Update on pulmonary infections in patients with hematologic malignancies and hematopoietic stem cell recipients

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The present article is an update of the literature on pulmonary infections in patients with hematologic malignancies and in hematopoietic stem cell recipients. A multidisciplinary group of Spanish physicians with an interest in these infections selected the most important papers produced in the field during 2005 and 2006. One of the members of the group discussed the content of each of the selected papers, with a critical review by other members of the panel.
After a review of the state of the art, papers from the fields of viral and fungal infections were discussed by the group.

Key words: **Pulmonary Infections. Respiratory Virus Infections. Fungal Infections. Hematologic Malignancies. Stem-cell Transplantation.**

Actualización de las infecciones pulmonares en los pacientes con procesos hematológicos malignos y en los receptores de células madre hematopoyéticas

El presente artículo es una actualización de la literatura sobre infecciones pulmonares en los pacientes con procesos hematológicos malignos y en los receptores de células madre hematopoyéticas.
Un grupo multidisciplinario de médicos españoles con interés en estas infecciones seleccionó los trabajos más importantes publicados sobre el tema durante 2005 y 2006. Un miembro del grupo discutió el contenido de cada artículo seleccionado, y otros componentes del panel efectuaron una revisión crítica del trabajo.
Después de una revisión del estado del arte, el grupo discutió los artículos sobre las infecciones víricas y micóticas.

Palabras clave: **Infecciones pulmonares. Infecciones por virus respiratorios. Infecciones fúngicas. Procesos hematológicos malignos. Trasplante de células madre.**

State of the art (M.A. Sanz, I. Jarque)

Pulmonary infections are common following hematopoietic stem cell transplantation (HSCT) and chemotherapy for hematologic malignancies. Pneumonia is a feared complication that may occur despite routine prophylaxis and empiric therapy of febrile neutropenia. Up to 15 to 25% of episodes of febrile neutropenia may develop pulmonary infiltrates[1], and despite diagnostic and therapeutic advances[2], atributable mortality continues to be high[3]. Pathogens include fungi, bacteria, and viruses, although it is difficult to distinguish between infectious and noninfectious causes, and etiologic diagnoses often cannot be established[4]. Lung infiltrates attributable to fungi, gramnegative bacteria, and viruses can produce mortality rates of up to 50%[5-7]. It should be noted that the course of immunosuppression and recovery in HSCT patients influences the type of infection.

This review will examine viral and fungal pulmonary infections as an introduction to the individual papers.

Viral infections

Community respiratory viruses such as influenza, parainfluenza, respiratory syncytial virus (RSV), and picornavirus are common causes of upper respiratory infection and usually occur in seasonal outbreaks. These viruses have been increasingly recognized as a possible cause of serious infections in patients with cancer[8-15]. Some patients, especially HSCT recipients with symptomatic upper respiratory tract infections, have a higher tendency to progress to severe pneumonia, with a mortality rate as high as 50 to 70%[16-20]. Most respiratory viruses have infection rates that peak in a seasonal pattern, with the exception of parainfluenza. RSV and influenza infections usually occur during the colder seasons (between December and February in the northern hemisphere). Parainfluenza type 1 and 2 may be present during the spring and fall and parainfluenza type 3 is most prevalent in the summer months. Preventing transmission from person to

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person throughout the respiratory virus season is recommended, especially in immunocompromised patients. Failure to follow fastidious infection control procedures inevitably leads to nosocomial transmission. Preventive measures include contact isolation, hand washing, education, and influenza vaccination of health care personnel and family members. In recent years, important advances in the management of these infections have been made, including the development of rapid diagnostic tests and the discovery of therapeutic agents for some of these infections.

Fungal infections

Fungal pneumonia is one of the main causes of morbidity and mortality after HSCT. The most common organism of fungal pneumonia is *Aspergillus* species, which is responsible for 90% of such infections, although other emerging opportunistic fungal pathogens have been reported over the last 2 decades[21-23]. Lesions in invasive mold infections are caused by vascular invasion and occlusion of small- to medium-sized pulmonary arteries by fungal hyphae. The resulting areas of hemorrhagic infarction are seen on computed tomography (CT) as nodules surrounded by areas of ground-glass attenuation (halo sign). High-resolution CT is of great value in the diagnosis of invasive pulmonary aspergillosis. Common findings include large nodules, frequently with a halo of ground-glass attenuation, and focal areas of consolidation. Histopathology allows the morphologic detection of fungi and demonstrates the pattern and degree of host response. However histopathology alone does not suffice to distinguish between fungal pathogens, such as *Aspergillus* and other hyalohyphomycetes, and definitive diagnosis requires fungal culture. Thus, histopathology and microbiology are complementary methods in the diagnosis of IFIs.

CT diagnosis

Diagnostic evaluation of pulmonary infiltrates in hematologic patients and HSCT recipients often starts with radiographic imaging[24]. When the chest radiograph is negative or shows only minimal changes, chest CT is useful for defining the location, extent, and configuration of pulmonary lesions. Early and accurate diagnosis of these complications is important because of the high morbidity and mortality associated with infection and because of the frequent complications associated with the treatment of fungal and viral infections[25]. Several authors have emphasized the importance of high-resolution CT in the diagnosis of pulmonary infections after bone marrow transplantation[26,27]. High-resolution CT may show pulmonary abnormalities in patients with normal findings on radiographs and is superior to radiography in depicting the pattern and extent of abnormalities. Reliable and timely diagnosis of invasive pulmonary aspergillosis remains an interesting clinical challenge. The diagnostic value of early CT scanning in patients with severe neutropenia who are developing respiratory symptoms and signs suggestive of invasive pulmonary aspergillosis was established by Caillot et al[28,29]. Timely recognition of aspergillosis shortens the delay of appropriate therapy, creating an opportunity to cure the disease at an early stage. The CT halo sign appears during the initial stages of invasive pulmonary aspergillosis, whereas the air crescent sign occurs later and is less useful for early diagnosis. It should be borne in mind that the widely accepted EORTC/MSG guidelines are of limited clinical value. In series of autopsy-proven invasive aspergillosis[30,31], only 36 to 47% of patients received antemortem diagnoses based on the EORTC/MSG criteria.

Serological markers

Laboratory methods available for the diagnosis of fungal infections in the HSCT population involve culture of the organism from clinical specimens, detection of antigens with serologic tests, or histopathologic inspection of tissue[32]. Serologic tests can detect circulating antigen released during invasive infection. The serum *Aspergillus* galactomannan (GM) assay has been accepted as a diagnostic adjunct of invasive aspergillosis in the EORTC/MSG consensus criteria[33]. Several variables can affect the performance of the GM assay[34,35] and may account for differences in the results of prospective studies. The sensitivity of the assay is reduced by concomitant mold-active antifungal agents[36,37]. False-positive results may be more common among children and allogeneic HSCT recipients[38]. Receipt of concomitant piperacillin-tazobactam can cause false-positive GM results[39,40]. A recent meta-analysis showed that the GM assay had a sensitivity of 70% and a specificity of 89% for proven invasive aspergillosis and that the accuracy of the test was variable among different patient populations[41]. (1→3)-β-D-glucan, a cell wall component of yeasts and filamentous molds, is detectable at high levels in blood during infection with *Aspergillus*, *Candida*, *Fusarium*, *Trichosporon*, *Saccharomyces*, and *Acremonium*. Detection of β-glucan has received US Food and Drug Administration approval for use in the presumptive diagnosis of IFI. Among patients with acute myeloid leukemia and myelodysplastic syndrome, the assay was highly sensitive and specific in detecting early IFIs[42]. Experience with the β-glucan assay in HSCT recipients is limited[43], and its use in this population requires additional study. Although valuable as diagnostic adjuncts to support a diagnosis of a probable IFI in patients with compatible host factors and radiological findings as defined in the EORTC/MSG criteria, the value of these laboratory markers as screening tools for IFIs is controversial, and more research is required. In neutropenic patients with fever without localizing symptoms or physical examination findings who have negative blood culture results and negative chest CT findings, a negative GM and/or β-glucan assay result lends additional support for the absence of a breakthrough IFI. Finally, PCR-based detection is considered to be investigational.

