Supportive care Neutropenia

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-ran-domized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

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Definitions

Neutropenia

Neutropenia is a reduction in absolute neutrophil count below the lower limit of normal. Clinically important is the reduction in neutrophil count below 1000/μL, which corresponds to at least grade 3 intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) classification. The term "agranulocytosis" is usually used when the neutrophil count is less than 100/μL, which is associated with a significantly higher risk of infection.

Febrile neutropenia

According to CTCAE version 5.0 [1], febrile neutropenia (FN) is defined as:

— a reduction in neutrophils count below 1000/μL and
— a fever (body temperature > 38.3°C in single measurement or at least 38°C lasting for at least 1 hour).

Febrile neutropenia is an adverse reaction of at least grade 3. In a life-threatening situation and the necessity of urgent medical intervention, FN is assigned grade 4.

FN definition of the European Society of Medical Oncology (ESMO) is the most commonly used in clinical practice. In comparison with the CTCAE criteria, ESMO definition [2] includes body temperature measured in the mouth > 38.3°C or > 38°C reported twice during 2 hours with accompanying decrease in the absolute number of neutrophils below 500/μL or predicted reduction below 500/μL. The IDSA (Infectious Diseases Society of America) and NCCN (National Comprehensive Cancer Network) definitions are similar [3, 4].

Incidence

Almost all patients receiving cytotoxic therapy develop neutropenia of different intensity (most often without associated symptoms and the need for treatment). Of clinical importance, especially in a context of prophylaxis, is an expected risk of FN. The risk depends primarily on chemotherapy regimen (Table 1). In addition to the type and dose of medications, other important factors include the line of ChT, advanced age, poor performance status, comorbidities (especially of cardiovascular system), previous exposure to bone marrow damaging factors (including radiation therapy), higher stage of cancer and occurrence of FN in the past.

Combinations of CDK4/6 inhibitors with hormone therapy are associated with a small (< 10%) risk of FN despite neutropenia grade 3/4 even in 50–60% of patients. In the majority of clinical studies the addition of anti-VEGF (vascular endothelial growth factor) drugs, anti-EGFR (epidermal growth factor receptor) antibodies as well as anti-PD1 (programmed death receptor 1) or anti-PD-L1 (programmed death-ligand 1) drugs to chemotherapy was not associated with a significant increase in the incidence of FN.

Pathogenesis

The most common cause of neutropenia in cancer patients is the disturbed production of neutrophils in the bone marrow due to dose-dependent myelotoxic effects of cytotoxic drugs. The period with the greatest reduction in the number of granulocytes is called nadir — it usually occurs 7–14 days after ChT administration, but with some drugs (nitrosourea) it can take even several weeks.

Drug-induced, dose-independent neutropenia (e.g. after phenylbutazone as one of the symptoms of bone marrow aplasia), neutropenia due to the formation of autoantibodies, as well as, vitamin B12 or folic acid deficiency is rarely seen.

Consequences

Neutropenia is one of the most important factors predisposing for infections, which occur in about half of patients with FN (approximately 10–25% of patients has bacteremia and 20–30% of patients clinically overt infection). The likelihood of infectious complications depends primarily on the duration and severity of neutropenia. The most important sign of neutropenia is a fever. Due to immunosuppresion other symptoms and signs often are less pronunced or atypical.

The consequence of asymptomatic neutropenia may be a decrease in treatment intensity following a delay in the administration of the next cycle of ChT and/or a reduction in the dose of drugs. It has been shown that in some patients this situation may lead to reduced treatment effectiveness (see — prophylaxis of neutropenia).

Etiology of infection during febrile neutropenia

The infection has been microbiologically documented in 21% of 750 patients with FN of low complications risk (risk assessment is discussed later in this chapter). Bacteremia was found in 58% of cases (12% of all FN patients) and urinary tract infections in 25% (5% of all patients). In 49% of patients the infection was induced by Gram-positive bacteria (most frequently staphylococcal species — coagulase-negative staphylococci [CNS]

Table 1. Probability of febrile neutropenia (FN) associated with selected chemotherapy (ChT) regimens [5, 13]

