

Diagnosis and treatment of infections in the oncohematological and stem cell transplant setting

Doctoral (PhD) theses

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Budapest, 2011

INTRODUCTION

Life expectancy and quality of life of patients treated at the oncohematological and stem cell transplant department is significantly influenced by infectious morbidity and mortality. Authors around the middle of the past century first unveiled a relationship between hematological malignancies and infections. A correlation between the absolute number of circulating neutrophil granulocytes (ANC) and the incidence and severity of infections was first described by *Bodey* and co-workers. The increasing amount of knowledge gathered from this field resulted in the development of the concept of empirical antibiotic therapy. In eight major clinical trials organized by the European Organisation for Research and Treatment of Cancer (EORTC) between 1978 and 1994, mortality of bacterial infections in neutropenic patients decreased from 21 % to 7 %, as a result of novel therapeutic concepts.

Trials investigating the efficacy of antimicrobials also yielded data on epidemiology. Until the mid nineteen-eighties a predominance of Gram-negative strains was seen in blood cultures taken from febrile neutropenic patients. Subsequently this proportion has changed to the opposite and Gram-negatives were outweighed by Gram-positive strains. The majority of blood cultures grew coagulase-negative staphylococci, viridans streptococci, *S. aureus* or *Enterococcus* spp. Around the turn of the millennium, however, a re-emergence of Gram-negative bacteria has been reported by several investigators. It is challenging that these Gram-negative strains markedly differ from those isolated in the nineteen-seventies. More and more often we have to face their representatives being resistant to several classes of antibiotics or even being multi- or panresistant. As a result of successful antibiotic strategy and a decrease of infectious mortality, more aggressive anti-leukemic protocols and later stem cell transplantation have gathered ground. At the same time the more prolonged and profound immunosuppression resulted in an increase of invasive mycoses. As methods for establishing a timely and specific diagnosis of these infections were lacking, along

with the analogy of antibacterial therapy a concept of empirical antifungal treatment has been created. *Pizzo* and co-workers used amphotericin B in neutropenic patients who failed to defervesce following antibiotic therapy. They came to the conclusion that with an early empirical institution of amphotericin B serious consequences of invasive mycoses could be prevented. Widespread use of the compound later declined as a result of its significant toxicity. With the expanding antifungal armamentarium options for an empirical therapy could be reconsidered. The institution of more potent but less toxic compounds rendered an antifungal therapy guided solely by clinical factors more appealing

With the widespread use of fluconazole, candida infections have become less prevalent and were largely replaced by moulds, most notably *Aspergillus* spp. Mortality caused by invasive mycoses have remained high throughout all affected patients' groups. At the turn of the millennium results of amphotericin B therapy in hematological patients with invasive aspergillosis were rather disappointing. In patients with acute leukemia and lymphoma, mortality was as high as 49.3 %. The outcome in transplant patients was even more dismal peaking up to 86.7 %. Even in our days of modern medicine establishing an early diagnosis of invasive mycoses remains challenging. The level of proof for the disease will differ by each and every patient.

To prove invasive aspergillosis a biopsy for histopathology is needed. This procedure, however, is often hampered by the bleeding tendency of oncohematological patients. Non-invasive diagnostic options are based on one hand on imaging techniques and on the other hand on the detection of some structural components of the fungus using sensitive assays. In acute invasive aspergillosis high-resolution chest CT (HR-CT) show macronodular lesions often surrounded by an area of ground glass opacity (halo-sign). In a later stage central necrosis of the nodule will result in gas production (air-crescent-sign). Among non-culture-based diagnostic assays, detection of galactomannan and beta-D-glucan antigens are mostly used. In neutropenic patients our greatest part of knowledge is related to the detection of aspergillus-specific galactomannan antigen by enzyme-immunoassay (EIA). This method has a sensitivity of 78 % and a specificity of 81%.

