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Management of infections during intensive treatment of hematologic malignancies

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Abstract In febrile neutropenic patients with high-grade hematologic malignancies, empirical antimicrobial intervention is mandatory. Large randomized clinical trials have elucidated the benefit of broad-spectrum beta lactam antibiotics used as single drugs or in combination with aminoglycosides in order to provide activity against gram-negative aerobes as well as against streptococci and *Staphylococcus aureus*. As a result, infection-related mortality was reduced to less than 10% also in patients undergoing intensified remission induction or consolidation therapy for acute leukemias. Distinct subgroups of patients have been identified who need an empirical modification of antimicrobial treatment, i.e., patients with catheter-related infections, patients with pulmonary infiltrates, and patients with unexplained fever not responding to first-line antibiotics. In two consecutive, prospectively randomized trials conducted by the Paul Ehrlich Society it was demonstrated that empirical antifungal therapy is beneficial for second-line treatment in patients with persistent unexplained fever and should be part of the first-line approach in patients with lung infiltrates. The empirical addition of glycopeptides, however, should be restricted to patients with catheter-related infections due to coagulase-negative staphylococci.

Key words Infection · Treatment · Neutropenia · Leukemia · Fever

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Introduction

The improvement of diagnostic techniques and antimicrobial treatment options has contributed substantially to the availability of new therapeutic perspectives for patients with high-grade hematologic malignancies such as acute leukemias. Although the duration of severe neutropenia induced by double-induction regimens containing high-dose cytosine arabinoside is markedly prolonged compared with standard remission induction, the rate of treatment-related mortality has not increased. However, infections still represent the dominant cause of death among patients undergoing myeloablative chemotherapy. Also, the character of infections has changed considerably during the past 15 years. Mycoses with deep organ involvement have become the most critical complication and can be found in the majority of patients autopsied. Bacteremic infections due to alpha hemolytic streptococci fostered by severe mucosal damage are diagnosed with increasing frequency and may cause life-threatening complications. At the same time, venous catheter-associated in-

fections from coagulase-negative staphylococci predominate among microbiologically documented infections. Their adequate treatment is controversially discussed with respect to the emergence of resistance against glycopeptide antibiotics. The options and limitations of diagnostic procedures and therapeutic interventions in febrile neutropenic patients others than allogeneic bone marrow transplant recipients are reviewed here.

Epidemiology of infections in neutropenic patients

Patients with profound neutropenia induced by intensive myeloablative chemotherapy have an approximately 90% risk of acquiring infectious complications. The causative micro-organism remains unknown in 70% of all febrile episodes, the majority of which therefore represent unexplained fever or "fever of unknown origin" (FUO). The majority of these cases can be successfully treated with antimicrobial agents even in the absence of sufficient numbers of neutrophil granulocytes, whereas discontinuation of antimicrobial treatment may result in fatal septic infections [1, 2].

In microbiologically documented infections, i.e., 30% of all febrile episodes, the pattern of micro-organisms involved has changed markedly over the past two decades. Before the introduction of antimicrobials with high activity against gram-negative aerobes including *Pseudomonas* species, i.e., acylaminopenicillins, third-generation cephalosporins, carbapenems, and fluoroquinolones, these pathogens dominated by far [3]. Since oral antimicrobial prophylaxis with substances such as trimethoprim-sulfamethoxazole or fluoroquinolones has become widely used in order to reduce the incidence of gram-negative infections and, at the same time, long-term indwelling venous catheters are inserted with increasing frequency, gram-positive cocci have become the dominating organisms isolated in these patients. If cytotoxic agents inducing mucosal damage such as high-dose cytosine arabinoside are administered, bacteremic infections due to alpha hemolytic streptococci further enhance the dominance of gram-positive cocci. With the prolongation of drug-induced neutropenia, the frequency of secondary or "super" infections caused by pathogens resistant to the established broad-spectrum antimicrobial regimens, above all, pathogenic fungi, will increase.

In 30% of infectious episodes, a clinically conclusive focus can be identified by physical examination and/or imaging procedures. These findings may provide useful evidence with respect to the causative micro-organisms (Table 1).

