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

K.R. Lausch[a,*], M. Søgaard[b,c], F.S. Rosenvinge[d,e], H.K. Johansen[f], T. Boysen[g], B. Røder[h], K.L. Mortensen[a,i], L. Nielsen[j], L. Lemming[i], B. Olesen[j], C. Leitz[k], L. Kristensen[i,l], E. Dzajic[m], L. Østergaard[a], H.C. Schønheyder[n,o], M.C. Arendrup[f,p,q]

[a] Dpt. of Infectious Disease, Aarhus University Hospital, Aarhus, Denmark
[b] Dpt. of Cardiology, Aalborg University Hospital, Denmark
[c] Aalborg Thrombosis Research Unit, Dpt. of Clinical Medicine, Faculty of Health, Aalborg, Denmark
[d] Dpt. of Clinical Microbiology, Odense University Hospital, Odense, Denmark
[e] Dpt. of Clinical Microbiology, Lillebaelt Hospital, Denmark
[f] Dpt. of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark
[g] Dpt. of Clinical Microbiology, Hvidovre Hospital, Hvidovre, Denmark
[h] Dpt. of Clinical Microbiology, Slagelse Sygehus, Slagelse, Denmark
[i] Dpt. of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark
[j] Dpt. of Clinical Microbiology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark,
[k] Dpt. of Clinical Microbiology, Viborg Regionshospital, Viborg, Denmark
[l] Dpt. of Clinical Microbiology, Herning Regionshospital, Denmark
[m] Dpt. of Clinical Microbiology, Sydvestjysk Sygehus, Denmark,
[n] Dpt. of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark
[o] Dpt. of Clinical Medicine, University of Aalborg, Aalborg, Denmark
[p] Unit of Mycology, Statens Serum Institute, Copenhagen, Denmark
[q] Dpt. of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

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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.,

* Corresponding author at: Dpt. of Infectious Diseases, Q Research, Aarhus University Hospital, Skejby Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: karelaus@rm.dk (K.R. Lausch).

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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.