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Infections in the outpatient cancer care

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Infections in the outpatient cancer care

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- Guideline
- Conflict of interests

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1 Summary

Infections are a common complication in patients with hematologic and oncologic diseases, also in the outpatient setting. They lead to distressing morbidity and can delay or compromise the delivery of effective antineoplastic therapy. Identification of risk factors for complicated infections reduces morbidity and mortality. Prevention of bacterial and viral infections through drug prophylaxis and consistent vaccination are key elements of this strategy. Precise clinical evaluation of patients with febrile neutropenia enables outpatient oral empiric therapy in many cases and avoids unnecessary hospitalization.

These recommendations are based on guidelines prepared by the German Infectious Diseases Working Party (AGIHO) for the prophylaxis, diagnosis and therapy of these patients and are available as short versions in Onkopedia. They are based on systematic literature searches, a uniform assessment of the strength of evidence (Table 1), and a consensus-building process.

Table 1: Strength of evidence (ESCMID)

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 systemic 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)

2 Basics

2.1 Definition and basic information

Systemic therapy of hematologic and oncologic diseases can be performed in most cases on an outpatient basis. Even fragile, comorbid and elderly patients with tumor diseases are increasingly treated this way.

Patients with hematologic and oncologic diseases are *per se* immunosuppressed, even if no specific therapy has been administered. The risk of opportunistic infections increases with the type and intensity of specific therapy and correlates with the underlying disease, remission status and general condition of the patient. The spectrum of infectious complications is very heterogeneous and largely depends on the cellular immune status and the duration and depth of neutropenia. Infectious complications play an important role in morbidity and mortality in this population and are a major cause of therapy-associated deaths.

A large number of guidelines and recommendations for the management of opportunistic infections are available. These are usually written for specific patient populations (e.g., stem cell transplantation), for specific microbiologically confirmed infections or for a defined measure (prophylaxis or therapy). The aim of this review is to provide algorithms for prophylaxis, diagnosis and therapy of opportunistic infections in the outpatient setting. The recommendations are based on the current guidelines of the AGIHO. The algorithms apply to different constellations:

- "watch and wait" situation
- specific tumor therapy

- follow-up after treatment
- Symptom-oriented care without specific tumor therapy

The recommendations refer to adult patients.

6 Therapy and prophylaxis

6.1 Prophylaxis

6.1.1 Antibacterial prophylaxis

The indication for antibacterial prophylaxis is risk-adapted [1]. Besides the expected duration of neutropenia (see Table 2), additional clinical factors play an important role in assessing the risk of complicated infections, see Table 3.

Table 2: Estimation of the risk of febrile complications as a function of the duration of neutropenia

Clinical situation	Intention	Intervention	SoR[1]	QoE[1]
Neutropenia >7 days	Estimation of the risk for febrile neutropenia	High risk	A	I
Neutropenia 7 days and clinical risk factors.[2]		High risk	B	II
Neutropenia 7 days without clinical risk factors		Standard risk	A	I

Legend:
[1] SoR =Strength of recommendation; QoE = quality of evidence;
[2] Assessment of the indication for G-CSF administration and estimation of the risk under this aspect

Table 3: Estimation of the risk of febrile neutropenia depending on clinical factors

Clinical risk factors[1]
Diagnosis and stage of the underlying disease
Type and dose of chemotherapy
First treatment cycle
Heart failure
Renal failure
Pre-existing leukopenia
Elevation of alkaline phosphatase and bilirubin

Legend:
[1] Factors independently associated with risk of febrile neutropenia in multivariate analysis.

The recommendations for the use of antibacterial prophylaxis are derived from this risk assessment. These are shown in Table 4 in relation to the clinical situation and the desired treatment goal.

