

# Aspergillosis in the ‘Nonimmunocompromised’ Host

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Invasive aspergillosis has been classically associated with certain risk factors: cytotoxic chemotherapy, prolonged neutropenia, corticosteroids, transplantation, AIDS. However, the literature is growing that this mycosis, particularly pulmonary aspergillosis, can be seen in patients lacking these factors. Many of the latter patients are in the intensive care unit. Other associated conditions include influenza, nonfungal pneumonia, chronic obstructive lung disease, immaturity, sepsis, liver failure, alcoholism, chronic granulomatous disease and surgery. Certain focal sites, such as sinusitis or cerebral aspergillosis, have additional risk factors. This emphasizes the potential importance of a positive culture for *Aspergillus* in the critically ill, the need for awareness about possible aspergillosis in patients lacking the classical risk factors, and readiness to proceed with appropriate diagnostic maneuvers.

**Keywords** Aspergillosis, Immunocompetence, Intensive care.

## INTRODUCTION

A problem with understanding the dimensions of the problem of aspergillosis in the immune-competent is one of definition. Review of the aspergillosis literature indicates there is a set of classical risk factors (Walsh and Stevens, 2011): cytotoxic chemotherapy, prolonged neutropenia, corticosteroids, transplantation (and concomitant immunosuppression), and most recently, AIDS (Denning et al., 1991). The understanding is that virtually all patients with

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*invasive* aspergillosis will have 1 or more of these underlying factors, and indeed that is the case for  $\geq 90\%$  of patients in the literature. A problem is that some publications on the “nonimmunocompromised” have included patients receiving steroids, some who were neutropenic, and even some who have received some cytotoxic chemotherapy. There is no consensus on what the cutoff dose for steroids or leukocyte count should be to call an individual “immunocompromised”.

That invasive aspergillosis could occur in the nonimmunocompromised might have been realized by an epidemiological observation that relies on our veterinary colleagues. It has been long known that, peculiarly, otherwise robust German Shepherd dogs are susceptible to invasive aspergillosis (Kahn and Line, 2010), presumably on some genetic basis.

*The noncompromised aspergillosis patient in the hospital and the intensive care unit (ICU).* However, a good starting place for the human-oriented literature is an important review that appeared (Karam and Griffin, 1986) reporting 3 cases who were “not immunocompromised, . . . not leukopenic, . . . never received either corticosteroids or cytotoxic chemotherapy”, and, importantly, reviewed the literature up to that date. Their 3 cases included one patient with alcoholism, one with chronic obstructive lung disease (COPD), and one with no significant medical history. In their institution, over 5 years, of 10 patients who had pulmonary infiltrates and a positive sputum culture for *Aspergillus*, 2 (20%) were proven to have invasive aspergillosis. Of 5 with infiltrates and a positive bronchoalveolar lavage culture, 2 (40%) were proven to have invasive aspergillosis. The conclusion was that a high percentage of nonimmunocompromised patients with a culture positive for *Aspergillus* had invasive disease. Their literature review included some patients who would meet standard definitions (EORTC/MSG; De Pauw et al., 2008) for “probable” and “possible” aspergillosis, but 25 were compatible with a diagnosis of “definite” aspergillosis. Of these 25, 4 had alcoholism, 3 had influenza, and 3 had diabetes or glucose intolerance (Karam and Griffin, 1986). However, 11 others had *no* underlying disease, and 1, nonrelevant medical issues. Their conclusion was: “In recent years, the number of cases of invasive pulmonary aspergillosis reported in nonimmunocompromised adults has been increasing . . .”, and their take-home message we believe was “. . . invasive pulmonary aspergillosis should be considered when *Aspergillus* species is isolated in respiratory secretions and presence of pneumonia.”

An important review (Meersseman et al., 2004) covered 1850 admissions to the ICU, 127 of which (7%) met criteria for proven or probable aspergillosis. This gives a picture of the problem as seen by ICU physicians, but hematology patients were one of the prominent constituents, as were COPD, solid organ transplant patients, and those with autoimmune diseases, where immunosuppressives are also common. The mortality in the proven cases was 97%, and in those in whom steroids were started after admission to the ICU, the mortality

rate was 100%. In 4 of the 5 patients with proven invasive aspergillosis, the positive sputum cultures were regarded as contaminants.

