Current Epidemiology and Prevention of Infectious Complications in Cancer Patients

Corrado Girmenia[1] and Francesco Menichetti[2]

1. Assistant, Department of Haematology, Azienda Policlinico Umberto I, Rome;
2. Head, Infectious Diseases Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa

Abstract

Infections represent an important cause of morbidity and mortality in cancer patients, especially those patients receiving intensive chemotherapy or undergoing stem cell transplant. The changing epidemiological patterns of infections in cancer patients are characterised not only by the increasing incidence of some opportunistic pathogens, but also by the wide emergence of resistance to antimicrobials, particularly in bacteria. The management of these complications has improved greatly during the past decades, especially in the field of antimicrobial prophylaxis. In the last few years, new antimicrobial drugs have been investigated, with the aim of defining new strategies for prophylaxis against bacterial, fungal and viral infections. Based on the new evidence, international guidelines on antimicrobial prophylaxis have been recently updated, and targeted prophylaxis schedules have been proposed for different clinical settings. In the practice of antimicrobial prophylaxis, it is crucial to continuously keep abreast of new epidemiological data in order to monitor the emerging antimicrobial resistances and define tailored prevention strategies.

Keywords

Infections, cancer, leukaemia, stem cell transplant, epidemiology, prophylaxis

Disclosure: Corrado Girmenia has received honoraria from Gilead Sciences, Schering-Plough, Astellas Pharma, Merck and Pfizer Pharmaceuticals. He has been a speaker for Gilead Sciences, Schering-Plough, Merck and Pfizer Pharmaceuticals. Francesco Menichetti has received honoraria from Gilead Sciences, Merck, Bayer, Novartis and Pfizer Pharmaceuticals. He has been a speaker for Gilead Sciences, Merck, Novartis and Pfizer Pharmaceuticals.
Received: 26 September 2011 **Accepted:** 17 October 2011 **Citation:** *European Oncology & Haematology*, 2011;7(4):270–7 *DOI: 10.17925/EOH.2011.07.04.270*
Correspondence: Corrado Girmenia, Dipartimento di Ematologia, Azienda Policlinico Umberto I, Via Benevento 6, 00161 Rome, Italy. E: girmenia@bce.uniroma1.it

Infections remain an important cause of morbidity and mortality in cancer patients, mainly those affected by haematological malignancies and those undergoing stem cell transplant (SCT).[1–3] With the improvement of cancer care in the past decades, patients live longer, and immunosuppression from the underlying disease and from more intensive and prolonged treatments renders more and more of them susceptible to infections.

The epidemiological evolution of infectious complications in cancer patients is characterised not only by the increasing incidence of some opportunistic infections, such as invasive fungal diseases (IFDs), but also by the emergence of antimicrobial resistance in several bacteria and some fungi. Additionally, viruses are a serious and frequently underestimated cause of infection in cancer patients, particularly those subjected to SCT procedures, in whom careful surveillance and an antiviral prophylaxis strategy are required.

Thanks to the availability of new laboratory and imaging diagnostic tools and to the development of tailored surveillance strategies, a better knowledge of the epidemiology and risk/prognostic factors of infections has been gained in cancer centres in recent years. This epidemiological awareness is crucial to define prevention strategies adapted to the various categories of patients with different infection risks, and to chose treatment protocols likely to contain the above-mentioned phenomenon of resistance to antimicrobials. In this article, recent epidemiological findings on, and current prevention strategies against, bacterial, fungal and viral infections in cancer patients are reviewed and critically commented on.

Epidemiology of Infections in Cancer Patients

Despite increasing attention to the clinical and therapeutic aspects of infection in cancer patients, few data are available on the incidence, microbiological characteristics and clinical outcomes of infectious complications in this population. Recent epidemiological data almost exclusively derive from retrospective studies and few prospective data are available. The susceptibility pattern to bacterial and fungal pathogens has been occasionally evaluated in the cancer population and most data derive from large microbiological studies in patients with various underlying conditions. Again, most data in the cancer setting derive from neutropenic patients affected by haematological malignancies and/or undergoing SCT.

Bacterial Infections

Over the past decades, the epidemiological spectrum of bloodstream bacterial isolates obtained from febrile neutropenic patients has continuously changed. During the 1960s and 1970s, gram-negative bacilli represented the predominant pathogens causing life-threatening infections. During the 1980s and 1990s, gram-positive organisms

became more common, probably due to the increased use of venous catheters and systemic prophylaxis with fluoroquinolones, which can allow entry of, and colonisation by, gram-positive skin and intestinal flora.[4–7] Currently, coagulase-negative staphylococci continue to be the most common blood isolates; however, the emergence of infections by *Enterobacteriaceae* (e.g., *Escherichia coli* and *Klebsiella* species) and non-fermenting gram-negative pathogens (e.g., *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*) has been observed in several centres.[8–19]

In particular, drug-resistant gram-negative bacteria species are causing an increasing number of infections in febrile neutropenic patients. *Klebsiella* species and *E. coli* strains with acquired extended-spectrum beta-lactamase (ESBL) genes frequently show a broad range of beta-lactam antibiotic resistance. These ESBL producers are often only susceptible to carbapenems, antibiotics with a very broad spectrum of activity but whose use may induce the selection of bacteria with even greater resistance patterns. Indeed, the use of carbapenems increases the risk of infections by carbapenemase-producing *Klebsiella* species and *P. aeruginosa* strains that are resistant to carbapenems and other classes of antibiotics. This phenomenon may represent a devastating problem, with the spread of infections by multi-drug-resistant (MDR) gram-negative strains, considering also that the molecules recently added to the antibacterial armamentarium are mainly oriented against gram-positive bacteria.

Information regarding incidence, risk factors and clinical findings for resistant gram-negative bacteraemia in cancer patients and its outcomes is scarce and dispersed. Only a few single-centre experiences have been published in recent years and the real epidemiological impact of such infections is little known. In a prospective survey in an adult Spanish cancer centre conducted during the period 2006–2009, about 50 % of bacteraemias were caused by gram-negative bacilli and 14 % of them were caused by MDR strains. The most frequent mechanism of resistance was ESBL production (45 %), mainly in *E. coli*, followed by AmpC cephalosporinase hyperproduction (24 %). Patients with MDR gram-negative bacteraemias more frequently received inadequate initial antibiotic therapy (69 % versus 9 %, p<0.001), and time to adequate therapy (after 48 hours) was longer in this group (41 % versus 4 %, p<0.001). Patients in the resistant group more frequently required intensive care unit admission (14 % versus 5 %, p=0.023), had greater need of mechanical ventilation (14 % versus 3 %, p=0.005) and had a higher overall case fatality rate (41 % versus 21 %, p=0.003).[15]

A very high rate of resistant gram-negative isolates in patients with haematological malignancies was observed in an Italian centre.[18] Out of 62 episodes of bacteraemia caused by *E. coli*, overall incidences of ESBL production and fluoroquinolone resistance were 41.9 % and 62.9 %, respectively. The overall 30-day mortality rate was 21 %. In a multivariate analysis, the significant predictors of mortality were inadequate initial antimicrobial therapy (odds ratio [OR]=14.96, 95 % confidence interval [CI] 1.95–114.51, p=0.009), infection caused by ESBL-producing isolates (OR=8.84, 95 % CI 1.48–52.91, p=0.01) and prolonged neutropenia (OR=8.10, 95 % CI 1.29–50.57, p=0.02).

