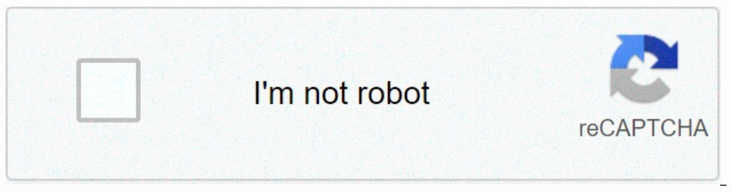

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Esmo guidelines febrile neutropenia

Singkatnya terapi voriconazole sebagai faktor risiko kambuhnya aspergillosis paru invasif. Shin DH, Yoo SJ, Jun KI, Kim H, Kang CK, Song KH, Choe PG, Park WB, Bang JH, Kim ES, Park SW, Kim HB, Kim NJ, Oh MD. Shin DH, dkk. Sci Rep. 2020 Sep 30;10(1):16078. doi: 10.1038/s41598-020-73098-w. Sci Rep. 2020. PMID: 32999399 Artikel PMC gratis. Neutropaenia Febrile (FN) didefinisikan sebagai suhu oral >38,3°C atau dua pembacaan berturut-turut sebesar >38,0°C selama 2 jam dan jumlah neutrofil absolut (ANC) <0.5 ×= 109/l,= or= expected= to= fall= below= 0.5= ×= 109/l.despite= major= advances= in= prevention= and= treatment,= fn= remains= one= of= the= most= frequent= and= serious= complications= of= cancer= chemotherapy= (cht).= it= is= a= major= cause= of= morbidity,= healthcare= resource= use= and= compromised= treatment= efficacy= resulting= from= delays= and= dose= reductions= of= cht.= mortality= from= fn= has= diminished= steadily,= but= remains= significant.most= standard-dose= cht= regimens= are= associated= with= 6–8= days= of= neutropaenia,= and= fn= is= observed= in= ~8= cases= per= 1000= patients= receiving= cancer= cht.= fn= is= responsible= for= considerable= morbidity= as= 20%–30%= of= patients= present= complications= that= require= in-hospital= management ,= with= an= overall= in-hospital= mortality= of= ~10%.= the= mean= cost= per= hospitalisation= in= western= countries= is= ~13= 500€= (15= 000= us$).there= is= a= clear= relationship= between= the= severity= of= neutropaenia= (which= directly= influences= the= incidence= of= fn)= and= the= intensity= of= cht.= currently,= the= different= regimens= are= classified= as= producing= a= high= risk= (=>sebesar 20%), risiko menengah (10%–20%) atau risiko rendah <10%) of= fn.it= has= been= shown= that= several= factors,= other= than= cht= itself,= are= responsible= for= increasing= the= risk= of= fn= and= its= complications.= among= them,= age= plays= a= major= role= [ii,= iii]= with= older= patients= having= a= higher= risk= of= fn= following= cht,= with= worse= morbidity= and= mortality= rates.= other= factors= having= a= similar= role= are= as= follows:the= risk= of= fn= and= its= complications= increases= when= one= or= several= co-morbidities= are= present= in= the= patient.= these= considerations= will= be= instrumental= in= deciding= whether= a= cht-treated= patient= should= receive= primary= prophylaxis= to= decrease= the= potential= risk= of= fn.in= the= case= of= fn,= prognosis= is= worst= in= patients= with= proven= bacteraemia,= with= mortality= rates= of= 18%= in= gram-negative= and= 5%= in= gram-positive= bacteraemia= [for= bacteraemias= due= to= coagulase-negative= staphylococcus= (cns)= only ,= no= attributable= mortality= has= been= reported]= [1klastersky= j.= ameye= l.= maertens= j.= et= al.bacteraemia= in= febrile= neutropenic= patients.]. = the= presence= of= a= focal= site= of= presumed= infection= (e.g.= pneumonia,= abscess,= cellulitis)= also= makes= outcome= worse.= mortality= varies= according= to= the= multinational= association= of= supportive= care= in= cancer= (mascc)= prognostic= index= (table= 1):= lower= than= 5%= if= the= mascc= score= is= ≥21,= but= possibly= as= high= as= 40%= if= the= mascc= score= is=></10%)> <15 [2Klastersky J. Paesmans M. Rubenstein E.B. et al. The Multinational Association for Supportive [2klastersky= j.= paesmans= m.= rubenstein= e.b.= et= al.the= multinational= association= for= supportive=></15 [2Klastersky J. Paesmans M. Rubenstein E.B. et al. The Multinational Association for Supportive > (</0.5> (</0.5> in the cancer risk index: a multinational assessment system for identifying low-risk fever neutropenic cancer patients.]. Table 1MASCC febrile neutropaenia risk indexPatients with a score ≥21 low-risk complications. The points associated with the variable 'disease load' are not cumulative. Therefore the maximum theoretical score is 26 [2Klastersky J. Paesmans M. Rubenstein E.B. et al. Multinational Association for Supportive Care in Cancer risk index: a multinational assessment system for identifying low-risk neutropenic fever cancer patients.]