Incidence GN	Diagnosis	ChT regimens
> 20%	Breast cancer	TAC (docetaxel, doxorubicin, cyclophosphamide), AT (doxorubicin, docetaxel)
	Gastric cancer	DCF (docetaxel, cisplatin, fluorouracil)
	Lymphomas	BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), ICE (ifosfamide, cisplatin, etoposide)
	Germ-cell tumors	VeIP (vinblastine, ifosfamide, cisplatin), TIP (paclitaxel, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin)
	Small cell lung cancer	Topotecan
	Soft tissue sarcomas	MAID (doxorubicin, ifosfamide, dacarbazine)
10–20%	Breast cancer	AC → T (100 mg/m^2) (doxorubicin, cyclophosphamide → docetaxel), CEF (cyclophosphamide, epirubicin, fluorouracil)
	Gastric cancer	ECF (epirubicin, cisplatin, fluorouracil), ECX (epirubicin, cisplatin, capecitabine)
	Lymphomas	R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
	Germ-cell tumors	BEP (bleomycin, etoposide, cisplatin)
	Small cell lung cancer	PE (cisplatin, etoposide), CAV (cyclophosphamide, doxorubicin, vincristine)
	Non-small cell lung cancer	Docetaxel, PE (cisplatin, etoposide)
	Ovarian cancer	Topotecan
	Bladder cancer	M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin)
	Head and neck cancer	TPF (docetaxel, cisplatin, fluorouracil)*
	Soft tissue sarcomas	Ifosfamide (9 g/m^2)
< 10%	Breast cancer	CMF (cyclophosphamide, methotrexate, fluorouracil), AC (doxorubicin, cyclophosphamide), docetaxel (75 mg/m^2), FAC (fluorouracil, doxorubicin, cyclophosphamide) TC** (docetaxel, cyclophosphamide) TCH*** (docetaxel, carboplatin, trastuzumab)
	Gastric cancer	EOX (epirubicin, oxaliplatin, capecitabine), trastuzumab + PF (cisplatyna, fluorouracyl), docetaksel
	Pancreatic cancer	FOLFIRINOX*** (calcium folinate, fluorouracil, irinotecan, oxaliplatin); gemcitabine + nab-paclitaxel; OFF (oxaliplatin, calcium folinate, fluorouracil)
	Colon cancer	FOLFIRI (calcium folinate, fluorouracil, irinotecan), FOLFOX (calcium folinate, fluorouracil, oxaliplatin), CAPOX (capecitabine, oxaliplatin), FOLFOXIRI (calcium folinate, fluorouracil, oxaliplatin, irinotecan), capecitabine, LVFU2 (calcium folinate, fluorouracil)
	Non-small cell lung cancer	PN (cisplatin, vinorelbine), PG (cisplatin, gemcitabine), cisplatin with pemetrexed, pemetrexed
	Ovarian cancer	Carboplatin with paclitaxel
	Germ-cell tumors	GP (gemcitabine, paclitaxel), GO (gemcitabine, oxaliplatin)
	Prostate cancer	Docetaxel with prednisone
	Bladder cancer	PG (cisplatin, gemcitabine)
	Head and neck cancer	PF (cisplatin, fluorouracil)
	Soft tissue sarcomas	Doxorubicin (75 mg/m^2)

*Depending on the drug dosing regimen in the TPF protocol, the risk of FN was 5% and 12% in 2 phase III studies; in both studies, ciprofloxacin was used prophylactically on days 5–15 of the cycle

**In the pivotal study fluoroquinolone prophylaxis was recommended; in the meta-analysis of mostly retrospective studies FN risk > 20%

***In clinical trials the primary prophylaxis with G-CSF was allowed; in some retrospective analyzes the risk of FN > 20%

and *Staphylococcus aureus*, as well as streptococci and enterococci), in 36% of patients Gram-negative bacilli (most often *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) were isolated, and in 15% of patients, the etiology of infection was mixed [6]. In the group of almost 2,150 unselected patients with FN (including 17% undergoing intensive ChT due to acute leukemia) bacteremia was found twice as often (23% of patients), and the cause in most patients was also Gram-positive bacteria (usually coagulase-negative staphylococci) [7]. The most common etiology of bacteremia in patients with FN are presented in Table 2. Fungal infection is rarely the main cause of fever in patients with neutropenia, however, the risk of infection with fungi (especially *Candida sp.* and *Aspergillus sp.*) is increased with longer duration (> 7 days) of neutropenia.

Assessment of risk associated with febrile neutropenia

The risk of serious FN complications (e.g. renal failure, respiratory failure, hypotension, heart failure, disseminated intravascular coagulation, consciousness disorders) is about 13% (risk of death — about 5%). Patients with some hematopoietic malignancies (e.g. acute leukemia) are at least 2 times more likely to die.

The probability of FN complications occurrence depends on many factors, among which the most important are the following:

— type and stage of cancer and cancer control;
— method of cancer treatment;
— FN occurrence during hospitalization;
— duration and intensity of neutropenia;
— presence of an organ infection;
— comorbidities;
— other organs injuries (including mucous membranes);
— age and performance status.

