Introduction

*Candida* spp. are opportunistic pathogens of the endogenous flora, which may cause (serious) infections or ‘candidiasis’ (also called candidosis). ‘Superficial’ candidiasis (e.g. vaginal and oropharyngeal candidiasis) is considered the most prevalent fungal infection, although it does not compromise survival. Nevertheless, *Candida* spp. may also cause life-threatening infections, the so-called ‘invasive candidiasis’, by invading the bloodstream (candidemia) and/or deep-seated organs. Despite its severity, little is known about deep-seated candidiasis, although its occurrence is closely related to that of candidemia. The host factor is paramount in the development of both candidemia and deep-seated candidiasis, since it mainly occurs in highly debilitated patients. Consequently, invasive candidiasis is generally found in severely ill patients, such as patients in the intensive care unit (ICU) or immunocompromised patients [1–3].

Most literature on invasive candidiasis predominantly describes candidemia, which is usually catheter-associated, and relatively easy to diagnose, for example, through positive blood cultures. Candidemia has been associated with increased morbidity, mortality and increased hospital costs and is the most prevalent form of invasive candidiasis among the critically ill [4,5]. Although often secondary to or associated with candidemia, only a few studies describe deep-seated candidiasis. Basically, deep-seated candidiasis can be present in every organ, organ space, or normally sterile tissue. Because of the difficult diagnosis (requiring biopsies) reliable estimates of the prevalence of these infections are lacking. As such, deep-seated candidiasis may be an underestimated problem in the ICU. Therefore, this article gives an overview of the most important manifestations of deep-seated candidiasis in the ICU, including the often difficult diagnosis, prevalence, and mortality.

Pathogenesis

*Candida* spp. are ubiquitous on the skin and mucosa of humans, and are present in small concentrations in the gastrointestinal tract (GIT) of healthy individuals. Nevertheless, they can cause a broad range of infections [5]. Therefore, it is not surprising that candidiasis is the most prevalent fungal infection in humans, occurring also in hospital settings such as the ICU [1,6,7]. Deep-seated candidiasis is, in general, only present in seriously ill patients. It may originate from candidemia but can also develop secondary to mucocutaneous colonization through locally spreading infections or through invasive procedures [8]. Continuous exposure to risk factors is then responsible for further invasion with possible secondary haematogenous dissemination [8]. It has, however, been postulated that all forms of deep-seated candidiasis follow an episode of candidemia [9].

Histological differentiation

Three histological varieties of candidiasis can be distinguished: (i) superficial candidiasis (skin or mucosa), (ii) locally invasive candidiasis and (iii) deep or systemic candidiasis. The superficial infection is most common and is characterized by infections limited to lining surfaces such as skin, oropharynx and the GIT [10]. The other two entities are considered ‘invasive candidiasis’, as sterile body sites are invaded. Locally invasive candidiasis
presents with typical ulcers with fairly sharp margins, and may be present as e.g. cystitis and oesophagitis (although these entities can also be secondary to candidemia) [10]. Ulcerative or necrotic lesions indicate deeper tissue invasion, which is usually haematogenously spread. These lesions are most frequently encountered in the intestinal, upper-respiratory and genitourinary tract. The differentiation between locally invasive and deep invasive forms is usually based on microscopy. Distinct features of the haematogenously spread candidiasis are the symmetric occurrence (e.g. both kidneys) and miliary distribution. Vascular invasion may also be present [10].

Definitions used in clinical practice

The histologic classification of candidiasis is not routinely used in clinical practice, where invasive candidiasis, or the invasion of normally sterile body sites, is usually classified as candidemia or as deep-seated candidiasis, which may co-exist [5,11].