. Reprinted with permission. © American Society of Clinical Oncology 2000. All rights reserved. BP, blood pressure. The rate of positive microbiological detection based on standard blood grains varies depending on whether the patient has received prophylactic antibiotics or not. Overall, bacteraemia can be detected in ~ 20% of patients with FN; this definitely helps to better tailor antibiotic therapy. It is important to understand that different centers experience different frequency patterns of pathogens causing different causes. Therefore, these guidelines are intended to be used in common with appropriate local antimicrobial policies tailored to central epidemiology. Over the past few decades, shifts have occurred from FN associated primarily with Gram-negative bacteria to FN associated with Gram-positive organisms. Currently, most centers report Gram-positive and Gram-negative bacteraemia in 50% of patients with FN, although centers that do not use fluoroquinolone prophylaxis report gram-negative bacterial predomination. Increased antibiotic-resistant strains have been noted, such as extended spectrum &bgr;-lactamase (ESBL)—producing Gram-negative bacteria, vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA). An increasing number of infections with flukonazole-resistant candida strains (e.g. Candida krusei and Candida glabrata) have also been reported [3Moghnieh R. Estaitieh N. Mugharbil A. et al. Third generation cephalosporin resistant Enterobacteriaceae and gram-negative multidrug resistant bacteria that cause bacteriumemia in adult cancer patients with fever neutropenia in Lebanon, broad-spectrum antibiotics are used as major risk factors, and correlation with poor prognosis.]. Antimicrobials (the first antibiotics that cannot be absorbed and then, co-trimoxazole) have been used for a long time for the prevention of FN episodes in CHT-treated patients. Since the 1990s, fluoroquinolones have been widely used for chemoprophylaxis. Most studies have shown that fluoroquinolones reduce the incidence of infection and, in some studies, also infection-related deaths, but at the expense of the appearance of quinolone-resistant strains. It should, on make prophylaxis useless; in addition, this strain jeopardizes the use of fluoroquinolones as a therapeutic therapy in low-risk patients, as will be discussed elsewhere. For all these reasons, the use of antimicrobials, including fluoroquinolones, should be discouraged. Guidelines from the EORTC (European Organisation for Research and Treatment of Cancer) and the American Society of Clinical Oncology (ASCO) recommend that doctors limit the use of antibacterial prophylaxis for patients at high risk for FN; others recommend avoidance only from such practices for the prevention of FN. The latest update of Cochrane's meta-analysis still recommends the use of ciprofloxacin or levofloxacin in cancer patients undergoing intensive ChT [4Gafter-Gvili A. Fraser A. Paul M. Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients.]. Several meta-analyses showed that primary prophylaxis with G-CSF (i.e. G-CSF administered immediately after cycle 1 ChT) reduced fn risk by at least 50% in patients with solid tumors without significantly affecting tumor response or overall survival [I][5.Clark O.A. Lyman G.H. Castro A.A. et al. Colony stimulating factors for chemotherapy-induced fever neutropenia: meta-analysis of randomized controlled trials., 6.Cooper K.L. Madan J. Whyte S. et al. Factors stimulating granulocyte colonies for neutropenia fever prophylaxis after chemotherapy : Systematic review and meta-analysis., 7.Kuderer N.M. Dale D.C. Crawford J. Lyman G.H. Impact of primary prophylaxis with stimulating factors of granulocyte colonies in fever neutropenia and death in adult cancer patients receiving chemotherapy: systematic review.]