

Primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with hematological malignancies and solid tumors

Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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Received: 22 January 2013 / Accepted: 2 February 2013 / Published online: 15 February 2013
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Abstract Bacterial infections are the most common cause for treatment-related mortality in patients with neutropenia after chemotherapy. Here, we discuss the use of antibacterial prophylaxis against bacteria and *Pneumocystis* pneumonia (PCP) in neutropenic cancer patients and offer guidance towards the choice of drug. A literature search was performed to screen all articles published between September 2000 and January 2012 on antibiotic prophylaxis in neutropenic cancer patients. The authors assembled original reports and meta-analysis from the literature and drew conclusions, which were discussed and approved in a consensus conference of the Infectious Disease

Working Party of the German Society of Hematology and Oncology (AGIHO). Antibacterial prophylaxis has led to a reduction of febrile events and infections. A significant reduction of overall mortality could only be shown in a meta-analysis. Fluoroquinolones are preferred for antibacterial and trimethoprim–sulfamethoxazole for PCP prophylaxis. Due to serious concerns about an increase of resistant pathogens, only patients at high risk of severe infections should be considered for antibiotic prophylaxis. Risk factors of individual patients and local resistance patterns must be taken into account. Risk factors, choice of drug for antibacterial and PCP prophylaxis and concerns regarding the use of prophylactic antibiotics are discussed in the review.

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Keywords Prophylaxis · Bacterial infection · *Pneumocystis* · Neutropenia

Introduction

Patients with hematological and oncological diseases are at increased risk for bacterial infections and pneumonia caused by *Pneumocystis jirovecii* (PCP) because of their disease-related and therapy-induced immunosuppression. As infections are the leading cause for non-relapse mortality, broad-spectrum antibiotic therapy is introduced as soon as an infectious problem is suspected. Despite early empirical antibiotic therapy, the infection-related mortality in neutropenic cancer patients is 4–7 % [1, 2]. The administration of systemic antibacterial prophylaxis may aim at a reduction of severe infections, a delay of the onset of such infections to a later phase of neutropenia, avoidance of infection-related treatment delays, reduction of hospitalization, reduction of treatment costs or a combination of

these goals. To reduce the risk of infectious complications during the period of chemotherapy-induced neutropenia, various prophylactic approaches including the systemic use of antibiotics were introduced and widely studied. The decision for or against the administration of a prophylactic antibiotic regime is guided by the risk of an individual patient to acquire a severe, life-threatening infection, carefully balanced against the potential risks of long-term administration of a broad-spectrum antibacterial agent with systemic activity. Several studies have shown that antibacterial prophylaxis led to a reduction of febrile events and documented infections, their tolerability is generally good and hospitalization may be avoided or shortened, resulting in cost saving. On the other hand, the concept of antibiotic prophylaxis is challenged because of possible side effects such as development of resistance and toxicity of the drugs.

For this review, papers on antibacterial and PCP prophylaxis published in scientific journals from September 2000 to January 2012 were searched and evaluated according to the 2001 evidence-based medicine criteria used by the Infectious Diseases Society of America (IDSA) (Table 1) [3]. The authors assembled in January 2012 to develop practice recommendations based on the recent literature. These recommendations were then extensively discussed at the Infectious Diseases Working Party of the German Society of Hematology and Oncology (AGIHO) plenary meeting, resulting in an agreement regarding each recommendation. This manuscript summarizes the recommendations on antibacterial and PCP prophylaxis for neutropenic cancer patients resulting from this process.

Guidelines for antiviral and antifungal prophylaxis can be found in other publications of the AGIHO [4, 5]. Furthermore, prophylaxis of patients with allogeneic stem cell transplantation is addressed in a separate guideline of the AGIHO [6].

Definitions

Neutropenia

Neutropenia is defined as a neutrophil count below 500/ μl or <1,000/ μl with predicted decline to less than 500/ μl within the next 2 days, or leukopenia <1,000/ μl when there is no differential leukocyte count available.