This overlap of recognized classical risk factors with non-classical patients in the ICU is further recognized in a recent abstract (Vazquez et al., 2010). If we eliminate 69 patients who received steroids, 39 who received immunosuppressives, and 33 with solid organ transplants, there were 28 whose risk factor was diabetes, 28 on mechanical ventilation, 22 with COPD, and 19 with sarcoidosis.

*Invasive pulmonary aspergillosis.* An article on an important subset concerned acute community-acquired pneumonia due to *Aspergillus* in presumed immunocompetent hosts (Clancy and Nguyen, 1998a), which these authors called "a rare but fatal disease". Their report included 12 patients, 100% of whom died, and 4 were not recognized antemortem. The underlying diseases recognized included influenza, alcoholism, COPD, cirrhosis, and exposure to a large inoculum of *Aspergillus* in an agricultural setting (the last issue to be discussed further later). The symptoms and time course were similar to pneumonia due to bacteria and viruses. Eight had bilateral diffuse infiltrates, and the remainder progressed to bilateral disease quickly. The sputum culture was positive in 7/10, and BAL culture positive in 3/3. Tissue biopsy was diagnostic in 83%. The clues that helped distinguish the aspergillosis subset were diffuse infiltrates, influenza, a new cavity, a positive culture for *Aspergillus*, and no confirming bacterial or viral diagnosis in that group of patients.

That aspergillosis in the apparently immunocompetent is not limited to North America or Europe is indicated in a report from Pakistan (Karim et al., 1997). Their report of chronic invasive disease included 9 with sinus disease (most had allergic sinus disease preceding invasive), 3 with pneumonia (and we wish to return to discussion of chronic pneumonia; 1 of these had mediastinitis), 2 with brain abscess, 2 with lymph node disease, and 1 with osteomyelitis of the foot. None of the patients had received steroids, cytotoxic therapy, or had an immunosuppressive disease.

It is worth digressing to talk about the entity chronic pulmonary aspergillosis, a disease that occurs largely in the nonimmunocompromised and uncommonly does become invasive (Geftter et al., 1981; Schiraldi et al., 2003; Hope et al., 2005). There are 4 major, and sometimes overlapping, forms: aspergilloma, chronic cavitary disease, chronic necrotizing disease (also called "subacute invasive aspergillosis"), and chronic fibrosing disease, which is a late stage. The most common setting is prior tuberculosis; almost a third of these, whereas other commonly predisposing conditions are pneumothorax and bullae, COPD, and allergic bronchopulmonary aspergillosis (ABPA). Lung cancer, sarcoidosis, pneumonia of diverse etiologies, lung resection and rheumatoid arthritis would, in that order, be the next common underlying conditions.

*Risk factors.* So what, from the discussion so far, should make the doctor, and especially the ICU doctor, consider aspergillosis in the differential diagnosis in the immunocompetent host? The identified risk factors for invasive aspergillosis in ICU patients without classical immunosuppression are listed in Table 1. That diabetics have impaired host response to infection has been long known (Robson, 1970; Thornton, 1971; Robertson and Polk, 1974). What steroid dose should be considered to make one immunocompromised? The EORTC/MSG criteria, referred to previously, considered 3 weeks of steroid therapy a risk factor for aspergillosis, whereas some consider a dose administered (with different opinions on duration) that exceeds an endogenous stress level of steroids. Of note, invasive aspergillosis has been reported in patients who only received inhaled steroids with their limited systemic absorption (Leav et al., 2000; Chow et al., 2002; Barouky et al., 2003). There are recognized aggravating factors in ICU patients with risk factors but without classical immunosuppression (Table 2) (Anaissie, 2008). *Aspergillus tracheobronchitis* may predispose to invasive pulmonary aspergillosis, especially in mechanically ventilated patients (Kramer et al., 1991; Kemper et al. 1993).

