine grading system according to the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).

Strength of recommendation (SoR)	
Grade	Definition
A	ECIL strongly supports a recommendation for use
B	ECIL moderately supports a recommendation for use
C	ECIL marginally supports a recommendation for use
D	ECIL supports a recommendation against use
Quality of evidence (QoE)	
Level	Definition
I	Evidence from at least 1 properly designed randomized, controlled trial (orientated on the primary endpoint of the trial)
II	Evidence from at least 1 well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Added index for source of level II evidence	
Index	Source
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, that is, results from different patient cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trial
a	Published abstract (presented at an international symposium or meeting)

monoclonal antibodies). In addition, new cellular therapy procedures, such as chimeric-antigen receptor T (CAR-T) cell treatments, are now increasingly used. Therefore, at the ECIL-10 meeting in September 2024, a detailed review of the recent literature was conducted, with the agreed proposals summarized in this review.

METHODOLOGY

The methodology of the ECIL conferences has previously been reported [1, 3].

A working group of experts in the field was nominated several months in advance of the biennial conference and was charged with reviewing the literature published since the last update of the guidelines.

A literature review was performed using the PubMed database for publications up from September 2015 and the working group co-authoring this manuscript reviewed all publications identified. Recommendations drawn from data available only as abstracts were provisionally graded, pending the publication of the full papers. The quality of evidence and strength of recommendation were graded according to the EBM grading system of ESCMID (Table 1) [5].

The working group compiled a slide set discussed in several consecutive online group meetings and electronic communication until two weeks before the ECIL-10 plenary meeting held on September 20th, 2024. The final slide set, approved by all group members, was sent by email to all ECIL-10 participants before the plenary. On the day of the meeting (September 20, 2024), the slides were presented by the working group and interactively discussed during a plenary session. The comments made during the plenary discussion were reviewed by the members of the working group in a closed session and recommendations revised accordingly.

The final set of recommendations was thereafter discussed with the ECIL-10 plenary until consensus was reached.

The approved slide set was published on the ECIL website (https://ecil-leukaemia.com/en/resources/resources-ecil), with comments invited for over a month (November 2024). All members of the working group then approved the final set of recommendations.

The final manuscript has been written and revised by all co-authors.

ACUTE MYELOID LEUKEMIA (AML)

Two new major issues have been addressed since the publication of the previous ECIL guidelines on antifungal prophylaxis [4].

Oral isavuconazole has been studied for primary antifungal prophylaxis in 65 patients undergoing remission induction chemotherapy in an open-label phase II study [6]. One patient developed a proven IFD and another 3 a probable IFD. When compared with posaconazole and voriconazole in a retrospective analysis of 277 patients with newly diagnosed AML, the incidences of breakthrough IFD were 2.9% for posaconazole, 4.8% for voriconazole, and 5.7% for isavuconazole ($p = 0.55$) [7]. While isavuconazole is not approved for antifungal prophylaxis in Europe (nor in the United States), the expert panel consider that isavuconazole may be considered for antifungal prophylaxis in selected adult patients undergoing remission induction therapy for AML and for whom posaconazole is not appropriate (e.g., liver function abnormalities, QTc prolongation, drug-drug interactions, intestinal absorption issues).

The benefit from systemic antifungal prophylaxis in patients undergoing consolidation chemotherapy for AML was retrospectively analyzed in a large SEIFEM study [8]. Among 2588 adult and pediatric patients, invasive aspergillosis was diagnosed in 34/1137 (2.9%) patients receiving no antifungal prophylaxis, compared with 22/1451 (1.5%) patients who were given antifungal prophylaxis ($p = 0.01$). The number needed to treat to prevent one invasive aspergillosis was 71 patients [8]. Systemic antifungal prophylaxis has been given a B-IIu recommendation for AML patient undergoing consolidation chemotherapy.

For patients undergoing AML treatment with one of the newer systemic agents such as venetoclax, FLT3 inhibitors, or ivosidenib,

the recommendations on indications and the proper selection of agents for systemic antifungal prophylaxis, as given by the ECIL-9 guideline [9], are reinforced by the present updated guideline. Recommendations for appropriate dose adjustments in case of relevant pharmacological drug-drug interactions were thereby addressed as well.

Beyond these issues, the grading of recommendations has been modified for itraconazole (from B-I to C-I) and micafungin (from C-II to B-II), and a recommendation for "super bioavailable" (SUBA)-itraconazole has been added (C-II).

In comparison to posaconazole, itraconazole was shown to be less effective and less reliable concerning drug levels than posaconazole in AML patients [10, 11]. As SUBA-itraconazole has become available, "classic" itraconazole has been slightly downgraded (C-I).

SUBA-itraconazole has been clinically investigated for pharmacokinetics, tolerability, and safety in several cohort studies including patients with hematologic malignancies and allogeneic HSCT recipients as well as solid organ transplant recipients [12, 13].

In our former recommendations, echinocandins as a group were graded as "C-II", because of their narrower spectrum of antifungal activity when compared to amphotericin B and most triazoles, and sparse clinical data on their use as antifungal prophylaxis in patients with hematologic malignancies. As more detailed data for the efficacy and safety of micafungin are now available for AML and myelodyplastic syndromes (MDS) patients as well as for allogeneic HSCT recipients, micafungin has now been upgraded to B-II [14–16].

Table 2 shows the new recommendations compared to those suggested during ECIL-5.

Myelodysplastic Syndromes (MDS)

For patients with low-risk MDS receiving transfusion-supportive treatment or treated with growth factors (i.e. erythropoietin), no increased risk of IFD has been reported, and therefore no antifungal prophylaxis is indicated (D-I). The introduction of luspatercept does not change this recommendation. The COMMANDS study comparing luspatercept versus erythropoietin which enrolled over 600 patients, did not report any case of IFD [17].

For patients with high-risk MDS receiving intensive AML-like induction (and consolidation) chemotherapy treatment, the recommendation to administer antifungal prophylaxis has not changed (A-I) [4]. The situation is different for intermediate and high-risk patients receiving treatment with azacytidine. A review of the literature in recent years shows an increased risk of IFD, especially during the first 4 cycles of treatment with an incidence ranging from 3% to 12% [18]. When antifungal prophylaxis was administered in most patients, the rate of IFD was 3-8% [18–20], while in series where the proportion of patients receiving antifungal prophylaxis was very low, the rate of IFD rised to 8-12% [21–27]. The new recommendation for these patients is therefore to use antimold prophylaxis during the first 4 cycles of azacytidine treatment (B-IIu).

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Regarding patients with chronic myeloid leukemia treated with TKIs (imatinib, dasatinib, nilotinib, ponatinib, asciminib) and Philadelphia chromosome-negative myeloproliferative neoplasms, including those treated with ruxolitinib [28–34] an increased risk of IFD is not reported and antifungal prophylaxis is not indicated (D-I).

