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High incidence of candidaemia in a nationwide cohort: Underlying diseases, risk factors and mortality

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ABSTRACT

Background: Denmark has a high incidence rate of candidaemia. A Nordic study suggested a higher Danish prevalence of haematological malignancies as an underlying reason. This nationwide study ascertained clinical characteristics of Danish candidaemia patients and investigated potential factors contributing to the high incidence and mortality.

Methods: Microbiological and clinical data for candidaemia patients in 2010-2011 were retrieved. 30-day mortality was estimated by hazard ratios (HR) with 95% confidence intervals (CI, Cox regression).

Results: Data were available for 912/973 candidaemia episodes (93.7%). Intensive care unit (ICU) held the largest share of patients (43.2%). Prevalent host factors were multi-morbidity (≥2 underlying diseases, 74.2%) and gastrointestinal disease (52.5%). Haematological disease was infrequent (7.8%). Risk factors included antibiotic exposure (90.5%), CVC (71.9%) and *Candida* colonisation (66.7%). 30-day mortality was 43.4%, and 53.6% in ICU. Mortality was lower for patients with recent abdominal surgery (HR 0.70, 95% CI: 0.54-0.92).

Conclusion: A substantial prevalence of multi-morbidity and a high 30-day mortality was found. We hypothesise, that an increasing population of severely ill patients with prolonged supportive treatment and microbiological testing may in part explain the high candidaemia incidence in Denmark. Nationwide studies are warranted to clarify this issue.

Introduction

Candida species account for the majority of fungal bloodstream infections (BSIs) and the 30-day mortality ranges from 22-70% (Puig-Asensio et al., 2016; Lortholary et al., 2014; Chakrabarti et al.,

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2015; Nucci et al., 2013; Chen et al., 2006; Cleveland et al., 2012; Luzzati et al., 2016).

Denmark is known for a consistently high annual incidence rate of candidaemia of 7.6-11.0 episodes per 100,000 inhabitants since nationwide surveillance was introduced in 2004. In comparison, annual rates of 3.9-4.4 episodes per 100,000 inhabitants have been reported in similar studies from neighbouring Scandinavian countries (Arendrup et al., 2013; Hesstvedt et al., 2017; Arendrup et al., 2008). Nationwide annual data from other countries are sparse and limited to Australia with 2.4 per 100,000 inhabitants (Chapman et al., 2017), and Scotland with 4.1 per 100,000 inhabitants (Rajendran et al., 2016). Multiple regional population-based studies have been conducted, most of which have also reported lower incidence rates than in Denmark, with exception of Atlanta (13.3/100,000) and Baltimore (26.2/100,000) in 2008-11 (Cleveland et al., 2012). A recent comparison of candidaemia incidence across the Nordic countries suggested that a higher prevalence of haematological malignancies and higher utilisation of certain anti-bacterial drugs in Denmark could potentially explain the higher candidaemia rate (Hesstvedt et al., 2017). However, clinical characteristics of candidaemia patients, including underlying diseases and common risk factors, have not previously been included in nationwide studies.

The aim of this nationwide cohort study was to ascertain clinical characteristics of Danish candidaemia patients to identify high-risk patient groups in order to identify potential factors contributing to the high incidence in Denmark, and to assess prognostic factors associated with 30-day mortality in candidaemia patients.

Materials and methods

Setting, study population and data collection

The Danish health care system provides tax-supported health care for all citizens. There is free access to primary care provided by general practitioners, secondary care in non-university hospitals, and tertiary care in university hospitals. Departments of medicine provide both specialised and general care and are operated by multiple sub-specialities. Each resident in Denmark is assigned a unique personal identification number at birth or immigration, which allows individual-level linkage between health care registries.

This study included all unique episodes of *Candida* BSI in Denmark 1st January, 2010 to 31st December, 2011. Cases were identified as part of the ongoing national fungaemia surveillance programme, where the national Reference Mycology laboratory ensured completeness of cases through comparison with local laboratory reports (Arendrup et al., 2013, 2011a). Local clinical microbiologists collected patient data using an abstraction form including information on underlying diseases, department at time of candidaemia diagnosis, surgical procedures, central venous catheter (CVC), total parenteral nutrition (TPN), and antibacterial treatment. Paediatric cases (age <16 years of age) were included in the initial analyses of cases and departments, but later excluded, due to their separate risk factors and mortality rates.

