Review article

Central nervous system infections by members of the *Pseudallescheria boydii* species complex in healthy and immunocompromised hosts: epidemiology, clinical characteristics and outcome

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Summary

Infections caused by members of the *Pseudallescheria boydii* species complex are currently among the most common mould infections. These fungi show a particular tropism for the central nervous system (CNS). We reviewed all the available reports on CNS infections, focusing on the geographical distribution, infection routes, immunity status of infected individuals, type and location of infections, clinical manifestations, treatment and outcome. A total of 99 case reports were identified, with similar percentage of healthy and immunocompromised patients (44% vs. 56%; $P = 0.26$). Main clinical types were brain abscess (69%), co-infection of brain tissue and/or spinal cord with meninges (10%) and meningitis (9%). The mortality rate was 74%, regardless of the patient's immune status, or the infection type and/or location. Cerebrospinal fluid culture was revealed as a not very important tool as the percentage of positive samples for *P. boydii* complex was not different from that of negative ones (67% vs. 33%; $P = 0.10$). In immunocompetent patients, CNS infection was preceded by near drowning or trauma. In these patients, the infection was characterised by localised involvement and a high fatality rate (76%). In contrast, CNS infection in immunocompromised patients was presented as rapidly progressive disseminated lesions at various degrees of evolution. Major risk factors for CNS infection were the aspiration of polluted water in near-drowning episodes in immunologically intact patients and medical immunosuppression in the remaining patient groups. As the therapeutic options were poor, the treatment was difficult in general and the prognosis was poor.

Key words: *Scedosporium apiospermum*, *Pseudallescheria boydii*, central nervous system infections, brain abscess, cerebral infections, fungal meningitis, near-drowning.

Introduction

The members of the *Pseudallescheria boydii* species complex can be commonly found in soil, sewage, mud, and the polluted waters of streams and ponds with still water.[1] Currently, the species of this complex are, after *Aspergillus*, one of the most prevalent moulds causing human infections. Recent molecular studies have demonstrated that *P. boydii* is a complex that includes several phylogenetic species[2] and that *S. apiospermum*, traditionally considered as the anamorph (asexual state of *P. boydii*), and *P. boydii* are two different species.[3] However, since the degree of involvement of which individual species in human infections has not been determined, the present review will use the name *P. boydii* complex. Several sites of *P. boydii* complex infection have been described in both immunocompromised and

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immunocompetent individuals. Among them, an increasing number of cases of CNS infections have been reported. In the literature, there are a few restricted reviews on CNS infections caused by *P. boydii* complex each covering a special subgroup associated with some particular conditions or patient populations.[4–10] However, many aspects of *P. boydii* complex CNS infections, including the risk factors and underlying conditions, route of entry and systemic spread, pathogenesis, diagnostic factors, management and outcome remain poorly understood. In this study, overall case reports have been reviewed chronologically to provide a global insight into CNS infections focusing on geographic diversity, incidence, infection routes, immune status of infected individuals, type and location of infections, clinical manifestations, treatment and outcome. This review summarises the overall impact and highlights the key features of CNS infections caused by *P. boydii* complex.

Methods

Literature search

A computerised search of the MEDLINE database (National Library of Medicine, Bethesda, MD, USA) was performed for cases reported in the literature between 1948 and mid-2007, with (by cross-referencing) the terms '*Pseudallescheria boydii*' and '*Scedosporium apiospermum*', 'cerebral', 'brain abscess', 'meningitis', 'central nervous system infection', 'disseminated' and 'near-drowning'. Additional search terms included were '*Allescheria boydii*,' '*Monosporium apiospermum*,' and '*Petriellidium boydii*' as referring to prior or other nomenclature for this fungus. These key words were used alone and/or in combination with an 'and' statement. Additional cases were obtained by scanning the references cited in the original articles. Original full texts of all the relevant articles were obtained via MEDLINE, TUBITAK-ULAK-BIM (Turkish Academic Network and Information Center), or personal communication of the authors and/or other international libraries and were used for the analysis.

Cases were included in the study when the presence of lesion and clinical syndrome consistent with CNS infection was documented and *P. boydii* complex was recovered from the lesion, usually from the brain tissue, CSF or aspirate from an abscess. One disseminated case with CNS infection, but in which *P. boydii* complex was isolated from vitrectomy material[11] and a metastatic case diagnosed based on head computed tomography (CT) in the setting of disseminated pseudallescherial disease[12] were also included.

Definitions

Infection types that refer to a single site involvement such as brain abscess or panencephalitis were evaluated and categorised as reported by the authors. Duplicate publications were excluded and follow-up reports were regarded as associated with a single case together with the previous report. The following data were picked up for each patient, if stated: age and gender, geographical location; predisposing factors, including underlying diseases and associated medical conditions, clinical symptoms, white blood cell count (WBC) and differential cell counts of CSF samples, mode and time to diagnosis, other pathogens isolated or observed in specimens if any, antimicrobial agents administered, regimens and duration of antifungal therapy, invasive or surgical procedures, duration of hospitalisation and patient outcome.

Statistical analysis

Categorical variables were analysed by chi-squared or Fisher exact tests. $P \leq 0.05$ was considered to be statistically significant.

Results

The first report of *P. boydii* complex CNS infection was by Benham *et al.* [13]. After this, further 98 cases have been described. Of those, 96 were detailed individually,[4–6,14–90] and three were summarised in general reports on CNS aspergillosis,[91] brain abscesses following marrow transplantation,[92] and treatment of central nervous system fungal infections.[93] Recurrence of CNS infection was documented in one case.[15] A metastatic case because of possible reactivation of a latent infection during immunosuppressive therapy was reported on one occasion.[69] A further possible case of reactivated latent infection as a result of endogenous colonisation in the setting of increased immunosuppression was also reported in a heart transplant farmer who was frequently exposed to soil and manure.[57]

Demographic and geographic features

Most of the 99 cases were reported from America (67/99, 68%), primarily from the United States (61/99, 62%) followed by Germany (5/99, 5%), France (4/99,

Table 1 Frequency and geographical distribution of the cases of CNS infection by *Pseudallescheria boydii* complex

Country	*n* (%)
USA	61 (62)
Canada	3 (3)
Argentin	1 (1)
Brazil	1 (1)
Trinidad	1 (1)
Germany	5 (5)
France	4 (4)
Italy	2 (2)
Spain	2 (2)
Austria	1 (1)
Belgium	2 (2)
Greece	1 (1)
Swizerland	1 (1)
UK	1 (1)
South Africa	1 (1)
China	1 (1)
India	2 (2)
Nepal	1 (1)
Japan	1 (1)
Lebanon	1 (1)
Malaysia	1 (1)
Taiwan	2 (2)
Thailand	2 (2)
Papua New Guinea	1 (1)

4%), and Canada (3/99, 3%). Sporadic cases were reported in 20 other countries (Table 1). Of those, 32 (32%) were female, 68 (69%) male and gender was not indicated in one case.[94] Age range was from 16 months to 77 years (Fig. 1, Table 2).