Antifungal therapy

The development of newer antifungal agents with activity against yeasts and molds and with superior safety and tolerability, compared with amphotericin B deoxycholate (AmB-D), has substantially improved the therapeutic armamentarium against IFI and may change classical antifungal therapy[44]. For instance, caspofungin was at least as effective as and less toxic than liposomal am-

photericin B as empirical therapy in persistently febrile patients with neutropenia[45]. The success rate in each arm, using a prespecified composite outcome, was only 34%, with most treatment failures being driven by a lack of resolution of fever during the neutropenic period. This trial raises 2 questions. First, should persistent fever without evidence of a breakthrough IFI be a criterion for failure in antifungal prophylactic and empirical trials? Several empirical antifungal studies have employed a composite outcome in which fulfillment of several prespecified criteria were required for a successful outcome[46]. In studies comparing voriconazole with liposomal amphotericin B and caspofungin with liposomal amphotericin B, the proportion of patients with a successful outcome in the different treatment arms was 26% to 34%. However, the proportion of patients with breakthrough IFIs, poorly controlled baseline IFIs, or mortality was relatively small. The most common reason for treatment failure was lack of resolution of fever during neutropenia. The rationale for including fever resolution as a criterion for a successful outcome is that this is precisely the trigger used to initiate empirical antifungal therapy. However, fever is neither a sensitive nor a specific sign of IFI. Fever resolution was the least clinically meaningful end point in the composite outcome, and yet it accounted for most of the treatment failures, with the potential to mask more-relevant clinical outcomes[47]. The second question relates to whether empirical modification of the antifungal regimen is warranted solely on the basis of persistent neutropenic fever in patients receiving mold-active prophylaxis. No studies specifically address this question. The availability of effective and safe mold-active prophylaxis creates the need for a new paradigm to diagnose breakthrough IFIs early and to modify the antifungal regimen only in those patients who meet pre-specified criteria.

Pneumocystis infections

Pneumocystis is an atypical fungus causing severe pneumonia in immunocompromised patients, particularly among HSCT recipients[48,49]. Molecular analysis has revealed genomic diversity of the organism in different host species: *P. carinii* infects rodents, and *P. jiroveci* infects humans[50]. Acquisition seems to be through inhalation of aerosolized organisms, and disease may occur either by primary exposure or by reactivation of latent infection. Recent studies have reported that patients with chronic lung disease or bacterial pneumonia as well as immunocompromised HIV-infected and uninfected patients could be asymptomatic carriers of *P. jiroveci*[51,52]. Since the use of effective prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX), less than 5% of HSCT recipients develop *P. jiroveci* pneumonia. Recent data from the TRANSNET surveillance program reported that pneumocystosis accounts for 2% of IFI in the transplant population[53]. However, late onset *P. jiroveci* pneumonia in patients discontinuing prophylaxis after the first 6 months post-transplant has been reported. Alternatively, acute graft-versus-host disease and high-dose steroids and cyclosporine in these patients could have triggered *P. jiroveci* pneumonia despite the use of prophylaxis, maybe because of low intestinal absorption of the prophylactic regimen or resistance of *P. jiroveci* to sulfonamides through the selection of mutations in the dihydropteroate synthase gene[54]. TMP/SMX or sulfadoxine-pyrimethamine are the preferred regimens because they are the most effective and also prevent *Toxoplasma gondii* reactivation. Aerosolized pentamidine, atovaquone, or disulone are acceptable alternatives in case of intolerance but are probably less effective[55]. The typical presentation of *Pneumocystis* pneumonia includes increasing dyspnea, nonproductive cough, fever, and occasionally chest pain. In seriously ill patients, hypoxemia is often present, and elevated lactate dehydrogenase levels reflect the extent of tissue injury. Radiographic imaging reveals bilateral interstitial infiltrates, although atypical images such as unilateral infiltrates, alveolar infiltrates, nodules, and cavities have been seen. As noted previously, widespread use of prophylaxis for *Pneumocystis* pneumonia has decreased rates of infection and improved survival. Breakthrough infections in patients receiving TMP/SMX with adequate systemic absorption are rare, but when they do occur, the clinical presentation is often atypical, and diagnosis may require lung biopsy. Breakthrough *Pneumocystis* infections have also been reported in transplant patients receiving low-dose atovaquone[56] and aerosolized pentamidine[55].

Below, a group of Spanish physicians with an interest in the field of pulmonary infections discusses the most remarkable papers produced in this area during the last 2 years. The following are the publications selected for discussion.

Infection by community respiratory viruses

Erard V, Chien JW, Kim HW, Nichols WG, Flowers ME, Martin PJ, et al. Airflow decline after myeloablative hematopoietic cell transplantation: the role of community respiratory viruses. JID. 2006;193:1619-25.

Severe airflow decline (SAD), otherwise known as airflow obstruction or bronchiolitis obliterans, is a frequent, serious and often fatal complication occurring in long-term survivors of hematopoietic cell transplantation (HCT). SAD has been defined as a > 5%/year decline in the percentage of predicted FEV_1 during year 1, with the year 1 FEV_1:FVC ratio < 0.8 (definition recently validated; Chien et al; Am J Respir Crit Care Med 2003;168:208-14). In this paper, the authors retrospectively analyze the effect of community respiratory virus (CRV) infections occurring in the immediate post-transplant period on the development of SAD.

A cohort of 1131 patients who underwent their first myeloablative allogeneic HSCT at the Fred Hutchinson Cancer Research Center in Seattle (USA) was studied. Among those patients, 132 (12%) had a documented CRV infection during the first 100 days post-HSCT. The infection affected the upper respiratory tract in 114 cases and the lower respiratory tract in 18 cases.

Two hundred and ninety-nine patients (26%) presented with SAD by year 1 (SAD1). Several factors were associated with a significantly increased risk of having SAD1: patient age > 20 years old (OR: 2.1), patient age > 60 years old (OR: 5.9), baseline FEV_1:FVC < 80% (OR: 2.6), baseline FEV_1:FVC < 70% (OR: 4.5), chronic GVHD (OR: 2.1), lower respiratory tract RSV infection (OR: 3.6), and lower respiratory tract parainfluenza-virus infection (OR: 17.9).

Therefore, along with other widely recognized factors influencing the development of SAD, lower respiratory tract infections by RSV and parainfluenza-virus were found to enhance the risk of late SAD. The most significant decline relative to CRV infection was observed between the day of HCT and day 100, during which time the viral infection occurred. During the months after infection (day 100 to year 1), there was a slight improvement in lung function, but none of the patients returned to their baseline values.

On the contrary, among patients who suffered from CMV (9 cases) and *Aspergillus* pneumonia (16 cases) during the initial 100 days post-HSCT and survived the infection, the risk of late SAD did not increase.

Comments

CRV are well known as a significant cause of morbidity and mortality after HCT by causing fatal pneumonia. However, according to this study, some CRV infections (lower respiratory tract parainfluenza-virus and RSV infection) might also contribute to increased overall mortality by causing a long-term decline of lung function. The authors suggest that CRV might activate an inflammatory process in the LRT that, in patients who survive the acute phase of the infection, might lead to irreversible damage to the tissue of the small airways independently of viral replication. The authors conclude that these data would benefit from further research into the mechanisms by which viruses can lead to SAD and, ultimately, into the role of viral infections in other airway diseases, such as asthma.