**Table 1:** Potential risk factors for invasive aspergillosis in ICU patients without classical immunosuppression.

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Extended ICU stay
Hemodialysis
Advanced liver disease
Antibiotics
Low-dose steroids
Congestive heart failure
COPD
Mechanical ventilation
Diabetes
Near-drowning
Transfusion-associated hemosiderosis

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**Table 2:** Potential aggravating ingredients in ICU patients with risk factors but without classical immunosuppression.

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Intubation interferes with first line of defense
Steroids for septic shock
Sepsis-associated immunoparalysis
Malnutrition
Transfusion of allogeneic blood products
Poorly controlled glycemia
COPD pts. have abnormal T helper cell profiles <sup>1</sup>

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<sup>1</sup>(Zhu et al., 2009).

For the septic patient, often *in* the ICU, there is an explanation for susceptibility to aspergillosis that involved immunosuppression, induced by sepsis itself (Table 3). Why are cirrhotics identified among the risk groups of patients not classically recognized as immunodeficient? There are explanations that also relate to immunodeficiencies identified in patients with liver failure (Table 4). Patients who are alcoholic also have defined immunosuppressive factors that relate to deficient host phagocyte functions (Table 5).

To help the ICU physician identify patients at higher risk, some factors have been defined that statistically favor invasive aspergillosis in the ICU patient with a positive sputum culture for *Aspergillus*, as opposed to those with only colonization (Vandewoude et al., 2006): those with higher APACHE scores, hemodynamic instability or acute respiratory failure. The diagnostic problem should not be underestimated. In one institution, 47% of the invasive aspergillosis in the hospital was in the ICU, other studies have indicated 60%

**Table 3:** Sepsis-associated immunoparalysis.

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SIRS leads to anti-inflammatory response, negative feedback  
 Decrease of innate and adaptive immunity  
 Decrease of all cellular immune functions  
 -Occurs via IL-10, apoptosis, decrease of MHC class II molecules, increased regulatory T cells and myeloid suppressor cells  
 Decreased HLA DR marker on monocytes- marker for monocyte energy, predictor of secondary infections  
 Decreased number of myeloid dendritic cells leads to increased risk infection  
 Septic peritonitis (bacterial) mouse model- increased susceptibility to aspergillosis <sup>1</sup>

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<sup>1</sup>(Benjamin et al., 2003).

**Table 4:** Factors potentially predisposing cirrhotics to fungal infection.

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Decreased opsonization due to complement deficiencies  
 Decreased phagocytosis due to neutrophil dysfunction  
 Impaired chemotaxis  
 Defects in Kupffer cell function  
 Concomitant bacterial infections + antibiotics  
 Inability to make diagnosis because of bleeding diathesis (leading to prior underestimate of frequency)

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**Table 5:** Factors potentially predisposing alcoholics to fungal infection.

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Impaired phagocytes  
 Mobilization  
 Chemotaxis  
 Adherence  
 Phagocytosis  
 Superoxide production

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of invasive aspergillosis in the ICU did not have either neutropenia or hematologic cancer, and <50% of patients in the ICU with invasive aspergillosis had sputum cultures positive for *Aspergillus* (vandeWoude et al., 2006; Dutkiewicz and Hage, 2010) (supporting the data in the early paper cited; Karam et al., 1986). The prognosis is not good—studies have indicated the mortality of invasive aspergillosis is  $\geq 70\%$  in ICU patients, and 100% if the patients also have cancer (Meersseman et al., 2004).

*Why the burgeoning literature?* Why does invasive aspergillosis appear to be rising in “nonimmunocompromised” hosts? Is it because we have an older population with more co-morbidities? Is it because patients are living longer as a result of advances in medicine, but with risk factors and/or immune-depressing conditions, making them more susceptible to opportunists? Is it because of wider use of broad-spectrum antibacterials, and anti-*Candida* therapeutics, both for therapy and prophylaxis? Is it because of more invasive monitoring and procedures? Is it due to increased recognition of the disease— including better testing modalities for aspergillosis? Does the rise in drug addiction, a recognized risk factor for aspergillosis contribute to the numbers? Is there an increased reliance on the ICU for seriously ill patients? Or is this only a statistical phenomenon of center-to-center variation relating to local ecology? These are the questions we can ponder to explain the phenomenon.

