ORIGINAL ARTICLE

Primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with hematologic malignancies and solid tumors: 2020 updated guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO/DGHO)

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Abstract

Hematologic and oncologic patients with chemo- or immunotherapy-related immunosuppression are at substantial risk for bacterial infections and *Pneumocystis jirovecii* pneumonia (PcP). As bacterial resistances are increasing worldwide and new research reshapes our understanding of the interactions between the human host and bacterial commensals, administration of antibacterial prophylaxis has become a matter of discussion. This guideline constitutes an update of the 2013 published guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). It gives an overview about current strategies for antibacterial prophylaxis in cancer patients while taking into account the impact of antibacterial prophylaxis on the human microbiome and resistance development. Current literature published from January 2012 to August 2020 was searched and evidence-based recommendations were developed by an expert panel. All recommendations were discussed and approved in a consensus conference of the AGIHO prior to publication. As a result, we present a comprehensive update and extension of our guideline for antibacterial and PcP prophylaxis in cancer patients.

Keywords Neutropenia · Prophylaxis · Bacterial infections · Resistance · Pneumocystis

Introduction

During recent years, the advent of an increasing amount of targeted drugs and other strategies of personalized medicine has resulted in rapid changes in treatment paradigms for hematologic and oncologic patients. Thus, since the previous version of this guideline many new substances have received approval in high-risk hematology treatment indications (e.g., idelalisib in follicular lymphoma/CLL) while immunological effects and possible risks for opportunistic infections remain poorly examined. However, most new treatment strategies only delay disease progression and most patients still receive

conventional anti-cancer chemotherapy at some point of their treatment. As a consequence of immunotherapy- and chemotherapy-related immunosuppression and neutropenia, bacterial infections and *Pneumocystis jirovecii* pneumonia (PcP) are significant causes of morbidity and mortality [1–4]. Most authors define neutropenia as a neutrophil count below 500/µl or < 1000/µl with predicted decline to less than 500/µl within the next 2 days [5, 6]. If no neutrophil count is available or possible, neutropenia can be assumed during leukopenia with leukocytes < 1000/µl.

Although no prospective studies have formally compared possible management strategies, fever during an episode of neutropenia (febrile neutropenia, FN) is generally considered a medical emergency and usually entails rapid initiation of empiric treatment with broad-spectrum antibiotics and in most cases hospitalization. Besides the morbidity and mortality related to FN, the need for antibiotic treatment, treatment side

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effects, inpatient stay or frequent outpatient visits also impairs quality of life, especially for patients in palliative treatment situations and causes considerable costs [1].

The incidence of febrile neutropenia is highly variable depending on patient-related risk factors as well as type of treatment and ranges from close to 0% (low-intensity treatment for solid tumors) [7] to almost 100% (induction treatment for acute leukemia) [8]. Real-life incidence rates may in general be higher outside the controlled conditions of prospective clinical trials [9].

Many oncologists advocate the use of general preventative strategies aiming at reducing transmission of pathogens via infection control, hygiene, and/or behavioral recommendations, although most infections in neutropenic hosts are usually considered of endogenous origin [10]. Other than that, there are two established pharmacological interventions to reduce incidence of FN: (i) granulocyte colony-stimulating factors (G-CSF), which are the topic of another guideline and (ii) prophylactic antibiotic use [11, 12].

The administration of antibacterial prophylaxis and its impact on patient outcome has been extensively studied. It is generally accepted that this strategy reduces the incidence of febrile events and infections, while survival benefits have only been demonstrated in meta-analyses by including studies from different epochs [13]. Even though prophylactic regimens are generally well tolerated during short-term observation, recent breakthroughs in the understanding of resistance development, spread of multidrug-resistant organisms, and the general interactions between the human host and its commensal microbiota have to be considered in a risk–benefit assessment.

We updated our guideline to give an overview about current evidence on antibacterial prophylaxis strategies and the choice of drugs to prevent bacterial infection and PcP in neutropenic patients. In addition, we revisited patient risk stratification and bacterial epidemiology and considered the current discussion on potential adverse effects caused by antibiotic exposure.

Methods

This guideline is an update of the 2013 published version [12]. As established, an expert group of hematologists, oncologists, and infectious disease specialists, all of them members of the Infectious Disease Working Party of the German Society of Hematology and Medical Oncology (AGIHO), reviewed and discussed current evidence on antibacterial and PcP prophylaxis. Initially, a literature search of publications from January 2012 to March 2017 was performed and evaluated by subcommittees of two to six experts. The literature review was updated at the time of manuscript finalization (August 2020), which revealed no new breakthrough results necessitating further amendments to the recommendations. All statements and recommendations were discussed in meetings, in telephone conferences, and by electronic correspondence. Recommendations have been approved via expert consensus during the AGIHO plenary meeting on 13 March 2017 and the manuscript was reviewed by all co-authors prior to submission. Evaluation of strength of recommendation and quality of evidence was performed in consistence with other recently updated German and European guidelines (Table 1) [4, 14–16]. The detailed methodology is described in the guideline report.