. Most guidelines recommend that the G-CSF be given prophylaxis if fn risk is >20% for all planned treatment cycles [I, A]. Risk classifications according to the type of ChT have been published and updated [8Aapro M.S. Bohlius J. Cameron D.A. et al.2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factors to reduce the incidence of chemotherapy-induced fever neutropenia in adult patients with lymphoproliferative For patients with intermediate risk (10%–20%), it is important to consider the age of the patient and especially the morbidity that coexists, as already mentioned [8.Aapro M.S. Bohlius J. Cameron D.A. et al.2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factors to reduce incidence of chemotherapy-induced fever neutropenia in adult patients with lymphproliferative disorders and solid tumors. , 9.Smith T.J. Khatcheressian J. Lyman G.H. et al.2006 updates recommendations for the use of white blood cell growth factors: evidence-based clinical practice guidelines., 10.Sung L. Nathan P.C. Alibhai S.M et al. Meta-analysis: hematopoietic prophylactic effects of colony-stimulating factors on death and infection outcomes.]. The algorithm for decisions about the use of G-CSF primary prophylaxis is presented in Figure 1.Figure 1Algorithm for first first the use of stimulating factors of granulocyte colonies, adapted from the European Organization Guidelines for Research and Treatment of Cancer. FN, neutropaenia fever; G-CSF, a stimulating factor of granulocyte colonies. Reprinted from [8Aapro M.S. Bohlius J. Cameron D.A. et al.2010 Update of EORTC guidelines for the use of granulocyte-colony stimulating factors to reduce the incidence of chemotherapy-induced fever neutropenia in adult patients with lymphproliferative disorders and solid tumors.], with permission from Elsevier.In addition to this approach, G-CSF can be considered in patients with reduced bone marrow reserve due to extensive radiotherapy [III] or neutropaenic patients in the context of HIV infection [II]. The latest meta-analysis of randomized and controlled trials [11Wang L. Baser O. Kutikova L. et al. Primary prophylactic impact with stimulating factors of granulocyte colonies in fever neutropenia during chemotherapy: systematic review and meta-analysis of randomized controlled trials.] and experience in real-world settings [12Mitchell S. Li X. Woods M. et al.Comparative effectiveness of granulocyte colony-stimulating factors to prevent febrile neutropenia and related complications in cancer patients in clinical practice: a systematic review.] confirmed the extraordinary (>50% success) of primary prophylaxis with filgrastim or pegfilgrastim. With most ChT used for the treatment of common tumors, the risk of FN is maximal during the first course; thus, it makes sense to recommend primary prophylaxis for at-risk patients rather than systematically using secondary prophylaxis. Secondary prophylaxis (i.e. G-CSF given for ChT courses following courses with FN) is indicated if the dose reduction is below the threshold or cht delay is not desirable (e.g. treatment with curative intent). There are several complications associated with the administration of the G-CSF; The most common side effects are small or moderate bone pain that can usually be treated with standard analgesics. Use 5 &mgr;g/kg/day G-CSF subcutaneously (s.c.) 24–72 hours after the last day of ChT until sufficient/stable post-nadir ANC recovery (achieving an ANC target of >10–109/l is not required). Pegfilgrastim, injected s.c. as a single dose either 100 &mgr;g/kg (individually) or from a total dose of 6 mg (general approach), is considered equally effective [I, A]. The equivalent filgrastim dose was 5 &mgr;g/kg/day for ~10 days. There is not enough data for the reduction of numbers or alternate days or days of G-CSF instead of standard, either to be used on day 1 instead of on day 2. EMA/FDA approved biosimilars can be considered. Acute leukaemia therapy, autologous and allogeneic stem cell transplantation (TLs) lead to a higher risk of FN and potentially deadly complications [13Hämäläinen S. Kuittinen T. Matinlauri I. et al. Nerve fever and severe sepsis in acute myeloid leukemia patients (AML) who received intensive chemotherapy: the causes and consequences.]