



Mini-Symposium: Fungi and The Paediatric Lung

Candida and the paediatric lung

Alessandro C. Pasqualotto*

Infection Control Department, Santa Casa Complexo Hospitalar, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

ARTICLE INFO

Keywords:

candidiasis
candidaemia
pneumonia
Candida albicans
Candida parapsilosis

SUMMARY

Although systemic candidosis is common in hospitalised children, *Candida* involvement of lung parenchyma is rare and usually perceived only at autopsy. The purpose of this article was to review the evidence regarding lung involvement in *Candida* infections, with special attention to paediatric patients. Primary *Candida* pneumonia is rare and usually associated with aspiration of oropharyngeal contents. The majority of cases of *Candida* pneumonia are secondary to haematological dissemination of *Candida* organisms from a distant site, usually the gastrointestinal tract or the skin. The diagnosis of pulmonary candidosis is difficult because there is no specific clinical or radiological presentation. In addition, the presence of *Candida* in sputum or other respiratory specimens mostly represents contamination. A definitive diagnosis of *Candida* pneumonia requires histopathologic proof of lung invasion in association with inflammation. Children can also be affected by pulmonary allergic reactions caused by *Candida* species. Treatment of *Candida* pneumonia is essentially the same as for candidaemia. Preliminary evidence suggests that patients with severe asthma sensitised to *Candida* species may also benefit from antifungal drugs.

© 2009 Elsevier Ltd. All rights reserved.

INTRODUCTION

Invasive fungal infections have markedly grown in importance in recent decades. This has resulted from an increasing number of immunocompromised patients, in addition to aggressive interventions in modern medicine. The majority of fungal infections occurring in the hospital setting are caused by species of *Candida* or *Aspergillus*. Differently from aspergillosis, manifesting mainly as pneumonia in a neutropenic patient, *Candida* species are usually associated with bloodstream infections (candidaemia). Reports of *Candida* pneumonia are rare. Pulmonary candidosis was first described by Aldo Castellani in the early 1900s in adults,¹ with several cases reported since. The frequency of lung involvement in the candidosis is so low that some authors have suggested that this condition does not exist.² The rarity of lung involvement in candidosis has been attributed to a natural resistance of columnar epithelium to *Candida* invasion, in contrast to the greater susceptibility of stratified epithelium. This article provides a brief overview of lung involvement in *Candida* infections, with an emphasis on paediatric patients. However, due to the rarity of these infections, many of the references cited were obtained from

the adult literature. A summary of the main findings discussed in this review is shown in Table 1.

CANDIDA SPECIES ARE NORMAL INHABITANTS OF HUMAN MUCOSAE

Candida species live as commensals on the human skin and mucosae. Humans become colonised by *Candida* very early in life. Although the yeast *C. albicans* is the major agent inciting human mycotic infections, *Homo sapiens* and *Candida* usually coexist peacefully and the dynamics of *Candida* colonisation in humans is more complex than it may seem. Pregnancy, mainly in the last trimester, has been associated with increased growth of yeasts in the vagina, and neonates are thought to acquire *Candida* organisms mainly from the maternal vaginal mucosa. *Candida albicans* is described in vaginal secretions in up to 30% of women at the end of pregnancy³ and about 85% of these patients contaminate their newborns. Caramalac *et al.* (2007)⁴ recently confirmed the higher frequency of oral colonisation by *Candida* species in neonates born via vaginal route, in comparison to those born by caesarean sections (25% versus 3.6%, respectively). However, using molecular typing methods the authors observed genotypic concordance in only 6% of cases, suggesting that the vaginal mucosa was not the main route of transmission of *Candida* organisms to the oral cavity in those neonates. Since multiple sites of colonisation tend to occur in humans, other anatomical sites such as skin folds and the gastrointestinal tract may also be of importance. Interestingly, it

* Serviço de Controle de Infecção Hospitalar, Hospital Dom Vicente Scherer, Santa Casa Complexo Hospitalar. Av. Independência, 155, Porto Alegre, Brazil.
Tel.: +55 51 32148645; Fax: +55 51 32137235.
E-mail address: acpasqualotto@hotmail.com.

Table 1Summary of *Candida*-related lung diseases in paediatric patients.

	Comments
<i>Candida</i> and the respiratory tract	<i>Candida</i> species commonly colonise the respiratory tract, particularly in mechanically ventilated patients and in those treated with steroids or antibiotics
Primary <i>Candida</i> pneumonia	Rare condition that occurs after aspiration of oropharyngeal materials. Definitive diagnosis requires histopathologic proof
Secondary <i>Candida</i> pneumonia	Usually occurs in the context of a bloodstream infection (candidaemia)
Allergies	<i>Candida</i> allergy resulting in respiratory symptoms is far more common than invasive <i>Candida</i> pneumonia
Treatment	Same as for candidaemia. Patients with severe asthma with fungal sensitisation may benefit from steroids and antifungal therapy

has been demonstrated that the mucosal surfaces of the mouth, the gastrointestinal tract, and the vagina may be colonised with *C. albicans* in up to 80% of normal individuals.⁵ Colonisation rate is generally increased in patients admitted to the hospital, and hospitalised children can also acquire *Candida* species (particularly for *C. parapsilosis*) from the hands of healthcare workers.⁶

