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Candida parapsilosis is a Significant Neonatal Pathogen: A Systematic Review and Meta-Analysis

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Abstract

Background—*Candida* is the third most common cause of late-onset neonatal sepsis in infants born at < 1500 g. *C. parapsilosis* infections are increasingly reported in preterm neonates in association with indwelling catheters.

Methods—We systematically reviewed neonatal literature and synthesized data pertaining to percentage of *C. parapsilosis* infections and mortality by meta-analyses. We also reviewed risk factors, virulence determinants, antimicrobial susceptibility patterns and outlined clinical management strategies.

Results—*C. parapsilosis* infections comprised 33.47 % [95% CI, 30.02, 37.31] of all neonatal *Candida* infections. *C. parapsilosis* rates were similar in studies performed before the year 2000, 33.53 % [95% CI, 30.06, 37.40] (28 studies), to those after 2000, 27.00% [95% CI, 8.25, 88.37] (8 studies). The mortality due to neonatal *Candida parapsilosis* infections was 10.02% [95% CI, 7.66, 13.12]. Geographical variations in *C. parapsilosis* infections included a low incidence in Europe and higher incidence in North America and Australia. Biofilm formation was a significant virulence determinant and predominant risk factors for *C. parapsilosis* infections were prematurity, prior colonization and catheterization. Amphotericin B remains the antifungal drug of choice and combination therapy with caspofungin or other echinocandins may be considered in resistant cases.

Conclusion—*C. parapsilosis* is a significant neonatal pathogen, comprises a third of all *Candida* infections and is associated with 10% mortality. Availability of tools for genetic manipulation of this organism will identify virulence determinants and organism characteristics that may explain predilection for preterm neonates. Strategies to prevent horizontal transmission in the neonatal unit are paramount in decreasing infection rates.

Keywords

Neonate; *Candida parapsilosis*; systematic review; meta-analyses

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Introduction

Neonatal sepsis is frequently due to organisms colonizing the skin and mucosal surfaces, such as Coagulase negative Staphylococci and *Candida* (1). *Candida* is the third most common etiologic agent in late-onset neonatal sepsis (> 72 hrs of age) and is responsible for 8 to 15% of hospital-acquired infections (2). *Candida* infections are responsible for an 'attributable mortality' of 18–25%, significant morbidity and healthcare costs (7, 30, 53). Overall, hospital infections due to non-albicans *Candida* are increasing and *Candida parapsilosis* is among the three most common *Candida* blood isolates (3–10). Compared to *C. albicans*, mortality due to *C. parapsilosis* infections is lower in adults (3, 4, 11), but has not been adequately evaluated in very low birth weight (VLBW, birth weight < 1500 g) neonates.

Preterm infants have high *Candida* colonization rates compared to term infants and it is well established that colonization with *Candida* is inversely proportional to gestational age (12, 13). Colonization precedes invasive *Candida* infection and the number of colonization sites and density of skin colonization with *Candida* correlate with candidemia (14–16). Premature neonates including VLBW and extremely low birth weight (ELBW, birth weight < 1000 g) infants frequently require vascular catheters for administration of parenteral nutrition to meet nutritional needs. Adherence properties of *C. parapsilosis* that favor adherence to the skin and catheters may be responsible for increased incidence of infection in preterm neonates. Increases in *C. parapsilosis* infections and their associated morbidity and mortality make this organism a significant infectious burden in VLBW preterm neonates (17). In this article, we have specifically reviewed neonatal *C. parapsilosis* infections with respect to organism characteristics, epidemiology, risk factors, antimicrobial susceptibility and mortality.

Clinical Epidemiology of *C. parapsilosis* Infections

C. parapsilosis is ubiquitous in nature and is found as a commensal on the human skin. It is most frequently isolated from hands (subungual space) and the gastrointestinal (GI) tract (18–22). The presence of *C. parapsilosis* on human hands may contribute to the horizontal transmission of this organism in neonatal intensive care units (21–24). Neonatal risk factors for invasive *C. parapsilosis* infections are birth weight < 1500 g, prematurity, prior colonization (25), parenteral nutrition, intravascular catheters and use of antibiotics, steroids and H_2 blockers (3, 18, 20). Exogenous sources of infection may be important (26) but colonization of the skin, GI and the respiratory tract often precede neonatal invasive infections (16, 25). The increasing awareness of *C. parapsilosis* infections in neonates is exemplified by the increased number of publications related to this organism in the last 2 decades (Table. 1). We performed a systematic review and meta-analysis to discern the clinical epidemiology and mortality of neonatal infections due to *C. parapsilosis*. We followed published guidelines for reporting of 'Meta-analyses of Observational Studies in Epidemiology' wherever relevant (27). We hypothesized that *C. parapsilosis* is responsible for a significant proportion of neonatal *Candida* infections and is associated with significant mortality.