Table 3 shows the new recommendations compared to those suggested during ECIL-5.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Adults with ALL are usually treated with an intensive polychemotherapy regimen inducing prolonged neutropenia and receive corticosteroids. Therefore, these patients are at risk of developing IFD. The incidence of IFD in this population varies between 4 and 18%, which is rather similar compared to that observed in AML [35]. Although TKIs (e.g. imatinib, nilotinib, ponatinib) used for the treatment of Philadelphia chromosome-positive ALL have been associated with IFD, the actual IFD incidence seems to be low (< 1%) [36]. Novel specific monoclonal antibody therapies used for ALL (e.g. blinatumomab, inotuzumab ozogamicin) have not been associated with a higher IFD incidence compared to the standard of care in randomized controlled trials [37, 38].

Antifungal prophylaxis in this population is hampered by the drug-drug interaction between triazoles and vincristine, an important component of most ALL chemotherapy regimens. Concomitant use of triazoles may result in increased vincristine-related neurotoxicity because this later drug is metabolized by the CYP3A4 cytochrome. Studies in children with ALL suggest a significantly higher risk of vincristine-related neurotoxicity with voriconazole or itraconazole, while the use of fluconazole seems to be safer [39, 40]. However, data on adults are lacking. Studies assessing the efficacy of antifungal prophylaxis in ALL adult patients for the prevention of IFD are heterogeneous and scarce [41–43]. One randomized controlled study failed to demonstrate the benefit of twice weekly intravenous liposomal amphotericin B (5 mg/kg) versus placebo with a higher incidence of drug-related adverse events in the treatment arm [44].

Antifungal prophylaxis with a mold-active triazole, such as voriconazole or posaconazole, is not recommended because of interactions which could increase the toxicity of vincristine (D-II). Although data are still lacking, isavuconazole might be considered with caution, considering its lower inhibitory effect on CYP3A4 (C-III). Similarly, fluconazole might be considered with caution for prevention of yeast infection (C-III). Alternative anti-mold prophylaxis (e.g. liposomal amphotericin B, echinocandins) might be considered in high-risk patients (i.e. prolonged chemotherapy-induced neutropenia), but no benefit has been shown to date. No antifungal prophylaxis is recommended for ALL patients receiving only TKIs (D-III) (Table 4).

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

The incidence of IFD in patients with CLL is overall low (0.5 to 3%) and varies according to the type of treatment [45–48]. These patients present with a large and diverse spectrum of immunosuppression, from untreated patients with different degrees of neutropenia, patients treated with corticosteroids, anti-BCL2 (e.g. venetoclax), or BTKIs (e.g. ibrutinib). Treatment with ibrutinib or other BTKIs is associated with the highest IFI incidence in this population (2 to 3%) [46, 49, 50]. One small retrospective analysis showed a significantly lower IFD incidence among ibrutinib-treated CLL patients receiving antifungal prophylaxis (mainly fluconazole) versus no prophylaxis [51].

Antifungal prophylaxis is not routinely recommended in CLL patients (D-III) but may be considered in selected refractory cases with prolonged neutropenia or BTKIs therapy (C-II). In the case of co-administration of venetoclax, antifungal prophylaxis should be avoided or used cautiously because of drug-drug interactions (i.e. adjustment of venetoclax dosing is needed with therapeutic drug monitoring of the antifungal agent) (Table 4).

MYELOMA

Reported IFD incidences in myeloma patients treated with conventional chemotherapy combinations have been low (< 1%) despite the presence of risk factors for IFD such as high doses of corticosteroids, disease-related comorbidities, myeloma-related innate immunodeficiency and, in treatment-experienced patients, poor marrow function [52]. Since the publication of the previous ECIL guidelines, treatment with combinations of immunomodulatory

Table 2. Recommendations for antifungal prophylaxis in patients with AML receiving intensive remission induction/reinduction chemotherapy.

Intention	Intervention	SoR	QoE	ECIL 5-6
Prevent IFD in AML patients, excluding allogeneic HSCT	posaconazole, tablet 300 mg q24h p.o. (q12h on day 1)	A	I[1]	A-I
	amphotericin B, liposomal, inhalation[*2,3] 10 mg twice weekly	B	I	B-I
	fluconazole[4] 400 mg q24h, p.o. or i.v.	B	I	B-I
	voriconazole 6 mg/kg/12 h first day then 4 mg/kg q12h, i.v. or p.o.	B	IIu	B-II
	isavuconazole[2] 200 mg q8h p.o. first 2 days then 200 mg q24h	B	IIt	NR
	micafungin 50 mg q24h i.v.	B	II u,t	NR
	amphotericin B, liposomal, i.v.[2] 1-3 mg/kg q24h	C	II	C-II
	caspofungin[2] 50 mg q24h i.v. (70 mg on day 1, 70 mg q24h in patients >80 kg)	B	IIt	NR
	itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o.	C	I	B-I
	SUBA-itraconazole 200 mg q12h p.o.	C	IIt	NR

AML acute myeloid leukemia, *IFD* invasive fungal disease, *HSCT* hematopoietic stem cell transplantation, *NR* No recommendation.
1 = recommendation for AML under remission induction chemotherapy; 2 = no approval for prophylaxis of IFD; 3 = formulation not approved; 4 =Only recommended if the incidence of mold infections is low. Fluconazole may be part of an integrated care strategy together with a mold-directed diagnostic approach.
*Should be combined with systemic fluconazole.
Amphotericin deoxycholate is not approved for prophylaxis and should not be considered due to drug-related toxicity.

Table 3. Recommendations for antifungal prophylaxis in patients with MDS, CML, and MPN.

Population	Intervention	SoR	QoE	ECIL 5-6
MDS low-/intermediate No chemotherapy	Any prophylaxis	D	I	No recommendation
MDS Intermediate/High treated as AML with intensive chemotherapy	posaconazole prophylaxis 300 mg q24 p.o. (q12h on day 1)	A	I	As for AML
MDS Intermediate/High Treated with Azacytidine	posaconazole prophylaxis during the first 4 azacytidine courses	B	IIu	No recommendation
CML Treated with TKIs	Any prophylaxis	D	I	No recommendation
MPN No chemotherapy	Any prophylaxis	D	I	No recommendation
MPN Treated with Ruxolitinib	Any prophylaxis	D	I	No recommendation

MDS Myelodysplastic Syndromes, *CML* Chronic Myeloid Leukemia, *MPN* Myeloproliferative Neoplasms, *AML* acute myeloid leukemia, *TKIs* tyrosine kinase inhibitors.

drugs, proteasome inhibitors, monoclonal antibodies, and autologous HSCT have been the standard of care. While no prospective study specifically reporting on IFD in this setting has been published, retrospective studies have reported a somewhat higher IFD incidence than with conventional chemotherapy, 2.7%, 3.5%, and 5.6%, respectively [46, 53–60]. Recently, two new types of antibody treatments have been introduced, bispecific antibodies activating a T-cell response by binding to both myeloma cells and T-cells, and B-cell binding antibodies conjugated with a cytotoxic compound (antibody-drug compound, ADC). Although neither prospective trials nor retrospective studies of treatment with bispecific antibodies have reported the exact numbers of IFD, their overall incidence after excluding Pneumocystis pneumonia has been low (< 2%) [47, 61–64]. The only registered ADC is belantamab mafotidin, which has now been withdrawn as a single agent but is currently under consideration as part of a combination treatment. The incidence of IFD was not specifically reported in the treatment trials leading to its registration, but the total infection rates were low with a 3% total incidence of pulmonary infections in the largest trial including 218 patients [61]. Routine antifungal prophylaxis is thus not recommended in myeloma patients, regardless of treatment with bispecific antibodies (D-II) (Table 4). Expert panels suggest to consider mold active prophylaxis in high-risk populations such as prolonged neutropenia or prolonged steroid treatment or secondary prophylaxis (no trials).