A prospective study of infections in nine Italian tertiary care centres or university hospitals among adult patients diagnosed with haematological malignancies was started in 2009.[19] The analysis of patients with *P. aeruginosa* bacteraemias showed 71 % MDR strains. In particular, the percentages of resistance to carbapenems (imipenem and meropenem), anti-pseudomonal cephalosporins (ceftazidime and cefepime), amikacin and ciprofloxacin were 60 %, 42 %, 50 % and 66 %, respectively, whereas the percentage of resistance to piperacillin was 24 %. Mortality within 30 days of the first positive blood culture occurred in 40 % of MDR *P. aeruginosa* bacteraemias and in 9 % of non-MDR *P. aeruginosa* bacteraemias. In a multivariate analysis, inadequate initial antibacterial therapy was independently associated with mortality (p=0.006).

All these studies show the increasing epidemiological burden of severe infections by resistant bacterial pathogens. A crucial problem in the management of such infections is the choice of prophylaxis and initial antibacterial therapy, considering that it may dramatically affect the outcomes of such complications. A continuous microbiological survey at each cancer centre is required to monitor the trend of resistant micro-organisms and to guide the use of antimicrobials.

Fungal Infections

IFDs, especially those caused by *Candida* and *Aspergillus* species, historically represent a major cause of death in cancer patients, especially after intensive chemotherapy and receipt of SCT. However, a continuous modification in epidemiology and outcomes has been observed over the last decades, as a result of prevention strategies and changes in host characteristics and treatment modalities.[20–22] Another factor that may greatly impact on epidemiological findings in IFDs is the type and quality of surveillance studies. In fact, different results have been obtained according to whether studies were retrospective or prospective, and single-centre or multicentre. Until a few years ago, most epidemiological and outcome data regarding IFDs in cancer patients came from single centres using different analysis criteria, which raised questions about the ability to generalise their findings. Only in the last few years have multicentre surveillance studies, which also evaluated the impact of host and chemotherapy and/or transplant factors on outcomes, been published.[23–25]

Very recent clinical data from a general population of patients with candidaemia were extracted from the Prospective Antifungal Therapy Alliance database, a comprehensive North American registry that collects information regarding IFDs.[23,24] Contemporary epidemiology and outcomes of candidaemia in multiple centres were evaluated in a total of 2,019 patients enrolled from 2004 to 2008.[23] Overall, patients treated in general medicine (66 %), who underwent non-transplant surgery (33 %) or had solid tumours (17 %) were the most represented, whereas 9.8 % and 2.9 % of the candidaemia episodes were documented in patients with haematological malignancies and in SCT recipients, respectively. Non-albicans *Candida* species accounted for the large majority of isolates (72.6 % in haematological malignancies, 77.6 % in SCT and 52.4 % in solid tumours).

The same registry was evaluated to analyse IFDs that occurred specifically among SCT recipients.[24] Out of 250 IFDs, invasive aspergillosis was the most frequent (59 %), followed by candidiasis (25 %) and infections caused by other moulds (14 %). A surprising finding was the unexpected lower 12-week mortality in patients with invasive aspergillosis compared with patients with invasive candidiasis (36 % versus 49 %, respectively). However, improved survival after the diagnosis of invasive aspergillosis was consistent with that observed in prior single-centre and multicentre studies in

Table 1: European Conference on Infections in Leukaemia (ECIL) Guidelines on Antimicrobial Prophylaxis in Haematology Patients

Type of Prophylaxis and Clinical Condition	Recommendations (Grading)
Antibacterial Prophylaxis	
Patients with acute leukaemia and adult SCT recipients after myeloablative therapy	A fluoroquinolone with systemic activity, including against *Pseudomonas aeruginosa*, should be used • Levofloxacin: 500 mg od oral (AI) • Ciprofloxacin: 500 mg bid oral (AI) • Norfloxacin: 400 mg bid oral – less effective than ciprofloxacin (BI) • Ofloxacin: 200–300 mg bid oral – less tested than ciprofloxacin in randomised controlled trials and at variable daily doses, lower activity against *P. aeruginosa* and less effective than ciprofloxacin (BI)
Antifungal Prophylaxis	
Leukaemia patients, induction chemotherapy	• Posaconazole: 200 mg tid (AI) • Fluconazole: 400 mg qd (CI) • Itraconazole oral solution: 2.5 mg/kg bid (CI) • Echinocandins: IV (insufficient data) • Polyenes: IV (CI) • Aerosolised liposomal AmB plus fluconazole (BI)
Allogeneic SCT recipients, initial neutropenic phase	• Fluconazole: 400 mg qd (AI) • Itraconazole: 200 mg IV followed by oral solution 200 mg bid (BI) • Posaconazole: no data • Voriconazole: 200 mg bid oral (provisional AI) • Micafungin: 50 mg qd IV (CI) • Polyenes: IV (CI) • Aerosolised liposomal AmB plus fluconazole (BII)
Allogeneic SCT recipients, GVHD phase	• Posaconazole: 200 mg tid oral (AI) • Fluconazole: 400 mg qd (CI) • Itraconazole: 200 mg IV followed by oral solution 200 mg bid (BI) • Voriconazole: 200 mg bid oral (provisional AI) • Echinocandins (insufficient data) • Polyenes: IV (CI) • Aerosolised liposomal AmB plus fluconazole (insufficient data)
Antiviral Prophylaxis	
Herpes simplex virus (HSV)	Antiviral drug prophylaxis is not recommended in HSV-seronegative leukaemic patients during chemotherapy or after SCT (DIII). HSV-seropositive patients undergoing allogeneic HSCT for acute leukaemia should receive antiviral drug prophylaxis (AI). HSV-seropositive patients treated for acute leukaemia by chemotherapy alone should be considered for antiviral drug prophylaxis (BIII). Intravenous (5 mg/kg q12h) or oral acyclovir (from 3 x 200 mg/day to 2 x 800 mg/day) (AI) or oral valaciclovir (2 x 500 mg/day) (BIII) should be given prophylactically for three to five weeks after start of chemotherapy or after allogeneic SCT, and for longer periods of time in children treated for acute leukaemia. Allogeneic SCT recipients who develop GVHD or receive immunosuppressive treatment, including steroids, usually require prolonged HSV prophylaxis (BII)
Varicella zoster virus (VZV)	Passive immunisation with IV VZIG (0.2–1 ml/kg) or IM ZIG or IVIG (300–500 mg/kg) should be given within 96 hours after exposure to VZV-seronegative leukaemic patients on chemotherapy and patients receiving steroids, as well as to VZV-seronegative SCT recipients, patients who have chronic GVHD, patients who are on immunosuppressive treatment, and patients who received SCT within the past two years (AII). Where passive immunisation is not available, post-exposure prophylaxis with aciclovir (800 mg four times daily; 600 mg/m^2 four times daily for children), valaciclovir (1,000 mg tid; 500 mg tid for <40 kg body weight) or famciclovir (500 mg tid) is recommended, starting within 3 days of exposure and continuing for 21 days (AIII). If a second exposure occurs more than 21 days after a dose of passive immunisation or after the administration of the antiviral prophylaxis, a prophylaxis should be readministered (CIII). Prophylaxis in VZV-seropositive patients is optional (CIII). Determination of VZV immunoglobulin serostatus before transplant is recommended for all SCT candidates (AIII). Prophylaxis with oral acyclovir (800 mg bid) or valaciclovir (500 mg od or bid) is recommended for seropositive allogeneic SCT recipients for one year (AII) or longer in the presence of GVHD and immunosuppressive therapy (BII). Prophylaxis in autologous SCT is controversial
Cytomegalovirus (CMV)	A pre-emptive antifungal strategy based on the monitoring of CMV infection by antigenaemia and quantitative PCR represents the most widely used approach, not only in the allogeneic SCT setting but also in other categories at risk of CMV infection and disease, such as patients with chronic lymphocytic leukaemia under alemtuzumab therapy. Antiviral chemoprophylaxis is an alternative to pre-emptive therapy in subgroups of patients at high risk of CMV disease. Intravenous ganciclovir prophylaxis is an effective strategy for the prevention of CMV disease and could be used in subgroups of allogeneic SCT patients at high risk of CMV disease (BI). Aciclovir or valaciclovir can be used as prophylaxis against CMV in allogeneic SCT patients (BI). However, their use must be combined with monitoring and pre-emptive therapy (AI). Immunoglobulin has no role as prophylaxis against CMV infection (EII). Valganciclovir prophylaxis is effective and reduces the risk of symptomatic CMV infection in patients receiving alemtuzumab (BII)