Methods of the Systematic review and Meta-analyses

We searched Pubmed from 1990 to April 2012, using the search terms '*Candida parapsilosis*' and the root word 'neonat*'. Our search strategy yielded 226 publications, whose citations were reviewed to identify those that included a significant neonatal component.

Inclusion criteria—Observational studies (cohort and case-control studies) or randomized trials (studies of anti-fungal agents, where data regarding the incidence of *Candida* infections and mortality were extractable) were included. Publications that reported 10 or more neonatal patients or neonatal clinical isolates were selected and data regarding incidence rate of *C. parapsilosis* infections as a component of total *Candida* infections and mortality were extracted by author MP (Table 2). All studies without a neonatal component (less than 10 patients or clinical isolates) or where data for neonates or *C. parapsilosis* could not be separately extracted were excluded.

Data Synthesis and Analysis

The extracted *C. parapsilosis* incidence and mortality rates were synthesized and summarized by meta-analyses. Expecting considerable heterogeneity in the included studies, which were mostly observational, we used the random-effects model and the inverse variance method for meta-analysis. Variances and binomial 95% confidence intervals for incidence and mortality rates were calculated using the statistical software STATA, version 11 (StataCorp, College Station, USA). The software Review Manager (RevMan, Version 5.1., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used for meta-analyses and generation of forest plots. We assessed heterogeneity between studies by visually assessing the forest plots for degree of overlap of confidence intervals and formally estimated statistical heterogeneity by the chi squared statistic (28). Inconsistency across studies was calculated by I^2 test (28). In subgroup analyses; we calculated the percentage of *C. parapsilosis* infections in studies performed before and after the year 2000 to analyze temporal trends and also percentage by geographical regions.

Results

The combined percentage of *C. parapsilosis* infections of all neonatal Candida infections estimated from 37 studies was 33.47% [95% CI, 30.03, 37.31] (Fig. 1). Subgroup analysis showed that there was no significant difference in the studies performed before the year 2000, 33.53 % [30.06, 37.40] (28 studies) compared to those performed after the year 2000, 27.90 % [8.91, 88.39] (9 studies, wide and overlapping confidence intervals). The largest study in our review was Fridkin *et al,* which was weighted based on sample size and influenced the outcome the most (9). Sensitivity analyses performed by eliminating the study by Fridkin *et al* changed the summary estimate insignificantly and with larger confidence intervals, 26.97% [95% CI 15.38, 47.29]. Studies were also sub grouped into 5 different regions to evaluate geographic trends; North America (12 studies), South America (2 studies), Europe (12 studies), Asia (7 studies) and Australia (2 studies) (Fig. 2). *C. parapsilosis* infection percentages were lowest in Europe 19.10% [95% CI 7.44, 49.03] followed by Asia 24.71% [95% CI 6.57, 92.92], South America 29.06% [95% CI 2.58, 327.86], North America 33.78% [95% CI 30.26, 37.71] and Australia 35.77% [95% CI 3.33, 384.32]. The mortality due to neonatal *C. parapsilosis* infections was 10.02 [95% CI, 7.66, 13.12] from 10 studies (Candidemia and meningitis data from Benjamin et al (29) were analyzed separately) (Fig. 3). During the same period, the mortality of *C. albicans* infections from 11 studies was 12.97% [95% CI, 12.65, 13.29] and mortality from all *Candida* infections was 14.50% [9.54, 22.03] from 23 studies. We did not find significant statistical heterogeneity in the evaluated outcomes among included studies (Chi squared test, p values > 0.10) and I^2 statistic for inconsistency not significant for any of the analyses.

Genetics and Molecular Characteristics of *C. parapsilosis*

Until recently, before the year 2005, *C. parapsilosis* isolates were classified into Groups I, II and III (30, 31) but evidence has identified sufficient genetic differences to support the designation of each group as a separate species. Group I isolates remained as *C. parapsilosis*

sensu stricto and Groups II and III were renamed *C. orthopsilosis* and *C. metapsilosis* respectively (32). Other species may yet be identified; sequencing of the internal transcriber (ITS) region of ribosomal DNA and the mating type loci of several isolates suggests that there are at least 4 groups represented by *C. parapsilosis* isolates (33, 34). All *C. parapsilosis* species are members of the "CTG clade", which translate the codon "CTG" as serine rather than leucine (35). *C. parapsilosis* is the most common clinical isolate but 1 to 24% of these isolates may actually be *C. orthopsilosis,* misidentified as *C. parapsilosis* (36, 37). In addition, *Lodderomyces elongisporus*, a more distant relative of the *C. parapsilosis* group, may be responsible for up to 0.8% of infections previously assigned to *C. parapsilosis* (38). *C. metapsilosis* is an environmental organism, rarely isolated from clinical specimens and is less virulent than *C. parapsilosis* in several models of infection (39, 40).

