Chapter 2
Current Trends in Candidiasis

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Abstract In the 1940s, coincident with the introduction of antibacterial antibiotics into therapeutic strategies, a gradual increase in the number of reports of serious, deep organ candidal infections began to appear in the medical literature. Since then, there has been an abrupt increase in the incidence of hematogenously disseminated candidiasis and its complications. Candidiasis now represents the third-to-fourth most frequent nosocomial infection in hospitals in the US and worldwide. An important reason for this is that *Candida* species have a propensity to infect devices, and there has been a highly significant increase in the implantation of devices including indwelling catheters, artificial hips, knees and shoulders and prosthetic heart components, in recent years. The gravity of the situation deepens with the emergence of novel multidrug resistant species of *Candida*, such as *C. auris*, and the inability of existing diagnostic techniques to identify such species. Here, we discuss the current trends in the field of Candidiasis: epidemiology, most common or unusual clinical manifestations, and latest development in the areas of immunology and diagnostic testing. While this chapter is not meant to be exhaustive in content related to *Candida*, we have attempted to inform most recent updates in the field.

2.1 Introduction

In the 1940s, coincident in timing with the introduction of antibacterial antibiotics into modern medical therapeutic strategies, a gradual increase in the number of reports of serious, deep organ candidal infections began to appear in the medical

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literature. It was during this time that widespread use of antibiotics was introduced, and since then, there has been an abrupt increase in the incidence of hematogenously disseminated candidiasis and its complications. Currently, there are approximately 2000 references per year on *Candida* and infections caused by the species. One important reason for this increase in infections is that *Candida* species have a propensity to infect devices, and there has been a highly significant increase in the implantation of devices including indwelling catheters, artificial hips, knees and shoulders and, prosthetic heart components.

Candidiasis now represents the third-to-fourth most frequent nosocomial infection in hospitals in the US and worldwide (Beck-Sague and Jarvis 1993; Edmond et al. 1999; Wisplinghoff et al. 2014; Wright and Wenzel 1997). The incidence of systemic candidiasis in the US is approximately 20 cases per 100,000 people (or about 60,000 cases per year) and in high-risk hospitalized patients this incidence increases by a factor of 50. Of note, these rates represent a 20-fold increase compared with just two decades ago, mostly as a result of an expanding population of immunocompromised patients (Edmond et al. 1999; Hajjeh et al. 2004; Viudes et al. 2002; Wright and Wenzel 1997). Disseminated candidiasis carries unacceptably high mortality rates, about 40–60%, even with treatment using antifungal agents. This high mortality may be due to poor diagnosis, inappropriate disease management, associated septic shock, or the general critical condition of the patient. The total estimated direct cost of candidiasis to the US health care system was ~ $2–4 billion yearly in the year 2000 (Wilson et al. 2002; Zaoutis et al. 2005b).

Deep organ, or disseminated candidiasis, is more likely to occur when the skin or gastrointestinal barriers are disrupted. The skin and mucosal infections may be more superficial and mild such as intertrigo, esophageal, and oropharyngeal candidiasis. In more serious situations, the superficial infections can advance toward an invasion of the bloodstream (blood stream infections) and dissemination to different organs in the body (hematogenously disseminated candidiasis). Invasive candidiasis (IC) itself includes severe complications such as endophthalmitis, meningitis, peritonitis, pancreatitis, endocarditis, arthritis, central nervous system infections, and osteomyelitis, besides others elaborated in their respective sections of this chapter.

Risk factors for invasive candidiasis include but are not limited to surgery, prolonged stay in an intensive care unit, severe burns, prior administration of broad-spectrum antibiotics and immunosuppressive agents, organ transplantation (especially liver), total parenteral nutrition, hemodialysis, antineoplastic chemotherapy, and catheter use (Pappas 2006; Bouza and Muñoz 2008; Playford et al. 2008). In addition to these risk factors, neonates and children are also susceptible if they are born premature, have low birth weight or any congenital malformations, or have low APGAR (American Pediatric Gross Assessment) score (Simonsen et al. 2014). An overall comprehensive picture of the pathogenesis of invasive candidiasis is explained elegantly in a review article by Kullberg and Arendrup (2015), and summarized in Fig. 2.1.