AmB = amphotericin B; bid = twice daily; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplant; IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; od = once daily; PCR = polymerase chain reaction; q12h = every 12 hours; qd = each day; SCT = stem cell transplant; tid = three times daily; VZIG = varicella zoster immunoglobulin; ZIG = zoster immunoglobulin.

See notes at the bottom of Table 2 *for an explanation of the grading system adopted for the recommendations.*

Table adapted from Bucaneve et al., 2007,[45] Maertens et al., 2011,[46] Styczynski et al., 2009[47] and Ljungman et al., 2008.[48]

Table 2: Infectious Diseases Society of America (IDSA) Guidelines on Antimicrobial Prophylaxis in Neutropenic Patients

Type of Prophylaxis and Clinical Condition	Recommendations (Grading)
Antibacterial prophylaxis in high-risk neutropenic patients	Fluoroquinolone prophylaxis should be considered in high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/mm^3) of over seven days (BI). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred where there is an increased risk of oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended (AII). Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended (AI)
Antibacterial prophylaxis in low-risk neutropenic patients	Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for less than seven days (AIII)
Prophylaxis against *Candida* infections in high-risk neutropenic patients	Recommended in patient groups in whom the risk of invasive candidal infections is substantial, such as allogeneic SCT recipients or patients undergoing intensive remission induction or salvage induction chemotherapy for acute leukaemia (AI). Fluconazole, itraconazole, voriconazole, posaconazole, micafungin and caspofungin are all acceptable alternatives
Prophylaxis against *Aspergillus* infections in high-risk neutropenic patients	Prophylaxis with posaconazole should be considered for selected patients over 13 years of age who are undergoing intensive chemotherapy for AML/MDS in whom the risk of invasive aspergillosis without prophylaxis is substantial (BI) Prophylaxis against *Aspergillus* infection in pre-engraftment allogeneic or autologous transplant recipients has not been shown to be efficacious. However, a mould-active agent is recommended in patients with prior invasive aspergillosis (AIII), anticipated prolonged neutropenic periods of at least two weeks (CIII) or a prolonged period of neutropenia immediately prior to HSCT (CIII)
Antifungal prophylaxis in low-risk neutropenic patients	Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is less than seven days (AIII)
Antiviral prophylaxis during neutropenia	HSV-seropositive patients undergoing allogeneic HSCT or leukaemia induction therapy should receive aciclovir antiviral prophylaxis (AI). Other herpesvirus infections occur in the post-HSCT setting, including infections due to cytomegalovirus and human herpesvirus 6. However, neutropenia is not a predisposition to reactivation of either virus, thus prevention strategies for these two herpesviruses are not discussed

AML = acute myeloid leukaemia; ANC = absolute neutrophil count; HSCT = haematopoietic stem cell transplant; HSV = herpes simplex virus; MDS = myelodysplastic syndrome; SCT = stem cell transplant.
Quality of evidence and strength of recommendations according to the Infectious Diseases Society of America grading system (Source: Freifeld et al, 2011[49]).
Strength of recommendation: A = good evidence to support a recommendation for or against use; B = moderate evidence to support a recommendation for or against use; C = poor evidence to support a recommendation.
Quality of evidence: I = evidence from >1 properly randomized, controlled trial; II = evidence from >1 well-designed clinical trial, without randomization; from cohort or case controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments; III = evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Table adapted from Freifeld et al., 2011.[49]

the US and Europe.[26–29] The better knowledge of epidemiology as well as of risk and prognostic factors, and the recent advances made in the prevention, diagnosis and treatment of *Aspergillus* infections probably justify such advances in the management of IFDs.

For fungi also does the reduced susceptibility to antifungal drugs represent a challenging problem. The phenomenon of *Candida* species resistance to triazoles has been largely reported for fluconazole and itraconazole since their first use more than two decades ago, and it continues to be an important issue for the second-generation triazoles posaconazole and voriconazole.[30–34] Resistance to triazoles has also been observed for *Aspergillus* species in some European countries, although, according to multinational surveys, the phenomenon seems uncommon. An *in vitro* study of triazole cross-resistance performed among more than 700 clinical isolates of *Aspergillus* species collected between 2000 and 2006 as part of a global antifungal surveillance programme showed a pattern of resistance (minimum inhibitory concentration [MIC]>2 µg/ml) for itraconazole in about 2 % of isolates, and in less than 1 % of the isolates for voriconazole and posaconazole.[35]

Viral Infections

Several viruses may cause infections in patients with cancer, and important advances have been made in recent years in their molecular diagnosis. Herpesviruses and hepatitis viruses may cause serious infections after chemotherapy or after SCT, generally as a result of viral endogenous reactivation. Up to 80 % of adult cancer patients are herpes simplex virus (HSV)-seropositive and HSV lesions occur in more than 50 % of these patients as a consequence of the reactivation of a latent virus – whereas primary infection is unusual. Among seropositive recipients without prophylaxis, following allogeneic SCT, the risk of HSV infection is approximately 80 %, the risk of cytomegalovirus (CMV) infection is 20–30 %, and the risk of varicella zoster virus (VZV) infection is 20–50 %.[36–39] Reactivation of chronic hepatitis B in patients undergoing immunosuppressive or antineoplastic treatment occurs in approximately 20–50 % of hepatitis B surface antigen (HBsAg)-positive patients and can result in fulminant hepatitis.[40] Patients with malignant lymphoma, especially those treated with anthracyclin-containing chemotherapy, are at significantly higher risk.[41] HBsAg-positive allogeneic SCT patients are at risk of developing severe and possibly fatal hepatic disease, and therefore anti-hepatitis B surface (HBs)-negative donors for HBsAg-positive patients should be vaccinated before stem cell collection. Conversely, transplantation of an HBsAg-negative patient with stem cells from an HBsAg-positive donor is associated with a high risk of transmission, but few patients develop aggressive acute infection or chronic hepatitis B.[42–44]

The detection and diagnosis of infections associated with community respiratory virus have improved substantially with the use of various polymerase chain reaction (PCR) techniques, but the routine application of these tests is limited to a few settings in cancer patients; therefore, the real epidemiological impact of respiratory virus infections is probably underestimated. Early identification using rapid and reliable diagnostic methods and strategies to contain the infection and prevent nosocomial spread are essential to prevent the devastating consequences caused by outbreaks of community respiratory viruses.

