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A Nationwide Cohort

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Pediatric Candidemia Epidemiology and Morbidities: A Nationwide Cohort

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Abstract

Introduction

Candidemia is the most frequent pediatric fungal infection, but incompletely elucidated in population-based settings. We performed a nationwide cohort study including all pediatric patients with candidemia in Denmark from 2004-2014 to determine age, incidence, species distribution, underlying diseases, patient management and outcomes.

Methods

All candidemia episodes were identified through the active nationwide fungemia surveillance program. Susceptibility testing followed the EUCAST E.Def 7 reference method. Chi-squared test, Fisher's exact test and Venn diagrams were used for statistical analyses.

Results

153 pediatric patients (≤15 years) with 158 candidemia episodes were identified. The overall annual incidence rate was 1.3/100,000 population, higher for neonates (5.7/100,000 live births) and low birth weight (LBW) neonates (103.8/100.000 live births). From 2004-9 to 2010-2014, the proportion of *C. albicans* decreased from 74.4% to 64.7%, whereas fluconazole resistance increased from 7.8% to 17.7%. Virtually all patients had at least one underlying disease (98.6%) and multi-morbidity was common (43.5%, ≥2 underlying diseases). Underlying diseases differed by age with heart malformations and gastrointestinal disease prevalent in children younger than 3 years. The overall 30-days mortality was 10.2% and highest for neonates (17.1%). Mortality increased from 2004- to 2010-14, driven by an increase among older children.

Discussion

This first nationwide epidemiologic study of pediatric candidemia confirmed a high incidence among neonates and a substantial burden of comorbidities. Moreover, an increasing proportion of

fluconazole resistant non-albicans species was observed. Our findings underline the importance of choosing correct treatment and continuous surveillance of pediatric candidemia.

Introduction

Candidemia is the most frequent invasive fungal infection in pediatric patients, but remains a rare disease as indicated by the few previous population-based studies. Annual incidence rates have been reported in the range of 0.81-10.5/1000 admissions in single and multi-hospital studies (1–4). Incidence rates from population-based studies also vary extensively, but are consistently higher for infants (<1 year) than non-infants with rates in infants ranging from 6.9 to 96.4/100.000 live births (5–11). The diverging incidence rates call for further insights into clinical characteristics of pediatric candidemia. For instance, it is not clear whether changes in species distribution towards non-albicans species have taken place in children as well as in adults (12). Most studies have been limited to well-recognized risk groups such as patients in neonatal intensive care units (NICU) and patients with hematological diseases. Population-based studies describing clinical characteristics of pediatric candidemia patients are sparse.

We aimed to investigate incidence, species distribution, underlying diseases, patient management and outcome by age and time in a nationwide cohort study of pediatric candidemia patients during an 11-year period.

Methods and Materials

Health care system

The Danish health care system is tax financed and divided into 5 health regions. Children up to the 15 years of age are admitted to pediatric departments. Treatment guidelines distinguish between pediatric and adult patients.

Study population

The Danish population increased from 5,397,640 to 5,627,235 during the study period. Candidemia patients were identified through the national reference mycology laboratory and completeness was ensured in collaboration with all departments of clinical microbiology as previously described

(13,14). Collaboration with local pediatricians was established for review of patient charts as instructed by the National Health Authorities. Data were collected using structured questionnaires in REDCap (Research Electronic Data Capture), a secure web-based application hosted at Aarhus University (15).

Clinical data included 1) underlying diseases; preterm birth, low birth weight (LBW≤2500 g), gastrointestinal disease, prior infection, heart malformations, hematological diseases (malignancies (n=30), hemophagocytic lymphohistiocytosis (n=1), aplastic anemia (n=2)), solid cancers, hepatobiliary disorders and others, 2) treatment regimens; use of central venous catheter (CVC), chemotherapy, corticosteroids, mechanical ventilation, total parenteral nutrition (TPN) and surgery, 3) antifungal treatment; compound, date of initiation and termination, 4) stay in ICU, and 5) information on length of hospital stay (Supplemental Table 1; http://links.lww.com/INF/D307).

Optimal antifungal treatment (AFT) upon species identification was assessed according to susceptibility classification (EUCAST) (16). Microbiological data on blood cultures and colonization (examinations of colonization performed 7 days before to 3 days after candidemia) were collected from the laboratory information systems. Date of death was obtained from patient charts up until the date of data collection yielding minimum 2 years of follow-up for all patients; the local clinicians evaluated if death was attributable to candidemia, or not possible to assess.