This guideline gives recommendations on antibacterial and PcP prophylaxis in neutropenic cancer patients. Recommendations on the diagnosis and empirical treatment of fever of unknown origin during neutropenia can be found in a distinct guideline of the AGIHO [4]. Information on antiviral and antifungal prophylaxis as well as information on infection prevention in patients undergoing allogeneic and autologous stem cell transplantation can also be found in separate AGIHO publications [15–18].

Patients and risk factors

Reliable identification of hematologic and oncologic patients at risk for febrile neutropenia and infection is a prerequisite to evaluate the need for prophylactic treatment. The chance of infection during neutropenia increases over time; therefore, severity and duration of neutropenia are unequivocal risk factors for the development of infection following chemotherapy [5, 6]. In line with other guidelines [4, 19, 20], we recommend to stratify neutropenic patients into two different risk groups according to the anticipated duration of neutropenia. Patients likely to develop prolonged neutropenia (> 7 days) should be considered as high-risk patients (A-I), whereas patients with estimated duration of neutropenia of seven days or less should not be considered at high risk (A-I), unless additional risk factors are present (B-II) [21, 22] (Table 2).

Prophylaxis with granulocyte colony-stimulating factors (G-CSF) or granulocyte-macrophage colony-stimulating factors (GM-CSF) should be considered for risk stratification as G-CSF prophylaxis reduces the incidence of FN and bacterial infection by shortening the length of neutropenia [11]. Use of G-CSF is recommended if the anticipated risk for FN is above 20% [11, 23]. There is insufficient clinical evidence to compare clinical outcome for prophylaxis with colony-stimulating factors versus use of antibiotics [23]. If sufficient risk reduction can be achieved by G-CSF administration, that should be the preferred strategy, based on superior tolerability and the absence of selective pressure to bacteria by G-CSF in contrast to antibacterials (B-II).

Numerous studies have assessed risk factors for FN that could potentially guide individual decisions towards antibacterial prophylaxis. Major dilemma is caused by the

Table 1 Grading

Category, grade	Definition
Strength of recommendation	
A	Strongly supports a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use
Quality of evidence—level	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, 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
Quality of evidence—index (for level II)	
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 is a historical control
u	Uncontrolled trial
a	Published abstract (presented at an international symposium or meeting)

heterogeneous assessment of discriminating subsets of highly interacting risk factors (e.g., age, comorbidity, performance score, and renal function). This limitation necessitates great caution when comparing results from different studies.

Most established guidelines compile lists of risk factors reported in one or more publications [25–28]. However, this strategy will inevitably lead to an overstatement of the actual risk by disregarding the interactions. We therefore extracted risk factors only from those epidemiological analyses which assessed the risk of FN by multivariable analysis.

Our strategy still revealed a concerning heterogeneity of results between studies. No single patient-related risk factor other than duration of neutropenia and intensity of

chemotherapy was consistently identified as an effective predictor of FN. For example, age is generally considered a risk factor for FN and listed as such in all major guidelines [20, 25–27, 29], although 15 of 19 identified studies controlling for confounders with 68,007 of 70,466 patients did not identify age as an independent risk factor in multivariable analysis. The administered dose of chemotherapy has been considered a risk factor for infection during neutropenia [22, 30, 31], while the impact of the chemotherapeutic regimen remains unclear. It has been shown that infection rates differ between treatment regimens [32–34] but not all studies showed statistically significant differences. The risk of febrile neutropenia and infection was shown to be higher during the first than

Table 2 Risk factors for bacterial infection during neutropenia

Clinical situation	Intention/recommendation	Intervention	SoR	QoE	References
Patients with prolonged neutropenia (> 7 days)[a]	Identify patients at risk for FN	Consider as high-risk patients	A	I	[5, 19, 23]
Patients with neutropenia > 0 and ≤ 7 days[a] and significant additional risk factors[b]		Consider as high-risk patients	B	II	[5, 21–23]
Patients with neutropenia ≤ 7 days without additional risk factors		Consider as low-risk patients	A	I	[5, 19, 24]

SoR strength of recommendation, *QoE* quality of evidence

[a] This estimation should consider potential G-CSF prophylaxis. If sufficient risk reduction can be achieved by G-SCF, that should be the preferred strategy

[b] See Table 3

during subsequent cycles of chemotherapy [30, 35–37]. The overall burden of comorbidities, but not low performance scores, seems to be independently associated with the risk for FN; however, no single comorbid condition can be identified as the main driver of FN risk.

Some of the more frequently detected independent factors associated with FN are listed in Table 3. Other additional risk factors, e.g., immunoglobulin deficiency, prior infections, and specific rare comorbidities may play a role in selected patient groups and should be part of individual considerations. However, patients with neutropenia duration of 7 days or less should not be considered at high risk because of one potential risk factor, but by clinical judgment based on comprehensive assessment of patient status and intended treatment. The decision should not only account for clinical risk factors but also patient management aspects (e.g., outpatient/inpatient treatment, estimated compliance, distance from hospital, home environment, and social support).