Prophylaxis Against Infections in Cancer and Stem Cell Transplant Patients

Until recently, the impact of prophylaxis against infections in cancer patients had been controversial, but new data now suggests that chemoprophylaxis might be able not only to reduce the incidence of infectious complications, but also to allow the continuation of treatment of the underlying malignancy, with a possible impact on long-term overall survival. Current European and US guidelines on antibacterial, antifungal and antiviral prophylaxis have been summarised in *Table 1* and *Table 2*, respectively.[45–49]

Antibacterial Prophylaxis

The risk of bacterial infection is directly related to the severity and duration of neutropenia. The practice of chemoprophylaxis for the prevention of bacterial infections in neutropenic cancer patients derived from the observation that most of the bacterial pathogens causing infection came from the patient's endogenous flora of the gastrointestinal tract.[1] Oral and gastrointestinal chemotherapy-induced mucositis represents a major risk of bacterial entry directly into the bloodstream. Selective intestinal decontamination with oral fluoroquinolones, which not only operate directly in the gastrointestinal tract but also act systemically, has been the most attractive antibacterial prophylactic strategy in neutropenic patients for 20 years. Patients who derive particular benefit from prophylaxis are those with a duration of neutropenia of more than seven days, as they are at high risk of bacterial infections.

In view of the need to re-evaluate the role of prophylaxis with fluoroquinolones in neutropenic cancer patients after a wide use in clinical practice, and to better define the categories of patients who might most benefit from it, two large multicentre controlled trials were conducted in Europe and the results published in 2005.[50,51] The Gruppo Italiano Malattie Ematologiche dell'Adulto (Italian adult haematological disease group) (GIMEMA) conducted a double-blind, placebo-controlled trial in 760 hospitalised high-risk adult patients with prolonged neutropenia (<1,000 neutrophils/mm^3 for more than seven days).[50] The trial included patients with acute leukaemia, lymphoma and solid tumours receiving high-dose chemotherapy. Participants were randomised to receive levofloxacin or placebo from the start of chemotherapy until resolution of neutropenia. The study demonstrated a statistically significant reduction in the incidence of fever in patients receiving levofloxacin compared with the placebo group (65 % versus 85 %, p<0.001), associated with a non-significant decrease in mortality in the levofloxacin arm.

The second study, the British Simple investigation in neutropenic individuals of the frequency of infection after chemotherapy ± antibiotic in a number of tumours (SIGNIFICANT) trial, look ated 1,565 patients receiving cyclical chemotherapy for solid tumours or lymphoma at risk of temporary neutropenia and classified as being at low risk.[51] Patients randomly received either levofloxacin or placebo for seven days during the expected neutropenia period. A significant reduction in febrile episodes was documented in the levofloxacin group during the first cycle of chemotherapy (3.5 % versus 7.9 %, p<0.001) and all cycles of treatment (10.8 % versus 15.2 %, p=0.01), but no effect on documented infections was observed.

These two studies indicate a potentially important role of levofloxacin prophylaxis in high-risk patients with prolonged neutropenia, but not in low-risk patient populations.

The major drawback of the routine use of prophylaxis is the emergence of fluoroquinolone resistance in both gram-positive and gram-negative organisms. The phenomenon has been observed since the 1980s and the clinical implications of fluoroquinolone resistance continue to be investigated.[52–57] A systematic review of the effect of quinolone prophylaxis in neutropenic patients showed that prophylaxis was associated with a decreased overall incidence of infection, a non-significant increase in colonisation with resistant organisms and no difference in the number of infections caused by resistant organisms.[57]

In summary, the problem of resistance during fluoroquinolone prophylaxis in cancer patients and its clinical implications remain controversial. In any case, fluoroquinolone resistance with possible cross-resistance to other antibiotics should be carefully monitored and the efficacy of the practice of antibacterial prophylaxis periodically re-evaluated.

Antifungal Prophylaxis

Antifungal prevention strategies are based on environmental precautions and antimicrobial treatment. While there is general agreement on the role of air filtration in the control of airborne filamentous fungal infections, the indication for pharmacological prophylaxis is still debated.[58–60] The use of antifungals for prophylaxis against deep-seated IFDs has become standard practice of care in some haematological and transplant patients, whereas, in patients with solid tumours, who are at lower risk of invasive infections, antifungal prophylaxis is mainly directed to the prevention of superficial mycoses.

Until a few years ago, fluconazole and, to a lesser extent, itraconazole were the only drugs recommended for primary prophylaxis against *Candida* infection in neutropenic patients and allogeneic SCT recipients.[61,62] However, a major limitation of a *Candida*-oriented prophylaxis is its lack of activity against moulds, which now represent the most frequent cause of IFDs in these patient populations. In recent years, awareness of the epidemiological impact of invasive aspergillosis and of infections caused by less common moulds, including zygomycetes, *Fusarium* species and *Scedosporium* species, has increased worldwide. At the same time, new broad-spectrum and well-tolerated antifungal drugs, in particular second-generation triazoles and echinocandins, have become available, and prospective controlled trials have been conducted to investigate their ability to prevent IFDs in high-risk haematological patients.[63–69]

Posaconazole and voriconazole – second-generation triazoles with a broad spectrum of activity – have been compared with fluconazole or itraconazole in phase III clinical trials of prophylaxis in leukaemia and SCT patients.[63–66] Posaconazole prophylaxis was associated with a significantly lower rate of invasive aspergillosis, both in neutropenic

patients with acute myeloid leukaemia and in allogeneic SCT recipients with graft-versus-host disease (GVHD), but only in the leukaemia setting did patients who received posaconazole prophylaxis experience a significantly longer survival.[63,64]

Two controlled studies of primary antifungal prophylaxis with voriconazole have been conducted in allogeneic SCT patients.[65,66] In the first study, in which voriconazole was compared with fluconazole, only a trend towards fewer *Aspergillus* infections was observed with voriconazole, and the fungal-free survival (primary endpoint of the study) was similar in the two groups.[65] However, it should be considered that, in the subgroup of patients with acute myeloid leukaemia – a population at higher risk of infection – voriconazole significantly reduced IFDs and improved fungal-free survival compared with fluconazole.[70] In the second study, voriconazole was superior to itraconazole considering a primary composite endpoint that included efficacy and tolerability criteria; however, no difference in the incidence of IFDs was observed in the two arms, probably due to the overall low rate of infections observed in the study.[66]

