Supportive care
Prophylaxis and treatment of infections

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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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Introduction

Patients treated for malignant tumours are at increased risk of infections. Immunosuppression associated with cancer treatment and the malignancy itself affects the intensity of infections and the risk of complications. The clinical course of infections in this group of patients can be unpredictable and limits the possibility of effective oncological treatment, leading to serious complications or death in extreme cases. Rational prevention, diagnosis, and treatment of infections can significantly improve the prognosis in patients with malignant tumours.

Infections risk assessment

The following factors should be taken into account when assessing the overall risk of infection in a patient diagnosed with cancer (Table 1):
— cancer type and stage;
— type of antineoplastic treatment;
— status of the underlying disease (e.g. remission phase, active disease, progression);
— previous chemotherapy or radiotherapy;
— use of immunosuppressive treatment;
— individual state of the immune system (e.g. impairment of non-specific immunity resulting from damage of the natural barriers of the immune system).

Prevention of bacterial infections

Indications for the prophylaxis of bacterial infections depend on the infection risk assessment. In the majority of patients with solid tumours receiving chemotherapy there are no indications for routine antibacterial prophylaxis (I, A).

During asymptomatic neutropenia resulting from anti-cancer therapy, antimicrobial prophylaxis may be considered in the following patients (IV, A):
— undergoing haematopoietic stem cell transplantation;
— receiving alemtuzumab;
— receiving purine analogues;
— diagnosed with acute lymphoblastic leukaemia;
— with at least grade 3 neutropenia according to CTCAE scale lasting > 7 days;
— treated for lymphoma, multiple myeloma, or chronic lymphocytic leukaemia (indications should be considered on an individual basis due to the heterogeneous clinical course of the disease) (IV, C).

Fluoroquinolones (preferably levofloxacin) are recommended for patients qualified for the prophylaxis of bacterial infections (I, B). In the case of contraindications or poor tolerance of fluoroquinolones, trimethoprim/sulfamethoxazole or oral III generation cephalosporin may be used.

In patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) and receiving chronically high doses of glucocorticosteroids (> 20 mg of prednisone per day) due to graft versus host disease (GVHD) more potent antibacterial prophylaxis can be used with a combination of several antibiotics (e.g. penicillin combined with trimethoprim/sulfamethoxazole) (IV, B).

Prevention of pneumonia caused by *Pneumocystis jirovecii* [1]

Trimethoprim/sulfamethoxazole is a drug of choice for therapy and prophylaxis of infections caused by *Pneumocystis jirovecii*. Preventive treatment is indicated for patients:

Table 1. Infection risk classification in patients with cancer [1]

General risk of infection in cancer patient	Examples of risk factors
Low	— Standard chemotherapy for most solid tumours — Expected duration of neutropenia less than 7 days
Moderate	— Auto HSCT — Treatment with purine analogues — Diagnosis of lymphoma, multiple myeloma, chronic lymphocytic leukaemia* — Expected duration of neutropenia 7–10 days
High	— Allo-HSCT — Acute myeloid and lymphoblastic leukaemia during treatment — Alemtuzumab treatment — Graft versus host disease (GVHD) treated with high doses of glucocorticosteroids (> 20 mg of prednisone daily) — Expected duration of neutropenia of over 10 days

*The type of treatment and clinical disease stage affect the individual risk assessment
Auto-HSCT — autologous haematopoietic stem cell transplantation; allo-HSCT — allogeneic haematopoietic stem cell transplantation

— undergoing allo-HSCT (I, A);
— receiving alemtuzumab (IV, A);
— diagnosed with acute lymphoblastic leukaemia undergoing anticancer treatment (I, A).

In addition, it should be considered in patients (IV, B):
— receiving purine analogues;
— undergoing autologous haematopoietic stem cell transplantation (auto-HSCT);
— receiving intensive corticosteroid therapy due to cancer;
— receiving temozolomide combined with radiation therapy.

Antifungal prophylaxis [1]

Antifungal prophylaxis should not be the standard of care (SOC) in all patients with neutropenia (IV, C).

This should be considered in patients:
— with prolonged neutropenia (e.g. in the course of aplastic anaemia) (IV, C);
— undergoing chemotherapy for acute myeloid leukaemia or myelodysplastic syndromes (I, A);
— after haematopoietic stem cell transplantation (especially after allo-HSCT) (I, A);
— undergoing immunosuppressive therapy due to GVHD (I, A).