The genome of *C. parapsilosis* was sequenced in 2009 along with 5 other *Candida* species. The diploid chromosomes of *C. parapsilosis* are highly homogeneous, with a single nucleotide polymorphism (SNP) frequency of about 1/15000, compared to 1/200 in *L. elongisporus* (41). Individual isolates of *C. parapsilosis* are also very similar, and are difficult to distinguish except by microsatellite analysis (42, 43). Early annotations of the *C. parapsilosis* genome were used for large-scale comparative studies (41, 44) and for the design and application of transcriptional microarrays (45, 46). *C. parapsilosis* shares some features with other pathogenic *Candida* species, such as an enrichment of cell wall families, including Glycosylphosphatidylinositol (GPI)-anchored adhesins (41). However, there are also substantial differences; for example, unlike *C. albicans*, the CFEM (common in fungal extracellular membranes) family of cell wall genes in *C. parapsilosis* is not associated with adhesion or biofilm development (47). Recently, RNA-seq analysis was used to generate a comprehensive and detailed annotation of the *C. parapsilosis* genome, and to determine the transcriptional response to hypoxic conditions (48). Almost 400 new protein-coding genes were identified, together with many novel transcriptional active regions (nTARs). In addition, comparison with the recently sequenced genome of *C. orthopsilosis* suggests that the Hyr/Iff family of cell wall proteins is expanded in *C. parapsilosis*, which may be associated with virulence. There is also substantial expansion of multidrug transporter families (49).

Molecular genetic studies of *C. parapsilosis* using gene knockouts have been hindered by the fact that the genome is diploid (42, 50, 51) and the lack of a characterized sexual cycle (34). Prior to 2007 an efficient method for targeted gene disruption of *C. parapsilosis* did not exist. Two groups subsequently adapted a dominant nourseothricin resistance marker developed for *C. albicans* (52, 53) to knock out lipase genes, and a regulator of biofilm development (54, 55). Although this method is efficient, it is very slow; the resistance marker must first be recycled from the first allele before it can be used to disrupt the second. More rapid methods have been developed in *C. albicans* either by the use of transposon-directed mutagenesis (56–58), or by using two different auxotrophic markers to target each of the two alleles (59). Screening collections of deletions of transcription factors and protein kinases in *C. albicans* led to the identification of genes and networks involved in biofilm development, virulence and iron metabolism (60–63). A similar set of deletions is currently being constructed in *C. parapsilosis* (Holland et al. unpublished data). It is likely that screening these deletions will lead to the identification of species-specific factors in *C. parapsilosis* that are important for virulence.

Virulence Determinants in *C. parapsilosis*

Virulence factors identified in *C. albicans* include adherence, hyphal morphogenesis, biofilm formation and secretion of enzymatic hydrolases including proteases, phospholipases and lipases. However, virulence determinants in *C. parapsilosis* have not been well characterized. Adherence to epithelial tissues that facilitates colonization of biomaterials and

initiation of biofilm formation may be important virulence determinants. Enhanced adherence of *C. albicans* to neonatal buccal epithelial cells, especially those from premature neonates may increase the risk of oral candidiasis (64, 65). *C. parapsilosis* adheres to epithelial cells and biomaterials similarly to *C. albicans* (66–68) and that adherence can be decreased by nystatin (68). Strain variations in adherence have been reported with superficial skin isolates more adherent than systemic isolates (66).

Biofilm formation is an important virulence determinant in *C. parapsilosis.* Biofilms are sessile microbial communities, adherent to a surface and encased in an extracellular matrix composed of polysaccharides, proteins and extracellular DNA (69). Biofilm developmental stages include adhesion, maturation and dispersal. Main risk factors for *C. parapsilosis* infection are the presence of indwelling vascular catheters and administration of parenteral nutrition, both of which predispose to the formation of catheter biofilms. In *C. albicans,* biofilm morphology consists of a compact basal yeast layer and a thicker but less compact hyphal layer (70). *C. parapsilosis* forms only pseudohyphae (not true hyphae) and its biofilms are thinner and less complex than *C. albicans* (71). Although *C. parapsilosis* biofilms are thinner than *C. albicans* biofilms, antifungal drug resistance to amphotericin and azoles is similar to *C. albicans* biofilms (72, 73). Hyphal morphogenesis is essential for biofilm formation and virulence in *C. albicans* (63, 74, 75). Amino acids stimulate morphogenesis from yeast cells to pseudohyphae in *C. parapsilosis* (76), and this may explain the high incidence of *C. parapsilosis* infections in catheterized neonates who are on amino acid rich parenteral nutrition solutions. Recent studies of *C. parapsilosis* biofilms have shown that *BCR1*, a transcription factor essential for the expression of cell surface antigens, is required for biofilm development both *in vitro* and *in vivo* (47, 55) (Fig. 4).