Definitions

We included first episodes of candidaemia and recurrent episodes as defined in the Supplementary Table 1, where also definitions of baseline characteristics, treatment before blood culture collection (BCC), and underlying diseases are provided. Candidaemia was defined as a blood culture positive for *Candida* and a recurrent episode if more than 30 days between isolates (Nucci et al., 2013; Cleveland et al., 2012; Puig-Asensio et al., 2014; Barchiesi et al., 2015). Multi-morbidity was defined as the presence of two or more underlying and pre-existing diseases (Whitson and Boyd, 2017). The Candida Score was used to assess multiple risk factors (≥3 points) assigning one point each for TPN, abdominal surgery, colonisation, and two points for sepsis (León et al., 2006; Leroy et al., 2011).

Data on *Candida* species identification and susceptibility were extracted from the national reference laboratory at Statens Serum Institut. Procedures and isolates within the study period have been described elsewhere (Arendrup et al., 2013).

Data on hospital admissions and mortality

Rate of incidence per 100,000 population-year were calculated using population data and rates according to hospital admission were expressed as numbers of cases per 1000 admissions, using data obtained from Statistics Denmark (www.statistikbanken.dk). Data on Intensive Care Unit (ICU) admissions were obtained from the Danish Intensive Care Database Annual report from 2011 (Fynbo Christiansen, 2011). Mortality data were obtained from the Danish Civil Registration System, in which the vital status of all Danish citizens, including deaths and emigrations, are registered and updated daily (Pedersen, 2011). Early mortality was defined as death before blood culture results became available to the treating physician.

Ethics approval

Data collection was approved by the Danish Health authorities (Journal no 3-3013-364/1/) and the Danish Data Protection Agency (Journal no 2004-54-1627).

Statistical analyses

Quantitative variables were reported as median with interquartile range (IQR) and qualitative variables were reported as numbers (%). Categorical data were analysed using the chi-squared or Fisher exact test. Significance was set at a p-value of <0.05. For survival analysis follow-up was initiated on the collection date for the positive blood culture. Prognostic factors associated with 30-day mortality were assessed using Cox regression modelling to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the main risk factors and commonly associated underlying diseases. Only the first episode of candidaemia was included in survival analysis to preserve the assumption of independence of observations. Directed acyclic graphs (DAG) were used to evaluate confounders potentially influencing the relationship between mortality and candidaemia according to the published literature for the multivariate analyses (Supplementary Figure 2-10) (Textor et al., 2017). All statistical analyses were performed with Stata®, vs 14 (StataCorp).

Results

A total of 973 episodes of candidaemia were identified during the 2-year study period. Clinical data were available for 912 (93.7%) episodes, hereof 882 adults (Supplementary Figure 1). The national annual incidence rate of first episodes of candidaemia was 8.8 episodes per 100,000 population-years, 0.38 episodes per 1,000 admissions; the rate was 6.08 episodes per 1,000 ICU admissions, specifically.

Most candidaemia episodes were diagnosed in the ICU (43.2%) (Table 1). General departments of medicine and surgery accounted for 19.3% and 16.8%, respectively, whereas other departments each accounted for <5% of the cases including gastroenterology (4.4%), haematology (3.9%) and oncology (1.2%). Paediatric patients accounted for 3.3% of cases.

Table 1
Type of department at the time of candidaemia diagnosis and basic demographic data.

	Patients		Age (years)			Male gender
	No	%	Median	IQR[a]	% >75 y	%
Total	912	100.0	66	56-75	28.3	59.9
Intensive care unit	394	43.2	67	58-75	25.9	61.7
Departments of medicine	306	33.6	65	54-76	28.4	59.9
General Medicine	176	19.3	70	58-80	40.9	58.5
Gastroenterology	40	4.4	54	47-62	5.0	65.0
Haematology	36	3.9	59	48.5-68	11.1	67.4
Cardiology	18	2.0	64.5	59-71	16.7	83.3
Nephrology	14	1.5	58.5	57-76	28.6	50.0
Oncology	12	1.2	66	61.5-70.5	8.3	25.0
Infectious Diseases	9	1.0	45	34-69	11.1	55.6
Neurology	1	0.1	17	-	-	100.0
Departments of Surgery	166	18.2	70	61-78	35.5%	54.8
General Surgery	153	16.8	70	62-78	35.3	54.9
Urology	13	1.4	63	56-75	38.5	53.9
Paediatrics	30	3.3	1	0-4	0	60.0
Emergency department	16	1.8	81.5	60-87.5	62.5	56.3

[a] IQR: Interquartile range.