Secondary prophylaxis is indicated in patients with a history of invasive mycosis undergoing treatment with a risk of long-term neutropenia (III, B).

Antiviral prophylaxis [1]

Prevention of reactivation of HSV, VZV, and CMV infections

Patients undergoing HSCT, receiving chemotherapy for acute leukaemia, and treated with alemtuzumab, high-dose corticosteroids, or purine analogues due to impairment of cellular immunity are at increased risk of reactivation of latent viral infections. Antiviral prophylaxis is indicated in seropositive patients receiving the aforementioned therapies (IV, B).

Prevention of reactivation of HBV infection

In accordance with the American Society of Clinical Oncology (ASCO) recommendations, screening for the detection of chronic HBV infection (HBs antigen, anti-HBc antibodies) is indicated in cancer patients qualified for chemotherapy with significant immunosuppressive potential or patients with a history of hepatitis B because of more frequent reactivation of the infection (I, A) [2]. If a chronic infection is detected, prophylactic treatment should be initiated after evaluation of viraemia (in Poland a lamivudine drug program in lymphoma patients with planned rituximab treatment) (I, A).

Diagnostics for the detection of clinically silent HCV and HIV infection is indicated in patients planned for treatment with significant immunosuppressive potential (e.g. high-dose chemotherapy, rituximab, alemtuzumab) (III, B). In other cancer patients the advisability of virological diagnostics (HBs-Ag, anti-HBc, anti-HCV, anti-HIV) should be assessed individually (IV, C), although according to the National Cancer Comprehensive Network (NCCN) recommendations all patients for whom chemotherapy or immunosuppressive treatment is planned should be screened [1].

Protective vaccinations [1, 3]

Vaccination with live attenuated viral vaccines is contraindicated in patients with impaired immunity, due to the significantly higher risk of inducing infection as compared to healthy individuals (IV, B). Vaccines with inactivated pathogens do not have such potential and can be safely used in immunocompromised patients.

Yearly influenza vaccination is recommended for:
— patients with either haematopoietic or lymphoid malignancies or solid tumours (IV, B) — inactivated vaccines;
— immediate family members, caregivers, and healthcare professionals (IV, B) — also attenuated vaccines (attenuated vaccines are contraindicated only in persons in the immediate vicinity of patients with a significant reduction in immunity).

In cancer patients (mainly with haematopoietic or lymphoid malignancies) at various stages of the therapeutic procedures, depending on the planned treatment and estimated risk of infection or pathogen invasion, vaccination against HBV (IV, B) as well as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b (IV, C) should also be considered. Revaccination against hepatitis B should be considered in cancer patients undergoing immunosuppressive therapy, depending on anti-HB antibody levels (IV, C).

Respiratory tract infections

The signs and symptoms of respiratory tract infections are not characteristic and include, among others: cough, shortness of breath, fever above 38°C, and chest pain. Differential diagnostics in patients undergoing anticancer treatment with respiratory symptoms and radiological abnormalities in the lungs is difficult and requires consideration of the possibility of cancer progression, cardiovascular disease, adverse drug reactions, and exacerbation of concomitant respiratory diseases.

The laboratory tests helpful in differential diagnosis include:
— complete blood count (CBC) with smear;

— microbiological examination of blood and sputum (before starting antibiotic therapy);
— computed tomography (CT) of the chest;
— in the case of diagnostic difficulties, bronchofiberoscopy with microbiological examination of bronchial lavage for bacterial, viral, fungal, and atypical infections (especially in cases of resistance to previous empirical therapy).

Pneumonia is suspected when auscultatory changes during examination are accompanied with one of the following symptoms: tachycardia > 100 beats/minute, tachypnea > 24 breaths/minute, or fever > 38°C. In such situation chest X-ray is mandatory (II, A).

Pneumonia in patients without neutropenia

If pneumonia is suspected in a patient undergoing systemic anticancer treatment without neutropenia, it is necessary to carefully collect the medical history, taking into account the time of symptoms onset and exposure to environmental infectious agents (infections in people around the patient, contact with animals, travels, air-conditioning system-connected infections, etc.).

Community acquired pneumonia

In the vast majority of cases community acquired pneumonia (CAP) in adults is caused by bacteria (Table 2). Routine bacteriological testing is not necessary in all patients with CAP without indications for hospitalisation (IV, B). Microbiological examination, in particular sputum culture, should be considered when risk factors for infection with a multidrug-resistant (MDR) microorganism are found, or when signs and symptoms of infection suggest a different etiology.