On the other hand, these data support the recommendation to screen for CRV in symptomatic patients in order to prevent transmission to other patients and, if possible, to prevent progression of infection from the upper to the lower respiratory tract. Therefore, a nasopharyngeal throat wash or swab for viral direct fluorescent antibody (DFA) staining and viral culture should probably be a standard practice for all patients with upper respiratory tract infection symptoms. Viral DFA and culture should also be performed in all bronchoalveolar lavage and lung biopsy samples. Once a patient is known to be infected, he/she should be placed in respiratory isolation. Finally, preventing progression of upper respiratory tract infections to lower respiratory tract CRV infections should be an important goal of medical management. Although there are no prospective randomized studies, several papers suggest that pre-emptive antiviral therapy of upper respiratory tract RSV infections reduces the likelihood of progression to pneumonia (lower respiratory tract infection). Therefore, this approach should be considered, at least in selected groups of HSCT and other immunosuppressed patients.

Chemaly RF, Ghosh S, Bodey GP, Rohatgi N, Saldar A, Keating MJ, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients. A retrospective study at a major cancer center. Medicine. 2006; 85:278-87.

Before 1990, very little information was available on the frequency of infections caused by community respiratory viruses (CRV) in cancer patients. However, recent studies involving HSCT recipients recorded CRV infections with varying frequencies in patients with respiratory symptoms, from less than 5 to almost 40%. Many CRV infections are limited to the upper respiratory tract and resolve favorably without treatment, although in other cases they can progress to pneumonia and death.

In this retrospective study carried out in one of the world reference centers, the M.D. Anderson Cancer Center of the University of Texas, in Houston, CRV infections diagnosed by CRV in adult patients with hematologic malignancies and HSCT recipients over a 2-year period (July 2000-June 2002). Patients with respiratory samples that were positive for influenza virus, parainfluenza virus, RSV or picornavirus were selected. A total of 343 infections were identified in 306 patients with hematological malignancies and HSCT. Data were collected on the underlying hematological malignancy, age, sex, type of infection, and absolute neutrophil and lymphocyte counts. Finally, patient characteristics and response to antiviral therapy were analyzed, as were risk factors for progression to pneumonia and death.

With the limitations inherent to retrospective studies, information that is relevant to clinical practice can be extracted from this extremely wide series of patients. Most infections (70%) occurred in HSCT recipients, mainly in those receiving allogeneic transplant. Infections by influenza (mainly influenza A), parainfluenza (type 3 predominance), and RSV accounted for most cases and had a similar frequency (around 30% each). Picornavirus (including rhinovirus) caused only 9% of cases.

Infection progressed to pneumonia in 119 patients (35%) and occurred with a similar frequency in infections by RSV, influenza virus, and parainfluenza virus. Patients with leukemia, those aged over 65 years, and those with severe lymphopenia or neutropenia had a greater risk of developing pneumonia. The risk factors for pneumonia in HSCT recipients were allogeneic transplant, graft-versus-host disease, infection within 100 days after transplantation, corticosteroids, age over 65 years, severe lymphopenia and neutropenia. Severe lymphopenia (absolute lymphocyte count $\leq 200/\mu L$) was associated with the development of pneumonia caused by influenza. Global mortality was 15%, similar for the 3 main viruses.

The results of therapy for the 112 patients with influenza virus infection are particularly surprising. Of 41 patients treated with oseltamivir when they had upper respiratory tract symptoms, only 4 (10%) developed pneumonia, whereas of the 71 who were not treated, 30 (42%) developed pneumonia, a clearly significant difference. Similarly, there were more deaths by pneumonia in untreated patients (27%) than in treated patients (9%). With respect to patients with infection by RSV, there was also less progression to pneumonia when treatment with aerosolized ribavirin was administered. The absence of therapy targeting RSV and age were associated with the development of pneumonia.

Comments

In summary, this study indicates that infection by CRV is common in immunocompromised patients. In patients with upper respiratory tract symptoms, cultures should be taken immediately and antigenic testing should be performed. In CRV infection, oseltamivir administered in infections of the upper airways by influenza and ribavirin in RSV seems to reduce progression to pneumonia in high-risk patients with

hematological malignancies (age ≥ 65 years, severe lymphopenia) and, therefore, the possibility of death.

FUNGAL INFECTIONS

Pediatric patients

Castagnola E, Cesaro E, Giacchino M, et al. Fungal infections in children with cancer. Pediatr Inf Dis J. 2006;25:634-9.

Background: Fungal infections are an important complication in cancer patients, particularly those suffering from leukemia and those undergoing a bone marrow transplant. Clinical and epidemiological data come mainly from different adult series; however, few studies (mainly retrospective) analyze clinical findings, risk factors, and survival after fungal infections in children.

Objective: To obtain epidemiological, clinical, and survival information about fungal infections in children with cancer who were followed up for a 2-year period in Centers of the Association of Hematology and Oncology in Italy.

Methods: This was a multicenter, prospective study of fungal infections in children receiving antineoplastic therapy in 15 centers.

Patients: The patients were registered in a single center (demographic data, data on the illness and stage of the illness) where the fungal infection developed. Therapy was moderately aggressive or aggressive. Cases were defined according to EORTC/MSG criteria.

Results: A total of 96 episodes of fungal infection were diagnosed (42 proven, 17 probable, and 37 possible). Aggressive chemotherapy was used in 73% of the episodes, 21% were allogeneic transplants, and only 6% occurred after moderately aggressive chemotherapy. Neutropenia was present in 77% of episodes. Prolonged deep neutropenia correlated with deep mycosis vs. fungemia (p = .020). Of the non-neutropenic patients, 75% presented lymphopenia. Children with probable fungal infection have a 25.7 times greater risk of dying than those who do not present fungemia. The risk of death is 3.8 times greater in those patients who were receiving antifungal therapy at the time of diagnosis compared with those who do not receive it.

Conclusions: Among children with cancer, aggressive therapy, duration and severity of neutropenia and lymphocytopenia in non-neutropenic patients are associated with fungal infection.

Mortality in children is lower and, curiously, it is significantly lower in those patients who have not received antifungal therapy.

Steinbach WJ. Pediatric Aspergillosis: disease and treatment differences in children. Pediatr Inf Dis J. 2005;24:358-64.

There is little information on invasive aspergillosis in pediatric patients. Some aspects are similar to those of adults, but there are important differences in epidemiology, pathophysiology, and treatment.

Epidemiology of invasive aspergillosis: The incidence of invasive aspergillosis in children is not well known and is not examined in epidemiological studies of this disease. In patients undergoing stem cell transplant, the most relevant study is that by Benjamín et al (Pediatr Infect Dis J. 2002;21:227-34), in which the incidence of proven aspergillosis is 4.79%. A multivariate analysis shows that the disease is associated with graft-versus-host disease.

Distribution of isolated species is different in adults and children in some studies. In adults, *Aspergillus fumigatus* (70%) and *A. flavus* (5-10%) are more common. In studies from the Hospital for Sick Children in Toronto (Pediatr Infect Dis J. 1993;12:673-82) and St. Jude's Children's Hospital (Clin Infect Dis. 1999;29:1210-9), the most commonly isolated species was *A. flavus*. Nevertheless, more recently (Pediatr Infect Dis J. 2002;21:240-8), *A. fumigatus* seems to be more frequent. In children, it seems that *A. flavus* is related to cutaneous aspergillosis and *A. fumigatus* with lung disease.

Diagnosis: Radiographic studies seem to show that the radiological spectrum is clearly related to age. The galactomannan test in children is not reliable and produces false negatives and positives.

Treatment: No studies analyze children in particular. There is also the problem of pharmacokinetics and pharmacodynamics, which are different in children. The metabolism of voriconazole is different in children and in adults, and elimination is linear after a dose of 3-4 mg/kg/12 hours.

Exposure to voriconazole based on AUC with a dose of 4 mg/kg/12 hours in children is similar to a dose of 3 mg/kg/12 hours in adults, which suggests that children are more able to eliminate the drug.

