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

Appendix: Evidence per search question

1. For which patient groups is this guideline written?

1.1 Are there trials describing/investigating antimicrobial management in non-chemotherapy-induced neutropenic patients?

IDSA, 2011, Freifield et al.	None
Korean guideline, 2011, Lee, D.G. et al	None
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	None
AGIHO FUO, 2017, Heinz, W. J. et al	None
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	None
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: no (no recommendations are made)

Search string:
((((((antimicrobial) OR management) OR guideline)) AND (neutropen* OR neutropaen* OR granulocytopen* OR granulocytopaen*))) NOT (((((""hematology""[MeSH Terms]) OR cancer) OR chemotherapy) OR stem cell transplant) OR marrow transplant) Filters: Clinical Trial"
Publication date: 1-1-2010 to 1-1-2020
Hits: 8
Relevant hits upon screening title and abstract: None

1.2 Fever

IDSA, 2011, Freifield et al.	a single oral temperature measurement of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a 1-h period.
Korean guideline, 2011, Lee, D.G. et al	body temperature to over 38.0℃, using a tympanic thermometer, or to over 37.5℃, using an axillary thermometer

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ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	at least 38.3°C (or at least 38.0°C on two occasions)
NICE, 2013, Bate, J. et al (+ full guideline)	temperature higher than 38°C, including one isolated fever.
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h
AGIHO FUO, 2017, Heinz, W. J. et al	either a temperature measured orally of ≥ 38.3 °C once or ≥ 38.0 °C lasting for at least 1 h or being measured twice within 12 h or a method shown to be equivalent to these results may be used to define fever.
ASCO children, 2017, Lehrnbecher, T. et al	a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained over a 1-hour period.
SEOM, 2018 Carmona-Bayonas, A. et al	>38.3°C
ASCO outpatient, 2018, Taplitz, R. A. et al	a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over 1 hour.
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: Yes

1.3 Neutropenia and the definition of high- and standard-risk neutropenia

IDSA, 2011, Freifield et al.	ANC of <500 cells/mm3 or an ANC that is expected to decrease to <500 cells/mm3 during the next 48 h. The term ‘‘profound’’ is sometimes used to describe neutropenia in which the ANC is <100 cells/mm3 High-risk neutropenia: Patients with anticipated prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count [ANC] <100 cells/ mm3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Low-risk neutropenia:

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	anticipated brief (≤7 days duration) neutropenic periods or no or few comorbidities. Formal risk classification may be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system. References: yes
Korean guideline, 2011, Lee, D.G. et al	an absolute neutrophil count less than 500/mm^3 or expected to be less than 500/mm^3 within 2-3 days. To determine the risk of serious infectious diseases in febrile neutropenic patients, the risk index of the Multinational Association for Supportive Care in Cancer (MASCC) can be used. References: yes
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	an absolute neutrophil count less than 0.5 X 10^9 cells/L, or with or less than 1.0 cells/L and predicted fall to lower than 0.5 X 10^9 cells/L. The current guidelines advocate a preferred approach, which incorporates the MASCC-score, to risk stratification. References: yes
NICE, 2013, Bate, J. et al (+ full guideline)	Neutrophils 0.5×10^9/l or lower Risk assessment of septic complications: A validated scoring system should be used to assess a child's risk of septic complications. This is the modified Alexander rule in paediatric practice (see box 1). References: yes
ECIL4, 2013, Averbuch, D. et al	Recommendations for high-risk neutropenic patients only. No definition of neutropenia and high-risk was given.
ESMO, 2016, Klastersky, J. et al	an absolute neutrophil count (ANC) of <0.5 × 10^9/l, or expected to fall below 0.5 × 10^9/l.

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	High-risk patients: patients with FN who are at high risk as assessed by the MASCC criteria (<21), or have high-risk features as judged by the admitting doctor. low-risk FN patients: patients who are haemodynamically stable, do not have acute leukaemia or evidence of organ failure, and do not have pneumonia, an indwelling venous catheter or severe soft tissue infection [I, A]. Precise criteria were not defined as they varied between the trials reviewed. References: yes
AGIHO FUO, 2017, Heinz, W. J. et al	a neutrophil count (segments and bands) < 500/µl or < 1000/µl with a predicted decline to < 500/µl within the next 2 days defines neutropenia. Standard risk: expected duration of neutropenia of up to 7 days and High risk: expected duration of neutropenia of at least 8days. Those assigned to the standard-risk group may exhibit individual characteristics justifying their allocation to the high-risk population as well. These individual factors can be identified by the use of the Multinational Association of Supportive Care in Cancer (MASCC) criteria. References: yes
ASCO children, 2017, Lehrnbecher, T. et al	an absolute neutrophil count < 1,000/µL (equivalent to < 1.0 × 109/L), severe neutropenia as absolute neutrophil count < 500/µL (equivalent to < 0.5 × 109/L), and profound neutropenia as < 100/µL (equivalent to < 0.1 × 109/L). The period of neutropenia is considered protracted if it lasts for ≥ 7 days. Adopt a validated risk stratification strategy (Table 3) and incorporate it into routine clinical management (strong recommendation, low-quality evidence) References: yes

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SEOM, 2018 Carmona-Bayonas, A. et al	Neutrophil<0.5 × 109/l, or expected to fall below 0.5 × 109/l Severity is graded according to symptoms and signs, and risk assessment scores should only be applied when said signs and symptoms rule out clinical instability (see below) [III, B]. References: yes
ASCO outpatient, 2018, Taplitz, R. A. et al	Neutropenia as an ANC , 1,000/mL (equivalent to , 1.0 3 109/L), severe neutropenia as ANC , 500/mL (equivalent to , 0.5 3 109/L), and profound neutropenia as , 100/mL (equivalent to , 0.1 3 109/L). High risk: presence of clinical judgment criteria (Table 1) or MASCC score <21 (Table 2) or Talcott's groups 1–3§ (Table 3) Low risk: absence of clinical judgment criteria or MASCC score ≥21 (or Talcott's group 4) Consider outpatient management or CISNE tool (Table 4) for "low-risk" patients with solid tumors who have undergone mild- to moderate-intensity chemotherapy and appear to be clinically stable References: yes
AGIHO sepsis, 2019, Kochanek, M. et al	Neutropenia: ANC < 500/ µL or < 1000/µL with predicted decline to 500/µL within next 2 days. No definition of standard- or high-risk neutropenia. Guideline only addresses neutropenic patients with sepsis. References: no

Consensus: Yes

2. Most common microbiological causes of febrile neutropenia

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

For this chapter, data on prevalence of pathogens were extracted from the studies represented in the meta-analysis of Mikulska et al.[1] that included most recent studies (2004-2016) in which fluorochinolon prophylaxis was compared to no prophylaxis. For epidemiology in children, these data were supplemented with the seminal publication of Alexander S. et al, 2018[2].