Beyond this typical association of clinical findings with causative micro-organisms, the spectrum of involved pathogens changes according to the time of their detection after the onset of fever. In early microbiologically documented infections, the proportion of gram-positive cocci is approximately 50%, that of gram-negative aerobes about 40%, whereas fungi, mostly *Candida* and *Aspergillus* spp., are isolated infrequently, apart from mucosal infections involving *Candida* spp. In infections with delayed microbiological documentation, i.e., samples positive after more than 5 days from the onset of fever, fungi can be isolated in more than 50% of cases, whereas the proportions of both gram-negative and gram-positive bacteria decline to about 25% each [2]. The incidence of bloodstream infections due to coagulase-negative staphylococci may not decline, regardless of established antimicrobial therapy, in patients with central venous catheters in place. In patients with pulmonary infiltrates, however, this pattern of isolated micro-organisms is markedly different, with (mostly filamentous) fungi dominating also in early microbiologically documented cases [4, 5].

Table 1 Typical pathogens associated with characteristic clinical symptoms

Clinical symptoms	Typical pathogens
Erythema/pain at venous access	Coagulase-negative staphylococci
Mucosal ulcers	*Herpes simplex* virus, *Candida* spp., alpha hemolytic streptococci (blood cultures)
Multi point-like skin lesions	Gram-positive cocci, corynebacteria, *Candida* spp.
Necrotizing skin lesions	*Pseudomonas aeruginosa, Aspergillus* spp.
Retinal infiltrates	*Candida* spp.
Diarrhea, meteorism	*Clostridium difficile*
Enterocolitis, perianal lesion	Polymicrobial, incl. anaerobes
Lung infiltrates ± sinusitis	*Aspergillus* spp., mucoraceae
Interstitial lung infiltrates	*Pneumocystis carinii, viridans* streptococci
Interstitial lung infiltrates + retinal hemorrhage	*Cytomegalovirus*

Empirical antimicrobial approach to febrile neutropenic patients

Since it was demonstrated that infections in neutropenic patients can be associated with 50% mortality when not treated appropriately [6], numerous clinical studies during the past 30 years have elucidated the use of prompt empirical broad-spectrum antimicrobial treatment. The marked discrepancies between reported results of these studies were caused by the heterogeneity of criteria for patient selection and for response assessment. Therefore, recommendations for the design and reporting of results of clinical trials were elaborated by consensus conferences of the Immunocompromised Host Society as well as of the Infectious Disease Society of America in the early 1990s [7–9]. Since then, the majority of large-scale clinical studies have been conducted in accordance with these recommendations and have shown more consistent results [10–15] (Table 2). Criteria for the institution of empirical antimicrobial treatment in neutropenic patients are clearly defined

Table 2 Large-scale clinical studies on antimicrobial treatment in febrile neutropenic patients published since 1992 (*FUO* fever of unknown origin or unexplained fever)

Reference	*n*	Treatment groups	Complete response without modification (%)			Remarks
			Total	FUO	Documented infection	
Rolston et al. 1992 [14]	750	Ceftazidime 1 g q 4 h	59	69	49	Nonbacterial and mycobacterial infections excluded 33% solid tumor
		+amikacin 800 mg/m^2/d	71	75	65	
		Imipenem 12.5 mg/kg q 6 h	72	79	62	
		+amikacin 800 mg/m^2/d	76	84	67	
De Pauw et al. 1994 [12]	784	Ceftazidime 2 g 8 h	35	38	31	18% solid tumor or lymphoma
		Piperacillin 3 g q 4–6 h +tobramycin 1.7–2 g q 8 h	33	42	26	
Freifeld et al. 1995 [13]	399	Ceftazidime 90 mg/kg q 8 h	46	61	16	66% FUO 26% children 56% solid tumor
		Imipenem 12.5 mg/kg q 6 h	53	66	27	
EORTC-IATCG 1995 [10]	706	Piperacillin-tazobactam 4.5 q 8 h +amikacin 200 mg/kg/d	61	67	58	Children included 17% solid tumor
		Ceftazidime 2 g q 8 h +amikacin 20 mg/kg/d	54	67	45	
EORTC-IATCG+ GIMEMA-IP 1996 [11]	958	Meropenem 1 g q 8 h	56	66	46	20% children 16% solid tumor
		Ceftazidime 2 g q 8 h +amikacin 20 mg/kg/d	52	64	40	

(Table 3). A careful physical and radiological examination is mandatory to discriminate cases of unexplained fever (FUO) from those with a clinically documented focus of infection. Standard procedures for microbiological analysis, particularly repeated venous blood cultures, help to identify microbiologically defined infections, the latter being differentiated into those with and those without bacteremia. Recommendations for diagnostic procedures in febrile neutropenic patients are given in Table 4.

