The Dutch Working Party on Antibiotic Policy (SWAB) recommendations for the diagnosis and management of febrile neutropenia in patients with cancer

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1. Summary and rationale of current guideline

Fever is often the only sign of onset of infection in the neutropenic patient. In case of fever, prompt initiation of adequate empirical antimicrobial therapy reduces the risk of morbidity and mortality. To provide evidence-based recommendations for treatment of neutropenic patients with fever, we sourced all relevant clinical guidelines published since 2010 (Appendix A). If there was no consensus in these guidelines, we performed a systematic search of the recent literature (2010-2020). This guideline aims to provide clinicians guidance in choosing the best antibiotic strategy for patients with chemotherapy-induced febrile neutropenia in The Netherlands. When available, recommendations in this guideline distinguish between high- and standard-risk episodes and between pediatric and adult patients.

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2. Questions answered in this guideline

For this guideline a number of key questions was formulated. These questions were all separately investigated for patients with high-risk neutropenia (absolute neutrophil count (ANC) < 0.5 * 10^9/L neutrophils for > 7 days). And for standard-risk neutropenia (ANC < 0.5 * 10^9/L for ≤ 7 days). Questions were investigated separately for both children and adults.

1. For which patient groups is the current guideline written?
2. What are the most common microbiological causes of febrile neutropenia?
3. What is the most suitable empirical treatment for febrile neutropenia?
4. How is treatment adjusted in case of clinical or microbiological diagnosis?
5. What is the optimal duration of treatment for fever of unknown origin (FUO)?
6. What is the predictive value of surveillance cultures for infections with multi-resistant bacteria?
7. What are the indications for removal of central venous catheters in patients with febrile neutropenia?
8. What is the role for granulocyte colony-stimulating factor (G-CSF) in treatment of febrile neutropenia?
9. What additional investigations should be done to rule out an infection in patients with FUO?

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3. Synopsis of recommendations

1. For which patient groups is this guideline written?

Recommendation	Strength	Quality of evidence
1. Recommendations in this guideline are based on literature in which patients with chemotherapy induced neutropenia are included. No evidence-based recommendations can be made for febrile patients with neutropenia due to disease (e.g. MDS or aplastic anemia) or non-chemotherapeutical agents (e.g. hypomethylating agents, venetoclax).	Strong	High
2. Fever is defined as a temperature of ≥ 38.3 °C measured once, or ≥ 38.0 °C measured multiple times during one hour. For practical implementation, treatment threshold of 38.5 °C may be used.	Strong	Very low
3. Definition of neutropenia is absolute neutrophil count < 0.5 * 10^9/L.	Strong	High
4. Chemotherapy induced neutropenia in adults may be divided in standard-risk vs. high-risk based on expected duration of neutropenia. Standard-risk: ≤ 7 days, high-risk > 7 days.	Strong	Very low

3. What is the most suitable empirical treatment for febrile neutropenia?

Recommendation	Strength	Quality of evidence
1. Adult patients with fever of unknown origin (FUO) and high-risk neutropenia should be treated with monotherapy with one of following beta-lactam antibiotic drugs with antipseudomonal activity: 1st choice: Ceftazidime 2000mg q8hr Cefepime 2000mg q8hr Piperacillin-tazobactam 4000/500mg q6hr 2nd choice: Meropenem 1000mg q8hr Imipenem-cilastatin 500/500mg q6hr	Strong	High
2. Since no reliable risk stratification can be made, all children with FUO should be treated with one of following beta-lactam antibiotic drugs with antipseudomonal activity: 1st choice: Ceftazidime Cefepime Piperacillin-tazobactam 2nd choice: Meropenem Imipenem-cilastatin For dosages, see *www.kinderformularium.nl*	Strong	Low

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3. In adults with FUO and standard-risk (e.g., ≤ 7 days expected) neutropenia, antibiotic treatment should be based on clinical burden and severity of illness as quantified using Multinational Association for Supportive Care in Cancer (MASCC) score or equivalent.	Strong	High
4. Adult patients with FUO during standard-risk neutropenia and a high MASCC score indicating low risk for serious complications can be treated with: Amoxicillin-clavulanate 500/125mg p.o. q8hr + ciprofloxacin 500mg p.o. q12hr, or with moxifloxacin 400mg p.o. q24hr monotherapy.	Strong	High
5. In patients with central venous catheters (CVC), addition of empirical Gram-positive coverage (e.g., glycopeptide or oxazolidinone such as vancomycin or linezolid) is only recommended when infection of the CVC is clinically apparent.	Strong	High
6. In hemodynamically instable patients that are admitted to the ICU, vancomycin may be added in patients in which a CVC is present prior to development of fever.	Moderate	Very low
7. Adult patients with FUO and standard-risk neutropenia and a low MASCC score, indicating high risk for serious complications should be treated as per the local treatment protocol for sepsis.	Strong	Very low
8. Indication for empirical treatment with antifungal agents for covering of yeast infections (e.g. *Candida*) should be restricted to settings with high local incidence of invasive non-mold fungal infections in patients with high burden of disease (e.g. ICU admission, enterocolitis) in combination with one or more of following: Persistence of fungal spp. in surveillance culture Patient has not received antifungal prophylaxis	Adult: Moderate Children: Moderate	Adult: moderate Children: very low

4. How is treatment adjusted in case of clinical or microbiological diagnosis?

Recommendation	Strength	Quality of evidence
1. In patients with a probable clinically apparent infectious origin for fever, antimicrobial coverage of empirical therapy should be expanded to include targeting of causative pathogens for that specific infection.	Strong	Moderate
2. When fever is possibly caused by a clinically apparent infection, and no microbiological investigations identify a specific pathogen, antibiotic treatment should be streamlined according to this infection after 48 hours of initial empirical therapy, after resolution of fever in a patient that is clinically stable.	Weak	Very low (Expert opinion)
3. In case of neutropenic enterocolitis, antibiotic treatment is expanded to cover anaerobic bacteria when initial empirical therapy has no antianaerobic activity (e.g. addition of	Strong	Low

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metronidazole 500mg q8hr in case of initial ceftazidime or cefepime treatment).		
4. Upon identification of a causative organism from blood cultures, prompt adjustment of initial empirical therapy is advised. Gram positive bacteria should be interpreted with caution due to the risk of contamination.	Strong	Very low (Expert opinion)

5. What is the optimal duration of treatment for FUO?

Recommendation	Strength	Quality of evidence
1. If no fever persists, blood cultures are negative and the patient is clinically stable, empiric therapy should be discontinued after a total treatment duration of 48 hours (and revert to prophylaxis).	Strong	Low
2. In patients that remain hospitalized and are clinically stable with negative blood cultures but with persisting fever: consider discontinuation of antibiotic treatment (revert to prophylaxis).	Weak	Very low

6. What is the predictive value of surveillance cultures for infections with resistant bacteria?

Recommendation	Strength	Quality of evidence
1. In patient colonized with third generation cephalosporin resistant *Enterobacterales* or resistant *P. aeruginosa* empirical antimicrobial treatment in high-risk neutropenia should be adapted to cover these bacteria.	Strong	Very low

7. What are the indications for removal of central venous line in patients with febrile neutropenia?

Recommendation	Strength	Quality of evidence
1. Removal of a CVC is advised in all patients with fever and no medical requirement for the CVC.	Strong	Low
2. Removal of CVC in case of catheter associated blood stream infections should be in concordance with CLABSI guideline.	High	Very low

8. What is the role for granulocyte colony-stimulating factor (G-CSF) in treatment of febrile neutropenia?

Recommendation	Strength	Quality of evidence
1. Treatment with G-CSF as adjunctive modality in febrile neutropenia yields no survival benefit or reduction in infection related mortality at a cost of more adverse effects and is therefore not routinely recommended.	Strong	High

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9. What additional investigations should be done to rule out an infective focus in patients with FUO?