Predisposing factors, underlying conditions

Forty-four patients (44%) were previously healthy and 55 (56%) had one or more underlying diseases and/or predisposing factors. Twenty-four of the previously healthy patients (24/44, 55%) had a history of aspiration of polluted water in association with near drowning, including a tsunami survivor,[84] or motor vehicle accidents.[51–53] In 18 cases (18/44, 50%), the infection was disseminated. In the patient group associated with aspiration of polluted water, seven cases were disseminated (7/24, 29%). An unusual disseminated case was described in an immunocompetent host who was not near drowned.[59] Nine of the previously healthy patients were posttraumatic cases (10/44, 23%), and five of them were disseminated (5/10, 50%). Fifty-five patients (55/99, 56%) had one or more underlying disease and/or predisposing factor. Of those, 20 (37%) cases occurred in transplant recipients, 16 being solid organ transplant recipients. Dissemination was similarly frequent in immunocompromised and immunocompetent patients (71% vs. 50%; $P = 0.32$). Apparent major risk factors for CNS infection were: aspiration of polluted water in near drowning episodes in immunologically intact patients and medical immunosuppression in the remaining patient groups (Fig. 2; Table 2).

Cases following near drowning

Near downing, an unexpected submersion episode related to accidental death, is a common cause of pulmonary and neurological damage and infection is a potential life-threatening complication.[94] *P. boydii* complex infections associated with near drowning, were reported in 25 cases.[5,10,26,28,30,33–35,44,49,51,53,55,60,67,68,72,76,80,83–87,95] The first reported case, by Van der Vliet [95], reports that infection was acquired because of cadaveric organ transplantation from a near drowned infected donor to two kidney recipient patients, one with a fatal outcome.

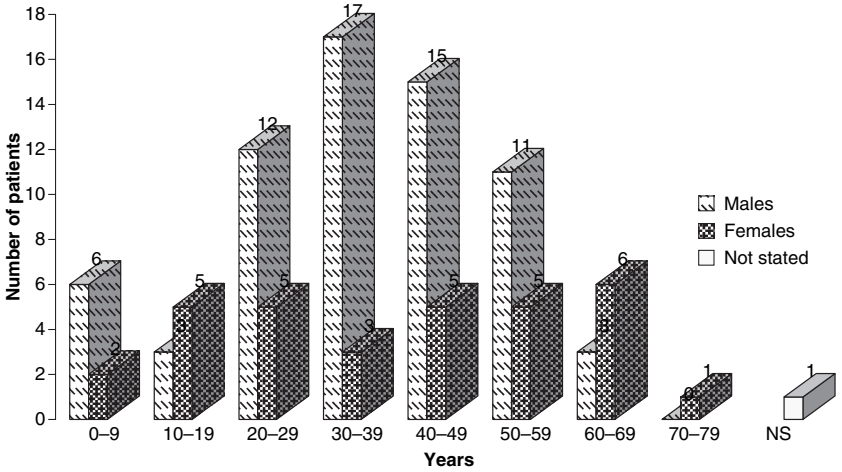

Figure 1 Age and sex distribution of 99 patients with CNS infection caused by *Pseudallescheria boydii* complex, 1948–2007.

Table 2 Demographic and clinical characteristics of 99 patients with *Pseudallescheria boydii* complex CNS infections, 74 of whom died

Characteristics	All patients	Proportion (%) of patients who died
Age, years		
Mean (range)	37.5 (16 months–77 years)	
Sex		
Male	68/99 (69)	46/68 (68)
Female	32/99 (32)	28/32 (88)
Not stated	1/99 (1)	
No underlying condition at time of infection[1]		
Overall	44/99 (44)	25/44(57)
Immunocompetent	4/99 (4)	4/74 (5)
Aspiration of contaminated water	24/44(55)	17/24 (71)
Trauma	10/44 (23)	4/10 (40)
Alcohol abuse	4/44 (9)	2/4 (50)
Injection drug abuse	1/44 (2)	
Pregnancy	1/44 (2)	1/1 (100)
Underlying condition at time of infection[1]		
ALL	5/99 (5)	3/5 (60)
AML	8/99 (8)	8/8 (100)
CML	1/99 (1)	1/1 (100)
Aplastic anaemia	1/99 (1)	1/1 (100)
Non-Hodgkin's lymphoma	3/99 (3)	3/3 (100)
Solid organ transplantation		
Renal	8/99 (8)	7/8 (88)
Liver	6/99 (6)	6/6 (100)
Heart	2/99 (2)	2/2 (100)
Lung	1/99 (1)	1/1 (100)
Bone-marrow transplantation	3/99 (3)	2/3 (67)
Immunosuppressive therapy[2]	36/99 (36)	33/36 (89)
Corticosteroids	32/99 (32)	31/32 (97)
Others[3]	20/99 (20)	18/20 (90)
Cytotoxic drug receiving/radiotherapy	11/99 (11)	9/11 (82)
Diabetes mellitus	7/99 (7)	6/7 (86)
Other[4]	17/99 (17)	15/17 (88.5)
IA	3/99 (3)	3/3 (100)
Hepatitis B, C	3/99 (3)	2/3 (67)
Aspiration pneumonia/ nosocomial lung infection	5/99 (5)	5/5 (100)
Previous surgery	6/99 (6)	2/6 (33)
Previous antifungal prophylaxis/treatment	4/99 (4)	4/4 (100)

Values in parentheses are expressed in percentage (%).

ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; CML, chronic myelogenous leukaemia; IA, invasive aspergillosis.

[1]Total of percentages is not 100% because some patients had more than one factor.

[2]Total of percentages is not 100% because some patients had received more than one immunosuppressant.

[3]Cyclosporin, tacrolimus, azathioprine, anti-IL-2 receptor antibodies therapy.