Based on the analysis of FN course in a group of more than 1,000 patients with various cancers, the Multinational Association for Supportive Care in Cancer (MASCC) [8] proposed a practical risk index score for assessing the risk associated with this complication (Table 3). In patients with low MASCC risk (≥ 21 points), the incidence of serious neutropenia complications is 6% (risk of death — 1%). If the number of points is less than 21, then the risk of serious complications is as much as 39% (risk of death — 14%). The MASCC score due to its simplicity and ease of use is routinely used in clinical practice to assess the risk related to FN.

The occurrence of bacteremia worsens the prognosis. Serious complications affect 10% of patients with sterile blood cultures (death — 3%), while in patients with bacteremia, the complications risk is 21% (death — 10%). Mortality in the course of FN with bacteremia depends on the type of pathogen. Mortality associated with bacteremia caused by Gram-positive and Gram-negative microorganisms is about 5% and about 20%, respectively [9]. Bacteremia etiology adds additional prognostic value to the MASCC score, especially in patients at high risk of complications (Table 4).

Table 2. The most common etiology of bacteremia in patients with febrile neutropenia [7]

Cause	Type of staining	Bacteria	Incidence (%)
Infections with one microorganism			90
	Gram-positive		57
		Staphylococcus (coagulase-negative)	28
		Streptococcus	15
		Staphylococcus (coagulase-positive)	5
	Gram-negative		34
		Escherichia coli	14
		Pseudomonas aeruginosa	8
		Klebsiella pneumoniae	4
Mixed infections			10
	At least one Gram-negative		6
	Gram-positive only		4

Table 3. MASCC risk index score for febrile neutropenia complications [8]

Characteristics	Points
Clinical symptoms	
— absent or minor	5
— moderate	3
Systolic blood pressure > 90 mm Hg	5
Absence of chronic obstructive pulmonary disease	4
Non-hematological or hematological cancer if there was no previous fungal infection	4
Absence of dehydration	3
Occurrence of symptoms outside the hospital	3
Age < 60 years	2

The points assigned to individual characteristic are added. If the clinical symptoms are significant, no points are assigned. The maximum and possible number of points is 26. A low risk of complications is considered when the number of points is ≥ 21

Table 4. Mortality in patients with febrile neutropenia and bacteremia depending on the type of pathogen and risk according to the MASCC index score [7]

Number of MASCC points	Mortality (%)	
	Gram-positive	Gram-negative
≥ 21	2	6
15–20	6	23
< 15	28	43

Febrile neutropenia — diagnostic procedures

Medical history

The medical history should provide information regarding: cancer type and stage, date of administration of last ChT cycle and doses of the drugs, recent surgical procedures and other methods of anticancer treatment, comorbidities, previous episodes of fever or infection, exposure to infectious agents, additionally used medicines (including antibiotics and glucocorticosteroids), results of microbiological tests, accompanying symptoms that may indicate the location of the infection (e.g. cough, abnormal urination, diarrhea, sore throat), drug allergies.

Physical examination

The physical examination provides an assessment of patient's general condition, hydration status, and potential sites of infection (skin, anal area, respiratory system, oral cavity, site of venous catheter insertion). Blood pressure measurement is necessary. Due to neutropenia, symptoms of infection can be very weakly expressed or even latent; and the clinical manifestation of infection may be distorted during glucocorticoids use or in the elderly.

Some patients with infectious complications of neutropenia do not have a fever, and body temperature may be even lower than normal. Situations in which neutropenia is accompanied by symptoms suggesting an inflammatory process (e.g. abdominal pain, focal lesions on the skin or erosions of mucous membranes) should be considered as an active infection (IV, B). Concomitant significant weakness, hypotonia, and decrease in body temperature in individual with neutropenia can suggest the possibility of sepsis (especially caused by Gram-negative bacteria).

Additional evaluations

In all cases the following tests must be performed (IV, A):

— complete blood counts (CBC) with leukocyte smear and platelet count;
— serum concentration of urea, creatinine, sodium, potassium and bilirubin;
— serum level of asparagine (AST) and alanine aminotransferase (ALT);
— blood cultures taken from 2 sites, but in case of a central venous catheter or chemotherapy port implanted it is strongly recommended to collect blood from a peripheral vein puncture as well as the second from a catheter/port); the sample should be taken before antibiotic administration.

It is also recommended to perform chest X-ray (IV, C) in all patients with FN (in patients with symptoms suggestive of pulmonary infection it is absolutely necessary and computed tomography (CT) of the chest should be also considered).