Recommendation	Strength	Quality of evidence
1. In neutropenic patients with fever, routine conventional chest radiography (CXR) is not recommended.	Strong	Moderate
2. Obtain imaging (CXR or CT) within 24 hours in patients with clinical signs and symptoms of pneumonia. A CT-scan is preferred due to a higher sensitivity.	Adult: Strong Children: Strong	Adult: Low Children: Moderate
3. Urine culture should be performed when a urinary tract infection (UTI) is clinically suspected or the patient has a history of recurrent UTI's.	Weak	Low

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Febrile episode	Treatment[$]	Additional considerations	Streamline/adjust	Discontinue
Adults: **High-Risk Neutropenia** (duration of neutropenia > 7 days) **Children:** (all duration of neutropenia)	1st choice: Ceftazidime 2000mg q8hr Cefepime 2000mg q8hr Piperacillin-Tazobactam 4000/500mg q6hr 2nd choice: Meropenem 1000mg q8hr Imipenem-Cilastatin 500/500 mg	Suspected CLABSI/ICU transfer → Remove CVC. If CVC removal is not possible: add glycopeptide/ oxazolidones ICU transfer: no information on 3GCR** colonization → consider expanding/escalating. Clinical apparent infectious origin → Expand antimicrobial coverage of empirical therapy to include targeting of causative pathogens***	Identification of a causative organism → prompt streamlining/adjustment Clinically apparent focus , clinically stable, no microbiological identification → streamline after 48 hours.	>48 hours of empirical therapy, clinically stable, negative blood cultures: Without fever: Discontinue empirical antibiotics (revert to prophylaxis) Persistent fever: Consider discontinuation of empirical antibiotics****
Adults: **Standard-Risk Neutropenia** (duration of neutropenia ≤ 7 days)	**High risk (low MASCC score)** Per protocol sepsis of unknown origin. **Low risk (high MASCC score)** Amoxicillin-Clavulanate 500/125 mg p.o. q8hr + ciprofloxacin 500mg p.o. q12hr. Moxifloxacin 400mg p.o. q24hr.			

[$] for dosages in children, see www.kinderformularium.nl
*this dose differs from the EUCAST recommended therapeutic dose for treatment of invasive *P. aeruginosa* infection, for rationale see chapter 3.
**3GCR: third-generation-cephalosporin resistance (e.g. ampC or ESBL). This is only relevant in case a cephalosporin is used.
***Skin: Gram-positive coverage (e.g. flucloxacillin); CVC: Gram-positive coverage including CNS (e.g., glycopeptide or oxazolidinones such as vancomycin or linezolid); neutropenic enterocolitis: anaerobic coverage (e.g. metronidazole).
****In case of neutropenic enterocolitis, no streamlining or discontinuation is advised except for addition of gram positive coverage based on blood cultures.

Figure 1 flow chart for treatment

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4. Introduction

The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch Society for Infectious Diseases, the Dutch Society for Medical Microbiology, and the Dutch Association of Hospital Pharmacists, coordinates activities in the Netherlands aimed at optimization of antibiotic use, containment of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By means of the evidence-based development of guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own, local antibiotic policy. SWAB yearly reports on the use of antibiotics, on trends in antimicrobial resistance and on antimicrobial stewardship activities in The Netherlands in NethMap (available from www.swab.nl), in collaboration with the National Institute for Public Health and the Environment (RIVM-CIb).

Purpose and scope of this guideline

Patients that suffer from neutropenia as a result of chemotherapeutic treatments are at high risk for infectious complications resulting in significant morbidity and mortality [1]. Fever may be the only clinical symptom at the onset of infection and should prompt rapid initiation of empirical treatment with broad-spectrum antimicrobial therapy. This treatment reduces the risk of death for patients with febrile neutropenia [2]. There are currently no Dutch national guidelines available to guide the choice of empirical antimicrobial therapy in this patient population, leading to a variety of empirical therapy approaches across The Netherlands [3].

This guideline aims to provide clinicians guidance in choosing the best antibiotic strategy for patients with febrile neutropenia.

5. Methodology

The guideline committee consisted of members delegated by their respective professional bodies; the Dutch Society for Infectious Diseases, Dutch Society for Medical Microbiology, Dutch Society for Hematology, Dutch Society for Medical Oncology, Dutch Association of Hospital Pharmacists, and Dutch Society for Pediatrics. No patient input was sought for the development of this guideline. After consultation with the members of these professional societies, the definitive guideline was drawn up by the delegates and approved by the board of SWAB.

This guideline was developed according to the Dutch Antibiotic treatment Working Group (Stichting Werkgroep Antibioticabeleid, SWAB) tool guideline development and the AGREE-II tool for guideline development [4, 5]. The guideline committee consulted the European Committee on Antimicrobial

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Susceptibility Testing (EUCAST) breakpoints and their respective dosages for antimicrobial susceptibility. Empirical therapy advices were based on standard dosages that cover treatment of most pathogens, but often are not advised for therapy of invasive infections with *Pseudomonas aeruginosa*. In case clinical trials consistently used other dosages, these were advised (which was the case in imipenem-cilastatin, also see chapter 3). Nine clinically relevant research questions with subquestions were formulated based on committee members' clinical experience.

As literature source, the committee used a selection of clinical guidelines that had been published since 2010, presented in appendix A. The recommendations concerning the preformulated research questions in these guidelines were compared to each other and provided the basis for this new SWAB guideline. Comparisons were made on three levels: the recommendation itself, the strength of the recommendation and the level of evidence. Whenever source guidelines had high level of agreement, advice was adopted. Discrepancies between the guidelines lead to a new literature search.

For the review of the literature, references quoted in the respective guidelines were complemented with published articles on the subject found in PubMed up until 1-1-2020. Search terms were used (see appendix B for details) and all articles were screened based on title and abstract for full text review. Full text review of selected articles was carried out by a subgroup of at least three people of the guideline committee, which led to a recommendation that was plenary discussed by the full guideline committee and adopted after consensus was reached.

For classification of the strength of the recommendation the GRADE system was used [6]. The GRADE system is a method of classifying quality of evidence and the strength of the accompanying recommendation. The strength of recommendations was graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (Figure 2). Quality of evidence is inherently linked to the strength of the recommendation: higher quality evidence leads to more certainty on effect of the intervention.

GRADE[6]

Strength of recommendation	Quality of evidence
Strong	High
Weak	Moderate
	Low
	Very low

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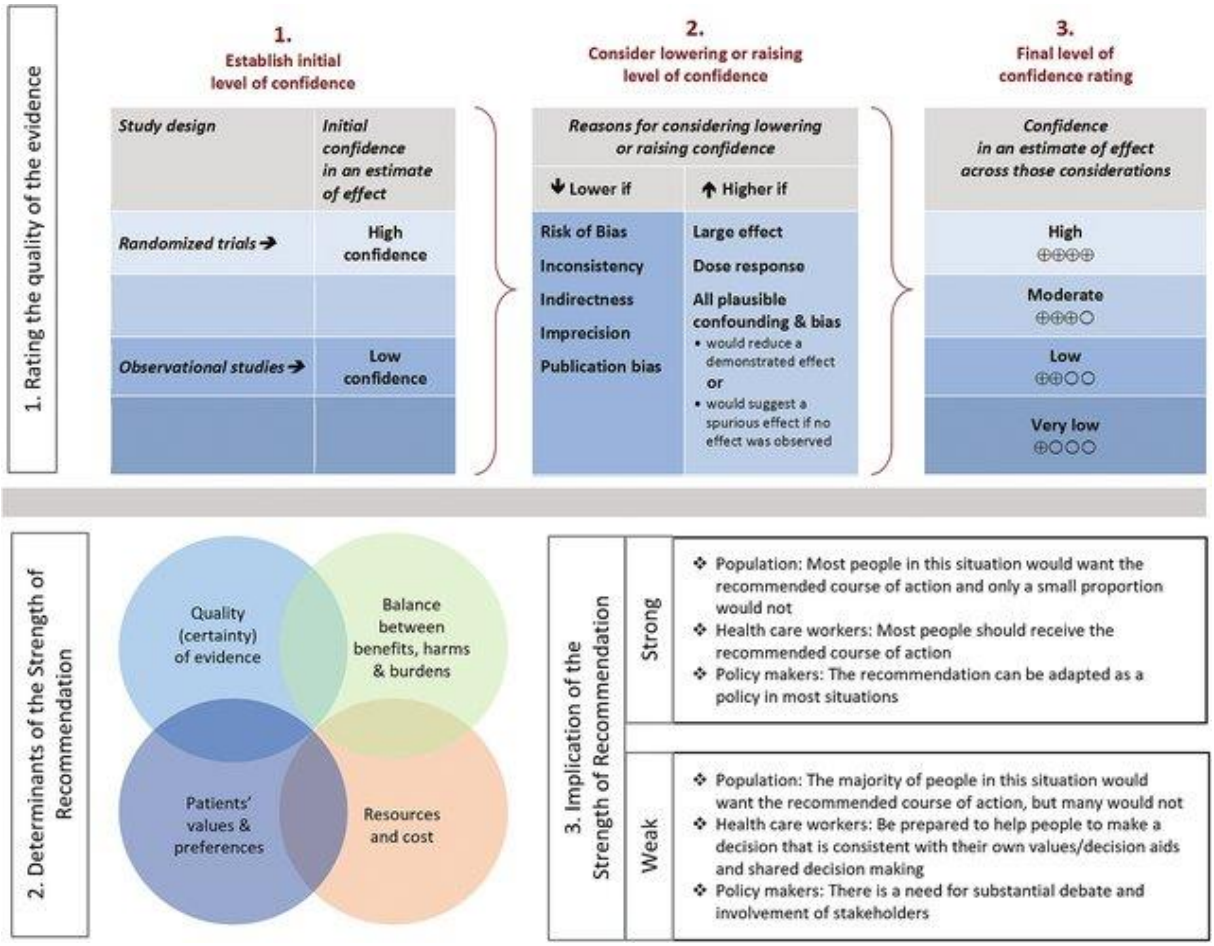