IDSA grading system for ranking recommendations

Regarding the IDSA grading system for ranking recommendations, see Table 1.

Patients and risk factors

The risk of developing an infection following chemotherapy depends on the severity and duration of neutropenia [7, 8]. In a

Table 1 Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations [3]

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

guideline published a decade ago, the AGIHO defined three risk groups depending on the duration of neutropenia — patients with an expected duration of neutropenia of less than 5 days generally are at low risk, whereas patients with an expected duration of neutropenia of more than 10 days are at high risk, with a risk of acquiring an infection exceeding 90 % [9]. Patients with an expected duration of neutropenia between 6 and 10 days were classified as intermediate risk group. Other guidelines divide the patients into two risk groups with neutropenia of more or less than 7 days based on two recently published clinical trials [1, 10–12]. Importantly, none of these classifications are based on prospective studies. However, judging the risk of an individual patient on his expected duration of neutropenia has become clinical practice in many centers. We will also assume two risk groups for easier applicability, the low-risk group being patients with an expected duration of neutropenia of less than 7 days and the high-risk group those patients with duration of neutropenia of 7 days or more or with additional risk factors.

Additional factors which may increase the risk of infection are the type and stage of the underlying malignancy, the remission status, disruption of physiological skin or mucosal barriers as well as age and comorbidities of an individual patient. Furthermore, the number and type of pretreatments or the use of other immunosuppressive agents such as high-dose

glucocorticosteroids or lymphocyte-depleting substances may have an impact on the risk of infection. Patients receiving their first cycle of chemotherapy are at a higher risk of infection than in following cycles. However, if a febrile episode occurred during the first cycle, the risk of infection is increased in subsequent cycles of chemotherapy. Moreover, the “social environment,” including the availability of a direct caregiver, telephone, option of quick transportation from home to hospital, residence within a defined maximum distance from the hospital and appropriate verbal communication and intellectual understanding of an individual patient should be considered for the decision of anti-infective prophylaxis [8, 13–16] (Table 2).

In patients with autologous stem cell transplantation, the risk of infection depends primarily on the length of neutropenia which is usually longer than 7 days. More detailed information can be found in the relevant guideline [17].

The use of the anti-CD20 antibody rituximab or anti-CD52 antibody alemtuzumab leads to an increased incidence of fungal, viral or protozoal infections [18–21], while a substantially increased risk of bacterial infections has not been reported [22–26].

Clinical presentation and spectrum of pathogens in neutropenic infections

In most cases of infection in a neutropenic patient, fever is the first sign [27]. Typical clinical symptoms such as local signs of infection as part of an inflammatory response may be missing. In approximately half of the patients, a focus of infection cannot be detected at the onset of fever; therefore, it is classified as fever of unknown origin (FUO). In up to a third of patients, bacteremia can be diagnosed [1, 28], with coagulase-negative staphylococci, α -hemolytic streptococci and *Staphylococcus aureus* being predominant among gram-positive pathogens. With regard to gram-negative pathogens, enterobacteria such as *Escherichia coli* and *Klebsiella* spp. as

well as non-fermenters such as *Pseudomonas aeruginosa* predominate [29–31]. A gram-negative sepsis is still associated with substantial mortality [32]. For this reason, antibiotic prophylaxis using agents active against gram-negative bacteria, particularly fluoroquinolones, was introduced in many hospitals, resulting in an overall decrease of bacteremias, but also in an increased proportion of infections caused by gram-positive bacteria [33]. At present, the proportion of gram-positive pathogens in neutropenic patients with microbiologically documented infections is typically around 60–70% [29, 31, 34, 35]; however, as this may differ substantially between cancer centers [36], the local epidemiology should always be considered before deciding on an antibacterial prophylaxis regimen.

