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Empirical antimicrobial treatment in haemato-/oncological patients with neutropenic sepsis

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ABSTRACT

Neutropenic sepsis in haemato-/oncological patients is a medical emergency, as infections may show a fulminant clinical course. Early differentiation between sepsis and febrile neutropenic response often proves to be challenging. To assess the severity of the illness, different tools, which are discussed in this article, are available. Once the diagnosis has been established, the correct use of early empirical antibiotic and antifungal treatment is key in improving patient survival. Therefore, profound knowledge of local resistance patterns is mandatory and carefully designed antibiotic regimens have to be established in cooperation with local microbiologists or infectious diseases specialists. In the following, identification, therapy and management of high-risk, neutropenic patients will be reviewed based on experimental and clinical studies, guidelines and reviews.

INTRODUCTION

Certain populations of patients are at increased risk for developing infectious complications during the course of their disease and/or treatment. Due to continuous development of treatments and therapies and accompanied increase of average overall life expectancy, we see ourselves faced with growing incidence of malignant diseases.[1] And although biologicals show ever increasing use, cytotoxic antineoplastic therapy remains an important cornerstone of most treatment regimens. Identifying the patient at risk for neutropenic sepsis can be challenging as in most cases no early warning signs apart from fever are present. Additionally, physicians responsible for the treatment of haemato-/oncological patients are more and more faced with multidrug-resistant organisms complicating the empirical treatment of neutropenic sepsis.[2] It is imperative that patients are evaluated individually for risk of infection to minimise the occurrence of infection-related complications.

Identifying the patient at risk

Febrile neutropenia—often the first sign of infection in neutropenic patients with cancer—is a medical emergency as bacterial infections may show fulminant progression.[3] Therefore, early recognition of patients at risk for severe neutropenic sepsis is key in improving the probability of patient survival.[4 5] As in any septic patient, mortality rises with every hour of delayed sufficient therapy.[4] Patients at increased risk may be identified by several key points: Multinational Association for Supportive Care in Cancer risk index <21, far progressed haematological disease, steroid therapy and, not at last, MDR Gram-negative sepsis, or transfer to intensive care unit (ICU).[6] However, these criteria are either not available on admission or have been proven to be not specific enough.[7] To overcome these difficulties, recently a new score for the risk assessment in neutropenic patients has been published (table 1).[8] The higher the score, the higher the probability of unfavourable outcomes as well as bacteraemia, with 1.1% unfavourable outcomes in class I representing a low score of zero to two versus 29.8% in class III representing a high score of 9 to 18 points.

A relatively new tool for the early recognition of patients in need of intensive care is the quick Sepsis-related organ failure assessment (qSOFA) score included in the Sepsis 3 guidelines.[9] This score, aimed for use by outpatient clinicians and physicians in general wards or emergency departments, uses three parameters most physicians use every day in a non-structured fashion to gauge the disposition of patients: respiratory rate (positive if >22/min), altered mentation and systolic blood pressure (positive if <100 mm Hg). If two of these criteria are deemed positive, the patient's death risk is increased 3-fold, if three criteria are positive, mortality increases 14-fold. In both cases, admission to an ICU is advisable. Although not specifically validated for neutropenic patients, the qSOFA score might present a useful tool to recognise those at highest risk and in need of intensive care.

Table 1 New prognostic model for chemotherapy-induced febrile neutropenia, as described by Anh *et al*[8]

Characteristics	Points
Age ≥60	2
Procalcitonin ≥0.5 ng/mL	5
ECOG performance score ≥2	2
Oral mucositis grade ≥3	3
Systolic blood pressure <90 mm Hg	3
Respiratory rate ≥24 breaths/min	3

Class I: <0–2 points, low risk; class II: 3–8 points, intermediate risk; class III: 9–18 points, high risk of unfavourable outcome and/or bacteraemia. ECOG,Eastern Cooperative Oncology Group.