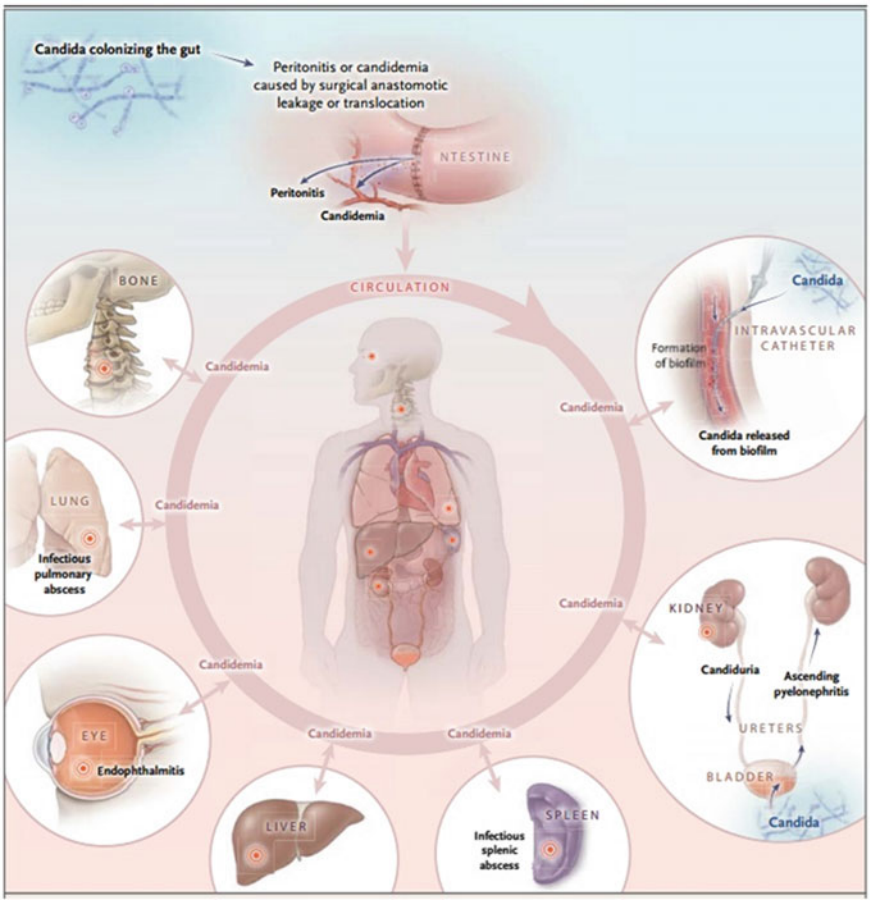

Fig. 2.1 Pathogenesis of invasive candidiasis (Courtesy Dr. Maiken C. Arendrup) (Kullberg and Arendrup 2015)

2.2 Epidemiology

C. albicans isolates have been recovered from soil, animals, hospital environments and food, and non-albicans spp may also be found in animal environments. Of the 150 known species of *Candida*, only 15 have caused infections in humans. These pathogens include *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida guilliermondii*, *Candida lusitaniae*, *Candida dubliniensis*, *Candida pelliculosa*, *Candida kefyr*, *Candida lipolytica*, *Candida famata*, *Candida inconspicua*, *Candida rugosa*, and *Candida norvegensis* (Pfaller et al. 2005). Of significance is the newly isolated species *C. auris* (http://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html), which will be discussed below.

The specific prevalence of infection depends on the patient population, geographical, and clinical settings. For instance, *C. parapsilosis* is known to colonize the skin and is more commonly found in catheter related infections. *C. krusei* affects recipients of hematopoietic stem cells or those neutropenic leukemia patients administered with fluconazole. *C. glabrata* tends to affect the elderly and neoplastic patient populations (Pappas 2006; Pfaller and Diekema 2007b). In the last 2–3 decades, 95% of the infections are caused by 5 *Candida* species including *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (Pfaller and Diekema 2007b; Diekema et al. 2012b; Lewis 2009). Historically, *C. albicans* alone has been responsible for 50% of all invasive candidiasis and candidemia. However, recent rise in the frequency of occurrence of the disease has been attributed to other *Candida* species including *Candida glabrata* and *Candida krusei* (Zaoutis et al. 2005a). This gradual epidemiologic shift from species susceptible to azole antifungals to resistant strains is particularly troubling for public health. The Infectious Disease Society of America (IDSA) has recommended the use of echinocandins as a first choice of treatment for patients with moderate to severe systemic candidiasis, and those with prior exposure to azoles (Pappas et al. 2016). However, recently European Society of Clinical Microbiology and Infectious Diseases recommends the use of echinocandins for all patients with systemic candidiasis (Cornely et al. 2012).