New anti-cancer agents and antibacterial prophylaxis

The use of new anti-cancer agents, e.g., immune-modulating drugs, antibodies, and molecular targeted agents in clinical routine increases constantly. Many of these agents received fast-track approval by regulatory authorities based on successful phase II–III trials while the impact of such drugs on the incidence of infections is not yet fully determined. Infections have been identified as a potential side effect of several anti-cancer drugs, though exact numbers remain unknown. In the absence of further individual risk factors, we recommend to not classify such patients as high-risk patients of FN when considering antibiotic prophylaxis [38].

To date, antibacterial prophylaxis in non-neutropenic patients is only recommended in those treated with the C5-antibodies eculizumab or ravulizumab without previous

Table 3 Patient-related risk factors

Patient-related risk factors[a]
Prolonged neutropenia (> 7 days)
Type and stage of underlying malignancy
Administered type and dosage of chemotherapy
First chemotherapy cycle
Cardiac insufficiency
Low baseline creatinine clearance
Low baseline leukocyte count
Elevated baseline levels of alkaline phosphatase and bilirubin

[a] Factors that were found independently associated with development of fever during neutropenia in multivariable analyses of either the majority of studies or the majority of patients in studies testing that risk factor

meningococcal vaccination (or vaccination < 2 weeks prior to drug administration) to prevent infection by *Neisseria* spp. [39, 40]. Prophylaxis should be performed with penicillin V 250 mg every 12 h, or ciprofloxacin 500 mg daily for at least 4 weeks after complete immunization or until protective titers are documented (A-II$_u$), comparable to the situation around surgical splenectomy.

Spectrum of pathogens in infections of neutropenic patients

While bacteremia is the most commonly identified cause of infection during FN, almost half of the febrile events are ultimately classified as fever of unknown origin (FUO), since no infectious focus can be identified [2]. In cases of microbiologically documented gram-positive bacteremia, the dominant species are typically coagulase-negative staphylococci, α-hemolytic streptococci, and *Staphylococcus aureus*. Sepsis due to gram-negative pathogens is associated with high mortality and often caused by enterobacteria such as *Escherichia coli* or *Klebsiella* spp. and by non-fermenters, in particular *Pseudomonas aeruginosa* [41–44].

In past observations, implementation of antibacterial prophylaxis with activity against gram-negative bacteria was associated with a decrease of gram-negative but an increase of gram-positive bacteria isolated from patients with FN [42, 45]. In the last decade, a new shift towards higher rates of gram-negative pathogens in bacteremia has been described in hematologic patients [43, 44, 46–48]. These observations have recently been confirmed by large multicenter surveillance studies [49–51]. Of note, no significant trend for blood stream infection due to resistant bacteria (methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*) was described. However, the surveillance was performed in patients undergoing hematopoietic stem cell transplantation (HSCT) and the situation for patients with other malignant diseases and other treatment regimens may differ. To better understand the impact of fluoroquinolone (FQ) prophylaxis on local epidemiology, continuous microbiological surveillance is highly recommended. This should not only focus on FQ-resistant pathogens but also on rates of *Clostridioides difficile* infection (CDI) [52–54].

Resistance development

Bacterial resistance increases globally, which bears two potential implications for prophylactic use of antibiotics: (i) the effectiveness of prophylactic antibiotics may decrease and (ii) the use of broad-spectrum antibiotics in large patient populations without infection undermines current demands for

rational anti-infective prescription. The prevalence of colonization due to ESBL *Enterobacteriaceae* increases worldwide, while prior colonization with ESBL-producing pathogens in hematologic/oncologic patients constitutes an important risk factor for subsequent development of ESBL-associated blood stream infections [50, 51, 55]. Concerns about resistance development therefore led some experts to vote against antibacterial prophylaxis in neutropenic patients [19, 24].

The prevalence of resistant pathogens, especially *Escherichia coli* and *Enterococcus faecium*, is higher and increases more rapidly in the hematologic/oncologic compared to other patient populations [47, 48, 56, 57]. Recent studies demonstrated that FQ use may expedite the emergence and colonization with bacterial strains resistant to the administered drug as well as other drugs with genetically linked resistance genes [58, 59]. Studies on discontinuation of antibacterial prophylaxis detected reappearance of gram-negative bacteria in blood culture isolates after FQ restriction, while a decrease in the proportion of FQ-resistant organisms was observed [43, 55, 60]. Yet, an increase of resistance was not uniformly observed across studies during antibiotic prophylaxis [61]. Gudiol et al. described a decrease in FQ resistance (71% versus 37%; $p < 0.001$); an observed concurrent increase in multidrug-resistant gram-negative blood stream infections (BSI) (1% versus 6%, $p < 0.001$) was probably attributable to global changes in the epidemiology of resistant bacteria [43]. Of note, a recently published study demonstrated that the patients' 30-day mortality was higher when developing bacteremia from FQ-resistant than from FQ-sensitive gram-negatives [62].

We do not generally recommend to use a threshold of FQ resistance among gram-negative bacteria in a given population for instituting FQ prophylaxis (D-III). However, to avoid amplification of resistant clones, we do not recommend to initiate prophylaxis with FQ if colonization of a patient with FQ-resistant gram-negative bacteria is known prior to the onset of prophylaxis (D-II$_{t,u}$). Surveillance of resistance development (A-III) and antibiotic prophylactic efficacy (B-III) should be performed. Considering the local epidemiology, prospective studies are needed for evaluation of FQ prophylaxis in areas with high local rates of FQ resistance among gram-negative bacteria.