As for caspofungin, some studies suggest that 70 mg/m^2/day as the initial dose followed by 50 mg/m^2/day seems to be more appropriate than 1 mg/kg/day.

In any case, these data suggest that the correct dose in pediatrics is not known, but that higher doses than those used in adults may be necessary.

Autopsy studies

Chamilos G, Luna M, Lewis RE, Bodey GP, Chemaly R, Tarrand JJ, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). Haematologica. 2006;91:986-9.

Invasive fungal infections (IFI) are now the main cause of infectious death in allogeneic stem cell transplantation (SCT), and an important cause of morbidity and mortality in patients with hematological malignancies treated with chemotherapy, mainly acute leukemia and myelodysplastic syndromes. The high mortality (50-90%) associated with these infections has remained essentially unchanged for the last 30 years, particularly for mold infections[5,57,58].

There have been three main changes in the epidemiology of IFI during the last 20 years in oncology-hematology patients. First, an increase in the overall incidence (2-4 times) and a change in the most frequent fungal pathogen[59-61]. Nowadays the main IFI in oncology-hematology patients and the cause of most deaths caused by fungal infections are not *Candida* but *Aspergillus* species. There has been a 50% decrease in the incidence and mortality of invasive candidiasis[62] and a 4- to 8-fold increase in invasive aspergillosis[61,63,64]. Second, there has been a

shift toward a non-*albicans Candida* species and an increase in non-*fumigatus Aspergillus* species, especially *A. terreus*. These facts have therapeutic consequences. Some non-*albicans Candida* species are less susceptible (*C. glabrata*) or resistant to fluconazole (*C. krusei*). *A. terreus* is less susceptible to amphotericin B *in vitro* and *in vivo* than *A. fumigatus* and has the potential to cause fulminant invasive infections in immunocompromised patients. And third, there has been an increase in the incidence of infections caused by difficult-to-treat opportunistic molds such as *Zygomycetes*, *Fusarium*, and *Scedosporium* species and yeasts such as *Trichosporon* species.

It is difficult to perform an early and timely diagnosis of IFIs. Two good examples illustrate the limitations of culture-based methods for IFI diagnosis. About 30% to 60% of patients with tissue-proven invasive candidiasis at autopsy had *Candida* isolated from blood during life[65]. This figure decreases dramatically to 20% if the patient received prophylaxis with fluconazole[64]. If this happened with invasive candidiasis, one of the IFI with the highest rates of fungemia, it is easy to imagine that the situation for IFIs due to molds should be worse, as in fact it is. Not surprisingly, but quite disappointingly, the proportion of patients without a clinical diagnosis of invasive aspergillosis who had evidence of disease at autopsy (68%) has remained unchanged for 40 years (1953 to 1992)[59,66]. Due to these difficulties in the diagnosis of IFI, autopsy studies are an important tool to evaluate the epidemiology of these infections.

The study by Chamilos et al[67] is the largest single-institution study of autopsy-proven IFI in oncology-hematology patients and the largest autopsy study published in the last 7 years: it is of enormous value in helping us understand the epidemiology of IFIs. Chamilos et al[68] summarize the M.D. Anderson Cancer-Center autopsy experience in oncology-hematology patients over 3 periods (1989-93, 1994-98, and 1999-2003). A total of 10,017 autopsies were performed over a 15-year period. The autopsy rate declined significantly over time, from 67% in the first period to 26% in the last one ($P < .0001$). This is in line with the experience of other centers showing an alarming worldwide tendency toward a lower autopsy rate.

Proven IFI were identified in 314 patients (31%). The prevalence of IFI remained constant throughout the study period. This is an interesting finding, since most studies show an increase in prevalence over time. The reasons for this stabilization are not clear. It is possible that the negative impact of higher risk patients was counterbalanced by better preventive and therapeutic strategies. As expected, most IFIs were diagnosed in leukemic patients (77%), allogeneic HSCT recipients, and in patients with active malignancies (78%). In line with the experience of other large HSCT centres[69], IFI tend to present late after allogeneic transplants (> 100 days) and are frequently associated with graft-versus-host disease. Severe (< 100/mm^3) and prolonged neutropenia is an important and well-known risk factor for the development of IFIs. Nonetheless, as seen in other series, the number of non-neutropenic cases is increasing. In this study, the proportion of patients with IFI who had severe neutropenia decreased after the first period (1989-93, 90%; 1994-98, 81%; 1999-2000, 70%; $P = .007$), and the percentage of patients with IFI who received a significant dose of corticosteroids increased (1989-93, 5%; 1994-98, 46%; 1999-2000, 32%; $P < .0001$).

Only 25% of the IFI were diagnosed antemortem as proven or probable IFI according to the EORTC/MSG criteria[33]. This reflects the difficulties in IFI diagnosis even in large oncologic centers in recent years, and confirms previous experience[69], which shows that most patients with proven IFI at autopsy had no proven or even probable IFI diagnosis during life.

As for the etiology of IFI, an interesting trend was found in the study by Chamilos et al[67]. In spite of the stable prevalence of overall IFI, there was an increase in the prevalence of invasive mold infections (19 vs. 25%; $P = .05$) and a decrease in the prevalence of invasive candidiasis (13 vs. 8%; $P = .07$). This confirms the shift from *Candida* to *Aspergillus* as the most frequent fungal pathogens seen since 1990 in other epidemiologic studies[60,61]. The increase in mold infections occurred despite the fact that the prevalence of aspergillosis, which was the predominant IFI in each study period, remained stable. Zygomycosis was the only mold infection that increased significantly after the first period (1989-93, 1%; 1994-98, 4%; 1999-2000, 3%; $P = .03$), in line with the experience of other oncology centers. Cases due to *Fusarium* and *Scedosporium* remained stable and low. In relation to the species isolated, this study confirms the pattern observed in other studies. Non-*albicans Candida* accounted for 66% of all *Candida* isolates, a proportion that increased after the first period (1989-93, 50%; 1994-98, 70%; 1999-2000, 80%; $P < 0.01$). Infections due to non-*albicans Candida* increased by a factor of more than 2 from the beginning of the period to the end (1989-93, 3.2 vs. 1999-2000, 7.8%; $P < .01$). The same occurred for the non-*fumigatus* species of *Aspergillus*: they represent 68% of all the infections, a proportion that experienced a marked increase after the first period (5%, 46%, 32%; $P < 0.001$). As already mentioned, this shift in *Aspergillus* species has a clinical and therapeutic impact[70].

Finally, only 40% of invasive mold infections had a positive culture, a proportion that remained stable during all 3 periods, a figure similar to that observed in previous studies[71]. It is known that culture has a low sensitivity for diagnosing mold infections: only 30% to 50% of tissues with histopathologic evidence of invasive mold infection have a positive culture. This has practical diagnostic consequences since the histologic appearance of different fungi is the same (*Aspergillus* = *Fusarium* = *Scedosporium*).

Aspergillosis: Clinical-radiological correlation

Brodoefel H, Vogel M, Hebart H, Einsele H, Vonthein R, Claussen C, et al. Long-term CT follow-up in 40 non-HIV immunocompromised patients with invasive pulmonary aspergillosis: kinetics of CT morphology and correlation with clinical findings and outcome. AJR. 2006;187:404-13.

This study analyzes 310 high-resolution computed tomography (HRCT) images from 40 patients diagnosed with proven or probable invasive pulmonary aspergillosis (IPA); 23 of the patients had undergone a stem cell transplant. The study aimed to describe the long-term outcome of the radiological lesions and establish the initial impact of the lesions in HRCT, risk factors related to radiological outcome, and clinical progress of the patient.

The images were analyzed by radiologists who were not aware of the clinical symptoms and progress of the patient. The first HRCT was carried out when IPA was first suspected (baseline) or on diagnosis and weekly thereafter during the pregraft period according to the patient's status, with a mean of 7.7 HRCTs per patient and an average follow-up of 112 days.

