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# Update on febrile neutropenia in patients with malignancy

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## Introduction

Infection complicating post-chemotherapy neutropenia has long been a major killer in patients with malignancy. In the following discussion, we will focus on the contemporary diagnostic and therapeutic approach to this clinical problem. Here we define fever as a single temperature of 38.3$^{o}$C or more and a febrile state with a temperature of 38$^{o}$C for at least one hour, and neutropenia is defined as an absolute neutrophil count (ANC) of less than 0.5 x $10^9$/L or a count of less than 1.0 x $10^9$/L with a predicted decline to less than 0.5 x $10^9$/L in the ensuing 24 to 48 hours.

## Pathophysiology and microbiology

In patients with febrile neutropenia, the severity and duration of neutropenia are most important predictors for risk of infection and mortality. An ANC below 0.5 x $10^9$/L greatly increases the risk of infection and the chance of infection approaches 100% if ANC is persistently below 1.0 x $10^9$/L for 3 weeks or longer. Of note, febrile neutropenia seldom occurs by itself and presence of other risk factors e.g. impaired cellular and/ or humoral immunity due to underlying disease, mucositis as a result of intensive chemotherapy, and presence of indwelling vascular catheter and other external devices, etc, will modify the risk of infection as well as spectrum of pathogens encountered.

Primary bloodstream infection is the commonest documented infection in patients with febrile neutropenia, and Gram-positive organisms have emerged in recent decades as predominant pathogens in this setting. This is due to (1) frequent occurrence of mucositis as a result of aggressive chemotherapy, and (2) use of intravascular catheter or other external devices. Other common sites of infection included respiratory tract (sinusitis, pneumonia), gastrointestinal tract (enterocolitis, perirectal infection), and integuments (skin and soft tissue, indwelling device insertion sites). Gram-negative, anaerobic and polymicrobial infection are more commonly found in lower respiratory and gastrointestinal tract. Despite vigorous effort in hunting the offending pathogen, approximately 50% of patients with febrile neutropenia do not have a documented infection.

Among the Gram-positive pathogens, coagulase-negative staphylococci are most frequently isolated, in particular from the bloodstream. Although they are less virulent, they often exhibit methicillin resistance and some strains also have intermediate to high level to vancomycin resistance as well. Other frequently encountered Gram-positive organisms included viridans-group streptococci, enterococci, and S*taphylococcus aureus.* Emergence of vancomycin resistant pathogens (e.g. vancomycin resistant enterococci (VRE), glycopeptide intermediately resistant staphylococci (GISA), *Leuconostoc spp, Pediococcus spp,* etc) is an imminent problem. Among the Gram-negative organisms, *Escheria coli, Klebsiella spp* and *Pseudomonas aeruginosa* were used to be the predominant pathogens; however, as a result of selection pressure, organisms with intrinsic or acquired resistance to empiric antimicrobial therapy for febrile neutropenia are increasingly recognized. Examples included *Acinetobacter spp, Stenotrophomonas maltophilia,* non-aeruginosa *Pseudomonas spp*, etc. Fungal infections generally occur later during the course of febrile neutropenia and are often secondary, with *Candida* and *Aspergillus* being the primary pathogens. Like the bacterial pathogens, we observed a changing paradigm of fungal pathogens and opportunistic fungal infections (e.g. *Fusarium spp*, *Scedosporium spp*, *Mucor spp*, etc) are on a rising trend. Common viral pathogens in febrile neutropenia included cytomegalovirus (CMV), human

herpesvirus-6 (HHV-6), and respiratory viruses like respiratory syncytial virus (RSV).

**Patient assessment**

The goals are (1) stratify patient's risk of infection and complication, (2) determine which kind of infections and pathogens are most likely.