*Influenza.* Influenza has already been mentioned as an association. One of the key papers (Fischer and Walker, 1979) described 2 patients, both of whom died. Both had lymphocytopenia, as had been noted previously in other post-influenza aspergillosis case reports in the literature. The authors cogently indicate as a possible mechanism: “Influenza is known to cause transient intradermal anergy and decrease in circulating T cells, as well as destruction of the mucociliary escalator.” Subsequent to this report, 15 patients were reported in the literature with post-influenza aspergillosis. Most currently, with the pandemic H1N1 2009 influenza virus circulating, 2 patients with invasive aspergillosis were reported (Lat et al., 2010). In addition to the immunologic defects and impairment of ciliary clearance, these authors added steroids prescribed for influenza-associated adult respiratory distress syndrome as a risk factor to be considered in predisposing otherwise immunocompetent patients to invasive influenza aspergillosis.

*COPD.* COPD has already appeared in our discussion of associated morbidities predisposing to invasive aspergillosis. Several important studies have documented the emergence of aspergillosis in COPD. COPD accounts for about 10% of cases of invasive aspergillosis in some institutions, and is there a more common predisposing condition for invasive aspergillosis than hematological malignancy, and these cases have 70% mortality (Guinea et al., 2008). In some series, 22% of COPD patients with a sputum culture positive for *Aspergillus* had invasive aspergillosis, and in one series, 5 of 6 patients

with disseminated aspergillosis had positive cultures antemortem that were regarded as colonizers (Dimopoulos et al., 2003).

One study reported 13 cases of invasive pulmonary aspergillosis in COPD admitted to the ICU (Ader et al., 2005). Bronchospasm was a prominent finding. Steroid treatment was often continued, despite the isolation of *Aspergillus* in the sputum. The mortality rate was 100%, and the diagnosis was proven at autopsy. Another important study (Bulpa et al., 2001) reported 23 COPD ICU patients, 16 with EORTC/MSG criteria for proven invasive pulmonary aspergillosis and 7 with probable (repeated isolation of *Aspergillus* in sputum). These patients had recently been treated with steroids, or had their steroid regimen intensified. Severe bronchospasm was the case for 12 of the 23. All required mechanical ventilation. The mortality rate was 100%, as an overview of the literature also had indicated (Rello et al., 1998).

A longitudinal study of COPD patients (Guinea et al., 2010) helps us assess the risk. For 14,618 COPD cases, the incidence of invasive pulmonary aspergillosis was 3.6 cases/1000 admissions. The odds ratio for developing aspergillosis for risk factors was 4.57 if the patient received steroids during their admission, 2.98 if steroids had been given prior to the admission, 2.57 if antibiotics had been given prior to admission, and 2.41 if the patient was admitted to the ICU. Of note, only 6% of the patients with invasive aspergillosis had a "halo sign" (a common and useful radiographic finding in immunocompromised hosts, to suggest invasive pulmonary aspergillosis) (Hsu et al., 2011) on chest radiography.

Risk factors for invasive aspergillosis in patients with chronic lung disease have been defined, and include mechanical ventilation, lengthy hospitalization, prior fluconazole (which lacks anti-*Aspergillus* activity), and a prednisone dose exceeding 20 mg/day for >1 mo. (Bulpa et al., 2007; Caston et al. 2009). A large series of COPD patients with aspergillosis (Patel et al., 2010) found that mortality, length of stay, and costs were all increased if the patient had been started on fluconazole first, as opposed to starting on voriconazole (the drug of choice in treatment of invasive aspergillosis) (Walsh et al., 2008) first.

*Diagnostic problems.* Meersseman et al. (2007) have pointed out the problems in the diagnosis of aspergillosis in the critically ill, not immunocompromised, patient. The classical radiology findings are not present. The well-studied diagnostic tools (Hsu et al., 2011) galactomannan, beta glucan and PCR, have been little studied outside the setting of hematologic malignancies. Beta glucan can be elevated in ICU patients without invasive mycoses, though persistently high levels are suggestive (Presterl et al., 2009).