At the time of diagnosis, 45% (18/40) presented nodules > 3 cm^2 and a mean of 3 lesions. The halo sign was observed in 87.5% (35/40) of HRCT and lasted around 5 days. The crescent sign appeared in 45% of IPA at around day 13 and 55% (20/40) of the lesions were cavitated a mean of 21 days after diagnosis.

The kinetics of radiological lesions during the clinical outcome of IPA is very interesting: 90% (26/40) of the lesions increase in size (to a mean of 12.5 cm^2) until day 9 (median and mean with range: 1-36 days). There is a parallel increase in the number of lesions with a peak of 5.2. From day 9 onward, stabilization was observed in the size of the nodules or condensations lasting 3.5 days, until 12 days after diagnosis, with a discreet fall in the number of lesions (17% reduction). From this point on, the lesions decreased in size and 62.5% (25/40) of the IPA showed a 50% reduction in size and number on about day 31. In approximately 42.5% of IPA there was a remission of lesions on day 80, and it was observed that in those cases with cavitation, remission time is 2.5 times longer (90 vs. 38.9 days). Nine patients underwent thoracic surgery for different reasons, and afterwards the same rate of relapse of IPA was observed in patients who had undergone surgery and in those who had not. This is 1 of the few studies to report this rate and this may have been observed because the follow-up was longer.

It is very interesting that 7 cases of IPA were fulminant and that the kinetics described was not observed in any of them. There was no increase in the size or number of the lesions and the patients died 20 days later with no crescent sign or cavitation.

Survival in the series was 60% (24/40): those patients with cavitated lesions had a greater survival (OR = 8.4; CI, 1.07-176) that could be explained by the fact that the cavitation was the result of an increase in the number of leukocytes releasing proteases that affect the reabsorption of necrotic tissue.

Comments

This study is interesting, since it shows the usefulness of HRCT in the diagnosis and follow-up of IPA, establishes kinetics for the lesions, and, even though the number is not very high, shows that patients with no increase in the number and size of lesions may present another infection during the early stage. In this study, surgery does not seem to have prevented relapses of IPA.

Greene RE, Schlamm HT, Oestmann JW, Stark P, Durand C, Lortholary O, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis. 2007;44:373-9.

This study retrospectively analyzes the images that appear on HRCT at onset of IPA in an attempt to establish the prevalence of radiological findings and evaluate the clinical usefulness of the halo sign in the early diagnosis and start of therapy. The cases were obtained from the Data Review Committee (DRC) of the Global Comparative Aspergillosis Study (National Library of Medicine clinical trials registry NCT00003031 and NCT00001646). Diagnosis of IPA was according to the criteria of EORTC/MSG, taking the halo sign in a hematology patient with neutropenia as probable IPA.

A total of 235 patients (203/86% hematological disease) were analyzed: 94% (222/235) presented at least 1 macronodule (> 1 cm), 79% presented multiple macronodules, and 60% were bilateral, the halo sign was present in 61% (143/235), and 8 of these patients did not have an underlying hematological condition. As the HRCT were taken at baseline, cavitation and the crescent sign were observed in only 20% and 10% of cases, respectively.

In order to evaluate the response to treatment and the involvement of the halo sign, 222 patients with macronodules were analyzed (143 with halo and 79 without). At 12 weeks, the global response was 52% in the halo group compared with 29%, a statistically significant difference. The same occurs with survival at 12 weeks: 71 vs. 53%. The best response in this group was from patients treated with voriconazole, 62% (48/77) of whom presented the sign and the worst response was from the 16% (6/38) who did not and received amphotericin B deoxycholate.

Comments

This study once again shows the value of HRCT in the diagnosis of API. The halo sign, common in the hematological patient, confers a better prognosis and survival; however, for the moment, this cannot be extrapolated to other populations with a high incidence of IPA, with the result that further radiological studies are necessary in these patients in order to establish diagnostic-prognostic patterns.

Antifungal therapy

Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis. 2005;41:1242-50.

Despite the fact that it is based on limited scientific evidence and in a different epidemiological environment, empiric antifungal therapy in patients with prolonged febrile neutropenia–or recurring fever during the same episode of neutropenia[72] –is considered the gold standard and has been recommended in the main clinical guidelines for almost a quarter of a century[73,74].

However, we must remember the following: 1) the positive predictive value of persistent/recurrent fever in the neutropenic patient is low (only 10% to 20% of patients who start empiric therapy suffer from mycosis); 2) recurrence involves overtreatment of many patients, which is especially important in terms of toxicity and cost, and 3) regardless of this empiric antifungal treatment, breakthrough IFI continues to affect at least 3 to 5% of these patients[75].

In recent years, the diagnostic arsenal has grown with the inclusion of techniques such as panfungal PCR, detec-

tion of beta-D-glucan and galactomannan, and high resolution computed tomography (HRCT). The latter 2 are more introduced in clinical practice. Although the sensitivity and specificity of these techniques can vary according to the clinical context, most authors agree on their high negative predictive value[29,76]. Furthermore, the detection of galactomannan–although not exempt from false positives–presents high specificity in the neutropenic patient. Even more important, and despite the fact that it is questioned by some authors, these techniques enable us to diagnose IFI in the initial stages, which in turn allows us to start therapy early[29]. Similar to the treatment of CMV infection in stem cell recipients, these techniques form the basis of early antifungal therapy as an alternative to empiric therapy.

This study by Maertens et al is both daring and right to include these "new" techniques as part of the routine management of 136 episodes of neutropenia in very high-risk patients in an attempt to study the possibility of replacing antifungal empiric therapy with early treatment. All the patients received antifungal prophylaxis with fluconazole only.

In their algorithm, the patients did not receive antifungals based on the classic criteria of persistent/recurrent fever. On the contrary, they received liposomal amphotericin B (not voriconazole) if galactomannan was detected on 2 consecutive occasions (cut-off > 0.5) or there was evidence of pathology in HRCT images and positive microbiology in bronchoalveolar lavage.

Using this strategy, Maertens et al were able to reduce the percentage of patients treated with antifungals from 35 to 7.8% (even though, on 10 occasions, treatment was started based on detection of galactomannan in patients who did not have persistent fever). No cases of aspergillosis were diagnosed, even taking into account autopsy studies of patients who died. Survival was 63% in cases of IFI. Only 1 patient was affected by zygomycosis that was diagnosed antemortem, although the patient did not meet the criteria for starting empiric antifungal therapy.

What criticisms can be leveled at these encouraging results of early treatment instead of traditional empiric therapy?

In the first place, it is inherently difficult to transfer this methodology to daily clinical practice in general hospitals (daily galactomannan detections analyzed 3 times per week, HRCT ± CT of airways in 24 hours, and early bronchoalveolar lavage if CT is positive). Although the authors do admit that it takes galactomannan 2 to 3 days to show positive levels, which would enable the test to be carried out only twice per week, it is nevertheless difficult to carry the test out with this frequency.

Second, the conclusions of Maertens et al should be taken in the context in which they were drawn–prolonged neutropenia in high-risk patients–and cannot be extrapolated to other groups (for example, non-neutropenic transplant recipients with graft-versus-host disease) in which the sensitivity and specificity of these early diagnostic tests are different.

Third, we must not forget the need to carry out cultures and other diagnostic tests when there is clinical suspicion of infection, as demonstrated by the fact that the authors detected 2 cases of breakthrough candidemia (despite prophylaxis with fluconazole) and 1 case of zygomycosis.

Fourth, we must ask whether this methodology allows us to advance in diagnosis with respect to empirical therapy. Although the study by Maertens et al was not designed to deal with this question (CT was carried out when galactomannan reached positive levels), other studies[77,78] were unable to show any advance in the diagnosis of aspergillosis.