The following points should be carefully assessed in history taking: (1) nature of chemotherapy (drugs, cycle, and date of last chemotherapy); (2) history of antimicrobial prophylaxis; (3) recent documented infection, pathogens involved, susceptibility pattern and treatment received; (4) recent surgical procedure and placement of indwelling device; and (5) drug allergy. A thorough physical examination is essential, and sites that are often overlooked include skin, vascular access sites, perineum, eyes (including fundoscopic examination) and oropharynx. For the investigations, two sets of blood culture should be drawn. If a vascular catheter is in place, then blood should be drawn from peripheral vein and each lumen of the catheter for culture. Other microbiological tests are performed as clinically indicated. Full blood count and biochemistry panel should be done initially and monitored regularly. It is prudent to include chest radiograph as part of the initial work-up, and the need of other imaging modality will depend on the initial clinical findings.

It is important to realize that patients with febrile neutropenia often fail to mount an appropriate inflammatory response to infections and the absence of physical/ laboratory abnormalities commonly seen in immunocompetent patients (e.g. lung infiltrate in chest radiograph) does not exclude active infections.

**Therapeutic approach**

Empiric antimicrobial therapy should be commenced promptly after initial assessment. In deciding the drugs of choice, the first step is to stratify patient's risk. Different scoring systems have been described, e.g. Multinational Association for Supportive Care in Cancer (MASCC) Risk Index. In essence, a patient is regarded as having low risk if the following criteria are met: ANC equals or greater than $1.0 \times 10^9$/L and duration of neutropenia is less than 7 days at presentation, resolution of neutropenia within 10 days is expected, underlying malignancy in remission, no significant comorbidity, patient is stable and no evidence of infective focus clinically, clear chest radiograph, and normal results of hepatic and renal function tests. Patients belonged to low risk subgroup can be managed in out-patient setting with oral co-amoxiclav and ciprofloxacin as empiric antibiotic therapy. For those who cannot tolerate oral drugs, ambulatory parenteral antimicrobial therapy is a viable option.

For patients requiring hospitalisation, the recommended empiric antimicrobial therapy consists of monotherapy with a 3$^{rd}$ or 4$^{th}$ generation cephalosporin possessing anti-pseudomonal activity (e.g. cefepime, ceftazidime) or a carbepenem (e.g. imipenem, meropenem), or combination therapy of the above drugs with an aminoglycoside (e.g. gentamicin, tobramycin, amikacin). Combination of an anti-pseudomonal penicillin (e.g. piperacillin) with an aminoglycoside is another alternative. Piperacillin-tazobactam, an anti-pseudomonal penicillin/ beta-lactamase inhibitor combination, has also been shown to be an effective monotherapy in this setting; however, its use has not been studied as extensively as that of other agents. Combination therapy with aminoglycosides provides synergistic activity, widens the spectrum of bacterial coverage and possibly reduces risk of emergence of resistance. However, this agent is potentially nephrotoxic, it increases the cost of therapy, and previous studies comparing combination therapy with aminoglycoside and monotherapy with drugs listed above did not show any significant difference in efficacy. In

general, the choice of agents is largely determined by local prevalence of pathogens and their susceptibility patterns, as well as patient-specific factors like initial clinical presentation, prior antibiotic exposure, drug allergy and presence of organ dysfunction (e.g. renal impairment). Whatever the choice is, it should be given in high enough dose to achieve maximum therapeutic effect.

The use of vancomycin in febrile neutropenia merits further discussion. It has been shown that inclusion of vancomycin as a component of initial therapy reduces need of subsequent antifungal therapy; however, it does not improve overall mortality rate, and the potential of selecting resistant organisms like VRE is a concern. Therefore, the use of vancomycin empirically should be based on risk assessment and it is appropriate to include vancomycin up front in the following scenarios: suspected intravenous catheter infection, known history of colonization or infection by penicillin- or cephalosporin-resistant organisms like MRSA, evidence of circulatory failure at presentation, or microbiological culture yields a Gram-positive organism pending further identification. It can be stopped if culture remains negative by day 3 to day 4 of therapy.