Figure 2. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

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6. Guideline content

1. *Scope of the guideline/For which patient groups is this guideline written?*

1.1 Chemotherapy-induced neutropenia

During neutropenic episodes, the innate immune response against microbial disease is largely attenuated and fever may be the sole symptom of a life-threatening infection. Although neutropenia may result from myriad causes such as bone marrow failure, auto-immune disease or congenital syndromes, best recognized and studied causes of neutropenic episodes -during which fever should promptly be treated- result from myelosuppressive chemotherapy [1, 7, 8]. Treatment with these agents causes not only myelosuppression, but may also result in mucositis. Febrile episodes in patients that suffer from the combination of a disrupted epithelial barrier in combination with lack of neutrophils has been extensively investigated. In contrast, no trials have been performed in febrile neutropenic patients in which neutropenia results from causes other than chemotherapy. Therefore, the recommendations given in this guideline are applicable foremost to the classical chemotherapy-induced neutropenia population. For neutropenic patients treated with agents that are not categorized as classical chemotherapeutical agents (e.g., but not limited to hypomethylating agents (HMA) or venetoclax) or in whom neutropenia results from hematological disease (e.g., but not limited to MDS, aplastic anemia or cytokine release as seen upon treatment with CAR-T cells), no recommendations can be made based on clinical trials, and treatment should be tailored individually.
To distinguish between high- and standard-risk neutropenic episodes, depth and duration of neutropenia is most often used. Often, high-risk patients receive prophylactic antibiotics, are hospitalized for the total duration of the neutropenic period for supportive treatment of cytopenias and mucositis, and are at higher risk for non-bacterial causes of infections such as invasive fungal disease. Whenever possible, advice in this guideline distinguishes between high- and standard-risk episodes. Moreover, when possible, recommendations distinguish between pediatric and adult patient populations.

1.2 Fever

In clinical guidelines and trials on the topic of febrile neutropenia, the definitions of fever and methods by which body temperature is measured are not consistent. Most consistently, fever is defined as a temperature measured orally of ≥ 38.3 °C measured once, or as ≥ 38.0 °C lasting for at least 1 h or measured twice within 12 h [9]. The guideline committee recognizes that a pragmatic approach of defining fever as a temperature of ≥ 38.5 °C at one time point is often employed and long-term experience with this approach has confirmed its safety.

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1.3 High- and standard-risk neutropenia

Pre-emptive risk stratification for infectious complications can be done by anticipating the depth and duration of neutropenia [10]. We utilized the following definition of high-risk versus standard-risk neutropenia in adults [9].

High-risk: absolute neutrophil count (ANC) < 0.5 * 10^9/L or an ANC that is expected to decrease to < 0.5 * 10^9/L over the next 48 hours with an expected duration of neutropenia > 7 days

Standard-risk: ANC < 0.5 * 10^9/L or an ANC that is expected to decrease to < 0.5 * 10^9/L over the next 48 hours with an expected duration of neutropenia ≤ 7 days

Patients assigned to the standard-risk group may exhibit individual characteristics, such as critical illness, justifying escalation of antibiotic treatment. We therefore propose different treatment for patients in which admission to the intensive care unit (ICU) is required for support of the febrile episode (see paragraph 3.5).

In absence of a generally accepted risk-score for children and little data on oral outpatient treatment, there is no distinction between standard-risk and high-risk neutropenic episodes in children with FUO.

Recommendation	Strength	Quality of evidence
1. Recommendations in this guideline are based on literature in which patients with chemotherapy induced neutropenia are included. No evidence-based recommendations can be made for febrile patients with neutropenia due to disease (e.g. MDS or aplastic anemia) or non-chemotherapeutical agents (e.g. hypomethylating agents, venetoclax).	Strong	High
2. Fever is defined as a temperature of ≥ 38.3 °C measured once, or ≥ 38.0 °C measured multiple times during one hour. For practical implementation, treatment threshold of 38.5 °C may be used.	Strong	Very low
3. Definition of neutropenia is absolute neutrophil count < 0.5 * 10^9/L.	Strong	High
4. Chemotherapy induced neutropenia in adults may be divided in standard-risk vs. high-risk based on expected duration of neutropenia. Standard-risk: ≤ 7 days, high-risk > 7 days.	Strong	Very low

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2. *Most common microbiological causes of febrile neutropenia*

In case of fever in the neutropenic patient microbiological documentation is only possible in 20–30% of the cases and blood cultures are positive in 10–25% with a blood stream infection (BSI) incidence as high as 13–60% in myeloablative hematopoietic stem cell transplantation (HSCT) recipients [11-13]. In studies describing prevalence of bacteremia, patients were included with both fever of unknown origin as well as with fever in the context of clinically apparent foci [14-24]. These studies can thus be used to identify pathogens that are found in blood cultures of these patients, but specific prevalence and distribution in cases of fever of unknown origin (which is the most common cause of antibiotic treatment) is largely unknown.

Staphylococcus aureus is a rarely encountered pathogen during febrile neutropenia, (0-3%, Table 1 and 2 which includes patients with clinical symptoms other than fever) and infection is most often accompanied by clinical symptoms involving skin or central venous catheter. *S. aureus* is thus an infrequent cause of fever of unknown origin.

2.1 Most common microbiological causes of febrile neutropenia in high-risk neutropenic adult patients

A summary of trials describing microbiological results of adult high-risk febrile neutropenic patients with and without antibiotic prophylaxis was made (Table 1) [15-19, 25]. Gram-positive bacteria were most frequently (3-31%) identified in high-risk neutropenic patients, in all [15-18, 25, 26] but one study [19]. In comparison, Gram-negative bacteria were less frequently found. The proportion of patients with febrile neutropenia with Gram-negative pathogens in blood cultures differed between the group receiving antibiotic prophylaxis (with fluoroquinolones) compared to the group without prophylaxis; 1-8% in patients with and 4-13% in patients without antibiotic prophylaxis. Of the study patients, 0-4% had positive blood cultures for *P. aeruginosa* (Table 1).

2.2 Most common microbiological causes of febrile neutropenia in high-risk neutropenic pediatric patients

In high-risk neutropenic pediatric patients, the same distribution of pathogens was found as in the adult patients described above. In a randomized controlled trial that included 617 children with high-risk neutropenia (198 children with acute leukemia and 419 children undergoing stem cell transplants) the likelihood of bacteremia between those receiving levofloxacin prophylaxis was compared to those without prophylaxis [14]. Gram-positive bacteremia was most frequent with viridans group streptococci as most common pathogens. None of the children receiving levofloxacin prophylaxis developed a *S. aureus* bacteremia. Prophylaxis with levofloxacin reduced Gram-negative bacteremia (GNB) from 34 without prophylaxis to 11 in the groups with prophylaxis.

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		Gram-positive bacteria, n (%)	*S. aureus, n (%)*	**Gram-negative bacteria, n (%)**	*P. aeruginosa, n (%)*	**Fungal**	**Total N**
Chong 2011 Adult	With prophylaxis (N = febrile neutropenic episodes)	**51 (6.7)**	2 (0.3)	**9 (1.2)**	2 (0.3)	**N/A**	**762**
	Without prophylaxis (N = febrile neutropenic episodes)	**71 (7.6)**	2 (0.2)	**75 (8.1)**	23 (2.5)	**N/A**	**931**
Garnica 2014 Adult	With prophylaxis (N = patients)	**N = 28**	4 (1.8)	**N = 29**	3 (1.4)	**N/A**	**219**
	Without prophylaxis (N = patients)	**N = 24**	1 (0.9)	**N = 17**	4 (3.6)	**N/A**	**110**
Sohn 2012 Adult	With prophylaxis (N = autologous stem cell transplantation cases)	**8 (7.0)**	2 (1.8)	**5 (4.4)**	N/A	**0 (0.0)**	**114**
	Without prophylaxis (N = cycles of chemotherapy)	**10 (8.5)**	4 (3.4)	**5 (4.2)**	N/A	**1 (0.8)**	**118**
Vehreschild 2012 Adult	With prophylaxis	**1 (2.9)**	1 (2.9)	**2 (5.9)**	1 (2.9)	**0**	**34**
	Without prophylaxis	**5 (15.6)**	1 (3.1)	**4 (12.5)**	0 (0.0)	**0**	**32**
Wolska 2012 Adult	With prophylaxis	**5 (10.0)**	N/A	**4 (8.0)**	N/A	**N/A**	**50**
	Without prophylaxis	**1 (1.9)**	N/A	**7 (13.0)**	N/A	**N/A**	**54**
Alexander 2018 Paediatric	With prophylaxis	**37 (12.1)**	0 (0.0)	**11 (3.6)**	1 (0.3)	**9 (2.9)**	**306**
	Without prophylaxis	**54 (17.5)**	4 (1.3)	**34 (11.1)**	6 (2.0)	**6 (2.0)**	**307**