Host conditions can also facilitate proliferation of *Candida* in the human body. For instance, diabetes mellitus has been associated with a 20% increase rate of oral colonisation and a fourfold increase in the density of oral colonisation by *Candida* species.⁷ Smoking and high ethanol intake have also been associated with an increased prevalence of the yeast in the oropharynx.² Oral colonisation by *Candida* species seems also particularly frequent amongst asthmatic patients, and the rate of colonisation may increase due to medical interventions such as treatment with inhaled steroids.

In addition to the oral mucosa, several other anatomical sites can become colonised by *Candida* species. *Candida* can involve the upper respiratory tract in asthmatics treated with inhaled steroids. *Candida* species have been found in 3–84% of sputum specimens in several studies, depending on the population surveyed and the techniques used for isolation.⁸ In an investigation of the fungal microbiota in the human lung of 159 autopsy cases, yeasts – particularly *Candida* species – were encountered in 33% of lungs showing no evidence of inflammation or any pathology.⁹ The isolation rate of yeasts in cases treated with antimicrobial agents was remarkably higher than in cases not receiving these drugs.

The significance of the recovery of *Candida* species in the sputum or other respiratory specimens is uncertain, but probably represents colonisation only.⁸ The meaning of this finding for immunocompromised patients is less clear. For some patients, *Candida* recovery from the respiratory tract may be a marker for higher severity of illness. In one study of mechanically ventilated children,¹⁰ the recovery of *Candida* species from the respiratory tract was associated with the presence of air leaks and a marker of poor outcome. It remains however to be elucidated if *Candida* infections/colonisation have any role in the aetiology of air leaks in these patients. In a study with cystic fibrosis patients,¹¹ *Candida* colonisation of the respiratory tract was associated with a ~10% reduction in FEV₁ values at all ages, in comparison to controls. This was not observed with either *Staphylococcus aureus* or *Haemophilus influenzae* infections. Tracheobronchial colonisation by *Candida* species has also been implicated as a potential risk factor for ventilated-associated pneumonia by *Pseudomonas aeruginosa* in mechanically ventilated patients, which has been linked to biofilm formation.¹²

CANDIDA SPECIES IN THE BROCHOALVEOLAR LAVAGE (BAL) FLUID IN MECHANICALLY VENTILATED PATIENTS

Candida species are frequently recovered from cultures of tracheal aspirates in intubated patients admitted to a paediatric intensive care unit (ICU). That occurs predominantly in individuals receiving antimicrobial therapy, and in those with a longer duration of mechanical ventilation. A recent study demonstrated

that 20% of intubated patients ventilated for >48 hours had evidence of tracheobronchial *Candida* colonisation.¹³ This proportion increased with the duration of mechanical ventilation to 20%, 31% and 34% after 5, 15 and 30 days, respectively. Therapy with steroids has also been associated with a higher rate of *Candida* pneumonia or colonisation in critically ill patients. Wood *et al.*¹⁴ investigated the clinical meaning of *Candida* spp. isolated from diagnostic BAL cultures in critically ill trauma patients over a 3-year period. The prevalence of positive BAL cultures for *Candida* was 8%. Based on the physician's decision to treat, 92% of episodes were thought to be colonisation only, 3% ventilation-associated pneumonia, and 5% inconclusive. No patient developed a systemic *Candida* infection, despite the lack of antifungal therapy. Accordingly, current guidelines for both ventilation-associated pneumonia and *Candida* infections recommend that the isolation of *Candida* spp. from BAL in immunocompetent patients should not trigger antifungal treatment. However, a study showed that 24% of ICU physicians would prescribe antifungal therapy for an immunocompetent, mechanically ventilated patient with *Candida* spp. isolated from a tracheal aspirate.¹⁵ This over treatment can increase costs, toxicity and drug-drug interactions, potentially increasing the risk for antifungal resistance to occur.

At least 2 post-mortem studies have demonstrated that *Candida* recovery from the respiratory tract in non-neutropenic patients does not correlate with the histopathologic findings.^{16,17} In one of these studies,¹⁶ *Candida* was isolated from 40% of pulmonary biopsies, but definite *Candida* pneumonia was diagnosed in only 1 patient (4%) (1 additional patient had *Candida* isolated from the pleural fluid). *Candida* colonisation was found to be uniform throughout different regions of the lung. Quantitative BAL cultures for *Candida* were also not helpful to differentiate colonisation from infection.¹⁶ This contrasts with bacterial infections in which several thresholds have been proposed to help distinguish colonisation from infection.