Receipt of initial antibiotic regimen for 3 to 5 days is generally required to determine its efficacy. Four factors determine the subsequent mode of therapy: ANC, microbiological work-up result, result of prior risk assessment, and patient's condition. If a pathogen is identified, antibiotic regimen should be adjusted to optimise efficacy. However, broad-spectrum coverage should be maintained to avoid breakthrough bacteraemia. If defervescence is observed within first 3 to 5 days of therapy and no etiology is identified, switching to oral antibiotics can be considered for low risk patients; whereas for high risk patients, one should continue the initial antimicrobial therapy. For febrile patients and no etiology is identified, one can continue the antibiotic regimen if patient's condition is stable. If there is deterioration of patient's condition, broadening of antimicrobial spectrum is indicated. If fever persists by day 5 and resolution of neutropenia is not imminent, addition of an antifungal agent is warranted. In the past, amphotericin B was the usual agent of choice. There are a number of new antifungals in the market at present, namely liposomal amphotericin B, voriconazole, and caspofungin. These agents have been demonstrated to have non-inferiority in overall success rate and better tolerance when compared with conventional amphotericin B therapy in well-designed randomised controlled trials. In particular, higher chance of survival at day 7 and resolution of baseline fungal infections were reported for caspofungin when compared with liposomal amphotericin B. However, these new agents are much costly when compared with conventional amphotericin B preparation.

In terms of the duration of empiric therapy after the first 3 to 5 days, ANC is the single most important determinant. For those with ANC greater than $0.5 \times 10^9$/L for 2 days, antibiotics can be stopped after 48 hours of defervescence. The minimum duration of therapy is 5 to 7 days. If patients remain febrile despite recovery of ANC to greater than $0.5 \times 10^9$/L, one can stop the therapy 4 to 5 days after recovery of ANC and monitor them closely. Management of patients with ANC persistently below $0.5 \times 10^9$/L depends on their clinical conditions. For low risk patients with stable condition, one can stop the antibiotics after a total of 5 to 7 afebrile days and monitor them closely. Antibiotics should be continued for high risk patients or those with one or more of the following features: ANC below $0.1 \times 10^9$/L, unstable clinical condition, persistent fever, and severe mucositis. In patients with prolonged neutropenia and hematologic recovery cannot be anticipated, one can consider stopping antibiotic therapy after 2 weeks, provided that no site of infection has been identified and the patient can be observed carefully. In all patients with persistent fever, low ANC, or both, a vigorous search of fungal infection should be taken. The duration of empiric antifungal therapy is not clearly defined.

## Adjunctive therapy

Apart from the supportive management and empiric antimicrobial therapy, efficacy of several adjunctive therapies has also been explored. Colony stimulating factors (CSF) have been shown to consistently shorten the duration of neutropenia. However, use of these agents have not consistently and significantly reduced other measures of morbidity, including duration of fever, use of antimicrobials, and no study has demonstrated a decrease in infection-related mortality rates. Routine use of CSF in management of febrile neutropenia is not recommended. Therapy with CSF may be considered in patients with anticipated worsening of the clinical course and long delay in recovery of the marrow. It may also be of value in patients who remain severely neutropenic and have documented infections that do not respond to appropriate antimicrobial therapy. Likewise, granulocyte transfusion is not recommended routinely. Potential complications of this therapy include transmission of blood borne pathogens like cytomegalovirus, alloimmunisation, and graft-versus-host reaction if granulocytes are not irradiated. For the time being, it is prudent to regard granulocyte transfusion as an experimental practice, and some authorities believe that it helps patients with profound neutropenia in whom the microbiologically documented infection cannot be controlled with optimal antibiotic therapy or by administration of a CSF, and in cases of severe uncontrollable fungal infections.