Table 4: Indication for antibacterial prophylaxis depending on the treatment setting

Clinical situation	Intention	Intervention	SoR[1]	QoE[1]
High risk and 1st cycle	Avoiding fever and infection	Antibacterial prophylaxis	A	I
High risk and all other cycles			B	I
Standard risk and 1st cycle			B	I
Standard risk and all other cycles			C	I
High risk		Mortality reduction	B	II
Standard risk			C	II
Therapy with eculizumab, ravulizumab or splenectomy/with functional asplenia without effective meningococcal vaccination	Prevention of meningococcal infection	Penicillin V 250 mg b.i.d. or ciprofloxacin 1 x 500 mg/day until 4 weeks after vaccination or documentation of protective titers	A	II_u

Legend:
[1] SoR =Strength of recommendation; QoE = Quality of evidence;

Both fluoroquinolones and cotrimoxazole can be used for antibacterial prophylaxis, see Table 5 and Table 6.

Table 5: Drugs of choice for antibacterial prophylaxis

Clinical situation	Intention	Intervention	SoR	QoE
Neutropenic patients with an indication for antibacterial prophylaxis	Avoidance of febrile neutropenia or death	Preference for FQ as drug when prophylaxis is indicated	A	I
	Avoidance of febrile neutropenia or death	Preference for a therapeutic dose of TMP-SMX as drug, when prophylaxis is indicated, is	B	II_t
	Avoidance of febrile neutropenia or death	Selective gut decontamination preferred vs. systemically acting antibacterial agents	*	
	Reduction of side effects	FQ preferred compared to TMP/SMX	A	II
	Avoidance of febrile neutropenia or death	Ciprofloxacin or levofloxacin as the FQ of choice	A	II
	Avoidance of febrile neutropenia and gram- positive infections	Combination of FQ with a substance active against gram-positive pathogens	D	II
Neutropenic patients with indication for antibacterial prophylaxis and known colonization with multidrug-resistant bacteria	Avoidance of febrile neutropenia or death	FQ prophylaxis for known colonization with gram-negative multidrug-resistant bacteria	D	$II_{t, u}$

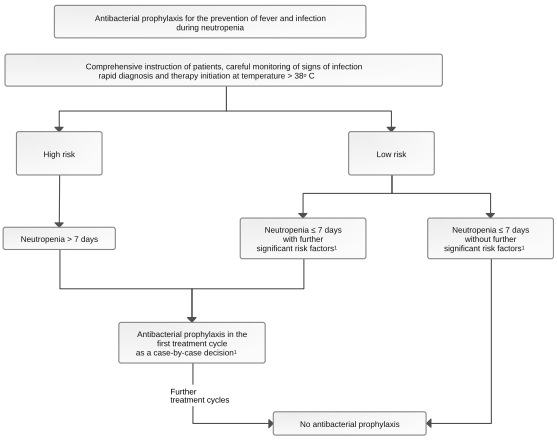
Table 6: Duration of antibacterial prophylaxis

Clinical situation	Intention	Intervention	SoR[1]	QoE
Indication for antibacterial prophylaxis and high risk for infection.	Avoidance of fever or infection	Start of antibacterial prophylaxis with the start of chemotherapy.	B	II_u
Indication for antibacterial prophylaxis and low risk for infection.		Start of antibacterial prophylaxis 5-8 days after the start of chemotherapy.	B	III
Initiation of empiric therapy with broad-spectrum antibiotics **OR** End of neutropenia	Reduction of side effects, avoidance of resistance development	Termination of antibacterial prophylaxis	A	II_u
Breakthrough infection in patients with FQ[2] Prophylaxis	Treatment of the infection	Use of FQ for empirical therapy	D	III

Legend:
[1] SoR =Strength of recommendation; QoE = Quality of evidence;
[2] FQ = Fluoroquinolone