Until recently, the standard definitions of disease (De Pauw et al., 2008) were based on the presentation in classically immunosuppressed patients. Diagnoses are often made at autopsy (in one series, in one third) (Roosen et al., 2000). Moreover, the appropriate therapy is unclear, as the clinical trials have

**Table 6:** Approach to the critically ill, not classically immunocompromised, patient with a respiratory culture positive for *Aspergillus*.

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Is the patient in a recognized risk group (as indicated in this article)?  
 Consider the diagnosis of invasive aspergillosis !!  
 Obtain imaging; test (recognizing the high rate of false negatives in this population) serum galactomannan, beta glucan, and (if available in your institution) PCR  
 Consider BAL (with stain, culture, and the molecular tests just mentioned)<sup>1</sup>  
 Depending on the results of the above test, consider tissue diagnosis and/or empiric antifungal therapy

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<sup>1</sup>(Meersseman et al., 2008).

not been done in the nonimmunocompromised population. Overall, the literature would suggest invasive pulmonary aspergillosis in critically ill patients has an overall crude mortality of 77%, with an attributable mortality of 19%. This leads us to an approach to diagnosis in these patients (Table 6).

*Chronic granulomatous disease (CGD).* Close examination of the literature results in some interesting observations. One of the papers cited by other articles as an early one describing invasive aspergillosis in immunocompetent persons is that by Strelling et al. (1966). However, the 2 children were siblings, living on a farm, both had granulomatous histopathology, and one had disseminated aspergillosis (she received 8 days' of steroids) and striking adenopathy. The authors cite 8 similar earlier cases in the literature, all children. All had granulomatous histopathology. Fever was not prominent in any. Two of the 8 were siblings. Three were infants. At least 6 had disseminated aspergillosis; 5 had CNS aspergillosis. Two had chest wall aspergillosis. Three lived on a farm, and one had inhaled timothy grass. The neutrophil disease, CGD (originally called "chronic granulomatous disease of childhood") was first described 9 years before this article (Berendes et al, 1957). Yet, this possible diagnosis is not mentioned in Strelling et al. In CGD, leukocytes (on a genetic basis) cannot make a respiratory burst, and progressive aspergillosis is a frequent fatal event. Many of the clinical characteristics described (here) in the 10 cases are compatible with a diagnosis of CGD.

Recently, a case was presented as fatal invasive aspergillosis in a nonimmunocompromised host, after gardening (Russell et al., 2008). However, no evidence for invasion was provided. As the authors suggest, "acute aspergillosis after contact with decayed plant matter may occur". However, alternative explanations need to be considered (Stevens, 2008). One such entity is extrinsic allergic alveolitis. This results from massive inhalation of *Aspergillus* spores, usually occurring in farm or malt workers.

The exposed persons develop symptoms (dyspnea, fever) within 24 h. The radiographic picture is diffuse micronodular infiltrates. Histopathology shows granulomas, not eosinophilia, and there is no invasion.

IgG precipitins and/or cellular immunity are implicated as the etiology. The treatment is steroids, but as there are purulent microfoci, antifungals need to be considered.

The other entity is so-called "mulch pneumonitis". This occurs in CGD, with onset typically in adults. The clinical picture is hypoxia, fever, and pulmonary infiltrates after inhaling a large inoculum of *Aspergillus*. The neutrophils have no respiratory burst, but the neutrophils infiltrate and damage the lung. Histopathology shows pyogranulomas, and no invasion. The case fatality rate appears to be 50%. The treatment is a prolonged course of steroids, with antifungals.