Understanding local resistance patterns

An important step in choosing the correct empiric antimicrobial therapy is knowledge of local resistance patterns. Those may differ largely between individual hospitals as well as between countries. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) only plays a minor role in Austria, France, UK, Germany and the Scandinavian countries, while Hungary, Romania or Greece (among others) show dramatic resistance rates between 20% and 57%.[10] In the USA and Canada, MRSA rates show a steady decrease over the last years with incident rates around 18 (number per 100 000 population per year) respectively 2.89 (number per 10 000 population per year).[11 12] Reliable data in these two countries however are sparse, as only few centres in selected areas report their resistance data to the Centers for Disease Control and Prevention or the Public Health Agency of Canada, respectively. From all available data, worldwide highest prevalence estimates of MRSA (resistance rates >50%) are found in Colombia, Malta, Romania, Iraq, Hong Kong, Singapore, Japan and South Korea.[13] Regarding Gram negatives, resistance to third-generation cephalosporins in *Escherichia coli* ranges between 5.7% in the Netherlands and up to 38.5% in Bulgaria.[10] Especially the emergence of carbapenem-resistant Enterobacteriaceae (CRE) places patients at risk to receive inappropriate empiric therapy.[14] Surveillance services report a worldwide increment of CRE over the last decade with different emphasis depending on the expressed carbapenemase.[14–16] Even though there are few data existing, we think the best strategy to reduce resistance rates and selective pressure is strict antimicrobial stewardship and a rigorous step-down approach of therapy once a pathogen has been identified.[17]

Pathogen distribution

Due to the adverse effects antineoplastic therapy has on the coherence of the gastrointestinal mucosa, patients are at increased risk of transmigration of bacteria from the gut into the bloodstream.[18] The more aggressive a chemotherapy regimen, the higher the chance of prolonged neutropenia and neutropenic fever. In a retrospective analysis of 2083 haemato-oncological patients with bloodstream infections during 2008 and 2013, 38.1% suffered from lymphoma, 30.9% from acute myeloid leukaemia, 10.7% from multiple myeloma, 7.9% from acute lymphatic leukaemia, 7.2% from myelodysplastic syndrome, only 3.6% from chronic myeloid leukaemia and 1.5% from chronic lymphatic leukaemia.[19] In this patient collective, 53.7% of all isolates were Gram negatives; of these, *E. coli* (13.8%), *Klebsiella pneumoniae* (9.5%), *Acinetobacter calcoaceticus–baumannii* complex (5.7%) and *Pseudomonas aeruginosa* (4.0%) were the most common isolated organisms. While 40.2% of all isolated organisms were identified as Gram positives, of these 20.5% were described as coagulase-negative staphylococci, which usually are a contaminant without pathogenic properties.[19] This is backed by the observation that since the 1980s there has been a shift of the bacterial spectrum from Gram negative to Gram positive and back to Gram-negative infections.[20] In another study, 17% of all Gram-negative bloodstream infections were caused by *P. aeruginosa*.[21] In this trial, no predisposing factors for *P. aeruginosa* bacteraemia aside increased severity of the underlying disease could be identified, leading to the conclusion that any neutropenic fever episode should be treated with antimicrobials active against *P. aeruginosa*. With rising resistance in Gram-negative as well as Gram-positive bacteria, the local and also the patients' personal resistance situation become important factors in the selection of the initial empiric therapy.

Choice of therapy

Antimicrobial treatment should start at the first signs of sepsis, but at least within the first 60 min after sepsis identification, as studies have shown that mortality increases every hour without adequate therapy.[5 22] In admitted patients, early catheter removal and change of injection site have shown to be beneficial in reducing overall mortality.[23 24] Beta-lactams are the cornerstone of antimicrobial therapy. For patients with limited previous antimicrobial exposure, that is, no antimicrobial therapy within the last months, a piperacillin/tazobactam therapy should be the first choice if local resistance profiles permit and no prior colonisation with resistant bacteria has been documented. If history of a type IV penicillin allergy (ie, drug exanthema) is present or suspected for the patient in question, alternatively an initial cefepime therapy with escalation to cefepime/linezolid is advisable. In patients with a history of anaphylactic shock during penicillin or aminopenicillin treatment, initial therapy should consist of aztreonam (first choice), meropenem or imipenem/cilastatin, as cross-reactions are extremely rare. Should previously found extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae exhibit resistance to piperacillin/tazobactam, empirical therapy should cover these resistances.[17] In escalation therapy, algorithms should favour meropenem or imipenem/cilastatin over cephalosporins, for example, cefepime or cefpirom, due to the latter drug's high tendency towards ESBL induction.[20] Considering significant differences in aetiology of bacteraemia and rapid changing patterns of resistance is

of the utmost importance in guiding the optimal empirical therapy.[25]