Antimicrobial prophylaxis during the early afebrile phase of neutropenia has been shown to reduce febrile episodes and infections. However, this benefit is offset by drug toxicity and emergence of resistant pathogens. Also, there is overall a lack of impact on patient mortality. At present, there is no consensus on the routine use of antimicrobial prophylaxis in afebrile neutropenic patients. This strategy may benefit selected subgroups of patients that are profoundly immunosuppressed (e.g. recipients of haematopoietic stem cell transplantation during the pre-engraftment period) or at risk of specific infections (e.g. cotrimoxazole prophylaxis against *Pneumocystis jiroveci* pneumonia in high risk patients, regardless of whether neutropenia is present). It is imperative that assessment of risk factors (ANC, timing of marrow recovery, presence of lesions or devices that break the mucous membranes and skin, history of instrumentations (e.g. endoscopy), severe periodontal disease, history of dental procedures, status of malignancy, and compromise of other immune responses) be performed prior to the decision of antimicrobial prophylaxis. Personal factors, such as drug compliance, personal hygiene, and environmental (i.e. hospital or home) circumstances, should also be considered. Drugs that have been shown to be useful for this purpose include fluoroquinolones, cotrimoxazole, and triazole antifungals.

## Conclusion

In recent decades, we witnessed a significant decline in mortality among patients with febrile neutropenia complicating malignancy. This is a result of several factors acting in concert: improvement of supportive care, better oncologic outcome as a result of more effective chemotherapy, advances in antimicrobial therapies, and refinement in individual risk assessment. The choice of antimicrobial therapy should be guided by the local prevalence of pathogens and their susceptibilities, as well as patient-specific factors. Emergence of pathogens resistant to broad spectrum antimicrobials remains to be a major challenge to clinicians.

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# Community acquired methicillin-resistant *Staphylococcus aureus* landed in Hong Kong

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## Introduction

*Staphylococcus aureus* can produce a wide range of diseases, from relatively benign skin infections to deep-seated and life-threatening conditions, including cellulitis, deep abscesses, osteomyelitis, pneumonia, sepsis and endocarditis. Before the introduction of penicillin in the 1940s, most of the *Staphylococcus aureus* are penicillin susceptible and they could be effectively treated with penicillin. But resistance to penicillin quickly emerged and methicillin was specially designed to overcome penicillin resistance. With only 2 years time of using methicillin, the first MRSA was reported in the United Kingdom in 1961, followed by report from other European countries, Japan and Australia. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a commonly known nosocomial pathogen worldwide. They are usually associated with risk factors like recent hospitalization or surgery, nursing home residence, renal dialysis and exposure to invasive medical devices. In recent years, there are reported cases from different parts of the world that cases without known risk factors of acquiring MRSA were also infected with strains of MRSA. In this article, the first reported case of community acquired MRSA landed in a local district hospital will be presented.

## The first local case

A 50-year old gentleman attended the Accident and Emergency Department of a local hospital in May 2004. He was referred from a general practitioner with an infected sebaceous cyst on the left and back side of the scalp for 1 week. The scalp abscess was 4 cm in diameter, fluctuant in nature with some purulent discharge. The patient was febrile with tympanic temperature of 38℃. Incision and drainage was done and a deep wound swab and sent for bacterial culture. A one-week course of oral ampicillin and cloxacillin was prescribed on discharge. A heavy pure growth of methicillin resistant *Staphylococcus aureus* was yielded from the swab culture which was resistant to only oxacillin while sensitive to other groups of antibiotics like erythromycin, gentamicin, clindamycin, ciprofloxacin, co-trimoxazole, fusidic acid, tetracycline, rifampicin and vancomycin. Following identification of the non-multiresistant MRSA, the patient was contacted by phone for further information. Direct questioning confirmed that risk factors like recent hospitalization or surgery, nursing home residence, renal dialysis and exposure to invasive medical devices were all negative in the previous 18 months. He had no history of exposure to person at risk for MRSA and none of his family members were healthcare workers. His neck wound gradually healed without the use of other antibiotics.

## Discussion

MRSA has become an important nosocomial pathogen that causes a variety of infections linked to hospitals. The presentations of the patients with community acquired and health care-associated MRSA are different. Skin and soft tissue infections are the most common manifestations of community acquired MRSA, but there are also some cases of serious invasive infection with occasional deaths occurred. Infection usually occurs in children or young fit adults rather than elderly or immunocompromised host. For soft tissue infections, there were reported outbreaks in prisons, military recruits, university football players, wrestlers or other athletes. The transmission of the organism was usually by sharing of towels, shavers or other personal items during the use of bathrooms or saunas. Necrotising pneumonia occurred in fatal cases.