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

For this chapter, data were extracted from studies included in the 2019 Cochrane systematic meta-analysis on "outpatient treatment for people with cancer who develop a low risk febrile neutropaenic event" by Rivas-Ruiz et al.[3] Studies on children were excluded for reasons mentioned in manuscript text. A number of studies in adults were excluded in these epidemiological data: Talcott (no data on specific pathogens)[4], Rubenstein (study not available for download or full text examination)[5].

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

3.1 High-risk and standard risk neutropenic episodes (standard risk with low risk for complications only) and risk stratification.

IDSA, 2011, Freifield et al.	High-risk patients: monotherapy with an antipseudomonal b-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is recommended (A-I). Low-risk patients may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria (A-I) Ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment (A-I). Other oral regimens, including levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin, are less well studied but are commonly used (B-III). References: yes
Korean guideline, 2011, Lee, D.G. et al	High-risk patients: Cefepime, imipenem/cilastatin, meropenem, or piperacillin/tazobactam is recommended as empirical monotherapy if the febrile neutropenic patient has no complications of infection (A-I). Ceftazidime can be considered as empiric monotherapy if the febrile neutropenic patient has no complications of infection, but clinicians should be aware of the possibility of breakthrough infections (from Gram-positive bacteria or drug-resistant Gramnegative bacteria) (B-II). Low-risk patients: The combination of ciprofloxacin and amoxicillin/ clavulanic acid is recommended as oral antibiotics for febrile neutropenic patients (A-I). The combination of ciprofloxacin and clindamycin is an acceptable alternative as oral antibiotics for penicillin-allergic patients (A-II). References: yes
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	Clinicians currently have several options for the empiric management of patients with neutropenic fever requiring hospital-based parenteral therapy: monotherapy with an anti-

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	pseudomonal beta-lactam (e.g. piperacillintazobactam, cefepime, ceftazadime or a carbapenem), or combination therapy with an anti-pseudomonal betalactam and a second agent, usually an aminoglycoside. References: yes
NICE, 2013, Bate, J. et al (+ full guideline)	Antibiotic treatment: β lactam monotherapy (eg, piperacillin-tazobactam) rather than dual therapy with an aminoglycoside (eg, gentamicin). Aminoglycosides should not be given unless there are patient specific or local microbiological indications. References: yes
ECIL4, 2013, Averbuch, D. et al	Escalation: Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) AI, Piperacillin-tazobactam AI, Other possible options include: - Ticarcillin-clavulanate, Cefoperazone-sulbactam or Piperacillin + gentamicin. De-escalation: Carbapenem monotherapy, Combination of anti-pseudomonal β−lactam + aminoglycoside or quinolone|| (with carbapenem as the β−lactam in seriously ill patients), Colistin + β−lactam ± rifampicin, Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) References: no
ESMO, 2016, Klastersky, J. et al	High-risk: Local epidemiological bacterial isolate and resistance patterns are crucially important in determining the first-choice empirical therapy, since coverage for MRSA or resistant Gram-negative bacteria may be required. A meta-analysis comparing monotherapy (e.g. an anti-pseudomonal cephalosporin like ceftazidime or cefepime, imipenem, meropenem or piperacillin–tazobactam) with combination therapy found equivalent efficacy [I, A]. This is less clear in the subsets at high risk of prolonged neutropaenia and those with bacteraemia, where the bactericidal activity and synergistic effect of a β-lactam antibiotic in combination with an aminoglycoside might be preferable; namely, in case of Pseudomonas aeruginosa sepsis or in centres with known intermediate susceptibility of Gram-negative bacilli to β-lactams. Low-risk: Single-agent quinolones (moxifloxacin) were not inferior to combinations (quinolone with amoxicillin plus clavulanic acid), but the latter are preferred given the rise in Grampositive FN episodes. References: yes

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AGIHO FUO, 2017, Heinz, W. J. et al	High-risk: Piperacillin/tazobactam, imipenem ,meropenem, cefepime or ceftazidime monotherapy. Low-risk patient: amoxicillin/ clavulanate with ciprofloxacin or monotherapy with moxifloxacin. References: yes
ASCO children, 2017, Lehrnbecher, T. et al	High-risk: monotherapy with an antipseudomonal b-lactam, a fourth-generation cephalosporin, or a carbapenem. Low-risk: consider oral antibiotics. References: yes
SEOM, 2018 Carmona-Bayonas, A. et al	High-risk: piperacillin/tazobactam, meropenem, imipenem–cilastatin, cefepime Low-risk: without prior fluorquinolones prophylaxis treat with amoxicillin–clavulanic and fluorquinolones (levofloxacin or ciprofloxacin). References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	Low-risk: fluoroquinolone (ie, ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate (or plus clindamycin for those with a penicillin allergy) is recommended. References: yes
AGIHO sepsis, 2019, Kochanek, M. et al	High-risk neutropenic patients with sepsis: initial treatment with piperacillin/tazobactam or meropenem or imipenem/cilastatin (AIII). A combination treatment with an aminoglycoside may be considered in neutropenic patients with septic shock (BIII). References: yes

Consensus: Yes

3.4 Addition of antibiotic agents for patients with CVC in situ.

IDSA, 2011, Freifield et al.	Vancomycin (or other agents active against aerobic grampositive cocci) is not recommended as astandard part of the initial antibiotic regimen for fever and neutropenia (A-I).These agentsshould beconsidered for specific clinical indications, including suspected catheter-related infection, skin orsoft-tissue infection, pneumonia, or hemodynamic instability.