The clinical use of both posaconazole and voriconazole requires knowledge of the pharmacokinetic characteristics of these drugs that explain why their concentration in blood varies between patients and in an individual patient over the course of treatment. Voriconazole metabolism is particularly affected by the different ability of patients to metabolise the drug via the CYP2C19 P450 enzyme, whereas erratic gastrointestinal absorption represents a frequent problem in patients receiving posaconazole. For both antifungals, the metabolism may be affected by the pharmacological interaction with other drugs. In view of the above, therapeutic drug monitoring is strongly suggested during voriconazole and posaconazole treatment to monitor whether target through blood levels are achieved.[71–75]

Several open issues regarding prophylaxis against IFDs in patients with haematological disorders deserve careful consideration. The recommendations contained in the international guidelines reflect the important progress made in the prevention of IFDs, including those caused by filamentous fungi; however, no consensus has been reached regarding the optimal prophylaxis against IFDs in the complex scenario of haematological disorders, particularly in the transplant setting. This problem was recently underlined in a consensus process conducted by the Gruppo Italiano Trapianto di Midollo Osseo (Italian bone marrow transplant group) (GITMO), which observed that the recommendations from international guidelines entail various problems, such as the lack of an approved mould-active prophylaxis during the engraftment phase in allogeneic SCT and the lack of an intravenous (IV) formulation of posaconazole, which limits the use of this drug in patients unable to tolerate oral medications or with altered intestinal absorption.[76]

Additional and well-designed studies are needed, not only to evaluate the efficacy of new antifungal drugs, but also to define risk stratification criteria and tailored prevention strategies. Being aware of, and keeping up-to-date with, new epidemiological data is required to individualise specific measures aimed at the prophylaxis against IFDs in the different clinical settings encountered in haematological disorders.

Antiviral Prophylaxis

Primary HSV infection in cancer patients, including those affected by leukaemia, is unusual, and antiviral drug prophylaxis is thus not recommended in HSV-seronegative patients during chemotherapy or after SCT. Conversely, prophylaxis with an HSV-active agent, such as aciclovir, should be offered to all HSV-seropositive autologous or allogeneic SCT recipients and patients with acute leukaemia undergoing induction or reinduction therapy.[47,49]

Seronegative leukaemic patients and SCT recipients are at high risk of varicella after face-to-face contact of five minutes or more with a person who has varicella or intimate contact (touching or hugging) with a person who has herpes zoster. Patients residing in the same household as a contagious person, or staying in hospital in the same room as, or (in large wards) in a bed adjacent to, a contagious person, are also at risk. Passive immunisation with IV varicella zoster-specific immunoglobulins or IV normal immunoglobulin should be given as soon as possible after exposure (<96 hours) to VZV-seronegative cancer patients on intensive chemotherapy, receiving steroids or undergoing SCT with chronic GVHD. The efficacy of antiviral agents for post-exposure prophylaxis in leukaemic patients and recipients of SCT is uncertain, but uncontrolled studies seem to suggest that aciclovir, valaciclovir or famciclovir prophylaxis may reduce the incidence of varicella and its severity. Although most SCT recipients are VZV-seropositive, they are at risk of virus reactivation for a prolonged period after transplant. Therefore, for VZV-seropositive allogeneic SCT recipients, prophylaxis with oral aciclovir or valaciclovir is recommended for one year, or longer in the presence of GVHD and immunosuppressive therapy.[47]

The different antiviral strategies for CMV disease include the use of chemoprophylaxis, pre-emptive therapy or treatment of symptomatic infection. A pre-emptive antifungal strategy based on the monitoring of CMV infection by antigenaemia and/or quantitative PCR represents the most widely used approach, not only in the allogeneic SCT patient, but also in other categories at risk of CMV infection and disease, such as patients with chronic lymphocytic leukaemia undergoing alemtuzumab therapy. The frequency of CMV infection in other subgroups of cancer patients may be high, but the risk of evolution to CMV disease is very low; therefore routine surveillance is unnecessary and prophylaxis not recommended in these patients.[48] As an alternative to pre-emptive therapy, IV ganciclovir prophylaxis is an effective strategy for the prevention of CMV disease in subgroups of allogeneic SCT patients at high risk of CMV disease, but acyclovir or valaciclovir at high doses can also be used. In any case, their use must be combined with monitoring and a pre-emptive approach.

Reactivation of hepatitis B is a well-characterised syndrome associated with the reappearance or rise of hepatitis B virus (HBV) DNA in the serum of a patient with previously inactive or resolved HBV infection, and is frequently accompanied by the reappearance of early or late hepatic disease activity. Reactivation of HBV has been reported not only in HBsAg-positive patients undergoing systemic chemotherapy, but also in a proportion of HBsAg-negative patients with hepatitis B core (HBc) antibody and/or HBs antibody. HBsAg-positive patients with haematological malignancies undergoing immunochemotherapy are at risk of developing severe hepatic disease. However, the most dramatic examples of HBV reactivation have been described in patients undergoing allogeneic SCT; in fact, vaccination before stem cell collection has been recommended for anti-HBs-negative donors to HbsAg-positive patients. Guidelines published by the US Centers for Disease Control and Prevention recommend that all patients about to receive chemotherapy for malignant disease be tested for HBsAg

before cancer treatment is initiated.[77] Controlled clinical trials and several subsequent meta-analyses have shown that prophylaxis with nucleoside analogues (e.g., lamivudine) decreases the incidence of HBV reactivation and the frequency of clinical hepatitis and death from HBV-associated liver injury in patients undergoing chemotherapy or SCT.[78–84] Such therapy should be commenced before the start of chemotherapy or before transplant and should be continued for at least six months after the end of chemotherapy, or for longer in case of long-term immune suppression.[85,86]

Conclusions

Infectious complications in cancer patients continue to represent a challenging issue that greatly affects the overall care of the underlying malignancy. Knowledge of the epidemiological phenomena of infections in such immunocompromised patients is required to better define surveillance and prevention strategies. Most epidemiological studies have been conducted in large patient populations with different tumour types, treatments and other patient characteristics, and may be unable to provide specific information for individual patient groups. Prophylaxis studies too have been conducted in large populations with some common risk factors but with a variety of different clinical characteristics. Consequently, current guidelines provide generic indications that can be difficult to apply to some specific subgroups of cancer patients. Knowledge of findings regarding infections in various clinical settings, according to the type of malignancy and the type of treatment, may be relevant to define targeted diagnostic and prophylactic strategies to fight infections in cancer patients. It is time to focus clinical research regarding infectious complications on specific cancer populations, in order to provide useful information for clinical practice. ■