Table 3 Criteria for the institution of empirical antimicrobial therapy in neutropenic patients

- Granulocyte count $< 1.0 \times 10^9$/l
- Oral temperature $\geq 38.5\,^{\circ}C$ or at least twice $\geq 38.0\,^{\circ}C$ within 12 h
- No evidence of noninfectious cause of fever
  - underlying malignancy
  - transfusion of blood products
  - drug reaction (e.g., cytokines, antimicrobial agents)

Unexplained fever (FUO)

Standard regimens for empirical first-line treatment in patients with FUO are based upon beta-lactam antibacterials with certain activity against gram-negative aerobes, particularly enterobacteriaceae and *Pseudomonas aeruginosa*, streptococci and methicillin-susceptible *Staphylococcus aureus* in combination with aminoglycoside antibiotics. Intent-to-treat analyses demonstrate complete response rates to unmodified first-line regimens of 50–60% in these patients. Significant differences between third-generation cephalosporins, acylaminopenicillins, or carbapenems for the beta-lactam compound or between different available aminoglycosides have not been consistently demonstrated [2, 10–15]. Very few data, however, are reported on escalating antimicrobial treatment regimens in patients not responding to first-line therapy. Thus, little is known about the character of these cases of persisting FUO. The only study group also investigating second- and third-line randomized treatment strategies is the Interventional Antimicrobial Strategy Study Group of the German Paul Ehrlich Society. They demonstrated that supplementation of two-drug first-line combinations with a third antibiotic in order to achieve a maximum antibacterial spectrum including multi-resistant pathogens, i.e., double beta-lactam plus an aminoglycoside or plus vancomycin, results only in 50% response rates, whereas 75–80% response can be achieved with the addition of antifungals [2, 16]. Therefore, supplementation of broad-spectrum antibacterials with a parenteral antifungal agent appears to be appropriate in patients not responding to standard antibacterial first-line therapy within 72–96 h, because a substantial proportion of persisting FUOs might represent occult fungal infections. The incorporation of an azole antifungal into the empirical first-line approach in FUO patients, shown to be beneficial in defined subgroups of neutropenic cancer patients [17], is more likely to represent an overtreatment of 50–60% of these patients because they can be expected to completely respond to standard antibiotics.

The criteria for response assessment in FUO patients as defined by consensus papers have been challenged with regard to the prognostic impact of persist-

Table 4 Recommended diagnostic procedures in febrile neutropenic patients

Clinical examination
- Clue findings, see Table 1
- Repeat daily until resolution of fever and other signs of infection are documented

Microbiological diagnostics
- Blood cultures (1–2 pairs from peripheral veins at different sites, another pair from venous catheter) before starting antimicrobial therapy
  – repeat daily in case of nonresponse
- Urine culture in patients with signs of urinary tract infection
- Stool culture plus *Clostridium difficile* enterotoxin in patients with diarrhea
- In patients with necrotizing skin lesions, consider culturing of wound secretion or tissue
- In case of catheter removal, microbiological culture from catheter tip

Fiberoptic bronchoscopy plus bronchoalveolar lavage
in patients with lung infiltrates. Workup with respect to:
- Infiltrates caused by underlying malignancy
- Pathogenic bacteria including mycobacteria and *Legionella* spp.
- Fungi
- *Pneumocystis carinii*

Radiological diagnostics
- Chest radiograph
  – in case of regular findings despite persisting fever: computed tomography of lungs
- Paranasal sinuses (sonography, if available)

Abdominal sonography in patients with symptoms of hepatosplenic candidiasis or other infection localized at abdominal organs