Secreted hydrolytic enzymes such as secreted aspartic proteases (SAP), phospholipases and lipases may cause tissue destruction and initiate pathogenicity (77). However, *C. parapsilosis* has been shown to have lower SAP activity than *C. albicans* (78). *C. parapsilosis* isolates vary in SAP activity, with skin and vulvovaginal isolates having more activity than blood isolates, which may indicate niche-specific adaptation of this organism (79–81). Environmental and epigenetic factors that may regulate the expression of SAPs in different host niches need to be explored. A recent study analyzed the role of *C. parapsilosis* secreted aspartyl proteinase isoenzyme 1 (SAPP1) in virulence (82). The SAPP1 mutant strain was hypersusceptible to human serum and was attenuated in its capacity to damage host-effector cells. The phagocytosis and killing of mutant cells by human macrophages was significantly enhanced relative to wild type (82). The role of lipases in *C. parapsilosis* (*CpLIP1* and *CpLIP2*) has also been studied. Lipase mutants form less biofilms and are less virulent in animal models of infection (54). In addition, lipase inhibitors decrease tissue damage in reconstituted human skin epidermal tissues (40). The role of phospholipases in the virulence of *C. parapsilosis* infections is not clear (79, 83, 84).

Antifungal Susceptibility Patterns of *C. parapsilosis* and Therapeutic Choices

Amphotericin B remains the mainstay in the therapy of neonatal invasive candidiasis including *C. parapsilosis* infections. *C. parapsilosis* resistance *in vitro* to amphotericin B has been reported but its clinical relevance is not clear (85). Fluconazole prophylaxis in VLBW preterm infants has been shown to be effective in decreasing invasive *Candida* infections and a composite outcome of invasive candidiasis or mortality (86–88). These results have led to wide adoption of targeted fluconazole prophylaxis strategy in neonatal intensive care units for VLBW infants to prevent invasive candidiasis (86, 87). Controversy remains as to whether widespread use of fluconazole in neonatal units has increased azole resistance among *Candida* isolates or altered the epidemiology of *Candida* infections towards non-*albicans Candida* infections. However, epidemiological studies so far suggest that there is very little change in azole resistance in clinical isolates of *Candida* infections (89). In a non-

human primate neonatal intensive care unit, fluconazole prophylaxis for a period of 4 years was associated with fluconazole-resistant *C. parapsilosis* infections (90). In a neonatal intensive care unit in Finland, long-term fluconazole prophylaxis has resulted in persistence of a fluconazole-resistant strain of *C. parapsilosis* causing repeated infections (91). In a study of 409 ELBW infants compared to historical controls, fluconazole prophylaxis significantly decreased invasive *Candida* infections and mortality due to *Candida* infections (92). In this study where fluconazole prophylaxis was continued for 4 years, no fluconazole-resistant *Candida* isolates or change in the epidemiology of *Candida* infections was observed. In another study, fluconazole prophylaxis targeted to VLBW infants on broad-spectrum antibiotics (n=206) and compared to a historical control (n=178), fluconazole prophylaxis significantly decreased invasive fungal infections and was cost-effective. Most of the infections in the control group (no fluconazole prophylaxis) were caused by *C. parapsilosis* (93). Some *C. parapsilosis* isolates (1.5 to 4%) show *in vitro* resistance to itraconazole, an azole that is rarely used in neonates (85). Approximately 1.9% of *C. parapsilosis* strains are resistant to voriconazole *in vitro* but most fluconazole-resistant strains are sensitive to voriconazole (89). The echinocandins, caspofungin, micafungin and anidulafungin, though not the first choice in the treatment of neonatal invasive candidiasis, may be useful in resistant cases. *C. parapsilosis* isolates show increased echinocandin minimum inhibitory concentrations (MIC) *in vitro* (85) but the clinical relevance of this is unclear as echinocandins have been effective *in vivo* (94–96). However, breakthrough infections have occurred in patients on caspofungin therapy. Caspofungin concentrations above the MIC paradoxically promote growth of *C. parapsilosis* in some instances (97). Increased caspofungin usage has also been associated with increased incidence of *C. parapsilosis* fungemia (98). These observations raise concern regarding widespread usage of caspofungin in neonates for the fear of selecting resistant *C. parapsilosis* infections.