It is estimated that for every 10 children or 7 adults, candidemia prevention could save one life (Zaoutis et al. 2005a). It is thus imperative to invest efforts in preventing candidemia in addition to developing therapies to cure the infections. Evidence-based studies emphasize on using proper hand hygiene, and the appropriate use and care of central venous catheters. It is also important to exercise caution when prescribing antimicrobials to limit the increase in resistant strains of *Candida*.

2.3 Emergence of *Candida auris*

The Centers for Disease Control and Prevention (CDC) has received reports from international healthcare facilities that *Candida auris*, an emerging multidrug-resistant (MDR) yeast, is causing invasive healthcare-associated infections with high mortality. *Candida auris* is a newly emerging form of the yeast, first described in 2009, when it was isolated from the ear discharge of a Japanese patient (Satoh et al. 2009). Since then, the organism has been reported across four continents in countries including India, Pakistan, South Korea, South Africa, Kuwait, UK, Venezuela, and Colombia (Pfaller and Diekema 2007a). It is not known why the species has emerged but it is likely that there are new selection pressures posed by humans, animals, or the environment for *C. auris* to evolve and increase its incidence over the years. Infections caused due to *C. auris* commonly occur in hospitals, several weeks into a patient's hospital stay. This species of fungus has been reported to cause bloodstream infections, wound infections, and ear infections

(Lee et al. 2011). While it has also been cultured from urine and the respiratory tract, it is unknown if isolation from these sites represented infection verses colonization. *C. auris* has been documented to cause infections in patients of all ages. Co-infection with other *Candida* spp. and detection of *C. auris* while the patient was being treated with antifungals have also been reported (Lee et al. 2011).

Diagnostic tests using traditional biochemical methods, API strips and VITEK-2 cannot differentiate *C. auris* from other *Candida* species and these isolates have been reported as "other *Candida* spp." http://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html. The CDC suggests that the clinical, state, and public health laboratories should be aware of this organism and of the limitations in its identification.

C. auris is also extremely drug resistant. Although no established minimum inhibitory concentration (MIC) breakpoints exist for *C. auris*, resistance testing of an international collection of isolates conducted by CDC demonstrated that nearly all isolates are highly resistant to fluconazole, based on breakpoints established for other *Candida* spp. More than half of *C. auris* isolates were resistant to voriconazole, 1/3rd were resistant to amphotericin B (AmB; MIC greater than or equal to 2), and a few were resistant to echinocandins. Some isolates have demonstrated elevated MICs to all three major antifungal classes, including azoles, echinocandins, and polyenes, indicating that treatment options would be limited.

2.4 Recent Trends in Anatomical Distribution of Candidal Infections

As the frequency of diseases due to *Candida* has increased, a relatively large number of manifestations, that were previously either not recognized or extremely infrequent, have become well documented. We have discussed them in the following sections.

2.4.1 Intra-Abdominal Candidiasis (IAC)

Our knowledge about intra-abdominal candidiasis (IAC) is limited, as most epidemiological studies, diagnostic studies, and antifungal clinical trials have focused primarily on candidemia. Since IAC occurs in different clinical presentations, has poor clinical diagnosis coupled with the fact that there are no standardized definitions for the disease, the scope of the research in this field has been limited (Bassetti et al. 2013; Blot et al. 2007; Montravers et al. 2015). Some studies define IAC to be comprised of primary peritonitis, secondary peritonitis, biliary infections, intra-abdominal abscesses, or infected pancreatic necrosis. (Bassetti et al. 2013; Blot et al. 2007; Lamme et al. 2006).