. Fn incident in the situation is as follows:FN related deaths are described as follows:Success in FN management requires rapid recognition of, and reaction to, potential infections. It is important to educate outpatients to monitor their symptoms, including body temperature, and to provide clear written instructions on when and how to contact the appropriate services in case of concern. In addition, effective written local policies are essential to ensure a quick response whenever the FN is suspected. Some patients may be present with FN in the Emergency Department, and in this situation, clear protocols must be re-established to properly manage these patients. The first therapy should be administered in the hospital within 1 hour of admission of the patient with FN. Delays in administering antibiotics have been linked to a significant extension of hospital stays and an increase in deaths. As already mentioned, the spectrum of infection in cancer patients differs from place to place and changes over time; therefore, paying attention to local epidemiology is very important [14Vitel infections are currently in cancer patients with neutropenia-related chemotherapy.]. Detailed history should be taken including given ChT properties, previous prophylactic antibiotics, concurrent steroid use, recent surgical procedures and the presence of allergies. To guide therapy, it is important to examine clinical records for past positive microbiology, in particular the presence of antibiotic-resistant organisms or previous bacteraemia. Initial assessment (Table 2) of circulatory and respiratory functions, with strong resuscitation if necessary, should be followed by careful examination for potential infection focus. Signs and symptoms of infection in neutropaenic patients can be minimal, especially in those receiving corticosteroids, or in elderly patients who may often present with a state of confusion. Table 2 Assessment and investigation of investigation.v., intravenously; CT, computed tomography.aUrinalysis, sputum and fesol culture only in case of suspected focus of infection on these sites. Vigilance is necessary in patients at risk for FN presenting unhealthy, hypotensive (compared to previous known blood pressure readings), with low-grade temperature or afebrile, as they may develop Gram-negative septicaemia, requiring rapid treatment. Urgent full blood count, to ensure the ANC along with other investigations listed in Table 2, is essential in guiding initial management. Two sets of blood cultures from peripheral veins and catheters of any indwelling venous veins should be taken as well as specimens for microbiological testing of suspected infectious sites, before the rapid institution of empirical broad-spectrum antimicrobial therapy. Urinary tract infections should be suspected even in asymptomatic patients with a past history of infection Most cases of FN, as managed according to the algorithm specified in Figure 2, 2, immediately for empirical therapy, does not suffer from major complications. A number of instruments have been developed in an attempt to predict these low-risk cases where complications are unlikely to occur. The most widely used instrument, the MASCC index, allows doctors to assess quickly, based solely on clinical, patient risk with FN. MASCC scores have been prospectively validated in several studies. Weighting criteria and scores are listed in Table 1. Low-risk cases are those that score ≥21. The rate of serious medical complications in low-risk cases is estimated at 6% and the mortality rate is below 1%. If the clear focus of infection is clear, antibacterials should be adjusted. Figure 2Inisi management of neutropaenia fever. ANC, absolute number of neutrophils; MASCC, The Multinational Association of Supportive Treatments in Cancer.A recent review has concluded that inpatient oral antibacterial therapy can be safely substituted for conventional intravenous treatment (i.e.) in some low-risk FN patients, i.e. those whose AgePrecise criteria are not defined because it varies between the trials reviewed. Single-agent quinolones (moxifloxacin) are not inferior to combinations (quinolone with amoxicillin plus clavulanic acid), but the latter is preferred given the rise in Gram-positive FN episodes. Oral quinolone therapy should not be used in patients who have taken antibacterial quinolone as a prophylaxis. The safety of early changes in oral combinations in afebrile patients after 48 hours on I.V. therapy was supported in reviews and favored by many physicians. Some low-risk patients may be treated with outpatient