In summary, the isolation of *Candida* from cultures of sputum, endotracheal aspirates, and bronchoscopic samples, may only represent colonisation of the tracheobronchial tree. The meaning of a positive culture for *Candida* in a severely immunosuppressed patient is however more obscure.

HISTOPATHOLOGIC PROOF IS REQUIRED TO DIAGNOSE CANDIDA PNEUMONIA

Histologic demonstration of the fungus in lung tissue with associated inflammation is the only widely accepted criterion for the definitive diagnosis of *Candida* pneumonia.^{8,18,19} Although used in several studies, the definitions for nosocomial infections established by the Centers for Disease Control and Prevention (CDC) are not appropriate for the diagnosis of *Candida* pneumonia. Due to the high frequency of *Candida* colonisation of mucosae, diagnoses of *Candida* pneumonia that are based solely on microbiological grounds are often incorrect. Additionally, it should be stated that a transbronchial approach is not satisfactory as histopathologic proof, owing to the possibility of oropharyngeal contamination of the specimens. Although BAL cytology has been

reported to improve the diagnostic yield, cytological tests are prone to a high rate of false-positive results due to *Candida* colonisation and therefore not recommended.

Percutaneous thin-needle aspiration biopsy of the lung has been proposed by some authors as a diagnostic tool in immunocompromised patients with lung infiltrates.²⁰ This procedure seems to be associated with a low yield (~30%) in the diagnosis of *Candida* pneumonia, with the potential for complications including air leak and bleeding. No iatrogenic complications occurred in another series in which children with malignancy were submitted to transthoracic lung puncture for the investigation of lung infections.²¹ Patients with platelet count $<50,000/\text{mm}^3$ were transfused platelet concentrates before and during the procedure. However, only one case of *C. tropicalis* pneumonia was included in this series. Due to the rarity of *Candida* pulmonary infections, diagnostic strategies have not been systematically evaluated, neither have the results obtained by initial reports been confirmed by multiple studies. Furthermore, biopsies cannot be performed in many patients due to severe illness and conditions such as thrombocytopaenia, commonly present in haematological patients at high risk for candidaemia. Even when pulmonary fragments are obtained false-negative results can occur due to sampling errors.

The morphology of *Candida* lesions in the lungs is varied. Grossly, bronchopneumonia, abscesses, granulomas, and intracavitary membranous exudates have all been described.²² Invasion and occlusion of large vessels – a finding frequently seen in cases of invasive aspergillosis – rarely occur in pulmonary candidosis. The presence of mycelial forms does not seem to provide good evidence of tissue invasion by *Candida*.

MAIN FORMS OF CANDIDA PNEUMONIA

Candida pneumonia seems to exist in two distinct forms. Primary *Candida* pneumonia is a rare condition that occurs after aspiration of oropharyngeal materials. Secondary *Candida* pneumonia is by far the most frequent form of pulmonary candidosis.²³ This usually occurs in the context of a bloodstream infection (candidaemia), following a gastrointestinal tract or cutaneous source. Cases of secondary pneumonia are often the result of fungal emboli to the lungs along with multiple other organs. Although it has been suggested that the route of infection can be deduced on the basis of its histopathologic features,²² these aspects may not be present in every case, and identification of the route of infection in individual cases may be problematic.²⁴ Despite this criticism, classical presentations of both forms of *Candida* pneumonia are briefly discussed here.

Independently of the mechanism involved in the disease, the signs and symptoms associated with *Candida* pneumonia are not specific and the clinical picture is usually dominated by the presence of sepsis.²² Features of respiratory distress syndrome and severe sepsis seem to be frequent amongst infants.²⁵ Rare cases of *Candida* empyema have also been reported, usually in lung transplant recipients or in the presence of surgical drains or chest tubes. *Candida* alone rarely involves enough parenchyma to compromise pulmonary function. The rare cases of extensive involvement are usually attributable to aspiration of *Candida* and occur in patients who are critically ill for a variety of other reasons.

The radiographic appearances of *Candida* pneumonia are also non-specific. It is noteworthy that *Candida* may cause pneumonia, either alone or in combination with other fungi, and bacterial pathogens,^{20,23} which may complicate the interpretation of radiological exams. The radiographic pattern can however be useful in excluding as well as including differential possibilities and can be correlated with bronchoscopic or lung biopsy findings. It is unusual to find a normal chest radiograph,²³ and the paucity of radiological findings in some studies may be attributed to technical

problems associated with portable examinations as those performed in some critically ill patients.^{23,25} Other unusual presentations of *Candida* pneumonias include cavitations and fungal balls. All of these features make the diagnosis of *Candida* pneumonias by chest radiograph difficult at best.