IAC has poor prognosis and afflicts 35–40% of patients who have had gastrointestinal surgery, necrotizing pancreatitis or recurrent gastrointestinal perforation (De Ruiter et al. 2009). After candidemia, IAC is the most prevalent type of invasive candidiasis, especially patients in intensive care units (Leroy et al. 2009). In postoperative patients suffering from IAC, *C. albicans* is the most frequently isolated pathogen (65–82%) followed by *C. glabrata* (Dupont et al. 2002; Sandven et al. 2002). Associated mortality rates for IAC range between 25 and 60%, while 10% of all peritonitis cases are caused by IAC (Dupont et al. 2002; Montravers et al. 2006). Among all causes of IAC, the highest mortality rates are attributed to primary and secondary peritonitis (88 and 75% respectively) (Vergidis et al. 2016). High mortality of IAC is due to difficulties in diagnosing the disease, since cultures have low sensitivity and specificity. Substantial delays in obtaining results, both before and after IAC, further complicates the diagnosis. In recent years, there is increasing evidence to suggest that IAC could act as a hidden reservoir for echinocandin resistant *Candida* (Shields et al. 2014).

Clinical evidence for the use of antifungal therapy for patients with suspected intra-abdominal invasive candidiasis is limited. Source control with adequate drainage and/or debridement is an important part of therapy of intra-abdominal candidiasis (Pappas et al. 2016). Preferred empiric therapy for this infection is an echinocandin, especially for patients likely to be infected by *C. glabrata* or *C. krusei*. Studies suggest that initiating treatment is more important than the choice of antifungal therapy (Morrell et al. 2005; Garey et al. 2006; Clancy and Nguyen 2012). It is thus essential to perform blood-based non-culture techniques such as β-D-glucan and polymerase chain reaction assays to quickly diagnose patients with IAC as compared to conventional cultures of intra-abdominal specimens (Nguyen et al. 2012; Clancy and Nguyen 2013, 2014). Needless to say, there is a need for the infectious diseases community to invest its efforts in developing standardized protocols for managing IAC, besides carrying out early diagnostic tests, and conducting research studies to gain insights about IAC.

2.4.2 Hepatosplenic Disease

Hepatosplenic candidiasis (HSC) is also called chronic disseminated candidiasis. It mainly involves liver and spleen. The disease is more likely to occur in patients with severe and prolonged neutropenia, especially those suffering from acute leukemia. The incidence of the disease ranges from 3 to 29%, but in recent years, there has been a steady decline (Rammaert et al. 2012; Masood and Sallah 2005). This decrease in disease incidence is attributed to the use of prophylactic antifungal therapy. With the use of newer antifungal agents, mortality has reduced, from 74 to 21% overall (De Castro et al. 2012). Lipid formulations of AmB have demonstrated

better efficacy, perhaps due to superior tissue concentrations (Gokhale et al. 1993; Masood and Sallah 2005; Sallah et al. 1999). A prophylactic treatment with fluconazole predisposes the patient to an increased risk of infection with a fluconazole-resistant organism. In such populations, a broader spectrum azole, or an echinocandin is considered more appropriate therapy (Cornely et al. 2007; De Castro et al. 2012; Lehrnbecher et al. 2010; Ostrosky-Zeichner et al. 2003; Poon et al. 2009; Rammaert et al. 2012). In recent years, corticosteroids have been used in addition to antifungal therapy. It is important to diagnose and treat HSC early as, any delays could result in negative patient outcomes (Legrand et al. 2008).

2.4.3 Neonatal Candidiasis

Close to four million neonates are born every year in the United States. About 11.4% of these babies are born preterm, 8% have low birth weight (LBW) and 1.4% are of very low birth weight (VLBW), bringing the cumulative sum of these delicate, susceptible population to 20.8% (~750,000 cases/yr) (Martin et al. 2015).

Of infants admitted to the NICU, 75% are colonized with *Candida* by the first month (Bendel 2005). Infection is acquired by; (1) vertical transmission during vaginal delivery; (2) postnatally from contact with maternal skin or the skin of direct care providers; or (3) direct transmissions via contaminated equipment or intravenous catheters. *Candida albicans* remains the most prominent pathogen in neonates, followed by significant cases due to *C. parapsilosis.* (Trofa et al. 2008; Hoffmann-Santos et al. 2013; Leibovitz et al. 2013) *Candida* infections are responsible for ~10–12% of nosocomial sepsis in VLBW (<1500 g) infants, with a collective incidence of up to 4% among all NICU admissions. (Botero-Calderon et al. 2015) In fact, *Candida* is the 3rd most frequently isolated organisms (after coagulase negative *Staphylococcus* spp. and *S. aureus*) in late onset sepsis in VLBW infants. (Bendel 2005) Despite empirical antifungal therapy, mortality related to the disease remains considerably high (20–30%), with even higher rates (59–73%) of long-term neurodevelopmental impairment in survivors. (Bendel 2005; Botero-Calderon et al. 2015).