parenteral regimen. The possibility of exclusive oral outpatient management for low-risk FN cases has become increasingly attractive on the grounds of patient comfort, economy [15Elting L.S. Lu C. Escalante C.P. et al. Outpatient outcomes and costs or inpatient management of 712 patients with fever neutropenia.] and reduced incidence of nosocomial infections. There is also evidence to support early release policies in these low-risk cases once they become clinically stable, without better symptoms and there is evidence of fever lysis after a minimum of 24 hours in the hospital [II, B], and provided there is an adequate understanding of the risks and that patient supervision is available [16.Freifeld A. Marchigiani D. Walsh T. et al. Double-blind comparison of empirical and intravenous antibiotic therapy for low-risk fever patients with neutropenia during cancer chemotherapy. , 17.Innes H. Lim S.L. Hall A. et al. Management of febrile neutropenia in solid tumors and lymphoma uses the Multinational Association for Supportive Care (MASCC) risk index, feasibility and safety in routine clinical practice., 18.Kern W.V. Marchetti O. Drgona L. et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: double-blind multicenter trial single daily moxofloxacin with with daily ciprofloxacin plus amoxicillin-clavulanic acid combination therapy - EORTC infectious disease trial group XV., 19.Pherwani N. Ghayad J.M. Holle L.M. Karpiuk E.L. Outpatient management of neutropenia fever associated with cancer chemotherapy: stratification of risk and treatment review.]. Patients with FN who are at high risk are assessed by mascc (<21) criteria, or have high-risk features as assessed by the admitted doctor, should be hospitalized and start on a broad-spectrum I.v. antibiotic, because the risk of bacterial sepsis is very high [infection 20Bloodstream in cancer patients with fever neutropenia.]. Isolation patterns and resistance of local epidemiological bacteria are essential in determining first-choice empirical therapy, since coverage for MRSA or Gram-negative resistant bacteria may be required [21Montassier E. Batard E. Gastinne T. et al. Recent changes in bacteriemia in patients with cancer: a systematic review of epidemiology and antibiotic resistance.]. Meta-analyses compared monotherapy (e.g. anti-pseudomonal cephalosporins such as ceftazidime or cefepime, imipenem, meropenem or piperacillin-tazobactam) with combination therapies finding equal efficacy [I, A] [22Furno P. Bucaneve G. Del Favero A. Monotherapy or a combination containing aminoglycoside for empirical antibiotic treatment of neutropenic febrile patients: meta-analysis., 23Comment on: empirical antibiotic monotherapy for fever neutropenia: a systematic review and meta-analysis of randomized controlled trials.]. This is less evident in the high-risk subset of prolonged neutropaenia and those suffering from bacteraemia, where bactericidal activity and the synergistic effects of antibiotics &bgr;-lactam in combination with aminoglycoside may be preferred; that is, in the case of pseudomonas aeruginosa sepsis or in centers with known vulnerability of medium Gram-negative bacilli to &bgr;-lactams [3Moghnieh R. Estaitieh N. Mugharbil A. et al. Third generation cephalosporin resistant Enterobacteriaceae and gram-negative multidrug resistant bacteria that cause bacteriumemia in adult cancer patients with fever neutropenia in Lebanon, broad-spectrum antibiotics are used as major risk factors, and correlation with poor prognosis.]. The main recommendations on the management of fever neutropenia are summarized in Table 3.Table 3Key recommendations for the management of FNFN, febril neutropaenia; ChT, chemotherapy; G-CSF, a stimulating factor of granulocyte colonies; MASCC, the Multinational Association of Supportive Treatments in Cancer.Apart from standard treatment with broad-spectrum antibacterial agents, there are a number of situations, in clinical practice, that require a certain regimen. The duration of treatment may vary and local antibacterial guidelines should be followed in these circumstances. If the patient has an i.v. catheter-related infection (CRI) it should be suspected, and the blood must be cultured from the catheter and peripherally to measure the differential positivity (DTTP), which is the time difference between the positivity of results between catheter culture and peripheral blood culture. DTTP ±2 h is an indicator of catheter-related bacteraemia [I, A] [24Seifert H. Cornely O. Seggewiss K. et al. Bloodstream infections in neutropenic cancer patients associated with short-term nontunnelled catheters are determined by quantitative blood culture, differential time for positivity, and molecular epidemiological typing with pulsating field gel electroesis.]