Efficacy of prophylaxis

The efficacy of systemic antibacterial prophylaxis was investigated in a multitude of clinical trials and several meta-analyses. The results of the two most important large double-blind, placebo-controlled studies are described briefly: Bucaneve et al. examined the use of levofloxacin in 675 patients with hematological malignancies or solid tumors and an expected length of neutropenia (neutrophil count less than 1,000/ μ l) of more than 7 days. A significant reduction of febrile episodes and microbiologically documented infections, especially gram-negative bacteremias, could be shown in the levofloxacin arm. Mortality was lower in the levofloxacin group, but the study was not powered to show this with statistical significance [1]. In the study by Cullen et al. [12], 1,565 patients with solid tumors or lymphomas receiving outpatient chemotherapy were given levofloxacin or placebo for an expected period of neutropenia of less than 7 days. The incidence of febrile episodes, probable infections and hospitalization for infection could be reduced significantly. Also, there were fewer severe infections and a lower overall mortality in the prophylaxis group, but this difference was not statistically significant [12].

These observations were confirmed in a large meta-analysis comprising a total of 13,579 patients from 109 studies conducted between 1973 and 2010 [37]. Most of the studies included high-risk patients with hematological diseases such as acute leukemias and compared different prophylactic strategies with placebo or no intervention. Due to the larger number of patients included in the meta-analysis compared to the single trials, a significant reduction of infection-related death with a risk ratio (RR) of 0.61 (95% confidence interval [CI], 0.48–0.77) and a reduction in all-cause mortality (RR 0.66; 95% CI, 0.55–0.79) were calculated for patients receiving antibacterial prophylaxis as compared to placebo or no intervention. A decrease in all-cause mortality could also be shown in the subgroup of 3,776 patients included from studies testing fluoroquinolone prophylaxis versus no prophylaxis

Table 2 Patient-related risk factors

Duration of neutropenia 500/ μ l
Type and stage of underlying malignancy
Number of cycles and type of cytotoxic/immunosuppressive pretreatment
Concomitant immunosuppressive therapy
First cycle of chemotherapy
Previous episode of febrile neutropenia
Disruption of physiological skin or mucosal barriers
Chronic wounds
Age
Comorbidities (e.g., diabetes mellitus, iron overload, chronic lung disease)
Social conditions

(RR 0.54; 95 % CI, 0.40–0.74). Microbiologically documented gram-negative as well as gram-positive infections including bacteremias were significantly reduced in patients receiving antibacterial prophylaxis. An increase of 3.6 % in adverse events due to prophylaxis as compared to no prophylaxis is reported with 2.1 % more events (3.9 % versus 1.8 %) leading to treatment discontinuation [37].

A meta-analysis including only randomized, blinded, placebo-controlled trials from 1987 to 2005 with a total of 2,721 patients could not demonstrate a significant, but only a trend towards, reduction of overall mortality [38], while efficacy data were consistent with the study from Bucaneve et al. and with the 2012 meta-analysis [1, 37]. It has to be kept in mind that this meta-analysis was strongly influenced by the non-infectious mortality among low-risk patients in the Cullen et al. study, which might obscure a potential survival benefit with regard to the infection-related mortality (Table 3).

Antibacterial prophylaxis, particularly with fluoroquinolones, can prevent febrile episodes, clinically or microbiologically documented bacterial infections including bacteremias and hospitalization of outpatients. A reduction in infection-related as well as all-cause mortality could be shown in a large meta-analysis [37]. In order to derive recommendations from the data described above, the risk reduction has to be weighed against adverse effects, especially the development of resistance to widely used antibacterial agents among clinically relevant pathogens. A reduction of overall mortality can be assumed in high-risk populations with a number needed to treat (NNT) below 50 (43 according to the study of Bucaneve et al., 34 according to the meta-analysis of Gafter-Gvili et al.) and avoidance of neutropenic fever with a NNT of around 5 [1, 37, 39]. As with other interventions, NNT decreases with increasing underlying risk. Therefore, prophylaxis is recommended in