NON-HODGKIN LYMPHOMA (NHL)

Patients with NHL have an overall low IFD incidence (0.5 to 3%) [46, 47]. The incidence among NHL patients receiving BKTIs (e.g.

Table 4. Recommendations for antifungal prophylaxis in patients with ALL, CLL, NHL, HL and MM.

Population		Intervention	SoR	QoE	ECIL 5-6
ALL	TKIs	Any prophylaxis	D	III	No data
	Chemotherapy including vincristine	posaconazole voriconazole	D	II	Against
		isavuconazole 200 mg q8h p.o. first 2 days then 200 mg q24h	C	III	No data
		Fluconazole 400 mg q24h, p.o. or i.v.	C	III	C-III
CLL	Conventional treatment	Any prophylaxis	D	III	No recommendation
	Refractory treated BTKIs and/or venetoclax	Mold-active prophylaxis	C	II	No recommendation
NHL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
	Refractory treated BTKIs or high doses steroids	Mold-active prophylaxis	C	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data
HL	Treated with chemotherapy	Any prophylaxis	D	II	No recommendation
MM	Treated with IMiDs	Any prophylaxis	D	II	No recommendation
	Treated with Bispecific antibodies	Any prophylaxis	D	II	No data

ALL Acute Lymphoblastic Leukemia, *CLL* Chronic Lymphocytic Leukemia, *NHL* non-Hodgkin's Lymphoma, *HL* Hodgkin's Lymphoma, *MM* Multiple Myeloma, *BTKIs* Bruton tyrosine kinase inhibitors; *IMiDs* immunomodulatory drugs.

ibrutinib) is roughly similar (about 1.5%) [49]. Some factors have been associated with a higher risk of IFD, such as primary refractoriness, use of two or more previous treatment lines, and occurrence of neutropenia [62].

Antifungal prophylaxis is not routinely recommended in patients with NHL (D-II) but might be considered in selected patients with refractory lymphoma and/or repeated intensive chemotherapies with neutropenia or high dose steroids or BTKI therapy (C-II) (Table 4).

HODGKIN LYMPHOMA (HL)

The risk for IFD tends to be low in patients with Hodgkin lymphoma. Two recent nationwide epidemiological studies in hospitalized HL patients reported a total IFD incidence of 0.5% in Australia and a 0.5% incidence of pulmonary aspergillosis in Spain [47, 63]. In line with previous recommendations, routine antifungal prophylaxis is not recommended (D-II) (Table 4).

ALLOGENEIC HSCT (ALLO-HSCT)

The main practice change since the previous ECIL recommendations [4] has been the development of haplo-identical allo-HSCT using post-transplantation cyclophosphamide (haplo/PTCy) as graft-versus-host-disease (GVHD) prophylaxis. Retrospective studies on haplo/PTCy allo-HSCT report a one-year incidence rate of IFD ranging from 6 to 17% [64–68]. In two retrospective studies, the IFD incidence (especially invasive mold infections) was significantly higher in haplo/PTCy than in patients transplanted from HLA-matched related and/or unrelated donors receiving calcineurin inhibitors with or without anti-thymocyte globulin (ATG) [66, 67]. However, as the reported IFD rates remained within the range of those in post allo-HSCT outside of the haplo/PTCy setting, haplo/PTCy was still considered at low risk of IFD by the expert panel. As previously highlighted, [4] allo-HSCT centers should monitor the incidence and epidemiology of IFD and be aware that construction works may alter environmental exposure, which may warrant local adaptation of primary antifungal prophylaxis strategy.

The use of isavuconazole as primary antifungal prophylaxis in allo-HSCT recipients has been reported in two prospective open-label studies [69, 70]. The reported rates of breakthrough IFD were low (3–5%) while the treatment was well tolerated (discontinuation rate for toxicity: 2–7%). Data are insufficient to recommend isavuconazole as first-line prophylaxis; however, the expert panel proposes to endorse the ASTCT (American Society of Transplantation and Cellular Therapy) recommendations allowing the use of isavuconazole in cases of QT prolongation, or intolerance to voriconazole or posaconazole (B-II) [71].

In Tables 5 and 6, the main changes in antifungal prophylaxis recommendation are reported (with two additional references in Table 5 [72, 73]).

ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS

Previously published ECIL guidelines did not include CAR-T cells [4]. The EBMT/JACIE (Joint Acreditation Committee International Society for Cellular Therapy (ISTC) EBMT) and EBMT/ASTCT guidelines recommend the use of an anti-*Candida* prophylaxis and suggest discussing an anti-mold prophylaxis in case of prolonged neutropenia and/or steroid use [74, 75].

Retrospective studies, along with two literature reviews, report a 1–15% incidence of IFD in patients treated with anti-CD19 CAR-T cells [76–80]. These studies highlight a significant association between the occurrence of cytokine release syndrome (CRS) and a higher incidence of infections, attributed to the use of systemic immunosuppressive agents. In the literature review by Garner et al. [80], a combination of pre-and post-infusion factors seemed to increase the risk of IFD. The panel endorses the proposal of Garner et al., published after the EBMT/ASTCT recommendations, and integrating new data not available at the time of publication of the EBMT/ASTCT recommendations. The use of anti-mold prophylaxis is thus proposed to patients with pre-infusion (such as neutropenia, previous IFD, previous allo-HSCT, refractory disease) and post-infusion (CRS/immune effector cell-associated neurotoxicity syndrome [ICANS] necessitating steroid therapy and/or tocilizumab, prolonged neutropenia, use of alternative immunosuppressive agent) risk factors for mold infections, while patients without these risk factors could receiveanti-yeast prophylaxis (B-II) [80].

AUTOLOGOUS HSCT

In the previous ECIL recommendations, patients undergoing autologous HSCT, for whatever underlying condition, were

Table 5. Recommendations for allo-HSCT recipients: pre-engraftment.