*Sinus.* Another described entity is invasive sinus aspergillosis in immunocompetent hosts (Clancy and Nguyen, 1998b; Siddiqui et al., 2004; Siddiqui et al., 2006; Webb and Vikram, 2010). Excluding cases of allergic sinusitis or mycetoma, 91 cases had been described by 2010. Three types are recognized: local (invasion into the walls of sinus) (10%), cranial (invasion into other cranial structures) (31%), and intracranial (59%) (e.g., invasion into arteries, brain). The presentation is indistinguishable from bacterial, viral, or allergic sinusitis. The initial histopathology and culture are unrevealing in more than one-fifth of cases. A delay in diagnosis is common, and has a bad prognosis. Computed tomography is unhelpful; magnetic resonance imaging reveals hypointense T2 sinus images, isointense T1, and bright T1 pictures with gadolinium (more than is seen with invasive sinusitis in immunosuppressed hosts).

In a global series, cases are caused in 59% by *A. flavus* and 28% by *A. fumigatus*. Multiple sinuses are involved in 83%, with the ethmoid, sphenoid, maxillary, and frontal involved in 83%, 79%, 48%, and 10%, respectively. The cure rate in the cranial form is 56%, and in the intracranial, 6%; mortality is 11% and 44%, respectively. The granulomatous type of histopathology tends to be in younger patients, outside North America, less lethal, and caused by *A. flavus*. The relative roles of surgical and medical therapy are unclear. If the disease can be completely resected, it does appear that the cure rate doubles. Preoperative itraconazole appears useful in the less invasive types. Suppressive therapy post-surgery fails in 27%.

*Central nervous system (CNS).* Cerebral aspergillosis is a devastating complication of disseminated disease, in any host. A report (Kim et al., 1993) brought to the fore 39 cases. The predisposing factors included 7 with complications of neurosurgery, 5 with chronic alcoholism, 4 drug addiction, 4 sinusitis, 3 hepatic failure, 2 "occupational" (farmers, millers), 2 Cushing's syndrome, 2 head trauma, 2 diabetes, 1 chronic otitis media, but also 4 with *no* known predisposing factor, and 2 with no obvious medical condition that could be connected as a risk factor for aspergillosis or immunosuppression. Only 6 of the cases survived, and these were treated with surgery + antifungal chemotherapy. This survival rate is comparable to what is reported in the literature for

survival of cerebral aspergillosis in the classically immunocompromised host (Schwartz and Thiel, 2003). Complications of local analgesia could also lead to CNS aspergillosis in persons otherwise without usual risk factors (Genzen and Kenney, 2009).

*Neonates.* Another category is aspergillosis in the neonate (Rowen et al., 1992; Groll et al., 1998). In the 1998 review, there had already been reported 44 cases. Few were neutropenic or had been given long-term immunosuppressives. The risk factors in this group would appear to be the immaturity of their phagocyte defenses and of cutaneous barriers. Impaired immune defenses in the immature result in weakened defense against infections, including those caused by fungi (Kethineni et al., 2006). Sixty-six % of those in the 1998 review were nosocomially acquired. Prematurity was associated with it in 43%, CGD 14%, and steroid therapy, 41%. The cutaneous form was seen largely in premature infants, was associated with *A. fumigatus*, and death was rare. With the pulmonary form, the majority was acquired outside the hospital, half had CGD, there were no premature infants; the cause was largely *A. fumigatus*, and more than half died. Of those with CNS infection, interestingly, all 4 were cured. With the widely disseminated form, all 14 died of aspergillosis, and the diagnosis was made in almost all at autopsy.

A problem in diagnosis in this patient group relates to the inefficacy of the galactomannan test, notably, false positives related to dietary factors and immature gastrointestinal tracts (Hsu et al., 2011). Overall, of the treated patients (mostly with amphotericin B, a drug better tolerated in neonates (Rex and Stevens, 2009)), 73% survived. Of note, an instance of intrauterine infection, resulting in a stillborn child, has also been reported (Rowen et al., 1992; Groll et al., 1998).

*Surgery and the surgical ICU.* The surgical ICU is also a site of these infections. For example, surgical ICU infections in the viscera have been reported after laparostomy, and the patient's isolate appeared to match isolates in the ICU air (Carlson et al., 1996).