The overall median age was 66 years (IQR 56-75 years) and 67 years (IQR 57-75 years) for adult candidaemia, but varied according to department and was highest for departments of emergency (81.5 years, IQR: 60-87.5), followed by departments of general medicine and surgery (median 70 years, IQR: 60-79) (Table 1). Males accounted for 59.9%.

Host and risk factors among adult patients

Prevalent host factors, found in more than half of the patients, were multi-morbidity (74.2%), including a third with ≥3 underlying conditions, and gastrointestinal disease (52.5%), including 106 patients (12.0%) with short bowel disease or pancreatic disease (Table 2). In contrast few patients had an underlying haematological disease (7.8%). Prevalent risk factors were prior antibiotic exposure (90.5%), CVC (71.9%), and colonisation with *Candida* (66.7%) The proportion of patients with a Candida score of ≥3 was highest in the ICU setting (22.6% vs. 15.4% overall). The proportion of patients receiving TPN was equal in all settings (overall 23.8%). Neutropenia was infrequent (3.3% of all patients) and associated with haematological disease in 79.3% (23/29) of the cases. Only 11 (1.2%) patients had no recorded underlying diseases, other than an "acute infection" diagnosed prior to their candidaemia.

Mortality

Mortality analyses included the 852 primary cases (Supplementary Figure 1). Across all departments, a substantial proportion of patients (6% in surgery, 13.3% in medicine, and 17.7% in ICU) died before the results of blood cultures were available (Table 2). Compared with patients surviving longer, these patients were characterized by higher age (median age 72 years (IQR: 60- 79) versus 66.5 (IQR 57- 75)), more prevalent ICU stays (56.9% vs 42.6%, p-value 0.003), and fewer had a CVC (62.6% vs 73.5%, p-value 0.013) or received TPN (16.3% vs 25.1%, p-value 0.033).

The overall 30-day mortality was 43.4%, ranging from 53.6% among ICU patients to 34.8% among non-ICU patients. Mortality was lowest for departments of general surgery (30-day mortality of 24.8%) (Table 2). The 30-day mortality rate was, in multivariate analysis, numerically lower for patients with gastrointestinal disease (adjusted HR 0.85 95% CI: 0.69 -1.04) or solid tumours (adjusted HR 0.81, 95% CI: 0.62 - 1.06), and significantly lower for patients with abdominal surgery (adjusted HR 0.70, 95% CI: 0.54 - 0.92) when compared with patients without these conditions (Table 3). Conversely, haematological disease was associated with a numerically higher mortality (age adjusted HR 1.35, 95% CI: 0.95 - 1.91). High level of multi-morbidity (≥3 underlying diseases) was associated with higher mortality compared to non-multi-morbidity (≤1 underlying diseases) (adjusted HR 1.21 95% CI: 0.92 - 1.59), whereas a Candida score ≥3 was not associated with increased mortality compared with patients with low score (adjusted HR 1.06, 95% CI: 0.80 - 1.41) (Table 3). There were no differences in mortality by infecting *Candida* species (data not shown).

Discussion

In this nationwide cohort study, the incidence of candidaemia was highest in the ICU, accounting for more than 40% of all cases. Essentially all patients had underlying diseases and the majority multi-morbidity. Most common conditions were gastrointestinal disease, lung disease, and solid tumours. Risk factors were common and most frequent among patients in the ICU: prior antibiotics, CVC, colonisation with *Candida*, BCC from internal line, prior infection, and abdominal surgery. The overall 30-day mortality was 43%, highest in ICU patients (53.6%). Mortality was significantly lower among patients with recent abdominal surgery and numerically lower in patients with gastrointestinal disease and solid tumours, compared with patients without these conditions.