Dosing of antifungal agents is substantially different for neonates than it is for older children and adults. Numerous studies examining fluconazole prophylaxis for the prevention of invasive candidiasis in neonates have consistently demonstrated efficacy and possibly reduced mortality (Kaufman et al. 2001; Manzoni et al. 2006, 2007) (for a complete list of these studies refer reference # (Pappas et al. 2016)). Enteral/orally administered nystatin has been shown to be effective in reducing invasive candidiasis in preterm infants (Howell et al. 2009; Violaris et al. 2010). Another antifungal drug, AmB deoxycholate (dose of 1 mg/kg daily) is also well tolerated in neonates without a high risk for nephrotoxicity (Benson and Nahata 1989). The duration of therapy is based primarily on adult and pediatric data, and there are no data to guide duration specifically in neonate (Pappas et al. 2016).

2.4.4 Genitourinary Candidiasis

The most frequent manifestations of genitourinary candidiasis include vulvovaginal candidiasis (VVC) in women, balanitis and balanoposthitis in men, and candiduria in both sexes. These diseases are remarkably common but occur in different populations, immunocompetent as well as immunocompromised. While VVC affects mostly healthy women, candiduria is commonly diagnosed in immunocompromised patients or neonates. In the majority of women, a diagnosis of VVC is made at least once during their childbearing years (Sobel et al. 1998). VVC is the second most common genital infection, after bacterial vaginosis and is diagnosed in up to 40% of women with vaginal complaints in the primary care setting (Anderson et al. 2004). *Candida* is also the most common infectious agent causing inflammation of the glans penis (Edwards 1996). In contrast to genital manifestations of candidiasis, candiduria is usually diagnosed in elderly hospitalized patients.

Over a decade ago, VVC was classified into uncomplicated (sporadic and infrequent) and complicated (recurrent and severe) cases, a classification that has been internationally accepted and adapted (Pappas et al. 2016; Sobel et al. 1998; Centers for Disease et al. 2006). Long-term suppressive antifungal therapy is commonly required to control complicated cases. However, recurrence often occur at rates of up to 50% after discontinuation of suppressive therapy (Sobel et al. 2004).

Candidal balanitis is defined as inflammation of the glans penis, often involving the prepuce (balanoposthitis), in the presence of *Candida* spp. and the absence of other infectious etiology. Candidal balanitis is generally sexually acquired and is often associated with the presences of diabetes (Edwards 1996). Diagnosis is based mostly on clinical appearance alone but should be confirmed by microscopy and/or culture if other differential diagnoses are considered.

A variety of topical and systemic oral agents are available for treatment of genital candidiasis. Uncomplicated infections can be effectively treated with either single-dose fluconazole or short-course fluconazole for 3 days, both of which achieve >90% response (Sobel et al. 1995; Watson et al. 2002). Complicated candidiasis requires that therapy be administered intravaginally with topical agents for 5–7 days or orally with fluconazole for the same duration (Sobel et al. 1998, 2001).

Women with type 2 diabetes mellitus (T2DM) are at increased risk for vaginal *Candida* colonization, perhaps because of glucosuria. Sodium glucose co-transporter 2 (SGLT2) inhibitors, in development for the treatment of T2DM, improve glycemic control by increasing urinary glucose excretion. Invokana (Canagliflozin) is one such drug. However, treatment with this drug was associated with an increase in genital candidiasis in both women and men suffering from T2DM (Nyirjesy et al. 2012).

2.4.5 Catheter-Associated Disseminated Candidiasis

Central venous catheters and other intravascular devices are important risk factors in the development and persistence of candidemia in non-neutropenic patients (Diekema et al. 2012a; Pfaller et al. 2012; Wagner et al. 2011). The rate of candidemia in such patients harboring central venous catheters (CVC) is between 50 and 70% (Diekema et al. 2012a; Pfaller et al. 2012; Wagner et al. 2011; Kett et al. 2011). The relationship of candidemia to CVCs has been assumed on the basis of observation, clinical experience, and an understanding of the role of biofilm in the genesis of bloodstream infections (Ruiz et al. 2013; Tumbarello et al. 2012). That candidemia in non-neutropenic patients is commonly due to contaminated CVCs is undeniable, but it is still unclear how best to distinguish a catheter-associated candidemia from one that is related to another source, such as the gastrointestinal tract. There have been no prospective clinical studies designed to examine CVC management as a primary measurement related to outcome. No prospective studies have been done on the relationship of early CVC removal and survival benefit to patients who have candidemia. However, several studies have demonstrated a shorter duration of candidemia and/or a trend toward improved outcomes (Garnacho-Montero et al. 2013; Lai et al. 2012; Kollef et al. 2012), also refer (Pappas et al. 2016), for a complete list of other related references.