Antifungal agent	Pre-engraftment risk of mold infection		ECIL 5-6	
	low	high	low	High
Fluconazole 400 mg q24h	A-I [a]	D-III	A-I [a]	A-III against
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1 or oral solution 200 mg q8h	B-II	B-II	B-II	B-II
Itraconazole 2.5–7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I	B-I	B-I	B-I
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I	B-I	B-I	B-I
Micafungin 50 mg q24h	B-I	C-I	B-I	C-I
Caspofungin and anidulafungin	no data	no data	no data	no data
Liposomal amphotericin B	C-II		C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	C-III		C-III	B-II
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [b]	B-II	B-II	no data	no data

[a]only when combined with a mold-directed diagnostic approach (biomarker and/or CT scan-based)or a mold-directed therapeutic approach (empirical antifungal therapy).
[b]Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole / voriconazole, or QTc prolongation.
Pre-engraftment risk of mold infection as previously defined: high risk includes active leukemia, cord blood transplantation and unrelated donor [72]. Haploidentical HSCT using post-transplantation cyclophosphamide should be considered at low risk (B-II) In case of prior IFD, secondary prophylaxis should be tailored according to the previous documentation [73].
HSCT hematopoietic stem cell transplantation.

Table 6. Recommendations for allo-HSCT recipients: post-engraftment.

Antifungal agent	Steroid treated acute GVHD	ECIL 5-6
Posaconazole tablet 300 mg q24h following a loading dose of 300 mg q12h on day 1, or oral solution 200 mg q8h	A-I [a, b]	A-I [a, b]
Itraconazole 2.5-7.5 mg/kg q24h i.v. or 200 mg q24h p.o	B-I [b]	B-I [b]
Voriconazole 6 mg/kg q12h first day then 4 mg/kg q12h i.v. or p.o.	B-I [b]	B-I [b]
Micafungin 50 mg q24h	C-II	C-II
Caspofungin and anidulafungin	no data	no data
Liposomal amphotericin B	C-II	C-II
Aerosolized liposomal amphotericin B (10 mg twice weekly) in combination with systemic fluconazole 400 mg q24h	no data	no data
Fluconazole 400 mg q24h	D-III	D-III
Isavuconazole 200 mg q24h following a loading dose of 200 mg q8h on days 1 and 2 [c]	B-II	no data

After engraftment, in patients without GVHD, fluconazole can be continued until D + 75.
[a] No difference compared with placebo was seen in patients with chronic GVHD.
[b] It is recommended to monitor serum drug concentration.
[c] Isavuconazole can be used as second-line mold active prophylaxis, in case of intolerance to posaconazole/voriconazole, or QTc prolongation.

considered at low risk of IFD. Primary antifungal prophylaxis is not recommended, although fluconazole (400 mg q24h) should be considered to prevent mucosal *Candida* infection during the neutropenic phase (B-III) [4]. There are no recommendations for change for autologous HSCT recipients.

PRIMARY ANTIFUNGAL PROPHYLAXIS IN PEDIATRIC HEMATOLOGICAL MALIGNANCIES

Mold-active antifungal prophylaxis is recommended for pediatric patients at high risk of IFD (incidence ≥10%), encompassing a subgroup of children with ALL, though their specific risk profile is less precisely defined [81].

A recent analysis of 6316 children with ALL enrolled in the international AIEOP-BFM ALL2009 trial reported an incidence of proven/probable IFDs at 3.8%, with a 12-week mortality rate of 11.2% [82]. In this cohort, 68% of infections were mold-related, with significant risk factors for IFD being ≥12 years of age and insufficient treatment response. A diagnoses of proven/probable IFD were associated with a elevated hazard ratio for event-free survival and overall survival [82]. Consequently, older children (≥ 12 years) with ALL and those with insufficient treatment response are identified as being at elevated risk for IFD and are now recommended to receive antifungal prophylaxis.

Since the 2021 update by ECIL, advances in pediatric antifungal development have been significant. A recent multicenter, non-randomized, open-label, phase 1b dose-escalation trial demonstrated that posaconazole intravenous solution (IV) and powder for oral suspension (PFS) were well tolerated in children, with safety profiles similar to adults [83]. Following this dose-finding trial, the European Medicines Agency (EMA) approved posaconazole IV and PFS in 2021 for high-risk patients aged ≥2 years and

weighing ≤40 kg, including those with AML/MDS or undergoing HSCT with GVHD [84]. Delayed-release tablets were approved for patients ≥2 years and >40 kg with the same conditions [84], although oral suspension remains unapproved by EMA [85].

Additionally, a prospective, randomized, open-label trial among pediatric allo-HSCT patients found caspofungin to be as effective as voriconazole and other triazoles in preventing IFD, including aspergillosis, with a 1.4% infection rate across both trial arms [86]. Hence, the caspofungin grade of recommendation has been updated to a B-I.

FUTURE PROSPECTS

The characteristics of an 'ideal' agent for antifungal prophylactic use include (a) broad spectrum of activity - covering both yeast and mold pathogens - with low risk of development of resistance, (b) availability in oral and parenteral formulations, (c) low potential for clinically problematic drug-drug interactions, (d) low risk of acute and chronic treatment-limiting toxicities, and (e) predictable pharmacokinetics. Several molecules with antifungal activity with a novel mechanism of action are currently in various stages of clinical development [87]. These new molecules tackle some of the shortcomings of the currently available aramamentarium.

- Rezafungin, a second generation echinocandin with enhanced PK/PD pharmacometrics, is active in vitro against most wild-type and azole-resistant *Candida* species (including C. auris), *Aspergillus* species (including azole-resistant A. fumigatus and cryptic species) and *Pneumocystis jirovecii*. The drug has minimal risk of drug-drug interactions and has recently been approved for the treatment of candidemia and invasive candidiasis [88]. Its prophylactic efficacy and safety, when given intravenously once weekly, is currently being tested in a phase 3 randomized double-blind study versus a standard antimicrobial regimen (including fluconazole/posaconazole plus trimethoprim-sulfamethoxazole) in allo-HSCT recipients (The ReSPECT Study) [89].
- Ibrexafungerp, a first-in-class oral glucan synthase inhibitor (a triterpenoid), is approved for the treatment of recurrent vulvovaginal *Candida* infection. The spectrum of activity is similar to the spectrum of rezafungin, but also includes *Alternaria* and *Cladosporium* species. The drug is generally well tolerated with a low risk for drug-drug interactions [90]. Ibrexafungerp has not yet been studied as prophylactic agent but has the potential for use in primary prophylaxis (similar to rezafungin).
- The fungicidal orotomide olorofim is a potent inhibitor of fungal dihydroorotate dehydrogenase. The drug is given orally, has a good tissue distribution and is generally well tolerated. Although olorofim has activity against a variety of mold pathogens (excluding Mucorales species) and dimorphic fungi, the drug displays no activity against yeast pathogens [91]. As such, olorofim is not a good candidate for primary prophylaxis, but may be used for secondary prophylaxis in patients with well documented prior mold infections (e.g., scedosporiosis or aspergillosis).
- Fosmanogepix (the active moiety is manogepix) targets fungal glycosylphosphatidylinositol-anchored cell wall transfer protein 1, inhibiting cell wall synthesis causing loss of viability. Manogepix has a very broad spectrum of activity covering most clinically important fungal pathogens. The drug is available as an oral and IV formulation, has a wide tissue distribution and displays linear pharmacokinetics. The drug has favorable drug-drug interaction and safety profiles [92]. A phase 1 safety and PK study has been performed in neutropenic leukemia patients receiving the drug prophylactically [93]. Given these characteristics, the drug has potential for being investigated as prophylactic antifungal agent.
- Opelconazole is an azole with activity against *Aspergillus* species and other fungi including various *Candida* sp. (including C. auris), *Rhizopus oryzae*, *Cryptococccus neoformans*, *Chaetomium globosum*, *Penicillium chrysogenum* and *Trichophyton rubrum*. Opelconazole was specifically designed for inhaled delivery; the drug accumulates in the lung and has a long residence time in airway cells, potentially enhancing the ability of host cells to clear the fungus, both in treatment and in prophylaxis. Systemic exposure is very low (ratio of lung: systemic concentrations is ~7000:1), resulting in a low risk for drug-drug interactions [94].