Change or removal of CVC was calculated among patients with CVC and surviving ≥2 days for CVC removal/change to be possible.

For the clinical evaluation, patients were categorized as neonates (age ≤28 days), infants (29 days-2 years), and older children (3-15 years).

Ethics

Ethical permission for data collection was obtained from the Danish Health authorities (journal no 3-3013-1427/1/) and the Danish Data Protection Agency (journal no *2007-58-0010*).

Statistical analyses

Incidence rates were calculated for all candidemia patients, and separately for neonates (<28 days), infants (<1 year) and non-infants (1-15 years) using denominators for corresponding years obtained from Statistics Denmark (http://www.statistikbanken.dk). Incidence rates for neonates were calculated by dividing the number of candidemias in neonates with the total number of live births. When calculating incidence rates for infants the denominator included neonates because it was not possible to separate neonates from the population of ≤1-year old infants obtained from Statistics Denmark.

In line with previous studies we categorized age as neonates (age ≤28 days), infants (29 days-2 years), and older children (3-15 years) in order to describe and compare clinical characteristics and outcomes across age (2,3). For each age group, we summarized continuous variables by median and interquartile range (IQR) and reported numbers and proportions for discrete variables. To assess changes over time, the study period was divided: 2004-2009 and 2010-2014. Chi-squared test was used for categorical data and Fisher's exact test for variables with less than 10 observations. Venn diagrams were used to visualize the distribution of underlying diseases according to age group using "Venn Diagram Maker online" (17). Patients were followed from the collection date for the positive blood culture and we assessed all-cause mortality at day 2, 14 and 30. In these analyses, only first-time episodes of candidemia were included in order to preserve the assumption of independent observations. Statistical analyses were performed with Stata®, v. 14 (StataCorp).

Results

Patients and incidence rates

From January 2004 to December 2014, 153 pediatric patients with 158 episodes of candidemia were identified (Figure 1). One episode was poly-fungal and five children had two episodes of candidemia. Clinical data was available for 91.8% (145/158) of all candidemia episodes of which

24.1% (35/145) were neonates, 39.3% (57/145) were infants, and 36.6% (53/145) were older children. The median age for non-neonatal patients (29 days-15 years) were two years (IQR: 0-6 years).

The annual number of patients varied from 12 episodes in 2005 and 2012 to 18 in 2009 with the majority of patients (93.1%, 147/158) being admitted at one of the four large university hospitals at the time of diagnosis. The overall annual incidence rate for candidemia episodes was 1.3/100,000 population, whereas the age specific annual incidence rate varied from 10.2/100,000 population for children aged <1 year to 0.8/100,000 population for children aged 1-15 years (Figure 2). The annual incidence rate for neonates was 5.7/100,000 live births; in LWB neonates it was 103.8/100.000 LWB births. Overall, the incidence remained stable over time (Figure 2a).

Species distribution

The species distribution and proportion of isolates with fluconazole resistance differed by age group and study period (Figure 2b). *Candida albicans* remained the predominant species across all age groups during the study period. Nonetheless, the proportion of *C. albicans* declined over time, in particular among the oldest children (70.6% in 2004-2009 to 54.2% in 2010-2014) (Figure 2b). Among non-*C. albicans* species, *C. parapsilosis* was most prevalent in infants in both periods (19.7%) and in older children in the first period (2004-2009; 14.7%), whereas *C. krusei* and *C. glabrata* was most common among the older children in the most recent period (2010-2014; 25%). Overall, fluconazole resistance among *Candida* isolates was 12.0% and the prevalence increased from 7.8% in 2004-2009 to 17.7% in 2010-2014 (p=0.051). Fluconazole resistance was most prevalent in the older children in whom resistance rose from 8.8% to 33.3% during the study period (p=0.023).