[4]Includes idiopathic thrombocitopenic purpura, haematopoietic stem cell transplantation, cystic fibrosis, graft vs. host disease, haemolysis, elevated liver enzymes and low platelets syndrome, HIV+/AIDS, pulmonary tuberculosis, glomerulonephritis, chronic pancreatitis, peritonitis

In 24 cases (24/25, 96%), CNS infection was reported. Twenty of them (20/24, 83%) were otherwise healthy individuals and four had different underlying conditions. These were an insulin-dependent diabetes mellitus patient, a hepatitis patient, a cirrhosis patient and an i.v. drug abuser with AIDS. Of those, seven (7/24, 29%) were female and 17 (17/24, 71%) male. Patients were relatively young subjects, 13 of them were under 30 years (mean age 25.3; Fig. 3). Seventeen patients (71%) with aspiration of polluted water showed clinical evidence of pulmonary infection with diffuse or localised lung infiltrates on chest X-ray. Chest radiograms did not show any infection focus in two patients[44,87] and was not stated in the remaining cases. Sputum and/or other respiratory sample cultures grew bacteria belonging to numerous genera.

Seventeen patients (71%) had lesions suggestive of brain abscess on CT scan and seven patients (29%) had a normal image result on admission; however, all developed brain lesions during their clincal course. Nineteen patients had single or multiple brain abscesses, one had meningitis, one had meningoencephalitis, one had panencephalitis, and two had brain abscesses and meningitis. Brain abscesses occurred at diverse locations in the cerebrum and/or cerebellum, mostly located in frontal lobe followed by parietal region. Single abscess was present in six and several abscesses occurred in 13 patients.

Antifungal treatment alone was given in 14 patients and combined with surgery in 10. Seventeen cases (17/24, 71%) were fatal (Fig. 4) between 16 days and 6.5 months (mean 89 days). Of those, nine were aged <30 years, five were 30–49 years, and three were ≥50 years. In this patient group, mortality rate was remarkably high at each stage in the lifetime. Although the cerebral abscess of the patient with AIDS was reported as stable after amphotericin B and voriconazole therapy on 2 months of follow-up,[60] scedosporiosis following near drowning was indeed associated with high mortality even in immunocompetent hosts (15/20, 75%), The brain lesion of the patient with hepatitis was resolved after 1 year of treatment with voriconazole alone, without surgery.[76] Aspiration of contaminated water seemed to have been associated with high mortality independently of patients' age and immunological status.

It is remarkable that ante mortem diagnosis of *P. boydii* complex pulmonary infection following a near drowning episode was quite rare.[26,76,95] This may be attributable to the fact that the first symptoms of these patients are usually evident in the brain. Pulmonary involvement was demonstrated in only eight of the

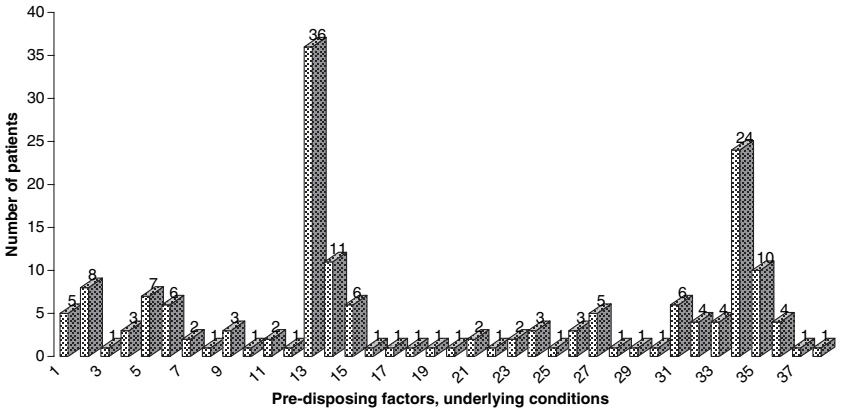

Figure 2 Frequency of predisposing factors and/or underlying conditions reported in 99 cases of CNS infection of *Pseudallescheria boydii* complex. Numbers: 1, ALL; 2, AML; 3, CML; 4, non-Hodgkin's lymphoma; 5, renal transplantation; 6, liver transplantation; 7, heart transplantation; 8, lung transplantation; 9, BMT; 10, haematopoietic stem cell transplantation; 11, aplastic anaemia; 12, graft vs. host disease, 13, immunesuppressive agent(s) receiving; 14, cytotoxic drug receiving, radiotherapy; 15, diabetes mellitus; 16, idiopathic thrombocytopenic purpura; 17, autoimmunehaemolytic anaemia; 18, lepromatous lepropsy; 19, systemic lupus erythematous; 20, haemolysis, elevated liver enzymes and low platelets syndrome, 21, cirrhosis; 22, cystic fibrosis; 23, HIV+/AIDS; 24, invasive aspergillosis; 25, pulmonary tuberculosis; 26, hepatitis B/C; 27, aspiration pneumonia/nosocomial lung infection; 28, glomerulonephritis; 29, chronic pancreatitis; 30, peritonitis; 31, previous surgery; 32, previous antifungal prophylaxis/treatment; 33, immunocompetent; 34, near-drowned/aspiration of contaminated water; 35, trauma; 36, alcohol abuse; 37, injection drug abuse i.v. drug use, 38, pregnancy.

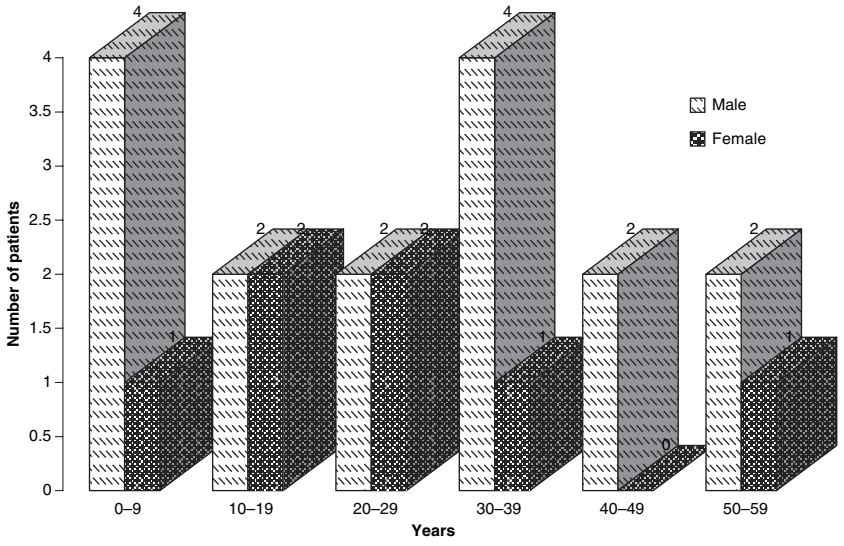

Figure 3 Age and sex distribution of 24 patients in association with aspiration of polluted water.

overall (8/25, 32%) near drowning episodes, five cases being revealed at autopsy. However, in 18 (18/25, 72%) of the reported cases that involved solely the CNS, no visceral organ involvement was demonstrated at autopsy. Together with CNS, the kidney and skin were involved in two cases each (2/24, 8%), and the liver, heart, bone and joint, and the eye in one case each (1/24, 4%). This may strongly support the suggestion of primary neurotropism of this angioinvasive fungus.