Table 1. Distribution of bloodstream isolates recovered from patients with or without ciprofloxacin or levofloxacin prophylaxis during neutropenia. N/A: data not available

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2.3 Most common microbiological causes of febrile neutropenia in standard-risk neutropenic adult patients

Likewise, a summary of microbiological data from trials describing standard-risk adult neutropenic patients with low risk for infectious complications, who were eligible for outpatient treatment, was made. In these studies, definition of risk was not standardized. Most studies included patients with an estimated duration of neutropenia less than 7 days and low burden of disease (these patients had a high Multinational Association for Supportive Care in Cancer (MASCC) risk index (or MASCC score), or would be expected to have a high MASCC score) (Table 2) [20-24, 27].

In this standard-risk patient population with a low burden of disease (high MASCC score) *P. aeruginosa* (≤ 1.3%) and *S. aureus* (≤ 1.2%) bloodstream infections are rare. Overall Gram-positive bacteria were more prevalent compared to Gram-negative bacteria in blood cultures from standard-risk patients, 1.6-6.4% versus 2.3-4.4%.

	Gram-positive bacteria, n (%)	*S. aureus*, n (%)	**Gram-negative bacteria, n (%)**	*P. aeruginosa*, n (%)	**Total, N**
Hidalgo 1999	5 (6.4)	0 (0.0)	3 (3.8)	1 (1.3)	78
Innes 2003	2 (1.6)	0 (0.0)	3 (2.3)	1 (0.8)	126
Kern 2013	20 (5.9)	N/A	15 (4.4)	2 (0.6)	341
Malik 1995	6 (3.6)	2 (1.2)	6 (3.6)	2 (1.2)	169
Minotti 1999	11 (6.0)	1 (0.5)	6 (3.3)	0 (0.0)	183

Table 2. Distribution of bloodstream isolates recovered from standard-risk adult neutropenic patients.

2.4 Most common microbiological causes of febrile neutropenia in standard-risk neutropenic pediatric patients

In pediatric patients, no generally accepted definition exists to identify patients with a low risk for complications and pediatric studies included in the aforementioned meta-analysis all had different in- and exclusion criteria, of which some studies included only patients with negative blood cultures and are therefore of little value.

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3. *Choice of initial empirical antimicrobial therapy/ What is the most suitable empirical treatment for febrile neutropenia?*

In patients without any sign of infection, prompt initiation of empirical therapy, awaiting blood culture results, is necessary to reduce mortality [2]. This therapy is focused on treating pathogens based on prevalence and severity of disease caused. Pathogens that cause the highest risk of severe morbidity and mortality are Gram-negative bacteria. Although *P. aeruginosa* is rarely encountered in the current age of antibiotic prophylaxis, untreated this pathogen carries high morbidity and mortality, moreover, all reference guidelines advise targeting this pathogen in empirical therapy. Thus, initial empirical therapy is foremost focused on adequate treatment of Gram-negative bacteria (including *P. aeruginosa)* with antipseudomonal beta-lactams. Empirical treatment advised in this guideline may differ from optimal therapeutic regimens for invasive infections with *P. aeruginosa* with respect to dose and mode of administration, but may be altered accordingly upon identification of this pathogen. Arguments for advised dose and mode of administration consist of toxicity, non-inferiority in randomized trials and central venous lumen occupation. This is indicated in the text below.

The most encountered Gram-positive pathogens (coagulase-negative staphylococci (CoNS), enterococci and streptococci) most often do not cause a high burden of disease or overt sepsis, and additions to empirical therapy targeting these bacteria does not lead to better outcomes in non-septic patients [28]. Of these Gram-positive pathogens, viridans group streptococci may cause more burden of disease than CoNS and enterococci and the need to empirically treat these bacteria is debated.

As stated above, occurrence of *S. aureus* in blood cultures is in most cases accompanied by additional clinical symptoms, for which additional considerations are described in chapter 4.1. Thus, additional empirical antibiotic treatment will be initiated at time of treatment.

3.1 High-risk neutropenic episodes

The practice of treating with antipseudomonal beta-lactam antibiotics dates from the 1960s when *P. aeruginosa* emerged as a common cause of blood-stream infection in the immunocompromised. Despite a declining incidence since, *P. aeruginosa* remains a serious cause of bacteremia with a very high mortality rate, ranging from 18% to 61% in neutropenic patients in more recent literature [29, 30]. When comparing antipseudomonal beta-lactam monotherapy treatments, the most recent Cochrane meta-analysis showed that - besides cefepime - carbapenems, ceftazidime and piperacillin-tazobactam have comparative efficacy and toxicity and can all be used for febrile neutropenia [31]. Although all-cause mortality was lower with piperacillin-tazobactam versus all other antibiotics, no statistical significant difference was found for infectious-related mortality and clinical failure overall [31].

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Cefepime

The possible excess mortality of cefepime demonstrated in an earlier meta-analysis was not confirmed by a data re-evaluation performed by the US FDA, which resulted in maintenance of the FDA approval for cefepime [32-34]. Difficulties with interpretation of the earlier mentioned meta-analysis included that although cefepime treated patients had slightly but significantly increased mortality, no infection related mortality difference was demonstrated. Moreover, the cefepime dose used in several of the studies was lower than the currently advised cefepime dose based on EUCAST. Based on this re-evaluation and extensive clinical experience, all but one of reference guideline have included cefepime as primary empirical treatment, with none recommending against. Cefepime is a fourth generation cephalosporin with broad coverage of Gram-negative bacteria including *P. aeruginosa* and *ampC* carrying *Enterobacterales* such as *Enterobacter* spp. Moreover, cefepime is effective against streptococci (including streptococci with reduced penicillin sensitivity) and methicillin sensitive *S. aureus*. It is not effective against anaerobic bacteria and ESBL producing *Enterobacterales*. Even though cefepime has been used internationally for more than 25 years it has only recently been registered in The Netherlands for treatment of patients with fever and neutropenia and other indications. Several Dutch hospitals have adopted its use since.

Ceftazidime

Although initial empirical therapy is foremost focused on treating Gram-negative bacteria, the more limited coverage of Gram-positive bacteria by ceftazidime should be addressed, since no EUCAST breakpoints are provided for the treatment of *S. aureus* and streptococci. As stated previously, initial treatment of *S. aureus* is not required in patients without clinical symptoms indicating CVC or skin infection and initial treatment of streptococci is debated, since streptococcal infections, just as CoNS or enterococcal infections, often have low clinical burden. Furthermore, the advised dosage of ceftazidime of 2000mg q8h potentially provides adequate coverage of wild-type viridans streptococci based on pharmacokinetic/pharmacodynamic (PK/PD) data. In addition, treatment with ceftazidime was found to be non-inferior compared to piperacillin-tazobactam, cefepime, or carbapenems [31], and empirical addition of agents targeting Gram-positive bacteria (e.g. glycopeptides, beta-lactams and other) did not result in better patient outcomes, although treatment failure (including requirement to start additional treatment upon identification of pathogens) was increased [28]. The combination of low virulence, antistreptococcal activity of ceftazidime, and clinical non-inferiority, support the recommendation of ceftazidime as a viable agent for the treatment of high-risk neutropenic patients.

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Aminoglycosides

A large number of trials, summarized in a systematic meta-analysis, evaluated the use of aminoglycoside-containing combination therapy compared to antipseudomonal monotherapy. No advantage has been identified for the combination regimens, although toxicity emanating from these agents can occasionally be problematic [35-37]. For children with high-risk febrile neutropenia, intravenous monotherapy with antipseudomonal beta-lactams was found to be similarly appropriate [38].