CONCLUSION

IFDs remain potentially fatal events in patients with hematological malignancies undergoing chemotherapy, transplantation or cellular therapies. Identification of the main risk factors is necessary to establish appropriate antifungal prophylaxis.

In recent years, various antineoplastic drugs directed against specific surface proteins or molecular targets have been developed for almost all hematological malignancies. This has opened new therapeutic possibilities, but has also increased the population at risk of developing IFDs. Development of cellular therapies, i.e. CAR-T therapy, and increasing use of allo-HSCT has further expanded the number of patients at risk of IFD. The main differences in this updated ECIL guidelines is the inclusion of recommendations for these new risk groups, such as venetoclax combined with azacytidine in patients with AML, treatment with bispecific antibodies, and CAR-T cell therapies.

We aimed to give solid indications based on randomized clinical trials, but in some cases, in the absence of randomized trials, clinical evidence from observational studies has been the base for a grading of recommendation (i.e. isavuconazole in AML).

New bispecific monoclonal antibodies have been introduced during the past 5 years for the treatment of myelomas and lymphomas, but current knowledge on the possible epidemiology of IFDs in these settings is still very limited and does not allow us to suggest any recommendation.

Until now, in Europe, lymphoma patients have been identified as receiving the most benefit from CAR-T cell therapies. However, the number of these procedures is constantly increasing, including myeloma and ALL patients, while their timing is changing, shifting from "the last line therapeutic change" to earlier treatment settings, and now being also used as a bridge to allo-HSCT.

The expectations for the near future are the introduction of new antineoplastic agents that will be more effective but which will also lead to increased immunosuppression. At the same time, we expect that new antifungals with greater efficacy and fewer pharmacological interactions will be available, which will hopefully have an important impact not only on the treatment of IFD but also on prophylaxis.

REFERENCES

1. Cordonnier C, Calandra T. The first European Conference on Infections in Leukaemia: why and how?. Eur J Cancer. 2007;5:2–4–4.
2. Maertens JA, Frère P, Lass-Flörl C, Heinz W, Cornely OA. Primary antifungal prophylaxis in leukaemia patients. Eur J Cancer. 2007;5:43–48–8.
3. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frêre P, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3–2009 update. Bone Marrow Transpl. 2011;46:709–18.
4. Maertens JA, Girmenia C, Brüggemann RJ, Duarte RF, Kibbler CC, Ljungman P, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from European Conference on Infections in Leukemia. J Antimicrob Chemother. 2018;73:3221–30.
5. Ullmann AJ, Akova M, Herbrecht R, Viscoli C, Arendrup MC, Arikan-Akdagli S, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012:

adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18:53–67.
6. Bose P, McCue D, Wurster S, Wiederhold NP, Konopleva M, Kadia TM, et al. Isavuconazole as primary antifungal prophylaxis in patients with acute myeloid leukemia or myelodysplastic syndrome: an open-label, prospective, phase 2 study. Clin Infect Dis. 2021;72:1755–63.
7. Rausch CR, DiPippo AJ, Jiang Y, DiNardo CD, Kadia T, Maiti A, et al. Comparison of mold active triazoles as primary antifungal prophylaxis in patients with newly diagnosed acute myeloid leukemia in the era of molecularly targeted therapies. Clin Infect Dis. 2022;75:1503–10.
8. Del Principe MI, Dragonetti G, Verga L, Candoni A, Marchesi F, Cattaneo C, et al. 'Real-life' analysis of the role of antifungal prophylaxis in preventing invasive aspergillosis in AML patients undergoing consolidation therapy: Sorveglianza Epidemiologica Infezioni nelle Emopatie (SEIFEM) 2016 study. J Antimicrob Chemother. 2019;74:1062–8.
9. Maschmeyer G, Bullinger L, Garcia-Vidal C, Herbrecht R, Maertens J, Menna P, et al. Infectious complications of targeted drugs and biotherapies in acute leukemia. Clinical practice guidelines by the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). Leukemia. 2022;36:1215–26.
10. Kallee S, Scharf C, Schroeder I, Paal M, Vogeser M, Irlbeck M, et al. Comparing posaconazole and itraconazole for antifungal prophylaxis in critically ill lung transplant recipients: Efficacy and plasma concentrations. Transpl Infect Dis. 2021;23:e13675.
11. Copley MS, Waldron M, Athans V, Welch SC, Brizendine KD, Cober E, et al. Itraconazole vs. posaconazole for antifungal prophylaxis in patients with acute myeloid leukemia undergoing intensive chemotherapy: A retrospective study. Int J Antimicrob Agents. 2020;55:105886.
12. Nield B, Larsen SR, van Hal SJ. Clinical experience with new formulation SUBA®-itraconazole for prophylaxis in patients undergoing stem cell transplantation or treatment for haematological malignancies. J Antimicrob Chemother. 2019;74:3049–55.
13. Whitmore TJ, Yaw M, Lavender M, Musk M, Boan P, Wrobel J. A novel highly bioavailable itraconazole formulation (SUBA®-Itraconazole) for anti-fungal prophylaxis in lung transplant recipients. Transpl Infect Dis. 2021;23:e13587.
14. Epstein DJ, Seo SK, Huang YT, Park JH, Klimek VM, Berman E, et al. Micafungin versus posaconazole prophylaxis in acute leukemia or myelodysplastic syndrome: A randomized study. J Infect. 2018;77:227–34.
15. Wingen-Heimann SM, Cornely OA, Vehreschild MJGT, Wisplinghoff H, Franke B, Schons M, et al. Clinical and pharmacoeconomic evaluation of antifungal prophylaxis with continuous micafungin in patients undergoing allogeneic stem cell transplantation: A six-year cohort analysis. Mycoses. 2021;64:437–44.
16. Kang WH, Song GW, Lee SG, Suh KS, Lee KW, Yi NJ, et al. A multicenter, randomized, open-label study to compare micafungin with fluconazole in the prophylaxis of invasive fungal infections in living-donor liver transplant recipients. J Gastrointest Surg. 2020;24:832–40.
17. Platzbecker U, Della Porta MG, Santini V, Zeidan AM, Komrokji RS, Shortt J, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402:327–85.
18. Lorenzana N, Avila LF, Alonso S, Colado E, Bernal T. The impact of antimicrobial prophylaxis in morbidity and infections during azacitidine treatment. Ann Hematol. 2017;96:1833–40.
19. Tey A, Shaw B, Cardamone L, Shepherd S, Paul E, Rogers B, et al. Risk factors for invasive fungal infection in 5-azacytidine treated patients with acute myeloid leukemia and myelodysplastic syndrome. Eur J Haematol. 2021;107:181–9.
20. Kang KW, Lee BH, Jeon MJ, Yu ES, Sik Kim D, Lee SR, et al. Efficacy of posaconazole prophylaxis in acute myeloid leukemia and myelodysplastic syndrome patients treated with hypomethylating agents. Ther Adv Hematol. 2020;11:2040620720966882.
21. Pomares H, Arnan M, Sánchez-Ortega I, Sureda A, Duarte RF. Invasive fungal infections in AML/MDS patients treated with azacitidine: a risk worth considering antifungal prophylaxis?. Mycoses. 2016;59:516–9.
22. Schuck A, Goette MC, Neukirchen J, Kuendgen A, Gattermann N, Schroeder T, et al. A retrospective study evaluating the impact of infectious complications during azacitidine treatment. Ann Hematol. 2017;96:1097–104.
23. Trubiano JA, Dickinson M, Thursky KA, Spelman T, Seymour JF, Slavin MA, et al. Incidence, etiology and timing of infections following azacitidine therapy for myelodysplastic syndromes. Leuk Lymphoma. 2017;58:2379–86.
24. Mądry K, Lis K, Biecek P, Młynarczyk M, Rytel J, Górka M, et al. Predictive model for infection risk in myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia patients treated with azacitidine; azacitidine infection risk model: the polish adult leukemia group study. Clin Lymphoma Myeloma Leuk. 2019;19:264–74.e4.
25. Latagliata R, Niscola P, Fianchi L, Aloe Spiriti MA, Maurillo L, Carmosino I, et al. Pulmonary infections in patients with myelodysplastic syndromes receiving frontline azacytidine treatment. Hematol Oncol. 2020;38:189–96.
26. Kim GYG, Burns J, Freyer CW, Hamilton KW, Frey NV, Gill SI, et al. Risk of invasive fungal infections in patients with high-risk MDS and AML receiving hypomethylating agents. Am J Hematol. 2020;95:792–8.
27. Kirkizlar TA, Kirkizlar O, Demirci U, Umut A, Iflazoglu H, Umit EG, et al. Incidence and predisposing factors of infection in patients treated with hypomethylating agents. Leuk Res. 2023;127:107043.
28. Polverelli N, Breccia M, Benevolo G, Martino B, Tieghi A, Latagliata R, et al. Risk factors for infections in myelofibrosis: role of disease status and treatment. A multicenter study of 507 patients. Am J Hematol. 2017;92:37–41.
29. Landtblom AR, Andersson TM, Dickman PW, Smedby KE, Eloranta S, Batyrbekova N, et al. Risk of infections in patients with myeloproliferative neoplasms-a population-based cohort study of 8363 patients. Leukemia. 2021;35:476–84.
30. Breccia M, Andriani A, Montanaro M, Abruzzese E, Buccisano F, Cedrone M, et al. Ruxolitinib in clinical practice for primary and secondary myelofibrosis: an analysis of safety and efficacy of Gruppo Laziale of Ph-negative MPN. Ann Hematol. 2017;96:387–91.
31. Palandri F, Tiribelli M, Benevolo G, Tieghi A, Cavazzini F, Breccia M, et al. Efficacy and safety of ruxolitinib in intermediate-1 IPSS risk myelofibrosis patients: Results from an independent study. Hematol Oncol. 2018;36:285–90.
32. Polverelli N, Palumbo GA, Binotto G, Abruzzese E, Benevolo G, Bergamaschi M, et al. Epidemiology, outcome, and risk factors for infectious complications in myelofibrosis patients receiving ruxolitinib: A multicenter study on 446 patients. Hematol Oncol. 2018. https://doi.org/10.1002/hon.2509.
33. Sylvine P, Thomas S, Pirayeh E. French network of regional pharmacovigilance centers. infections associated with ruxolitinib: study in the french pharmacovigilance database. Ann Hematol. 2018;97:913–4.
34. Tremblay D, King A, Li L, Moshier E, Coltoff A, Koshy A, et al. Risk factors for infections and secondary malignancies in patients with a myeloproliferative neoplasm treated with ruxolitinib: a dual-center, propensity score-matched analysis. Leuk Lymphoma. 2020;61:660–7.
35. Stafylidis C, Diamantopoulos P, Athanasoula E, Solomou E, Anastasopoulou A. 2022. Acute lymphoblastic leukemia and invasive mold infections: a challenging field. J Fungi. 2022;8:1127.
36. Gold JAW, Tolu SS, Chiller T, Benedict K, Jackson BR. Incidence of invasive fungal infections in patients initiating ibrutinib and other small molecule kinase Inhibitors-United States, July 2016-June 2019. Clin Infect Dis. 2022;75:334–7.
37. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376:836–47.
38. Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019;125:2474–87.
39. van Schie RM, Bruggemann RJ, Hoogerbrugge PM, te Loo DM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother. 2011;66:1853–6.
40. Yang L, Yu L, Chen X, Hu Y, Wang B. Clinical analysis of adverse drug reactions between vincristine and triazoles in children with acute lymphoblastic leukemia. Med Sci Monit. 2015;21:1656–61.
41. Doan TN, Kirkpatrick CM, Walker P, Slavin MA, Ananda-Rajah MR, Morrissey CO, et al. Primary antifungal prophylaxis in adult patients with acute lymphoblastic leukaemia: a multicentre audit. J Antimicrob Chemother. 2016;71:497–505.
42. Oh SM, Byun JM, Chang E, Kang CK, Shin DY, Koh Y, et al. Incidence of invasive fungal infection in acute lymphoblastic and acute myelogenous leukemia in the era of antimold prophylaxis. Sci Rep. 2021;11:22160.
43. Wang Y, Xing Y, Chen L, Meng T, Li Y, Xie J, et al. Fluconazole versus mould-active triazoles for primary antifungal prophylaxis in adult patients with acute lymphoblastic leukemia: clinical outcome and cost-effectiveness analysis. Int J Hematol. 2018;107:235–43.
44. Cornely OA, Leguay T, Maertens J, Vehreschild M, Anagnostopoulos A, Castagnola C, et al. Randomized comparison of liposomal amphotericin B versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. J Antimicrob Chemother. 2017;72:2359–67.
45. Infante SM, Fernandez-Cruz A, Nunez L. Severe infections in patients with lymphoproliferative diseases treated with new targeted drugs: A multicentric real-world study. Cancer Med. 2021;10:7629–40.
46. Tisi MC, Hohaus S, Cuccaro A, Innocenti I, De Carolis E, Za T, et al. Invasive fungal infections in chronic lymphoproliferative disorders: a monocentric retrospective study. Haematologica. 2017;102:e108–e11.