An algorithm for the use of antibacterial prophylaxis is shown in Figure 1. Antibacterial prophylaxis can successfully reduce febrile episodes and bacterial infections in neutropenic patients, although overall survival has not been shown to improve. The indication for antibiotic prophylaxis should be critically considered because of the associated side effects and with respect to increasing resistance. Furthermore, due to the continuous influence of antibiotic application on the composition of the intestinal microbiota as well as the selection of resistant bacterial strains, it is unclear whether the positive effect of prophylaxis is maintained during serial therapy cycles. Therefore, the evidence on the efficacy of antibacterial prophylaxis was analyzed and evaluated separately between the first cycle of therapy and subsequent cycles. If, from a clinical point of view, an indication for antibiotic prophylaxis can be made solely on the basis of the reduction of fever and infection after careful consideration of the adverse effects (development of resistance, toxicity, side effects), there is a high level of evidence for its effectiveness (A I) for the first cycle of therapy. The evidence for this strategy in patients at standard risk is significantly less strong (B I). The same applies to all subsequent therapy cycles for both risk groups: in view of the development of resistance and the lack of evidence, the effectiveness of prophylaxis for the prevention of fever and infections cannot be assessed with certainty here (high-risk B I - low-risk C I).

Figure 1: Risk-adapted algorithm for antibacterial prophylaxis



Legend:
[1] First cycle of therapy
Heart failure
Renal failure
Leukocytopenia at start of therapy
Alkaline phosphatase and bilirubin elevated
Type and stage of underlying disease
Type and dose of chemotherapy

6.1.2 Pneumocystis jirovecii prophylaxis

Pneumocystis jirovecii pneumonia is a serious complication in the treatment of hematology patients. The risk for the occurrence of this infection increases with the extent of cellular immunosuppression. A risk stratification is shown in Table 7.

Table 7: Risk factors for Pneumocystis jirovecii pneumonia

High risk	Intermediate risk	Special indication
• Acute lymphoblastic leukemia • Allogeneic stem cell transplantation • Long-term steroid therapy >20 mg q.d.[1] prednisone equivalent >4 weeks • Fludarabine + cyclophosphamide + rituximab	• R-CHOP14 or BEACOPP escalated • Nucleoside analogs • Whole brain irradiation + high dose steroids. • CD4 cell count <200 /µL	• Alemtuzumab • Idelalisib • Whole brain irradiation + temozolomide.

Depending on the clinical risk, drug prophylaxis can be performed [1]. A selection of possible drugs in relation to the clinical question is shown with the corresponding recommendation grade in Table 8 and Table 9.

Table 8: Indication for prophylaxis of Pneumocystis jirovecii pneumonia

Clinical situation	Intention	Intervention	SoR[1]	QoE[1]
High risk	Prophylaxis of the infection	TMP/SMX[2]	A	I
Intermediate risk			C	III
Special indication			A	$II_{u,\ t}$
High risk	Mortality reduction	TMP/SMX	A	II_{r}
Low risk			C	III

Legend:
[1] SoR =Strength of recommendation; QoE = Quality of evidence;
[2] Trimethoprim-Sulfamethoxazole (Cotrimoxazole)

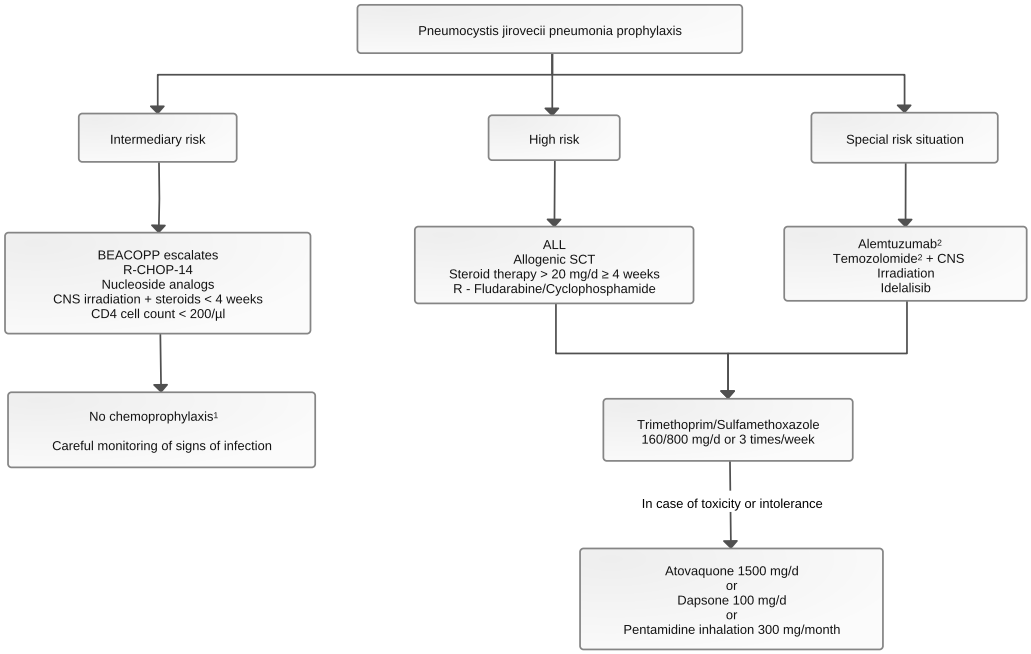
Table 9: Drugs recommended for prophylaxis of Pneumocystis jirovecii pneumonia