Invasive candidiasis has also been described as four overlapping clinical entities [9,10]: catheter-related candidemia (which is due to colonization/biofilm formation of a vascular catheter) and three sub-classifications of deep-seated candidiasis: (i) acute disseminated candidiasis, (ii) chronic disseminated candidiasis and (iii) deep-organ candidiasis. In acute disseminated candidiasis, candidemia is present (which may be catheter-related) but candidiasis is also present in one or more organs. Chronic disseminated candidiasis, often described as hepatosplenic candidiasis, occurs almost exclusively following prolonged episodes of bone marrow dysfunction and neutropenia. The liver, spleen, and sometimes kidney are prominently infected with Candida spp. Blood cultures are rarely positive at this point, although presumably they were positive at the time the infection was initiated. Deep-organ candidiasis can virtually occur in any organ, either in isolation or in combination. At the time of presentation, no candidemia can be detected and the focal infection is the only manifestation. This is the feature that sets these manifestations apart from hepatosplenic candidiasis.

Aetiology

The epidemic relevance of Candida spp. is limited by its predominantly endogenous origin [1,6], with a low risk of outbreaks. Consequently, Candida prevention is low-priority in hospital infection control [1]. In the 1980s, a major increase of fungal infections was reported, which was probably related to an increased use of antibiotics and corticosteroids, but also due to an advance in medicine, leading to an increasing number of more vulnerable patients at risk for opportunistic infections [1,12]. Thanks to the introduction of fluconazole, effective antifungal prophylaxis and empirical therapy, an important decrease in cases of ICU candidemia was noted during the 1990s [1,13]. This decrease was completely due to a reduction of C. albicans candidemia, consequently leading to a relative increase of non-albicans candidemia in the ICU [1]. In studies investigating candidemia, half of the episodes are caused by C. albicans [14,15]. A shift to non-albicans spp. has also been described. In particular C. glabrata (after previous exposure to azoles) and C. parapsilosis (in children under total parenteral nutrition) are gaining importance. In patients with recent exposure to fluconazole, non-albicans spp. are more prevalent because fluconazole seems to lead to selection of less susceptible strains [16,17], although C. parapsilosis is usually very susceptible to fluconazole. C. glabrata is less susceptible or dose-dependent susceptible to fluconazole. C. krusei is intrinsically resistant but an increase in infections with this species has not yet been reported [17-20].

Risk factors

Since virtually all cases of deep-seated candidiasis had a previous or co-existing candidemia, the risk profile is similar. Since candidemia is an aspecific clinical entity, a-priori risk analysis is important for identifying patients at risk. Prolonged ICU admission (>7-10 days) is considered the single most important risk factor [2,6,21,22]. Previous administration of broad spectrum antibiotics, corticoids and/or parenteral nutrition, peritonitis, abdominal surgery, multiple lumen catheters, prior (mucosal Candida colonization (in multiple body sites), renal replacement therapy, and mechanical ventilation are considered to be major risk factors for developing candidemia, and also describes the patients most at risk of developing deep-seated candidiasis [3,6,21,23-26]. Major risk factors specifically described for deep tissue invasion with Candida spp. are antibiotic and corticosteroid therapy, neutropenia and chemotherapy [27].

The Candida colonization index is used to quantify the risk of developing candidemia, since candidemia is usually secondary to colonization [8,26]. The colonization index is defined as the ratio of positive non-blood samples to all analysed non-blood samples taken at the same time [26,28,29]. This colonization index was developed to predict candidemia in high risk patients, and was validated in a cohort of surgical patients [26]. However, a relationship between mortality and the risk for candidemia and the colonization index could not be confirmed [1,26,30]. Consequently, prediction models to guide the initiation of antifungal treatment (e.g. the Candida score) should also include other risk factors [31]. However, the predictive value of such scoring systems remains low. Therefore, starting antifungal treatment based only on colonization without other arguments for invasive candidiasis is controversial [32].