During the past fifteen years marked progress was seen in the field of antifungal therapy. In invasive aspergillosis the real breakthrough took place as voriconazole has become available. By its use survival rate was significantly improved (70.8 % vs. 52.8 %), when compared to traditional amphotericin B. Management strategies should be considered as important as finding an optimal place for each antifungal drug on the therapeutic palette. In addition to the aforementioned empirical and targeted therapy, as well as antifungal prophylaxis being outlined below, more emphasis is placed on the so-called pre-emptive approach. The framework of this can best be studied in the paper published by *Maertens* and co-workers. In this trial authors were able to reduce the proportion of patients requiring antifungal therapy from 35% to 7.7%-ra by regular detection of *Aspergillus galactomannan* antigen, HR-CT scanning and use of bronchoalveolar lavage (BAL). At the same time this strategy also proved safe, as none of the invasive aspergillosis cases had been missed.

To preclude infections, a prophylactic approach has also been used in the oncohematological and stem cell transplant setting. Struggling bacterial infections the marketing of novel fluoroquinolones, especially ciprofloxacin and later levofloxacin, can be considered as a breakthrough achievement. A new scene in the prophylactic concept was set, as *Gafter-Gvili et al.* have published their meta-analysis in 2005. They came to the conclusion that by using a fluoroquinolone prophylaxis overall mortality can significantly be reduced in neutropenic patients (RR = 0.52). In addition, infection related mortality, number of febrile episodes as well as the incidence of clinically and microbiologically documented infections could also be lowered. At the same time increasing prevalence of fluoroquinolone-resistant bacteria and adverse events related to antibiotic use were also seen in patients under prophylaxis. These side effects however were not considered to be significant by the authors.

With regard to anti-aspergillus prophylaxis, in an open, randomized study comparing posaconazole with traditionally used fluconazole/itraconazole in patients with acute leukemia and myelodyslasia, posaconazole has been found superior to improve survival and to effectively reduce the incidence of invasive mycoses.

In another randomized, double-blind trial posaconazole and fluconazole were compared in severe GvHD. Primary endpoint was the incidence of proven and probable invasive mycoses. Here no significant difference could be shown (posaconazole 5.3 %, fluconazole 9 %, OR: 0.56 [CI] 0.3 – 1.07, $p = 0.07$). Posaconazole however was found to be superior to prevent breakthrough fungal infections, particularly invasive aspergillosis (2.3 % vs. 7%, OR: 0.30 [CI] 0.13 – 0.75, $p = 0.006$).

OBJECTIVES

Aims of the present research work were the following:

1. To investigate autopsy-proven infectious causes of death in the allogeneic stem cell transplant population.
2. To study the performance of diagnostic methods by comparing cases uncovered in vivo and post mortem.
3. To study the efficacy of posaconazole prophylaxis in stem cell transplant patients.
4. To develop care pathways for the optimal management of mould infections in international cooperation.
5. To assess the incidence of fluoroquinolone-resistance in Gram-negative strains causing bloodstream infection and colonization in oncohematological patients.
6. To describe the effect of fluoroquinolone prophylaxis on the incidence of Gram-negative bacteremia and on antibiotic resistance.

METHODS

Clinical, pathological and imaging results from adult and pediatric patients treated with chemotherapy for hematological malignancies, mainly acute leukemia, or undergoing stem cell transplantation for any approved indication, were analyzed. Patients were treated at the author's primary working place, Department of Hematology and Stem Cell Transplantation at Szent László Hospital – later renamed as United Szent István és Szent László Hospital. As the centre was moved to a different location, data between the years 2005-2007 come from the Department of Hematology and Stem Cell Transplantation of the National Medical Centre where the group was temporarily active.

Treatment algorithms were used in concordance with institutional, national and international protocols.

Infectious causes of death and diagnostic performance of invasive mycoses in allogeneic stem cell transplantation

Between January 2003 and October 2006 data from 97 adult and paediatric patients undergoing allogeneic stem cell transplantation were analyzed.

Key points of antifungal strategy are shown in Figure 1.