Primary *Candida* pneumonia

As the mechanism of primary *Candida* pneumonia involves aspiration, lesions are usually distributed with clusters of pseudohyphae and/or yeasts around the bronchioles. Necrosis and intra-alveolar haemorrhage are common findings, and acute inflammation with associated bronchopneumonia and abscess formation has also been reported. In the series by Haron *et al.*¹⁸ patients with *Candida* pneumonia associated with aspiration were identified by excluding those individuals with associated candidaemia and disseminated infection. The concomitant presence of oesophageal candidosis in some patients supported aspiration of oropharyngeal contents as the proposed mechanism of entry of the infection. Accordingly, the lungs were the only organs involved at autopsy, and a high percentage of intra-bronchial and intra-alveolar involvement by *Candida* was found. No vascular invasion was observed. *Candida* pneumonia directly contributed to the death of 84% of the cancer patients included in this series.

Colonisation of the upper respiratory tract by *Candida* species is frequently seen in cases of primary *Candida* pneumonia, sometimes with ulcerated mucosal surfaces.²⁵ From these sites *Candida* organisms can spread down the airways and to invade terminal air spaces. Grossly, these lungs can show areas of consolidation and haemorrhage. Microscopically, a thick mat of *Candida* pseudohyphae line the conducting airways, bronchioles, and terminal air spaces, ulcerating the mucosal surfaces and invading adjacent tissues. *Candida* organisms are occasionally seen in pulmonary veins and lymphatics but not in the pulmonary arteries.

The radiological findings of primary *Candida* pneumonia are typically those of patchy bilateral consolidation in a peribronchovascular distribution. Air bronchograms and obscuration of a cardiac border or hemidiaphragm are additional non-specific findings. The parenchymal consolidations are frequently basilar, bilateral, and rarely localised to one segment. Endobronchial spread of the fungi from an initial focus to other sites within the same lung or the contra-lateral lung is another potential source of airway dissemination. This can lead to a nodular pattern in the newly infected lung, although proliferation in the pulmonary parenchyma is rare in any clinical setting. Early in the course of disease the affected sites may be difficult to distinguish from the radiographic findings often seen with haematogenous pulmonary seeding (discussed below). With time and with further endobronchial spread of the organisms the nodules may coalesce to the more diffuse pneumonic aspect.²³

Haematogenous (secondary) pulmonary candidosis

Pulmonary inoculation of *Candida* species can occur during haematogenous spread of these organisms from a distant site. This usually initiates in the gastrointestinal tract – as an example, the typical neutropenic patient with extensive mucositis, receiving therapy with antibiotics and steroids; or the patient submitted to gastrointestinal operation. Alternatively, *Candida* can disseminate from the skin, which is facilitated by the use of central venous catheters. Regardless of the source, *Candida* can spread to virtually infect any organ in the body, including small arterioles and capillaries in both lungs. With fungal growth and invasion of the adjacent pulmonary tissue, a miliary nodular pattern can be seen.²⁰ This is usually manifested as small (2 to 4 mm) nodules or multiple larger nodules with ill-defined borders which are randomly

distributed in the pulmonary parenchyma. These nodules are characterised by areas of central necrosis with varying amounts of acute inflammation. The centre of the nodules usually contains clusters of both pseudohyphae and budding yeasts. In a recent study,²⁶ including 17 haematopoietic stem cell transplant recipients with pulmonary candidosis, multiple nodules varying in size from 3–30 mm were the most common abnormalities (88%). Consolidation was found in 65% of cases,²⁶ and this is usually a manifestation of more advanced disease. In some patients the miliary nodular radiographic pattern may be a pre-terminal event related to inability to control the infection.²³

Mediastinal and/or hilar adenopathy, when present, are usually secondary to metastases and not fungal lymphadenitis.²⁰ Pleural effusions may be present in approximately half of patients, but are usually related to either concomitant bacterial infections of the pleural space, pleural metastases, or cardiac failure.²³

Humphrey and Weiner²⁴ found evidence of invasive gastrointestinal candidosis in all 9 cases of pulmonary candidosis identified at autopsy (3 of which were children). Debilitating underlying diseases and broad-spectrum antibacterial drugs had been used for all of these patients; other important risk factors were therapy with steroids (77.8%) and neutropaenia (44.4%). The majority of patients showed extensive pulmonary infiltrates (88.9%) and *Candida* was cultured from ante-mortem specimens in only 55.5%.

The manifestations of pulmonary candidosis at high-resolution computed tomography have recently been described, in comparison with patients with invasive aspergillosis.²⁶ Centrilobular nodules were significantly more common in aspergillosis (96%) than in candidosis (52%). On the contrary, random nodules were significantly more common in patients with candidosis (48%) than in individuals with aspergillosis (4%), suggesting the possibility of haematological dissemination in the first group. As expected, consolidation was more common in aspergillosis (84%) than in candidosis (50%).

INCIDENCE AND POTENTIAL RISK FACTORS FOR CANDIDA PNEUMONIA

The real incidence of *Candida* pneumonia is hard to determine, in many studies histopathologic proof was not required to diagnose this condition. Most of the reports were based on persistent isolation of *Candida* from the sputum in the absence of other likely pathogens.²² This sort of association was the basis for Rosen von Rosenstein's original suggestion in 1771 that *Candida* was a respiratory pathogen, and for Castellani's report in early 1900s of an occupational disease of tea tasters in Ceylon.¹ Data from several studies including different populations show an incidence varying from 0.23–4.5%.^{18,22} Most of these reports included cases where the lungs were involved in the context of a disseminated infection (secondary *Candida* pneumonia), and information concerning *Candida* pneumonia in non-neutropenic patients is even more limited.