high-risk patients. Concerning avoidance of fever and infections, this is a strong recommendation; concerning mortality reduction, the recommendation is weaker (Table 4). In low-risk patients, a reduction of neutropenic fever and avoidance of hospitalization can be achieved. This effect is most pronounced during the first cycle of chemotherapy. On the other hand, a reduction of mortality was not unequivocally shown for low-risk patients. One meta-analysis showed a mortality reduction with a NNT of 72 [39], but it included older studies with an unacceptably high baseline event rate to be attributed to low-risk patients. Assuming that in low-risk patients a similar relative risk reduction as in high-risk patients can be achieved, the NNT to prevent one infection-related death would be around 250 at a baseline risk of 1 % and a relative risk of 0.6 (i.e., otherwise healthy individuals with low-intensity chemotherapy). In addition, the prophylactic administration of a fluoroquinolone in low-risk patients would prohibit the use of a fluoroquinolone for treatment of infection in the outpatient setting. Therefore, antibacterial prophylaxis can generally not be recommended in low-risk patients. In specific situations such as the first chemotherapy cycle [15], aggressive cytostatic regimens with high baseline infection rate or in elderly patients; however, it may be considered because it reduces the incidence of infections and febrile episodes.

Substances for antibacterial prophylaxis

Studies conducted in the 1970s used non-absorbable antibiotics such as colistin, polymyxin B or neomycin for selective bowel decontamination. Due to the lack of systemic activity, gastrointestinal tolerability problems and the risk of selection of resistant bacteria, most institutions have switched to

Table 3 Overview of risk reduction rates in studies on antibacterial prophylaxis in cancer patients

Study	N	All-cause mortality		Infection-related mortality		Fever	
		Baseline risk	RR	Baseline risk	RR	Baseline risk	RR
Gafter-Gvili et al. [37] (meta-analysis, drug vs. none)	5635	8.8 %	0.66**	5.6 %	0.61**	60.7 %	0.80 **
Gafter-Gvili et al. [37] (meta-analysis, quinolone vs. none)	3776	5.3 %	0.54**	2.9 %	0.51 **	53.8 %	0.74 **
Bucaneve et al. [1] (low and high risk, levofloxacin vs. placebo)	760	5.0 %	0.54 ns	3.9 %	0.63 ns	84.8 %	0.76 **
Cullen et al. [12] (low risk, levofloxacin vs. placebo)	1565			0.5 %	1.00		0.71 **
- Cumulative		4.6% ^a	0.86			15.2 %	0.44 **
- First cycle		2.3 %	0.67			7.9 %	
Imran et al. [38] (meta-analysis, quinolone vs. placebo)	2721	5.3 %	0.76 ns			39.7 % ²	0.76 ns ^b

N number of patients, RR relative risk, ns not significant

^a Overall mortality reported as personal communication in reference [38] and as 30-day mortality in reference [39]

^b Heterogeneous data. Only first cycle from Cullen et al. [12] is used for this analysis

**Significant

trimethoprim–sulfamethoxazole (TMP/SMX) or fluoroquinolones. These substances have a broad spectrum of activity and are well absorbed from the gastrointestinal tract. TMP/SMX is not active against *P. aeruginosa*, and resistance to this drug combination among gram-negative target pathogens such as *E. coli* or *Klebsiella* spp. has been observed already in the 1990s. However, significant differences in clinical efficacy have not been shown in direct comparisons [40–42]. Both types of drugs show similar risk reductions of the outcome parameters mentioned above in comparison to placebo [37].

TMP/SMX is less well tolerated as compared with fluoroquinolones (relative risk for side effects requiring discontinuation about 2 compared to quinolones by both direct and indirect comparison [37]), and it may be associated with bone marrow toxicity in patients given this drug combination daily for more than 2–3 weeks.

Therefore, if a high local resistance rate and an individual intolerance to fluoroquinolones are excluded, a fluoroquinolone should be preferred in patients in whom systemic antibacterial prophylaxis is indicated (A-II, Table 4).