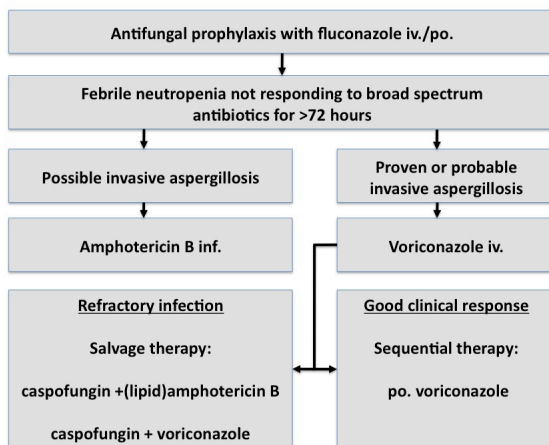


Figure 1
Antifungal strategy in febrile neutropenic patients following allogeneic stem cell transplantation

Clinical findings, imaging and microbiological (culture, microscopy, antigen detection) findings, data from cytological and histopathological studies as well as endoscopic (bronchoscopy) examinations were collected and analyzed.

Pathologic processes behind the fatal outcome were analyzed driven by the autopsy findings. Causes of death were designed as non infection-related and infection-related. Within the latter group, cases with invasive mycoses and infections caused by bacteria, viruses and protozoa were separately evaluated. For the classification of invasive mycoses definitions approved by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were used. Cases with an invasive mycosis were further classified according to additional parameters. Proportions of different fungal infections within all infectious fatalities were calculated. In addition the rate of invasive mycoses diagnosed on clinical basis ante mortem was also assessed.

Use of anti-mould prophylaxis in different risk-groups of patients with allogeneic stem cell transplantation

In this study 36 allogeneic stem cell transplant patients received primary or secondary antifungal prophylaxis between November 2007 and October 2008. The first group of patients was treated with 3 x 200 mg posaconazole oral suspension started after the pretransplant conditioning regimen. Following engraftment, prophylaxis was only carried on in those cases where GvHD developed (group „B”). In other individuals prophylaxis was stopped (group „A”). An additional group did not receive any posaconazole after during the neutropenic phase and was started on prophylaxis only after having developed GvHD (group „C”). (Figure 2)

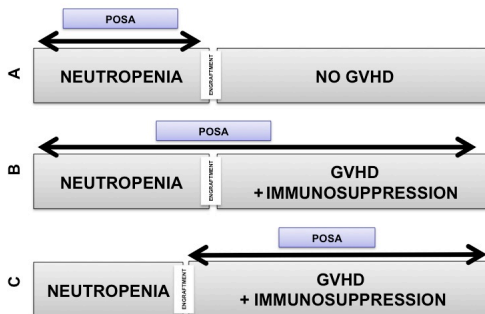


Figure 2
Posaconazole prophylaxis in different risk groups of patients

Study endpoint was success of prophylaxis at the end of the observation period. *Success* was defined as a case where no invasive mycosis developed and there was no need for the administration of additional antifungal drugs, either. *Success with modification* was determined when no mycosis developed but other antifungals were used according to the decision of the clinician. *Failure* meant any

event of proven or probable invasive fungal infection (EORTC/MSG) throughout the observation phase.

Setting up optimized care pathways for the management of mould infections in hematological and stem cell transplant patient population (international co-operation)

In 2010, professor *J.P. Donnelly* has funded an independent international workgroup under the auspices of Nijmegen University (The Netherlands) to optimize the management of invasive mould infections in immunocompromised patients. A group of experts dealt with prognosis and risk factors, a second one with diagnostic methods and a third one with treatment and timing. The remaining part of attendees was responsible for the synthesis of achievements from the former groups and for developing care pathways. I have been invited to participate in the latter group. The final document has been created through the following stages: a/ group leader, in group 4 *S. Agrawal* (St. Bartolomew's Hospital, London, UK), proposed a working material based on the review of literature and suggestions of group members, b/ in June 2010 a two days' symposium has been organized in Amsterdam, to discuss basic points, harmonize statements with the other workgroups and to condense near-final stage proposals into flowchart diagrams, c/ by circulating an electronic version all group members agreed on the finalized text, d/ then the description of care pathways appeared in print.