Novel considerations regarding microbiome and resistome

New sequencing techniques have led to an abundance of new insights on host–microbiota interactions which may ultimately in part redefine our understanding of the pathogenesis of many infections and other diseases [63]. Two recent studies by Chong et al. analyzed the impact of prior FQ prophylaxis on the gut microbiota [64, 65]. After the first administration of prophylaxis, disappearance of quinolone-susceptible *Enterobacteriaceae* and emergence of FQ-resistant bacteria were observed. Even though levels of FQ-susceptible *Enterobacteriaceae* could recover during subsequent cycles of prophylaxis, detection rates of FQ-resistant bacteria significantly increased after repeated prophylaxis (8/35 samples versus 20/33 samples, $p = 0.0028$). Moreover, detection frequency seemed to increase with the number of prophylactic treatment cycles [64]. Other studies have shown that antibiotic exposure causes long-lasting disturbances of the gut microbiota, which may be a necessary step towards acquisition of multidrug-resistant colonization [66, 67].

There is growing concern regarding a possible effect of microbiota composition on oncogenesis and response to anti-cancer treatment. After two independent studies in mice demonstrated the dependency of cisplatin and cyclophosphamide efficacy on prevalence of distinct bacterial groups in the gut microbiota [68, 69], several clinical studies have confirmed that antibiotic exposure and/or gut microbiota composition may influence outcomes of human cancer patients as well [70–75]. Additional studies have highlighted the interconnection of antibiotic treatment and dysbiosis with the emergence of CDI, bloodstream infections and graft-versus-host disease (GvHD) in allogeneic stem cell recipients [76–80]. More recently, antibiotic use and dysbiosis have been linked to worse outcomes of viral infections, possibly as result of impaired T cell activation [81–83].

Further studies are needed to better understand the molecular mechanisms of the observed effects. There are currently no studies specifically reporting a potential effect of FQ prophylaxis on tumor response. However, it should be kept in mind that administration of antibiotic drugs may have considerable interaction with anti-cancer treatment. Any decision for antibiotic prophylaxis must be carefully balanced against the potential for resistance induction, immediate drug-related adverse events (e.g., rash, nausea, QT prolongation, and tendinopathy), and microbiota-mediated adverse events (e.g., CDI, antibiotic-associated diarrhea, GvHD, reduced effectiveness of anti-cancer treatment). It is imperative that future studies on antibiotic prophylaxis consider these new insights to fully evaluate the consequences of FQ exposure.

Efficacy of prophylaxis

Antibacterial prophylaxis has been shown to be effective and safe in preventing febrile episodes and bacterial infections in neutropenic patients [5, 6, 13, 84–86]. A large meta-analysis conducted by Gafter-Gvili et al. included data from 13,579 patients out of 109 trials and compared prophylactic strategies (FQ, trimethoprim–sulfamethoxazole/TMP-SMX, other systemic drugs, non-absorbable drugs) with placebo or no intervention [13]. A significant reduction of infection-related and

all-cause mortality could be shown in patients receiving antibacterial prophylaxis. Moreover, a significant decrease in rates of microbiologically documented infection and bacteremia could be observed. However, the meta-analyses included numerous historical studies from a different era of bacterial resistance and when proper empirical treatment strategies for FN were not universally established. Administration of antibacterial prophylaxis was generally associated with more side effects [13].

Following publications on the rapid and profound effect of antibiotics on selection of resistant bacteria and microbiota composition, it has become a matter of debate how a single drug prophylaxis can maintain effectiveness over a prolonged period of time, i.e., multiple chemotherapy cycles. Indeed, only one of the included studies [35] discriminated the outcome of overall and infection-related mortality between the first and each subsequent cycle while one additional study reported on outcomes during first and during all chemotherapy cycles [6]. It was therefore decided to separate evidence rating and recommendation for first and subsequent chemotherapy cycles.

Since the last version of this guideline [12], a comprehensive literature search by multiple researchers did not reveal new evidence from prospective, randomized clinical trials in adult cancer patients. The results of the recently published TEAMM trial indicate that prophylaxis with levofloxacin is significantly associated with a reduction in febrile episodes and death during the first 12 weeks of multiple myeloma (MM) therapy [87]. This led the authors to the conclusion that levofloxacin prophylaxis should become standard of care for newly diagnosed MM patients, although overall survival during the 1-year follow-up period of the trial was lower than in the placebo group. A major limitation of the TEAMM trial is that incidence of neutropenia was not reported for the patient cohorts, while administration of antibiotic prophylaxis in prolonged neutropenia is known to show a direct benefit for affected patients. A new meta-analysis evaluating the impact of antibiotic prophylaxis in multiple myeloma (MM) patients including the TEAMM trial indicated that antibiotic prophylaxis for the first 3 months following MM diagnosis decreases the incidence of infection, while this decrease did just reach the threshold of statistical significance. Moreover, no evidence for a decrease in mortality could be noted [88]. The modest benefit of antibacterial prophylaxis in MM patients has thus to be weighed carefully against the risk of resistance development, toxicity, and its impact on following therapies. Given the established quality of evidence, after thorough review of the identified literature, it was thus decided that the methodology of most new studies was insufficient to allow relevant new conclusions on prophylactic efficacy [55, 89–96].