Even more, antifungal prophylaxis (itraconazole or posaconazole, for example) may be chosen by many groups for these high-risk patients. There is some doubt as to whether using this prophylaxis against filamentous fungi, in addition to the frequency of sampling, can reduce the usefulness of galactomannan[37]. Another technique, β-D-glucan, is not influenced by antifungal prophylaxis.

The literature mentions 2 further studies that have used early treatment, although it was based on PCR. In 1 of them[79], a reduction in the use of empiric antifungal drugs had no effect on patient safety. In the other, the use of antifungals was more extended in the early treatment group, although there was less mortality secondary to IFI in these patients than in those treated empirically[80].

However, and bearing all these questions in mind, the study by Maertens et al puts forward the possibility of developing a series of studies that allow us to determine the role of this strategy in comparison with classic antifungal empiric therapy, a clinical situation in which greater rationality and less empiricism are probably necessary[75].

Patterson TF, Boucher HW, Herbrecht R, Denning DW, Lortholary O, Ribaud P, et al. Strategy of following voriconazole versus amphotericin b therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: impact of other therapies on outcome. Clin Infect Dis. 2005;41:1448-52.

In their classic study, Herbretch et al demonstrated the superiority of voriconazole over amphotericin B deoxycholate for first-line treatment of invasive aspergillosis in terms both of antifungal efficacy and of survival[81]. In the present study, Patterson et al focus on patients who received another salvage antifungal drug due to intolerance or resistance to the initially assigned treatment arm: 80% of those initially randomized to amphotericin B deoxycholate and 36% of those randomized to voriconazole. More patients in the amphotericin B deoxycholate group received antifungal treatment than in the voriconazole group due to intolerance (70 vs. 24%).

If we exclude patients who received long-term antifungal therapy to avoid prevent reactivation of aspergillosis, antifungal salvage therapy consisted of lipid amphotericin (44.5%), amphotericin B deoxycholate (22.6%, at low doses if amphotericin was also the initial antifungal drug, since many patients could not tolerate 1 to 1.5 mg/kg/day), itraconazole (24.2%), and combined treatment with amphotericin and itraconazole (8%). Only 1 patient was treated with caspofungin.

Salvage therapy was more efficacious in patients treated initially with voriconazole compared with those who received amphotericin B deoxycholate (48 vs. 38%) (table 1).

Limitations: The study has the advantage that the first-line treatment was homogeneous. However, due to the period when the study was carried out, salvage therapy did not include caspofungin, micafungin, or posaconazole,

TABLE 1. **Salvage antifungal therapy: response rate (complete + partial)**

	First-line therapy: Voriconazole	First-line therapy: Amphotericin B
Global:	48%	38%
In refractory patients	26%	19%
In intolerant patients	50%	38%
With lipid amphotericins	36%	30%
With amphotericin B deoxycholate	45%	64%*
With itraconazole	65%	50%
First-line therapy + salvage therapy	53%	32%

*These patients were treated with lower doses of amphotericin B deoxycholate.

whose efficacy rates are at least similar to those of drugs used in the study by Patterson[82-84].

Another limitation is that the study did not include patients taking combined therapy based on caspofungin, which has shown encouraging results both in first-line therapy[85] and in salvage therapy[86-88] against invasive aspergillosis.

Conclusions: First, the study by Patterson shows that salvage therapy with lipid amphotericin in patients with invasive aspergillosis already treated with amphotericin B deoxycholate is clearly insufficient: 32% response in intolerant patients and only 12% in patients with resistance to therapy.

We wonder whether the results would have been the same if a lipid amphotericin formulation had been used as first-line therapy. Obviously, the only way to answer this question is by means of a randomized study, although 2 conclusions drawn by Herbrecht and Patterson make it unlikely that the results with lipid amphotericin would be better than those obtained with voriconazole:

1. Initial treatment was changed to salvage antifungals due to progression of aspergillosis in 38.9% of those who received amphotericin and in "only" 27.8% of those treated with voriconazole. Given that lipid amphotericin improves tolerance but not antifungal therapy[89], it seems unlikely that initial therapy with lipid amphotericin would have increased efficacy by more than 10%.

2. When patients treated with amphotericin only (first line + salvage), the response rates were very different from those obtained with first-line voriconazole (30 vs. 55%).

3. Although data from the Ambiload study (liposomal amphotericin B for first-line therapy of aspergillosis)[90] showed response rates around 50%, these good results were not confirmed in another recent study in which liposomal amphotericin B had a response rate of only 27%[85].

Second, and despite the feared hypothetical antagonism of sequential therapy with amphotericin in patients previously treated with voriconazole, the Patterson study shows that treatment with polyenes can rescue 41% of patients treated previously with voriconazole. This efficacy rate is even higher that that obtained in patients treated only with first and or second line polyenes (28%), thus supporting the use of first-line voriconazole.

Finally, we emphasize the importance of early treatment with maximum efficacy in invasive aspergillosis. In this sense, we must point out the following: 1) first-line antifungal therapy with voriconazole was more efficacious than the sum of the efficacy rates of first- and second-line treatments in patients who had initially received amphotericin B deoxycholate, and 2) despite the fact that more patients in the amphotericin B deoxycholate group received another antifungal due to intolerance (in theory making this group one of lower risk), the salvage therapy was more efficacious in the group treated initially with voriconazole.

In summary, the studies by Herbrecht and Patterson support voriconazole as the initial therapy against invasive aspergillosis due to its greater first-line efficacy and the fact that it does not compromise the efficacy of salvage therapy. If combination therapy–for which there are high hopes–offers better results, it can only be studied in randomized trials[91].

Infections by *Pneumocystis jiroveci*

De Castro J, Neuville S, Sarfati C, Ribaud P, Derouin F, Gluckman E, et al. Occurrence of *Pneumocystis jiroveci* pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. BMT. 2005;36:879-83.

Before the systematic use of prophylaxis, *Pneumocystis jiroveci* pneumonia (PCP) was a frequent (5-16%) and very serious complication (mortality rate of up to 76%) of allogeneic HSCT, particularly during the first 3 months after transplant. Since the effective use of prophylaxis, PCP is considered a rare event in HSCT patients. In this paper, the authors retrospectively study the occurrence of PCP among all the patients who underwent allogeneic HSCT between January 1997 and December 2002 at the Saint-Louis Hospital in Paris (France). PCP prophylaxis was started 2 weeks pre-HSCT and maintained for at least 6 months after HSCT. Sulfadoxine-pyrimethamine once a week and trimethoprim-sulfamethoxazole (TMP-SMX) 3 times a week were the regimens used.

PCP was diagnosed in 13 out of the 519 allogeneic HSCT patients (2.5%); 11 cases had received conventional conditioning regimens and 2 cases reduced-intensity conditioning regimens. Two to three cases of PCP were diagnosed each year, with no temporal clustering.

Three of the 13 patients presented with "early-onset PCP," since the infection occurred within the first 6 months after-HSCT (2.5, 4, and 5 months, respectively). All of these patients were receiving prophylaxis at the time of PCP diagnosis. All 3 had a low parasitic burden in BAL (no trophozoites and only rare cysts were detected)

and had concomitant invasive aspergillosis (IA). Two of these patients died, but their deaths were apparently not related to *P. jiroveci*.

The remaining 10 cases of PCP were diagnosed after the first 6 months post-HSCT (median: 14.5; range: 7.5-44) ("late-onset PCP"). At the time of diagnosis, none of these patients were receiving PCP prophylaxis–it had been discontinued 3 to 8.5 months before (median: 4.8). This decision was based on suspected bone marrow toxicity or intolerance in most cases. Seven patients (70%) were receiving immunosuppressive therapy for chronic GVHD and 3 patients (30%) had a relapse of their hematological malignancy. Nine cases (90%) had lymphopenia (median counts: 970/µL; range: 160-1400/µL), and the median count of CD4+ T cells was 131/µL (range: 1-368), with just 1 patient having more than 200/µL. Unlike cases with early-onset PCP, the clinical and radiological features of the late-onset group were typical of PCP, and most of them had a high parasitic burden in BAL. Four patients had concomitant infections: 2 IA, one lower respiratory tract RSV infection and one infection by varicella-zoster virus. One patient died from PCP pneumonia despite appropriate treatment, 2 developed chronic respiratory failure, and 7 recovered fully from PCP.