Incidence of fluoroquinolone-resistant Gram-negative bacteria and the effect of fluoroquinolone prophylaxis on spectrum and outcome of Gram-negative bacteremic episodes

During the first stage, in 2006 spectrum and prognostic factors of bloodstream infections developing in acute leukemia patients treated at the Department of Hematology were studied. Spectrum of bacterial pathogens isolated from neutropenic bloodstream infections (Gram-positive, Gram-negative and polymicrobial infections) has been estimated together with mortality caused by individual species. In a subsequent survey that took place during the same year, patient admitted to the hematological centre

were studied with regard to intestinal colonization by resistant bacteria. In co-operation with associates from the Microbiology Laboratory proportion of patients colonized by fluoroquinolone-resistant Gram-negatives has been calculated.

At the same time spectrum and outcome of bloodstream infections developing in patients treated for acute leukemia has also been assessed. Ratio of Gram-positive and Gram-negative isolates cultured from blood samples has been estimated. In the latter group, incidence of fluoroquinolone-resistant strains was determined together with its correlation with intestinal colonization.

In the next phase of the survey the effect of fluoroquinolone prophylaxis has been studied in oncohematological patients. In the year of 2008 no prophylaxis was used in individuals at risk. From January 1, in concordance with international guidelines, patients were either given 500 mg levofloxacin or 2 x 500 mg ciprofloxacin orally. Prophylaxis was started after the completion of chemotherapy cycles expected to cause bone marrow aplasia. After the second year of observation parameters from the period before and during prophylaxis were compared in a retrospective fashion. Incidence of Gram-negative bacteremic episodes, species distribution, rate of fluoroquinolone-resistance as well as mortality of patients with bacteremia were studied. During analysis patient flow facts were taken into account and primary data corrected accordingly.

RESULTS

Infectious causes of death and diagnostic performance of invasive mycoses in allogeneic stem cell transplantation

From the 97 allogeneic transplant patient followed during the observation period, a total of 38 individuals have died after median 125 (14 - 416) days post transplant. The fatal outcome was due to an invasive mycosis in 10 cases [invasive aspergillosis 6, invasive candidiasis and mucormycosis (zygomycosis) 2-2 cases each]. Within this group, 3 patients with aspergillosis, 1 with candidiasis and both cases of mucormycosis were only diagnosed post mortem.

Details of the group are shown in Table 1.

	Donor type	Invasive mycosis	Diagnosed in vivo	Diagnostic results	Comments
1	HLA-matched related	Invasive aspergillosis (pulmonary)	yes	Galactomannan antigen (BAL+serum)	
2	HLA-matched related	Invasive aspergillosis (pulmonary+ CNS)	no		Elevated galactomannan on one instance
3	HLA-matched unrelated	Invasive aspergillosis (CNS)	no		
4	HLA-matched related	Invasive aspergillosis (pulmonary)	no		
5	HLA-matched unrelated	Invasive aspergillosis	yes	Galactomannan antigen (BAL)	
6	HLA-matched related	Invasive aspergillosis (CNS)	yes	Galactomannan antigen, CT, brain biopsy	
7	HLA-matched unrelated	Acute disseminated candidiasis	no		Multiple candida colonization
8	HLA-matched unrelated	Candida pneumonia	igen	Blood culture, catheter, tissue culture	
9	HLA-matched unrelated	Mucormycosis (pulmonary)	no		
10	HLA-matched unrelated	Mucormycosis (pulmonary)	no		

CNS: central nervous system, BAL: bronchoalveolar lavage

Table 1

Parameters of stem cell transplant patients dying of invasive mycosis according to the spectrum of infections and timing of diagnosis

Use of anti-mould prophylaxis in different risk-groups of patients with allogeneic stem cell transplantation

Data from altogether 36 patients undergoing stem cell transplantation were analyzed. A total of 31 patients received primary antifungal prophylaxis while in further 5 cases secondary

prophylaxis was used. Median duration of prophylaxis was 81 (11-311) days. Patients were followed for median 275 (21-481) days.

Treatment was judged to be successful in 29/36 (81 %) of all patients on prophylaxis. Success with modification was seen in (8 %) of cases, and failure occurred in 4/36 (11 %) of patients. Results are shown in Figure 3.