Mode of infusion

In non-neutropenic patients with sepsis, current guidelines advise extended or continuous infusion of specific beta-lactam antibiotics to optimize achievement of appropriate pharmacokinetic/pharmacodynamic (PK/PD) targets [39]. It has been advocated that PK/PD targets may be higher in patients without alternative defense mechanisms, such as neutropenic patients [40], and administration by prolonged infusion may yield the highest chances of reaching the required targets. Moreover, in febrile neutropenic patients with hematological malignancies, certain underlying conditions may alter the pharmacokinetics of hydrophilic antibiotics such as beta-lactams, further compromising pharmacodynamic target attainment for *P. aeruginosa* and *Enterobacterales* using standard intermittent infusion regimens [41]. Administration by prolonged infusion may be imperative to reach the required PK/PD target, with both extended and continuous infusion having proven to be successful dosing strategies in pharmacokinetic studies with antipseudomonal beta-lactams [41-45]. Clinical data on effects of the beta-lactam infusion mode in neutropenic patients, however, are scarce. A retrospective study showed that 4-hr extended infusion of meropenem led to better clinical outcome than conventional intermittent infusion [46]. It was independently associated with clinical success at day 5, fewer additional antibiotics, faster defervescence and more rapid decrease of C-reactive protein but no differences in length of hospital stay or mortality were found. A randomized open label trial performed in Israel has studied efficacy of extended infusion of ceftazidime and/or piperacillin-tazobactam versus bolus infusions in the neutropenic patient population. In this study it was shown that extended infusion was superior in reaching a composite endpoint of clinical infectious response. No differences were found analyzing any of the single components of the outcome (defervescence, clinical failure, antibiotic switch, persistent BSI, mortality, length of hospitalization)[47]. Another study comparing extended (3 hour) infusion of cefepime to standard 30 minute infusion reported a shorter time to defervescence in neutropenic patients with fever receiving extended infusion, but no differences were found for clinical success, in-hospital mortality, length of hospital stay, and need for additional antimicrobials [48].

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Currently, a multicenter, open label, randomized, superiority clinical trial is being conducted in hematological neutropenic patients treated with cefepime, piperacillin-tazobactam, or meropenem to assess the clinical efficacy of extended versus intermittent beta-lactam infusion [49]. Based on the clinical evidence available, continuous or extended infusion treatment modalities are advised in septic patients. For non-septic patients, while awaiting further scientific evidence, mode of treatment infusion (bolus, continuous or extended infusion) can preferably be advised. When using continuous infusion, a loading dose should be administered in order to rapidly achieve adequate serum concentrations.

Carbapenems

In an era of increasing antimicrobial resistance, restricting the use of carbapenems is considered good practice and antimicrobial resistance can be threatening on the population level as well as for the individual patient [50]. Benefits of carbapenems emanate from its broad antibiotic spectrum (including activity against 3rd generation cephalosporin resistant (3GCR, e.g. ampC and ESBL) *Enterobacterales*, methicillin-sensitive *S. aureus*, and viridans group streptococci, and the equal efficacy compared to other antipseudomonal beta-lactam antibiotics in the treatment of febrile neutropenia). The broad spectrum of carbapenems may result in reduced requirement of additional antibiotic agents, which in turn could cause medication interactions or toxicity. Its disadvantages, encompassing collateral damage to the (intestinal) microbiome that is caused by the use of unnecessary broad-spectrum antibiotics, is increasingly recognized. In particular, use of carbapenems may be associated with selection of multidrug-resistant bacilli, predisposition to fungal infections and development of *Clostridioides difficile* associated diarrhea [51-54]. However, in addition to reduced prescription of carbapenem antibiotics, antibiotic stewardship depends on proper indication and timely discontinuation of antibiotics. Local bacterial epidemiology, prevalent resistance patterns and patients risk factors for infection caused by resistant bacteria (e.g., ESBL-colonization), should be taken into account when selecting an agent for empirical antibiotic therapy. Based on these considerations, a majority of the guideline committee members favored the recommendation of non-carbapenem agents (ceftazidime, cefepime, piperacillin-tazobactam) as a 1st choice for the treatment of neutropenic patients during high-risk episodes. Carbapenems (meropenem, imipenem-cilastatin) are 2nd choice. The advised dose of imipenem-cilastatine (500mg/500mg q6hr) differs from the dose that is advised according to EUCAST for treatment of *P. aeruginosa* (1000mg/1000mg q6hr). Reasons for this discrepancy are that the lower dose is most often used in clinical studies evaluating efficacy of imipenem-cilastatin, in which efficacy was equal to all other advised beta-lactams. In addition, increasing the imipenem-cilastatin dose may result in increased toxicity (most notably nephrotoxicity) while adequately targeting a larger proportion, but not all wildtype *P. aeruginosa* strains. These data

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caused the commission to advise a dose of 500mg/500mg q6hr. Upon identification of *P. aeruginosa* in blood cultures, treatment should be altered accordingly.

In conclusion, we recommend to use any of the following beta-lactam antibiotic drugs with antipseudomonal activity for adult patients with FUO and high-risk neutropenia and all children with FUO: 1st choice: ceftazidime 2000mg q8hr; cefepime 2000mg q8hr; piperacillin-tazobactam 4000/500mg q6hr. 2nd choice: meropenem 1000mg q8hr; imipenem-cilastatin 500/500mg q6hr. Dosages for children should be altered according to age and weight (www.kinderformularium.nl).

3.2 Standard-risk neutropenic episodes – risk assessment

For standard-risk neutropenic patients, oral and outpatient treatment can be considered if there is an individual low-risk for serious complications. To aid risk identification for the individual patient the following risk scores are frequently recommended by international guidelines: Multinational Association for Supportive Care in Cancer (MASCC) risk index [55], the Talcott risk-scoring system [56], or the Clinical Index of Stable Febrile Neutropenia (CISNE). For patients with solid tumors, the CISNE is recommended, and some guidelines suggest performing CISNE scores in all patients in which MASCC scores indicate low risk for complications (ASCO/IDSA 2018) [57]. Although different risk-scores may thus be used, most experience is obtained with the MASCC score, and a score of 21 or higher may support the notion that the patient is at a low risk of complications. Furthermore, trials using this score included patients with both solid tumors and hematological malignancies, making it a simple scoring method that can be performed in all emergency departments (the MASCC scoring system is available in a number of online calculators such as on mdcalc.com).

The ASCO guideline for pediatric patients with febrile neutropenia cited 6 different risk-scores that rely on a single assessment at presentation and that have been validated in different pediatric populations, but were unable to clearly recommend any single prediction rule [58-64]. In addition, these scores were not used in trials examining oral outpatient treatment in children at low risk for complications. Due to the absence of a generally accepted risk-score for children and little data on oral outpatient treatment, all children with FUO should initially be treated with intravenous antibiotic agents.

3.3 Standard-risk neutropenic patients with a low-risk of serious complications

For low-risk neutropenic patients (standard-risk neutropenia and a high (≥ 21) MASCC score), oral antibiotic treatment is safe. Several clinical trials have demonstrated equal efficacy of the combination of amoxicillin-clavulanate in combination with a fluoroquinolone in comparison to intravenous antibiotics [21, 65, 66]. In two trials, monotherapy with moxifloxacin was also shown to be safe and

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effective [22, 67] although moxifloxacin has no activity against *P. aeruginosa* [68, 69]. Due to exceedingly low prevalence of *P. aeruginosa infections* in this low-risk patient population (≤1%) and due to the fact that patients with invasive *P. aeruginosa* infections will likely be identified by high burden of illness, there is no clear preference between moxifloxacin or the combination of amoxicillin-clavulanate plus ciprofloxacin [22]. In settings with a high prevalence of 3GCR *Enterobacterales* and fluoroquinolone resistance, inpatient treatment with a carbapenem should be considered in low-risk neutropenic patients [70]. In The Netherlands, national surveillance data (Nethmap) on inpatient departments shows a background fluoroquinolone resistance of *Enterobacterales* and non-fermenters of 4-14% (ciprofloxacin resistance of *E. coli, K. pneumoniae, P. mirabilis, E. cloacae* complex*, P. aeruginosa* and *Acinetobacter* spp.) and an estimated percentage of ESBL carrying *E. coli* and *K. pneumoniae* of 6-9% [71]. Considering the Dutch antimicrobial resistance rates, both the combination of amoxicillin-clavulanate plus ciprofloxacin, or moxifloxacin monotherapy can be used in this population. In patients that have gastrointestinal complaints, a once-daily single pill regimen as with moxifloxacin may be regarded as more favorable, but drug interactions may cause prolonged QTc-time.

Although fluoroquinolone prophylaxis is not advised in non-high risk neutropenic patients that generally have short duration neutropenia, in selected cases, patients may still receive such treatments. Since all oral treatment regimens contain a fluoroquinolone, oral outpatient treatment is not recommended for patients in which fever develops during prophylactic treatment with fluoroquinolones. These patients should be regarded as at high risk for complications, and hospital admission and intravenous antibiotic treatment is advised.