Optionally other tests could be performed, depending on the clinical situation: cultures from other places, X-ray of paranasal sinuses, ultrasound (US) of the abdominal cavity, CT — depending on the clinical indications — of the chest, abdomen and pelvis or central nervous system (CNS) (in case of suspected inflammation, it is also necessary to perform lumbar puncture to collect cerebrospinal fluid for testing), urinalysis and urine culture, examination of stool for anaerobic bacteria (primarily *Clostridium difficile* toxins A and B) and other pathogens, blood gas test, C-reactive protein (CRP), procalcitonin, coagulogram and other (IV, C).

In every patient with suspected infection, a diagnosis of sepsis should be carried out (IV, A). As part of the current consensus (Sepsis-3) [10], the initial qSOFA test (blood pressure ≤ 100 mm Hg, respiratory rate ≥ 22/min, disorders of consciousness) allows estimating the risk of sepsis (greater when at least 2 factors are present). To diagnose sepsis, it is necessary to document organ failure based on the SOFA score (sudden change of ≥ 2 points) taking into account oxygenation index, platelet count, bilirubin and creatinine concentration, mean arterial pressure, and level of consciousness according to Glasgow Coma Scale (GCS).

Treatment

The management depends on the risks associated with FN. There are several possibilities: hospital treatment, short-term hospitalization with the continuation of therapy in outpatient settings or completely outpatient treatment.

According to the NCCN recommendations [4], hospitalization is necessary (high-risk FN), among others, in the following situations:

— the number of points in the MASCC scale is less than 21 or
— at least one of the following characteristics occurs:
  • FN occurred during hospitalization,
  • significant diseases co-occur or the clinical condition is unstable,

- the expected duration of agranulocytosis (neutrophil count < 100/μL) is at least 7 days,
- symptoms of hepatic insufficiency occur (ALT or AST level 5 times above the upper limit of normal),
- symptoms of renal insufficiency occur (creatinine clearance < 30 mL/min),
- disease progression or no complete remission in patient with acute leukemia,
- pneumonia or any other clinically significant infection occurs,
- alemtuzumab treatment is used,
- grade 3 or 4 mucositis is found.

Remaining patients (from the so-called low-risk FN group) may be treated in outpatient or hospital settings. The decision on a completely outpatient treatment is also significantly influenced by organizational, social and psychological conditions (constant home care, time of arrival from the patient's place of residence to the hospital ≤ 1 hour, easy telephone contact with the oncological center, good compliance with medical recommendations, etc.) (IV, C).

The most important treatment component in patients with FN is empirical broad-spectrum antibiotic therapy, which should cover potentially the most important pathogens (Table 5) (I, A), as well as take into account the epidemiological situation in healthcare unit (including the incidence of infections with individual pathogens and their antibiotic sensitivity) and data regarding carrier state (e.g. MRSA, Methicillin-resistant *Staphylococcus aureus*) (IV, A).

It is recommended to initiate antibiotic therapy as soon as possible after a diagnosis of FN, preferably within 1 hour (III, B).

After pathogen identification and determining its sensitivity to antibiotics, empirical treatment should be replaced with antimicrobial therapy according to culture results (I, A).

Treatment of low-risk FN patients [2, 4]:

— empirical oral antibiotic therapy with ciprofloxacin and amoxicillin with clavulanic acid (I, A) [or moxifloxacin alone (I, A) or levofloxacin (II, B)] or intravenous antibiotic therapy (in hospitalized patients). Quinolones should not be used in patients who have received ciprofloxacin as prophylaxis of FN (IV, A);
— it is recommended to administer the first dose of antibiotics in the hospital and observe the patient's clinical condition and tolerance of the treatment for at least 4 hours before discharge (in patients not requiring hospitalization) (IV, B);
— patients who required hospitalization and the use of intravenous antibiotics may continue oral treatment in outpatient settings in case of stable general condition, clinical improvement and fever resolution after 48 hours of in-hospital stay (IV, C).

Treatment of high-risk FN patients [2, 4]:

— intravenous broad-spectrum antibiotic therapy in hospital settings (I, A).

As part of the initial treatment, antibiotics can be used as monotherapy (the risk of nephrotoxicity is smaller) or in combination, depending on the clinical situation. In patients with a higher risk of long-term neutropenia, with bacteremia, complicated FN or resistance to treatment, the combination of a beta-lactam antibiotic with activity against *Pseudomonas spp*. in combination with aminoglycoside (I, C) or sometimes with vancomycin should be considered (I, C).