2.5 Host Defense Against Candidiasis

A primary defense mechanism against *Candida* is intact skin and mucosal membranes. Any process causing skin disruption or mucosal harm leaves the involved site susceptible to *Candida* invasion, even in healthy individuals. In recent years, the importance of the dendritic cell for maintaining skin and mucosal integrity and as an immune effector cell has been recognized (d'Ostiani et al. 2000).

Figure 2.2, modified from Lionakis (Lionakis and Netea 2013), summarizes current topics regarding the cell surface pattern recognition receptors involved in the recognition of *Candida* by the innate immune system, and findings related to STAT1, Dectin-1, and CARD9.

STAT1p is a signal transducer protein that modulates cellular response to a variety of cytokines and growth factors (Lionakis 2012). Individuals having a deficiency in the production of the STAT1 protein display a proclivity for having a defect in their defense against mucocutaneous candidiasis. This deficiency results in insufficient production of interferon-γ, IL-17, and IL-22,—important regulators of a variety of inflammatory cells. Another population of patients with a propensity for recurrent episodes of mucocutaneous candidiasis are patients with Job Syndrome, who have varying degrees of deficiency in the STAT3 gene product and have cutaneous infections of both *Candida* and *Staphyloccus* (Chandesris et al. 2012).

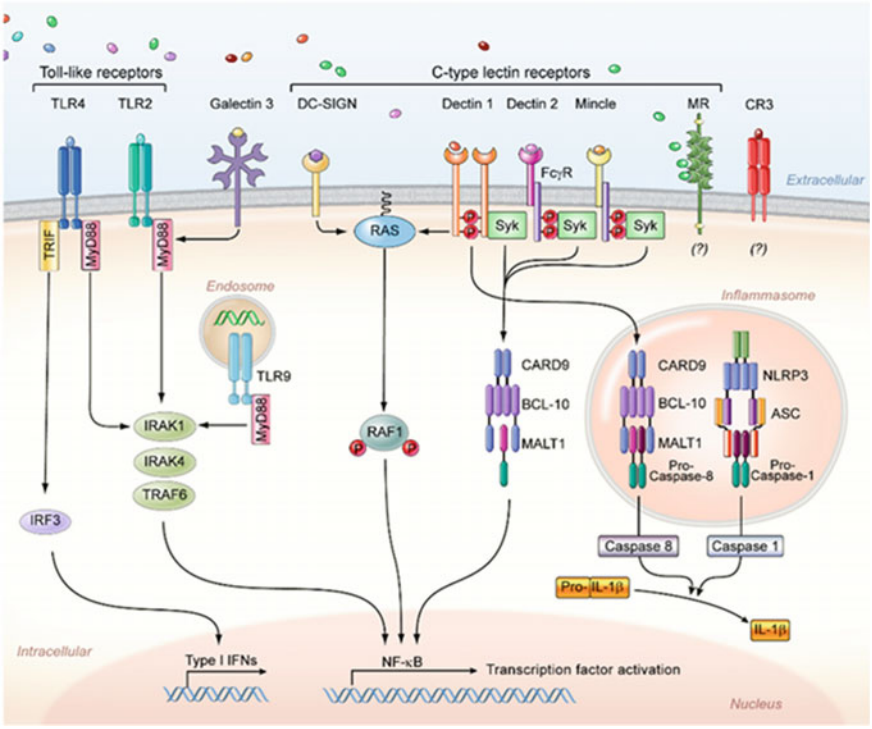

Fig. 2.2 Pathways involved in immune defense against *Candida* (*Courtesy* Dr. Mihailis Lionakis)

Dectin-1 has been found to be a major recognition factor for β-glucan on *Candida* and participates in the CARD9 pathway (Gow et al. 2007) (Fig. 2.2). Defective surface expression of Dectin-1 results in impaired cytokine response in monocytes and macrophages but not neutrophils. Homozygous mutations in CARD9 result in chronic mucocutaneous candidiasis, *Candida* brain abscess and deep dermatophytosis (Glocker et al. 2009).