. All CRI cases in FN settings require decision making on the choice and duration of antibiotics, and the need for catheter removal. When CRI is suspected, and the patient is stable, the catheter should not be removed without microbiological evidence of infection [25Raad I. Kassar R. Ghannam D. et al. Catheter management in catheter-related staphylococcal bacteria documented: remove or maintain?.]. Glycopeptides such as vancomycin should be administered over the line whenever possible to cover gram-positive organisms [III, A]. Teicoplanin is a useful alternative because it can be given once a day as a key line. Success in treating CRI without eliminating catheters depends on pathogens isolated in blood culture. In CRI due to CNS, efforts to preserve catheters can be made if the patient is stable [III, B]. Catheter retention has no impact on the resolution of CNS bacteraemia but is a significant risk factor for relapse in patients where the catheter is maintained. Removal of lines is indicated in the context of tunnel infections, pocket infections (implant port systems) [III, B], persistent bacteraemia despite adequate care, atypical mycobacterial infections and candidaemia. With regard to duct infections caused by S. aureus, literature is divided. The desire to preserve the line should be balanced against the risk of metastatic spread by seeding the bloodstream. The recommendation is to remove the line if possible, while acknowledging that, with careful management, it is possible to maintain it for a short time. Persistent fever and bacteraemia although proper antibiotics are indications for the removal of the ducts. If outpatient pneumonia is diagnosed either on clinical grounds and/or on the basis of radiological imaging, antibiotic cover can be expanded to treat atypical organisms such as Legionella and Mycoplasma by adding macrolide or fluoroquinolone antibiotics to antibiotics &bgr;-lactam [V, D]. Consideration for infection with Pneumocystis jirovecii should be given to patients present with high respiratory levels and/or desaturate ready from oxygen or at minimal exertion. Predisposing factors include previous corticosteroid therapy, use of immune suppressor after organ TPL and exposure to purine analogues, as well as a reliable lack of chemoprofilsis with co-trimoxazole [26Evolving health effects hundred years of advances in diagnosis and treatment.]. In high-risk patients with deep prolonged neutropaenia and lung infiltration,

early treatment with mold active antifungal agents is recommended. Patients with AML during ChT induction remission and those undergoing haematopoietic allogeneic TPL stem cells with the previous condition ChT are at risk of invasive yeast infection (i.e. aspergillosis) due to prolonged and profound neutropaenia [27Maschmeyer G. Carratalà J. Buchheidt D. et al. Diagnosis and therapy of lung infiltration antimicrobials in fever neutropenic patients (excluding allogeneic SCT): latest guidelines from the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO).]. Frequent assessment of the initial response to antibacterial therapy is essential, and, in the absence of a quick fix, further investigation is warranted. If invasive aspergillus is suspected, a high-resolution chest computing tomography (CT) scan should be performed on the same day, looking for distinctive features such as nodules with halo or ground glass changes, and galactomannan should be measured in serum. If any intruders are found, bronchoalveolar lavage should be carried out if possible. Advice from an infectious disease specialist (ID) or clinical microbiologist is recommended, and appropriate therapy against infection with fungi or pneumocystis species should be instituted. The choice of antifungal agents will depend on the center, individual patients and previous use of prophylactic therapy [28Marr K.A. Schlamm H.T. Herbrecht R. et al.Combination antifungal therapy for invasive aspergillosis: randomized trials.]