In some clinical situations, the recommendations are modified as follows [2, 4]:

— sepsis — aminoglycoside and vancomycin should be added (I, A) to broad-spectrum beta-lactam antibiotic (cefepime, meropenem, imipenem/cilastatin, piperacillin/tazobactam), empirical antifungal therapy should be considered (IV, B);
— septic shock — also fluid therapy, oxygen therapy, vasopressors and possibly corticosteroids — e.g. hydrocortisone 50 mg *i.v.* every 6 hours (IV, A);

Table 5. Most commonly used antibacterial drugs in empirical therapy in patients with febrile neutropenia [2, 4]

Way of treatment	Drugs
Intravenous antibiotic therapy	
— combined	— aminoglycoside + piperacillin with tazobactam
	— aminoglycoside + ceftazidime
	— ciprofloxacin + piperacillin with tazobactam
	— aztreonam + vancomycin (in case of penicillin allergy) (IV, B)
— monotherapy	— imipenem/cilastatin
	— meropenem
	— ceftazidime
	— piperacillin/tazobactam
	— cefepime
Oral antibiotic therapy	— ciprofloxacin + amoxicillin with clavulanic acid
	— ciprofloxacin + clindamycin (in case of penicillin allergy) (IV, B)

— pneumonia — the combination is expanded to include an active drug against *Mycoplasma* (macrolide) (IV, B), and if *Pneumocystis* etiology is suspected, cotrimoxazole is the drug of choice (IV, A);
— diagnosis of Gram-positive bacteremia prior to the final identification of the pathogen — vancomycin adding is advisable (IV, A);
— diarrhea — metronidazole or vancomycin (oral) should be added to the combination and a fecal test for e.g. *Clostridium difficile* toxins should be performed (IV, B);
— suspected bacteremia associated with the presence of a venous catheter — including a glycopeptide (e.g. vancomycin) is recommended to consider (II, A). It is absolutely necessary to obtain the microbiological diagnosis as soon as possible. A useful and simple (although requiring an automatic device for detection of bacterial growth) method of recognizing bacteremia associated with the presence of a vascular catheter is to perform two cultures of blood samples taken simultaneously from the catheter and the peripheral vein and note the time to obtain a positive result [11]. If the time to bacterial growth for a catheter sample is shorter by at least 2 hours compared to a peripheral vein sample, this is likely to indicate an infection associated with the presence of a vascular catheter (I, A) that in some situations should be removed [especially in case of infection of implanted vascular port (II, B), prolonged fever and bacteremia despite antibiotic therapy, in case of *Candida*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* infection or venous thrombosis];
— intra-abdominal or pelvic infections — metronidazole is included in the combination (unless patient receives carbapenem or piperacillin/tazobactam) (IV, B);
— skin and subcutaneous tissue infections — it is recommended to consider adding a glycopeptide (IV, C);
— suspected viral infection: HSV or VZV (mucosal vesicles, herpes zoster) — acyclovir (I, A) is included in the combination, in case of suspected influenza virus infection — zanamivir or oseltamiwir (IV, C);
— suspected fungal infection (necrotizing ulceration of oral mucosa, symptoms of oral candidiasis, painful swallowing) — microbiological diagnostics for mycosis should be implemented and an antifungal drug should be added to the combination (if the clinical symptoms suggest candidiasis — fluconazole) (I, A);
— infections in patients during intensive ChT with massive mucosal damage (higher risk of penicillin-resistant streptococcal infection) — vancomycin should be considered as part of the initial treatment, especially when ceftazidime was previously initiated (IV, B);
— infections preceded by quinolones prophylaxis — vancomycin should be considered as part of the initial treatment (IV, B).

During the empirical treatment, the patient's clinical condition should be monitored daily and additional tests (CBC, serum creatinine and other, depending on the clinical situation) should be repeated until the fever has resolved and the stable increase in neutrophil count to at least 500/μL is observed (IV, A). If the patient's condition is stable, assessment of treatment response is made after 48 hours. Further management depends on the clinical situation and should be as follows (Fig. 1):