Depending on the suspected pathogens, broadening the spectrum of activity towards MRSA and ampicillin-resistant enterococci by adding glycopeptides, preferably teicoplanin, should be considered.[26] If located in an environment with an MRSA rate over 20%, initial empiric therapy with teicoplanin should be considered.[10] It is, however, essential to perform therapeutic drug monitoring, as teicoplanin serum levels show high interpatient variability. Alternatively, a combination with a fifth-generation cephalosporin like ceftarolin may be chosen to cover MRSA, however leaving enterococci uncovered. In areas of Vancomycin resistant enterococci (VRE) endemicity, ampicillin or piperacillin as antienterococcal agents may be considered, as VRE tend to be susceptible to aminopenicillin treatment and vice versa ampicillin-resistant enterococci have often shown to be sensible to glycopeptide treatment.[27] Daptomycin has a low significance in patients with neutropenic fever as most suffer from respiratory tract infections, and daptomycin shows no activity in pulmonary tissue due to inhibition by pulmonary surfactant.[28] High-risk patients with prior ICU admission and/or prolonged steroid exposure showing signs of partial respiratory insufficiency and high lactate dehydrogenase (LDH) levels should receive treatment with trimethoprim/sulfametrole targeting *Pneumocystis jirovecci*. With persisting fever and all other means exhausted, we see tigecycline as a drug of last resort in unstable neutropenic patients, but further study is required.[29] Receiving an effective antimicrobial regimen, neutropenic patients suffering from solid organ tumours will show defeverence within 2 days, while those suffering from haematological malignancies may suffer from fever for up to 5 days.[30] In patients who present stable but continue to show fever, there is no need to change the empiric antimicrobial therapy during the first 4 days of therapy.[30] High-risk patients with sustained fever on day 5 should be rescreened for infection sites and in cases of unexplained fever an empiric antifungal therapy should be added.[30] After cessation of fever, antimicrobial treatment should be discontinued after 2 days, regardless of neutrophil count.[30–32] However, a swift restart of antimicrobial therapy in case of fever relapse is indicated. A decision tree for antibacterial therapy in neutropenic fever may be found in figure 1.

Carbapenem-sparing agents

Appropriate use of carbapenems is of particular concern as they are often used against increasingly difficult-to-treat Gram-negative pathogens such as *P. aeruginosa*. Alternatives to carbapenems are successively more and more needed due to the emergence of carbapenemase-producing Enterobacteriaceae.[33] In addition, carbapenem-sparing agents might be considered in patients to expand activity within multidrug-resistant Gram-negative (MRGN) organisms, but their high rate of ESBL induction should always be kept in mind.[34] Typical regimens are piperacillin/tazobactam, meropenem/teicoplanin, cefepime/linezolid or aztreonam/linezolid, in this order. If no pathogen has been detected, depending on the initial course of treatment, cefepime and subsequently aztreonam might be considered as the latter has shown in vitro activity against metallo-β-lactamase-producing pathogens despite its slow hydrolysation by New Delhi metallo-β-lactamase (NDM).[35 36] Ceftazidime poses another possibility if MRGN pathogens—in particular *P. aeruginosa*—are suspected, but has a less significant role than aforementioned antibiotics. Ceftazidime shows no effect in Gram-positive infections and has a high tendency to induce ESBL, which is why it should only be administered as a last resort in combination with agents covering the Gram-positive spectrum.[37]

New β-lactams and β-lactamase inhibitors

An attempt to circumvent resistances is the development of new β-lactamase inhibitors that are able to inhibit a wide range of problematic β-lactamases including serin-based carbapenemases and cephalosporinases.[38] In patients showing continued neutropenic fever despite sufficient treatment duration, the use of these novel agents might be considered as a therapeutic option against highly resistant Gram-negative organisms. Comparing surveillance data for these new substances from different areas has shown to be difficult due to the variety of laboratory test methods existing and the fact that with most surveillance programmes, reporting is done on a voluntary basis.[39] Ceftolozane/tazobactam shows good effect against multidrug-resistant *P. aeruginosa* but is more susceptible to ESBL-producing Enterobacteriacae, whereas ceftazidime/avibactam seems to induce resistance faster.[38 40] These agents would best be used after piperacillin/tazobactam in treating neutropenic fever and sepsis as carbapenem-sparing agents to take weight from carbapenems, although current resistance patterns as well as treatment cost-effectiveness prohibit the broad use of these novel therapeutics. In Austria and other areas with high and/or increasing rates of carbapenem-resistant *P. aeruginosa* (rates ≥20%), however, early use of these new drugs should be considered.[11] By tendency, we see ceftolozane/tazobactam before ceftazidime/avibactam as some reports already suggest development of resistance against ceftazidime/avibactam in carbapenem-resistant *K. pneumoniae*.[40–42] Aztreonam/avibactam is another novel combination that has shown good activity against NDM regardless of its slow hydrolysation by this enzyme.[33 36 43 44] Recent in silico and in vivo studies have proven aztreonam/avibactam to be an attractive treatment option for infections with metallo-β-lactamase-producing Gram-negative bacilli that coproduce ESBL or AmpC.[44 45] Moreover, it poses an effective alternative when treating multidrug-resistant *P. aeruginosa*.