In conclusion, we recommend to treat adult patients with FUO and standard-risk neutropenia and a high MASCC score, indicating low risk for serious complications, with the combination of amoxicillin-clavulanate 500/125 mg p.o. q8hr plus ciprofloxacin 500mg p.o. q12hr, or with monotherapy moxifloxacin 400mg p.o. q24hr.

3.4 Standard-risk neutropenic patients with a high-risk of serious complications

Patients with standard risk neutropenic episodes that are at high risk for complications (e.g. MASCC score of <21) usually have a high burden of disease. Often, therapy that causes short term neutropenia (< 7 days) results in mild mucositis and thus alternative foci that are at the root of their problems should be investigated. Epidemiology of pathogens in this patient group is elusive, since these patients are almost invariably excluded from trials and form a small subgroup. Often, these patients require medical support to such an extent that discharge is not possible and oral treatment in this group is not investigated nor advised. In patients that have standard risk neutropenia, *P. aeruginosa* prevalence is

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low and a number of studies have evaluated safety and efficacy of alternative treatment regimens, such as with ceftriaxone monotherapy [72], or combination therapy with ceftriaxone and gentamicin [73], confirming safety in this patient population. No specific trials have been performed on the patient population with standard risk duration (<7 days), but with high risk for complications (MASCC <21). Treatment with broad spectrum antibiotics containing beta-lactams targeting Gram-negative, but due to burden of disease also Gram-positive pathogens, is advised. This will be achieved by treatment with a regimen used for community acquired sepsis. For adjustments based on clinically apparent foci in this population, see chapter 4.1.

3.5 *Additional treatment for patients with central venous catheters*

A number of trials summarized in a systematic meta-analysis [28] have shown that empirical addition of Gram-positive coverage using glycopeptides or addition of beta-lactam antibiotics directed against Gram-positive pathogens (e.g. flucloxacillin or amoxicillin-clavulanic acid) used for treatment of febrile neutropenia does not improve clinical outcome (defined as survival or infection related mortality) at the cost of increased side effects. This only applies when there is no clear CVC entry infection. Patients included in the trials that were reviewed in this meta-analysis were not stratified according to the presence of a CVC, but the majority of the patients in the trials did have a CVC. Most bacteria associated with CVC infection that are insufficiently treated with single agent beta-lactam regimens advised for febrile neutropenia are low-virulence organisms (CoNS and enterococci) which do not require immediate empirical antimicrobial treatment. Treatment of these low-virulence pathogens can be initiated when identified from blood cultures. Therefore, additional Gram-positive coverage (e.g., but not limited to vancomycin) is reserved for settings in which infection of the CVC is clinically apparent. This recommendation does not apply to neutropenic patients admitted to the ICU, as these patients were not included in any of the trials included in the aforementioned systematic review [28].

3.6 Hemodynamically unstable neutropenic patients/neutropenic patients admitted to the ICU

Randomized controlled trials of neutropenic patients admitted to the ICU are lacking, and ICU referral is often a study endpoint. Therefore, recommendations are based on expert opinion. Moreover, most neutropenic patients that are hemodynamically unstable at presentation of fever have been excluded from clinical trials examining use of empirical antibiotic regimens. Although antipseudomonal beta-lactam monotherapy is the first choice for all high-risk neutropenic patients, guidelines commenting on the hemodynamically unstable (requiring relocation to the ICU) patients, leave room for the addition of a second Gram-negative agent or a glycopeptide [11, 12, 50, 64, 74-76]. The IDSA guideline

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only recommends to broaden coverage for resistant Gram-negative bacteria in hemodynamic unstable patients with persistent fever after initial doses with standard agents for neutropenic fever [11].

Evaluating the evidence for non-ICU patients, the addition of aminoglycoside, as described above, was not associated with better survival in high-risk neutropenic patients with fever. The routine addition of glycopeptides in high-risk neutropenic patients does not influence survival [28, 77]. Intravenous antipseudomonal beta-lactams remain the first-choice empirical therapy for children and high-risk neutropenic adult patients admitted to the ICU, and should be given without delay [76]. Although surveillance cultures adequately display colonization with resistant *Enterobacterales* and *P. aeruginosa*, these cultures may not have been routinely performed. Therefore, in order to target these bacteria (e.g. 3GCR *Enterobacterales* and *P. aeruginosa)* in patients with lack of adequate surveillance cultures, potential escalation of the beta-lactam regimen, or addition of a second agent targeting Gram-negative bacteria may be considered based on clinical grounds. Furthermore, in neutropenic hemodynamically unstable (requiring ICU admission) patients with a CVC, the addition of a glycopeptide or oxazolidinone (e.g., vancomycin, teicoplanin, linezolid) to treat possible CLABSI with CoNS or enterococci may be considered, pending microbiological results. Empirical treatment for non-mold fungal infections (e.g., *Candida* spp.) can be considered in settings associated with increased prevalence of non-mold fungal infections: high risk neutropenia without prophylaxis against fungal spp. or patients in which colonization with fungal spp. persist despite prophylaxis, especially when accompanied by mucositis. Starting treatment with empirical *Candida*-active agents (e.g., echinocandins) should only be considered in patients with high burden of disease (e.g., ICU admission, enterocolitis) in settings with high local incidence.

There is no evidence supporting a difference in the treatment of sepsis and septic shock in patients with neutropenia compared to non-neutropenic septic patients. We therefore recommend to treat adult patients with FUO and standard-risk neutropenia and a low MASCC score (indicating high risk for serious complications) as per the local treatment protocol for sepsis [39].

Recommendation	Strength	Quality of evidence
1. Adult patients with fever of unknown origin (FUO) and high-risk neutropenia should be treated with monotherapy with one of following beta-lactam antibiotic drugs with antipseudomonal activity: 1st choice: Ceftazidime 2000mg q8hr Cefepime 2000mg q8hr Piperacillin-tazobactam 4000/500mg q6hr 2nd choice: Meropenem 1000mg q8hr	Strong	High

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Imipenem-cilastatin 500/500mg q6hr		
2. Since no reliable risk stratification can be made, all children with FUO should be treated with one of following beta-lactam antibiotic drugs with antipseudomonal activity: 1st choice: Ceftazidime Cefepime Piperacillin-tazobactam 2nd choice: Meropenem Imipenem-cilastatin For dosages, see *www.kinderformularium.nl*	Strong	Low
3. In adults with FUO and standard-risk (e.g., ≤ 7 days expected) neutropenia, antibiotic treatment should be based on clinical burden and severity of illness as quantified using Multinational Association for Supportive Care in Cancer (MASCC) score or equivalent.	Strong	High
4. Adult patients with FUO during standard-risk neutropenia and a high MASCC score indicating low risk for serious complications can be treated with: Amoxicillin-clavulanate 500/125mg p.o. q8hr + ciprofloxacin 500mg p.o. q12hr, or with moxifloxacin 400mg p.o. q24hr monotherapy.	Strong	High
5. In patients with central venous catheters (CVC), addition of empirical Gram-positive coverage (e.g., glycopeptide or oxazolidinone such as vancomycin or linezolid) is only recommended when infection of the CVC is clinically apparent.	Strong	High
6. In hemodynamically instable patients that are admitted to the ICU, vancomycin may be added in patients in which a CVC is present prior to development of fever.	Moderate	Very low
7. Adult patients with FUO and standard-risk neutropenia and a low MASCC score, indicating high risk for serious complications should be treated as per the local treatment protocol for sepsis.	Strong	Very low
8. Indication for empirical treatment with antifungal agents for covering of yeast infections (e.g. *Candida*) should be restricted to settings with high local incidence of invasive non-mold fungal infections in patients with high burden of disease (e.g. ICU admission, enterocolitis) in combination with one or more of following: Persistence of fungal spp. in surveillance culture Patient has not received antifungal prophylaxis	Adult: Moderate Children: Moderate	Adult: moderate Children: very low

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4. *How is treatment adjusted in case of clinical or microbiological diagnosis?*

4.1 Should empirical antibiotic therapy be adjusted in case of a clinically apparent focus?

In the majority of febrile episodes in neutropenic patients, no specific origin can be identified. Nevertheless, fever should always prompt clinical evaluation including patient history and physical examination, since upon finding a potential infectious focus site specific cultures may be taken and empirical antibiotic therapy may be altered. It should be taken into account that a clinically apparent infection in neutropenic patients may have other causative agents than in otherwise healthy patients (e.g., Gram-negative pathogens in skin infections[78]), and that omitting antibiotic treatment targeting Gram-negative bacteria may have an unfavorable outcome. Certain foci may require expansion of the spectrum of the initial empirical antibiotic regimen. For example, in skin infections, coverage of Gram-positive agents including *S. aureus* is warranted, especially in hospitals in which ceftazidime is the empirical treatment. For suspected urinary tract infections (UTIs) and pneumonia, no additional treatment is required, unless less common pathogens are suspected on clinical grounds (e.g., *S. aureus* pneumonia during influenza season, especially when ICU admission is necessary). Special care should be taken in case of a suspected central nervous system infection, and immediate consultation with a specialist should be initiated. Therapy should be targeted to treat a clinical apparent focus in clinically stable patients with resolution of fever after 48 hours of initial empirical therapy as addressed as in chapter 3, based upon the spectrum of microorganisms typically involved in the respective clinically documented infection.