In patients requiring hospitalisation, coughing up purulent sputum, and with moderate or severe symptoms, it is necessary to perform a microbiological examination of sputum and two blood cultures before starting antibiotic therapy. In the case of severe pneumonia not responding to beta-lactam antibiotic therapy, determination of antigens of *Streptococcus pneumoniae* and *Legionella pneumophila* in urine is recommended.

Antibiotic therapy for community-acquired pneumonia should include an antibiotic effective against *Streptococcus pneumoniae* (e.g. oral amoxicillin 3 × 1 g) (I, A). In patients with mild community-acquired pneumonia it is possible to use macrolide in the first line (I, B). In moderate community-acquired pneumonia, amoxicillin/clavulanic acid 3 × 1.2 g intravenously or oral amoxicillin/clavulanic acid with sustained release (SR) at a dose of 2000/125 mg every 12 hours could be used (IV, B). In patients with severe pneumonia, the use of ceftriaxone or cefotaxime in combination with macrolide is recommended (II, B). The recommended duration of treatment of uncomplicated community-acquired mild-to-moderate pneumonia is app. seven days or app. three days after clinical stabilisation.

Hospital-acquired (nosocomial) pneumonia

Hospital-acquired pneumonia is an infection that occurs at least 48 hours after admission and was not during incubation at the time of admission [5].

The etiology of nosocomial pneumonia varies and depends on the epidemiological situation in the hospital. Prior to antibiotic administration, microbiological tests are recommended in all patients — blood and sputum culture or bronchoalveolar lavage.

Treatment should depend on the results of microbiological tests and the risk assessment of infection with a multidrug-resistant bacterial strain. The risk of infection with MDR strain increases with the duration of hospitalisation (> 4 days), in patients who previously received antibiotics or were previously hospitalised (up to 90 days before admission).

Gastrointestinal infections

Bacterial, viral, or fungal gastrointestinal (GI) infections in the course of neutropenia may have similar clinical characteristics, and only microbiological ex-

Table 2. Microorganisms most commonly causing hospital-acquired (nosocomial) and community-acquired pneumonia [4]

Hospital-acquired pneumonia	Community-acquired pneumonia
Klebsiella pneumoniae	*Streptococcus pneumoniae* (30–42%)
Pseudomonas aeruginosa	*Klebsiella pneumoniae* (20%)
Staphylococcus aureus	*Mycoplasma pneumoniae* (10–15%)
Escherichia coli	*Chlamydophila pneumoniae* (3–40%)
Streptococcus pneumoniae	*Haemophilus influenzae* (8–10%)
Legionella pneumophila	Viruses — respiratory syncytial virus (RSV), rhinoviruses (8–10%)
Mycobacterium sp.	*Staphylococcus aureus* (4–5%)
Viruses	*Legionella pneumophila* (3–18%)
	Unidentified (30%)

amination of the material sampled from the infection site makes diagnosis possible. The planned therapy should take into account the probability of various pathogens co-occurrence, therefore, apart from the use of broad-spectrum antibiotic therapy, simultaneous antiviral and/or antifungal therapy may be indicated in clinically justified situations (IV, C).

Esophagitis [6]

The main cause of esophagitis is yeast infection or reactivation of HSV infection. The presence of thrush in the mouth is more indicative of candidiasis, but their absence does not preclude fungal infection. An unambiguous diagnosis can be made after endoscopic examination with sampling material for microbiological examination; however, it is a procedure with a risk of complications, especially in patients with neutropenia or thrombocytopenia. If candidiasis is suspected, empirical treatment with fluconazole should be initiated (I, A). However, in the case of clinical signs and symptoms of esophagitis in patients with neutropenia or undergoing immunosuppressive therapy, the use of fluconazole and acyclovir should be considered (IV, B).

Diarrhoea

The etiology of GI infections in cancer patients may be typical (e.g. *Salmonella*, *Shigella*, *Yersinia*, rotaviruses, adenoviruses, and noroviruses). Anticancer treatment may result in pathological proliferation of bacteria (*Klebsiella, Proteus, Enterococcus sp.*) and fungi (most often *Candida*). Therefore, quite often, endogenous flora is the cause of the infections. Moreover, drug-induced damage of mucous membranes significantly increases the risk of invasion of endogenous pathogens into blood and peritoneum.