1. Schimpff SC, Young V, Greene E, et al., Origin of infection in acute nonlymphocytic leukemia: significance of hospital acquisition of potential pathogens, *Ann Intern Med*, 1972;77:707–15.
2. Maschmeyer G, Haas A, The epidemiology and treatment of infections in cancer patients, *Int J Antimicrob Agents*, 2008;31:193–7.
3. Neuburger S, Maschmeyer G, Update on management of infections in cancer and stem cell transplant patients, *Ann Hematol*, 2006;85:345–56.
4. Viscoli C, Bruzzi P, Castagnola E, et al., Factors associated with bacteraemia in febrile, granulocytopenic cancer patients. The International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), *Eur J Cancer*, 1994;30A:430–7.
5. Viscoli C, EORTC International Antimicrobial Therapy Group. Management of infection in cancer patients. studies of the EORTC International Antimicrobial Therapy Group (IATG), *Eur J Cancer*, 2002;38(Suppl. 4):S82–7.
6. Zinner SH, Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria, *Clin Infect Dis*, 1999;29:490–4.
7. Wisplinghoff H, Seifert H, Wenzel RP, et al., Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States, *Clin Infect Dis*, 2003;36:1103–10.
8. Cattaneo C, Quaresmini G, Casari S, et al., Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution, *J Antimicrob Chemother*, 2008;61:721–8.
9. Oliveira AL, de Souza M, Carvalho-Dias VM, et al., Epidemiology of bacteremia and factors associated with multi-drug-resistant gramnegative bacteremia in hematopoietic stem cell transplant recipients, *Bone Marrow Transplant*, 2007;39:775–81.
10. Aubron C, Poirel L, Fortineau N, et al., Nosocomial spread of Pseudomonas aeruginosa isolates expressing the metallo-beta-lactamase VIM-2 in a hematology unit of a French hospital, *Microb Drug Resist*, 2005;11:254–9.
11. Morris PG, Hassan T, McNamara M, et al., Emergence of MRSA in positive blood cultures from patients with febrile neutropenia-a cause for concern, *Support Care Cancer*, 2008;16:1085–8.
12. Weinstock DM, Conlon M, Iovino C, et al., Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant, *Biol Blood Marrow Transplant*, 2007;13:615–21.
13. Wang SS, Lee NY, Hsueh PR, et al., Clinical manifestations and prognostic factors in cancer patients with bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae, *J Microbiol Immunol Infect*, 2011;44:282–8.
14. Chong Y, Yakushiji H, Ito Y, Kamimura T, Clinical impact of fluoroquinolone prophylaxis in neutropenic patients with hematological malignancies, *Int J Infect Dis*, 2011;15:e277–81.
15. Gudiol C, Tubau F, Calatayud L, et al., Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes, *J Antimicrob Chemother*, 2011;66:657–63.
16. Arnan M, Gudiol C, Calatayud L, et al., Risk factors for, and clinical relevance of, faecal extended-spectrum β-lactamase producing Escherichia coli (ESBL-EC) carriage in neutropenic patients with haematological malignancies, *Eur J Clin Microbiol Infect Dis*, 2011;30:355–60.
17. Gudiol C, Calatayud L, Garcia-Vidal C, et al., Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome, *J Antimicrob Chemother*, 2010;65:333–41.
18. Trecarichi EM, Tumbarello M, Spanu T, et al., Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies, *J Infect*, 2009;58:299–307.
19. Trecarichi EM, Tumbarello M, Caira M, et al., Multidrug resistant Pseudomonas aeruginosa bloodstream infection in adult patients with hematologic malignancies, *Haematologica*, 2011;96(1):e1–3.
20. Maschmeyer G, Invasive fungal disease: better survival through early diagnosis and therapeutic intervention, *Expert Rev Anti Infect Ther*, 2011;9(3):279–81.
21. Pagano L, Caira M, Nosari A, et al., Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne, *Clin Infect Dis*, 2007;45:1161–70.
22. Pagano L, Caira M, Candoni A, et al., The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study, *Haematologica*, 2006;91:1068–75.
23. Horn DL, Neofytos D, Anaissie EJ, et al., Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry, *Clin Infect Dis*, 2009;48:1695–703.
24. Neofytos D, Horn D, Anaissie E, et al., Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry, *Clin Infect Dis*, 2009;48:265–73.
25. Kontoyiannis DP, Marr KA, Park BJ, et al., Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database, *Clin Infect Dis*, 2010;50:1091–100.
26. Upton A, Kirby KA, Carpenter P, et al., Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality, *Clin Infect Dis*, 2007;44:531–40.
27. Nivoix Y, Velten M, Letscher-Bru V, et al., Factors associated with overall and attributable mortality in invasive aspergillosis, *Clin Infect Dis*, 2008;47:1176–84.
28. Cordonnier C, Ribaud P, Herbrecht R, et al., Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers, *Clin Infect Dis*, 2006;42:955–63.
29. Parody R, Martino R, Sanchez F, et al., Predicting survival in adults with invasive aspergillosis during therapy for hematological malignancies or after hematopoietic stem cell transplantation: Single-center analysis and validation of the Seattle, French, and Strasbourg prognostic indexes, *Am J Hematol*, 2009;84:571–8.
30. Espinel-Ingroff A, Mechanisms of resistance to antifungal agents: yeasts and filamentous fungi, *Rev Iberoam Micol*, 2008;25:101–6.
31. Rogers TR, Antifungal drug resistance: limited data, dramatic impact?, *Int J Antimicrob Agents*, 2006;27(Suppl. 1):7–11.
32. Chamilos G, Kontoyiannis DP, Update on antifungal drug resistance mechanisms of Aspergillus fumigatus, *Drug Resist Updat*, 2005;8:344–58.
33. Verweij PE, Mellado E, Melchers WJ, Multiple-triazole-resistant aspergillosis, *N Engl J Med*, 2007;356:1481–3.
34. Verweij PE, Snelders E, Kema GH, et al., Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use?, *Lancet Infect Dis*, 2009;9:789–95.
35. Pfaller MA, Messer SA, Boyken L, et al., In vitro survey of triazole cross-resistance among more than 700 clinical isolates of Aspergillus species, *J Clin Microbiol*, 2008;46:2568–72.
36. Gratwohl A, Brand R, Frassoni F, et al., Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time, *Bone Marrow Transplant*, 2005;36:757–69.
37. Kernan NA, Bartsch G, Ash RC, et al., Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program, *N Engl J Med*, 1993;328:593–602.
38. Maltezou HC, Kafetzis DA, Abisaid D, et al., Viral infections in children undergoing hematopoietic stem cell transplant, *Pediatr Infect Dis J*, 2000;19:307–12.
39. Sandherr M, Einsele H, Hebart H, et al., Antiviral prophylaxis in patients with haematological malignancies and solid tumours: Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO), *Ann Oncol*, 2006;17:1051–9.
40. Rossi G, Pelizzari A, Motta M, et al., Primary prophylaxis with lamivudine of hepatitis B virus reactivation in chronic HbsAg carriers with lymphoid malignancies treated with chemotherapy, *Br J Haematol*, 2001;115:58–62.
41. Yeo W, Chan P, Ho WM, et al., Lamivudine for the prevention of Hepatitis B Virus reactivation in Hepatitis B s-Antigen seropositive cancer patients undergoing cytotoxic chemotherapy, *J Clin Oncol*, 2004;22: 927–34.
42. Locasciulli A, Testa M, Valsecchi MG, et al., The role of hepatitis C and B virus infections as risk factors for severe liver complications following allogeneic BMT: a prospective study by the Infectious Disease Working Party of the European Blood and Marrow Transplantation Group, *Transplantation*, 1999;68:1486–91.
43. Chiba T, Yokosuka O, Goto S, et al., Successful clearance of hepatitis B virus after allogeneic stem cell transplantation: beneficial combination of adoptive immunity transfer and lamivudine, *Eur J Haematol*, 2003;71:220–3.
44. Locasciulli A, Alberti A, Bandini G, et al., Allogeneic bone marrow transplantation from HbsAg+ donors: a multicenter study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO), *Blood*, 1995;86:3236–40.
45. Bucaneve G, Castagnola E, Viscoli C, et al., Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients, *Eur J Cancer*, 2007;5(Suppl. 2):5–12.
46. Maertens J, Marchetti O, Herbrecht R, et al., European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 Update, *Bone Marrow Transplant*, 2011;46:709–18.
47. Styczynski J, Reusser P, Einsele H, et al., Second European Conference on Infections in Leukemia, Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia, *Bone Marrow Transplant*, 2009;43:757–70.
48. Ljungman P, de la Camara R, Cordonnier C, et al., European Conference on Infections in Leukemia, Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT, *Bone Marrow Transplant*, 2008;42:227–40.
49. Freifeld AG, Bow EJ, Sepkowitz KA, et al., Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America, *Clin Infect Dis*, 2011;52:e56–93.
50. Bucaneve G, Micozzi A, Menichetti F, et al., Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia, *N Engl J Med*, 2005;353:977–87.
51. Cullen M, Steven N, Billingham L, et al., Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas, *N Engl J Med*, 2005;353:988–98.
52. Kotilainen P, Nikoskelainen J, Houvien P, Emergence of ciprofloxacin resistant coagulase negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin, *J Infect Dis*, 1990;161:41–4.
53. Trucksis M, Hooper DC, Wolfson JS, Emerging resistance to fluoroquinolones in staphylococci: an alert, *Ann Intern Med*, 1991;114:424–6.
54. Kern WV, Andriof E, Oethinger M, et al., Emergence of fluoroquinolone-resistant Escherichia coli at a cancer center, *Antimicrob Agents Chemother*, 1994;38:681–7.