Management Strategies for Neonatal *C. parapsilosis* Infections

A typical patient with invasive *C. parapsilosis* infection is a preterm VLBW infant with a central line receiving parenteral nutrition and on antibiotics. Management includes removal of the central venous line and systemic amphotericin B therapy. Delayed removal of central line in patients with candidemia increased the duration of blood culture positivity by a median of 3 days irrespective of the *Candida* species and increased mortality in *C. albicans* infections (99). In this study, it is also noteworthy that there was a significant difference of mortality between *C. albicans* and *C. parapsilosis* infections (24 vs. 4%). In a prospective cohort study of over 4500 infants born at < 1000 g from the National Institute of Child Health and Human Development sponsored Neonatal Research Network, delayed (≥2 days) removal of catheter in infants with positive blood cultures for *Candida* was associated with increased death or neurodevelopmental impairment in multivariate regression analysis [odds ratio 2.69 (1.25–5.79), p=0.01] (29). Also a trend toward delayed clearance of *Candida* from the blood was observed in the delayed removal group; 7.3 vs. 5 days, p=0.11. Persistence of candidemia for 5 days or more is associated with an increased risk of ophthalmologic, renal or cardiac dissemination compared to infants with lower duration of candidemia (100). Hence prompt removal of the infected central venous catheter is recommended after diagnosis of candidemia.

Systemic amphotericin B therapy is continued via a peripheral intravenous line until blood cultures are clear of *C. parapsilosis* for at least 2 cultures, after which replacement of the central venous line can be considered. Also, in any patient with an invasive fungal infection, additional foci of infection should be explored by cultures of urine and CSF, echocardiogram, fundoscopy and sonograms of the kidneys and the liver. Liposomal amphotericin may be an option in neonates with renal or hepatic dysfunction and *in vitro* studies demonstrate higher efficacy of liposomal amphotericin against biofilms of *Candida*

than amphotericin B (101–103). However, a recently published large retrospective cohort study with 730 neonates with candidiasis has reported higher mortality and higher therapeutic failure rates in neonates treated with amphotericin lipid products (that includes liposomal amphotericin) compared to conventional amphotericin or fluconazole (104). Nearly a fourth of invasive *Candida* infections are associated with a concurrent bacterial infection (often Coagulase negative Staphylococci and Enterococci) that need appropriate antibiotic therapy (100, 105, 106).

Persistence of *C. parapsilosis* fungemia in spite of removal of central venous line should prompt evaluation of antifungal susceptibility of the isolate and consideration of echinocandins (caspofungin or micafungin) as 'add on' or replacement therapy. Combination of amphotericin B with echinocandins is effective *in vitro* but there are very few studies that have tested them *in vivo* (107). Duration of antifungal therapy is 2 to 3 weeks after the last positive blood culture in candidemia and 1–2 weeks for isolated urinary tract infection (108). However, *Candida* in the urine may be the first manifestation of candidemia and hence systemic evaluation for candidemia is necessary. Longer duration of therapy of 4 weeks is considered in the presence of meningitis, 6–12 weeks for endopthalmitis and at least 6 weeks in endocarditis with or without surgical therapy. Empirical antifungal therapy has been advocated in neonates at high risk of nosocomial infections such as those on cephalosporins or other clinical and laboratory parameters but needs careful consideration (109).

Prevention of *C. parapsilosis* Infections

Prevention should target the horizontal transmission of *C. parapsilosis* in the neonatal unit. Monitoring and surveillance for *C. parapsilosis* infections, awareness and compliance with hand hygiene, bundled strategies for prevention of central venous catheter infections and antifungal prophylaxis are important strategies (110). The benefit of isolation measures such as cohorting or single room isolation of neonates who are colonized or infected with *Candida* is not clear (111). It is also paramount to create awareness, institute educational policies for health care staff and provide feedback as a part of a quality improvement initiative.

General preventive strategies include initiation of early human milk feeding to decrease dependence on central venous lines and parenteral nutrition. Judicious use of antibiotics, avoiding broad-spectrum antibiotics such as cephalosporins, steroids, H_2 blockers and proton pump inhibitors is recommended. Antifungal prophylaxis strategies may be useful in decreasing colonization and subsequent invasive fungal infections. A meta-analyses of 638 infants in 7 trials found that prophylactic fluconazole significantly decreased invasive fungal infection [RR 0.23 (95% confidence interval 0.11, 0.46)] but not mortality prior to hospital discharge [RR: 0.61 (95% confidence interval 0.37, 1.03)] (88). However, the baseline fungal infection rate was high in the placebo arm in the included trials. Targeted fluconazole prophylaxis in VLBW or ELBW infants with risk factors is an alternative strategy that may be effective. Follow-up of ELBW infants at 8–10 years, who received fluconazole prophylaxis in the neonatal period revealed no adverse effects on neurodevelopment or quality of life (112). Another meta-analysis of 1625 infants in 3 trials found that oral or topical non-absorbed antifungal prophylaxis (nystatin or miconazole) significantly decreased invasive fungal infections [RR 0.19 (95% confidence interval (CI) 0.14, 0.27)] but not mortality [RR 0.88 (95% CI 0.72, 1.06)] (113). The choice of nystatin vs. fluconazole prophylaxis in preventing invasive *Candida* infections including their relative efficacies and safety has been debated (114).