Apart from the difference in clinical presentations from the health care-associated MRSA, their susceptibility pattern to antibiotics were also different. The community acquired MRSA were usually resistant to cloxacillin or oxacillin only while susceptible to other class of antibiotics like macrolides, aminoglycocides, fluoroquinolones, co-trimoxazole, tetracycline, clindamycin which hospital MRSA were usually resistant. Other than this phenotypic distinction, they are genetically different from the classical MRSA by possessing a Panton-Valentine leukocidin (PVL) gene. PVL increases the virulence of this organism, causing more severe soft tissue infection and increased prevalence of toxic shock cases. PVL is a member of a toxin known as synergohymenotropic toxins. They act on cell membranes by the synergy of 2 proteins that form a pore. Only 2% of the *S. aureus* isolates produce PVL and this toxin is the most leukocytolytic toxin in the family and causing dermo-necrosis. This gene can be used as one of the characteristics of the community acquired MRSA since all countries with reported cases of community acquired MRSA had similar findings.

The isolate from the case reported in Hong Kong is also PVL gene positive which coincide with the findings in other parts of the world. The organism is non-multiresisitant and there was absence of risk factors for acquiring MRSA. This case has illustrated that the spectrum of MRSA infection has expanded in Hong Kong. The emergence of this resistant and virulent organism may pose a threat to our community. We have to alert when we see cases with MRSA with multi-sensitive pattern. Soft tissue infection caused by these organisms usually can be treated with drainage and dressing of the abscess alone. For invasive infection, parenteral antibiotics will be needed. The organisms can be treated with the susceptible agents instead of using vancomycin in the treatment of classical multi-resistant MRSA.

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# Pulmonary *Pseudallescheriasis* in an immunocompetent woman

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## Introduction

*Pseudallescheria boydii* has been increasing recognized as an opportunistic organism, causing invasive and disseminated infection in immunocompromised hosts. Infection in immunocompetent host is uncommon. We reported a case of pneumonia caused by *Pseudallescheria boydii* in an immunocompetent woman.

## Case report

A 53-year-old lady was admitted to our medical ward for left sided pleuritic chest pain for one day. She also complained of three episodes of blood-streaked sputum in the past two months. She had minimal dry cough otherwise. There was no systemic symptom including fever or weight loss. She reported no recent travel history. She had background history of asthma and she was on inhaled bronchodilator only. Concerning her social history, she worked as a cleaner in a Chinese herbal factory. She was a regular swimmer. On admission, she was afebrile and not in respiratory distress. Blood pressure was 120mmg/80mmg and pulse was 85 beats per minute. Oxygen saturation was 97% with room air. Crepitation could be heard over left lower zone of the chest at the back. Otherwise, physical examination was unremarkable. Blood tests for complete blood picture, renal and liver function tests were all normal. Chest X-ray showed left lingular shadow. She was prescribed with oral ampicillin-sulbactam and clarithromycin and was discharged two days later.

Her chest X-ray on follow-up three weeks later showed persistent left lingular shadow. Computer tomographic scan of the thorax was performed, showing left lingular mass and old tuberculosis change at right apex. There was no mediastinal lymph node. Bronchoscopy showed mucosal swelling at left lingular opening, which was covered with a layer of greyish necrotic tissue. Bronchial-alveolar lavage revealed septated and branched fungal hyphae, suggestive of *Aspergillus*. Suppurative granulomatous inflammation and numerous septated hyphae with dichotomous branching, compatible with *Aspergillus*, were also noticed in the transbroncial biopsy.