1. Resolution of fever + no signs of infection + sterile blood culture + neutrophil count at least 500/μL:
   a) low risk — continuation of oral antibiotic therapy (possibly in outpatient settings) (II, A);
   b) high risk — the continuation of intravenous antibiotic therapy (possible discontinuation of aminoglycoside) (IV, B);
   c) if fever does not occur for another 24–48 hours — discontinuation of antibiotic therapy (IV, A);
   d) antibiotic therapy can also be discontinued if the neutrophil count is less than 500/μL and the fever has not been present for at least 5–7 days.
2. Persistence of fever + patient's stable condition + absence of infection symptoms + sterile blood culture — continuation of current treatment to meet the conditions as above. If the fever lasts 3–5 days, despite empirical antibiotic therapy, and the bacterial pathogen has not been isolated from repeated blood cultures, the implementation of microbiological diagnostics for fungal infection should be considered and intravenous empirical antifungal therapy with fluconazole (in case of low risk of aspergillosis) or amphotericin B in various forms, itraconazole (injectable preparations are not available in Poland), echinocandin (e.g. caspofungin) or optionally voriconazole should be initiated (I, A). CT scan of chest with liver and spleen is also recommended. In case of probable or confirmed fungal infection targeted treatment should be implemented, depending on the clinical situation and the results of the microbiological test (I, A).
3. Microbiological identification of the pathogen — treatment in accordance with the antibiogram (treatment duration depends on the clinical situation, usually at least 10–14 days, and in case of confirmed fungal infection — several weeks) (I, A).
4. Persistence of fever + unstable patient's condition + no pathogen identification — repeating of additional tests (including diagnostics for non-infectious cause, non-bacterial or bacterial infection with drug-resistant pathogens) and change of current antibiotic therapy (adding an antifungal drug

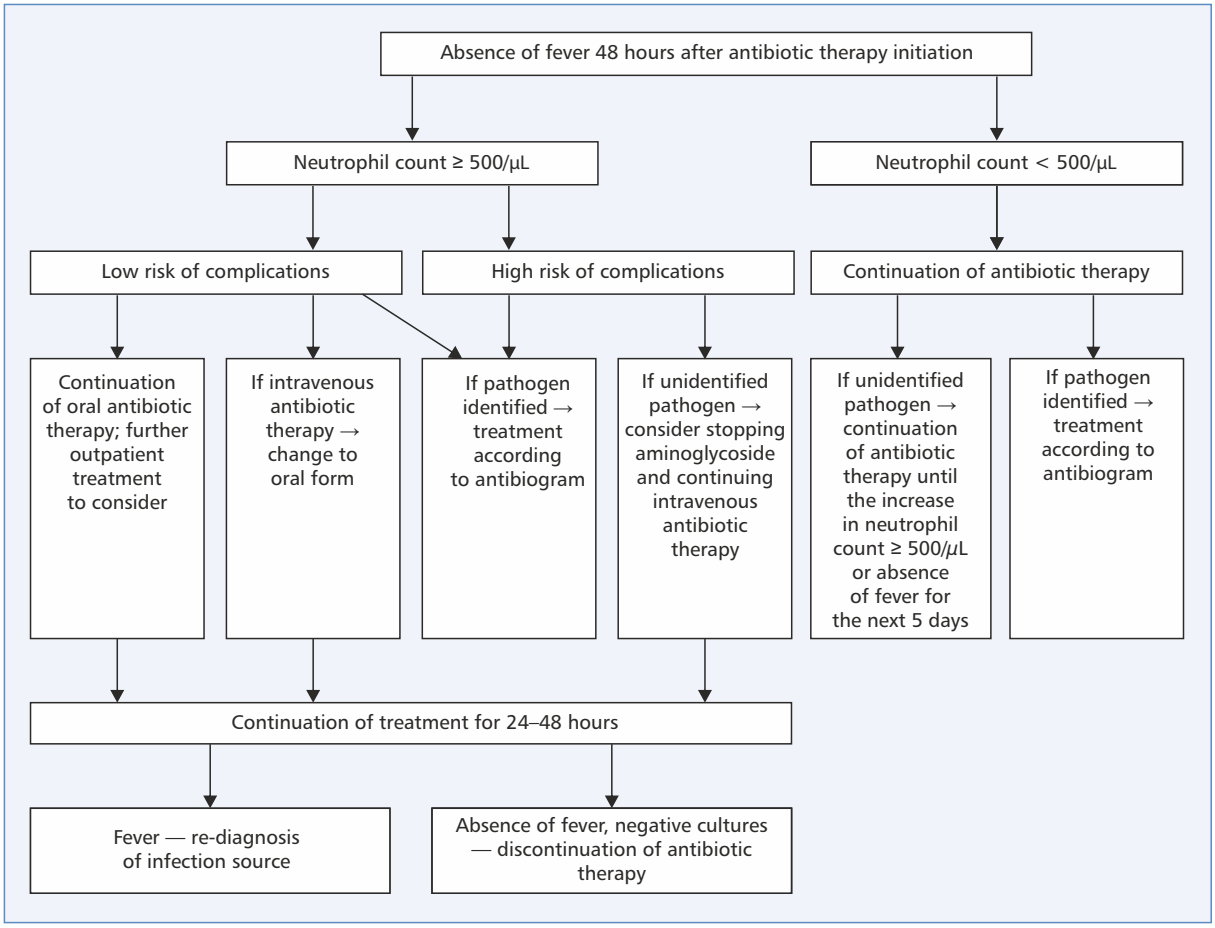

Figure 1. Treatment algorithm for patients without fever after 48 hours of antibiotic therapy

in accordance with the above recommendations, adding a glycopeptide, possible use of carbapenem, if not previously used) and consultation of a hospital microbiologist (IV, A).