Incubation period of the CNS infection

In general, in previously healthy patients, the time of onset of CNS infection caused by *P. boydii* complex is particularly affected by both the infection route and inoculum size. Caya *et al.* [41] reported that a frontal lobe abscess secondary to bilateral *P. boydii* complex endophthalmitis occurred in a cadaveric kidney recipient 1 year prior to admission. The patient underwent

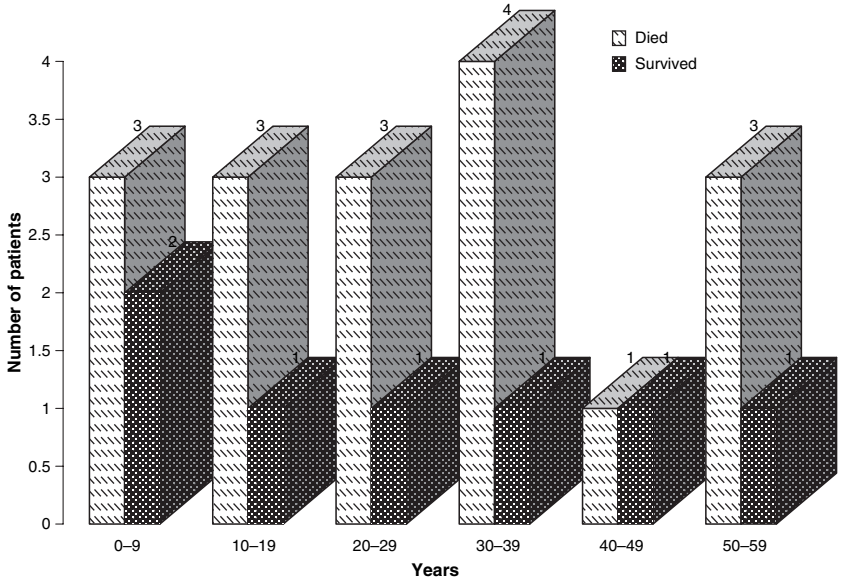

Figure 4 Mortality associated with near-drowning episodes followed by *Pseudallescheria boydii* complex CNS infection.

neurosurgical drainage on day 95, but died on day 110. In near-drowned patients who have aspirated a sufficient inoculum, the incubation period can be estimated as approximately 1–3 weeks. Rüchel *et al.* [55] reported a case of a nearly-drowned child whose clinical condition began to deteriorate 1 week after the accident and on day 21, a CT scan of the brain revealed hypodensic foci, suggestive of cerebral abscess. In another case, the patient suffered a massive intracerebral haemorrhage and became comatose approximately 20 days after the accident.[26] A fatal primary neurological *P. boydii* complex infection[80] causing meningismus 15 days after nearly drowning was also described. In a further case, the onset of neurologic symptoms from CNS infection because of this fungus associated with near drowning appeared 22 days later.[68]

The time of onset of the disease in immunocompromised patients varies enormously, and recognition of the symptoms can often be delayed because of silent or non specific symptoms. In a case reported by Van der Vliet *et al.* [91], the infection spread from a near-drowned donor's infected kidney to the recipient's CNS and death occurred 2 weeks after transplantation.

Portals of entry and routes of infection

It has been hypothesised that one of the most common routes of infection can be by inhalation of airborne conidia,[22,32,59] which can be spread to the brain by the haematogenous route.[17,34,45,57,59,69] Lung infection was reported in 23 of the 99 cases (23%) with CNS infection. Although it is also likely that after an invasive pneumonitis, the fungus can reach CNS by haematogenous spread, it may be facilitated by immunosuppressive therapy. Cells of *P. boydii* complex may possess appropriate virulence factors or specific surface receptors, to cross the blood–brain–CSF barriers and escape the action of host mechanisms. But many other mechanisms of CNS invasion have been documented, such as direct inoculation through penetrating injury or surgery including ventriculoperitoneal shunting;[20,29,64] haematogenous spread from a primary site of infection, usually lung or kidney[17,45,95] or extension via lumens and walls of vessels;[32,41] direct extension from an infection site adjacent to the brain, usually paranasal sinuses;[12,24,31] direct entry by massive aspiration from pharynx, through sinuses close to brain and ethymoid bone, during submersion in contaminated water, as mentioned above, or iatrogenically through epidural anaesthesia[13,14] or catheter.[42] No site of entry for the organism was found in three non-immunocompromised patients.

Signs and symptoms

The predominantly reported symptoms were headache (17/99, 19%), altered mental status (16/99, 18%), seizures (7/99, 8%), hydrocephalus (6/99, 7%), infarcts, eye pain, arm and leg weakness (each in 5/99, 6%), vomiting, vision loss and back pain (each in three cases), neck stiffness, haemiparesis, general convulsions, lethargy and confusion (each in two cases), and dizziness, facial paresis, nausea, skin rash, photophobia, abnormal behaviour (each in one case).

Thirteen (15%) of the patients had coma on admission. Eleven patients (12%) had no complaints and/or had no abnormal neurological signs.