Definitive evidence of pulmonary involvement by *Candida* species is best obtained in studies in which autopsies were performed. Reviewing paediatric autopsy records, Kassner *et al.*²⁵ found 14 infants with significant pulmonary involvement associated with systemic candidosis. In a series of 149 autopsies in patients who had undergone haematopoietic stem cell transplantation,²⁷ 9 cases of *Candida* pneumonia were described. In addition to the lungs, the most frequent sites of *Candida* involvement were the gastrointestinal tract ($n = 15$), the kidneys ($n = 7$), and the heart ($n = 6$). Only 30 cases of suspected *Candida* pneumonia were described in a large series involving 2 hospitals in New York City.²² The study included data from all lung biopsies performed during a 4 year-period, in addition to 1,960 autopsies. The majority of the

patients with *Candida* pneumonia had leukaemia or lymphoma (73.3%), and 80% of patients had had neutropaenia for >10 days. Half of patients had been treated with high doses of corticosteroids and has pulmonary infiltrates. Only one patient had biopsy-proven *Candida* pulmonary infection. The main routes of infection were considered to be aspiration (53.3%), haematogenous spread to the lungs (33.3%) or unknown (13.3%). Blood cultures were positive for *Candida* in only 23.3% of patients. For almost all patients, there was little clinical significance for *Candida* pulmonary involvement. For instance, amongst 61 post-mortem lung cultures that were positive for *Candida* species, *Candida* was seen histologically in only 3. Consequently, experience from several centres supports the view that *Candida* is rarely seen histologically in lung aspirates or biopsy specimens.

In addition to premature infants (discussed further in this review), pulmonary *Candida* infections seem to particularly affect immunosuppressed patients with AIDS, patients with chronic granulomatous diseases, transplant recipients, and patients with malignancies. Candidosis is far less common than invasive aspergillosis in chronic granulomatous disease patients – *Candida* species are isolated in about 2% of cases of pneumonia in these patients.²⁸ In lung transplant recipients, *Candida* species can colonise and invade necrotic tissues and bronchial anastomoses. Accordingly, it has been recommended that the isolation of *Candida* from a patient with pulmonary infiltrates after lung transplantation should not be dismissed as benign colonisation.²⁹ Nevertheless, histological confirmation is also required to prove invasive disease.

Several investigators have also emphasized the particular importance of endotracheal intubation as a risk factor for disseminated *Candida* infections in paediatric patients.^{30,31} We have previously demonstrated that children are more commonly exposed to mechanical ventilation before candidaemia than adult patients.³¹ Also, the risk associated with intubation seems to increase with the number of days and with *Candida* colonisation of the tube. It remains to be elucidated however if endotracheal intubation is an independent risk factor for *Candida* pneumonia. It is also unknown what the risk for *Candida* dissemination from the lungs is in these patients.

MAIN CANDIDA SPECIES INVOLVED

Most of the reports so far have implicated *C. albicans* as the agent of *Candida* pneumonia. This may just reflect the predominance of *C. albicans* over other *Candida* species as the aetiology of invasive candidosis, including candidaemia. Apparently, there is no clinical or pathologic evidence for any differences amongst the *Candida* species with regard to their potential to cause pulmonary lesions.

Recent studies have reinforced the growing importance of *C. parapsilosis* in paediatric patients. Candidaemia caused by *C. parapsilosis* is more frequently found in children than in adults.³¹ In contrast, paediatric patients are less frequently infected by *C. glabrata*, which tends to infect adults.³¹ Invasive infections caused by *C. parapsilosis* have been associated with the use of central venous catheters and parenteral nutrition, often required in the immunocompromised paediatric population. Candidaemia was also found to be more persistent in children when compared to adults.³¹ Disseminated *Candida* infection to the central nervous system is also more frequent in children (11.4%) than in adults (0.8%).³² The reasons for these are poorly understood. Accordingly, it is also unclear if disseminated conditions such as secondary *Candida* pneumonia occur more frequently in children than in adults, although there is a suggestion that this may happen. Whilst the prognosis of candidaemia has been shown to be better for children than for adults,^{30,31} the same is unknown for *Candida* pneumonias.

Since the majority of cases of *Candida* pneumonia occur secondarily to a disseminated candidosis, the detection of *Candida* species in the blood may potentially diagnose pulmonary involvement by *Candida* at an early stage. Although blood culture is still the standard test for the diagnosis of candidaemia, it has to be said that the sensitivity of blood cultures for detection of *Candida* can be as low as 50%. The use of other diagnostic tests, including biochemical markers, antigen assays, and polymerase chain reaction, is currently limited but remains under active investigation. More sensitive and reliable diagnostic tests are required to more promptly diagnose invasive *Candida* infections.