55. Caratalla J, Fernandez-Sevilla A, Dominguez MA, et al., Emergence of fluoroquinolone-resistant flora of cancer patients receiving norfloxacin prophylaxis, *Antimicrob Agents Chemother*, 1996;40:503.
56. Cometta A, Calandra T, Bille J, et al., Escherichia coli resistant to fluoroquinolone prophylaxis in patients with cancer and neutropenia, *N Engl J Med*, 1994;330:1240–1.
57. Gafter-Gvili A, Paul M, Fraser A, et al., Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis, *J Antimicrob Chemother*, 2007;59:5–22.
58. Bow EJ, Laverdière M, Lussier N, et al., Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials, *Cancer*, 2002;94:3230–46.
59. Robenshtok E, Gafter-Gvili A, Goldberg E, et al., Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis, *J Clin Oncol*, 2007;25:5471–89.
60. Girmenia C, Prophylaxis of invasive fungal diseases in patients with hematologic disorders, *Haematologica*, 2010;95:1630–2.
61. Stevens DA, Kan VL, Judson MA, et al., Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America, *Clin Infect Dis*, 2000;30:696–709.
62. Rex JH, Walsh TJ, Sobel JD, et al., Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America, *Clin Infect Dis*, 2000;30:662–78.
63. Cornely OA, Maertens J, Winston DJ, et al., Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia, *N Engl J Med*, 2007;356:348–59.
64. Ullmann AJ, Lipton JH, Vesole DH, et al., Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease, *N Engl J Med*, 2007;356:335–47.
65. Wingard JR, Carter SL, Walsh TJ, et al., Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation, *Blood*, 2010;116:5111–8.
66. Marks DI, Pagliuca A, Kibbler CC, et al., for the IMPROVIT Study Group, Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation, *Br J Haematol*, 2011;155:318–27.
67. Van Burik JA, Ratanatharathorn V, Stepan DE, et al., Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation, *Clin Infect Dis*, 2004;39:1407–16.
68. Mattiuzzi GN, Alvarado G, Giles FJ, et al., Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies, *Antimicrob Agents Chemother*, 2006;50:143–7.
69. Rijnders BJ, Cornelissen JJ, Slobbe L, et al., Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial, *Clin Infect Dis*, 2008;46:1401–8.
70. Girmenia C, Aversa F, Micozzi A, Voriconazole prophylaxis and the risk of invasive fungal infection after allogeneic hematopoietic cell transplantation, *Blood*, 4 February 2011, e-letter in reply to Wingard JR, Carter SL, Walsh TJ, et al., Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation, *Blood*, 2010;116:5111–8.
71. Krishna G, Ma L, Vickery D, et al., Effect of varying amounts of a liquid nutritional supplement on the pharmacokinetics of posaconazole in healthy volunteers, *Antimicrob Agents Chemother*, 2009;53:4749–52.
72. Kohl V, Müller C, Cornely OA, et al., Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation, *Antimicrob Agents Chemother*, 2010;54:207–12.
73. Trifilio S, Ortiz R, Pennick G, et al., Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients, *Bone Marrow Transplant*, 2005;35:509–13.
74. Smith J, Safdar N, Knasinski V, et al., Voriconazole therapeutic drug monitoring, *Antimicrob Agents Chemother*, 2006;50:1570–2.
75. Trifilio S, Pennick G, Pi J, et al., Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients, *Cancer*, 2007;109:1532–5.
76. Girmenia C, Barosi G, Aversa F, et al., Prophylaxis and treatment of invasive fungal diseases in allogeneic stem cell transplantation: results of a consensus process by Gruppo Italiano Trapianto di Midollo Osseo (GITMO), *Clin Infect Dis*, 2009;49:1226–36.
77. Weinbaum CM, Williams I, Mast EE, et al., Recommendations for identification and public health management of persons with chronic hepatitis B virus infection, *MMWR Recomm Rep*, 2008;57:1–20.
78. Lau GK, Yiu HH, Fong DY, et al., Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy, *Gastroenterology*, 2003;125:1742–9.
79. Hsu C, Hsiung CA, Su IJ, et al., A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial, *Hepatology*, 2008;47:844–53.
80. Kohrt HE, Ouyang DL, Keeffe EB, Systematic review: lamivudine prophylaxis for chemotherapy induced reactivation of chronic hepatitis B virus infection, *Aliment Pharmacol Ther*, 2006;24:1003–9.
81. Katz LH, Fraser A, Gafter-Gvili A, et al., Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis, *J Viral Hepat*, 2008;15:89–102.
82. Lau GK, He ML, Fong DY, et al., Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic stem cell transplantation, *Hepatology*, 2002;36:702–9.
83. Hui CK, Lie A, Au WY, et al., Effectiveness of prophylactic anti-HBV therapy in allogeneic hematopoietic stem cell transplantation with HBsAg positive donors, *Am J Transplant*, 2005;5:1437–45.
84. Tsutsumi Y, Tanaka J, Kawamura T, et al., Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma, *Ann Hematol*, 2004;83:58–60.
85. Kusumoto S, Tanaka Y, Mizokami M, Ueda R, Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma, *Int J Hematol*, 2009;90:13–23.
86. Lubel JS, Angus PW, Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management, *J Gastroenterol Hepatol*, 2010;25:864–71.