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Korean guideline, 2011, Lee, D.G. et al	The use of glycopeptides as empirical antimicrobial therapy is recommended if the patient'sblood cultures are positive for Gram-positive bacteria, a catheter-related infection is suspected,there is colonization with MRSA or a history of MRSA infection, the patient has severe sepsis or shockpending the results of cultures, or the patient has a skin or soft tissue infection (A-II
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	none
NICE, 2013, Bate, J. et al (+ full guideline)	Empiric glycopeptide antibiotics (eg, vancomycin, teicoplanin) should not be offered to patients withsuspected neutropenic sepsis who have central venous access devices unless there are patient-specific or local microbiological indications
ECIL4, 2013, Averbuch, D. et al	Situations in which antibiotics vs. resistant Gram-positive bacteria is indicated to combine in the first-line regimen CIII for all. Suspicion of serious catheter-related infection e.g. chills or rigors with infusion through catheter and cellulitis around the catheter exit site or Skin or soft-tissue infection at any site
ESMO, 2016, Klastersky, J. et al	None
AGIHO FUO, 2017, Heinz, W. J. et al	Current evidence shows that the addition of anti-Gram-positive treatment, namely glycopeptides, before documentation of a Gram-positive infection, does not improve outcomes in febrile neutropenia
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	it is recommended to associate vancomycin, linezolid (of choice if the focus is either pulmonary or cutaneous, but not recommended in catheter-related infections), or daptomycin (of choice in severe patients with quick SOFA ≥ 2 points and suspicion of cutaneous or catheter focus) to initial antibiotherapy. Tigecycline should be used only as a last option

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ASCO outpatient, 2018, Taplitz, R. A. et al	Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: yes

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

IDSA, 2011, Freifield et al. References: 38-41	Hemodynamically unstable neutropenic patients with persistent fever without a clear source should have their antimicrobial regimen broadened to ensure adequate coverage for drug-resistant gram-negative and gram-positive organisms, as well as for anaerobes. This may be achieved by a change from an initial cephalosporin to an anti-pseudomonal carbapenem, such as imipenem or meropenem, as well as by the prompt addition of an aminoglycoside, ciprofloxacin, or aztreonam together with vancomycin. References: no
Korean guideline, 2011, Lee, D.G. et al	In particular, clinically unstable febrile neutropenic patients with hypotension a combination of broad-spectrum β-lactam antibiotics (imipenem/ cilastatin, meropenem, or piperacillin/tazobactam) and an aminoglycoside to extend the antibacterial spectrum and to obtain an synergistic effect against some Gram-negative bacteria. References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	Antibiotic treatment: β lactam monotherapy (eg, piperacillin-tazobactam) rather than dual therapy with an aminoglycoside (eg, gentamicin). Aminoglycosides should not be given unless there are patient specific or local microbiological indications

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	References: no
ECIL4, 2013, Averbuch, D. et al	Combination of beta-lactam (carbapenem in seriously ill patients) and aminoglycoside or quinolone (BIII) References: no
ESMO, 2016, Klastersky, J. et al	This is less clear in the subsets at high risk of prolonged neutropaenia and those with bacteraemia, where the bactericidal activity and synergistic effect of a β-lactam antibiotic in combination with an aminoglycoside might be preferable; namely, in case of Pseudomonas aeruginosa sepsis or in centres with known intermediate susceptibility of Gram-negative bacilli to β-lactams. Refences: yes
AGIHO FUO, 2017, Heinz, W. J. et al [92]. [96–98]. [99].	A combination might be useful in institutions with a high prevalence of multidrug-resistant bacteria (AIIr) [92]. An antipseudomonal beta-lactam should always be included, with an aminoglycoside or a fluoroquinolone such as levofloxacin and ciprofloxacin as the combination partner (AIIt). For standard-risk patients without critically impaired renal function, the combination of an aminoglycoside with a third- or fourth generation cephalosporin can be considered (AI) [96–98]. When aminoglycoside antibiotics are given, therapeutic drug monitoring is mandatory (AIIu) and once-daily dosing is appropriate (AIIr) [99]. References: yes
ASCO children, 2017, Lehrnbecher, T. et al	reserve the addition of a second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (strong recommendation, moderate-quality evidence). References: yes
SEOM, 2018 Carmona-Bayonas, A. et al	qSOFA ≥ 2 points associate amikacin 15–20 mg/kg/day IV (Strongly supports a recommnedation for use, evidence from at least 1 well-deigned clinical tril, without randomization) References: no

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ASCO outpatient, 2018, Taplitz, R. A. et al	Other antimicrobials (eg, aminoglycosides, fluoroquinolones, vancomycin) may be added to the initial regimen for management of complications (eg, hypotension, pneumonia) or if antimicrobial resistance is suspected or proven. References: no
AGIHO sepsis, 2019, Kochanek, M. et al	Empirical antimicrobial treatment using anti-pseudomonal broad-spectrum antibiotics must be started immediately in neutropenic patients with sepsis (AIIrt). We recommend initial treatment with piperacillin/tazobactam or meropenem or imipenem/cilastatin (AIII). A combination treatment with an aminoglycoside may be considered in neutropenic patients with septic shock (BIII). There is no evidence that sepsis and septic shock in patients with neutropenia need to be treated differently to non-neutropenic patients according to the sepsis guidelines 2016 (AIII). References: no

Consensus: no
Search string
Search terms: (((intensive care[mesh terms] OR intensive care[text word] OR "critical care"[mesh terms] OR critical care[text word]))) AND (neutropen*)
Publication date: 1-1-2010 to 1-1-2020
Hits: 477
Relevant hits upon screening title and abstract:
Ten Berg S. et al, 2019[6]
Kern W.V. et al, 2019[7]
Azoulay E. et al, 2017[8]
Blijlevens N.M.A. et al, 2017[9]
Van Beers E.J. et al, 2016[10]

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

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

4.1 Pneumonia

Table with conclusion and references per guideline

IDSA, 2011, Freifield et al.	Other antimicrobials agents active against aerobic Gram-positive cocci may be added to the initial regimen for management of pneumonia.