However, skin prick test and antibody level to *Aspergillus* were negative. Immunoglobulin E level was elevated to 250IU/mL but the specific immunoglobulin E level to *Aspergillus* was normal. Later bronchial-alveolar lavage culture came back to grow *Pseudallescheria boydii*. Fasting glucose was 4.5mmol/L. Autoimmune markers including antinuclear antibody, rheumatoid factor and ANCA as well as anti-HIV antibody were all negative.

Our patient was then treated with oral itraconazole 100mg twice daily. Her chest X-ray repeated two months after treatment showed resolution of left lingular shadow. Treatment was maintained for six months.

**Discussion**

*Pseudallescheria boydii* is a saprophytic fungus that can be found worldwide, mainly in soil, sewage and polluted water. It exists in sexual and asexual form namely *Scedosporium apriosporum*. *P. boydii* is often misdiagnosed histopathologically as *Aspergillus* species. Microscopically, both are hyphae with regular septa and dichotomous branching, which are basically indistinguishable from each other. Both are well stained with haematoxylin and eosin (H&E) stain and best shown with Grocott methenamine silver (GMS) and Periodic acid-schiff (PAS) stain. Although both grow readily in routine mycologic medium e.g. Sabouraud dextrose agar, *Aspergillus* species are more thermophilic that it can grow at temperature of up to 45 degree Celsius while *Pseudallescheria* has maximal growth at temperature around 37 degree Celsius. The colonies of *Pseudallescheria* initially appear white macroscopically and then turn to dark grey after a few days due to the pigment excreted by this organism whereas colonies of *Aspergillus* remain white in colour.

The clinical spectrum of Pseudallescheriasis is wide, affecting all systems in the body. The most common infection is cutaneous pedal mycetoma, also named “Madura foot”. Infection in immunocompetent hosts is usually localized, and mostly associated with drowning or direct inoculation through trauma (1,2). There were case reports of pneumonia and fatal cerebral Pseudallescheriasis in near-drown patients (3,4,5). On the other hand, Pseudallescheriasis affecting the central nervous system could also occur in the absence of any predisposing factor. A case of meningitis in an immunocompetent man without any identifiable predisposing factor was reported recently (6).

Pulmonary manifestations of Pseudallescheriasis resemble those of Aspergillosis, ranging from mycetoma colonizing pre-existing pulmonary cavities, allergic bronchopulmonary reactions, intra-bronchial lesion, pneumonia to invasive diseases. In immunocompetent hosts, majority of lung infections reported were colonization of preformed tuberculous or sarcoid cavities. Most cases of invasive infections occurred in immunosuppressed patients. Our case is rather atypical in view of its clinical presentation as pneumonia in an immunocompetent adult.

Diagnosis of Pseudallescheriasis usually relies on histologic sections and fungal culture. More recently, in-situ hybridisation and polyerase chain reaction are other method of choices. Serology using specific immunoglobulin is also useful, especially in the diagnosis of allergic bronchopulmonary reactions. A recent study looked into the efficacy of in-situ hybridisation

for the differentiation of Aspergillus, Fusarium, and Pseudallescheria species in tissue section, using oligonucleotide DNA probes targeted against ribosomal RNA of the fungi. It was found that morphological examination had 100% sensitivity in detection of the fungi while DNA probes allowed 100% identification of the organisms, including mixed fungal infections. No cross-reactivity was found when Pseudallescheria probes were tested against cases of Aspergillus and Fusarium (7).

Distinguishing P. boydii from Aspergillus sp is important for effective treatment. P. boydii is notoriously resistant to anti-fungal agents including amphotericin B. The drug of choice are imidazoles. In vitro studies showed better result with voriconazole than itraconazole. Surgical intervention also plays a role in certain circumstances, for example in osteomyelitis or brain abscesses surgical debridement is mandatory for adequate treatment.

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## Journal Review

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**Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. N Engl J Med. 2004; 351: 2295-301.**

**Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. N Engl J Med. 2004; 351: 2286-94.**

Flu vaccine shortages and ongoing concerns about avian and human influenza pandemics serve to emphasize the need for further optimization of flu vaccine usage. One potential approach is to employ novel immunization routes. Intradermal immunization, one such method delivering the antigen directly to the skin where large numbers of antigen-presenting dendritic cells reside, may hold promise for the future. Two research groups recently investigated this approach and their results were published in the *New England Journal of Medicine*.