ESH
EUROPEAN
SCHOOL OF
HAEMATOLOGY

- **3-4 FEBRUARY,** 2012 - Paris, France
  ESH-Enerca Training Course
  In association with the "Club du Globule Rouge et du Fer"
  DIAGNOSIS AND MANAGEMENT OF VERY RARE ANAEMIAS: A CHALLENGE
  CHAIRS: P. Aguilar-Martinez, H. Heimpel, R. Van Wijk, L. Ribeiro, A. Zanella

- **9-10 FEBRUARY,** 2012 - Paris, France
  ESH Updates in
  CLINICAL HEMATOLOGY
  CHAIRS: E. Gluckman, B. Löwenberg, E. Montserrat

- **12-14 MARCH,** 2012 - Muscat, Oman
  ESH-EHA Type II Hematology Tutorial
  Diagnostic Work-Up of Hematological Diseases
  FOCUS ON MYELOID MALIGNANCIES
  CHAIRS: S. Alkindi, N. Fawaz, S. McCann

- **20-22 APRIL,** 2012 - Mandelieu, France
  ESH-EHA Scientific Workshop on
  ANTI-INFLAMMATORY & IMMUNE MODULATORY PROPERTIES OF MESENCHYMAL STROMAL CELLS
  CHAIRS: W. Fibbe, F. Dazzi, K. Le Blanc
  SCIENTIFIC COMMITTEE: D. Fearon, A. Keating, F. Locatelli, S. Mendez-Ferrer, D. Scadden, L. Sensebé

- **22-25 APRIL,** 2012 - Sofia, Bulgaria
  ESH-EBMT Training Course on
  HAEMOPOIETIC STEM CELL TRANSPLANTATION
  CHAIRS: J. Apperley, E. Carreras, E. Gluckman, T. Masszi
  LOCAL ORGANIZER: D. Konstantinov

- **MAY,** 2012 – Kiev, Ukraine
  ESH-EHA Type II Hematology Tutorial
  FOCUS ON LYMPHOID MALIGNANCIES
  CHAIR: TBA

- **24-27 MAY,** 2012 - Dublin, Ireland
  ESH International Conference on
  MYELODYSPLASTIC SYNDROMES
  CHAIRS: M. Cazzola, P. Fenaux, E. Hellström-Lindberg
  LOCAL ORGANIZER: S. McCann

- **20-23 SEPTEMBER,** 2012 - Baltimore, USA
  ESH-ICMLF 14th International Conference on
  CHRONIC MYELOID LEUKEMIA
  CHAIRS: J.M. Goldman, J. Cortes, T.P. Hughes
  CO-ORGANIZERS: T. Holyoake, F.X. Mahon, D. Perrotti, J. Radich

- **4-6 OCTOBER,** 2012 – Vienna, Austria
  ESH International Conference on
  MYELOPROLIFERATIVE NEOPLASMS
  CHAIRS: T. Barbui, T. Green, H.L. Pahl, R. Skoda, W. Vainchenker

- **28-30 OCTOBER,** 2012 – Marseille, France
  ESH International Conference on
  LYMPHOMAS
  CHAIRS: A.M. Carella B. Coiffier, P. Johnson

EUROPEAN SCHOOL OF HAEMATOLOGY

IUH, Centre Hayem, Hôpital Saint Louis – 1, Avenue Claude Vellefaux – 75475 Paris Cedex 10, France –
Tél. +(33) 1 57 27 68 37 Fax. +(33) 1 57 27 68 38
Please visit our new website: www.esh.org

E-MAILS: didi.jasmin@univ-paris-diderot.fr **or** ghyslaine.lebougault@univ-paris-diderot.fr **or** nancy.hamilton@univ-paris-diderot.fr **or** maude.brunet-lecomte@univ-paris-diderot.fr **or** nicolas.jaillard@univ-paris-diderot.fr **or** camille.frank@univ-paris-diderot.fr **or** sylvain.lepen@univ-paris-diderot.fr

Manchester, UK
October 25-27, 2012

SIOG

1st Announcement / Call for Abstracts

Geriatric Oncology: Cancer in Senior Adults

12th Meeting of the International Society of Geriatric Oncology
October 25-27, 2012
Manchester, UK

Scientific Chair:
Riccardo Audisio, Liverpool, UK

SIOG *(International Society of Geriatric Oncology)*
President: **Riccardo Audisio**, Liverpool, UK
Past President: **Martine Extermann**, Tampa, USA
Executive Director: **Matti Aapro**, Genolier, Switzerland

For more information, please visit: **www.siog.org**

SAVE THE DATE

The 12th International Symposium on MYELODYSPLASTIC SYNDROMES

May 8-11, 2013 | Berlin, Germany

ADVANCING RESEARCH & PATIENT CARE

Symposium Chairmen:

Arnold Ganser, M.D., Ph.D.
Hannover Medical School, Germany

Wolf-Karsten Hofmann, M.D., Ph.D.
University Hospital Mannheim, Germany

www.kenes.com/mds

MDS 2013 Symposium Secretariat c/o Kenes International
1-3 Rue de Chantepoulet, PO Box 1726, CH-1211 Geneva 1, Switzerland
Tel: + 41 22 908 0488, Fax: + 41 22 906 9140, E-mail: mds@kenes.com,

For MDS Foundation Contact: US number: 1-800-MDS-0839,
Outside the US: 1-609-298-1035

mds foundation
the myelodysplastic syndromes foundation, inc.

European Congress of Radiology

ECR 2012

Vienna

March 1–5

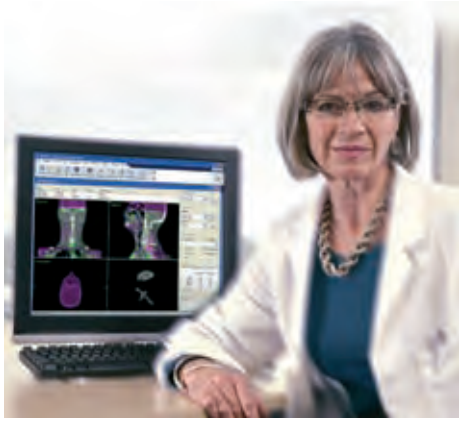
Join us in Vienna and register for the most innovative meeting in imaging at
myESR.org/registration2012

Travel & Accommodation Service now open
travelservice.myESR.org

Plan your schedule for ECR 2012 now! Check out the preliminary programme at
myESR.org/preliminary_programme2012

The annual meeting of ESR European Society of Radiology myESR.org

...***one*** software system that integrates your multiple locations



With MOSAIQ®, it's reality.

Effective data management across disparate departments and locations can be a challenge, particularly if each has unique hardware, workflow and administrative needs. As the standard in OIS scalability, MOSAIQ efficiently manages everything from the single physician practice to the most sophisticated provider networks.

LADMSQ110629 v1.0

Experience the Elekta Difference

More at elekta.com/imagine

ELEKTA