Patient characteristics and underlying diseases

Most patients were males (58.2%) though the male dominance decreased with increasing age (Table 1). ICU stay, sepsis, TPN and mechanical ventilation were most prevalent among neonatal patients and decreased with increasing age (Table 1). Conversely, body temperature and CRP were lower among neonates compared with older patients, as were the proportion of patients with CVC (Table 1). Removal or change of CVCs was performed in the majority of patients and slightly more frequently among the neonatal patients (88.2%). Four-fifths of non-neonatal patients had prior hospital contact before the current admission with candidemia in contrast to one-third of neonatal patients (80.2% vs. 32.4%). Surgery within the prior 30 days was most frequent among infants compared with neonates and older patients (44.2%) (Table 1). Virtually all patients had at least one underlying disease (98.6%) and with a considerable overlap between the underlying diseases (Figure 3). Multi-morbidity (defined as two or more underlying diseases) was present in 43.5% of patients, the highest proportion of multi-morbidity was found among the older children (47.2% vs. 42.9% in neonates and 40.4% in infants). The diversity of underlying diseases was highest among non-neonatal patients (Figure 3). Prematurity was common among the neonates (71.4% were born before a gestational age of 32 weeks), and all preterm neonates had LBW (76.0% had a birth weight <1000 g). The most frequent underlying disease for infants was gastrointestinal disease (35.1%), for older children it was hematological disease (39.6%). Heart malformations were especially prevalent in the two youngest age groups (22.9% in neonates and 12.3% in infants). The proportion of solid cancers and hematological disease increased with age (none in neonates, 12.3% and 21.1% in infants, 18.9% and 39.6% in older children, respectively). Patients with hematological diseases were distinct with regard to species distribution as less than half had *C. albicans* candidemia (*C. albicans* 48.5%), and a larger proportion had fluconazole resistant species compared to non-hematological disease patients (27.3% vs. 6.3%, p-value 0.002).

Antifungal treatment

One-fourth of all patients had received AFT within 7 days prior to the blood culture positive for candida was obtained. This proportion 2-3 doubled with age (Table 2). Prior AFT was given daily in all but one patient, and for more than seven days in 11% (2.7% of neonates, 12.0% of infants and 17.7% of older children). Prior AFT was most prevalent among patients with hematological disease (63.5% and 39.4% with ≥7 day's duration). Seven or more days of prior AFT was associated with higher proportion of non-albicans species (80.0%), whereas the species distribution was comparable among patients with less than 7 days prior AFT (16.7% non-albicans) and AFT naive patients (26.2% non-albicans) (p=0.000, non-albicans vs *C. albicans* in all three groups). Prior AFT was also associated with subsequent fluconazole resistant species compared to no prior AFT (27.3% vs. 4.9%, p-value 0.001). The proportion of fluconazole resistant species was greater in patients with ≥7 days duration of prior AFT compared to <7 days duration and no prior AFT (40.0% vs 18.5% and 5.8%, p=0.001).

The majority of children received AFT after blood culture collection (88.2%). Neonatal patients and older children most commonly received azoles (42.9% and 39.2%), whereas infants most commonly received amphotericin B (40.0%). Initial antifungal treatment was optimal for the majority of treated patients (95.8%) with no difference by age.

Outcome

The overall 30-day mortality was 10.2%, and for all time-points highest among neonates and lowest among infants (Table 1). Mortality was not associated with choice of AFT and numbers were too small to adjust for underlying diseases. The overall 30-day mortality was considered attributable to candidemia in five deaths (35.7%), unrelated to candidemia in five deaths (35.7%) whereas in four deaths (28.6%) it was not possible to assess the cause of death. 90-day mortality was 15.3% (21/137). Seven patients died from day 30-90; five of these deaths (71.4%) were assed as

attributable to candidemia and two deaths (28.6%) as "unrelated to candidemia". Thus, indicating an overall attributable mortality of 3.7% at day 30 and 7.3% at day 90.

The overall 30-day mortality for primary candidemia increased from 6.6% in 2004-2009 to 14.8% in 2010-2014 (p-value 0.099). This increase occurred among older children (30-day mortality was 0% (0/29) in 2004-9 vs. 27.3% (6/22) in 2010-2014) (p-value 0.003). Four of the six deaths occurred in patients with underlying hematological disease.

Discussion

This nationwide pediatric candidemia cohort study showed a stable incidence during 2004-2014. The incidence was substantially higher in neonates, and ten times higher in LBW neonates. *C. albicans* was the predominant species, though the proportion declined over time and with prior AFT for ≥7 days duration. Fluconazole resistance increased over time, in particular among the older children. Virtually all children had at least one underlying disease; most neonates were immature and acutely ill. Gastrointestinal disease and recent surgery was frequent in infants, whereas older children had solid cancers or hematological disease. Heart malformations and gastrointestinal disease were identified as important risk factors in neonates and infants. Choice of AFT varied across age groups but the proportion with optimal treatment was consistently high regardless of age. Overall 30-day mortality was 10.2%, highest among neonates (17.1%) and increasing over time.