The fluoroquinolones available for clinical use differ in their spectrum of activity. Ciprofloxacin and levofloxacin were most frequently tested in clinical trials. Compared to ciprofloxacin, levofloxacin is less effective against *P. aeruginosa*, but has the advantage of activity against gram-positive bacteria such as *Streptococcus* spp. In 2012, a warning regarding the off-label use of levofloxacin was issued because of rare but severe side effects including life-threatening hepatotoxicity. In Germany, levofloxacin is not approved for the prophylactic use in the setting of chemotherapy-induced neutropenia, whereas ciprofloxacin is. Considering this fact and in the light of the recent box warning, the authors recommend to prefer ciprofloxacin for antibacterial prophylaxis in neutropenic cancer patients.

While moxifloxacin has a broad activity against aerobic and anaerobic gram-positive and gram-negative

pathogens, it has no efficacy against *P. aeruginosa* and appears to be associated with a higher risk of *Clostridium difficile*-associated enterocolitis than levofloxacin [43]. As yet, no properly designed clinical study showing a benefit of moxifloxacin for antibacterial prophylaxis in neutropenic cancer patients has been reported. A recently published trial has demonstrated a reduction of bacteremias by moxifloxacin in a small number of patients undergoing autologous hematopoietic stem cell transplantation [44].

Combination of a fluoroquinolone with an agent active against gram-positive bacteria

In order to prevent gram-positive infections, combinations of fluoroquinolones with antibiotics active against gram-positive pathogens such as oral penicillin, vancomycin or a macrolide have been studied in neutropenic patients. A randomized placebo-controlled study investigated the use of ciprofloxacin in combination with roxithromycin versus no antibiotic prophylaxis in patients with small cell lung cancer during the first cycle of chemotherapy. In the prophylaxis group, the incidence of febrile leukopenia, documented gram-positive and gram-negative infections and infection-associated deaths were significantly reduced [45]. A comparison with single-agent ciprofloxacin was not included in this study. Several small trials compared combination prophylaxis with fluoroquinolone prophylaxis alone. Two meta-analyses including more than 1,200 patients found a significant reduction in gram-positive infections and septicemia with the addition of an antibiotic active against gram-positive pathogens, however, a significant reduction of clinically documented infections, febrile neutropenia or mortality could not be demonstrated [37, 46]. On the other hand, significantly more side effects were reported in patients

Table 4 Recommendations for antibacterial prophylaxis

Recommendation	Level of evidence
Antibiotic prophylaxis is indicated for	
Low risk, regarding fever and infection	B-I
Low risk, regarding mortality ^a	C-II
High risk, regarding fever and infection	A-I
High risk, regarding mortality	B-II
Fluoroquinolone prophylaxis should be preferred to TMP/SMX	A-II
Drug of choice: ciprofloxacin (500mg twice daily) or levofloxacin (500mg once daily) (not approved for this indication in Germany)	A-II
Addition of a gram-positive active agent to quinolone prophylaxis (discouraged)	E-II
Start of prophylaxis with onset of neutropenia in low-risk patients	B-III
Start of prophylaxis with start of cytostatic drugs in high-risk patients	B-III
Termination of prophylaxis with the start of empirical antibiotics or end of neutropenia	B-III
Use of FQ for empirical therapy if used for prophylaxis (discouraged)	E-III

^aConsider in special situations (see text)

on combination therapy. In particular, the administration of rifampin resulted in a significantly increased rate of side effects such as gastrointestinal intolerance or abnormal liver function tests.

In summary, the addition of prophylactic antibiotics with specific activity against gram-positive pathogens to a fluoroquinolone is not recommended (E-II, Table 4).

Beginning and duration of prophylaxis

There are no comparative studies addressing the question when to start prophylactic antibiotics and how long to administer them. In those patients with expected short duration of neutropenia (solid tumors, lymphomas), in whom antibacterial prophylaxis is considered at all, prophylaxis is usually started after the end of chemotherapy and given throughout the period of neutropenia [12, 45]. In high-risk patients, however, antibiotic prophylaxis in clinical trials was administered almost exclusively from the start of chemotherapy until the end of neutropenia or until the onset of systemic antimicrobial therapy [1, 47]. In patients receiving induction chemotherapy for acute leukemia, prophylaxis should begin with the first day of chemotherapy because of the functional neutropenia induced by the disease itself. With the end of neutropenia or onset of systemic antimicrobial treatment, antibiotic prophylaxis should be stopped (B-III). The use of quinolones for empirical treatment is not recommended if prior prophylaxis has been carried out with a fluoroquinolone (A-III, Table 4).