Conclusions

C. parapsilosis infections are a significant problem in the premature neonate and contribute significantly to neonatal mortality and morbidity. *C. parapsilosis* infections are responsible for a third of neonatal *Candida* infections and have a mortality rate of approximately 10%. The reasons for predilection of *C. parapsilosis* infection in neonates are not clear but adherence to skin and biomaterials leading to biofilm formation may be important determinants. Advances in microbial genetics and availability of tools for genetic manipulation will help us understand the virulence and other organism characteristics responsible for neonatal pathogenicity of *C. parapsilosis*. Amphotericin B remains the antifungal drug of choice and combination therapy with caspofungin or other echinocandins may be considered in resistant cases. Early enteral feeding with human milk and early removal of central venous lines, avoidance of steroids, H_2 blockers, judicious use of antibiotics and antifungal prophylaxis may decrease *C. parapsilosis* infections.

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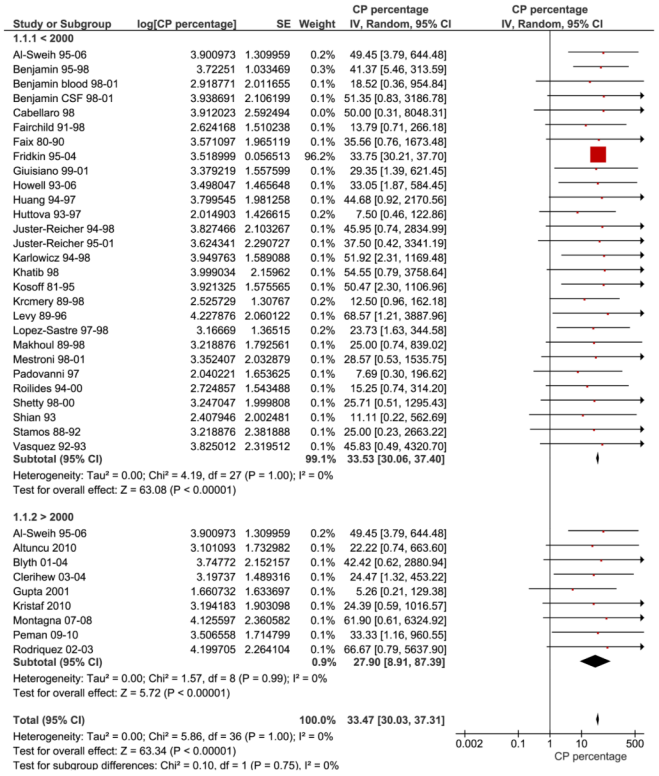

Fig. 1. Forest plot depicting percentage of *C. parapsilosis* infections

Red squares and black horizontal lines through the squares represent proportion with 95% confidence intervals. First subgroup labeled 1.1.1 represents studies that were predominantly performed before the year 2000 and the second subgroup labeled 1.1.2 represents studies performed after the year 2000. Abbreviations: CP – *Candida parapsilosis*, SE- standard error, IV- inverse variance, Random-Random effects model for meta-analyses, CI- confidence intervals.

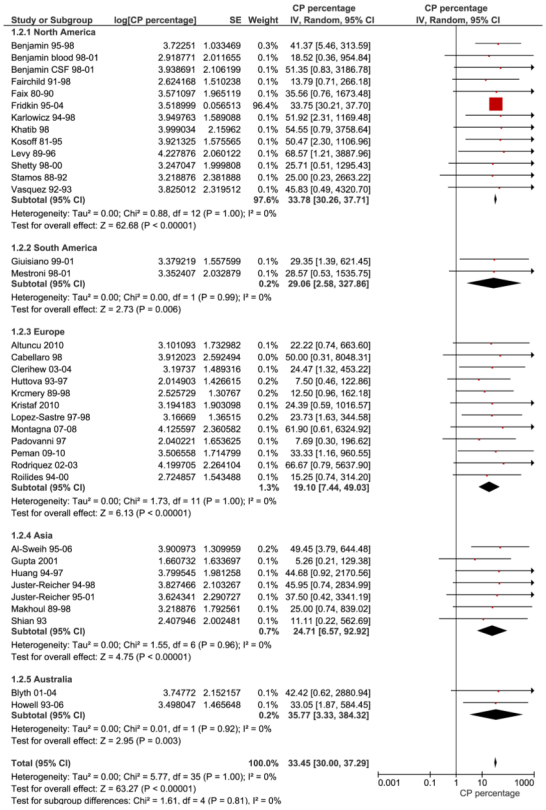

Fig. 2. Forest plot of percentage of *C. parapsilosis* infections by geographical regions