4.2 Neutropenic enterocolitis

Severe and prolonged neutropenia may result in reduced intramucosal defense against gut pathogens and enterocolitis may develop, often resulting in abdominal pain, diarrhea and cecal wall thickening in combination with “fat stranding” on CT scan, a clinical syndrome known as neutropenic enterocolitis or typhlitis. Neutropenic enterocolitis is difficult to distinguish from or may be accompanied by enterocolitis caused by *C. difficile*, and the imminent diagnosis warrants testing for *C. difficile* in all patients [79, 80]. Anaerobes and Gram-negative organisms predominate as causative agents in neutropenic enterocolitis, and treatment regimens may consist of a combination of an antipseudomonal cephalosporin plus metronidazole, or monotherapy with piperacillin-tazobactam or a carbapenem [11]. Furthermore, vigilance for infections with yeast species is warranted for patients that suffer from neutropenic enterocolitis, see chapter 3.6.

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4.3 Should empirical antibiotic therapy be streamlined or adjusted upon retrieval of possible causative pathogens from blood culture.

Antibiotic streamlining encompasses altering the empirical broad spectrum antibiotic treatment to specific and targeted treatment, in which narrowing of the antibiotic spectrum is pursued.

Although the quality of evidence is very low, guidelines are equivocal in advising that when a causative microorganism is identified, initial antimicrobial agents should be streamlined accordingly. When altering antibiotic therapy based on positive blood cultures it is important to consider the etiologic relevance of the positive blood culture. Although Gram-negative bacteria are generally considered of etiologic relevance, the clinical relevance of Gram-positive bacteria is variable depending on the bacterial species identified and may result from contamination. Moreover, blood cultures may yield multiple findings (during high-risk neutropenia, polymicrobial findings range from 0-4.5%[25]). Therefore, caution is advised during early streamlining or altering antibiotic therapy in case of Gram-positive pathogens.

Recommendation	Strength	Quality of evidence
1. In patients with a probable clinically apparent infectious origin for fever, antimicrobial coverage of empirical therapy should be expanded to include targeting of causative pathogens for that specific infection.	Strong	Moderate
2. When fever is possibly caused by a clinically apparent infection, and no microbiological investigations identify a specific pathogen, antibiotic treatment should be streamlined according to this infection after 48 hours of initial empirical therapy, after resolution of fever in a patient that is clinically stable.	Weak	Very low (Expert opinion)
3. In case of neutropenic enterocolitis, antibiotic treatment is expanded to cover anaerobic bacteria when initial empirical therapy has no antianaerobic activity (e.g. addition of metronidazole 500mg q8hr in case of initial ceftazidime or cefepime treatment).	Strong	Low
4. Upon identification of a causative organism from blood cultures, prompt adjustment of initial empirical therapy is advised. Gram positive bacteria should be interpreted with caution due to the risk of contamination.	Strong	Very low (Expert opinion)

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5. *What is the optimal duration of treatment for FUO?*

In patients with FUO (defined as fever with a lack of microbiological or clinically documented infection), no definitive evidence on optimal duration of treatment has been published. Traditionally, prolonged treatment was proposed until resolution of neutropenia. This practice was based on the assumption that fever resulted from translocation of bacterial antigens through a damaged digestive tract. Once a focus for infection, repeated bacterial translocation would ensue [11, 81]. To date, the American and Korean guidelines adhere to this advice [11, 74] and propose that long term experience with this strategy has resulted in confirmation of its safety and efficacy. More recently, antibiotic stewardship, bacterial resistance, and other negative implications of reducing microbiome diversity, such as possible long-term effects on graft versus host disease, have resulted in the tendency to shorten treatment courses. Several authoritative guidelines advocate this strategy [9, 50, 75, 82]. A number of studies, which have been performed primarily in children, have confirmed safety of stopping antibiotic treatment after defervescence after 48 hours [83, 84]. Of note, only children that had low risk of infectious complications were included in these studies (no reasons for prolonged hospitalization, underlying cancer in remission) and these children mostly had diagnoses of which treatment would have resulted in low-risk neutropenia in adults, being reflected in absence of mortality in these studies. In adults with high-risk neutropenia, prophylactic antibiotic regimens will mostly be resumed upon discontinuation of empirical antibiotics, resulting in maintained antibiotic treatment for the duration of neutropenia in most high-risk neutropenia patients. Several guidelines advise a treatment duration with empirical antibiotics of five days after defervescence [9, 11, 82], with little evidence-based support. A number of observational publications have advocated safety of a three-day treatment course in patients that have become free of fever [85, 86] and a Spanish observational study showed that the vast majority of blood cultures become positive within the first 24 hours, obviating the need for long-term treatment in order to cover pathogens that require long culture times [87]. A recently completed Dutch trial compared a three-day treatment course with nine days of treatment with meropenem. In this trial, antibiotics were also discontinued in patients that remained febrile. Results of this study have not been published. Presumed safety of short-term regimens in combination with a preference to treat as short as possible in order to reduce antimicrobial resistance led to the recommendation to discontinue empirical antibiotic treatment in stable patients if no fever persists. Although most guidelines advise discontinuation of empirical antibiotic treatment after 72 hours in these patients, considering the fact that a very small proportion of blood cultures will yield additional findings after 24 hours of culture, stopping empirical treatment after 48 hours is advised.

In patients that remain febrile, discontinuation of empirical antibiotic treatment is under increased scrutiny. Outside the aforementioned unpublished Dutch trial, no data underlie treatment advice. In patients in which antibacterial prophylaxis is given, reverting to this prophylactic regimen may be

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prudent in clinically stable patients that remain hospitalized with the goal of reducing treatment duration of broad-spectrum empirical antibiotics and complications resulting from these agents (e.g., *C. difficile* infections, candidemia) [88, 89]. Patients that are not treated with broad spectrum empirical therapy and remain febrile should remain under close scrutiny, since other symptoms than fever (e.g. frank rigors or hypotension) should prompt re-initiation of empirical antibiotic treatment. Patients with persistent fever that is not responsive to empirical antibiotic treatment have a worse prognosis than patients in which fever abates, and in these patients, other infectious causes should be considered (e.g. but not limited to hepatosplenic yeast infections, invasive mold infections).

Recommendation	Strength	Quality of evidence
1. If no fever persists, blood cultures are negative and the patient is clinically stable, empiric therapy should be discontinued after a total treatment duration of 48 hours (and revert to prophylaxis).	Strong	Low
2. In patients that remain hospitalized and are clinically stable with negative blood cultures but with persisting fever: consider discontinuation of antibiotic treatment (revert to prophylaxis).	Weak	Very low

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6. What is the predictive value of surveillance cultures for infections with resistant bacteria?

In previous studies, the sensitivity of colonization with Multi-Drug-Resistant (MDR) bacteria for MDR-BSI in the hematologic patient population ranged from 45-91% [90-97]. With most evidence for and very high negative predictive value of ESBL-E colonization for ESBL-E bacteremia (73.9-99.8%) [90, 92, 93, 95, 96]. Two studies showed that *P. aeruginosa* colonization independent of resistance can be predictive for infection [94, 98]. The ECIL-4 guidelines conclude that colonization or infection by resistant organisms is the most important risk factor for infection with resistant pathogens [50]. Adjustment of treatment based on colonization with specific pathogens or the selection of narrow-spectrum empirical antibiotic therapy based on the absence of (resistant) pathogens in routine surveillance cultures has not been studied. Most Gram-negative bacteria are covered by the empirical antibiotic therapy recommended by this guideline (chapter 3). When patients are colonized with 3GCR *Enterobacterales* or *P. aeruginosa,* i.e. resistant to the used empirical agents, empirical antimicrobial treatment should be adjusted accordingly. Carbapenem-resistant *Enterobacterales* or *P. aeruginosa* are still very rare in The Netherlands but studies from countries with high background resistance rates (e.g. Italy and India), demonstrate the association between colonization and infection with these very resistant bacteria [99-103]. These studies also demonstrated a significant association between carbapenem resistant Gram-negative bacteria (4/5 studies included only *Enterobacterales*) and mortality. We therefore recommend to adapt empirical treatment in patients colonized with these bacteria. Due to limited data and due to possible lower virulence and weak direct attributable mortality, non-fermentative Gram-negative bacteria (other than *P. aeruginosa*) resistant to the empirical treatment regimen (e.g. *Acinetobacter* species) are not included in these recommendations and should be discussed per individual case [104].