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	References: no
Korean guideline, 2011, Lee, D.G. et al	None
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	Risk factors for a complicated clinical course: 2. localized infection (e.g. **pneumonia**, enteritis, central venous catheter infections) Notably, ceftazidime has limited coverage for Gram-positive organisms (methicillin-susceptible staphylococci, viridans group streptococci, Streptococcus pneumoniae). If the patient deteriorates, or a resistant pathogen is isolated, therapy is 'escalated' to an antibiotic or a combination with a broader spectrum: e.g. a carbapenem plus an aminoglycoside. References: no
ESMO, 2016, Klastersky, J. et al	If pneumonia in an outpatient is diagnosed either on clinical grounds and/or on the basis of radiological imaging, antibiotic cover may be extended to treat atypical organisms such as Legionella and Mycoplasma by adding a macrolide or a fluoroquinolone antibiotic to a β-lactam antibiotic [V, D]. Consideration for infection with Pneumocystis jirovecii should be given in patients who present with high respiratory rates and/ or desaturate readily off oxygen or on minimal exertion. Predisposing factors include prior corticosteroid therapy, use of immune suppressants after organ TPL and exposure to purine analogues, as well as lack of reliable chemoprophylaxis with cotrimoxazole. References: yes
AGIHO FUO, 2017, Heinz, W. J. et al	None
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	In high-risk patients with suspicion of catheter-related infection or infection with a skin focus, pneumonia, or hemodynamic instability, it is recommended to associate vancomycin, linezolid (of choice if the focus is either pulmonary or cutaneous, but not recommended in catheter-related infections), or

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	daptomycin (of choice in severe patients with quick SOFA ≥ 2 points and suspicion of cutaneous or catheter focus) to initial antibiotherapy. Tigecycline should be used only as a last option. (II,A) References: yes
ASCO outpatient, 2018, Taplitz, R. A. et al	Additional Specific Clinical Criteria That May Be Used to Exclude Patients With Cancer Who Have Fever and Neutropenia From Initial Outpatient Care Even With a MASCC Score ≥ 21: Presence of a clear anatomic site of infection (eg, symptoms of **pneumonia**, cellulitis, abdominal infection, abnormal imaging or microbial laboratory cultures) Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. References: no
AGIHO sepsis, 2019, Kochanek, M. et al	Patients with severe neutropenia due to chemotherapy for acute leukemia or other aggressive hematologic malignancy. This subgroup of febrile neutropenic patients with LI should be treated with a broad-spectrum β-lactam with antipseudomonal activity, as used for empirical treatment of fever of unknown origin (A-II). Streptococci including cephalosporin-resistant strains must be included in the antimicrobial spectrum (**B**-II) References: yes

Consensus: no
Search string
(Lung infiltrate[Title] OR Pneumonia*[Title] OR Lung infection[Title] OR pulmonary[Title])
AND ("Neutropenia"[Mesh]) OR neutropen*[tiab])
AND (anti-bacterial agents mesh OR antibiotic*[tiab] OR meropenem[tiab] OR piperacillin[tiab] OR Tazobactam[tiab] OR cefepime[tiab] OR ceftazidime[tiab] OR metronidazole[tiab] OR flucloxacillin[tiab] OR vancomycin[tiab] OR cefazolin[tiab] OR daptomycin[tiab] OR tigecycline OR trimethoprim sulfamethoxazole OR TMP/SMX OR cotrimoxazole OR co trimoxazole OR aminoglycoside OR quinolon* OR fluorquinolon* OR macrolide
Publication date: 1-1-2010 to 1-1-2020
Hits: 132
Relevant hits upon screening title and abstract:
Di Pasquale et al. 2019[11]

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Gudiol et al. 2019[12]
Aguilar-Guisado M. et al 2011 (cross reference from pasquale et al. 2019)[13]

4.2 Urinary tract infection

IDSA, 2011, Freifield et al.	None
Korean guideline, 2011, Lee, D.G. et al	None
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	None
AGIHO FUO, 2017, Heinz, W. J. et al	None
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	Antibiotic treatment should last for at least 10–14 days in infections of the skin and soft tissue, pneumonias, and urinary tract infections (IIB) References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: no
Search string
(urinary[Title]) AND neutropen*[Title/Abstract]
Publication date: 1-1-2010 to 1-1-2020
Hits: 24
Relevant hits upon screening title and abstract:
Schneenerger C. et al, 2016[14]
Cunha B.A. et al, 2015[15]
Sandoval C. et al, 2012[16]
Crossreference from Cunha B.A. et al: Jacobs L. et al, 2006[17]

4.3 Skin infection

IDSA, 2011, Freifield et al.	Vancomycin (or other agents active against aerobic grampositive cocci) is not recommended as a standard part of the

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	initial antibiotic regimen for fever and neutropenia (A-I).These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. References: no
Korean guideline, 2011, Lee, D.G. et al	For newly observed skin lesions or those of unknown causes, biopsies should be conducted and the results of microbiological cultures and histopathological findings should be evaluated. In cases with bullous lesions on the mucous membranes or skin, the presence of herpes simplex virus (HSV) infection should be determined. The use of glycopeptides as empirical antimicrobial therapy is recommended if the patient's blood cultures are positive for Gram-positive bacteria, a catheter-related infection is suspected, there is colonization with MRSA or a history of MRSA infection, the patient has severe sepsis or shock pending the results of cultures, or the patient has a skin or soft tissue infection (A-II). Skin and soft tissue infection: 7-14 days (if Gram-negative sepsis, consider 10-14 days) References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	Situations in which antibiotics vs. resistant Gram-positive bacteria is indicated to combine in the first-line regimen CIII for all 3. Skin or soft-tissue infection at any site References: no
ESMO, 2016, Klastersky, J. et al	cellulitis. The addition of vancomycin broadens the cover against skin pathogens [V, D]. Linezolid and daptomycin are emerging alternatives to glycopeptides; however, more clinical experience is needed, especially in neutropaenic patients. References:

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	None
AGIHO FUO, 2017, Heinz, W. J. et al	A combination therapy including vancomycin or teicoplanin (DIIr) or linezolid (DIII) is generally discouraged for empirical first-line therapy [100] but might be considered in the case of (CIII) severe mucositis, skin or soft tissue infection, foreign body infection, or documented colonization of a patient with MRSA. References: no
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	In high-risk patients with suspicion of catheter-related infection or infection with a **skin focus**, pneumonia, or hemodynamic instability, it is recommended to associate vancomycin, linezolid (of choice if the focus is either pulmonary or cutaneous, but not recommended in catheter-related infections), or daptomycin (of choice in severe patients with quick SOFA ≥ 2 points and suspicion of cutaneous or catheter focus) to initial antibiotherapy. Tigecycline should be used only as a last option. (IIA) References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. References: no
AGIHO sepsis, 2019, Kochanek, M. et al	A combination therapy including vancomycin or teicoplanin (DIIr) or linezolid (DIII) is generally discouraged for empirical first-line therapy but might be considered in the case of (CIII) severe mucositis, skin or soft tissue infection, foreign body infection, or documented colonization of a patient with MRSA.

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	Clinicians should also consider whether fungal species are likely pathogens when choosing initial therapy. Risk factors for invasive fungal infections include: **Severe skin and soft tissue infections** References: no

Consensus: Yes, but no literature references.
Search string
(((((Skin) OR Soft tissue) OR cellulitis)) AND ("Neutropenia"[Mesh] OR neutropen*[tiab])) AND ((Anti-Bacterial Agents"[Mesh] OR antibiotic* [tiab] OR meropenem [tiab] OR piperacillin [tiab] OR Tazobactam [tiab] OR cefepime [tiab] OR ceftazidime [tiab] OR metronidazole[tiab] OR flucloxacillin[tiab] OR vancomycin[tiab] OR cefazoline[tiab]))
Publication date: 1-1-2010 to 1-1-2020
Hits: 150
Relevant hits upon screening title and abstract:
None

4.4 Neutropenic enterocolitis

IDSA, 2011, Freifield et al.	Patients who develop neutropenic enterocolitis should be treated with an expanded broad-spectrum regimen, although the most efficacious regimen is unknown. Because anaerobes and Gram-negative organisms predominate in causing neutropenic enterocolitis, monotherapy with piperacillin-tazobactam or a carbapenem or a combination of an anti-pseudomonal cephalosporin plus metronidazole are appropriate antibiotic regimens. There is less evidence to support routine additions of vancomycin or an antifungal agent to antimicrobial regimens. These patients should be evaluated by a surgeon in case a bowel resection is required for uncontrolled sepsis, bleeding, or ischemic bowel. References: yes
Korean guideline, 2011, Lee, D.G. et al	None
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None

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ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	None
AGIHO FUO, 2017, Heinz, W. J. et al	None
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	In high-risk patients with enterocolitis or perirrectal infection, metronidazole should be associated to a beta-lactam with antipseudomonal activity (II,A) In case of enterocolitis (typhlitis) or perirrectal infection, the previously mentioned β-lactams are active; however, given the risk of possible resistance, the recommendation is that parenteral metronidazole 500 mg/6 h be associated [II, A]. References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	In accordance with IDSA guidelines for patients with complicated abdominal infections in non-neutropenic patients and the guideline for antimicrobial therapy of unexplained fever in neutropenic patients of the AGIHO, we recommend administration of piperacillin/tazobactam or imipenem/ cilastatin or meropenem (BIII). There are no studies assessing the effect of additional metronidazole or vancomycin on patient outcome (CIII). Empirical antifungal therapy may be discussed if it has not yet been administered for the indication of persistent febrile neutropenia (BIII). The use of hematopoietic growth factors might be considered, even though corresponding evidence is not available (BIII). Antimicrobial therapy should be administered until resolution of clinical signs and neutropenia. While a surgical consultation should be obtained at an early stage of disease evolution, surgical interventions in the neutropenic and/or thrombocytopenic patient are reserved to severe cases, e.g., patients with bowel wall perforation (BIII). References: yes

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Consensus: no
Search string
neutropenic enterocolitis[ti] AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND English[lang])
Publication date: up to 1-1-2020
Hits: 25
Relevant hits upon screening title and abstract:
Cardona Zorilla A.F. et al, 2006[18]
Pugliese N. et al, 2017[19]

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

IDSA, 2011, Freifield et al.	The antibiotic spectrum can be appropriately narrowed to specifically treat the defined infection once fever has resolved. References: no
Korean guideline, 2011, Lee, D.G. et al	If the causative microorganism is identified, initial antimicrobial or antifungal agents should be changed accordingly. When the cause is not detected, the initial agents should continue to be used until the neutrophil count recovers References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	streamlining of initial therapy should be considered (Figure 2) including: i) discontinuation of any aminoglycoside, quinolone, colistin or any antibiotic directed against resistant Gram-positive pathogens, if given in combination; or ii) for patients with FUO initially treated with a carbapenem, change to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam or ticarcillin-clavulanate (the last two agents are not available in many European countries). References: no
ESMO, 2016, Klastersky, J. et al	Pathogen identified: consider specific antibacterial therapy. When the cause is