Source of infection and affected organs

Most Candida spp. causing infection are of endogenous origin, but exogenous transmission has also been reported, and can co-exist with endogenous colonization [8]. Basically all episodes of deep-seated candidiasis are preceded by or coexist with candidemia. About 80% of cases of candidemia arise from or evolve in the presence of a vascular access, including central venous catheters, haemodialysis catheters and implanted ports [3,33]. The primary source in non-neutropenic patients who develop deep-seated candidiasis may be an infected intravenous catheter or contamination of an infusion fluid, especially hyperalimentation fluid, but infection of the peritoneal cavity after complicated abdominal surgery may also occur [10].
The distribution of organ involvement is believed to be related to the site from which haematogenous dissemination has occurred and whether or not the patient had adequate bone marrow function [10]. Non-neutropenic patients who develop deep-seated candidiasis after abdominal surgery or with IV catheter-induced phlebitis tend to have myocardial, pulmonary, renal, ocular and cerebral involvement [10]. Liver and spleen lesions are unusual in these patients [10]. Every organ and implanted material can be contaminated, colonized or infected by Candida spp., although some of these are rarely described in the literature, e.g. infected pacemakers [7]. The most important manifestations of deep-seated candidiasis in the ICU are summarised as follows:

1. Gastro intestinal tract [GIT], liver, spleen and peritoneum

Deep-seated candidiasis may have originated from fungal translocation across an intact bowel wall, which is facilitated by the decreased intestinal mucosal barrier function as seen in ICU patients [4,29,34]. GIT involvement is invariably present in leukaemia patients and is therefore one of the major sources of infection including hepatosplenic involvement [10]. Deep-seated candidiasis may present as hepatosplenic (or chronic disseminated) candidiasis, which rarely occurs in non-neutropenic patients [10]. These patients usually have a disturbed liver function and experience fever not responding to antibacterial treatment.

Candida peritonitis is most often secondary to bowel perforation e.g. following surgery, trauma, or peritoneal dialysis, which is often polymicrobial [18]. Rarely, it is secondary to bowel perforation due to gastrointestinal Candida ulceration [18].

The importance of positive Candida cultures in secondary and tertiary peritonitis is controversial. Some authors reported Candida as the leading or second most frequently isolated pathogen in secondary or tertiary peritonitis. Yet, in other studies it was only the seventh most prevalent microorganism. A definite diagnosis of Candida peritonitis is possible only in patients with peroperatively documented Candida plaques on the peritoneum, or on histology [1,18].

2. Trachea and Lung

Fungal pneumonia is an uncommon entity, but important differences exist between infections caused by mould and yeasts: yeast will rarely cause pneumonia [35,36]. Candida pneumonia is thus an extremely rare disorder, even in the ICU population, occurring primarily as a result of haematogenous dissemination [36]. However, Candida spp. are often isolated from the tracheal aspirates of mechanically ventilated patients (~25%), which reflects the colonization of the bronchial tree [5]. The study of Meersseman et al. however, did not find any relationship between tracheal colonization with Candida spp. and Candida pneumonia [36]. So, unless there is prolonged neutropenia, Candida pneumonia is considered highly improbable. Antifungal therapy should therefore not be prescribed based on isolation of Candida spp. from respiratory specimens [36]. Because lung biopsies can often not be performed in critically ill patients [37,38], and yeast infections do not have typical features on computerised tomography, ante-mortem diagnosis remains difficult.

3. Urinary tract

In 20% of ICU patients, Candida is isolated from the urine mainly in patients with bladder catheterisation, most often representing colonization [10,39]. There is however, no reliable method to differentiate colonization from infection. High colony counts (> 10,000 cfu/ml) have been associated with infection in patients without indwelling catheter. Pyuria may be a sign of cystitis or pyelonephritis, but it can also be caused either by bacteria or mucosal trauma by catheterisation. Candidiasis can be ruled out in the absence of pyuria and low colony counts. Patients with candiduria are frequently colonized at other body sites, increasing the risk of developing candidemia. Candiduria is associated with an overall mortality rate of up to 50% and should rather be considered as an epiphenomenon or marker of severity [40]. Removal of the catheter is the cornerstone of treatment of candiduria, and is a sufficient measure in 40% of the patients [41]. When the candiduria persists after antifungal treatment, complementary examination (imaging) of the kidneys is recommended [5,10].