The incidence rate of 0.8/100.000 population among children aged 1-15 years is comparable with rates reported in previous studies (0.25-2.6 per 100.000 population) (5–7,11,18,19). Conversely, the incidence of 10.2/100.000 population for infants <1 year was higher than reported in our neighboring countries Finland and Norway (6.9 and 7.5/100.000 population) (5,7), but markedly lower than in other population-based studies (15.7-96.4/100.000 population) (6,8,10,11,18). A considerable decline in incidence rates from 52.1/100,000 population in 2009 to 15.7/100.000 in 2015 was observed in a study from the US (11). An improvement in infection control precautions

was suggested to have caused the decline. The low and stable Danish incidence rate for children contrasts the high incidence rates for adult candidemia, suggesting genetic predisposition is not an important cause of the latter (12,20). Despite the notable decline in incidence rates in the US study, the rate reported for neonates remained twice as high as in our study (10.7 vs. 5.7/100.000 population), whereas an Australian study reported similar incidence rate for neonates of 4.4/100.000 population (19). We are unaware of other reports of population-based incidence rates for neonates. Our study extends these findings by providing estimates for LBW infants in a nationwide perspective. Further comparisons could be valuable to clarify what drives the high incidence among infants as well as the large national difference.

In line with our findings, a recent US study also showed a decline in *C. albicans* with increasing age (11). The proportion of *C. parapsilosis* varies by setting and age, and was low in our setting (13.3%) compared to estimates from Australia (38-42%) (19), Latin America (27%) (4), Taiwan (27%) (21) and Turkey (22%) (2). This may suggest appropriate infection control practices, as *C. parapsilosis* is the species most commonly found on the skin and associated with device infections (22). The increasing fluconazole resistance over time has not previously been reported among children. We demonstrated that fluconazole resistance was associated with use of antifungal prophylaxis and hematological disease. This underlines the importance of monitoring species distribution and resistance and to adjust treatment guidelines according to local epidemiology.

Our finding that neonatal patients were acutely ill with a high proportion of ICU admission, mechanical ventilation, sepsis and TPN while older children most frequently had hematological diseases and solid cancers is in concordance with previous studies (4,11,19). The high burden of multi-morbidity have not previously been recognized and illustrates the heterogeneity of the pediatric candidemia population, and furthermore identify the underlying diseases for each age group. Heart malformations and gastrointestinal disease were identified as common underlying

diseases with few other studies focusing on these diseases. An international study from 2007-11 with 196 pediatric patients found 16% with gastrointestinal disease (23), whereas an Australian study from 2001-4 with 142 pediatric patients found zero cases with gastrointestinal disease among neonates and 9.1% among non-neonate pediatric patients (19). Congenital heart disease was found among 11% in a single center study from US (3), heart valve disorders and cardiomyopathy together accounted for 12.6% in a US study with 192 candidemia patients (24). The high proportion of patients who presented with gastrointestinal disease or heart malformations in the current study, as well as gastrointestinal disease being an established risk factor among adult candidemia patients warrants further investigation.

The proportion of patients receiving prior AFT was comparable to previous studies (10.7-36%)(3,11,21,24). In line with what has been reported for adults (25), prior AFT for ≥7 days was associated with higher prevalence of non-albicans species. Furthermore, prior AFT was associated with higher proportion of fluconazole resistance in subsequent species. To our knowledge, this has not previously been reported for children and underlines the importance of addressing prior AFT in children and of local surveillance programs.

Data on mortality of pediatric candidemia is sparse and often not age-specific. The 30-day mortality of 10.2% is in line with estimates of previous studies (10-18%) (1,2,11), except from the high mortality rates from Latin America (28-40%, children and neonates) (4), which likely reflect differences in socio-economic factors. Attributable mortality, though complicated to assess, was 7.3% and indicates that candidemia is an important complication in these severely ill patients.

This study has limitations. When calculating incidence rates for neonates and LBW neonates we used livebirths as denominator. This likely leads to an underestimation of the rates, as not all in the denominator survive 28 days. Nevertheless, this calculation is in line with previous studies and the estimates are therefore comparable. Information regarding the clinical indication for AFT given

prior to candidemia was not obtained. Therefore, we were unable to discriminate between prophylaxis and early empiric treatment. However, our focus was the effect of prior AFT on the subsequent candidemia species distribution, which is independent of indication. Moreover, we were unable to determine the cause of death in 28.6% of mortality cases. The principal strength of this study is the high level of data completeness due to the Danish fungal surveillance program and overall registration systems enabling detailed information on this rare disease.