Pseudomembranous colitis (*Clostridium difficile* infection) is most often a consequence of antibiotic therapy or hospitalisation itself, but it can also occur in the course of neutropenia [7]. The clinical picture covers a wide range of symptoms ranging from mild diarrhoea to megacolon toxicum. Diarrhoea is most often accompanied by painful abdominal cramps, fever, and leukocytosis. In each case of diarrhoea with a potentially infectious etiology in a patient receiving myelosuppressive therapy or antibiotic therapy, stool (two samples) should be examined, including multi-stage algorithms with the assessment of the presence of toxins or toxins genes A and/or B and glutamate dehydrogenase (GDH) (methods allowing a quick positive result) (IV, C). Stool culture is the most sensitive method but is impractical because of the duration of the culture.

Management of pseudomembranous colitis includes:
- isolation of the patient (IV, B);
- discontinuation of the antibiotic that is causing the infection (may be sufficient for patients with a mild form) (II, A);
- the use of oral vancomycin (I, A) or fidaxomicin (I, A); in the case of mild disease and limited access to these drugs, oral metronidazole (IV, C) may be used; in very severe forms, co-administration of intravenous metronidazole and oral vancomycin should be considered (III, A);
- surgical treatment: megacolon toxicum, perforations, symptoms of toxaemia not responding to conservative treatment (II, B).

Neutropenic enterocolitis is a life-threatening disease with a mortality rate of around 50% [8]. The most commonly identified pathogens are Gram-negative bacteria (less often Gram-positive), and in about 5% of cases fungal infections are the cause (*Candida albicans*). The main symptoms include: nausea, vomiting, flatulence and abdominal pain, fever, and diarrhoea, sometimes bloody. CT scans or ultrasound examination reveal colon wall thickening (> 4 mm). Stool and blood culture and differentiation with *Clostridium difficile* infection is required. Final diagnosis is possible based on histopathological examination; however, due to the significant risk of complications, endoscopic diagnostics is not indicated (IV, C).

Management of neutropenic enterocolitis includes:
- strict diet (except for the mild form) and hydration (IV, A) and possible parenteral nutrition (IV, B);
- the use of broad-spectrum antibiotic therapy covering *Clostridium difficile*, aerobic and anaerobic bacteria; most authors recommend monotherapy with carbapenem, piperacillin with tazobactam or a combination of III or IV generation cephalosporins with metronidazole (IV, A);
- considering the use of G-CSF (I, B);
- surgical treatment in the case of complications (IV, C);
- antifungal therapy if there is no response to antibiotic therapy (IV, B).

Infections of the skin, subcutaneous tissue, and soft tissues

In cancer patients, especially those undergoing immunosuppressive treatment or with deep neutropenia, the clinical features of skin and soft tissue infections often take on a less severe form and look different from those seen in individuals without cancer. Usually, the initial manifestations include delicate erythematous lesions, macular or maculopapular eruptions, nodules or signs of subcutaneous tissue inflammation. Infection

may primarily develop within these tissues or manifest as a generalised infection. The etiological factors include bacteria, viruses, fungi, as well as parasites.

Before starting treatment, it is advisable to collect material for histopathological and microbiological examination (IV, C), and in some patients imaging tests to assess the severity of inflammatory lesions (IV, C). Antibiotic therapy should cover Gram-positive bacteria (the most common etiology) (IV, A). In patients with febrile neutropenia and symptoms suggestive of skin, subcutaneous, or soft tissue inflammation, the use of vancomycin should be considered as standard antibiotic therapy (until cultures are obtained) (I, A), and in patients with long-term neutropenia, the addition of an antifungal drug should be also considered (IV, C).

Infections of the skin and soft tissues of the perineum are most often associated with Gram-negative or anaerobic bacteria. The spectrum of antibiotic therapy should include these groups of pathogens (IV, A).

Catheter-associated infections (connected with the intravascular line) may occur as local infections, catheter tunnel infections, phlebitis, or bloodstream infections. The etiological factors of most infections are Gram-positive bacteria (most often coagulase-negative *Staphylococci*) [9]. In the case of suspected catheter infection, cultures of blood drawn from the catheter and peripheral vein should be performed, time to positive culture should be determined (interpretation in the "Neutropenia" chapter), and vancomycin antibiotic therapy should be initiated (I, A). In patients diagnosed with febrile neutropenia, the suspicion of catheter-associated infection is an indication to add vancomycin to standard empirical antibiotic therapy until bacteriological confirmation (IV, A). Catheter removal is not absolutely necessary if the patient's state is stable and the microbial causative agent is not identified. The likelihood of successful treatment without removing the catheter depends on the clinical judgment and the type of pathogen responsible for the infection. Infection limited to the site usually (except in severe cases) does not require catheter removal; however, as well as from blood cultures, a swab should be taken from the suspected site, followed by antibiotic therapy covering the spectrum of the recognised pathogen.