The overall incidence rate per admission was similar to rates reported from other candidaemia studies (0.21-0.89) although population based incidence rates were high (Chen et al., 2006; Puig-Asensio et al., 2014; Trouvé et al., 2017). One plausible explanation for this discrepancy is different registration practises for numbers of admissions in different countries. In Denmark, patient referrals between departments are registered as separate admissions, which inflates the denominator. A higher number of overall admissions in Denmark might also be explained by Denmark's easily accessible public health care system. On the other hand, our finding of an incidence of 6.08 episodes/1.000 admissions in the ICU is markedly higher than ICU rates reported in studies from ICU settings in Italy (3.4 episodes/1000 admissions) (Barchiesi et al., 2015) and France (3.5 episodes/1,000 admissions) (Baldesi et al., 2017). Part of this may be explained by the

Table 2
Patient characteristics by specialty.

	Total (n = 882) No. (%)	ICU (n = 394) No. (%)	General Medicine (n = 176) No. (%)	General Surgery (n = 153) No. (%)
Baseline characteristics				
Prior infection	320 (36.3)	132 (33.5)	85 (48.3)	33 (21.6)
Sepsis	100 (11.3)	52 (13.2)	17 (9.7)	10 (6.5)
Neutropenia	29 (3.3)	5 (1.3)	1 (0.6)	0 (0)
LOS before BCC, median days (IQR)[a]	12 (5, 23)	10 (6, 19)	11 (5, 30)	17.5 (7, 32)
BCC from internal line[b]	245 (36.3)	166 (53.6)	19 (14.8)	17 (13.4)
Colonised with Candida before BCC	588 (66.7)	311 (78.9)	100 (56.8)	77 (50.3)
Candida score ≥3[c]	136 (15.4)	89 (22.6)	43 (7.4)	15 (9.8)
Treatment before BCC				
Antibiotics	775 (90.5)	373 (95.9)	140 (82.8)	122 (84.1)
Central venous catheter (CVC)	634 (71.9)	351 (89.1)	74 (42.1)	102 (66.7)
Abdominal surgery	234 (26.5)	133 (33.8)	14 (8.0)	69 (45.1)
Total parenteral nutrition (TPN)	210 (23.8)	100 (25.4)	39 (22.1)	39 (25.5)
Corticosteroids	167 (18.9)	92 (23.4)	26 (14.8)	14 (9.2)
Dialysis	141 (16.0)	99 (25.1)	9 (5.1)	6 (3.9)
Chemotherapy	77 (8.7)	20 (5.1)	6 (3.4)	8 (5.2)
Underlying diseases				
Gastrointestinal disease	463 (52.5)	203 (51.5)	72 (40.9)	109 (71.3)
Lung disease	231 (26.2)	136 (34.5)	48 (27.3)	24 (15.7)
Solid cancer	170 (19.3)	61 (15.5)	21 (11.9)	61 (39.9)
Chronical heart disease	168 (19.1)	100 (25.4)	31 (17.6)	18 (11.8)
Renal disease	142 (16.1)	44 (11.2)	32 (18.2)	20 (13.1)
Endocrine disease	133 (15.1)	59 (15.0)	39 (22.2)	15 (9.8)
Alcohol and/or iv abuse	111 (12.6)	52 (13.2)	29 (16.5)	9 (5.9)
Haematological disease	69 (7.8)	22 (5.6)	8 (4.6)	3 (2.0)
Multi-morbidity, ≥2[d]	654 (74.2)	302 (76.7)	131 (74.5)	106 (69.3)
Multi-morbidity, ≥3[d]	283 (32.1)	145 (36.8)	54 (30.7)	34 (22.2)
Mortality[e]				
Early mortality[f]	122 (14.3)	69 (17.7)	23 (13.3)	9 (6.0)
0-30 day mortality	371 (43.4)	209 (53.6)	63 (36.4)	37 (24.8)