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	found, continue on appropriate specific therapy [II, A]. References: no
AGIHO FUO, 2017, Heinz, W. J. et al	If diagnostic procedures reveal a clinically documented infection or if a causative pathogen has been isolated, the empirical antibacterial approach should be changed to targeted or preemptive therapy (AIIt). Pre-emptive antimicrobial treatment is chosen according to the spectrum of microorganisms typically involved in the respective clinically documented infection (Table 4). As prospective studies for second-line antimicrobial therapy in neutropenic patients with persistent FUO under clearly specified 1st-line treatment regimens are sparse [20] recommendation of treatment modification are partially based on clinical expertise. References: yes
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	In the event of microbiological documentation, the antibiotic spectrum can be decreased depending on the focus and severity of the infection, and the antibiogram of the microorganisms identified as the cause of the infectious disease [II, A]. References: yes
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	In case of clinically stabilizing patients or detection of pathogens sensitive to ß-lactam, it is recommended to stop the aminoglycosides (AIII). References: No

Consensus: no
Search string
(antibiotic[MeSH Terms]) AND (((((((narrowing) OR (de-escalation)) OR (streamline)) OR (targeted treatment)) OR (targeted antibiotic therapy)) OR (treatment modification)) OR (sequential therap*)) AND (neutropen*)

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Publication date: 1-1-2010 to 1-1-2020
Hits: 210
Relevant hits upon screening title and abstract:
Gustinetti G. et al, 2018[21]
Mokart D. et al, 2014[22]

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

IDSA, 2011, Freifield et al.	Continue antibiotic therapy until resolution of neutropenia. There is a strong advice against discontinuation of antibiotic therapy in patients that remain febrile. If no fever persists, antibiotic therapy may be discontinued after 4-5 days.
Korean guideline, 2011, Lee, D.G. et al	In case of fever of unknown origin, antibiotic treatment is continued until resolution of neutropenia.
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	Switch from intravenous to oral antibiotic therapy after 48 hours in low risk patients (based on alexander score)
ECIL4, 2013, Averbuch, D. et al	Discontinue antibiotic therapy after 72 hours of which 48 hours are afebrile.
ESMO, 2016, Klastersky, J. et al	After 5-7 days without fever, antibiotic therapy may be discontinued when neutropenia persists.
AGIHO FUO, 2017, Heinz, W. J. et al	After a minimum of 7 days without fever, antibiotic therapy may be discontinued.
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	None
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: no
Search string: (neutropen* AND fever) AND (duration OR discontinuation) AND (therapy OR antibiotics)

Publication date: 1-1-2010 to 1-1-2020
Hits: 1258

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Relevant hits upon screening title and abstract:
Lehrnbecher T. et al, 2002[23]
Miedema K.G. et al, 2016[24]
Santolaya M.E. et al, 1997[25]
Cohen K.J. et al, 1995[26]
Stern A. et al, 2019[27],
Cornelissen J.J. et al, 1995[28]
Talcott J.A. et al, 2011[4]
Horowitz H.W. et al, 1996[29]

Conclusion

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

IDSA, 2011, Freifield et al.	11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (B-III). These include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum b-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including Klebsiella pneumoniae carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity. i. MRSA: Consider early addition ofvancomycin, linezolid, or daptomycin (B-III). ii. VRE: Consider early addition of linezolid or daptomycin (B-III). iii. ESBLs: Consider early use of a carbapenem (B-III). iv. KPCs: Consider early use of polymyxin-colistin or tigecycline (C-III). VRE colonization is an important risk factor for subsequent invasive disease. Local and even individual patient patterns of bacterial colonization and resistance must be taken into account when choosing an initial empirical regimen for neutropenic patients at a given institution.[30] References: yes
Korean guideline, 2011, Lee, D.G. et al	Other factors that should be considered in choosing initial empirical antibiotics for

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	febrile neutropenic patients include the infection site (s), **history of MRSA infection or colonization**, organ dysfunction, history of the use of antibiotics, and bactericidal effects of antibiotics. References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	Ensure ongoing surveillance of antimicrobial resistance patterns in your centre. However, factors such as local antibacterial resistance patterns and individual patient drug allergy may determine that the use of piperacillin-tazobactam monotherapy is not appropriate. References: no
ECIL4, 2013, Averbuch, D. et al	The most important risk factor for infection with resistant pathogens is prior colonization or infection by resistant organisms. This applies for ESBL- and carbapenemase-producing Enterobacteriaceae; A. baumannii, P. aeruginosa, S. maltophilia; methicillin-resistant Staphylococcus aureus (MRSA) and VRE with recent reports also in the case of colistin-resistant K. pneumoniae. References: no
ESMO, 2016, Klastersky, J. et al	None
AGIHO FUO, 2017, Heinz, W. J. et al	Colonization by ESBL, VRE, or MRSA has been associated with an increased rate of bacteremia with these pathogens. References: no
ASCO children, 2017, Lehrnbecher, T. et al	A6b. Reserve the addition of a second gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (strong recommendation, moderate-quality evidence). References: no

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SEOM, 2018 Carmona-Bayonas, A. et al	Many factors should be considered when choosing empirical antibiotic treatment in patients with FN. These include the risk of infection associated with the severity of neutropenia (low versus high risk), possible focus of infection, clinical manifestations (e.g., hypotension, sepsis, septic shock), local epidemiology, **previous infection or colonization by multidrug-resistant organisms (MDROs)**, previous use of antibiotics, and presence of allergies and potential toxicities. References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood-culture results suspicious for resistant bacteria: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), extendedspectrum b-lactamase (ESBL)–producing gram-negative bacteria, and carbapenemase-producing organisms, including Klebsiella pneumoniae carbapenemase (KPC). **Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.** MRSA: Consider early addition of vancomycin, linezolid, or, in the absence of evidence for pneumonia, daptomycin. s VRE: Consider early addition of linezolid or daptomycin. ESBLs: Consider early use of a carbapenem. KPCs: Consider early use of polymyxin-colistin or tigecycline,[31] or a newer b-lactam with activity against resistant Gram-negative organisms as a less toxic and potentially more effective alternative. References: yes
AGIHO sepsis, 2019, Kochanek, M. et al	Importantly, colonization with resistant bacteria must be considered. References: no