Indications for catheter removal are as follows (IV, A):
— sepsis, unstable general state in patients with suspected catheter-associated infection;
— severe, clinically apparent infection of catheter tunnel or implantable port for chemotherapy;
— septic thrombophlebitis;
— persistent bacteremia despite antibiotic therapy;
— infection with atypical mycobacteria;
— candidemia;
— catheter removal should also be considered in case of infections: *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter, Bacillus*.

The most common causes of viral skin infections in cancer patients include reactivation of latent herpes simplex virus (HSV) or varicella zoster virus (VZV) [10]. They occur mainly as a vesicular rash; however, in patients with reduced immunity, they take on an atypical (e.g. VZV infection in the form of single or multiple lesions with an accidental location) or generalised form more often than in individuals with normal immunity. Diagnostic procedures involve the collection of a follicle (scraping) or fluid from inside for cytological examination, direct fluorescence examination or culture. Acyclovir treatment should be oral or intravenous depending on the severity of the symptoms (I, A).

Gangrenous ecthyma is a cutaneous manifestation of a generalised infection (most often *Pseudomonas aeruginosa*) [10]. It occurs in the form of rapidly progressing (within 24 hours) skin lesions eventually taking on the form of single or multiple ulcers. Treatment includes antibiotic therapy with high activity against this pathogen (I, A); surgical intervention is sometimes indicated (III, C). Similar skin lesions may accompany generalised infections of *Staphylococcus aureus*, *Streptococcus pyogenes*, Gram-negative bacilli, some fungi, and even HSV.

Necrotising fasciitis (NF) (sometimes with concomitant myositis) is an acute, rapid, subcutaneous tissue infection with common concomitant becteremia [10]. In cancer patients it is more often associated with Gram-negative bacteria or mixed flora infections than in individuals with normal immune function. For an accurate assessment of the inflammatory process severity magnetic resonance imaging is recommended (IV, A). Management of patients with neutropenia includes surgical treatment (in more advanced cases) (IV, A) and broad-spectrum antibiotic therapy (I, A); in some patients the inclusion of G-CSF should be considered (IV, C).

Urinary tract infections

In patients treated for cancer, the risk of developing a urinary tract infection may be affected by the following: urinary tract obstruction, urinary catheter insertion, damage of the urinary tract epithelium as a result of surgery and chemotherapy or radiotherapy, concomitant diseases, as well as kidney function impairment.

Symptoms of lower urinary tract infection (cystitis) include dysuria, polyuria, nocturia, and urinary

incontinence (UI) (involuntary urination). In addition, general symptoms (fever, chills, lumbar pain, nausea, and vomiting) and a positive Goldflam symptom are observed in inflammation of the kidneys (nephritis).

The most common etiological factors of urinary tract infections are *Escherichia coli* followed by *Pseudomonas* sp., *Klebsiella* sp., and *Enterobacter* sp. In hospitalised patients with risk factors (diabetes, immunosuppression, chronic catheterisation) fungal infections can also occur.

The key to determining antibiotic therapy is urine culture, but in cases not responding to treatment and in patients with complicated pyelonephritis (e.g. nephrolithiasis, other urological diseases, recurrent urinary tract infection), CT of the abdomen and pelvis is recommended (IV, A).

The choice of antibiotic in empirical therapy depends on infection severity, kidney function, and the risk of drug resistance. If local resistance to particular groups of drugs is below 20%, fluoroquinolone (ciprofloxacin, levofloxacin), cephalosporin (III–IV generation), aminopenicillin with beta-lactamase inhibitor, and aminoglycoside are most commonly used (II, A). In the case of treatment failure or severe clinical status, the use of piperacillin/tazobactam, carbapenem, or ceftazidime is justified (II, A). Duration of treatment should be 7–14 days, and if there is no improvement within 48–72 hours, it should be modified according to the result of the antibiogram [11].

There are no indications for control urinalysis when clinical effectiveness of the treatment is confirmed.

Conflicts of interest

The authors declare to have no conflict of interest.

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