Routine use of G-CSF is definitely not recommended for the treatment of all patients with FN. In a meta-analysis of 14 randomized clinical trials in which the use of granulocyte or granulocyte-macrophage colony-stimulating factors was compared to placebo in a group of approximately 1,500 patients, there was no improvement in overall mortality and infection-related mortality by the use of G-CSF (a shorter hospitalization time and time to increase neutrophil count were showed) [12] (I, A). However, adding G-CSF to antibiotic therapy should be considered in the following situations [13] (IV, A):

— there is no response to antibiotic therapy;
— severe and life-threatening infection or complications (sepsis, septic shock);
— FN is diagnosed, despite the prophylactic use of non-PEGylated growth factors;
— other factors increasing the risk of complications co-occur (age > 65 years, neutropenia < 100/μL or lasting > 10 days, fungal infections, the occurrence of FN during hospitalization, previous FN episodes).

There is no evidence that patients with FN may benefit from granulocyte transfusion.

Prophylaxis of neutropenia

Secondary prophylaxis

In case of post-ChT occurrence of FN, the use of secondary prophylaxis with G-CSF from the next cycle should be considered [13]. An alternative approach, preferred in most clinical situations, is to reduce the dose of drugs or to use a less myelotoxic ChT regimen. The decision depends largely on treatment intention. In selected cases, the indication for secondary prophylaxis may be not only FN but also asymptomatic neutropenia which is the reason for delaying of subsequent ChT cy-

cles. This relates to some cases with radical treatment where, reduction of dose intensity may adversely affect the prognosis (e.g. in adjuvant breast cancer therapy, treatment of some types of lymphoma and testicular cancer). Prophylactic use of G-CSF is not sufficient management in the presence of other significant adverse effects (e.g. thrombocytopenia or organ toxicity) as it does not reduce the risk of their occurrence. In the prophylaxis of FN, two groups of G-CSF preparations can be used — PEGylated (e.g. pegfilgrastim and lipegfilgrastim) or non-PEGylated (e.g. filgrastim) forms. Pegylated forms are used as a single injection (6 mg) after ChT (approximately 24 hours). PEGylated forms should not be used when the frequency of ChT cycles is less than 14 days. Prophylaxis with non-PEGylated G-CSF (e.g. filgrastim) is started between 24 and 72 hours after ChT (5 μg/kg with dose rounded to full ampoule) subcutaneously, daily, until the expected nadir disappears (usually ≥ 5–7 days) and obtaining a normal or slightly reduced but stable neutrophil count. There are no data indicating differences in the effectiveness of G-CSF preparations, including PEGylated and non-PEGylated [14].

Primary prophylaxis

The primary prophylaxis consists of G-CSF use from the first ChT cycle. The results of meta-analysis of controlled clinical trials show that primary prophylaxis reduces the incidence and the duration of FN, antibiotic therapy and hospitalization, and also reduces the risk of infections [15]. These benefits are evident when frequency of FN is higher than 20%. However, there was no effect of primary prophylaxis on reduction of the risk of death, which is independent of ChT myelotoxicity grade. Admittedly, meta-analyzes assessing the impact of primary prophylaxis on, among others, the survival of patients undergoing ChT, indicated a slight decrease in the mortality (despite the higher incidence of acute leukemia or myelodysplastic syndromes [16]), but this effect most likely depends on the assumed higher intensity of treatment in these groups of patients (among others, meta-analysis included studies on chemotherapy with G-CSF support in breast cancer patients). Analysis limited to studies comparing identical treatment regimens revealed only a statistically insignificant trend to prolong survival [17].

Primary prophylaxis is the subject of controversy, and due to the lack of impact on mortality, the pharmacoeconomic analyzes play an important role in determining indications to this procedure.