Kenney et al. enrolled 100 healthy adults aged 18 to 40 in a randomized, open-label trial comparing a single 0.5ml intramuscular (im) dose of the 2003-2004 inactivated flu vaccine (containing hemagglutinins from an H1N1 influenza A virus, an H3N2 influenza A virus, and an influenza B virus) with a single 0.1ml intradermal (id) dose of the same vaccine. On day 21, the two groups showed similar rates of seroconversion and seroprotection (defined as a strain-specific hemagglutination-inhibition antibody response more than or equal to 1:40) against all three influenza strains included in the vaccine. However, significantly more subjects receiving id vaccines experienced local reactions to the vaccine, including erythema (96% vs. 8%), pruritus (42% vs. 4%), swelling (84% vs. 10%), and induration (34% vs. 8%). No serious related adverse events were reported in either group.

In another open-label trial, Belshe and colleagues randomized 238 adults aged 18 years or above to receive a single 0.5ml im dose of the 2003-2004 inactivated flu vaccine or a single 0.1ml id dose of an experimental vaccine containing hemagglutinin from an H1N1 influenza A virus, an H3N2 influenza A virus, and an influenza B virus. In the 130 subjects aged less than or equal to 60, immune responses against all three influenza strains were comparable in the two groups. Among the 108 participants aged more than 60, a stronger immune response was seen in those who received the im vaccine; the difference was significant only for the antibody response to the H3N2 strain antigen. Nevertheless, 100% of the subjects receiving id vaccines aged 60 or above achieved seroprotective antibody levels against the H1N1 and B strains, and 93% had seroprotective levels against the H3N2 strain. Similar to the previous study mentioned above, signs of local inflammation were significantly more common in subjects receiving id vaccines; among subjects receiving id vaccines, injection-site pain occurred significantly less frequently in younger participants. Again, no serious vaccine-related adverse events were reported.

**Points to note:** Overall, these studies showed that id injection of inactivated flu vaccine elicited nearly the same immune response as did intramuscular injection, but with a lower dose of vaccine. Using lower doses could ease the current flu vaccine shortage in the U.S. and could also be potentially used to stretch supplies, should a flu pandemic occur. Nevertheless, these are only pilot studies, and large-scale investigations are needed to confirm the efficacy and safety of this vaccination dose and route before it could be widely adopted.

**Maertens J, Raad I, Petrikkos G, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis. 2004; 39: 1563-71.**

Invasive aspergillosis (IA) is an increasingly common cause of hospital-acquired infection among immunocompromised hosts and is often associated with poor outcomes. Treatment options are limited to amphotericin B formulations, including conventional and lipid preparations; the triazoles, such as itraconazole and voriconazole; and the echinocandins, including caspofungin. Although caspofungin has demonstrated in vitro activity against aspergillus and efficacy in animal models of IA, it has not been studied extensively as a treatment for IA in humans yet.

Maertens et al recently conducted this open-labeled, non-comparative trial involved 90 patients with proven or probable IA, who were recruited because of refractory disease or intolerance to previous antifungal therapy. Out of the 83 patients who could be successfully evaluated, 37 (45%) responded favorably with complete or partial clinical response after ≥1 month of caspofungin therapy. However, only 4 patients (5%) showed a complete response. Patients with hematologic malignancies were significantly more likely to respond favorably than were those with stem-cell transplants, and patients who were intolerant of previous antifungal therapy were more likely to respond than were those who had refractory diseases. The use of caspofungin was associated with clinically observed or lab-confirmed adverse events in 23 of the 90 patients (26%). However, only two of these events, namely the development of pulmonary infiltrates and hypercalcemia, were considered serious drug-related events.