Another area of intense evaluation has been the role of Th1 and Th17 cells in defense against invasion by *Candida* (Hernandez-Santos and Gaffen 2012). Several reports reveal that these cells play a role in defense against both mucosal and disseminated disease (Conti et al. 2009; Hernandez-Santos and Gaffen 2012; van de Veerdonk et al. 2011). In fact, vaccination with the N-terminus of *C. albicans* cell wall protein Als3, has been shown to increase IL-17 levels in humans (Schmidt et al. 2012; Spellberg et al. 2006).

Numerous other cells and components of the immune system (cytokines, defensins, platelets, complement components, macrophages and monocytes, Treg and natural killer (NK) cells, extracellular traps, Th2 cells and antibodies) play

critical roles in defense against *Candida* damage (Edwards 2015; Romani 2000, 2004; Shoham and Levitz 2005). A discussion of these entities will be found in other chapters of this publication.

2.6 Diagnosis

Diagnosis of candidiasis cultures of blood or other samples collected under sterile conditions have long been considered diagnostic gold standards for invasive candidiasis. Nonculture diagnostic tests, such as antigen, antibody, or β-D-glucan detection assays, and polymerase chain reaction (PCR) are now entering clinical practice as adjuncts to cultures. If used and interpreted judiciously, these tests can identify more patients with invasive candidiasis and better direct antifungal therapy. To fully realize the benefits of combining culture and nonculture tests, however, clinicians must carefully consider the types of invasive candidiasis, understand the strengths and limitations of each assay, and interpret test results in the context of the clinical setting.

2.6.1 Use of Cultures for Diagnosis of Systemic Candidiasis

Invasive candidiasis encompasses 3 entities: candidemia in the absence of deep-seated candidiasis, candidemia associated with deep-seated candidiasis, and deep-seated candidiasis in the absence of candidemia (Clancy and Nguyen 2013). The overall sensitivity of blood cultures for diagnosing invasive candidiasis is roughly 50% (Clancy and Nguyen 2013). While blood cultures are positive during active *Candida* bloodstream infections, they may be negative in cases of extremely low-level or intermittent candidemia, or deep-seated candidiasis in the absence of candidemia. Cultures of tissues or fluid recovered from infected sites during deep-seated candidiasis also exhibit poor sensitivity.

2.6.2 Antigen and Antibody Detection

Candida antigen and anti-*Candida* antibody detection has gained greater acceptance in Europe, where it is approved for use. The best-studied test is a combined mannan/antimannan antibody assay (Platelia *Candida* Ag and Ab; BioRad). In a meta-analysis of 14 studies, the sensitivity/specificity for the diagnosis of invasive candidiasis of mannan and antimannan IgG individually were 58/93 and 59/83%, respectively (Mikulska et al. 2010). Values for the combined assay were 83 and

86%, with best performances for *C. albicans*, *C. glabrata*, and *C. tropicalis* infections. This assay is not used widely in the United States, and its role in the diagnosis and management of invasive candidiasis is unclear.

2.6.3 β-D-Glucan Detection

β-D-glucan is a cell wall constituent of *Candida* species, *Aspergillus* species, *Pneumocystis jiroveci*, and several other fungi. A serum β-D-glucan assay (Fungitell; Associates of Cape Cod, East Falmouth, Massachusetts) has been approved by the FDA as an adjunct to cultures for the diagnosis of invasive fungal infections. True-positive results are not specific for invasive candidiasis, but rather suggest the possibility of an invasive fungal infection. β-D-glucan detection can identify cases of invasive candidiasis days to weeks prior to positive blood cultures, and shorten the time to initiation of antifungal therapy. The major concern about β-D-glucan detection is the potential for poor specificity and false positivity, which may be particularly problematic in the patient populations for which nonculture diagnostics would be most helpful. For example, false-positive results are rare in healthy controls, but decidedly more common among patients in an ICU. For example, a routine surveillance β-D-glucan testing in a recent study of lung transplant recipients revealed sensitivity/specificity and positive/negative predictive values of 64/9 and 14/50%, respectively (Alexander et al. 2010).