Antifungal therapy

Several predisposing factors exist for systemic mycosis, such as prior organ and/or stem cell transplantation

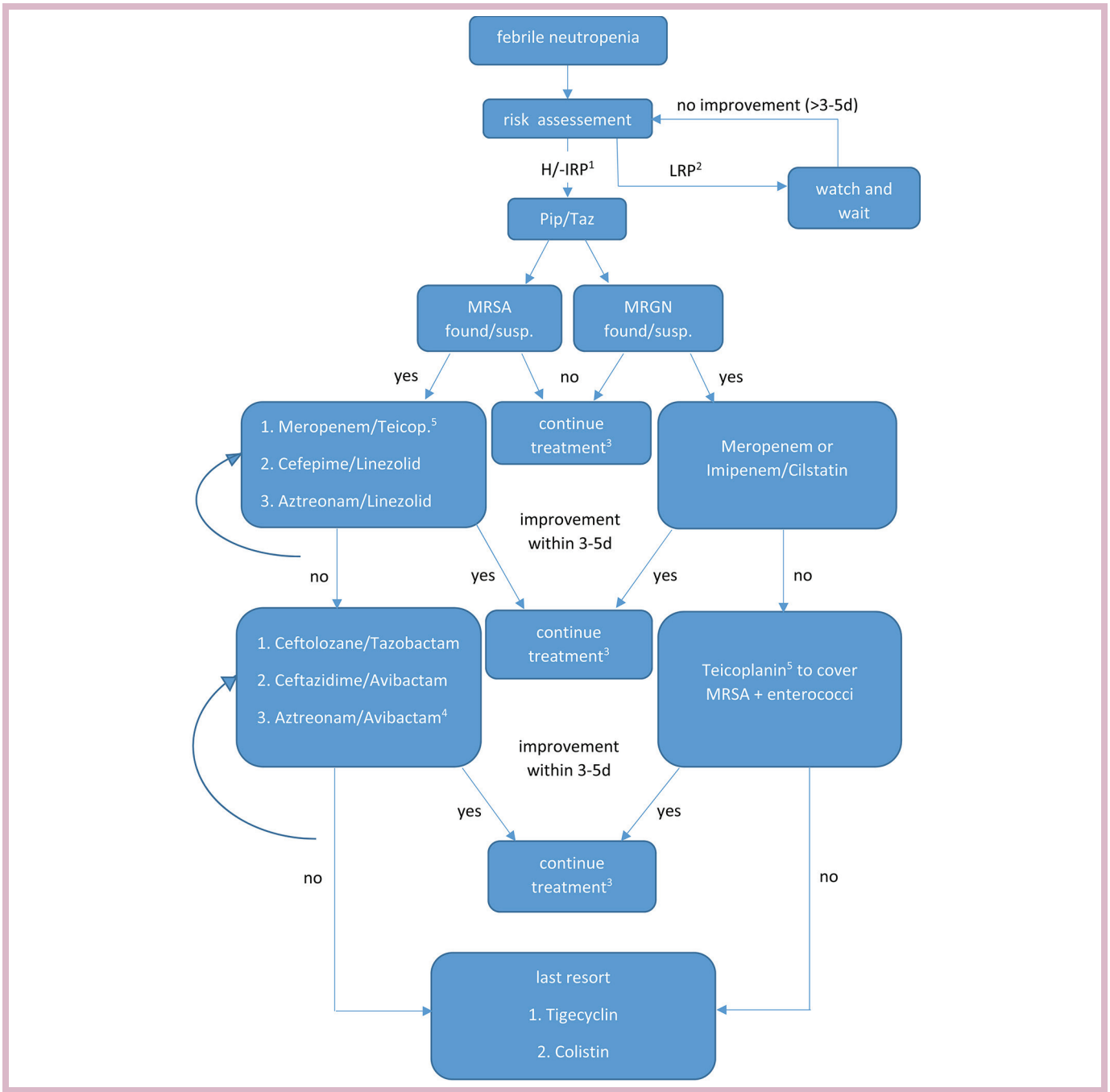

Figure 1 Therapeutic escalation approach in septic neutropenic patients. [1]High/intermediate risk, [2]low risk, [3]continue treatment, [4]currently under development, [5]use therapeutic drug monitoring, target values 40–60 mg/L. MRGN, multidrug-resistant Gram negative; MRSA, methicillin-resistant *Staphylococcus aureus*.

(HLA-matched related>unrelated donors), chemotherapy with prolonged neutropenia (>10 days), steroid therapy (>7 days), biologics therapy, HIV or prior admission to ICU (>7 days).[46] Empiric antifungal therapy is advised in neutropenic patients, who persist to be febrile on days 4–7 of antibacterial therapy or who present recurring fever.[47] We, however, only recommend empirical treatment in the presence of aforementioned predisposing factors to reduce selection of mucormycosis.[48] Patients at high or intermediate risk with expected, protracted neutropenia will often have already received prophylactic antifungal medication. Antifungal prophylaxis in these patients is usually performed with a triazole agent, either fluconazole, targeting yeast or posaconazole or voriconazole, targeting mould infectious agents. With voriconazole, therapeutic drug monitoring should be performed routinely, but at the latest in case of non-adequate response to treatment or side effects that occur with high plasma levels of voriconazole, especially neurological signs or elevated liver enzymes.[49] If patients show impaired renal function, isavuconazole poses a