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Consensus: no

Search string
neutropen*[tiab] AND colonization
Publication date: 1-1-2010 to 1-1-2020
Hits: 211
Relevant hits upon screening title and abstract:
Komurcu et al, 2020[32]
Cattaneo et al, 2018[33]
Satlin et al, 2018[34]
Ferreira et al, 2018[35]
Forcina et al, 2018[36]
Sadowska-klasa et al, 2018[37]
Cornejo-juarez et al, 2016[38]
Nguyen et al, 2016[39]
Nesher et al, 2015[40]

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

IDSA, 2011, Freifield et al.	CVC removal in case of: tunnel or pocket infect. Specific pathogens in blood culture: *p. aeruginosa*, *s. aureus*, fungal pathogens, mycobacterial pathogens or in all (other) cases of persisting blood stream infections for more than 72 hours after installation of adequate therapy.
Korean guideline, 2011, Lee, D.G. et al	CVC removal in case of: specific pathogens: fungi, non-tuberculous mycobacteria, *Bacillus* spp., *Corynebacterium jeikeium, S. aureus, Acinetobacter, P. aeruginosa, Stenotrophomonas maltophilia,* and vancomycin-resistant *Enterococcus* (A-II). Clinically instable patients. Persistent BSI
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	None
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	When a catheter related infection is suspected, and the patient is stable, the catheter should not be removed without microbiological evidence of infection.

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	remove: tunnel/pocket; candidemia, mycobacterial, persisting BSI. S. aureus: balance risk.
AGIHO FUO, 2017, Heinz, W. J. et al	CVCs not indispensable for patient care should removed in case of fever.
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	None
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	CVCs not indispensable for patient care should removed in case of fever.

Consensus: yes

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

IDSA, 2011, Freifield et al.	Prophylactic use of myeloid CSFs (also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is >20% (A-II). CSFs are not generally recommended for treatment of established fever and neutropenia (B-II). References: yes
Korean guideline, 2011, Lee, D.G. et al	None
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None
NICE, 2013, Bate, J. et al (+ full guideline)	There is too little evidence to recommend the use of routine G-CSF (granulocyte-colony stimulating factor) in children to prevent neutropenic sepsis. References: no
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	Several meta-analyses indicate that primary prophylaxis with GCSF (i.e. G-CSF administered immediately after cycle 1 of

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	ChT) reduces the risk of FN by at least 50% in patients with solid tumours without significantly affecting tumour response or overall survival [I]. Most guidelines recommend that G-CSF be administered prophylactically if the risk of FN is >20% for all planned cycles of treatment [I, A]. Classifications of the risk according to the type of ChT have been published and updated. An algorithm for the decisions about primary prophylactic G-CSF use is presented in Figure 1. References: yes
AGIHO FUO, 2017, Heinz, W. J. et al	The adjunctive use if granulocyte colony-stimulating factor (G-CSF) is not recommended for routine clinical practice in febrile neutropenic patients (DIIr). If G-CSF has not been started before the onset of neutropenia, its interventional use can be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors that are predictive of poor clinical outcomes, including expected prolonged (> 10 days) and profound (< 100/µl) neutropenia, age > 65 years, uncontrolled primary disease, or hospitalization at the time of fever development (BIIr). References: yes
ASCO children, 2017, Lehrnbecher, T. et al	None
SEOM, 2018 Carmona-Bayonas, A. et al	Therapeutic use of G-CSF is recommended in patients at high risk for infectious complications, with neutropenia < 100 neutrophils/mm3 or in the presence of risk factors (age > 65, clinical instability, widespread infection, or severe complication) [1,A] References: yes
ASCO outpatient, 2018, Taplitz, R. A. et al	None
AGIHO sepsis, 2019, Kochanek, M. et al	None

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Consensus: no
Search string ((neutropen* OR neutropaen* OR granulocytopen* OR granulocytopaen*) AND (G-SCF OR (granulocyte colony-stimulating factor)) AND (mortality OR Fever)
Publication date: up to 1-1-2021
Hits: 1680
Relevant hits upon screening title and abstract:
Mahler D.W. et al, 1994[41]
Uyl-de Groot C.A. et al, 1997[42]
Clark O.A. et al, 2005[43]
Mhaskar C. et al, 2014[44]
Aktas D. et al, 2015[45]

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

9.1 Imaging

IDSA, 2011, Freifield et al.	A chest radiograph is indicated for patients with respiratory signs or symptoms (A-III). References: no
Korean guideline, 2011, Lee, D.G. et al	If a respiratory manifestation is present, a chest X-ray should be taken. Additionally, even with no symptoms, basal chest X-rays are recommended for comparison with future images when respiratory symptoms are present. Although there may be no abnormality on chest X-rays because there is no inflammatory response in neutropenic patients, approximately half of these patients can show evidence of pulmonary infiltration on chest computed tomography (CT) images. References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	A chest X-ray is indicated for patients with respiratory symptoms or signs.[46] References: no
NICE, 2013, Bate, J. et al (+ full guideline)	– Stop doing chest radiographs routinely—only if clinically indicated. Chest radiograph should only be performed if clinically indicated. References: no
ECIL4, 2013, Averbuch, D. et al	Only recommendations for diagnostic testing in patients with persistent fever. No

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	recommendations for initial diagnostic approach. Recommended strategies at 72-96 hours in various circumstances when using an escalation or de-escalation approach unless the patient deteriorated earlier or the microbiological results justify an earlier modification: Chest X-rays and eventually computed tomography (CT) scans of the lungs, abdomen, sinuses and brain. References: no
ESMO, 2016, Klastersky, J. et al	Routine investigations: Chest radiograph References: no
AGIHO FUO, 2017, Heinz, W. J. et al	At onset of fever, a CT scan of the lungs is recommended in the case of respiratory tract symptoms (BIII). Conventional chest radiographs are discouraged (DIIt), as they show abnormalities in less than 2% of febrile neutropenic patients who have no clinical signs of lower respiratory tract infection References: yes
ASCO children, 2017, Lehrnbecher, T. et al	Obtain chest radiography (CXR) only in patients with respiratory signs or symptoms (strong recommendation, moderate-quality evidence). Two additional studies have been added to the initial systematic review[47] of the use of routine CXR during the initial assessment of pediatric FN. One was undertaken in a broad cohort of patients with FN and one in children undergoing HSCT. Both demonstrated rates of pneumonia of , 3% in an asymptomatic child. Asymptomatic children who did not undergo CXR had no significant adverse clinical consequences. Thus, no change was made to the strong recommendation to obtain CXR only in patients with respiratory signs or symptoms. References: yes
SEOM, 2018 Carmona-Bayonas, A. et al	The initial assessment should include the clinical history, physical examination,