Remarks
- Diagnostic procedures should not substantially delay the initiation of empirical antimicrobial therapy.
- Diagnostic findings might be discrete despite the presence of severe infection.
- Results of microbiological procedures serve as confirmation for the antimicrobial choice, as basis for treatment modification and for documentation of epidemiology.

ing febricity in the absence of any other clinical sign of infection [18]. In a recently published trial, the EORTC-IATCG allowed continuation of a randomly assigned treatment regimen also in case of persisting fever unless patients were clinically instable, thereby demonstrating that the median time to defervescence in FUO patients may exceed 96 h even if the allocated treatment is effective [11]. Data from a prospectively randomized trial comparing treatment modification with a continuation of the established regimen in patients with persisting FUO without any other clinical sign of infection are not available as yet.

Overall, a complete response, defined as stable defervescence without the need for any further antimicrobial treatment, can be achieved by systematically escalating antibacterial and antifungal therapy in approximately 95% of patients with FUO [2, 12]. Once patients being treated empirically for FUO have responded to antimicrobial treatment, the established regimen should be continued for at least 7 days in those who are persistently neutropenic, whereas in patients with neutrophil counts increasing to $>1.0\times10^9$/l treatment can be discontinued after 2 days of stable defervescence. A follow-up of at least 7 days after treatment termination should be mandatory, however, in order to record possible secondary treatment failure.

Clinically documented infections

The identification of a focus of infection by physical examination or imaging procedures can be used for a more sophisticated selection of antimicrobial drugs for empirical therapy. As outlined in Table 1, typical patterns of micro-organisms are found in association with distinct clinical symptoms of infection. Although this pattern does not allow a highly specified therapy, it gives reason to recommend that:

– In patients with abdominal and/or perianal signs of infection, anaerobic pathogens should be included in the spectrum of antimicrobial activity.
– In patients with skin or venous access infections, antibiotics with high activity against multi-resistant gram-positive cocci should be administered.
– In patients with pulmonary infiltrates, early parenteral antifungal treatment directed against filamentous fungi must be considered.
– In patients with single point-like erythemas, antimicrobial agents active against gram-positive cocci should be part of the empirical treatment regimen.
– In patients with symptoms of severe enterocolitis, oral metronidazole or even an oral glycopeptide should be administered empirically, at least until the results of stool cultures and toxin analysis are available.

With respect to the increasing frequency of vancomycin-resistant enterococci being selected in association with the widespread use of glycopeptide antibiotics, as well as to the high treatment costs and the potential for adverse events under vancomycin treatment, it must be pointed out that also in cases with evidence of skin and/or venous access infection, empirical supplementation of standard antimicrobial treatment with vancomycin or teicoplanin right from the start should be handled with caution. Numerous studies have demonstrated that delayed supplementation of these agents restricted to patients not responding to standard first-line regimens such as beta-lactam plus aminoglycoside, as well as to patients with multiply resistant staphylococci isolated from blood cultures, provides an overall efficacy equivalent to the first-line empirical addition of glycopeptides [19–22].

It must be underlined, however, that patients with pulmonary infiltrates documented by conventional chest radiography or CT scan have an extraordinarily high chance of having invasive fungal infections. Conventional microbiological analyses of bronchial secretions or bronchoalveolar lavage samples usually fail to detect these fungi. The same must be stated for serological procedures. Molecular diagnostics using the poly-

merase chain reaction in bronchoalveolar lavage (BAL) fluid samples have indicated a high proportion of cases suspect for a fungal pulmonary infection; however, this procedure may provide a high number of false-pathologic results and requires verification of its clinical benefit in sufficiently large, prospectively randomized trials [23]. Considering the prognostic significance of early antifungal intervention in these cases, it must be recommended that the empirical first-line approach should include amphotericin B, whereas fluconazole has no proven benefit in patients with pulmonary infiltrates not responding to a standard antibacterial first-line regimen [24]. The spectrum of micro-organisms other than fungi detected in neutropenic patients with pulmonary infiltrates includes gram-negative aerobic rods as well as streptococci and *Staphylococcus aureus*, and in rare cases also *Pneumocystis carinii* and *Legionella pneumophila* [4]. Since the last two pathogens can be easily detected in BAL samples by immunological methods, it is recommended to perform fiberoptic bronchoscopy and BAL in patients not responding to an empirical antimicrobial first-line therapy. The incorporation of drugs active against these two pathogens, i.e., high-dose trimethoprim-sulfamethoxazole and a macrolide antibacterial, into the empirical first-line treatment of patients with lung infiltrates is not encouraged.