PARTICULARITIES OF CANDIDA PNEUMONIA IN NEONATES

Invasive candidosis has become the third most common late-onset infection in most neonatal ICUs. The risk factors for invasive *Candida* infections in neonatal patients differ from those of older children. Birth weight is a particularly important variable. For instance, in one study the odds for developing candidosis were 3.22 for infants with a birth weight of 400–750 grams, compared with those infants born at 751–1,000 grams.³³ Data from another study revealed that multiple risk factors put neonates at risk for candidaemia, including gestational age <32 weeks, Apgar score of <5 at 5 minutes, shock, exposure to more than two antibiotics, parenteral nutrition for >5 days, use of intravenous lipids for >7 days, presence of a central catheter, exposure to an H2 blocker, length of stay in a neonatal ICU >7 days, and intubation.⁶ A more recent survey confirmed that, independent of birth weight, gestational age <26 weeks and a history of abdominal surgery significantly increased the risk of candidaemia for neonates.³⁴

Interestingly, the majority of babies were born at term (81.0%) in a review of 21 neonates with pulmonary candidosis.³⁵ Symptoms usually appeared at birth or within the first 4 weeks of life. Radiological signs were non-specific, and pleural effusion was uncommon. Of note, symptoms of pneumonia were usually preceded or accompanied by oral thrush (71.4%), suggesting that aspiration could be an important mechanism for *Candida* pneumonia amongst neonates. This may have occurred at birth or due to the presence of foreign bodies (endotracheal or pleural drainage tube).

Congenital pulmonary candidosis (i.e., an infection that is evident at birth or soon afterward) has also been described. This has usually been attributed to vaginal contamination or *Candida* amnionitis resulting from premature rupture of the membranes, even though the membranes were described as intact in several of the reported cases.²⁵ Whilst this process tends to be limited to the skin in healthy-term infants, a cutaneous infection may become invasive and produce acute disseminated candidosis in premature neonates or infants with low birth weight and prolonged rupture of cutaneous membranes.¹⁹

ALLERGIES ASSOCIATED WITH CANDIDA SPECIES

Over the past forty years the rates of allergy and asthma have markedly increased in the Western world, which seem to correlate with a higher use of antibiotics in clinical practice, by promoting changes in the faecal microbiota.³⁶ Antibacterial drugs can facilitate overgrowth of *Candida* species, which in turn can secrete potent prostaglandin-like immune response modulators. Even though *Candida* species may contain several antigenic components capable of stimulating immediate hypersensitivity responses, it is controversial whether the inhalation of these fungi is causative for their allergenicity.³⁷

Prevalence of type I allergy to *Candida* in the general population is about 8.5%; in atopics, it ranges from 23–44%.³⁸ Similarly, 25–87% of patients with atopic dermatitis show specific IgE reaction

against *C. albicans*.³⁹ Earlier studies found that sensitisation to this yeast was associated with chronic asthma and rhinitis, atopic dermatitis, and nasal polyps. The association between cutaneous fungal infections and worsening of asthma symptoms has also long been described. In a recent study of patients with severe asthma, sensitivity to *Candida albicans* occurred in 10% of patients with no hospital admissions and 33% for patients with >1 admission to the hospital.⁴⁰ Allergic patients with respiratory symptoms frequently react to *Alternaria* and *Candida* species.³⁸ Although younger patients seem to be more at risk for *Alternaria* sensitisation, *Candida* allergy seems to particularly affect young adult women. Accordingly, an association between recurrent vaginal candidosis and allergic rhinitis has been proposed.⁴¹

Atopic patients primarily sensitised by yeasts may develop allergic symptoms by exposure to other environmental yeasts due to cross-reacting IgE antibodies. It is well known that a subgroup of allergic bronchopulmonary aspergillosis (ABPA) patients also demonstrate IgE reaction against *Candida* species. The term 'allergic bronchopulmonary mycosis' has been proposed to group patients reacting not only to *Aspergillus*, but to different fungi including *Candida* species. Curiously, most cases of 'allergic bronchopulmonary candidosis' (69%) have a late onset of respiratory symptoms, usually after the age of 30 years.⁴² In another study, patients who were monosensitised to *C. albicans* were significantly older (58.4 years) than controls monosensitised to different airborne allergens (29.9 years).⁴³ This suggests that long-term exposure to the yeast is needed for sensitisation to occur. In a survey of 76 cystic fibrosis patients,⁴⁴ all patients sensitised to *C. albicans* (27%) showed a concomitant sensitisation to *A. fumigatus*, suggesting that IgE to *C. albicans* may be an immunologic marker related to the development of ABPA in patients with cystic fibrosis.