Candida pyelonephritis is grossly indistinguishable from acute bacterial pyelonephritis [10]. The kidneys are involved with the same frequency in neutropenic and non-neutropenic patients [10]. The medullary portion of the kidney is more frequently involved than the cortical portion [10]. Pyelitis, hydronephrosis, hydroureter, and cystitis are often present [10]. The haematogenous route of invasion is accepted as the most common way by which Candida spp. enter the renal parenchyma, because of the high vascularity of the kidneys and the large volume of blood circulating through them [10]. The absence of lower urinary tract pathology is one of the most reliable arguments in favour of the haematogenous route of renal infection [10].

4. Cardiovascular candidiasis

Myocardial micro abscesses with yeast and pseudohyphal elements are the most common manifestations of cardiac infection in disseminated candidiasis [10]. Because of the small size of the lesions, the heart compromised by candidiasis may manifest subtle alterations in its function, and therefore most Candida myocarditis is clinically undetectable [10]. Endocarditis and pericarditis are less common, but morbidity and mortality are disastrous [42]. Candida endocarditis has become a threat in patients after cardiac surgery particularly when prosthetic valves have been inserted, and is also encountered in drug addicts and in patients with long-term venous catheters [10,22,43]. Complications of Candida endocarditis include embolisms, congestive heart failure and sepsis [43]. The valvular vegetations tend to be bulkier than those caused by bacteria. In any of these circumstances, Candida may evoke little or no inflammatory reaction or may induce a suppurrative response [10]. Arterial emboli from Candida endocarditis are generally larger than from bacterial infection, and consequently, larger vessels are involved.
in the embolisation with subsequent infarction often seen in the spleen, kidneys, brain and lower extremities [10].

5. Central Nervous System [CNS]
Neonates are the group most at risk for Candida meningitis, but it has also been reported among other patient groups (e.g. HIV) as an occasional manifestation of disseminated candidiasis, after neurosurgery and surgery in the oral cavity [10,22,44-46]. Cerebral involvement with Candida spp. is often not recognized until autopsy examination, due to the typically severe underlying primary disease and the small and focal nature of the parenchymal CNS lesions in candidiasis [10]. Nevertheless, it is the most common cerebral mycosis found post-mortem, surpassing cryptococcosis which is clinically most frequently recognized [10].

6. Eye
Deep-seated candidiasis of the eye can be present as chorioretinitis and endophthalmitis, and is usually of endogenous origin. Chorioretinitis is, by definition, confined to the choroid and retina but may evolve to endophthalmitis, in which the vitreous cavity is also affected.

Of all cases of endophthalmitis, only 2-15% are endogenous [47,48], although most cases of endogenous endophthalmitis are caused by Candida spp., followed by Aspergillus spp. [10,47,49]. Candida chorioretinitis and endophthalmitis are usually caused by embolic spreading, and are therefore usually preceded by or coexisting with candidemia. The eye can even be the presenting site of a previously undiagnosed fungaemia [10,50].

Endogenous Candida chorioretinitis and endophthalmitis occur mainly in hospitalised patients with intravenous lines and other risk factors for candidiasis, such as underlying systemic debilitating diseases, e.g. diabetes mellitus, HIV, neutropenia, haematogenous malignancies, and intravenous drug abuse [47,49-51]. Some studies found that Candida endophthalmitis occurs in less than 2% in patients with candidiasis, although in one study almost 80% of autopsy proven invasive candidiasis, showed signs of retinal involvement [47,49,50,52,53]. Since the visual prognosis is poor, a fundoscopic examination is recommended in all patients with (suspected) candidemia.