Two major problems must be considered in febrile neutropenic patients with unexplained lung infiltrates:

1. Micro-organisms cultured from samples such as "sputum", saliva, nasal or oropharyngeal swabs, removed venous catheter material, or even from blood cultures must be interpreted cautiously with respect to their etiologic significance. In particular, coagulase-negative staphylococci or *Corynebacterium* spp. isolated from blood cultures as well as selected bacteria such as enterococci or *Candida* spp. cultured from samples of the oropharynx or the upper airways cannot be regarded as causative pathogens in patients with lung infiltrates. They may, however, indicate other infections in addition to pneumonia.
2. Noninfectious causes such as diffuse alveolar hemorrhage, adult respiratory distress syndrome, radiation-induced pneumonitis, drug toxicity, or lung involvement by the underlying malignancy may be present in approximately 20% of cases with unexplained lung infiltrates refractory to antimicrobial agents. In these cases, which may also present or persist beyond periods of neutropenia, transbronchial or open lung biopsy is recommended.

Microbiologically documented infections

Microbiological findings may be helpful for treatment modification in order to target antimicrobial activity and to avoid unnecessary toxicity. Beyond this, the pattern of micro-organisms as well as their susceptibility profile provides important guidelines for the selection of empirical first-line antibiotics in each institution. Therefore, microbiological diagnostics are mandatory in all cases of febrile episodes in neutropenic patients.

It must be emphasized, however, that the interpretation of microbiological findings should address the questions of the etiologic relevance in relation to the clinical presentation of an infection and of the possible involvement of additional pathogens not detectable by the applied diagnostic method. The false interpretation of microbiological findings associated with lung infiltrates has been discussed above. In patients with enterocolitis, the isolation of pathogens from fecal samples may miss important other micro-organisms involved in the pathogenesis. Also in patients with venous catheter-associated infections, pathogens other than coagulase-negative staphylococci isolated from blood cultures may be involved but not detected [25–27]. Considering these diagnostic pitfalls, it is not surprising that in prospective clinical trials on infections in neutropenic patients, microbiologically documented infections treated with targeted antimicrobial drugs have shown no higher response rates than clinically documented infections treated empirically [2, 4].

In cases of microbiological findings offering the opportunity of a more specific antimicrobial therapy, the selection of appropriate drugs should be based upon the criteria listed in Table 5. To meet these requirements, the close interdisciplinary cooperation of clinicians, microbiologists, radiologists, and clinical pharmacologists should be encouraged in order to optimize targeted antimicrobial treatment also in febrile neutropenic cancer patients. With respect to pharmacoeconomic aspects, however, the preference of presumably cost-saving products must be carefully balanced with regard to markedly higher treatment costs of multiple-drug "salvage" regimens and prolonged treatment duration required to achieve stable clinical response.

Response criteria and treatment duration in patients with documented infections

In contrast to patients with FUO, complete response of documented infections must include the resolution of all clinical signs of infection as well as the clearance of infected sites from the causative pathogens in addition to stable defervescence. Once these criteria have been fulfilled, the established successful treatment regimen

Table 5 Criteria for selection of antimicrobial drugs in microbiologically documented infections

- In vitro susceptibility profile of isolated pathogens
- Pharmacokinetic aspects (sufficient penetration to the focus of infection)
- Toxicity profile
- Patient-related contraindications
- Personal experience with standard regimens
- Pharmacoeconomic factors

should be continued according to the principles outlined above for FUO. In patients with invasive pulmonary fungal infections, this treatment period usually exceeds the time required for the resolution of other documented infections. In general, a cumulative administered dose of at least 2 g amphotericin B is required for those cases. It should be remembered that residual radiological findings may persist despite complete clinical response and may not necessarily represent active infection.