Clinical situation	Intention	Intervention	SoR[1]	QoE[1]
Indication for PjP[2] Prophylaxis	PjP prevention	TMP-SMX as the agent of first choice	A	$II_{t,\ r}$
		One 80/400 mg tablet daily or one 160/800 mg tablet either daily or three times a week	B	II_{t}
	Patients with intolerance[3] of or severe side effects from TMP-SMX.	Atovaquone as a 2nd choice agent • 1500 mg/day	A	II_{t}
		Dapsone as 2nd choice agent • 100 mg/day	A	II_{t}
		Pentamidine (aerosolized) as a 2nd-line agent. • 300 mg monthly	B	II_{t}

Legend:
[1] SoR =strength of recommendation; QoE = Quality of evidence;
[2]Pneumocystis jirovecii pneumonia;
[3] Desensitization may be considered in cases of known intolerance to cotrimoxazole (Pyle RC et., J Allergy Clin Immunol Pract, 2014, 2(1):52 - 8. [2]

The algorithm in Figure 2 outlines the prophylaxis of PjP infection according to the risk assessment.

Figure 2: Risk-adapted algorithm for prophylaxis of PjP infection



Legend:
[1] Deviating recommendations in tumor-related guidelines, if applicable
[2] see technical information in package insert

6.1.3 Antifungal prophylaxis

Invasive fungal infections are very rare outside the treatment of acute leukemias or in the context of allogeneic stem cell transplantation. The reason for this is the short duration of neutropenia, which is usually less than seven days in the treatment of solid tumor patients. These patients are therefore at standard risk of neutropenic infectious complications.

There is no general indication for antifungal prophylaxis in this patient population. Local antifungal prophylaxis of oropharyngeal or esophageal Candida infections may be indicated for long-term use (≥ 4 weeks) of glucocorticoids or during radiation or radiochemotherapy of head and neck or esophageal carcinomas.

6.1.4 Antiviral prophylaxis

6.1.4.1 General

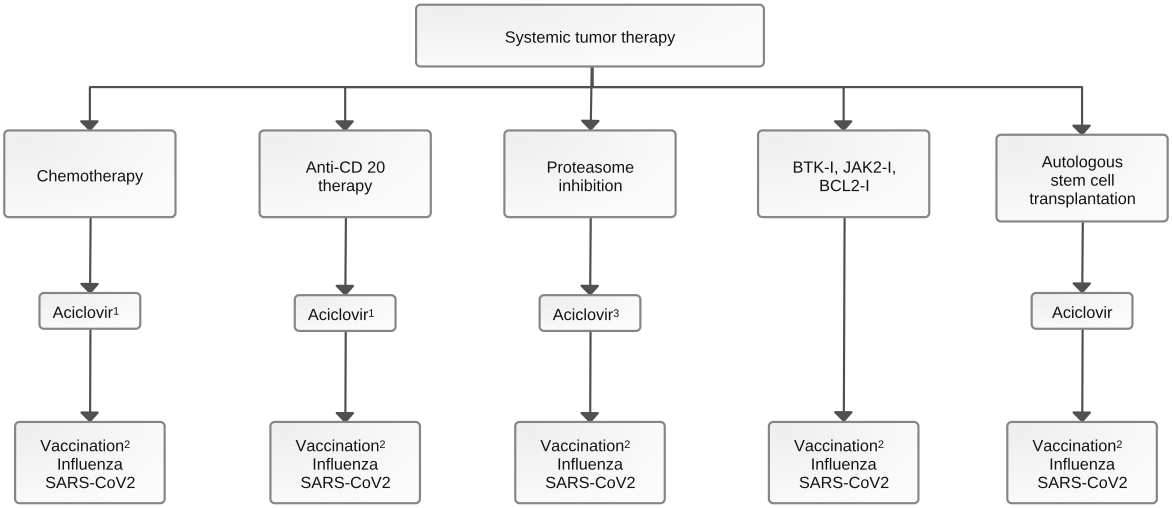
Viral infections are usually reactivations of pre-existing infections, such as hepatitis B or shingles. Primary viral infections occur primarily with respiratory or enteric viruses. The risk of reactivation correlates with the depth of cellular immunosuppression. Other risk factors include advanced age, prolonged neutropenia, advanced and uncontrolled underlying disease, and prolonged treatment with steroids. For antiviral prophylaxis in patients with hematologic/oncologic diseases outside of allogeneic stem cell transplantation, the following key principles apply in appropriate risk constellations [3]:

- the administration of aciclovir or valaciclovir for the prophylaxis of herpes zoster
- antiviral treatment to prevent reactivation of hepatitis B
- vaccination against influenza (see Onkopedia guideline Vaccinations in tumor patients).

- vaccination against SARS-CoV-2 (see Onkopedia guideline COVID-19 in patients with blood diseases and cancer)

The algorithm for antiviral drug prophylaxis is shown in Figure 3. Depending on clinical risk factors, drug prophylaxis with aciclovir or valaciclovir may be useful in specific clinical situations (AGIHO: moderate recommendation) [4].

Figure 3: Recommendations for antiviral prophylaxis

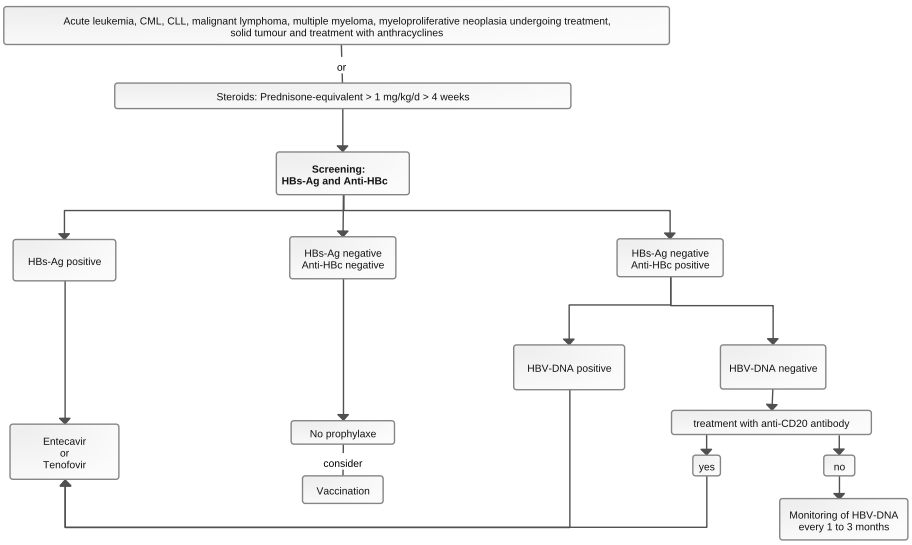


Legend:
[1] Individual risk assessment in the presence of risk factors: head and neck tumor + radiochemotherapy, steroids > 10 mg/d longer than 14 days, age > 60 years, > 1st line of therapy, therapy with bendamustine, maintenance therapy with anti-CD20 AB, history of febrile neutropenia or HSV/VZV infection.
[2] Observe boosters according to Onkopedia guideline "Vaccinations in tumor patients"
[3] Obligatory for prophylaxis of herpes zoster

6.1.4.2 Hepatitis B

Patients with hematologic diseases, especially those receiving CD20 antibodies, anthracyclines, or high-dose steroids, should be screened for previous hepatitis B infection. Depending on the serostatus, the procedure for prophylaxis is selected [3]. Recommendations for screening and prophylaxis are shown in Figure 4.