TREATMENT

No convincing data for any particular form of therapy exist for *Candida* pneumonias.¹⁹ Most of the available information is anecdotal and originated from case reports or small series of patients. In cases of secondary pneumonia associated with haematogenously disseminated infection, therapy directed at disseminated candidosis, rather than at *Candida* pneumonia in particular, is indicated. Although varied intrapulmonary penetration has been reported amongst currently available antifungal drugs,⁴⁵ the clinical meaning of these findings is controversial.

Immunotherapy with fungal extracts may become a therapeutic option in the future for the treatment of fungal allergies.³⁷ A recent placebo-controlled study has shown the benefit of antifungal treatment in patients with severe asthma and fungal sensitisation.⁴⁶ The majority of these patients had high titres of specific IgE against *C. albicans*, and a marginal benefit of antifungal therapy was also demonstrated to these patients. More research is clearly needed in the field.

CONFLICT OF INTEREST

In the past 5 years, Dr Pasqualotto has received grant support from Pfizer, Merck, CAPES, CNPq, The Fungal Research Trust, Sigma-Tau and Myconostica. He has been a speaker to or has received travel grants from Pfizer, Schering-Plough (now Merck), United Medical, Biometrix, Merck, and Bago.

REFERENCES

1. Castellani A. Observations on the fungi found in tropical bronchomycosis. *Lancet* 1902; 179: 13–15.

2. Cunha BA. Historical, physical, and laboratory clues to the diagnosis of pneumonia. In: Karetzky M, Cunha BA, Brandstetter RD, eds: *The Pneumonias*. Springer-Verlag: New York, 1993; pp. 106–144.
3. Blasschke-Hellmessen R. Vertical transmission of *Candida* and its consequences. *Mycoses* 1998; **41**: 31–36.
4. Caramalac DA, da Silva Ruiz L, de Batista GC, Birman EG, Duarte M, Hahn R et al. *Candida* isolated from vaginal mucosa of mothers and oral mucosa of neonates: occurrence and biotypes concordance. *Pediatr Infect Dis J* 2007; **26**: 553–557.
5. Gorbach SL, Nahas L, Lerner PI, Weinstein L. Studies of intestinal microflora. I. Effects of diet, age, and periodic sampling on numbers of fecal microorganisms in man. *Gastroenterology* 1967; **53**: 845–855.
6. Saiman L, Ludington E, Dawson JD, Patterson JE, Rangel-Frausto S, Wiblin RT et al. Risk factors for *Candida* species colonization of neonatal intensive care unit patients. *Pediatr Infect Dis J* 2001; **20**: 1119–1124.
7. Tapper-Jones LM, Aldred MJ, Walker DM, Hayes TM. Candidal infections and populations of *Candida albicans* in mouths of diabetics. *J Clin Pathol* 1981; **34**: 7060–7061.
8. Baum GL. The significance of *Candida albicans* in human sputum. *N Engl J Med* 1960; **263**: 70–73.
9. Okudaira M, Kurata H, Sakabe F. Studies on the fungal flora in the lung of human necropsy cases. A critical survey in connection with the pathogenesis of opportunistic fungus infections. *Mycopathologia* 1977; **61**: 3–18.
10. Briassoulis GC, Venkataraman ST, Vasilopoulos AG, Sianidou LC, Papadatos JH. Air leaks from the respiratory tract in mechanically ventilated children with severe respiratory disease. *Pediatr Pulmonol* 2000; **29**: 127–134.
11. Navarro J, Rainisio M, Harms HK, Hodson ME, Koch C, Mastella G et al. Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. *Eur Respir J* 2001; **18**: 298–305.
12. Ader F, Faure K, Guery B, Nseir S. *Pseudomonas aeruginosa* and *Candida albicans* interaction in the respiratory tract: from pathophysiology to a therapeutic perspective. *Pathol Biol (Paris)* 2008; **56**: 164–169.
13. Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR et al. Outcomerea Study Group. *Candida* colonization of the respiratory tract and subsequent *Pseudomonas* ventilator-associated pneumonia. *Chest* 2006; **129**: 110–117.
14. Wood GC, Mueller EW, Croce MA, Boucher BA, Fabian TC. *Candida* sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients. *Intensive Care Med* 2006; **32**: 599–603.
15. Azoulay E, Cohen Y, Zahar JR, Garrouste-Orgeas M, Adrie C, Moine P et al. Practices in non-neutropenic ICU patients with *Candida*-positive airway specimens. *Intensive Care Med* 2004; **30**: 1384–1389.
16. el-Ebiary M, Torres A, Fàbregas N, de la Bellacasa JP, González J, Ramirez J et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. *Am J Respir Crit Care Med* 1997; **156**: 583–590.