The *first* post-surgical case was probably a report in 1933 (Frank and Alton, 1933). A woman operated on for an abdominal tumor developed a dark ulcer under the dressing, and *A. niger* was grown from the dressings. A true estimate of the incidence/prevalence of postsurgical invasive aspergillosis wound infections is lacking, as most of the publications are case reports or outbreak investigations. There have been no prospective or surveillance studies. Estimates in the literature suggest a rate of 2/10,000 surgeries, though this figure is unsubstantiated.

A list of *Aspergillus* infections reported after surgery or after trauma has been provided (Carlson et al., 1996), broken into: during surgery, after surgery and trauma-related. The first category includes infection of vascular grafts and artificial valves, Hickman lines, sternotomies, bronchial stumps,

and those after procedures such as laminectomies or insertion of prosthetics. The "after surgery" category is dominated by a variety of postoperative wound infections. The "trauma" category includes burn wounds and tissue injuries, often accompanied by ischemia.

An extensive review (Pasquolotto and Denning, 2006) reported >500 cases of postoperative aspergillosis. The most prominent types of infection were related to cardiac surgery (n = 188), with ophthalmic and dental surgery next-ranked.

A review from one, 1750-bed, institution over a period of a little more than 7 years, reported 83 cases of invasive aspergillosis, 7 of which were post-surgical (8% of the total) (Jensen et al., 2009). Six were caused by *A. fumigatus*. Four were wound infections (57%), and 2 were mediastinitis (29%). The distribution was sporadic and occurred exclusively in patients with no classic predisposing conditions for invasive aspergillosis; diabetes was present in a few. The mean time from surgery to the first *Aspergillus* isolation was 25 days (range 11–376). Treatment involved surgical debridement and concomitant antifungal therapy in 6 patients. The galactomannan assay was negative in 5.

*Cardiac surgery.* Two important papers have described sternal wound infections after cardiac surgery. One (Vandecasteele et al., 2002) described 9 patients, whose *A. flavus* infections developed, insidiously, a median of 14 days after surgery (range, 5–147 days), and 4 patients presented with sternal wound infection 13 weeks after they had undergone surgery. Two had received high-dose steroids within a week of the surgery. Symptoms were only local (wound dehiscence, local inflammatory signs, pleural effusion, and formation of sterno-cutaneous fistulas and substernal fluid collections). Three had multiple relapses. Two had fulminant mediastinitis and died, although *Aspergillus* is a rarely reported cause of mediastinitis in the overall literature. The operating room air appeared to have high levels of *A. flavus* conidia. The other (Richet et al., 1992) reported 6 cases (all *A. fumigatus*) over a 21-month period. These were unrelated to construction or renovation projects, and environmental sampling did not suggest an air or surface source. The authors concluded, from case-control studies in randomly selected concurrent open-heart surgery cases, that COPD and/or lung disease is a risk factor for post-surgical invasive aspergillosis. It appeared likely previous colonization was translocated during surgery.

*Sources of surgical infection.* The main sources of infection implicated in the literature are contaminated grafts, contaminated sutures, intra-operative dispersion of spores, and post-surgical environmental exposure. Of interest, 2 papers (Gage et al., 1970; Mehta, 1990) have implicated pigeons and pigeon droppings contaminated with *Aspergillus* in the vicinity of the air supply to the operating rooms as a possible cause of such cases. Fomites, such as the

grilles of the heat exchanger used to maintain extracorporeal blood at the proper temperature, have also been implicated (Diaz-Guerra et al., 2000) in *A. flavus* infections, supported by RAPD genotyping of environmental and patient isolates.

Beyond excision of the infected tissue wherever possible, choice of therapy and duration relies on general practice guidelines for the treatment of aspergillosis (Walsh et al., 2008).

## CONCLUSION

It would be highly desirable that genetic research be pursued that will define polymorphisms of patients, particularly in the ICU, at increased risk of invasive aspergillosis and who lack the classical risk factors. The final message from this review: do not disregard a culture positive for *Aspergillus* in a critically ill patient. Consider and investigate its clinical significance, even in the absence of EORTC/MSG-defined (De Pauw et al., 2008) risk factors.

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