Red squares and black horizontal lines through the squares represent proportion with 95% confidence intervals. Studies were sub grouped into 5 different regions; North America (12 studies), South America (2 studies), Europe (12 studies), Asia (7 studies) and Australia (2 studies). Abbreviations: CP – *Candida parapsilosis*, SE- standard error, IV- inverse variance, Random-Random effects model for meta-analyses, CI- confidence intervals.

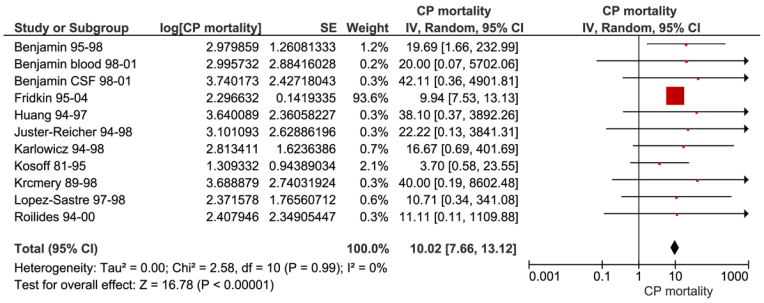

Fig. 3. Mortality of *C. parapsilosis* infections

Red squares and black horizontal lines through the squares represent proportion with 95% confidence intervals. The combined mortality of neonatal *C. parapsilosis* infection was 10.02 [95% CI 7.66, 13.12]. Abbreviations: CP – *Candida parapsilosis*, SE- standard error, IV- inverse variance, Random- Random effects model for meta-analyses, CI- confidence intervals.

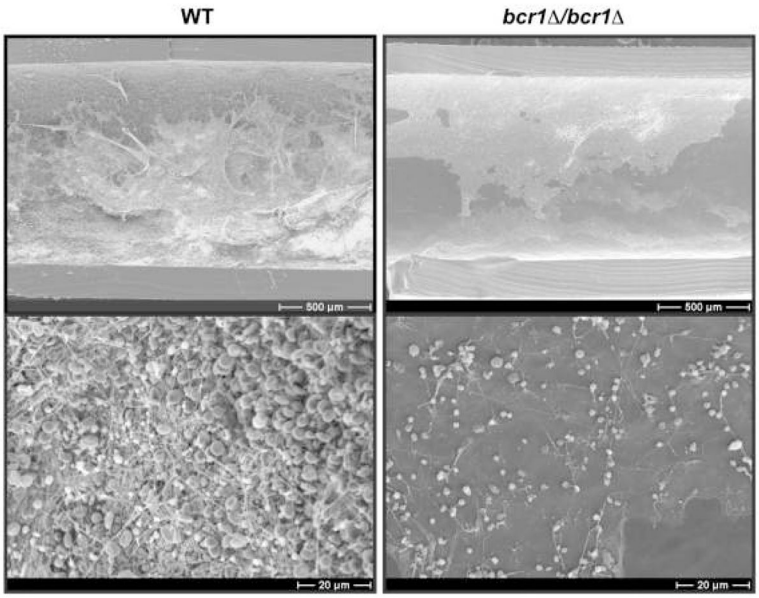

Fig. 4. Electron microscopy of *in vivo* biofilms

Biofilm formation on central venous catheters inserted into rats and inoculated with *C. parapsilosis* (wild type strain CLIB214) and a *bcr1* deletion (CDb71) strain. The catheters were removed after 24 hrs and visualized using scanning electron microscopy at two different magnifications. The wild type strain formed a thick biofilm, whereas the *bcr1* deletion strain displayed impaired biofilm formation, indicating the essential role of the transcription factor BCR1 in biofilm formation. [Reproduced with permission from Ding C, Vidanes GM, Maguire SL, Guida A, Synnott JM, Andes DR and Geraldine Butler. Conserved and divergent roles of Bcr1 and CFEM proteins in *Candida parapsilosis* and *Candida albicans*. PLoS One. 2011;6(12):e28151].

Table 1

Years of publication	Number of publications
1990–95	22
1996–2000	32
2001–05	68
2006–2010	79

Increasing awareness and reports of *C. parapsilosis* infections in neonates observed on review of literature. We searched for publications using the search terms '*Candida parapsilosis*' and 'neonat*' and plotted in epochs of 5 years.