. Therapy for suspected aspergillosis (for cases with typical infiltration of CT) can consist of voriconazole or liposomal amphotericin B [I, A] [29Cornely O.A. Maertens J. Bresnik M. et al. Liposomal amphotericin B as an initial therapy for invasive fungal infections: randomized trials comparing high-loading dose regimen with standard doses (AmBiLoad Trial)., 30Herbrecht R. Denning D.W. Patterson T.F. et al. Voriconazole versus amphotericin B for the main therapy of invasive aspergillosis.]. This antifungal can be combined with echinocandin in unresponsive diseases [IV, B]. Proper microbiological diagnosis is highly desirable in patients suspected of invasive fungal infections, since sensitivity to various antifungal agents varies among different species. High dose co-trimoxazole is the treatment of choice for suspected pneumocystis infection [I, A]. Once the right sample is taken, therapy with aciclovir should begin [I, A]. Ganciclovir (or foscarnet) should be replaced only when there is a high suspicion of invasive cytomegalovirus infection [I, A] [31Glenny A.M. Fernandez Mauleffinch L.M. Pavitt S. Walsh T. Interventions for the prevention and treatment of herpes simplex virus in patients treated for cancer., 32Torrez-Madriz G. Boucher H.W. Immunocompromised perspective in the treatment and prophylaxis of cytomegalovirus disease in solid organ transplant recipients.]. Lumbar punctures (if in any way possible before the institution of antibiotics) are mandatory in these rare cases. Bacterial meningitis should be treated with ceftazidime plus ampicillin (to cover listeria monocytogenes) or meropenem [II, A]. Viral encephalitis is treated with a high dose of aciclovir. The addition of vancomycin extends the cover against skin pathogens [V, D]. Linezolids and daptomycin are emerging alternatives to glcopeptides; However, more clinical experience is needed, especially in neutropaenic patients. If clinical or microbiological evidence of intra-abdominal or pelvic sepsis exists, metronidazole should begin [V, D], unless the patient is in carbapenem or piperacillin-tazobactam, which has adequate anaerobic coverage. Assessment for Clostridium difficile is required and, if suspected, oral vancomycin or metronidazole treatment should be administered [V, D]. Patients at risk of disdidiasis are those with prolonged neutropaenia and especially those with haematological malignancy undergoing myeloablative therapy [33van der Velden W.J. Blijlevens N.M. Feuth T. Donnelly J.P. Febrile mucositis in haematopoietic SCT recipients.]. Candidaemia can be diagnosed in blood cultures; however, culture may take several days to be positive. Empirical initiation of antifungal therapy is recommended in patients whose fever fails to respond to broad-spectrum antibiotics after 3-7 days of proper treatment [I, A]. CT scans of the liver and spleen should be done before starting anti-Candida treatment, looking for typical changes. Empirical treatment of the first line depends on what is known about the patient. Liposomal amphotericin B and antifungal echinocandin such as caspofungin are appropriate first-line treatments if the patient has azole or if the patient is known to be colonized with non-albicans candida [I, A]. Fluconazole can be given the first line as long as the patient is at low risk of invasive aspergillosis; Local epidemiological data shows low levels of azole-resistant isolates from Candida and patients have not received azole antifungals as prophylaxis. Once started, antifungal treatment should continue until neutropaenia has been resolved, or for at least 14 days in patients with the indicated invasive Candida infection. A special need to prevent other opportunistic infections is needed in patients with haematological malignancy, namely those undergoing haematopoietic stem cell transplantation [34Summary of guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients.]