Radiology

Head CT was performed in 51 patients (52%), magnetic resonanse imaging (MRI) in 16, and less frequently other techniques such as arteriography in four, myelography in three and isotopic scan in two patients. Diagnostic imaging procedure was not stated in the remaining cases (24%). CT and MRI scans showed the presence of brain abscess or cerebritis, areas of ischaemic infarcts and hydrocephalus and also the status of the ventricles. Single or multiple brain lesions of different sizes and at diverse locations suggestive of brain abscess were the most common finding in CT, reported in 65 of the 99 cases. They appeared as ring-enhancing lesions with low density, mostly located in frontal/bifrontal and parietal lobes followed by temporal region. Basal nuclei and/or thalami involvement was reported in three patients. Intracerebral, intraventricular or subarachnoid haemorrhage was identified in CT or MRI of five patients.[12,44,56,59,66] Mycotic aneurism was reported in two cases.[61,72]

Clinical presentations

The main clinical types of CNS infection by *P. boydii* complex are primary or secondary cerebral infections and meningitis. Brain abscess (solitary mass or multiple lesions) in cerebrum and/or cerebellum or the brainstem, were reported in 68 (69%) cases, co-infection of brain tissue and/or spinal cord with meninges in ten (10%), meningitis in eight (8%) and pachymeningitis in two (2%). Cerebral abscess and concomitant ventriculitis were reported in four cases (4%); subdural abscess and diffuse cerebritis each in one case (1%). Cerebral fungus ball was reported in two (2%) cases. Brain cavity lesion was described in one case. Optic nerve involvement was reported in one patient with brain abscess. The fungus also showed a high affinity for blood vessels, quickly affecting the cerebral vessels and causing ischaemia, brain infarction and/or intracranial mycotic aneurism followed by clinical brain death even prior to deterioration of brain parenchyma when inoculated directly into the vessels.[61] Aneurism of the brain vessels was described in four fatal cases.[12,33,61,72] The highest mortality was associated with co-infection of brain tissue and meninges (9/10, 90%) and brain abscesses (53/68, 78%; Fig. 5).

In approximately half of the patients with systemic infections, no site of infection was found other than the

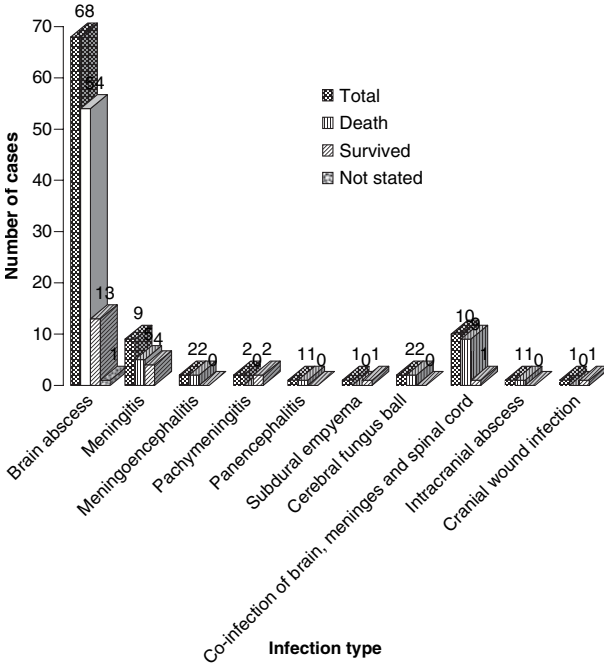

Figure 5 Mortality differences among patients with different patterns of CNS infection by *Pseudallescheria boydii* complex, 1948–2007.

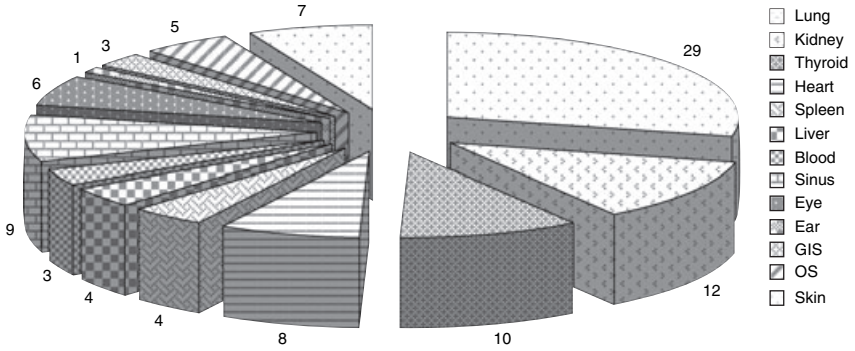

Figure 6 Other sites of involvement in 57 of 99 patients with CNS infection.

CNS (42/99, 42%), while in 57 (57%) more than one site of infection was documented. These additional sites were: the lung in 29 (29%), kidney in 12 (12%), thyroid in 10 (10%), sinusitis in nine (9%), heart or myocardium in eight (8%), skin in seven (7%), eye in six (6%), cranial or extra cranial osteomyelitis in five (5%), spleen, liver, and in four each (4%) and gastrointestinal system organs in three (3.4%; Fig. 6). Twenty-four (42%) patients with disseminated infection had multiple brain abscesses. A total of 48 of the 57 patients with disseminated infection died.

Khurshid *et al.* [59] described a fatal case with unusual widespread dissemination of *P. boydii* complex infection in an immunocompetent host. Autopsy revealed multifocal subarachnoid haemorrhages and also in cerebellar white matter, parietal cortex and putamen nucleus. A necrotic fungal mass was also observed in the left lung and invasion of the pulmonary artery, haematogenous dissemination to the liver, spleen, kidney and pancreas and formation of arterial fungal masses. This case is highly exceptional as there was no evidence of immunosuppression.

Although haemorrhagic features were reported in some CNS cases,[12,26,44,56,59,66,72,75] intracranial arteriography revealed occasional cases of cerebral aneurysms.[33,61,72] The clinical course in fatal cases was very variable, ranging from 27 h[19] to 10 months.[31]

Laboratory diagnosis

Direct examination of clinical samples was rarely performed and the septate hyphae of this fungus were only visualised in routine Gram-stained clinical samples in two patients.[41,67] In contrast, it was frequently cultured from different types of samples even on routine culture media. *P. boydii* complex was isolated from the brain or meningeal tissue in 37 patients, from CSF samples in 20, from aspirated pus in 22 and from extraneural sites in 15 patients. Occasionally, the fungus could be also isolated from the whitish material that filled the shunt,[30] fluid obtained by ventriculostomy,[38] or by cisternal tap.[51] Positive blood culture for *P. boydii* complex was only documented in three cases (3%). The kind of clinical specimen cultured was not stated in four cases. In two cases,[17,18] the diagnosis was made only histologically. The different types of clinical specimens from which *P. boydii* complex was first isolated are shown in Fig. 7. Diagnosis was established ante mortem in 66 (67%) cases, post mortem in 30 (30%) cases, and it was not mentioned in three cases.