This nationwide epidemiologic study adds to the knowledge and understanding of candidemia in pediatric patients. Pointing out new underlying diseases associated with candidemia and demonstrating changes over time underlines the importance of continuous surveillance to improve management of these severely ill patients.

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Pediatric candidemia epidemiology and morbidities: a nationwide cohort

Table 1. Patient characteristics, treatment and outcome by age

	Neonates (0-≤28d)	**Infants** (≥29d-2y)	**Older children** (3-15y)	**Total**
Male sex, %(n)	60.0 (21)	59.7 (34)	52.8 (28)	57.2 (83)
Prior hospital contact*, %(n)	32.4 (11)	72.6 (37)	88.0 (44)	68.2 (92)
LOS before BCC, median(IQR) (days)	11 (7-18)	17 (5-32)	12 (2-23)	13 (4-23.5)
Intensive care unit, %(n)	51.4 (18)	43.1 (22)	22.0 (11)	37.5 (51)
Colonised with ***Candida****, %(n)	81.8 (18)	57.1 (20)	67.7 (21)	67.1 (59)
BC drawn from internal catheter, %(n)	33.3 (9)	70.8 (34)	80.9 (38)	66.4 (81)
Bacteriemia*, %(n)	37.1 (13)	19.6 (11)	24.0 (12)	25.5 (36)
Sepsis*, %(n)	60.0 (21)	38.0 (19)	24.5 (12)	38.8 (52)
CRP at BCC, median (IQR)*	35.5 (17.5-72.5)	52 (13-135)	71.5 (30-160)	58 (19-123)
Temperature at BCC, median (IQR)*	37.4 (37.1-38.5)	39 (38.2-39.7)	38.9 (38.3-39.3)	38.8 (38-39.4)
Treatment				
Antibiotic, %(n)	77.1 (27)	82.4 (42)	80.0 (40)	80.2 (109)
Chemotherapy, %(n)	0	33.3 (17)	45.1 (23)	29.2 (40)
Corticosteroid, %(n)	0	30.0 (15)	35.4 (17)	24.1 (32)
Mechanical ventilation, %(n)	60.0 (21)	30.0 (15)	10.0 (5)	30.4 (41)
CVC, %(n)	67.7 (23)	88.2 (45)	88.5 (46)	83.2 (114)
CVC changed after candidemia*, %(n)	88.2 (15)	75.0 (33)	69.1 (29)	74.7 (77)
TPN, %(n)	60.0 (21)	25.5 (13)	32.0 (16)	36.8 (50)
Surgery, %(n)	25.7 (9)	44.2 (23)	18.4 (9)	30.2 (41)
Outcome[1]				
Mortality day 0-2, % (n)	5.7 (2)	0	1.9 (1)	2.2 (3)
Mortality day 0-14, %(n)	11.4 (4)	0	7.6 (4)	5.8 (8)
Mortality day 0-30, %(n)	17.1 (6)	4.1 (2)	11.3 (6)	10.2 (14)

Total 145 patients; Neonates n=35, toddlers n=57, older children n=53. Missing values varied on variable.
LOS: Length of Stay, BCC: blood culture collection, IQR: Inter Quartile Range, BC: Blood Culture, CRP: C-Reactive Protein, CVC: Central Venous Catheter, Total Parenteral Nutrition,
[1]Primary patients; 5 recurrent patients excluded, *Defined further in supplementary

Tabel 2. Antifungal treatment by age

Antifungal treatment	Neonates %(n)	Infants % (n)	Older children % (n)	Total % (n)
	n=35	n=50	n=51	n=136
AFT within 7 days prior to BCC	11.4 (4)	22.0 (11)	35.5 (18)	24.2 (33)
Azoles	11.4 (4)	18.0 (9)	15.7 (8)	15.4 (21)
Echinocandins	0	0	9.8 (5)	3.7 (5)
Amphotericin B	2.9 (1)	6.0 (3)	15.7 (8)	8.8 (12)
≥2 AFT[1]	2.9 (1)	2.0 (1)	3.9 (2)	2.9 (4)
≥7 days duration of prior AFT	2.9 (1)	10.1 (5)	17.6 (9)	11.0 (15)
	n=35	n=50	n=51	n=136
AFT after BCC	85.7 (30)	86.0 (43)	92.2 (47)	88.2 (120)
Azoles	42.9 (15)	28.0 (14)	39.2 (20)	36.0 (49)
Echinocandins	14.3 (5)	20.0 (10)	31.4 (16)	22.8 (31)
Amphotericin B	28.6 (10)	40.0 (20)	33.3 (17)	34.6 (47)
≥2 AFT[2]	0	2.0 (1)	11.8 (6)	5.2 (7)
Initial AFT optimal[3]	85.7 (30)	82.0 (41)	86.3 (44)	84.6 (115)