ICU: Intensive Care Unit, LOS: Length of stay, BCC: Blood culture collection, IQR: Interquartile range.
[a] 231 missing information on admission date.
[b] 207 missing information on BCC location.
[c] Points: Sepsis (2), TPN (1), Surgery (1), Colonisation (1).
[d] ≥2 underlying diseases and ≥3 underlying diseases.
[e] Including primary cases-n = 852.
[f] Mortality before blood cultures became positive for candidaemia.

correspondingly lower number of ICU beds in Denmark (6.7/100.000 population (Rhodes et al., 2012)) compared with Italy and France (12.5 and 11.6 beds/100,000 population, respectively), which requires a more rigorous patient selection process in Denmark. As such, differences in health care systems and organisations and patient selection processes complicates comparisons of incidence rates according to hospital admissions and emphasise the need for population-based epidemiological studies.

Compared with previous cohort studies, our patient cohort was older (median age 66 years versus 53-63 years (Lortholary et al., 2014; Puig-Asensio et al., 2014; Li et al., 2015; Horn et al., 2009)). Gastrointestinal disease was the most prevalent underlying disease and more than twice as common in Denmark as reported in Australia (52.5% versus 20.8%) (Chen et al., 2006). On the contrary, solid tumours were less frequent (26.2% vs 30-36%) (Chen et al., 2006; Luzzati et al., 2016; Puig-Asensio et al., 2014; Almirante et al., 2005), except in the departments of surgery (39.9%). Neutropenia was infrequent (3.2%) compared with previous studies (4.7% to 19%) (Chen et al., 2006; Luzzati et al., 2016; Puig-Asensio et al., 2014), and the proportion of Danish patients with haematological disease was low (7.8%) relatively to other rates (12.5-24.0%) (Lortholary et al., 2014; Chen et al., 2006; Tadec et al., 2016; Pfaller et al., 2012). Therefore, it seems less likely that the higher rate of haematological disease in Denmark compared to the other Nordic countries should explain the higher incidence of candidaemia as previously suggested (Hesstvedt et al., 2017).

To our knowledge, this is the first description of multi-morbidity in candidaemia patients. Unfortunately, this value cannot be directly compared to previous studies using clinical scores (e.g. Acute Physiologic And Chronical Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS)) (Nucci et al., 2013; Baldesi et al., 2017; Colombo et al., 2014). However, multi-morbidity is a simple and pragmatic measurement of the complexity of underlying diseases and it is applicable in varying settings (Ording and Sørensen, 2013). Our finding of 75% of patients with multi-morbidity illustrates a uniformity of severely ill patients at the time of candidaemia diagnosis This aligns with the observed higher overall 30-day mortality (43.4%) compared to a semi-national survey in Denmark in 2006 and to other population-based candidaemia studies (37% and 27-31%, respectively) (Chen et al., 2006; Cleveland et al., 2012; Puig-Asensio et al., 2014; Arendrup et al., 2011b). It also aligns with the notably high mortality among our candidaemia ICU patients (53.6%) compared to national 30-day mortality after ICU admission (21.2% overall, and 36.7% for patients with septic shock) in Denmark in 2011 (Fynbo Christiansen, 2011). A large ICU study from France compared candidaemia versus non-candidaemia ICU patients and found a similar difference of 34.6% point in 30-day mortality (Baldesi et al., 2017). We hypothesise that an increase in multi-morbidity rates over the past decades, associated with advances in the management of patients with complicated illnesses, prolonged intensive caring and blood culturing have contributed to the rise in

Table 3
30-day mortality according to major underlying diseases and risk factors.