47. Valentine JC, Morrissey CO, Tacey MA, Liew D, Patil S, Peleg AY, et al. A population-based analysis of invasive fungal disease in haematology-oncology patients using data linkage of state-wide registries and administrative databases: 2005-2016. BMC Infect Dis. 2019;19:274.
48. Visentin A, Gurrieri C, Imbergamo S, Lessi F, Di Maggio SA, Frezzato F, et al. Epidemiology and risk factors of invasive fungal infections in a large cohort of patients with chronic lymphocytic leukemia. Hematol Oncol. 2017;35:925–8.
49. Allouchery M, Brunet K, Tomowiak C, Singier A, Pambrun E, Pariente A, et al. Invasive fungal infection incidence and risk factors in patients receiving ibrutinib in real-life settings: A nationwide population-based cohort study. Mycoses. 2024;67:e13676.
50. Holowka T, Cheung H, Malinis M, Gan G, Deng Y, Perreault S, et al. Incidence and associated risk factors for invasive fungal infections and other serious infections in patients on ibrutinib. J Infect Chemother. 2021;27:1700–5.
51. Yasu T, Sakurai K, Hoshino M, Akazawa M. Oral azole antifungal prophylaxis in Japanese patients with chronic lymphocytic leukemia receiving ibrutinib: a nationwide cohort study. Leuk Lymphoma. 2023;64:730–3.
52. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006;91:1068–75.
53. Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW. Low rates of invasive fungal disease in patients with multiple myeloma managed with new generation therapies: Results from a multi-centre cohort study. Mycoses. 2021;64:30–4.
54. Tsai CK, Liu YC, Kuan AS, Lee KL, Yeh CM, Lee YT, et al. Risk and impact of invasive fungal infections in patients with multiple myeloma. Ann Hematol. 2020;99:1813–22.
55. Bahlis NJ, Costello CL, Raje NS, Levy MY, Dholaria B, Solh M, et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. Nat Med. 2023;29:2570–6.
56. Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk N, Rodríguez-Otero P, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med. 2022;387:2232–44.
57. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023;29:2259–67.
58. Mohan M, Monge J, Shah N, Luan D, Forsberg M, Bhatlapenumarthi V, et al. Teclistamab in relapsed refractory multiple myeloma: multi-institutional real-world study. Blood Cancer J. 2024;14:35.
59. Nooka AK, Rodriguez C, Mateos MV, Manier S, Chastain K, Banerjee A, et al. Incidence, timing, and management of infections in patients receiving teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study. Cancer. 2024;130:886–900.
60. Uttervall K, Tätting L, Lemonakis K, Majd M, Crafoord J, Olsson M, et al. Effectiveness and infectious complications of BCMA T-cell engagers in treating multiple myeloma: Real-world evidence from Sweden. Cancer Med. 2024;13:e7048.
61. Dimopoulos MA, Hungria VTM, Radinoff A, Delimpasi S, Mikala G, Masszi T, et al. Efficacy and safety of single-agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-3): a phase 3, open-label, randomised study. Lancet Haematol. 2023;10:e801–12.
62. Takaoka K, Nannya Y, Shinohara A, Arai S, Nakamura F, Kurokawa M. A novel scoring system to predict the incidence of invasive fungal disease in salvage chemotherapies for malignant lymphoma. Ann Hematol. 2014;93:1637–44.
63. Tamayo-Velasco Á, López-Herrero R, Gómez-García LM, Sánchez-de Prada L, Aguilar-Monserrate G, Martín-Fernández M, et al. COVID-19-associated pulmonary aspergillosis (CAPA) in hematological patients: Could antifungal prophylaxis be necessary? A nationwide study. J Infect Public Health. 2024;17:939–46.
64. Fayard A, Daguenet E, Blaise D, Chevallier P, Labussière H, Berceanu A, et al. Evaluation of infectious complications after haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning: a study on behalf of the francophone society of stem cell transplantation and cellular therapy (SFGM-TC). Bone Marrow Transpl. 2019;54:1586–94.
65. Lien MY, Yeh SP, Gau JP, Wang PN, Li SS, Dai MS, et al. High rate of invasive fungal infections after non-t cell depleted haploidentical allo-HSCT even under antifungal prophylaxis. Bone Marrow Transpl. 2021;56:1750–53.
66. Busca A, Cinatti N, Gill J, Passera R, Dellacasa CM, Giaccone L, et al. Management of invasive fungal infections in patients undergoing allogeneic hematopoietic stem cell transplantation: the turin experience. Frontiers in Cellular and Infection. Microbiology. 2021;11:805514.
67. Papanicolaou GA, Chen M, He N, Martens MJ, Kim S, Batista MV, et al. 'Incidence and impact of fungal infections in post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis and haploidentical hematopoietic cell transplantation: a center for international blood and marrow transplant research analysis'. Transpl Cell Ther. 2024;30:114.e1–114.e16.
68. Little JS, Shapiro RM, Aleissa MM, Kim A, Chang J, Kubiak DW, et al. 'Invasive yeast infection after haploidentical donor hematopoietic cell transplantation associated with cytokine release syndrome'. Transpl Cell Ther. 2022;28:508.e1–508.e8.
69. Stern A, Su Y, Lee YJ, Seo S, Shaffer B, Tamari R, et al. A Single-center, open-label trial of isavuconazole prophylaxis against invasive fungal infection in patients undergoing allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2020;26:1195–202.
70. Nguyen MH, Ostrosky-Zeichner L, Pappas PG, Walsh TJ, Bubalo J, Alexander BD, et al. Real-World Use of Mold-Active Triazole Prophylaxis in the Prevention of Invasive Fungal Diseases: Results from a Subgroup Analysis of a Multicenter National Registry. Open Forum Infect Dis. 2020;10:ofad424.
71. Dadwal SS, Hohl TM, Fisher CE, Boeckh M, Papanicolaou G, Carpenter PA, et al. American Society of Transplantation and Cellular Therapy Series, 2: Management and Prevention of Aspergillosis in Hematopoietic Cell Transplantation Recipients. Transpl Cell Ther. 2021;27:201–11.
72. Girmenia C, Raiola AM, Piciocchi A, Algarotti A, Stanzani M, Cudillo L, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transpl. 2014;20:872–80.
73. Puerta-Alcalde P, Champlin RE, Kontoyiannis DP. How I perform hematopoietic stem cell transplantation on patients with a history of invasive fungal disease. Blood. 2020;136:2741–53.
74. Yakoub-Agha I, Chabannon C, Bader P, Basak GW, Bonig H, Ciceri F, et al. Management of adults and children undergoing chimeric antigen receptor t-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica. 2020;105:297–316.
75. Kansagra AJ, Frey NV, Bar M, Laetsch TW, Carpenter PA, Savani BN, et al. Clinical Utilization of Chimeric Antigen Receptor T-Cells (CAR-T) in B-Cell Acute Lymphoblastic Leukemia (ALL)-an Expert Opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). Bone Marrow Transpl. 2019;54:1868–80.
76. Park JH, Romero FA, Taur Y, Sadelain M, Brentjens RJ, Hohl TM, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. Clinical Infect Dis. 2018;67:533–40.
77. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131:121–30.
78. Little JS, Aleissa MM, Beluch K, Gonzalez-Bocco IH, Marty FM, Manne-Goehler J, et al. Low incidence of invasive fungal disease following CD19 chimeric antigen receptor t-cell therapy for non-hodgkin lymphoma. Blood Adv. 2022;6:4821–30.
79. Cheok KPL, Farrow A, Springell D, O'Reilly M, Morley S, Stone N, et al. Mucormycosis after CD19 Chimeric Antigen Receptor T-Cell Therapy: Results of a US Food and Drug Administration Adverse Events Reporting System Analysis and a Review of the Literature. Lancet Infect Dis. 2024;24:e256–65.
80. Garner W, Palash S, Haidar G. Invasive fungal infections after anti-cd19 chimeric antigen receptor-modified t-cell therapy: state of the evidence and future directions. J Fungi. 2021;7:156.
81. Groll AH, Pana D, Lanternier F, Mesini A, Ammann RA, Averbuch D, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. Lancet Oncol. 2021;22:e254–69.
82. Lehrnbecher T, Groll AH, Cesaro S, Alten J, Attarbaschi A, Barbaric D, et al. Invasive fungal diseases impact on outcome of childhood ALL – an analysis of the international trial AIEOP-BFM ALL 2009. Leuk 2022 371. 2022;37:72–8.
83. Groll AH, Abdel-Azim H, Lehrnbecher T, Steinbach WJ, Paschke A, Mangin E, et al. Pharmacokinetics and safety of posaconazole intravenous solution and powder for oral suspension in children with neutropenia: an open-label, sequential dose-escalation trial. Int J Antimicrob Agents. 2020;56:106084.
84. Groll AH, Körholz K, Holterhus M, Lehrnbecher T. New and emerging options for management of invasive fungal diseases in paediatric patients. Mycoses. 2024;67:e13654.
85. Noxafil | European Medicines Agency (EMA). Accessed November 3, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/noxafil.
86. Dvorak CC, Fisher BT, Esbenshade AJ, Nieder ML, Alexander S, Steinbach WJ, et al. A randomized trial of caspofungin vs triazoles prophylaxis for invasive fungal disease in pediatric allogeneic hematopoietic cell transplant. J Pediatr Infect Dis Soc. 2021;10:417–25.
87. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R, et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. Drugs. 2021;81:1703–29.
88. Thompson GR 3rd, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive

candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2023;401:49–59.
89. xxx. https://clinicaltrials.gov/study/NCT04368559?cond=rezafungin&rank=7.
90. El Ayoubi LW, Allaw F, Moussa E, Kanj SS. Ibrexafungerp: A narrative overview. Curr Res Micro Sci. 2024;6:100245.
91. Vanbiervliet Y, Van Nieuwenhuyse T, Aerts R, Lagrou K, Spriet I, Maertens J. Review of the novel antifungal drug olorofim (F901318). BMC Infect Dis. 2024;24. 1256.
92. Almajid A, Bazroon A, Al-Awami HM, Albarbari H, Alqahtani I, Almutairi R, et al. Fosmanogepix: the novel anti-fungal agent's comprehensive review of in vitro, in vivo, and current insights from advancing clinical trials. Cureus. 2024;16:e59210.
93. Cornely OA, Ostermann H, Koehler P, Teschner D, Limburg E, Kramer WG, et al. Phase 1b safety and pharmacokinetics of intravenous and oral fosmanogepix in patients with acute myeloid leukaemia and neutropenia. Antimicrob Chemother. 2023;78:2645–52.
94. Neoh CF, Jeong W, Kong DCM, Beardsley J, Kwok P, Slavin MA, et al. New and emerging roles for inhalational and direct antifungal drug delivery approaches for treatment of invasive fungal infections. Expert Rev Anti Infect Ther. 2024;22:1085–98.

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All co-authors prepared a set of summary slides on each of the substances addressed in the manuscript, presented the slides at the ECIL-10 conference and revised the slide sets after the plenary discussion. LP prepared the manuscript, all co-authors revised the text and consented the final version.

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COMPETING INTERESTS

Livio Pagano (LP) was Board member of Gilead Science, MSD, Pfizer, Menarini-Stemline, Gentili, Jazz Pharmaceutical, Cidara and has received speaker's honoraria from Gilead Sciences, Kyowa Kirin, MSD, Pfizer Pharmaceuticals, Astellas Pharma, Novartis, Jazz Pharmaceutical, Janseen-Cilag, Astra Zeneca, F2G, Abbvie. Consultant for Menarini, Cidara. Georg Maschmeyer (GM) has received speaker's honoraria from Gilead Sciences. Frederic Lamoth (FL) reports research funding from Gilead, MSD, Pfizer and Novartis, and honoraria for conferences or advisory boards from Gilead, MSD, Pfizer, Mundipharma and Becton-Dickinson, outside of the submitted work. All contracts were made with and fees paid to his institution (CHUV). Ola Blennow has received speaker's honoraria from Gilead Sciences. Alienor Xhaard (AX) has received speaker's honoraria from Merck Sharp and Dohme and Pfizer Pharmaceuticals. Manuela spadea (MS) nothing to declare. Alessandro Busca (AB) was Board member of Gilead Science, Takeda, and has received speaker's honoraria from Gilead Kite Sciences, MSD, Pfizer Pharmaceuticals, Novartis, Jazz Pharmaceutical, Astra-Zeneca, Abbvie, Menarini Stemline, Takeda. Catherine Cordonnier (CC) has received speaker's honoraria from Gilead Science and MSD, and consulting fees from Cidara and Mundipharma. Johan Maertens (JM) reports consulting fees from Amplyx, Cidara, Gilead, Pfizer, Scynexis, F2G, Mundipharma, Takeda, and Basilea; Honoraria for lectures from Astellas, Gilead, Basilea, Mundipharma, Takeda, MedScape, Pfizer, and Shionogi; Participation on Advisory Board from Cidara, Pulmocide, Shionogi, Basilea, Sfunga.

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