However, the current studies underline that antibacterial prophylaxis continues to be effective in the current overall epidemiologic setting regarding predominant bacterial strains and resistances.

Based on the available evidence and under consideration of the defined risk groups, we recommend using antibacterial prophylaxis in high-risk patients receiving their first chemotherapy cycle if prevention of fever and infection is desired (A-I). This strategy may also be effective in reducing overall mortality, but ultimate evidence is lacking (B-II). Antibiotic prophylaxis in low-risk groups receiving their first chemotherapy cycle may be considered for prevention of fever and infection (B-I), but a reduction of mortality was not shown for this patient group (C-II). In this sense, low-risk patients with relevant individual risk factors should be considered as high-risk patients (Tables 2 and 3). Considering the increase of resistant bacteria and given lack of evidence, we downgraded our recommendation for antibiotic prophylaxis during subsequent chemotherapy cycles in high-risk (B-I) and low-risk patients (C-I) (recommendations summarized in Table 4).

Duration of prophylaxis administration

Data regarding timing of prophylaxis initiation and duration of administration are still scarce and comparative studies are warranted. In patients with high risk for development of FN and infection, prophylactic agents are mostly administered with the start of chemotherapy [5], while administration in low-risk patients is often initiated at the end of chemotherapy application [6]. We recommend starting antibacterial prophylaxis in high-risk patients with the start of the cytostatic regimen (B-II$_u$). To reduce side effects and to prevent resistance development, antibacterial prophylaxis should be terminated with the end of neutropenia or with the initiation of therapeutic broad-spectrum antibiotics, as it has been protocol standard in the respective landmark trials [5, 6] (A-II$_u$). In case of breakthrough infection during prophylactic administration of FQ, we recommend switching to another drug class for empiric therapy (A-III) (Table 5).

Drugs for antibacterial prophylaxis

Antibacterial prophylaxis in neutropenic patients is commonly performed with trimethoprim–sulfamethoxazole (TMP-SMX) in standard therapeutic dosing (800/160 mg every 12 h) or FQ. No significant differences regarding incidence of fever and infection as well as all-cause or infection-related mortality could be shown between both drugs [13, 99, 100]. The combination TMP-SMX is probably similarly effective as FQ for prevention of febrile neutropenia and death (B-II$_t$). However, FQ prophylaxis is associated with better tolerability as well as lower bacterial resistance [13, 101]. Therefore, we recommend preferring FQs over TMP-SMX to avoid side effects

Table 4 Indications for antibacterial prophylaxis

Clinical setting	Intention/recommendation	Intervention	SoR	QoE	References
High-risk patients receiving first chemotherapy cycle	Prevent fever and infections by using antibacterial prophylaxis[a]	Antibacterial prophylaxis	A	I	[5, 13, 66, 67, 70, 79, 97, 98]
High-risk patients receiving subsequent chemotherapy cycles			B	I	
Low-risk patients receiving first chemotherapy cycle			B	I	[6, 13, 66, 67, 70, 79, 97, 98]
Low-risk patients receiving subsequent chemotherapy cycles			C	I	
High-risk patients	Reduce mortality by using antibacterial prophylaxis		B	II	[5, 13, 84]
Low-risk patients			C	II	[6, 84, 98]
Patients receiving eculizumab, ravulizumab, or splenectomy or patients with functional asplenia without effective meningococcal vaccination	Prevent meningococcal disease	Penicillin V 250 mg b.i.d. or ciprofloxacin 500 mg q.d. until 4 weeks after immunization or documented protective titers	A	II$_u$	[39, 40]

[a] The recommendation levels refer to the efficacy in achieving the specific endpoint and not on the overall recommendation of antibacterial prophylaxis. Prevention of fever and infections is a non-critical clinical goal and must be weighed against selective pressure and adverse drug effects (see sections "Recent warnings regarding fluoroquinolone safety" and "Novel considerations regarding microbiome and resistome")

(A-II). Compared to FQ, TMP-SMX has the advantage of providing additional prophylaxis against PcP [100]. Of note, we could not identify a study addressing the situation that a patient needs antibacterial and PcP prophylaxis at the same time. It remains unknown whether TMP-SMX three times per week in combination with FQ is better tolerated and/or more effective than TMP-SMX in therapeutic dose without FQ.

The FQ ciprofloxacin and levofloxacin have both been evaluated in different studies and are the first-choice agents for antibacterial prophylaxis compared to other FQs (A-II). Oral absorption of ciprofloxacin following chemotherapy has been described to decrease after cytostatic treatment [102].

Levofloxacin shows inferior efficacy against *Pseudomonas aeruginosa* than ciprofloxacin but has the advantage of being active against gram-positive bacteria. To date, other than ciprofloxacin, prophylactic administration of levofloxacin in patients with chemotherapy-associated neutropenia is not approved in Germany. Moreover, severe side effects including life-threatening hepatotoxicity led to an official warning regarding the off-label use of levofloxacin. Although not part of the major studies, it may be considered to use intravenous FQ formulations in patients with expected poor resorption due to severe diarrhea and/or inability to swallow the drug.