	Hazard ratio[a] (95% CI)	Adjusted Hazard ratio[a] (95% CI)	Minimal adjusted model[b] (Link to causal diagram)
Sex			
Female	1 (Ref.)	1 (Ref.)	Sex (http://dagitty.net/dags.html?id=12Jr0q)
Male	1.10 (0.89-1.35)	-	
Age at candidaemia			
<75 years	1 (Ref.)	1 (Ref.)	Age (http://dagitty.net/dags.html?id=atUl8)
≥75 years	1.59 (1.29-1.97)	-	
Prior infection			
No	1 (Ref.)	1 (Ref.)	Prior infection, age, dialysis, haematology (http://dagitty.net/dags.html?id=uDszw0)
Yes	1.04 (0.84-1.28)	1.05 (0.85-1.30)	
Abdominal surgery			
No	1 (Ref.)	1 (Ref.)	Abdominal surgery, age, gastrointestinal disease: (http://dagitty.net/dags.html?id=T-hiQM)
Yes	0.73 (0.57-0.94)	0.70 (0.54-0.92)	
Total parenteral Nutrition			
No	1 (Ref.)	1 (Ref.)	TPN, age, gastrointestinal disease, multi-morbidity: (http://dagitty.net/dags.html?id=v8-ZGp)
Yes	0.83 (0.65-1.07)	0.91 (0.70-1.18)	
Gastrointestinal disease			
No	1 (Ref.)	1 (Ref.)	Gastrointestinal disease, age: (http://dagitty.net/dags.html?id=mDfau8)
Yes	0.82 (0.67-1.01)	0.85 (0.69-1.04)	
Solid cancer			
No	1 (Ref.)	1 (Ref.)	Solid cancer, age: (http://dagitty.net/dags.html?id=nbSlQ-)
Yes	0.92 (0.71-1.20)	0.81 (0.62-1.06)	
Multi-morbidity			
≤1	1 (Ref.)	1 (Ref.)	Multi-morbidity, age, haematology: (http://dagitty.net/dags.html?id=eF8Z94)
≥2	1.05 (0.80-1.36)	1.01 (0.78-1.32)	
≥3	1.23 (0.93-1.61)	1.21 (0.92-1.59)	
Candida score			
<3	1 (Ref.)	1 (Ref.)	Candida score, age, gastrointestinal disease, haematology, multi-morbidity: (http://dagitty.net/dags.html?id=hM9CLO)
≥3	1.04 (0.78-1.37)	1.06 (0.80-1.41)	

CI: Confidence Interval, -: no adjustments performed according to casual diagram.
Ref.: reference.
[a] Calculated using Cox Regression.
[b] Minimal adjustment sets for estimating the total effect of each exposure was defined according to casual diagrams and used in the multivariate analyses.

candidaemia rates and to the continued high mortality despite introduction of new diagnostics and therapeutic options.

This study has limitations. First, a potential heterogeneity in data-collection as multiple doctors contributed. The use of an abstraction form sought to minimize this potential bias, which if present may have led to an underestimation of underlying diseases and risk factors. Second, patient referrals between hospitals and departments and the fact that one third of patients BCs was obtained from an internal line allowing for possible contamination may have biased the estimation of incidence. Unfortunately, no other candidaemia studies have established benchmarks for these issues. However, the low prevalence of the skin associated *C. parapsilosis* suggest contaminations may not be a major bias (van Asbeck et al., 2009). Third, although intended, attributable mortality was not assessed due to significant challenges in ensuring an objective evaluation in this heterogeneous and multi-diseased patient population. Furthermore, it should be kept in mind that these data unite very different hospital settings and therefore cannot be used to describe local epidemiology for the different hospitals, but are useful for comparing with population-based studies.

In conclusion, this study described clinical characteristics of candidaemia patients based on nationwide data. The high incidence in Denmark was not explained by high prevalence of haematological malignancies as previously proposed (Hesstvedt et al., 2017). However, the underlying disease burden was evident by the high prevalence of multi-morbidity and high mortality with a substantial proportion of patients dying early. An increasing burden of multi-morbidity may be expected following better management of complicated illnesses and as such hypothesise that this may contribute to the high incidence rate and mortality associated with candidaemia in our country. This calls for continued surveillance of candidaemia to target clinical awareness towards these patients.

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Conflict of interest

Dr. Lausch et al. reports grants from Amplyx, Basilea, Cidara, F2G, Gilead, personal fees from Astellas, Basilea, Gilead, MSD, Pfizer, T2Biosystems, grants from Pfizer, personal fees from Astra Zeneca, personal fees from Horizon Pharmaceuticals, personal fees from MSD, Pfizer, personal fees from MSD, grants and personal fees from Gilead, outside the submitted work.

Ethical approval

Data collection was approved by the Danish Health authorities (Journal no 3-3013-268 364/1/) and the Danish Data Protection Agency (Journal no 2004-54-1627).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.08.010.

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