7. Endocrine organs
Haematogenous Candida lesions can be found in the endocrine organs at autopsy. The thyroid and adrenals especially may be involved but these lesions are not often clinically significant [10,54]. Since most patients with fungal thyroiditis had disseminated fungal infection with delay in diagnosis and treatment, the described overall mortality was high [54].

8. Osteo-articular
Candidiasis in bone and cartilage is uncommon in clinical practice and literature, and may be present as e.g. osteomyelitis, septic arthritis, spondylodiscitis and infected joint prostheses [55-59]. These infections are usually hematogenously spread, or related to surgery [57]. Because presenting features are often nonspecific, osteo-articular candidiasis can be difficult to recognize in the early stages, and therefore adequate treatment is often delayed [57].

Diagnosis
The diagnosis of deep-seated candidiasis is often difficult, as the clinical picture is non-specific and blood cultures have a low sensitivity, since not all cases of invasive candidiasis (including transient candidemia) are detected. For deep-seated candidiasis the differentiation with colonization is often problematic because critically ill patients are often heavily colonized, especially when receiving broad spectrum antibiotic treatment [5].

In invasive candidiasis, the necessity of antifungal treatment is generally acknowledged, but the clinical relevance of positive non-blood cultures is not clear. Although early diagnosis and treatment are associated with better prognosis, a definitive diagnosis of deep-seated candidiasis can only be obtained by histological confirmation, which is often not performed in the ICU setting because of the underlying condition of the patient (e.g. bleeding diathesis) [3]. The diagnosis is therefore usually based on clinical and laboratory findings but there is certainly a need for specific markers [21].

Laboratory markers
Serodiagnostic assays such as C. albicans germ tube antibodies (CAGTA), (1,3)-β-D-glucan and galactomannan detection and molecular techniques for the detection of fungal-specific DNA have been developed with controversial results in ICU settings [60]. (1,3)-β-D-glucan is a cell-wall component of most pathogenic fungi and can be used as a broad spectrum fungal marker which can detect invasive infections caused by Aspergillus, Candida, Pneumocystis etc. [23]. A high prevalence of false positive results (resulting from Gram positive bacteraemia, albumin etc.) makes it difficult to implement it in a clinical setting, and radiologic and microbiologic confirmation are essential [21]. The negative predictive value is however excellent [21]. Fungal DNA can be detected by polymerase chain reaction (PCR), which has a potential for rapid detection [21,23]. Yet, no standardised and validated commercial methods are currently available, and PCR is not therefore recommended for the detection of invasive fungal infections [21]. Indirect immunofluorescence assay is commercialised to detect antibodies such as CAGTA, with an overall sensitivity of 77-89% and specificity of 91-100%, and has been helpful in ICU populations [21]. CAGTA can also be detected in invasive infections with non-albicans species, and can be used for therapeutic monitoring for invasive candidiasis [21]. However, more studies are needed to validate this strategy in the critical care setting [21,60].

Microscopic examination and culturing
Conventional microbiology
Direct microscopic examination of clinical specimens is the crucial and fast (<1h) first-line procedure in detecting the presence of fungal elements, and is probably the most cost-effective means of diagnosing fungal infections [21]. However,
culturing is more sensitive, and consequently negative results of direct microscopic examination never rule out fungal infections [21]. Detection of fungaemia is useful in diagnosing opportunistic infections caused by yeasts but automatic continuous blood cultures may be negative in up to 50% when invasive candidiasis is present [21]. Identification of yeasts recovered from clinical specimens can be challenging because of their slow growth characteristics [21,61]. Isolation of Candida spp. from a normally sterile site provides evidence for starting a targeted antifungal therapy. Positive cultures of specimens from non-sterile body sites may be related to either colonization or infection, and distinguishing between both can be difficult [21].