Microbiological response should be documented by serial repetition of cultures until negative results are obtained (e.g., blood or urine cultures, fecal samples for *C. difficile* toxin). In microbiologically documented lung infiltrates identified by invasive procedures, however, microbiological response will not be demonstrable in patients with good clinical response, since (at least outside clinical studies) it is not acceptable to repeat these procedures only to document the clearance from pathogens.

Adjunctive therapy

The additional administration of adjunctive treatment elements in febrile neutropenic patients has been investigated for the past 25 years. Unfortunately, the majority of studies have not demonstrated a significant benefit in comparison to antimicrobial therapy alone.

Immunoglobulins

The prophylactic administration or additive interventional use of immunoglobulin preparations has been considered, with the intention of reducing the risk of infections as well as of improving the outcome of septic infections. Evidence of prophylactic or therapeutic benefit has been detected very rarely and was restricted to patient subgroups with documented humoral immunodeficiency and to single patients with high levels of endotoxin [28, 29]. The experimental administration of specific hyperimmune globulins also has failed to show any benefit in neutropenic patients [30].

Hematopoietic growth factors

The prophylactic use of recombinant hematopoietic growth factors such as granulocyte or granulocyte-macrophage colony-stimulating factor results in a significant reduction of neutropenia and thereby of febrile episodes in patients undergoing myelosuppressive chemotherapy. Beyond this, a functional activation of mature granulocytes is also induced by these cytokines. Therefore, their interventional administration in neutropenic patients with severe infections has been subject to randomized clinical trials comparing their efficacy in comparison to placebo. The majority of these trials have shown no significant benefit, but a higher incidence of adverse effects and a significant increase of treatment costs [e.g., 31, 32]. However, single studies have indicated a significant improvement of treatment outcome as well as a reduction of treatment costs [33–35], so that no definitive recommendation for clinical management can be given at this point. Optimization of drug selection and timing and dosing schedules might help to find a more appropriate place for growth factors in the setting of febrile complications in neutropenic patients. Therefore, further well-designed, randomized clinical studies on the efficacy of interventional growth factors are encouraged.

Granulocyte transfusions

Since the incidence and outcome of infections in cancer patients are closely related to the degree and the duration of neutropenia, the transfusion of donor granulocytes was extensively investigated in the early 1970s [36–38]. With respect to their poor efficacy, their very high logistic requirements, and the occurrence of possibly transfusion-related pulmonary complications, this modality of supportive care has been abandoned. Nevertheless, the increasing incidence of life-threatening pulmonary fungal infections, together with the availability of hematopoietic growth factors markedly increasing the achievable number of granulocytes harvested by leukapheresis, has prompted several investigators to reconsider the use of granulocyte transfusions from donors pretreated with G-CSF [39–41]. However, results from large-scale clinical trials on the usefulness of these transfusions are not yet available.

Future perspective

As demonstrated by large clinical studies, the efficacy of antimicrobial treatment strategies is excellent in neutropenic patients with unexplained fever (FUO) as well as in patients with clinically and/or microbiologically documented infections apart from pulmonary infiltrates. The early detection of lung infiltrates and the prompt initiation of antifungal treatment in these patients have resulted in a significant improvement of the treatment outcome. However, invasive fungal infections, particularly those caused by filamentous fungi, remain a major challenge for the management of infectious complications in patients with high-grade hematologic malignancies undergoing intensive myelosuppressive chemotherapy.

In the future, major improvements may be achieved by:

1. Minimally toxic yet highly effective beta-lactam antibiotics suitable for monotherapy
2. Highly effective oral antimicrobial drug regimens, allowing the avoidance or abbreviation of hospitalization for parenteral antimicrobial treatment

3. New antifungal agents with improved efficacy against *Aspergillus* infections
4. Effective approaches for chemo- and immunoprophylaxis of infection
5. Identification of significant prognostic factors, allowing for prospective stratification between high- and low-risk patients
6. Valid immunological techniques for noninvasive identification of infectious pathogens and for early detection of life-threatening septic infections, as well as for the reliable assessment of treatment response
7. More appropriate and more effective administration of recombinant hematopoietic growth factors.

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