**Points to note:** This well designed study demonstrates that caspofungin is effective in treating some patients with IA who have not responded to previous antifungal therapy. Response was more likely in patients who were less immunosuppressed (hematologic malignancies vs. stem cell transplants), and in patients whose initial antifungal therapy had failed because of toxicity rather than refractory disease. The authors concluded that further studies examining caspofungin and other echinocandins as primary therapy for IA should be conducted in future.

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|---|---|
| 22-25 March 2005<br>Edinburgh<br>Scotland<br>United Kingdom | **Teach-In: Infectious Diseases**<br>The Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh, EH2 1JQ<br>Phone: 44-0-1-312-257-324<br>Fax: 44-0-1-312-203-939<br>E-mail: c.pottingen@rcpe.ac.uk |
| 2-5 Apr 2005<br>Bella Center<br>Copenhagen,<br>Denmark | **15th European Congress of Clinical Microbiology and Infectious Diseases ECCMID 2005**<br>European Society of Clinical Microbiology and Infectious Diseases<br>Contact: Congress Secretariat, ESCMID Executive Office<br>P.O. Box 6, CH-4005 Basel Switzerland<br>Phone: +41-616-867-799<br>Fax: +41-616- 867-798<br>E-mail: info@escmid.org<br>Web: http://www.escmid.org |
| 9-10 April 2005<br>Washington DC<br>United States | **An Update in Sexually Transmitted Infections**<br>Contact: Continuing Medical Education, Boston University School of Medicine, 715 Albany Street, A 305, Boston, MA 02118<br>Phone: 617-638-4605<br>Fax: 617-638-4905<br>E-mail: cme@bu.edu |
| 22 April 2005<br>Omaha<br>NE United States | **25th Annual Infectious Diseases Symposium**<br>Contact: Continuing Medical Education Division, 601 North 30th Street Suite 2130-Omaha, NE 68131<br>Phone: 402-280-1830 / 800-548-2633<br>Fax: 402-280-5180<br>E-mail: cmeded@creighton,edu |
| 16 May 2005<br>London<br>United kingdom | **Emerging Resistance and Emerging Infections**<br>Contact: The Royal College of Physicians, 11 St Andrew Place, Regent's Park, London<br>Phone: 02-0-79-351-174<br>Fax: 02-0-74-875-218<br>E-mail: conferences@rcplondon.ac.uk |
| 23-27 May 2005<br>Bradenton-Sarasota<br>Florida<br>United States | **Pediatric Infectious Diseases**<br>Contact: Eva Easterwood or Cristina<br>American Medical Seminars Inc. at PO Box 49947, Sarasota, FL USA<br>Phone: 1-800-325-1961<br>Fax: 1-941-388-1766<br>E-mail: mail@ams4cme.com |
| 18-25 June 2005<br>Athens<br>Greece | **CME at SEA: Infectious Disease Update**<br>Contact: Sea Course Cruises<br>Phone: 1-888-647-7327<br>Fax: 1-888-547-7337<br>E-mail: cruises@seacourse.com |

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| 24-28 June 2005<br>Boston<br>MA<br>United States | **6th International Conference on Cryptococcus an Cryptococcosis**<br>Contact: Boston University School of Medicine Continuing Medical Education<br>Phone: 617-638-4605<br>Fax: 617-638-4905<br>E-mail: cme@bu.edu |
| 27-29 June 2005<br>Oxford<br>United Kingdom | **Infection and Immunity in Children 2005**<br>Contact: Mrs. Julia Bremble, University Department of Pediatrics at John Radcliffe Hospital, Oxford, USA OX3 9DU<br>Phone: 44-01-865-221-074<br>Fax: +44-01-865-221-889<br>E-mail: iic.2005@paediatrics.ox.ac.uk. |
| 24-27 Aug 2005<br>Hobart<br>Australia | **17th Annual Conference of the Australasian Society for HIV Medicine**<br>Contact: Nicole Robertson<br>Phone: 612-936-820-718<br>Fax: 61-293-316-537<br>E-Mail: conferenceinfo@ashm.org.au |