If a cytostatic treatment in acute leukemia patients is given without antibacterial prophylaxis, an intensive clinical monitoring is required to ensure an immediate start of antibiotic therapy in case of a suspected infection.

Concerns on resistance development

One of the main concerns regarding antibiotic prophylaxis in any patient population is the development or selection of multidrug-resistant pathogens. This has led some experts to withhold a recommendation for antibiotic prophylaxis in neutropenic cancer patients [11]. Regarding the risk of the emergence of resistance, several issues need to be considered:

1. Does antibacterial prophylaxis in cancer patients really lead to an excess increase in the proportion of multidrug-resistant pathogens?
2. Are infections due to fluoroquinolone-resistant pathogens more threatening than infections from sensitive strains of the same pathogen?
3. If there is an increase in multidrug-resistant pathogens, does it lead to an increased infection rate due to these pathogens and does this result in increased mortality?

4. As a consequence, should a recommendation for antibacterial prophylaxis in neutropenic cancer patients be restricted to centers with a low (e.g., <20 %) prevalence of resistance against the prophylactic antibacterials (typically fluoroquinolones) among target pathogens such as *E. coli* or *Klebsiella* spp. since in areas with a high prevalence of resistance no benefit from this prophylaxis can be expected?
5. Is it ethically justified to withhold a potentially beneficial antibacterial prophylaxis from cancer patients at risk for serious neutropenic infections today, in order to avoid an increasing risk of infections due to resistant pathogens in future patients?

While none of these questions can be answered definitely, there are some arguments to consider for most of them. Data regarding the additional effect of drug resistance on morbidity and mortality in hospital acquired infections are conflicting [48–50], whereas there is little doubt that hospital acquired infections by themselves pose a major problem and should generally be avoided if possible. This consideration rather favors the use of prophylactic antibiotics, since it has been shown that they reduce the likelihood of infections in neutropenic cancer patients. From a broader perspective, neutropenic cancer patients at risk of severe infections constitute a small proportion among patients who regularly receive antibiotic treatment, not to mention the widespread use of antibiotics in settings outside the health care system such as agriculture and livestock. Nonetheless, even such a small population may have an impact on the general epidemiology of infections, and reports of spread of resistant pathogens after the introduction of TMP/SMX or fluoroquinolone prophylaxis have to raise concern [51, 52]. In particular, multidrug-resistant *E. coli* and *P. aeruginosa* as well as methicillin-resistant *S. aureus* have been reported to play a relevant role [51]. However, this finding has not been confirmed unequivocally [53, 54]. The 2012 Cochrane meta-analysis on antibiotic prophylaxis in neutropenic cancer patients revealed an increase of infections due to resistant pathogens in patients receiving antibiotic prophylaxis with TMP-SMX, but not with fluoroquinolones [37]. Thus, it is not entirely certain if antibacterial prophylaxis using fluoroquinolones increases the incidence of infections with resistant strains. Also, moxifloxacin seems to have the most relevant potential for inducing *C. difficile* associated diarrhea [43], while studies on levofloxacin [55] or ciprofloxacin [56] prophylaxis did not report a similar increase in the incidence of *C. difficile*-associated enterocolitis [39].

In addition, in studies on discontinuation of antibacterial prophylaxis, an increase in (particularly gram-negative) bacteremias has been observed [52, 54, 57], sometimes even translating into a higher mortality rate [57]. Of note, although some authors report a lack of efficacy in case of a high incidence of resistance [58], this could not be

confirmed by others [52, 53, 57]. Thus, a fixed threshold of for example <20 % prevalence of quinolone resistance for instituting quinolone prophylaxis as suggested by Bow [59] cannot be generally advised (E-III). In contrast, it seems more advisable to monitor development of resistance (A-III) and efficacy (B-III) on a regular basis in centres implementing antibiotic prophylaxis. The overall clinical benefit can then be deduced from local data and experience.