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	complete blood count, and basic biochemistry, and **chest Rx** (III, B) Perform a computerized tomography of the chest in patients with clinically relevant respiratory symptoms and inconclusive chest Rx, or in patients with persistent fever (72 h or more) and risk factors for complications (II, B) References: yes
ASCO outpatient, 2018, Taplitz, R. A. et al	The initial diagnostic approach should maximize the chances of establishing clinical and microbiologic diagnoses that may affect antibacterial choice and prognosis. A systematic evaluation should include the following: e. Chest imaging study for patients with signs and/or symptoms of lower respiratory tract infection (Type of recommendation: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate) References: no
AGIHO sepsis, 2019, Kochanek, M. et al	As already stated in the interdisciplinary consensus statement of the DGHO, Austrian Society of Hematology and Oncology (OeGHO), German Society for Medical Intensive Care Medicine and Emergency Medicine (DGIIN), and Austrian Society of Medical and General Intensive Care and Emergency Medicine (ÖGIAIN), timely recognition, **diagnostic steps,** and rapid therapy initiation are of decisive importance for the prognosis of critical ill cancer patients Independent of the clinical presentation, chest computed tomography is recommended (A-IIt) References: yes

Consensus: no
Search string
neutropen* AND (((Chest x-ray[Title/Abstract]) OR (radiography[Title/Abstract])) OR (CXR[Title/Abstract]))
Publication date: 1-1-2010 to 1-1-2020
Hits: 40
Relevant hits upon screening title and abstract:

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Pereverzeva E. et al, 2019[48]
Estacio O. et al, 2018[49]
Zaleska-Dorobisz U. et al, 2017[50]
Gerritsen M.G. et al, 2017[51]
Yolin-Raley D. et al, 2015[52]
Philips B. et al, 2012[53]

Additional question: CT versus HRCT for initial work-up. Pragmatic because eventually a HRCT is needed to detect aspergillosis?
P: High/low risk/pediatric/adult neutropenic patient with FUO/febrile e.c.i.
I: HRCT
C: CT
O: Increased diagnostic accuracy/Therapy adjustment/Pneumonia/IPA

Publication date: from 1-1-2010 to 1-1-2020
Search terms: neutropen* AND ((Computed tomography) AND (High-resolution))
Hits: 9
Relevant hits upon screening title and abstract:
Kang M et al, 2013[54]
Cross reference:
Reichenberger J. et al, 2002[55]

9.1. Urine analysis

IDSA, 2011, Freifield et al.	Urine: Culture of urine samples is indicated if signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or the findings of urinalysis are abnormal. References: no
Korean guideline, 2011, Lee, D.G. et al	If necessary, based on symptoms, an arterial blood gas analysis or urinalysis should also be conducted. In cases with no sign or symptom of infection, specimens from the nasal cavity, oropharynx, urine, stool, and rectum do not need to be cultured, except for the purpose of hospital-related infection control Urine culture is recommended when there are symptoms of urinary tract infection, when a urethral catheter has been inserted, or when a urinalysis reveals abnormal findings. References: no
ACG, 2011, Lingaratnam, S. et al ACG, 2011, Tam S.C. et al	None

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NICE, 2013, Bate, J. et al (+ full guideline)	Children less than 5 years old should have urinalysis sent. References: no
ECIL4, 2013, Averbuch, D. et al	None
ESMO, 2016, Klastersky, J. et al	4 Routine investigations: Urinalysis and culture[a] [a]Urinalysis, sputum and stool cultures only in case of suspected focus of infection at these sites. Urinary tract infections have to be suspected even in asymptomatic patients with a past history of such infections. References: no
AGIHO FUO, 2017, Heinz, W. J. et al	Treatment algorithm for febrile neutropenic high-risk patients: 1, e.g., urine cultures, CT of sinuses, echocardiography, and viral PCR; Baseline laboratory tests include a blood count, liver enzymes (ASAT/SGPT, ALAT/SGOT, gGT), total bilirubin, alkaline phosphatase, LDH, creatinine, blood urea nitrogen, coagulation tests (INR, aPTT), C-reactive protein, and urinalysis (BIII). Except for urinalysis, it is recommended to repeat these tests regularly, e.g., twice a week, during long-lasting neutropenia (BIII). References: no
ASCO children, 2017, Lehrnbecher, T. et al	In terms of urinalysis and urine culture to detect urinary tract infections in pediatric FN, in one study, all patients with positive urine cultures were asymptomatic, strengthening the conclusion that restricting urine culture to those with symptoms is not adequate. The use of abnormal urinalysis to triage culture is also not recommended because pyuria was present in only 4% of urinary tract infection episodes during neutropenia and nitrite testing in younger children (without cancer) is less discriminatory than in older patients.[56] References: yes
SEOM, 2018 Carmona-Bayonas, A. et al	microbiological samples should be taken, depending on the clinical orientation (e.g.,

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	urine, sputum, mucosal or skin lesions, feces, cerebrospinal fluid, urinary antigens for pneumococcus and/or Legionella spp., nasal swab for flu virus during flu season, etc.) [III, A]. References: no
ASCO outpatient, 2018, Taplitz, R. A. et al	A systematic evaluation should include the following: d. Cultures from other sites, such as urine, lower respiratory tract, CSF, stool, or wounds, as clinically indicated (Type of recommendation: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate) References: no
AGIHO sepsis, 2019, Kochanek, M. et al	None

Consensus: yes

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References

1. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T *et al.* Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *Journal of Infection* 2018; **76**(1)**:** 20-37. doi: https://doi.org/10.1016/j.jinf.2017.10.009

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