2.6.4 Polymerase Chain Reaction

Candida PCR shares many of the potential benefits and shortcomings of β-D-glucan detection. Compared to cultures, PCR assays of various blood fractions have been shown to shorten the time to diagnosis of invasive candidiasis and initiation of antifungal therapy (Avni et al. 2011; McMullan et al. 2008). The pooled sensitivity and specificity of PCR for suspected invasive candidiasis in a recent meta-analysis were 95 and 92%, respectively (Avni et al. 2011). In probable invasive candidiasis, sensitivity of PCR and blood cultures was 85 and 38%, respectively. A major limitation of PCR studies is the lack of standardized methodologies and multicenter validation of assay performance. A multicenter US study assessing the performance of a self-contained instrument that amplifies and detects *Candida* DNA by PCR and T2 magnetic resonance (T2 Biosystems, Lexington, Massachusetts), respectively, has been completed (Mylonakis et al. 2015). This assay is FDA approved, but its role in the early diagnosis and management of candidemia remains unclear until more data are available. PCR has potential advantages over β-D-glucan or antigen-antibody assays, including the

capacity for species identification, detection of molecular markers for drug resistance, and multiplex formatting. Furthermore, the role of PCR in testing samples other than blood is not established.

2.7 Summary

In summary, the incidence of nearly all forms of candidal infections is predicted to increase, due partially to the ever increasing number of devices being implanted. *Candida* infections are predominantly becoming healthcare-related infections, with immunocompromised milieu as primary populations suffering from these diseases. Newer approaches to the management of diabetes will likely result in an increase in genital/urinary tract *Candida* infections.

Predicted also is an increasing risk of resistance, not only of *C. albicans*, but also other species of *Candida*. It is likely that the intense interest in the molecular mechanisms of resistance, coupled with increased stewardship will result in strategies to minimize its development. Of recent concern is the emergence of *C. auris*, which is resistant to all antifungals.

In recent years, there has been an increase in abdominal/peritoneal candidiasis, which poses complex diagnostic challenges. For reasons that are not entirely clear, there has been a significant reduction in the presence of hepatosplenic candidiasis.

Substantial efforts have been sustained in developing diagnostic tests for hematogenously disseminated candidiasis. Presently, their value is most significant for their strong negative predictive value, resulting in the withdrawal of unnecessary antifungal treatment. The development of hematogenous *Candida* endophthalmitis is an important physical finding in establishing a 90% likelihood of the presence of microabscesses in the brain, heart and kidney as well, and in that sense, is a valuable diagnostic tool.

In general, *Candida* species have a very high propensity to spread hematogenously to the eye. The organism is likely the most common organism causing endopthalmitis in hospitalized patients. Its presence not only is a helpful diagnostic tool (indicating widespread dissemination, but also necessitates careful observation due to its capability of causing irreversible blindness. Therefore, the IDSA (Infectious Disease Society of America) currently recommends that every non-neutropenic patient with candidemia have a dilated ophthalmoscopic examination (Pappas et al. 2016). However, we would recommend that every patient with candidemia have a dilated ophthamoscopic exam. The typical lesion is an off-white, cotton ball looking lesion, projecting out into the vitreous, and frequently accompanied by a vitreal haze (Edwards 2015).

A significant roadblock in the elimination of *Candida* infections is the presence of drug resistant biofilms. Fungal cells within the biofilms display resistance to azoles and polyenes (Taff et al. 2013) and echinocandins likely achieve better results against *Candida* biofilms. Recently, some compounds with known anti-inflammatory properties have been investigated for their antifungal activity.

The interplay between fungus and host, i.e., immune system and inflammatory milieu, is crucial in determining the tolerance or the disease status (Romani 2004). Drugs displaying dual activity, antifungal and anti-inflammatory, could thus represent novel approaches to treat biofilm-related infections. After a significant hiatus, the pharmaceutical industry has renewed efforts to develop newer antifungals, including drugs in new classes. These efforts are in early stage clinical trials, and will be discussed in subsequent chapters on drug resistance in this book.

A vaccine to prevent or ameliorate mortality from *Candida* sepsis is currently in clinical trials. This vaccine is based on the recombinant N-terminis of Als3p. It has shown safety and a signal of efficacy for recurrent *Candida* vaginitis in early phase 1b/2a clinical trials (Edwards 2016). Currently there are no vaccines approved by regulatory agencies for any fungal infections.

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