Antibiotic prophylaxis versus myeloid growth factors for infection prophylaxis

The administration of granulocyte (G-CSF) or granulocyte-macrophage colony-stimulating factors (GM-CSF) is another possibility to prevent infectious complications. In studies, a reduction of bacterial infections could be shown by shortening the length of neutropenia by the use of these myeloid growth factors. Therefore, the use is generally recommended if the risk of febrile neutropenia is above 20 % [60–62]. Two questions arise, which of these strategies is more efficient, and can both strategies be combined? A formal meta-analysis comparing both strategies directly could not be performed due to the different evaluation endpoints of the two small single studies [63]. Indirect comparisons give the impression, that growth factors and prophylactic antibiotics show roughly the same magnitude of efficacy. If antibiotic prophylaxis and growth factors are combined, it can be assumed from network analyses that efficacy of both strategies add to each other [63], so that indications for both these approaches to infection prevention should be considered separately.

P. jirovecii prophylaxis

Prophylaxis with trimethoprim-sulfamethoxazole is highly effective for prevention of *Pneumocystis pneumonia* (PCP)

and is associated with a decrease in mortality [64]. This could be demonstrated in studies with HIV patients, but has also been shown in patients undergoing allogeneic stem cell transplantation or patients with acute lymphoblastic leukemia (ALL) [65]. Green et al. [66] recommend the use of prophylaxis when the risk of PCP is greater than 3.5 %. Unfortunately, the studies included in this meta-analysis are outdated, and data on the actual risk of PCP in a broad range of hematological malignancies such as acute myeloid leukemia are sparse [65]. Generally, because of more intensive therapy and the use of newer protocols such as T-cell-depleting substances, an increased incidence can be assumed. In addition, patients with hematological malignancies appear to have a higher risk of mortality once they develop a PCP [67]. Thus, prophylaxis is recommended for patients deemed at significant risk (Table 5). It should be pointed out that non-neutropenic cancer patients given glucocorticosteroids for prolonged periods of time, typically those with brain metastases from solid tumors or cerebral involvement from non-Hodgkin's lymphoma, carry a substantial risk of PCP and should be candidates for TMP-SMX prophylaxis [68]. In some situations, for example, in patients receiving temozolomide and radiation therapy, the manufacturer recommends additional PCP prophylaxis although the evidence for an increased risk might seem weak. However, in these situations we recommend to follow the advice given by the manufacturer.

The drug of first choice for PCP prophylaxis is TMP/SMX (A-I). The efficacy and tolerability of a daily and thrice-weekly administration of 960 mg are comparable [66]. It is recommended to use the drug for the period of treatment-induced immunosuppression or until CD4 cell count increases above 200/μl. Due to a potential stem cell toxicity, it is recommended to begin TMP/SMX after engraftment in patients with stem cell transplantation. In case of intolerance, oral dapsone (100 mg/day), aerosolized pentamidine (300 mg every 4 weeks) or oral atovaquone (at least 1,500 mg/day) may be used [66].

Table 5 Recommendations for *Pneumocystis jirovecii* prophylaxis

Infection risk	Disease/therapy	Level of evidence
Strong evidence for increased risk ^a - ALL - Prolonged CD4 <200/μl - Long-term steroids ^b	TMP/SMX for the duration of therapy or until CD4 > 200/μl	A-I
Risk status not entirely conclusive - R-CHOP; BEACOPPesc - Prolonged neutropenia - Acute myeloid leukemia - High dose cytarabine	TMP/SMX for the duration of therapy	C-III
Consider PCP prophylaxis when recommended by the manufacturer (for example temozolomide and radiation)		

^aIncreased risk: if incidence greater than 3.5 % (NNT 15)

^bIncluding patients without neutropenia, e.g., cerebral metastasis from solid tumor

Conflict of interest The authors have declared no conflicts of interest.

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