The broad-spectrum FQ moxifloxacin has been shown to prevent bacteremia in patients undergoing autologous HSCT and to shorten the length of febrile episodes [103]. However, it has no proven superiority to ciprofloxacin or levofloxacin prophylaxis, while it seems to be related with higher risk for CDI [104]. Furthermore, bacteremia due to *P. aeruginosa* could be observed during moxifloxacin prophylaxis [103].

It has been studied whether combining FQs with agents active against gram-positive bacteria prevents FN by reducing the incidence of gram-positive infections in neutropenic

Table 5 Timing and duration of antibacterial prophylaxis

Clinical setting	Intention/recommendation	Intervention	SoR	QoE	References
Patients with indication for antibacterial prophylaxis at high risk for infection	Prevention of fever or infection	Start antibacterial prophylaxis with start of cytostatic drugs	B	II$_u$	[5, 6, 13]
Patients with indication for antibacterial prophylaxis at low risk for infection		Start antibacterial prophylaxis 5–8 days after beginning chemotherapy	B	III	
Start of empirical broad-spectrum antibiotic treatment	Reduce side effects, prevent resistance development	Termination of antibacterial prophylaxis	A	II$_u$	
OR					
End of neutropenia					
Patient with breakthrough infection receiving FQ prophylaxis	Treatment of infection	Use of FQ for empirical therapy	D	III	

patients [35, 105]. A meta-analysis by Paul et al. showed no significant differences in all-cause mortality after addition of anti-gram-positive antibiotics, while bacterial superinfections due to gram-positive pathogens were less frequently detected [106]. Adverse events and nephrotoxicity were significantly higher when additional antibiotics were administered. Based on these findings, we do not recommend the addition of prophylactic antibiotics active against gram-positive bacteria in neutropenic patients (D-II) (Table 6).

Recent warnings regarding fluoroquinolone safety

In recent years, a series of warnings regarding safety of FQs was released by several health authorities, including the German *Bundesinstitut für Arzneimittel und Medizinprodukte* and the US Food and Drug Administration. These warnings raise the issue of potentially disabling and permanent toxic effects on large blood vessels, muscles, tendons, joints, peripheral nerves, and the central nervous system [111–114]. Consequently, FQs should no longer be prescribed for non-severe and/or self-limiting infections (e.g., upper respiratory tract infections, urinary tract infection, acute exacerbation of chronic bronchitis, and COPD), traveler's diarrhea, and chronic non-bacterial prostatitis. Special attention is required for patients at risk of toxicity, i.e., elderly patients, patients with impaired renal function, solid organ transplantation recipients, and patients receiving concomitant corticosteroids. Patients showing any signs of tendinitis or tendon rupture, myalgia, muscle weakness, arthralgia, neuropathy, confusion, or hallucinations. In addition, a list of preconditions increasing the risk for aortic aneurysms is provided in the warning letters.

The warning letters were discussed by the guideline group and it was agreed upon that the new evidence does not change the overall rating of the evidence or the recommendation. This has also been extensively argued by another guideline group [115]. The decision not to change the recommendation was based on three primary reasons. Firstly, in the setting of neutropenia, for no other drugs, sufficient evidence regarding efficacy and tolerability is available. While TMP-SMX has comparable efficacy, it showed a higher rate of treatment-emergent adverse events in comparative trials. Secondly, hematologic and oncologic patients are typically closely monitored by the treating physician and toxic side effects could probably be detected earlier, allowing timely termination of FQ treatment. And finally, the guideline group felt that the overall low rate of severe side effects of FQs, especially compared to the severity of the underlying disease of neutropenic patients and the high efficacy of FQs in preventing infections, does not outweigh the potential benefits of FQ use.

Table 6   Drugs for antibacterial prophylaxis

Clinical setting	Intention/recommendation	Intervention	SoR	QoE	References
Neutropenic patients with indication for antibacterial prophylaxis[a]	Prevent FN or death	Use fluoroquinolone prophylaxis, if indicated	A	I	[13, 101, 107, 108]
	Prevent FN or death	Use therapeutic dose TMP-SMX instead of FQs, if indicated	B	II$_t$	[13, 101, 107, 108]
	Prevent FN or death	Prefer selective gut decontamination vs. systemically active antibacterials	*		[109, 110]
	Reduce side effects of antibacterials	Prefer fluoroquinolone prophylaxis vs. TMP-SMX	A	II	[13, 101, 107, 108]
	Prevent FN or death	Ciprofloxacin and levofloxacin as FQs of choice for prophylaxis	A	II	[5, 13, 103–105]
Prevent FN and reduce incidence of gram-positive infections	Combine fluoroquinolone with an agent active against gram-positive bacteria	D		II	[13, 35, 105, 106]
Neutropenic patients with indication for antibacterial prophylaxis and known colonization with multiresistant bacteria	Prevent FN or death	FQ prophylaxis if known colonization by FQ-resistant gram-negative bacteria	D	II$_{t, u}$	[50, 51, 58, 79]

*No recommendation due to lack of randomized studies and conflicting data

[a] Note that these recommendations are made provided that a patient was determined to receive an antibacterial prophylaxis under consideration of Table 4. A high level of evidence/recommendation in this table does not provide recommendation to the indication of prophylaxis, but only on the choice of drug if an indication is given

We advise physicians to inform patients about potential FQ side effects and discuss the risks and benefits of alternative strategies, i.e., standard-dose TMP-SMX (more acute side effects), an oral third-generation cephalosporin (lack of evidence), or no antibiotic prophylaxis (increased risk of fever and hospitalization).