Histology

The most characteristic histological findings in the brain tissue of patients infected by *P. boydii* complex were the presence of a neutrophylic inflammatory infiltrate,[56] granulomatous inflammation with multinucleate cellular tissue reaction[31,56] and microabscesses with hyphae invading cerebellar blood vessels.[56] Hyphae of *P. boydii* complex are usually well stained with the routine histological stains such as haematoxylin and eosin (H–E), gomori methenamine silver, periodic acid-Schiff (PAS), or even with potassium hydroxide.[42] Fluorescent antibodies have also been useful for the detection of the fungus.[24] However, exceptions also exist and in a case of cerebral infection, no microbial elements were detected by haematoxylin, Gram and PAS staining.[55] In general, the fungal structures observed in CNS infections were hyaline, septate and multiple acute angle[45] or dichotomously branched hyphae.[49] These hyphae are indistinguishable from those of other commonly pathogenic fungi such as *Aspergillus.* However, *P. boydii* complex has the ability, not found in *Aspergillus,* of sporulating in tissue. Thus, presence of pyriform, ovoid, brown conidia and even slender conidiophores of *P. boydii* complex have been reported in several cases of CNS infections.[17,18,36,37,42,47] Occasionally, globose, swollen cells (up to 20 μm in diameter) have also been seen.[36]

CSF findings

Lumbar or ventricular puncture was performed (once or many times) in 34 (34%) patients. In addition, in three

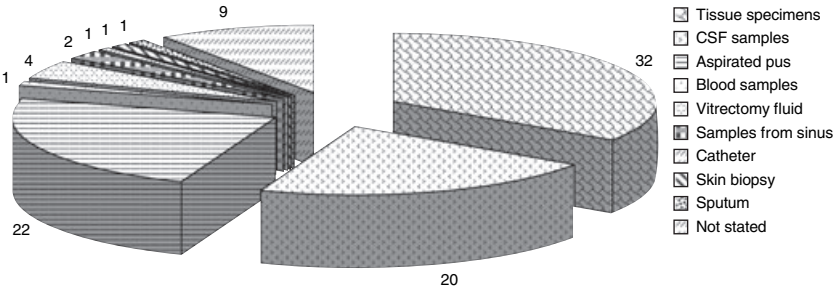

Figure 7 *Pseudallescheria boydii* complex first isolated materials from patients with CNS infection.

patients, CSF was obtained from shunt.[30,51,82] Samples of CSF were cultured in 31 cases, with no significant differences between positive and negative results for *P. boydii* complex (65% vs. 35%, $P = 0.01$). This relatively high percentage of CSF culture negativity might be attributed to the typical encapsulated abscess that the fungus forms in the brain. Positivity was higher in meningitis cases (12/20, 60%). All the negative cases were brain abscesses. In a pachymeningitis case secondary to pansinusitis, reported by Schiess *et al.* [31], CSF showed negative cultures, while *P. boydii* complex was isolated from a swab specimen obtained from sphenoid sinus.

Purulent CSF, revealing heavy infiltrate with polymorphonucleer leukocytes (PMN) and multinucleate giant cells, was reported in meningitis cases[27,55,64] as well as in cerebral granulomas[45] In general, CSF specimens showed high WBC counts with rise in percentage of PMN, which is considered to be of diagnostic significance. A number of patients had a predominance of neutrophyls with a total number $>10^7$.[7,13,16,22,27,28,30,38,48,51,55,64] CSF pleocytosis with increase of lymphocytes (>1000 cells mm^{-3}) was also present in some cases.[7,51] In one patient with cranial epidural abscess, CSF showed no abnormality.[31]

Treatment and outcome

In general, the treatment was unsuccessful and the overall death rate very high. Of the 99 patients with CNS infections by *P. boydii* complex a total of 74 died, 23 survived (74% vs. 23%; $P \leq 0.001$) and in two cases the outcome was not indicated (Fig. 8). There were significant differences between the mortality rate of patients treated with antifungal drugs alone (37/50) and those treated with a combination of antifungal drugs and surgery (8/26; 74% vs. 31%, $P \leq 0.001$. Four patients received only surgical therapy[16–19,73] and two of them (50%) survived. Twelve patients received no therapy and all died.[9,13–15,25,32,36,43,47,88,89] Treatment was not stated in seven patients,[7,20,54,61,81,88,90] five of whom died, and the outcome was unknown in the remaining two.[20,90]

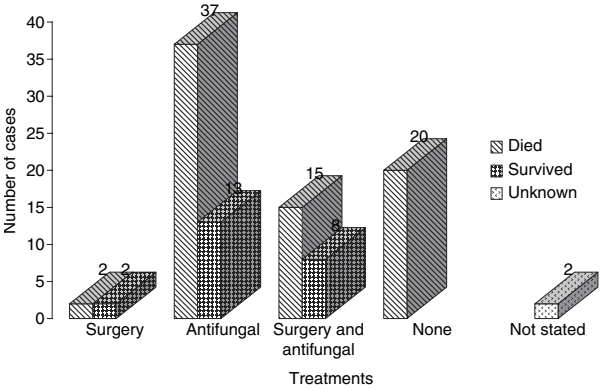

Figure 8 Treatment and outcome of 99 patients with CNS infections by *P. boydii* complex.

As numerous therapeutic approaches have been used, both monotherapies and combinations, with variable results, a general consensus for the treatment of these infections does not yet exist. Overall, a total of 70 patients received antifungals. The drug most frequently used alone was amphotericin B, which was administered to 16 of all antifungal recipients (16/70, 22%), followed by miconazole. In most cases, miconazole was delivered directly into the CSF because of its poor meningeal penetration. Itraconazole and terbinafine monotherapies were used in two and one patient, respectively, and all died. The novel azoles, voriconazole and posaconazole were also administered in a number of relatively recent cases. Voriconazole was given alone in two patients and combined with surgery in one and all survived[64,83,84] (Fig. 9).

Of the 23 survivors, 10 (44%) were submitted for surgical draining procedures of lesions and eight of these 10 were also treated with intravenous and intratechal miconazole (3/22, 13.6%); or amphotericin B (2/22, 9%), alone or combined with miconazole (2/22, 9%); or flucytosine (1/22, 4%). Among survivors, fluconazole was administered in one case (1/22, 4%), itraconazole in four (4/22, 18%) and terbinafine and caspofungin in one each (1/22, 4%) either subsequently or in combination. Therapy was finally changed to voriconazole in six of survivors (8/22, 36%); and to posaconazole in two (2/22, 9%).[71,78] Therapy was further changed to voriconazole in four of the non-survivors.