AFT: Antifungal Treatment, BCC: Blood Culture Collection,

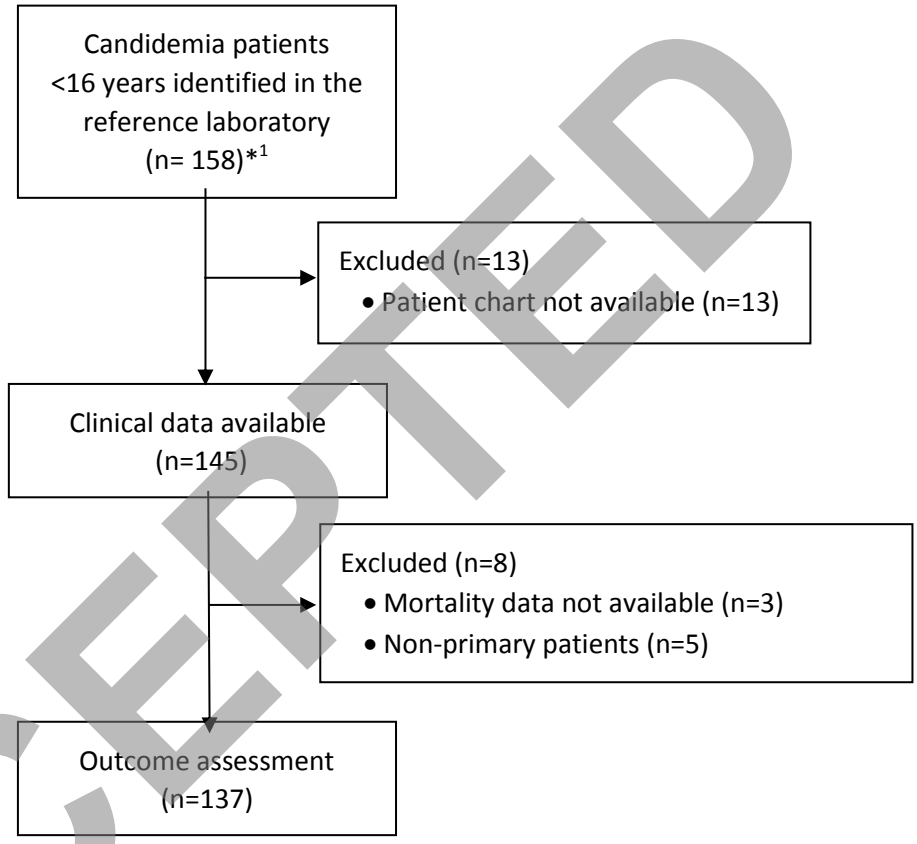
[1] Also included under each compund. Amphotericin B and fluconazole(1), amphotericin B and voriconazole(1), and caspofungin and voriconazole (1).

[2] Also included under each compound. Amphotericin B and caspofungin(4), amphotericin B and fluconazole(1), amphotericin B and voriconazole(1), one caspofungin and fluconazole(1).

[3]Non-optimally treated: 2 *C. parapsilosis* treated with echinocandins (MIC anidulafungin 1 µg/mL), 1 *C. krusei* treated with fluconazole (MIC fluconazole >16 µg/mL), 1 *C. guilliermondii* treated with echinocandins (MIC anidulafungin 2 µg/mL) and 1 *C. lusitaniae* treated with voriconazole (MIC voriconazole not performed in 2004).