A widely accepted indication is the need to use ChT with an expected risk of FN greater than 20%, and this indication is independent of other factors (Table 1) [13] (I, A). If the ChT is associated with a 10–20% risk of FN, the indication for primary prophylaxis may be the presence of additional risk factors for FN and its complications (e.g. age > 65 years, the occurrence of FN during previous ChT, advanced stage of cancer, metastases in the bone marrow, radiotherapy covering an area of the skeletal system containing a significant part of the bone marrow, poor performance status, malnutrition, female gender, anemia, impaired renal and liver function and others) (IV, C). The use of primary prophylaxis may be justified in the presence of several of these factors, especially in case of radical treatment. Primary prophylaxis of neutropenia is also an mandatory component of chemotherapy regimens given at shorter than standard intervals (so-called regimens with higher dose-density) (I, A). However, the possibility of replacing the ChT regimen with less myelotoxic one, delaying the start of treatment until normalisation of neutrophiles count or reduction of medications doses should always be considered. Treatment intention is of great importance during qualifying the patients for primary prophylaxis (as far as palliative chemotherapy is concerned, primary prophylaxis is less frequently used) [2, 14, 18].

The pattern of G-CSF administration is analogous to that used for secondary prophylaxis.

Primary prophylaxis is not justified in case of ChT regimens with low risk of FN.

Despite the fluoroquinolone activity demonstrated in FN prophylaxis in clinical studies, their standard use in patients with solid tumors is not recommended due to the increased risk of inducing the development of quinolone-resistant bacterial strains [3]. However, in the high-risk group of patients who are expected to develop long-term (over 7 days) and deep (100/μL) neutropenia, prophylaxis with ciprofloxacin or levofloxacin should be considered (IV, B).

Conflicts of interest

The authors declare to have no conflict of interest.

References

1. Common Terminology Criteria for Adverse Events (Version 5.0). Dostęp on-line: 10.01.2020 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).
2. Klastersky J, de Na, Rolston K, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2016; 27(supl. 5): v111–v118.
3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious Diseases Society of America. Clin Infect Dis. 2011; 52(4): e56–e93, doi: 10.1093/cid/cir073, indexed in Pubmed: 21258094.
4. NCCN Guidelines Version 1.2020. Prevention and treatment of cancer-related infections. Dostęp on-line: 10.01.2020.
5. Crawford J, Caserta C, Roila F, et al. ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO Clinical Practice

Guidelines for the applications. Ann Oncol. 2010; 21 Suppl 5: v248–v251, doi: 10.1093/annonc/mdq195, indexed in Pubmed: 20555091.
6. Kamana M, Escalante C, Mullen CA, et al. Bacterial infections in low--risk, febrile neutropenic patients. Cancer. 2005; 104(2): 422–426, doi: 10.1002/cncr.21144, indexed in Pubmed: 15937905.
7. Klastersky J, Ameye L, Maertens J, et al. Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents. 2007; 30 Suppl 1: S51–S59, doi: 10.1016/j.ijantimicag.2007.06.012, indexed in Pubmed: 17689933.
8. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol. 2000; 18(16): 3038–3051, doi: 10.1200/JCO.2000.18.16.3038, indexed in Pubmed: 10944139.
9. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. Int J Antimicrob Agents. 2008; 32 Suppl 1: S30–S33, doi: 10.1016/j.ijantimicag.2008.06.017, indexed in Pubmed: 18778919.
10. Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 801, doi: 10.1001/jama.2016.0287.
11. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med. 2004; 140(1): 18–25, doi: 10.7326/0003-4819-140-1-200401060-00007, indexed in Pubmed: 14706968.
12. Mhaskar R, Clark OA, Lyman G, et al. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev. 2014(10): CD003039, doi: 10.1002/14651858.CD003039.pub2, indexed in Pubmed: 25356786.
13. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic growth factors. Dostęp on-line: 15.11.2019.
14. Smith TJ, Bohlke K, Lyman GH, et al. American Society of Clinical Oncology. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015; 33(28): 3199–3212, doi: 10.1200/JCO.2015.62.3488, indexed in Pubmed: 26169616.
15. Sung L, Nathan PC, Alibhai SMH, et al. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med. 2007; 147(6): 400–411, doi: 10.7326/0003-4819-147-6-200709180-00010, indexed in Pubmed: 17876022.
16. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol. 2010; 28(17): 2914–2924, doi: 10.1200/JCO.2009.25.8723, indexed in Pubmed: 20385991.
17. Lyman GH, Dale DC, Culakova E, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol. 2013; 24(10): 2475–2484, doi: 10.1093/annonc/mdt226, indexed in Pubmed: 23788754.
18. Aapro MS, Bohlius J, Cameron DA, et al. European Organisation for Research and Treatment of Cancer. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011; 47(1): 8–32, doi: 10.1016/j.ejca.2010.10.013, indexed in Pubmed: 21095116.