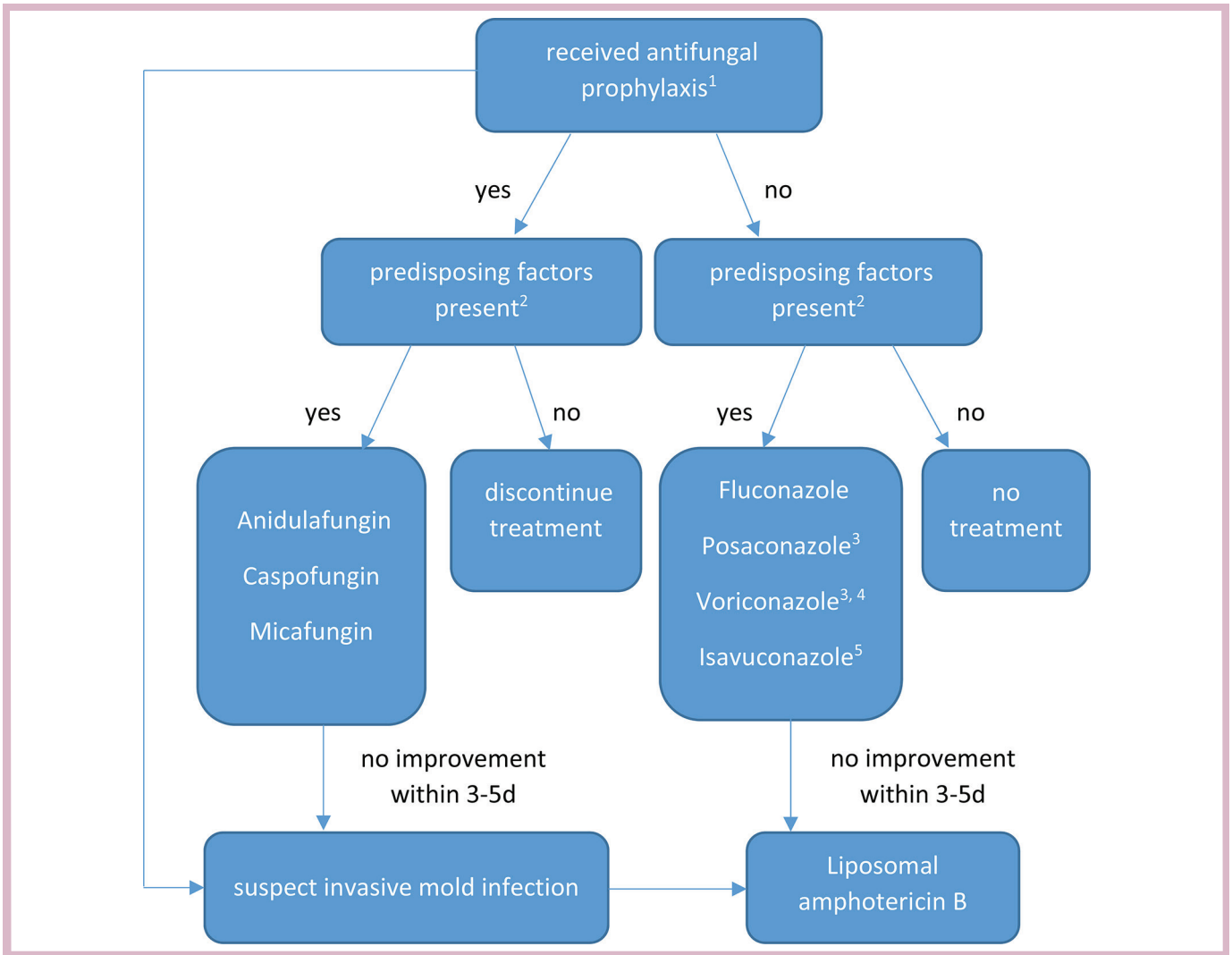

Figure 2 Antifungal prophylaxis and treatment in septic neutropenic patients. [1]Type of antifungal prophylaxis (fluconazole vs antimould agent) and underlying illness influence the likelihood if invasive mould infection; [2]factors predisposing for fungal infection: prior organ and/or stem cell transplantation (HLA-matched related>unrelated donors), chemotherapy with prolonged neutropenia (>10 days), steroid therapy (>7 days), biologics therapy, HIV or prior admission to intensive care unit (>7 days); [3]avoid intravenous administration due to renal toxicity of the solvent; [4]drug monitoring; [5] alternative in cases of renal impairment.

therapeutic alternative to intravenous voriconazole or posaconazole to treat mould infections. With these patients—bearing in mind that most commonly *Candida* spp. cause sepsis—an echinocandin (anidulafungin, caspofungin or micafungin) is recommended as initial therapy of systemic fungal infection in haemato-/oncological patients with neutropenia.[50] Liposomal amphotericin B should be used as initial therapy if a patient received antifungal prophylaxis with a mould active agent such as posaconazol or voriconazol or as second-line escalation if patients received fluconazole as prophylactic agent. Some studies have suggested the use of high-dose caspofungin as a first-line therapy to treat invasive aspergillosis.[51 52] Additionally, a recent trial has shown an improved 6-week survival compared with voriconazole monotherapy if anidulafungin is added.[53] However, we currently only recommend a combination therapy of voriconazole and anidulafungin as last-line treatment option after liposomal amphotericin B (figure 2). Collection of serial blood cultures is of great importance in management of neutropenic patients with suspected invasive fungal disease: first to detect possible bloodstream infections and second to re-evaluate treatment. Serological testing for galactomannan and β-D-glucan are suitable instruments for early diagnosis and to reassess treatment.