Figure 4: Recommendations for hepatitis B screening and prophylaxis



6.1.4.3 Vaccinations

Prevention of infectious complications is an important element in the reduction of morbidity and mortality from tumor therapy. In addition to avoidance of exposure and to drug prophylaxis, vaccination is an effective measure in prevention. The vaccination strategy depends on the extent of immunosuppression as a consequence of the underlying disease, the specific tumor therapy and the current vaccination status of the patients [5].

In principle, vaccinations with live vaccines should be avoided in immunocompromised patients. Vaccination with inactivated vaccines is usually safe. An overview of the recommendations for vaccination of hematological-oncological patients against specific pathogens is given in Table 9.

Patients receiving anti-CD20 therapy must be considered separately. The resulting B-cell depletion persists for at least 6 months after completion of treatment. However, B-cell function is necessary to establish an adequate vaccination response, therefore vaccination can only be useful after recovery of the humoral immune response. Vaccination strategy should follow these two main principles:

- Vaccination of patients against SARS-CoV-2 is definitely recommended.
- All vaccinations should be carried out according to individual benefit assessment. Household contacts of tumor patients should also be motivated to update their own vaccination protection. The protective effect of herd immunity for tumor patients is of primary importance if patients themselves cannot be vaccinated.

The evidence basis of the implementation of vaccination varies. Recommendations are summarized in Table 10.

Table 10: Disease-specific vaccination strategies

Pathogen	Acute leukemia	Lymphoma, Multiple Myeloma, Myeloproliferative Neoplasms	Solid tumors
Diphtheria	B-II$_t$[1]	A-II$_t$	A-II$_t$
Haemophilus influenza type B	C-II$_t$	C-II$_t$	C-II$_t$
Herpes zoster	-	A-II$_t$	B-I
Influenza	A-II$_{t,\ u}$	A-II$_t$	A-II$_t$
Hepatitis A	B-II$_t$	B-II$_t$	B-II$_t$
Hepatitis B	A-II$_t$	B-II$_t$	B-II$_t$
Measles[2]	B-II$_t$	B-II$_t$	B-II$_t$
Meningococci	C-III	C-III	C-III
Mumps[2]	B-II$_t$	B-II$_t$	B-II$_t$
Pertussis	B-II$_t$	A-II$_t$	A-II$_t$
Pneumococci	A-II$_t$	A-II$_t$	A-II$_t$
Rubella[2]	B-II$_t$	B-II$_t$	B-II$_t$
Tetanus	B-II$_t$[1]	A-II$_t$	A-II$_t$
Varicella[2]	C-III	C-III	C-III
SARS-CoV-2	B-III	A-II$_t$	A-II$_t$

Legend:
[1] Strength of recommendation and level of evidence,
[2] vaccination with live MMRV (measles, mumps, rubella, varicella) vaccines should not be performed (D-IIt); recommendation BIIt refers to vaccination after definitive cytoreductive treatment OR use of a dead vaccine, if applicable.

6.1.5 Febrile neutropenia

Fever in neutropenia is a major risk factor for morbidity and mortality after cytoreductive therapy and necessitates the immediate initiation of empiric antibiotic therapy. Fever in neutropenia is a hematologic emergency [6].

A microbiologically confirmed infection is practically never present at the time of fever onset. A thorough clinical examination to search for a source of infection is indispensable in order to be able to administer a calculated ("preemptive") antimicrobial therapy against a typical spectrum of pathogens, if appropriate. If no suspicious findings are found here either, the diagnosis is fever of unknown origin (FUO). This is treated empirically [6].

6.1.5.1 Diagnostics

Recommendations for diagnostics in patients with febrile neutropenia are summarized in Table 11.