Comments

The paper shows that PCP is still occurring after allogeneic HSCT, but that it is a very rare event when patients receive efficient prophylaxis.

In the 3 cases of early-onset PCP (all of them on prophylaxis), the authors believe that *P. jiroveci* might even be colonizing rather than infecting.

The occurrence of late-onset PCP after a premature discontinuation of prophylaxis has been observed in this and in several previous studies. Based on these data and CDC recommendations, the authors strongly encourage maintaining long-term PCP prophylaxis in all patients with one of these circumstances: CD4+ count under 200/µL, relapse of hematological malignancy, chronic GVHD, or immunosuppressive therapy (current or recent). The authors also note that hematological toxicity of the most commonly used PCP prophylaxis regimens is rare in patients who have undergone HSCT months before.

Reviews

Costa SF, Alexander BD. Non-*Aspergillus* fungal pneumonia in transplant recipients. Clinics in Chest Medicine. 2005;26:675–90.

A huge number of species of fungus have been described (between 100,000 and 200,000), but until now only 270 have been recognized as human pathogens. *Aspergillus* and *Candida* are still the most important in quantitative terms, although in recent years there has been an increase in the population of immunocompromised patients associated with the emergence of other, non-*Aspergillus* and non-*Candida* fungi as important causes of morbidity and mortality. The rate of infection by non-*Aspergillus* species in solid organ transplant (SOT) recipients has increased markedly during the last 20 years from approximately 2% to 27% of fungal infections caused by molds. A similar trend has been observed in HSCT recipients, with a noticeable increase in the number of infections by *Fusarium* and by *Zygomycetes*. The qualitative importance of these opportunistic fungi lies in the fact that they are ubiquitous and that they have reduced sensitivity to currently available antifungal drugs, thus making treatment extremely difficult. In addition, there are predisposing factors for pulmonary infection in transplant recipients that depend on the transplanted organ. For example, neutropenia and graft-versus-host disease have been linked to the development of fungal infection in HSCT recipients. In lung transplant recipients, direct communication between the graft and the environment and continuous exposure to potential pathogens are key factors, as is the reduced cough reflex and deficiencies in the function of the cilia and of lymphatic drainage.

In this review, 2 researchers from the Duke University Medical Center provide an exhaustive update of non-*Aspergillus* fungal pneumonia, one of the most relevant clinical manifestations in the practical management of transplant recipients. Below, we show some of the most important points made in the review.

As already mentioned, *Fusarium* infections have increased in transplant recipients. Fusariosis affects the lung in more than 80% of cases and its clinical manifestations vary according to the type of transplant. In SOT recipients, infection tends to be localized, fungemia is rare, it usually starts during the late post-transplant period, and mortality stands at around 33%. On the contrary, in HSCT recipients, infection is disseminated, there is fungemia in 20 to 70% of cases, it occurs shortly after the transplant, and mortality is high (70 to 100%).

Another emerging infection is that caused by the genus *Scedosporium*. One species, *Scedosporium prolificans*, is resistant to all available antifungal drugs and its mortality is around 80% in transplant recipients. Infection by *Scedosporium* has an earlier onset in HSCT recipients (median 1.2 months after transplant), than in SOT recipients (median 4 months). Similarly, fungemia is more frequent in HSCT.

Compared with *Fusarium* or *Scedosporium*, infection by *Zygomycetes* is not usually disseminated outside the respiratory tract and the lungs are involved in 55% of patients with zygomycosis. Most cases occur after 100 days post-transplantation and mortality is high (75 to 80%).

Other infections, such as endemic mycosis and cryptococcosis, are more common in SOT recipients than in HSCT recipients. Lastly, breakthrough infections by *Pneumocystis jiroveci* in patients taking cotrimoxazole are very rare, but when they do occur, the clinical presentation is usually very atypical and diagnosis may require a lung biopsy.

The clinical condition of the patient may limit the performance of diagnostic procedures. Blood cultures can be useful for the diagnosis of yeasts and molds that produce adventitious forms *in vivo* (*Fusarium*, *Scedosporium*, *Paecilomyces*, *Acremonium*). A patient may also be simultaneously affected by more than 1 mold; therefore, it could be necessary to use aggressive diagnostic methods when a patient presents progression of known lesions or develops new lesions while on treatment. We must remember that all hyalohyphomycetes, which include the different species of *Aspergillus*, are similar in the histological analy-

sis, with septate hyaline hyphae and vascular invasion, making culture of the fungus necessary to establish a definitive diagnosis.

Treatment is complicated, since many emerging pathogens have intrinsic or variable resistance to available antifungals. In addition, some interventions that could improve clinical response, such as surgery or drainage, may not be feasible. Success depends on ascertaining the causal agent. For example, in a *Paecilomyces* infection, it is important to distinguish between *P. variotii* (sensitive to amphotericin B) and *P. lilacinus* (resistant to amphotericin but sensitive to voriconazole *in vitro*). The main available agent for the treatment of infections by *Fusarium* and *Scedosporium* is voriconazole. The combination of voriconazole and terbinafine has proven synergistic *in vitro* against *Scedosporium*. Finally, the only azole with activity against *Zygomycetes* is posaconazole.

Neuburger S, Maschmeyer G. Update on management of infections in cancer and stem cell transplant patients. Ann Hematol. 2006;85:345-56.

Epidemiology of infections in patients with cancer: Patients with hematological conditions who are undergoing intensive chemotherapy and experience severe alteration of humoral and cellular immunity have a high risk of suffering from infections. Thus, in patients with acute leukemia, approximately 90% of chemotherapy cycles are complicated by fever and infection. Furthermore, 50% of febrile episodes in neutropenic patients do not have an infections focus or a causal pathogen and between 15 and 20% of episodes progress with bacteremia or lung involvement or another identified clinical or microbiological focus. During the last 20 years, there has been a marked change in epidemiology, and gram-positive entities now have a higher incidence owing to the antibacterial prophylaxis used (quinolones) and placement of long-term catheters. There is also an increase in fungal infections due to the higher number of transplants and aggressive treatments in patients with hematological conditions.

Infections in patients with neutropenia: The risk of acquiring an opportunistic infection is proportional to the degree of neutropenia. Organizations such as the EORTC, IDSA, GIMEMA, and DGHO have classified neutropenic patients into different risk groups depending on the duration of the neutropenia. Patients with neutropenia lasting between 5 and 7 days are considered low-risk, whereas patients undergoing intensive chemotherapy with neutropenia lasting more than 10 days are considered high-risk. Approximately 30% of febrile episodes occur in low risk patients. Combination therapy with amoxicillin-clavulanate plus ciprofloxacin would be a good option in this group of patients. However, in patients with a high risk of bacteremia, pneumonia, or sepsis, it is important to identify these conditions by using suitable diagnostic tests in order to initiate the correct treatment.

First-line empiric therapy in patients with fever of unknown origin: In febrile neutropenic patients, the infectious focus is not identified in approximately 50% of episodes; therefore, empiric treatment must be started early. Several randomized studies show the efficacy of monotherapy as efficacious early empiric therapy with cefepime, piperacillin/tazobactam, imipenem/cilastatin, or meropenem.