[54 55] In a recent study with 203 participants, investigators found that a negative slope of β-D-glucan correlated with a successful treatment outcome with a positive predictive value of 90%, and a positive slope in β-D-glucan levels correlated with treatment failure with a negative predictive value of 90%.[56] Antifungal treatment should continue 2 weeks after negative blood cultures and no sites of infection are present.[57]

Colony-stimulating factors

Usage of G-CSF (recombinant human granulocyte colony-stimulating factor; filgrastim, pegylated filgrastim) and GM-CSF (granulocyte-macrophage colony-stimulating factor; sargramostim) in neutropenic septic patients as an attempt to decrease infections is controversial.[58 59] While analysis have shown a positive effect on duration of neutrophile recovery and hospitalisation, it appears not to reduce overall mortality.[60] Side effects include bone and muscle pain, fatigue, vomiting, nausea, headaches and also severe but very rare complications such as acute respiratory distress syndrome, cardiopulmonary events and spleen rupture.[61] In non-neutropenic septic patients, usage has shown to be fairly safe but ineffective in decreasing mortality rates.[62] Currently, we do not recommend routine addition of G-CSF and/or GM-CSF to treatment for sepsis in neutropenic patients.

CONCLUSION

Early sufficient therapy of neutropenic sepsis reduces mortality. Choosing the correct antimicrobial regimen, however, requires knowledge of local resistance patterns to allow for maximum efficacy and minimal selective pressure.

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