. The frequency of clinical assessment is determined by severity but may be required every 2-4 hours if resuscitation is required. Daily assessment of trends in fever, bone marrow and kidney function is shown until the patient is afebrile and has 0.≥5 × 109/l (Figure 3) for 24 hours. Repetitive imaging may be required in patients with persistent pyrexia. Figure 3Assessment of the next response and management. ANC, absolute number of neutrophils; i.v., intravenously; ID, infectious disease. If the patient is afebrile and has an ANC ≥0.5 ×109/l at 48 hours, has a low risk and no cause of infection has been found, consider changing oral antibiotics [II, A]. If a high-risk patient with no cause is found and is on multiple therapies, aminoglycoside can be discontinued [V, D]. When the cause is found, proceed to the appropriate specific therapy [II, A]. If the patient is still feverish at 48 hours, but is clinically stable, early antibacterial therapy should continue. If the patient is clinically unstable, antibacterial therapy should be rotated or expanded if clinical development justifies this. Some haematological units will add glycopeptide to the regimen, while others will change the regimen to imipenem or meropenem and glycopeptide. This group of patients with persistent fever is at high risk of serious complications, and quick advice from an ID physician or clinical microbiologist should be sought. Unusual infections should be considered, especially in the context of rising C-reactive proteins, with a view to continuing imaging of the chest and upper abdomen, to exclude the possibility of yeast or yeast infections, or abscesses. When pyrexia lasts for >4-6 days, empirical initiation of antifungal therapy may be required [I, A]. If the ANC ≥0.5 × 109/l, the patient is not resonant and has been afebrile for 48 hours and the blood culture is negative, antibacterial can be stopped [II, A]. If the ANC is at ≤0.5 × 109/l, the patient does not suffer from complications and has been afebrile for 5-7 days, antibacterials can be stopped except in certain high-risk cases with acute leukaemia and follow high-dose ChT when antibacterials are often continued for up to 10 days, or until an ANC ≥0.5 × 109/l [II, A]. Patients with persistent fever despite neutrophil recovery should be assessed by an ID physician or clinical microbiologist and considered antifungal therapy [II, A]. The overall algorithm for response assessment and subsequent management is proposed in Figure 3.These clinical practice guidelines were developed in accordance with ESMO standard operating procedures for the development of clinical practice guidelines, . The relevant literature has been selected by expert authors. A summary of recommendations is shown in Table 3. The level of evidence and recommendation values have been applied using the system shown in Table 4. Statements without judgment are considered justified as standard clinical practice by ESMO experts and faculties. The manuscript has been the target of an anonymous peer review process. Table 4Levels of evidence and recommendation values (adapted from infectious diseases society of America–United Grading Systema Public Health Service)aBy permission from the Infectious Diseases Society of America [34Summary of guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients.]. JK has stated the speaker fee and consultation fee from TEVA. JdN stated there was no potential conflict of interest. KR has reported research support from Merck, Allergan, and JMI Laboratories and participation in the advisory board for Allergan. BR has reported advisory boards for Sandoz/Hexal, Amgen and Roche, research support from Sandoz/Hexal and speaker bureaus for Teva, Amgen and Roche. GM has reported personal expenses (beyond the proposed work) of Merck/MSD, Astellas, Gilead, Pfizer, F2G, Roche and Basilea. MA has reported consultations for Amgen, Hospira, Pfizer, Pierre Fabre, Roche, Sandoz, Teva and honoraria to study at symposiums for Amgen, Chugai, Hospira, Kyowa Hakko Kirin, Pierre Fabre, Roche, Sandoz, Sanofi, Taiho and Teva. JH has stated that he is a member of the advisory board of rolapitant for Tesaro.Bacteraemia in neutropenic fever patients. 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