Selective digestive tract decontamination

The rationale behind decontamination of the intestinal or digestive tract is to eliminate most bacteria which can cause endogenous infection by translocation from the digestive system ideally by non-absorbable anti-infective agents only [44]. Selective digestive tract decontamination (often termed SDD or SD) aims at leaving the anaerobic flora intact and many authors of comparative studies have claimed a benefit for SDD 15–20 years ago [116–118]. However, most studies used absorbable antibiotics like cotrimoxazole or FQ and are thus difficult to distinguish from systemically active antibiotic prophylaxis. After a decade of no new data on SDD, two retrospective studies comparing non-absorbable antibiotics (colistin or rifaximin) with antibiotic prophylaxis using FQ in patients who received an allogeneic HSCT found comparable efficacy of SDD versus systemic antibiotics with regard to infections [109, 110]. The most recent study observed a survival benefit for patients who received non-absorbable as opposed to systemic antibiotic prophylaxis; however, it remains unclear how rifaximin would have compared to placebo or other systemically active antibiotic prophylaxis [110]. Of note, both studies do not define their regimen for PcP prophylaxis, which might add a low level of systemic antibiotic activity if given.

A concern regarding SDD is the possibility of inducing resistance. A recent meta-analysis of SDD in critically ill patients found no short-term increase of a small set of specific resistant organisms/resistance genes in studies investigating SDD [119], while other data indicate that the composition of the intestinal microbiota and the resistome is importantly affected by SDD [66, 120, 121]. It could be shown that application of SDD in intensive care patients has considerable effects on the gut microbiota, including overgrowth by *Enterococcus* spp. [121, 122].

In summary, because of the lack of well-designed prospective trials and the lack of data from patients other than allogeneic HSCT recipients, a recommendation regarding SDD cannot be made.

Indication for *Pneumocystis jirovecii* prophylaxis

Infections caused by *Pneumocystis jirovecii* are a common complication in immunocompromised patients; the individual risk depends on the underlying disease and treatment regimen [123–126]. Trials on PcP in HIV-uninfected cancer patients are sparse, but several risk factors for development of PcP have been identified [127, 128].

Oncologic patients at significant risk for PcP are those treated for acute lymphoblastic leukemia, those treated with a combination of fludarabine, cyclophosphamide, and rituximab [129], and patients undergoing allogeneic HSCT [128, 130]. Moreover, long-term use of steroids (> 20 mg/day prednisone equivalent for 4 weeks) increases the risk of developing PcP [129, 131, 132]. Patients with hematologic malignancies appear to have higher mortality rates once they develop PcP [133]. The administration of chemoprophylaxis in patients with one of these three risk factors is thus strongly recommended to prevent PcP (A-I) and reduce mortality (A-II$_r$).

Other hematologic and oncologic patients may occasionally develop PcP, such as lymphoma patients treated with R-CHOP14 or escalated BEACOPP protocol, patients treated with nucleoside analogs or long-term anti-CD20 antibody therapy, patients receiving high-dose steroids in addition to a radiotherapy for brain malignancies, and patients with CD4 count < 200 cells/μl [127, 134, 135]. There are no studies demonstrating benefit of PcP chemoprophylaxis in these patient groups, though it is likely that the number needed to treat is considerably higher compared to the high-risk groups. Such patients at moderate risk may or may not receive chemoprophylaxis to prevent PcP (C-III) and to reduce mortality (C-III).

New immune-modulating agents might increase the risk for PcP [136–138]. Patients receiving idelalisib are at high risk for developing PcP and prophylaxis must be administered concurrently (drug label) [139–141]. Initiation of chemoprophylaxis at the beginning of therapy is recommended by the manufacturer and should be maintained for 2–6 months after stopping therapy. Increased rates of PcP and other opportunistic infections have been observed in a phase II pilot of alemtuzumab without administration of prophylaxis [142]. Some authors recommend chemoprophylaxis during treatment with alemtuzumab with TMP-SMX or an equivalent agent [143, 144]. If radiotherapy is combined with temozolomide, chemoprophylaxis is recommended and administered in clinical studies [145–147]. Based on the documented high-risk situation, we strongly recommend chemoprophylaxis against PcP for patients receiving temozolomide (in combination with radiotherapy), idelalisib, or alemtuzumab (A-II$_{u,t}$) (Tables 7 and 8).