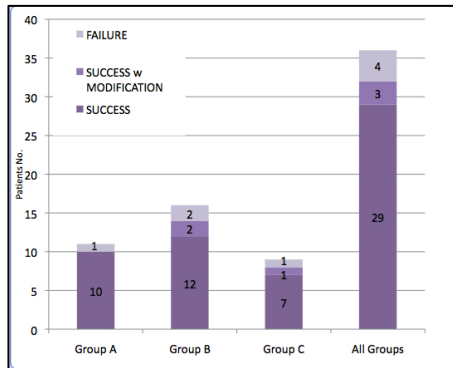


Figure 3
Efficacy of posaconazole prophylaxis in different risk groups of allogeneic stem cell transplant patients

Setting up optimized care pathways for the management of mould infections in hematological and stem cell transplant patient population (international co-operation)

Management of mould infections is a multidisciplinary task requiring high level of organization. Its effectiveness should rely on pre-defined, consensual programs affecting all health care providers. This should exactly describe duties of diagnostic, therapeutic, patient care and other supportive systems, together with their timing and conditions.

Care pathways

Empirical approach: With this strategy the use of diagnostic results will not be precluded only reserved for the later period of the process. (Figure 4).

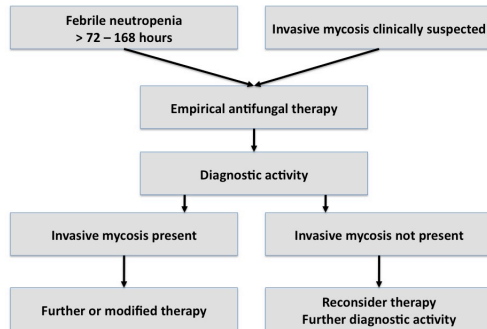
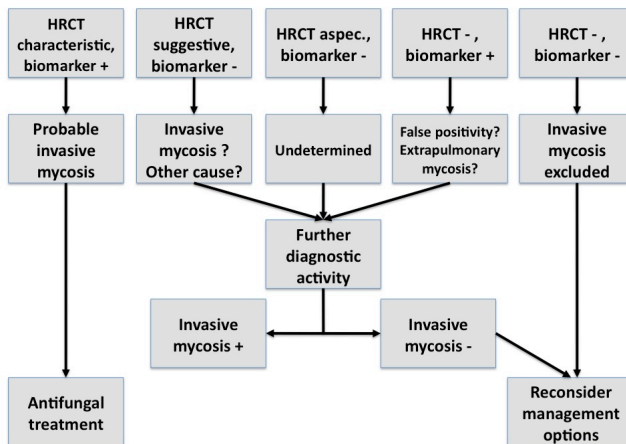


Figure 4. Empirical antifungal strategy

Diagnostic-based approach: In this strategy the start of an antifungal therapy is triggered by signals that are more specific than clinical signs (fever, respiratory symptoms). (Figure 5).



HRCT: high-resolution computer tomography

Figure 5.
Diagnostic-driven antifungal strategy

Incidence of fluoroquinolone-resistant Gram-negative bacteria and the effect of fluoroquinolone prophylaxis on spectrum and outcome of Gram-negative bacteremic episodes

Initially 93 acute leukemia patients admitted to the department of hematology were studied between 2005-2006. The group included 75 cases with acute myeloid leukemia, and 18 patients treated for acute lymphoid leukemia. Their median age was 51 (18-86) years. In the study population a total of 99 bacteremias were observed in 49 patients (53 %). From the blood stream infections 77 (78 %) were single Gram-positive, and 18 (18 %) single Gram-positive bacteremias. In further 4 (4%) cases a polymicrobial bacteremia could be confirmed. The mortality in Gram-positive bacteremic episodes was 4/77 (5.2 %), while 3/18 (16.6 %) of Gram-negative infections proved to be fatal.