Screening
Several studies have shown that ICU patients with mucosal Candida colonization, particularly if multifocal, are at a higher risk of invasive candidiasis, and that such colonization selects a population amenable to antifungal prophylaxis or anticipative therapy [6,62,63]. Therefore, routine surveillance cultures are performed in many ICUs to guide the initiate early pre-emptive treatment, although the overload of samples sent to the microbiology laboratory could limit the widespread use of this approach [21,29].

Outcome
In contrast to candidemia, little is known about mortality in deep-seated candidiasis. Candidemia is thus the only severe manifestation of candidiasis for which the precise impact has been repeatedly established [8,17,64-68]. Although an attributable mortality up to 71% has been described for invasive candidiasis [22,65], other studies showed that nosocomial candidemia does not adversely affect the outcome in ICU patients in whom mortality is attributable to age, the severity of underlying disease and acute illness [1,2].

Since deep-seated candidiasis is often preceded or accompanied by candidemia, mortality figures will be comparable to or higher than those of candidemia, since these are expected to be related with the severity of illness. The mortality associated with deep-seated candidiasis is also connected to the difficult diagnosis, since some manifestations are rarely diagnosed ante-mortem.

To conclude, although Candida spp. are prevalent among critically ill patients, the importance of local colonization and infection can easily be overestimated, but the importance of deep-seated candidiasis may be underestimated [1]. Early diagnosis and initiation of treatment is however essential to improve survival, especially in patients with a compromised health status.

Therapeutic options
In documented candidiasis and those patients highly suspected of having invasive candidiasis, the empirical treatment should be based on local epidemiology, essentially on azole exposure and resistance, and the presence of haemodynamic instability [22,69]. When the Candida spp. is determined, the treatment should be adjusted if required. Therapeutic options have been excellently reviewed by Pappas et al. of the Infectious Disease Society of America [7].

Economic impact
No data are available for the extra costs resulting from deep-seated candidiasis. Yet, the extra cost of an episode of candidemia in adults has been estimated up to € 31,150.00, or up to € 405.00 per day [7,70-73]. Almost 90% of healthcare costs due to candidemia are related to the extra length of hospital stay which can increase up to 24 days [70-72]. Consequently, the impact of candidiasis is considerable, especially considering that it affects an already expensive group of patients [72].

Conclusion
Scientific studies about deep-seated candidiasis are scarce, since it is a relatively rare entity in the ICU population, with an extremely difficult diagnosis. Especially for the non-neutropenic ICU population, most studies about invasive candidiasis only describe candidemia. However, the majority of deep-seated candidiasis appears to be haematogenously spread or at least associated with candidemia. According to some of the biggest clinical trials for antifungals in invasive candidiasis, the percentage of disseminated invasive candidiasis is between 3% and 20% [74-76]. Yet, clinical trials do not necessarily represent a consecutive sample of patients and therefore these incidence estimates must be interpreted with caution.

Although the prognosis mainly depends on early diagnosis and treatment, deep-seated candidiasis is often recognized too late. However, an overconsumption of antifungals is a major topic of discussion in cases of positive respiratory and urinary samples. The diagnostic and therapeutic approach of tissue invasion with Candida spp. is often based on clinical suspicion (risk factors), because histopathologic examination is often impossible. The differentiation with colonization in non-sterile body sites (tracheal aspirates, candiduria) is not standardised, and reference values are still lacking. Consequently colonization may be falsely classified as infection, but on the contrary, the diagnosis of deep-seated candidiasis is still often missed.

To conclude, deep-seated candidiasis can occur as a variety of clinical presentations, and is associated with important morbidity and mortality. Because of the difficult diagnosis, deep-seated candidiasis is thought to be underdiagnosed. On the one hand, this presents a real threat because delayed diagnosis results in delayed initiation of appropriate antifungal therapy with an increase in fatality figures. On the other hand, frequent clinical situations, e.g. isolation of Candida in respiratory and urinary samples, lead to overdiagnosis of infection and an overconsumption of antifungals.
References