Clinically documented infections

Pulmonary infiltrates

Diagnostic considerations: In neutropenic patients with pulmonary infiltrates, this could have an infectious or noninfectious origin and early diagnosis is important in order to modify empiric antibiotic therapy. To do this, it is necessary to carry out computed tomography of the chest or even bronchoalveolar lavage. There are also series that compare laboratory diagnostic techniques for the diagnosis of fungal infection such as PCR or *Aspergillus* antigen. At present, only computed tomography and *Aspergillus* antigen are considered validated for the diagnosis of fungal infection and PCR is not yet an accepted technique.

Therapeutic considerations: In patients with a high risk of neutropenia lasting more than 10 days, pulmonary infiltrates, initial antibiotic therapy, and persistent fever, an antifungal that is efficacious against filamentous fungi must be added.

Catheter infections: Catheter infections can occur at the entry site or tunnel or can take the form of catheter-related bacteremia. Most episodes can be cured with an early diagnosis and glycopeptides. The number of glycopeptide-resistant microorganisms is on the increase.

Abdominal infections: Patients with altered mucosa or those who have received high doses of ARA-C are at risk of suffering from abdominal infections. There are no clear criteria for establishing a diagnosis, but in cases with obvious symptoms it is important to design regimens that cover anaerobes.

Microbiologically documented infections: In patients who respond to initial empiric therapy and in whom a microorganism is subsequently identified, it is not necessary to change therapy but adapt it to the antibiogram. Antibiotics should be maintained for at least 5 days without fever, unless infection is by *S. aureus*, in which case they should be maintained for at least 14 days.

Documented fungal infections: Patients with candidiasis can be treated with fluconazole, caspofungin, and amphotericin–there is no drug of choice in any study.

Nevertheless, in patients with aspergillosis, the drug of choice is voriconazole, although lipid formulation amphotericin can also be used.

Pneumocystis jiroveci *pneumonia:* Treatment should be with trimethoprim at 20 mg/kg plus sulfamethoxazole at 100 mg/kg for at least 3 weeks. Treatment with corticosteroids is only efficacious in patients with HIV infection but not in neutropenic patients.

Infection by herpes simplex virus or varicella zoster virus: This type of infection should be treated with acyclovir at 10 mg/kg for 7 days in herpes simplex virus infections or 14 days in the case of varicella zoster infections.

Infections in patients with altered humoral immunity: High doses of chemotherapy and allogeneic transplant alter humoral immunity for at least 12 months. In these patients, determination of immunoglobulins is altered during the first year after transplant and treatment with monoclonal antibodies alters humoral immunity for 6 months. In this group of patients, the risk of viral infec-

tions is much higher, especially in the case of herpes simplex virus, varicella zoster virus, and cytomegalovirus. In high-risk situations, intravenous immunoglobulins may be recommended as support therapy.

Infection in patients with T cell dysfunction: Treatment with fludarabine and cladribine leads to immunosuppression of T cells. The new monoclonal antibodies such as alemtuzumab (anti-CD52) leads to deep lymphopenia, with the risk of other types of infection such as those by *Listeria monocytogenes*, mycobacteria, cryptococcus, fungi, and herpes virus, specifically adenovirus, cytomegalovirus, and herpes simples virus.

In order to prevent cytomegalovirus infection, the IDWP of the EBMT recommends weekly monitoring of cytomegalovirus antigenemia. If the determination is positive, treatment should start with oral valganciclovir or intravenous ganciclovir. If a positive antigenemia is accompanied by disease, immunoglobulins should be added to antiviral therapy.

Summary: Infections are the most important cause of morbidity and mortality in patients undergoing stem cell transplantation. The use of purine analogs, monoclonal antibodies such as anti-CD52 and anti-CD20, and an increase in mismatched transplants has led to an increase in the number of viral and fungal infections. Therefore, it is important to choose the correct antibiotic, antiviral, or antifungal therapy.

Silveira F, Paterson DL. Pulmonary fungal infections. Curr Opin Pulm Med. 2005;11:242-6.

The target organ of fungal infections in immunodepressed patients is the lung.

The last year has seen a series of changes in this type of infection in terms of epidemiology, new techniques for early diagnosis, and new therapeutic alternatives.

Changes in the epidemiology of pulmonary aspergillosis: The epidemiology of pulmonary aspergillosis is changing, not only with regard to the number of patients at risk of suffering from it (patients with prolonged neutropenia who are undergoing solid organ transplant and HSCT), but also in other risk groups, for example, patients on long-term corticosteroids, patients with other types of immunosuppression (HIV-infected patients), pediatric patients with chronic granulomatous disease, patients on monoclonal antibodies in non-neoplastic conditions (rheumatoid arthritis), and other patients with alterations of the specific neutrophil function, such as those suffering from cirrhosis.

Epidemiological changes are also affecting the fungi involved in this type of condition, with an increased incidence of *A. terreus* in infection of the lungs, bone, sinuses, and skin. This is compounded by the peculiarity that this type of fungus makes therapy difficult, as it is a filamentous fungus resistant to amphotericin.

Techniques for the early diagnosis of invasive aspergillosis: The clinical manifestations of pulmonary aspergillosis are varied and often nonspecific. Patients generally present cough, fever, pleural pain, and hemoptysis; however, when the clinical manifestations begin it is generally too late, with the result that methods to provide early diagnosis are necessary. At present, we can use the antigen galactomannan, which is a component of the wall of the *Aspergillus* cell and can be detected circulating in fungal infection. Nevertheless, the basic problem of this test is that its sensitivity is often very low and, therefore, it is of no help in neutropenic patients, patients undergoing solid organ transplant, and patients receiving antifungal prophylaxis with agents covering filamentous fungi. It can also lead to false positives in patients taking piperacillin/tazobactam.

Another early diagnostic test is available. 1-3 β-D-glucan is a component of the cell wall not only of *Aspergillus* but also of *Candida*, *Fusarium*, *Trichosporum*, *Acremonium*, and *Saccharomyces*. The few studies available show that this is a much more sensitive and specific test than the galactomannan test, although it is not yet available in most centers.

The ideal solution would be to use both tests in combination.

Management of invasive Aspergillus*:* Amphotericin has been the antifungal of choice in invasive aspergillosis for decades. However, evaluation of voriconazole in clinical trials has shown that voriconazole now seems to be the antifungal of choice, with the exception of specific infections, such as mucormycosis, in which amphotericin is the most efficacious drug.

At present, invasive fungal infections are one of the most important causes of morbidity and mortality in these patients and the mortality rate remains high, despite the appearance of new antifungals.

These results have led to new lines of therapy for invasive fungal infections, especially with combinations of therapy.

The combination of antifungals is based mainly on the model of bacterial infections. Combining drugs with different mechanisms of action could generate synergy reduce toxicity, and increase the response rate.

The clinical efficacy of antifungal combinations in humans is based on reports with low numbers of patients. Most published studies have a low number of cases and most patients have received combination therapy as a rescue regimen. Aliff et al[92] obtained a response rate of 57% in rescue therapy with amphotericin B and caspofungin, whereas Kontoyianis et al[93] found that, in proven and refractory forms, the response was only 18%. However, in this same series, the response to initial therapy in the proven forms was 53%. Marr et al[94] compare the combination of voriconazole and caspofungin with voriconazole alone in patients who were refractory to different formulations of amphotericin and show a greater survival rate in the group that received combined therapy.

Echinocandins (specifically caspofungin) have a low number of medication interactions, and can be used relatively safely in patients receiving several drugs. Therefore, the combination of caspofungin and voriconazole used to treat invasive pulmonary aspergillosis has shown synergy both *in vitro* and in animal models compared with different species of *Aspergillus* (*fumigatus*, *niger*, *flavus, terreus*).

The combination of caspofungin and voriconazole in these studies led to a serious reduction in minimum efficacious dose of both antifungals, which contributed to reducing toxicity (related to the dose) and the cost of treatment.

We can conclude that prospective observational and randomized studies are necessary to determine the efficacy and toxicity of the different combinations of drugs in invasive fungal infections to reduce their still high mortality rate.

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