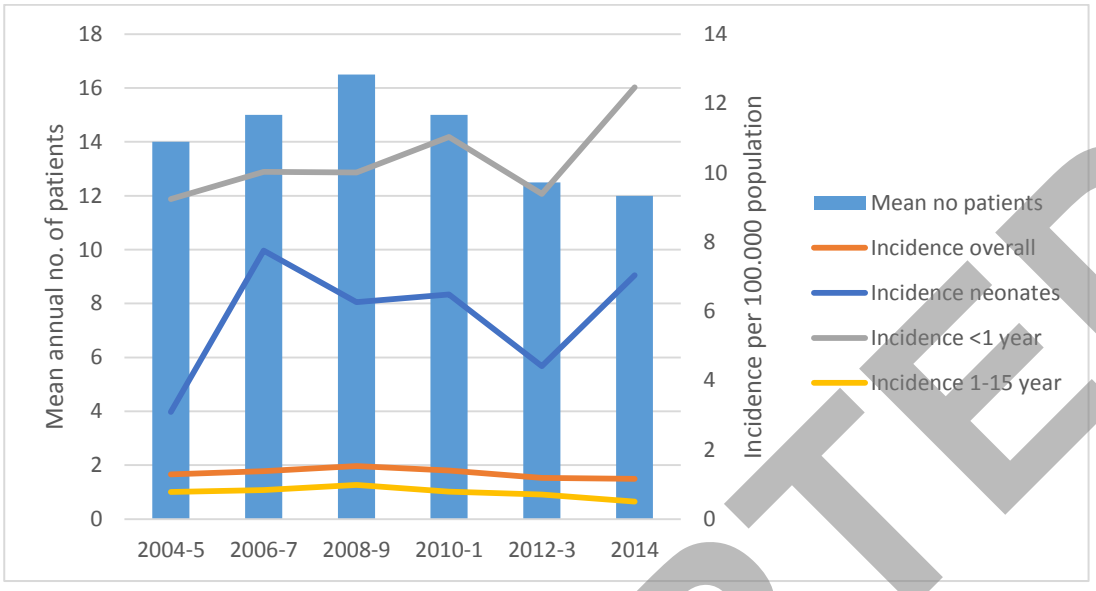
Tables and Figures

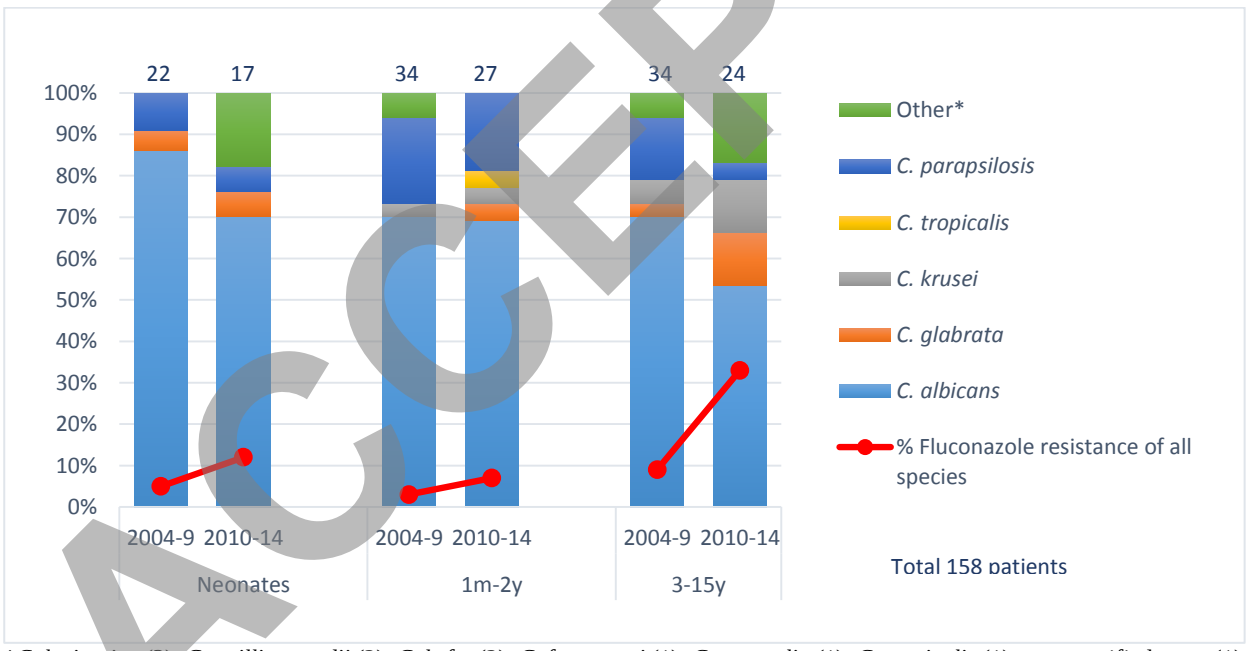
Figure 1. Flowchart of included patients