Choice of drugs and doses for PcP prophylaxis

Administration of PcP prophylaxis has been extensively studied in HIV-positive patients [153] and non-HIV patients [127, 133, 154]. Based on the available evidence, the most effective prophylactic agent is TMP-SMX,

Table 7 Risk factors and indications for *Pneumocystis jirovecii*

Significant risk	Intermediate risk	Special indications
• Acute lymphoblastic leukemia	• R-CHOP14 or escalated BEACOPP	• Alemtuzumab
• Allogeneic stem cell transplantation	• Nucleoside analogs	• Idelalisib (drug label)
• Long-term steroids with > 20 mg q.d. prednisone equivalent for > 4 weeks	• Brain irradiation with high-dose steroids	• Brain irradiation + temozolomide
• Fludarabine + cyclophosphamide + rituximab	• CD4 cell count < 200/µl	

which also offers protection for toxoplasmosis [153], nocardiosis [155], and actinomycosis. For these reasons, TMP-SMX is the first-choice agent for PcP prophylaxis (A-II$_{t,r}$). It is unknown whether the low doses of TMP-SMX used for PcP prophylaxis are also effective in preventing other infections. No relevant differences in efficacy of different dosing strategies for TMP-SMX, i.e., one single-strength tablet per day (80/400 mg) or one double-strength tablet (160/800 mg) daily or thrice a week, were shown in clinical studies [156, 157]. A study in HIV-infected patients observed a 43% lower risk of discontinuing TMP-SMX due to side effects if the double-strength tablet was given thrice a week instead of daily [153]. We recommend using any of these dosing regimens (B-II$_t$).

In patients with intolerance or severe adverse events related to TMP-SMX administration, atovaquone, dapsone, or pentamidine (aerosolized) can be used as alternatives. Atovaquone has been studied in HIV-infected patients [158–160], while only few studies in non-HIV-infected immunocompromised patients exist [161–163]. The drug was highly effective, generally well tolerated and not associated with hematologic toxicity. We therefore recommend atovaquone as first alternative to TMP-SMX as PcP prophylaxis in patients with underlying hematologic or oncologic malignancies. Low-dose atovaquone has been described to be less effective in PcP prophylaxis [164]; thus, 1500 mg atovaquone should be administered once daily (off-label use) (A-II$_t$). To increase bioavailability of atovaquone, it should be taken during a fatty meal [165, 166]. If hematologic toxicity is not a major concern, dapsone (100 mg/day) can be used (A-II$_t$). Efficacy of daily dapsone was equivalent to the administration of TMP-SMX in comparative studies [167–169]. Testing for glucose-6-phosphat dehydrogenase deficiency is recommended prior to administration of dapsone. If prophylaxis of toxoplasmosis is indicated, dapsone should be combined with pyrimethamine. The risk of dapsone-induced methemoglobinemia must be carefully considered.

Aerosolized pentamidine is a popular option for PcP prophylaxis, considering the lack of hematologic toxicity or drug–drug interactions and the long dosing interval of 28 days. However, efficacy is probably lower compared to systemic prophylaxes. Pentamidine has no efficacy against toxoplasmosis and bacterial infections, which is of concern, especially after allogeneic HSCT [170–173]. Some authors have reported a mild to moderate decline in pulmonary function after long-term exposure [174–177], while others found no effect [178]. Pentamidine inhalation has been shown to cause considerable exposure and respiratory side effects in healthcare workers [179, 180], and adequate measures are recommended to protect staff. Our recommendation to use aerosolized pentamidine (300 mg once/month) is moderate (B-II$_t$) (Table 9). There have been reports of successful use of intravenous pentamidine in prevention of PcP [187–189]. In the absence of comparative trials, no recommendation can be given for this regimen in favor of established ones.

Table 8 Indications for *Pneumocystis jirovecii* pneumonia prophylaxis

Clinical setting	Intention/ recommendation	Intervention	SoR	QoE	Reference
Patients at significant risk for developing PcP	Prevent PcP	Use chemoprophylaxis	A	I	[125–133, 148–151]
Patients at intermediate risk			C	III	[127, 134, 135]
Patients receiving idelalisib, alemtuzumab, or temozolomide (with radiation) treatment			A	II$_{u, t}$	[142, 144, 152]
Patients at significant risk for developing PcP	Reduce mortality	Use chemoprophylaxis	A	II$_r$	[127]
Patients at intermediate risk			C	III	[127]

Table 9 Drugs for *Pneumocystis jirovecii* pneumonia prophylaxis

Clinical setting	Intention/recommendation	Intervention	SoR	QoE	References
Patients with indication for PcP prophylaxis	Prevent PcP	Use TMP-SMX as first-choice agent	A	II$_{t, r}$	[126–128, 133, 153, 154, 181, 182]
		Use one single-strength (80/400 mg) tablet daily **or** one double-strength tablet (160/800 mg) either daily **or** thrice a week	B	II$_t$	[127, 153, 156, 157, 182–184]
Patients with intolerance or severe adverse effects due to TMP-SMX		Use **atovaquone** as second-choice drug - 1500 mg/day	A	II$_t$	[37, 157, 160–162, 164]
		Use **dapsone** as second-choice drug - 100 mg/day	A	II$_t$	[153, 160, 167]
		Use **pentamidine (aerosolized)** as second-choice drug - 300 mg once monthly	B	II$_t$	[153, 159, 168, 170, 185, 186]

Declarations

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