Table 11: Recommendations for the diagnosis of febrile neutropenia

Patients	Intention	Intervention	SoR[1]	QoE[1]
Febrile neutropenia	Identify infection focus	Medical history and physical examination	A	III
Febrile neutropenia	Document bacteremia	2 separate blood cultures before starting antimicrobial therapy.	A	II
Febrile neutropenia with CVC	Search for venous catheter infection	Take blood culture peripherally and centrally	A	II
Febrile neutropenia without respiratory distress	Search for pneumonia	Conventional chest radiograph	D	II
Febrile neutropenia with respiratory distress	Search for pneumonia	Thoracic CT scan (without contrast media)	B	III
Persistent febrile neutropenia > 96 h	Search for pneumonia	Thoracic CT scan (without contrast media)	B	II

Legend:
[1] SoR =Strength of recommendation; QoE = Quality of evidence;

6.1.5.2 Risk stratification

The main risk factor for the occurrence of febrile neutropenia and the associated complications is the duration of neutropenia [6]. Therapy-related neutropenia in outpatient tumor patients usually does not last longer than 7 days. These patients are therefore at standard risk for the occurrence of febrile neutropenia. Other risk factors include age, performance status, type and remission status of the underlying disease, extent of prior therapy, and comorbidity (impaired function of vital organ systems). Patients who are expected to have neutropenia for longer than seven days are considered to be at high risk for complicated febrile neutropenia. This is usually the case in patients with acute leukemias undergoing induction and consolidation therapies and allogeneic stem cell transplantation. The procedure for febrile neutropenia in this population requires inpatient care and is therefore not the subject of this guideline. We refer to the current AGIHO guideline on empirical antimicrobial therapy [6] and to the specific recommendations for suspected sepsis [7].

Patients who are expected to have neutropenia for ≤ 7 days may also be managed as outpatients with oral empiric antibiotic therapy under certain conditions. Numerous clinical parameters associated with a low risk of febrile complications help to assess the likely course of febrile neutropenia, see Table 12.

Table 12: Patients with febrile neutropenia - low risk (standard risk according to MASCC)

Parameter
Controlled underlying disease
ECOG status 0 or 1
Mild disease symptoms
Outpatients
Temperature < 39°C
Inconspicuous chest X-ray
Respiratory rate < 24/min
No chronic obstructive pulmonary disease
No diabetes mellitus
Inconspicuous neurological status
No relevant blood loss
No dehydration
No previous fungal infection
Normal serum albumin

The Multinational Association of Supportive Care in Cancer (MASCC) has established a risk score based on individual factors [8], see Table 13.

Table 13: MASCC score in febrile neutropenia

Characteristic	Weight
Febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic neoplasm without prior fungal infection	4
No dehydration, no indication for parenteral fluid replacement	3
Febrile neutropenia with moderate symptoms	3
Outpatient	3
Age <60 years	2

Validation of the score showed that patients with a score above 20 (73% of the total group) could be assigned to a low/standard risk cohort. The rate of complications was 6%, and the rate of death was 1%. 39% of patients with a score of <21 (27% of the total group) had complicated FN and a case fatality rate of 14%. Thus, these patients are at high risk for an unfavorable outcome of FN.