Initial empirical treatment does not include the coverage of VRE, penicillin resistant viridans streptococci and/or *Candida* species. VRE colonization is found to be predictive of VRE infection in several studies [93, 105-109], but enterococci are not covered in empirical antibiotic regimens for febrile neutropenia due to the fact that they are of low pathogenicity. Therefore, the adjustment of antibiotic therapy due to VRE colonization is only recommended when infection with enterococci is highly suspected, or in critically ill patients (e.g., ICU admission, see chapter 3.6). Evidence for the relationship between colonization and infection with penicillin-resistant viridans streptococci is scarce and no evidence-based recommendations can be made [110, 111]. Colonization with *Candida* species, especially multiple site colonization, is found to be a risk factor for candidemia or invasive candidiasis [112-114]. However, incidence of candidemia and/or invasive candidiasis is low and therefore the coverage of *Candida* species is not included in the empirical antimicrobial therapy recommended by this guideline (chapter 2). Initiating empirical antifungal therapy may result in excess costs and treatment-related toxicities that may not be justified. Therefore, empirical therapy with antifungal

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agents is not recommend. Pre-emptive antifungal therapy should be considered in patients with high burden of disease (e.g., ICU admission, enterocolitis) in combination with one or more of following (chapter 3.2):

- Persistence of yeast species in surveillance culture
- Absence of antifungal prophylaxis

Recommendation	Strength	Quality of evidence
1. In patient colonized with third generation cephalosporin resistant *Enterobacterales* or resistant *P. aeruginosa* empirical antimicrobial treatment in high-risk neutropenia should be adapted to cover these bacteria.	Strong	Very low

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7. What are the indications for removal of CVC in patients with febrile neutropenia?

All foreign bodies carry the risk of being a source for colonization and infection and consequently may cause fever. CVCs should be evaluated for potential site of infection in a febrile episode. In all patients, CVC removal is advised if there is no medical requirement.

Five trials specifically involving neutropenic patients with CVCs have been published [115-119]. In none of these CVC removal versus maintenance is investigated in the setting of a putative CVC infection. Therefore, the recommendation on CVC maintenance versus removal and CVC salvage using antimicrobial treatment is adopted from the IDSA guideline on catheter related infections in immunocompetent patients [120, 121]. Risk balance between recurrence of blood stream infection (BSI) and removal of CVC should be made in all patients with a CVC. A lower threshold of CVC removal in neutropenic patients that have had a Gram-negative bacteremia or who are critically ill is justified. Immediate CVC removal is indicated for bacteremia with *P. aeruginosa*, *S. aureus*, and *Candida* species as per the central line-associated BSI (CLABSI), *S. aureus* bacteremia [122] and candidemia guideline [123].

Recommendation	Strength	Quality of evidence
1. Removal of a CVC is advised in all patients with fever and no medical requirement for the CVC.	Strong	Low
2. Removal of CVC in case of catheter associated blood stream infections should be in concordance with CLABSI guideline.	High	Very low

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8. What is the role for G-CSF in treatment of febrile neutropenia?

In neutropenic patients that suffer from fever, reducing the duration of neutropenia may reduce the duration of the febrile period and aid in the treatment of febrile patients. To this end, treatment with granulocyte colony stimulating factor (G-CSF) has been evaluated in patients with cancer in a number of randomized controlled trials, largely summarized in a systematic review [124]. In these studies, febrile patients were treated with antibiotics and with G-CSF, in contrast with treatment with antibiotics alone. These studies equivocally exhibited reduced length of neutropenia without beneficial effects on mortality. Although these studies have not been powered to evaluate use in specific infections (e.g., mold infections), the guideline committee advises against standard use of G-CSF as adjunctive treatment in febrile neutropenia.

Recommendation	Strength	Quality of evidence
1. Treatment with G-CSF as adjunctive modality in febrile neutropenia yields no survival benefit or reduction in infection related mortality at a cost of more adverse effects and is therefore not routinely recommended.	Strong	High

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9. *What additional investigations should be done to rule out an infective focus in patients with febrile of unknown origin?*

The initial diagnostic approach of the neutropenic patient with fever aims to establish a clinical and microbiologic diagnosis, which leads to targeted (antibiotic) treatment and thereby improving the patient's prognosis. In neutropenic patients with fever, this should at least include clinical history, physical examination and the drawing of blood cultures before antibiotic therapy is administered (peripheral and CVC).

9.1 Imaging

In patients with clinical signs and symptoms of pneumonia radiographic imaging (conventional chest X-ray radiography (CXR) or chest CT-scan) is recommended and should be obtained within 24 hours. In one study, sensitivity, specificity, positive predictive value, and negative predictive value for conventional radiography were 36%, 93%, 50% and 88%, and for low-dose CT-scan 73%, 91%, 62% and 94% respectively [125]. Therefore, chest CT-scan is the preferred modality due to the higher sensitivity and specificity [125, 126]. The optimal timing of radiological imaging is not known, in studies and in clinical practice CXR or chest CT-scan are often performed within 24 hours [125, 127].

In asymptomatic children, previous studies show that chest radiography rarely shows a pneumonia, and if CXR was not obtained no significant adverse clinical consequences were observed [38, 128-130]. The lack of consequence of the rare abnormal CXR in absence of respiratory symptoms/signs has been confirmed in adults [127, 131]. Therefore, routine radiography in the work-up of febrile neutropenia (CXR or chest CT-scan) without symptoms of a respiratory infection is not recommended. This advice specifically concerns radiography in the first 24 hours of fever and does not involve chest imaging aimed at diagnosing invasive fungal infections in patients with persistent fever.

9.2 Urine analysis

During neutropenia, the diagnosis of a UTI can be challenging, as pyuria is not a reliable parameter in neutropenic patients with UTI [132]. In addition, UTI symptoms can be atypical or even absent [133], while a positive culture may reflect contamination of colonization instead of infection. However, for the diagnosis of a UTI, a positive urine culture combined with the clinical suspicion of an UTI remains the gold standard. Furthermore, routine urine analysis in absence of complaints may result in excessive invasive procedures (as catheterization may be required in children) or therapeutic delay in absence of therapeutic consequences.

In conclusion, routine urinalysis or urine cultures are not beneficial in patients that do not exhibit urinary tract complaints and may be unnecessarily invasive (e.g., requiring catheterization). Therefore,

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in both children and adults, urine cultures are recommended only when UTI is suspected or if the patient has a history of recurrent UTIs.

Recommendation	Strength	Quality of evidence
1. In neutropenic patients with fever, routine conventional chest radiography (CXR) is not recommended.	Strong	Moderate
2. Obtain imaging (CXR or CT) within 24 hours in patients with clinical signs and symptoms of pneumonia. A CT-scan is preferred due to a higher sensitivity.	Adult: Strong Children: Strong	Adult: Low Children: Moderate
3. Urine culture should be performed when a urinary tract infection (UTI) is clinically suspected or the patient has a history of recurrent UTIs.	Weak	Low

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7. Funding and Conflict of Interest

For the development of this guideline, the SWAB was funded by the National Institute for Public Health and the Environment (RIVM-CIb), the Netherlands.

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). All members of the guideline committee complied with the SWAB policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the guideline committee were provided the SWAB conflict of interest disclosure statement and were asked to identify ties to companies developing products or other parties that might be affected by the guideline. Information was requested regarding employment, honoraria, consultancies, stock ownership, research funding, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts: Inge Baas: onkostenvergoeding Roche voor adviesraad en reisonkostenvergoeding. Others: none.

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8. Applicability and Validity

The guideline articulates the prevailing professional standard in diagnosis and management of febrile neutropenia in patients with cancer and contains general recommendations for the antibiotic treatment of hospitalized adults and children and outpatient treatment of adults. It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances in which, in the interest of proper patient care, non-adherence to the guideline is desirable.

SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, on the basis of an examination of current literature. If necessary, the guidelines committee will be reconvened to discuss potential changes. When appropriate, the committee will recommend expedited revision of the guideline to the SWAB board.

Therefore, in 2026 or earlier if necessary, the guideline will be reevaluated.

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