Discussion

Pseudallescheria boydii complex can cause a wide spectrum of diseases, from localised to invasive infections in both immunocompetent and immunocompromised patients with various underlying diseases. It has also been described as one of the major fungal agents of chronic colonisation of airways in cystic fibrosis (CF) patients. Invasive infections caused by *P. boydii* complex are only rarely reported in CF after lung transplantation. However, the fungus was also recovered from the patient's CSF specimen in a fatal case of pulmonary pleuritis,[8] and in one of subacute-meningitis.[90]

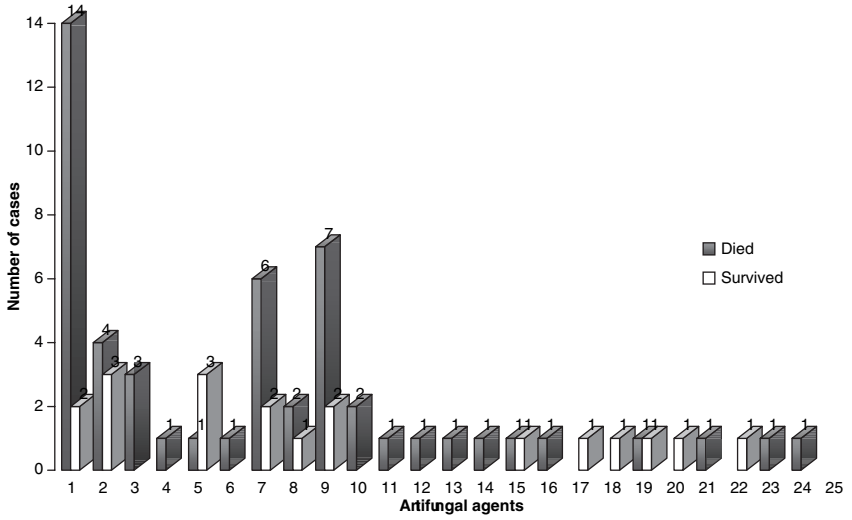

Figure 9 Reported antifungal treatments and outcome in CNS infections caused by *Pseudallescheria boydii* complex, 1948–2007. Numbers: 1, amphotericin B (AMB); 2, miconazole (MCZ); 3, itraconazole (ITZ); 4, terbinafine (TRB); 5, voriconazole (VRZ); 6, posaconazole (PSZ); 7, flucytosine (5FC); 8, AMB+5FC; 9, AMB, MCZ; 10, AMB, ITZ; 11, AMB, FLZ; 12, AMB, ketaconazole (KTZ), AMB (intratechally); 13, AMB, KTZ, MCZ; 14, AMB, VRZ; 15, AMB, MCZ, VRZ; 16, AMB, MCZ (intratechally); 17, AMB, ITZ, VRZ; 18, L-AMB, ITZ, PSZ; 19, AMB, KTZ, PSZ; 20, ITZ, AMB, PSZ; 21, ITZ, MCZ; 22, TRB, caspofungin, VRZ; 23, AMB, 5FC, saperconazole; 43, AMB, FLZ, ITZ, MCZ.

Invasiveness involves the ability of microorganisms degredation of anatomic barriers, to migrate into adjacent tissues or into circulation. The mechanisms by which *P. boydii* complex evades host defense to enter the body and establish invasive disease remain largely unknown. A surface glycoconjugate, peptidorhamnomanan antigen of the fungus was characterised and its role in adhesion to human epithelial cells was demonstrated.[96–99] Two distinct extracellular metallopeptidases (28 and 35 kDa), released by both conidia and mycelium, capable of cleaving different human serum proteins were recently described.[100,101] *In vitro* studies have shown that *P. boydii* complex conidia and hyphae are susceptible to phagocytosis[102] but in a variable manner.[103] However, alpha-glucan from *P. boydii* complex cell wall was demonstrated to lead inhibition of conidia phagocytosis.[104] Although fungal melanins may also play an important role in resistance to phagocytosis, being able to neutralise radicals produced after oxygenic burst,[105] *P. boydii* complex has been considered being non-melanised regarding its hyaline mycelium and Fontana–Mason staining negative hyphae present in infected tissue sections.[106] Some fungi may produce hyaline hyphae and melanised sclerotia, reproductive structures, or conidia.[105] To our opinion, the presence or absence of melanin or melanin-like pigments in dark coloured conidia and/or colour-less hyphae of *P. boydii* complex and other metabolic products to further involve its pathogenicity should be investigated. In addition, antioxidant systems including a Cu, Zn-superoxide-dismutase from *P. boydii* complex were recently detected[107] and further research is needed to gain insight into the immunopathogenesis of this fungus.

Pseudallescheria boydii complex shows a marked neurotropism and a high propensity to cause CNS infections. CNS is the most common site for *P. boydii* complex infections.[108] In most of the CNS associated disseminated cases, particularly the vascular organs such as the kidney, thyroid and heart have been also involved (Fig. 6)[15,19,22,26,37,43,54,81] probably because of the particular tropism for blood vessels and haematogenous spread of this fungus.[17,32,41,45,108] The usual portal of entry of CNS infection by *P. boydii* complex was presumed to be the respiratory tract with haematogenous spreading to the brain.[17,34,45,80] A case of possible reactivation of a latent infection resulted from endogenous colonising fungi during immunosuppressive therapy in a farmer who was frequently exposed to soil and manure.[57] The rather high prevalence of *P. boydii* complex in the respiratory tracts of susceptible patients[108] may also support this consideration. However, there are also some aspects that seem to go against this presumption. For instance, cases probably following inhalation and/or exposure to airborne conidia of this fungus were reported rather rarely.[22,32,59] Pulmonary involvement was demonstrated at autopsy in only 32% of the near drowned patients or isolation of *P. boydii* complex from outside and indoor air was extremely infrequent. However, at least other five portals of entry could be defined by analysing the reported cases of CNS infection.