6.1.5.3 Therapy of febrile neutropenia at standard risk based on the MASCC score

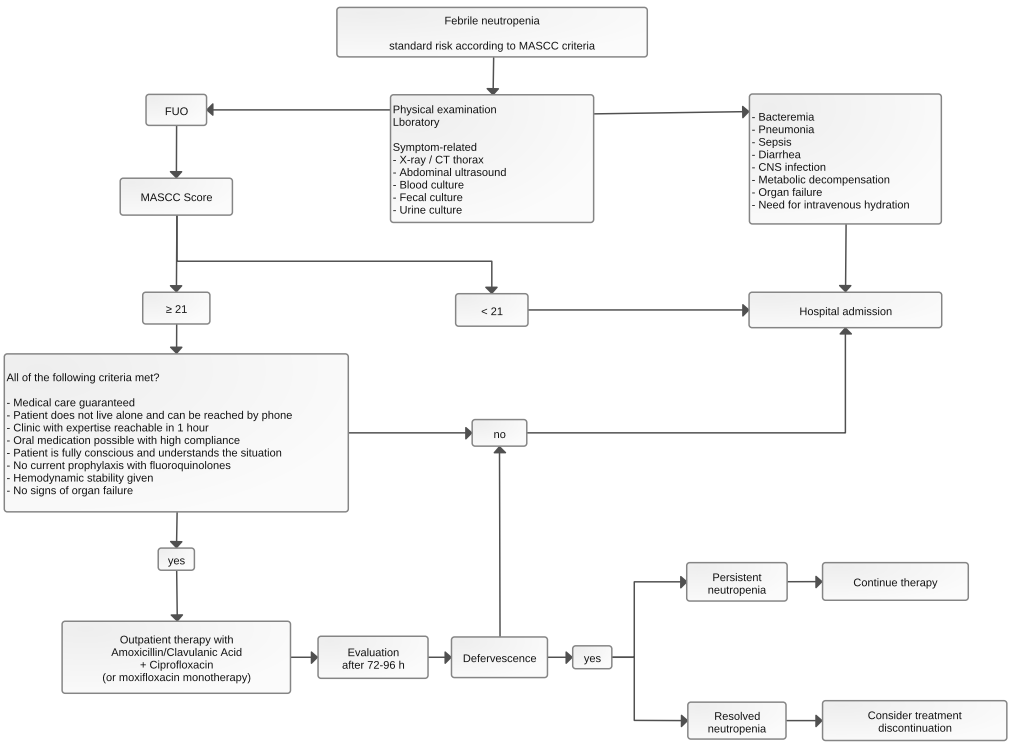
The MASCC score thus identifies patients at low risk for complicated FN using simple clinical parameters. Therefore, outpatient care can be targeted. However, further factors describing the social environment and compliance must be examined. These factors play an important role in the safe outpatient care of febrile patients. To evaluate use using a further risk checklist, see Table 14.

Table 14: Checklist for additional risk factors to assess potential outpatient therapy for febrile neutropenia

Parameter
Medical care is ensured
Patients are not alone and can be reached by phone
Clinic with hematologic-oncologic competence reachable in 1 hour
Oral medication can be safely administered with high compliance
Patients are fully conscious and understand the clinical situation
No prophylaxis with fluoroquinolones performed
Hemodynamic stability
No signs of organ failure

Consistent interrogation and assessment of risk leads to an algorithm for identifying patients with febrile neutropenia who can be referred to outpatient therapy, see Figure 5.

Figure 5: Algorithm for the outpatient treatment of patients with febrile neutropenia



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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Maschmeyer, Georg	Klinikum Ernst von Bergmann gGmbH Potsdam	**No**	**No**	**No**	**Yes** Vorträge und/oder Moderation von Symposien: Merck-Serono, Gilead Sciences, AstraZeneca, GlaxoSmithKline, Forum für Medizinische Fortbildung, RG Medizinische Fortbildung, MedUpdate, Uniklinik Kiel, Uniklinik Leipzig, Landesapothekerkammer Baden-Württemberg, OSHO Services	**No**	**No**	**No**
Rieger, Christina	Conflict of interest declarations pending							
Sandherr, Michael	MVZ Penzberg, Starnberger Kliniken GmbH	**Yes** Roche, BMS, Lilly	**No**	**No**	**Yes** Roche, BMS, Lilly	**No**	**No**	**No**

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

[2] - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

[3] - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

[4] - Relates to drugs and medical devices.

[5] - Honoraria for lecturing and training activities or paid authors or co-authorships on behalf of a company in the health care industry, a commercially oriented contracting institute or an insurance company.

[6] - Financial support (third-party funds) for research projects or direct financing of employees of the institution by a

company in the health care industry, a commercially oriented contract institute or an insurance company.

[7] - Other financial relationships, e.g., gifts, travel reimbursements, or other payments in excess of 100 euros outside of research projects, if paid by an entity that has an investment in, license to, or other commercial interest in the subject matter of the investigation.

[8] - Personal relationship with an authorized representative(s) of a healthcare company.