*[1]153 patients with 158 episodes of candidemia

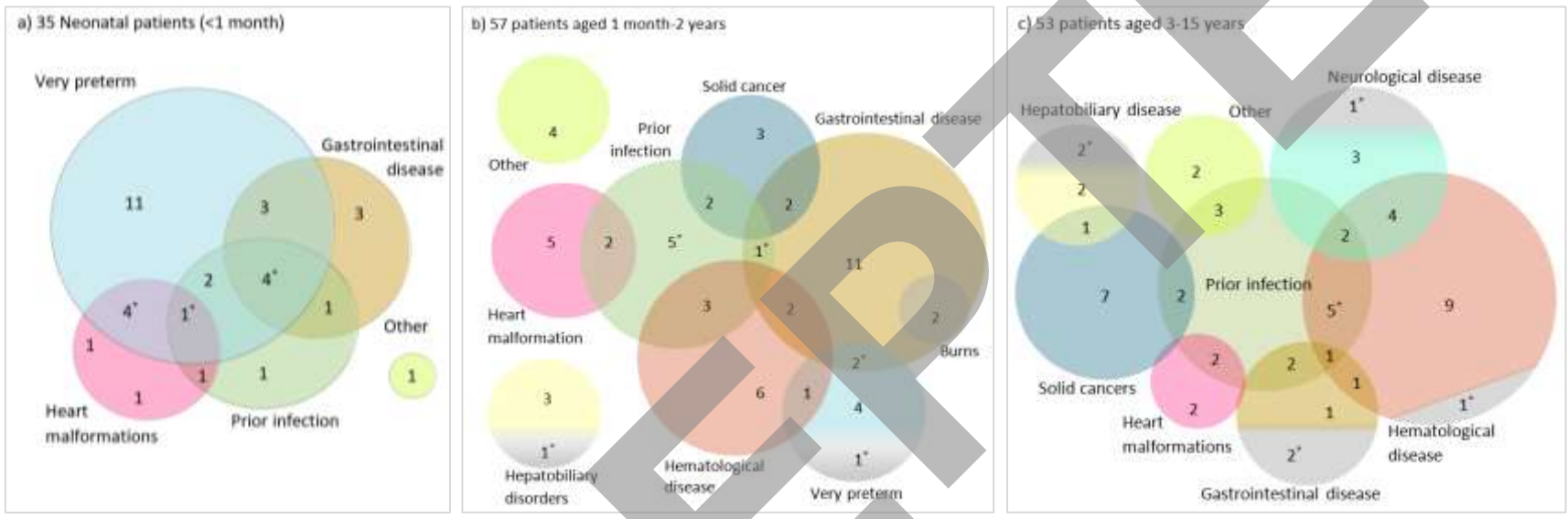
Figure 2. Epidemiology of pediatric candidemia in Denmark; (a) Number of patients and incidence rate of candidemia episodes; (b) and species distribution and fluconazole resistance proportion by age and study period





C. lusitaniae (3), *C. guilliermondii* (2), *C. kefyr* (2), *C. fermentati* (1), *C. magnolia* (1), *C. tropicalis* (1), non-specified yeast (1).

Figure 3. Venn diagrams of proportions of underlying diseases by age (from left to right neonates, toddlers and older children)



**Patients with more underlying diseases than possible to illustrate by overlapping circles. Full describtion of theese patients in supplementary Figure 1.*
a) 35 Neonatal patients (<1 month): Very preterm (71.4%); Gastrointestinal disease (31.4%); Prior infection (28.6%); Heart malformations (22.9%); Other (4.0%)
b) 57 patients age 1 month – 2 years: Gastrointestinal disease (35.1%); Prior infection (22.8%); Hematologic disease (21.1%); Very preterm (14.0%); Solid cancer (12.3%); Heart malformations (12.3%); Hepatobiliary disorders (7.0%); Other (7.0%); Burns (3.5%)
c) 53 patients age 3-15y: Hematologic disease (39.6%), Prior infection (32.1%), Solid cancer (18.9%), Neurological disease (18.9%), Gastrointestinal disease (13.2%), Hepatobilliar disease (9.4%), Other (9.4%), Heart malformations (7.6%).