Table 2

Reports of neonatal *C. parapsilosis* infections from 1990 to 2012 with > 10 clinical patients or isolates

Reference	Period of study	Reported	Place	Bwt	GA	No of infections				Mortality			Comments
						CP	CA	OT	Total	CP	CA	All	
Faix et al (115)	1980–90	1992	USA			16	29		45	0/16	7/29	7/45	
Shian et al (116)		1993	Taiwan			2	16		18			10/18	
Saxen et al (117)	55 mths	1995	Finland	Mean 817g	Mean 28 wks				58				Study of CP only
Stamos et al (118)	Jan 88–Oct 92	1995	USA		Preterm infants	4	9	3	16				65 pediatric patients
Padovani et al (119)		1997	Italy	Mean 1405 g	Mean 29 wks	2	23	1	26			11/26	
Vazquez et al (120)	1992–93	1997	USA	Mean 890 g	Mean 26 wks	11	7	24					
Huttova et al (121)	Jan 93–Dec 97	1998	Slovakia	Median 1290 g	Median 33.5 wks	3	37		40			8/40	
Cabellero 1998 (122)	Mar 94–Sep 97	1998	Spain		2 term and 12 preterm	7	7		14			3/14	
Kossoff et al (10)	Jan 81–Dec 95	1998	USA	Median 765g	Median 26 wks	54	50	3	107	2/54	13/50	29/107	
Levy et al (123)	1989–96	1998	USA			24	9	35				4/35	Study in children 0–20 yrs of age. (80 patients)
Khatib et al (124)		1998	USA			18	15		33				
Huang et al (125)		1999	Taiwan	Mean 1249g	Mean 29.2 wks	17	0		17				Study of CP only
Benjamin et al (109)	Jan 95–Jul 98	2000	USA	Mean 1178g	Mean 27.6 wks	19	15	3	37	8/19	5/15	13/37	
Karlowicz et al (99)	Jan 94–Dec 98	2000	USA	Range 426–3190 g	Range 23–40 wks	54	44	6	104	9/54	2/44	11/104	Study of Catheter-associated Candidemia
Juster-Reicher et al (103)	Sept 94–Jan 98	2000	Israel	Mean 847g	Mean 26 wks	9	12	3	24	2/9	2/12	4/24	Study of liposomal amphotericin
Huang et al (126)	Jan 94–Jul 97	2000	Taiwan	Range 768–3700 g	Range 25–42 wks	21	24	2	47	8/21	9/24	17/47	
Krcmery et al (127)	1989–98	2000	Slovakia			10	68	2	80	4/10	22/68	27/80	Slovakia fungal group
Gupta et al (128)	6 mths	2001	India			1	4	14	19				
Makhoul et al (129)	Jan 89–Dec 98	2001	Israel			13	21	18	52				
Fairchild 2002 (106)	1991–98	2002	USA			8	41	9	58				
Juster-Reicher 2003 et al (102)	Jul 95–Jan 01	2003	Israel	Median 860 g	Median 26 wks	17	15	5	37			1/37	Study of high dose liposomal therapy
Mestroni et al (130)	Nov 98–Aug 01	2003	Argentina			10	9	16	35				Included 46 adults.
Lopez-Sastre et al (131)	Jul 97–Dec 98	2003	Spain			28	62	28	118	3/28	5/62	12/118	
Roilides et al (132)	Oct 94–Dec 00,	2004	Greece	Mean 1457g	Mean 30 wks	9	38	12	59	1/9	15/38	17/59	
Giusiano et al (133)	Sept 99–01	2004	Argentina			27	32	33	92				
Shetty et al (134)	Oct 98–Sep 00	2005	USA	Median 685g	Median 25 wks	9	19	7	35			7/35	
Benjamin et al 2006 (29) Candidemia	Sept 1998–Dec 31 2001	2006	USA	< 1000 g		127	147	33	307	25/127	63/147	97/307	
Benjamin et al 2006 (29) meningitis	Sept 1998–Dec 31 2001	2006	USA	< 1000 g		5	20	2	27	1/5	7/20	8/27	

CP- *C. parapsilosis*, CA- *C. albicans* and CT-OT- Others which include *C. tropicalis, C. glabrata, C. lusitaniae, C. krusei, C. dublinensis and C. rugosa*

Studies **excluded** were Viudes et al (143) (neonatal data could not be extracted), Sarvikivi et al (91) (focused on fluconazole consumption and resistance in *C. parapsilosis*), Frezza 2005 (144) (pulmonary candidiasis only) and Rodriguez 2006 (145) (same as Rodriguez 2010 (25).