17. Rello J, Esandi ME, Diaz E, Mariscal D, Gallego M, Valles J. The role of *Candida* spp. isolated from bronchoscopic samples in non-neutropenic patients. *Chest* 1998; **114**: 146–149.
18. Haron E, Vartivarian S, Anaissie E, Dekmezian R, Bodey G. Primary *Candida* pneumonia. *Medicine (Baltimore)* 1993; **72**: 137–142.
19. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; **38**: 161–189.
20. Samuels BI, Pagani JJ, Libshitz HI. Radiologic features of *Candida* infections. In: Bodey GP, ed: *Candidiasis – Pathogenesis, Diagnosis and Treatment*. 2nd Edition. USA: Raven Press; pp. 137–157.
21. Kumar KG, Bakhshi S, Samantaray JC, Banerjee U, Arya LS. Transthoracic lung aspiration in etiology of pneumonia. *Indian J Pediatr* 2004; **71**: 129–132.
22. Masur H, Rosen PP, Armstrong D. Pulmonary disease caused by *Candida* species. *Am J Med* 1977; **63**: 914–925.
23. Pagani JJ, Libshitz HI. Opportunistic fungal pneumonias in cancer patients. *AJR Am J Roentgenol* 1981; **137**: 1033–1039.
24. Humphrey DM, Weiner MH. Candidal antigen detection in pulmonary candidiasis. *Am J Med* 1983; **74**: 630–640.
25. Kassner EG, Kauffman SL, Yoon JJ, Semiglia M, Kozinn PJ, Goldberg PL. Pulmonary candidiasis in infants: clinical, radiologic, and pathologic features. *AJR Am J Roentgenol* 1981; **137**: 707–716.
26. Franquet T, Muller NL, Lee KS, Oikonomou A, Flint JD. Pulmonary candidiasis after hematopoietic stem cell transplantation: thin-section CT findings. *Radiology* 2005; **236**: 332–337.
27. Wakayama M, Shibuya K, Ando T, Oharaseki T, Takahashi K, Naoe S et al. Deep-seated mycosis as a complication in bone marrow transplantation patients. *Mycoses* 2002; **45**: 146–151.
28. Winkelstein JA, Marino MC, 155–169.
29. Nicod LP, Pache JC, Howarth N. Fungal infections in transplant recipients. *Eur Respir J* 2001; **17**: 133–140.
30. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* 2003; **37**: 634–643.
31. Pasqualotto AC, Nedel WL, Machado TS, Severo LC. A 9-year study comparing risk factors and the outcome of paediatric and adults with nosocomial *Candida*emia. *Mycopathologia* 2005; **160**: 111–116.
32. Krupova Y, Sejnova D, Dzatková J, Kaiserova E, Kiskova M, Babela R et al. Prospective study on fungemia in children with cancer: analysis of 35 cases and comparison with 130 fungemias in adults. *Support Care Cancer* 2000; **8**: 427–430.
33. 712–718.
34. Shetty SS, Harrison LH, Hajjeh RA, Taylor T, Mirza SA, Schmidt AB et al. Determining risk factors for candidemia among newborn infants from population-based surveillance: Baltimore, Maryland, 1998–2000. *Pediatr Infect Dis J* 2005; **24**: 601–604.
35. Patriquin H, Lebowitz R, Perreault G, Yousefzadeh D. Neonatal candidiasis: renal and pulmonary manifestations. *AJR Am J Roentgenol* 1980; **135**: 1205–1210.
36. Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol* 2004; **12**: 562–568.
37. Simon-Nobbe B, Denk U, Poll V, Rid R, Breitenbach M. The Spectrum of Fungal Allergy. *Int Arch Allergy Immunol* 2008; **145**: 58–86.
38. Mari A, Schneider P, Wally V, Breitenbach M, Simon-Nobbe B. Sensitization to fungi: epidemiology, comparative skin tests, and IgE reactivity of fungal extracts. *Clin Exp Allergy* 2003; **33**: 1429–1438.
39. Faergemann J. Atopic dermatitis and fungi. *Clin Microbiol Rev* 2002; **15**: 545–563.
40. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. *BMC Pulm Med* 2005; **5**: 4.
41. Moraes PS. Recurrent vaginal candidiasis and allergic rhinitis: a common association. *Ann Allergy Asthma Immunol* 1998; **81**: 165–169.
42. Sandhu RS, Mehta SK, Khan ZU, Singh MM. Role of *Aspergillus* and *Candida* species in allergic bronchopulmonary mycoses. A comparative study. *Scand J Respir Dis* 1979; **60**: 235–242.
43. Asero R, Bottazzi G. Clinical features of patients showing *Candida* hypersensitivity: an observational study. *J Invest Allergol Clin Immunol* 2004; **14**: 309–311.
44. Maiz L, Cuevas M, Quirce S, Cañón JF, Pacheco A, Sousa A et al. Serologic IgE immune responses against *Aspergillus fumigatus* and *Candida albicans* in patients with cystic fibrosis. *Chest* 2002; **121**: 782–788.
45. Paterson PJ, Seaton S, Prentice HG, Kibbler CC. Treatment failure in invasive aspergillosis: susceptibility of deep tissue isolates following treatment with amphotericin B. *J Antimicrob Chemother* 2003; **52**: 873–876.
46. Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitisation (SAFS), the FAST study. *Am J Resp Crit Care Med* 2009; **179**: 11–18.