It is likely that the fungus enters the CNS directly from the pharynx, through sinuses close to the brain and ethymoid bone during submersion into contaminated water. The relatively short incubation period of CNS infection after aspiration reinforces this hypothesis. Remarkably, direct entry by aspiration of contaminated water from the pharynx, through sinuses close to brain

and ethymoid bone seemed the most frequent portal of entry regarding the 16 near-drowned cases in whom no pulmonary involvement was observed (16/99, 16%).

Persistent neutrophylic meningitis is a poorly described variant of chronic meningitis characterised by the persistence of neutrophils in the CSF overextended periods of time (>1 week) in association with ongoing signs of meningeal inflammation and negative CSF cultures for bacteria or other pathogens. Persistent neutrophilia in the serial CSF analysis along with negative cultures for *P. boydii* complex were reported in four cases.[14,48,51,82] In one case,[14] neutrophylic pleocytosis persisted over a 4-month period. In the report by Tan *et al.* [82], CSF obtained at days 63 and 67 gave positive cultures for *P. boydii* complex. The patient died a month after proven diagnosis, despite the use of antifungal therapy. Therefore, in patients with persistent neutrophilic meningitis suspected by *P. boydii* complex, multiple CSF cultures and prolonged incubation (14–28 days) should be recommended.

It is usually difficult to isolate fungi including *Aspergillus* and others, from CSF because of the low organism concentration.[109–111] It was suggested that many lumbar punctures must be made and enough liquid must be taken to increase success, a minimum of 5 ml with the ideal quantities being between 10 and 15 ml.[109,112] In cases because of *P. boydii* complex, CSF culture positivity was higher in meningitis cases than in brain abscesses (60% vs. 40%). In some cases[14,20,27] subsequent CSF samples were persistently culture positive. Regarding our review results, CSF examination is significant in establishing the diagnosis of *P. boydii* complex meningitis. However, imaging studies and a brain biopsy are necessary in most patients, particularly in those who have brain abscess, to make a definite diagnosis.

Pseudallescheria boydii complex fungemia have rarely been reported even in patients with disseminated infection[9,37,39,113,114] and AIDS.[115] Blood culture findings positive for *P. boydii* complex were reported only in three disseminated cases with CNS involvement (3%).[37,39] This could probably be because of (i) the low fungal cell content of blood fluid despite of aboundant hyphal growth extending through the vessel wall, destructing its structural integrity and resulting in infarcts. Indeed, in many arters, wall destruction of all layers of the vessel wall with infiltration by fungal hyphae was reported in CNS involved cases by *P. boydii* complex.[40,51] (ii) Active phagocytic host defence to hyphae and conidia[103,116] and substances normally found in blood, which are inhibitory to fungal growth may further cause the circulating blood to contain insignificant numbers of *P. boydii* complex cells and also reduce the isolation rate from blood samples. To support this hyphothesis, all of the fungemia detected patients were with haematological malignancy and/or allogenic bone marrow transplantations except one with AIDS. In addition, opsonised hyphae of single isolates were demonstrated to show differences in their interactions with and susceptibilities to phagocytes.[103] Alpha-glucan from *P. boydii* complex cell wall was shown to lead to a dose dependent inhibition of conidia phagocytosis.[104] These factors may possibly affect, on the contrary, blood culture positivity. To our understanding, immunopathogenesis of *P. boydii* complex should be studied.

Early diagnosis of the infection might be difficult,[5,117] and the onset of neurological symptoms revealing *P. boydii* complex CNS invasion might be late (several weeks, and even months).[5,64] In some cases, death occurred within 1 day from diagnosis before therapy could be given.[88] Therefore, clinical suspicion should be maintained particularly in near-drowning cases and immunosuppressed patients to make possible early diagnosis of *P. boydii* complex infection and detection of CNS dissemination.

In some aspects such as underlying medical conditions, length of hospital stay, or sites of other organ involvement CNS infections by *P. boydii* complex are difficult to differentiate from CNS aspergillosis.[91] Clinically applicable serological tests to allow a presumptive diagnosis are not currently available and isolation by culture remains the gold standard for diagnosis. It is to be expected that in the near future, progress in molecular testing may provide accurate and rapid diagnostic methods to detect *P. boydii* complex in patients' CNS samples.

Central nervous system infection caused by *P. boydii* complex has a poor prognosis. The overall death rate in

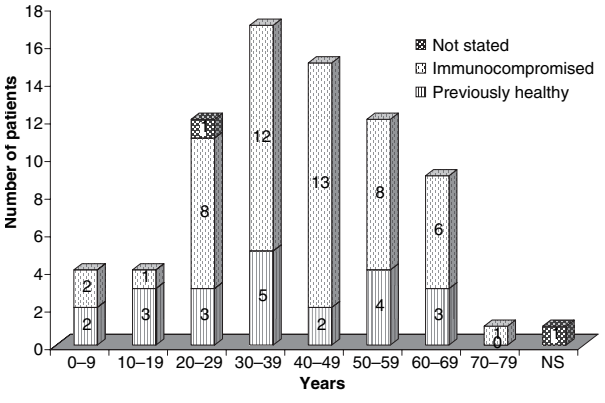

Figure 10 Relative mortality for previously healthy patients compared with immunocompromised patents with CNS pseudallescheriasis according to the age groups.

these patients has been 74%, while the predictors of outcome remain largely unknown. Sixty-five of the survivors were previously healthy patients. According to the analysed data, mortality rates were high regardless of the patient's immune status (Fig. 10); or the infection type and/or location (Fig. 5); but probably affected by infection route and inoculum size (Fig. 4). In some cases, the evidence of fungal infection was obtained too late for a successful antifungal therapy.[87]

Pseudallescheria boydii complex is resistant to conventional antifungal drugs, including amphotericin B. This has also been demonstrated clearly in a cerebral murine model.[118] Voriconazole seems to be effective in CNS cases and constitutes a promising therapeutic option. It has shown *in vitro* activity[119–121] and has been approved by the US Food and Drug Administration for the treatment of serious infections caused by *P. boydii* complex in patients who are intolerant to other antifungal agents. Correlation of the results of *in vitro* susceptibility testing with clinical outcome (success or failure) from patients with CNS infection will be determined in the future by accumulating the data.

Important clinical characteristics influencing the outcome of *P. boydii* complex infection have not been well defined. Current therapeutic options for frequently fatal infections are limited. However, regarding the analysed data, surgical removal of the abscess, when possible, appears as important as antifungal therapy. Rapid identification and targeted therapy are essential, so improved diagnostic and treatment options are needed to optimise management of CNS infections caused by *P. boydii* complex.

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