According to the isolated species, mortality rates were the following: coagulase-negative staphylococcus: 2/61 (3.3 %), Enterobacteriaceae : 1/8, *Enterococcus* spp.: 4/8, *P. aeruginosa*: 3/7. In the age group between 18-40 years mortality was 1/36 (2.7 %). In patients between 41-60 years however the mortality rate increased to 5/43 (11.6 %). In individuals above the age of 60 the rate of fatal outcome reached 3/20 (15%).

Intestinal colonization caused by fluoroquinolone-resistant species: In this stage data from 85 patients admitted to the department of hematology and stem cell transplantation were studied. Among them 41 individuals (48 %) were already colonized on admission by bacteria resistant to fluoroquinolones.

Effects of fluoroquinolone prophylaxis on the spectrum of Gram-negative bacteremias, antibiotic resistance of isolates and mortality: While on fluoroquinolone prophylaxis the number of

patients with Gram-negative bacteremias decreased from 45 to 38. This – corrected for patient flow – represents a non-significant absolute risk reduction (ARR = 0.024 [- 0.027 – 0.076, 95 % CI]). The number of bloodstream infections caused by *E. coli* was reduced from 24 to 22 (ARR = 0.008 [- 0.032 – 0.048, 95 % CI]).

For all Gram-negative isolates the proportion of fluoroquinolone-resistant strains increased during prophylaxis from 24 % to 59 % (p = 0.001). An even more prominent change was seen in *E. coli*, where resistance rate changed from 16 % to 75 (p < 0.001). (Figure 6.)

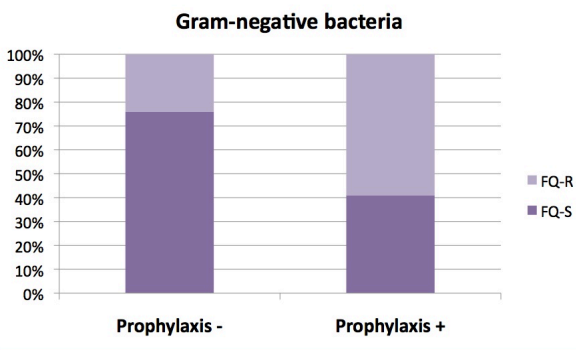


Figure 6.

Rates of fluoroquinolone resistance of Gram-negative bacteria in the year before and during prophylaxis (FQ-R: fluoroquinolone-resistant, FQ-S: fluoroquinolone-susceptible)

As a result of fluoroquinolone prophylaxis, mortality of Gram-negative bacteremia increased in a non-significant manner. For 7 days mortality ARR = - 0.006 [- 0.029 – 0.017, 95 % CI], and for 30 days mortality ARR= - 0.024 [- 0.054 – 0.005, 95 % CI]. Bloodstream infections caused by fluoroquinolone-resistant species had a higher mortality rate compared to episodes with susceptible bacteria (19 % vs.13 %, difference not significant).

CONCLUSIONS

1. In about 40% of fatalities following hemopoetic stem cell transplantation, death is caused by infections, most frequently invasive aspergillosis. In 60 % of cases a diagnosis of invasive fungal diseases can only be established post mortem.
2. In 81% of high-risk allogeneic stem cell transplant patients invasive mycoses can be prevented by the prophylactic use of posaconazole.
3. Centres treating oncohematological patients should develop care pathways for the management of invasive mould diseases. Technical and logistical conditions permitting, a diagnostic-based approach is preferred.
4. In the acute leukemia setting Gram-positive bacteremia is predominant (78%). Subsequent mortality is lower (5.2%) than in Gram-negative bacteremia (16.6%).
5. On admission to the hospital, 48 % of oncohematological patients all already colonized by fluoroquinolone-resistant Gram-negative strains.
6. Under current epidemiological circumstances the incidence of Gram-negative bacteremia does not change significantly with the use of fluoroquinolone prophylaxis. At the same time a marked increase in the proportion of fluoroquinolone-resistant Gram-negative strains causing bacteremia was seen (24 % vs. 59 %) ($p = 0.001$). The phenomenon was even more pronounced in *E. coli* (16 % vs. 75 %) ($p < 0.001$) representing the most prevalent Gram-negative bloodstream pathogen.

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