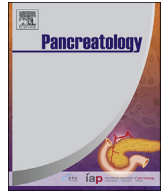




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Increased risk of candidemia in patients with necrotising pancreatitis infected with candida species

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ABSTRACT

Background and objectives: Candida infections are frequent in necrotising pancreatitis. Candidemia is associated with very high mortality and its risk due to infected pancreatic necrosis is unknown. So we aimed to assess potential risk factors and the risk of candidemia in necrotising pancreatitis.

Methods: We retrospectively searched our clinical database for the diagnosis necrotising pancreatitis from 2007 till March 2017 and entered relevant information in a database for statistical analysis.

Results: in total, 136 patients met the inclusion criteria. Candida infected pancreatic necrosis were found in 54 patients and 7 patients developed candidemia. Patients with Candida infected necrosis had a significantly higher in hospital mortality (35.2% versus 13.4%, $p = 0.003$). The highest mortality was observed in patients with candidemia (57.1% versus 20.2%, $p = 0.042$). Male gender (OR 0.32, CI 0.13–0.78, $p = 0.013$) and post-ERCP pancreatitis (OR 4.32, CI 1.01–18.36, $p = 0.048$) had a significant impact on the risk of Candida infections of pancreatic necrosis. Candidemia was significantly more frequent in patients with Candida infected necrosis (11.1% versus 1.2%, $p = 0.016$). Candida albicans was the most common species followed by Candida glabrata.

Conclusion: Candidemia is a relevant complication of necrotising pancreatitis and associated with high mortality. If patients do not respond to antibiotic therapy empiric antifungal therapy should be discussed.

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1. Introduction

With an incidence of 30–45/100.000 person years acute pancreatitis is a frequent disease [1–3]. The overall mortality is about 5% but strongly depends on the severity of the disease [4,5]. According to the revised Atlanta classification of 2011, acute pancreatitis can be classified as mild, moderately severe or severe. Moderately severe and severe pancreatitis is characterized by local and systemic complications. Typical local complications include acute necrotic collections in the early phase and walled-off necrosis in the late phase of the disease [6]. This so called necrotising pancreatitis evolves in about 4–47% of the patients with acute pancreatitis and, particularly in case of infected necrosis, it is associated with high morbidity and mortality rates [4,7,8]. Fungal infections of necrosis in acute pancreatitis are very common and especially *Candida albicans* is one of the most frequently cultured

pathogens [7]. In the available data of fungal pancreatic infections, pancreatic pseudocysts are usually not distinguished from walled-off necrosis. But pseudocysts and walled-off necrosis are characterised by a divergent course of the disease and distinct complications [9–11].

While fungal colonisation, e.g. of the respiratory tract, is mainly considered as risk factor for fungal infections and is a common finding in severely ill patients, invasive mycosis itself has a substantial mortality. In particular, candidemia has a mortality rate of over 60% and, similar to other pathogens, source control within 24 h and early effective antifungal therapy can significantly reduce mortality in candidemia [12]. Accordingly, treatment of fungal infections of pancreatic necrosis is recommended by current guidelines [13]. However, treatment is often delayed by the insensitivity and time needed to yield growth in cultured necrotic specimen [13,14]. Furthermore, neither the actual risk nor the role of markers like 1,3 Beta - d - Glucan or risk scores of candidemia have been evaluated in necrotising pancreatitis [13].

Considering the high prevalence of candida infections in pancreatic necrosis, we aim to assess the prevalence and potential

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risk factors of invasive candidiasis and candidemia in necrotising pancreatitis by this retrospective analysis.

2. Materials and methods

We performed a unicenter retrospective analysis of patients with necrotising pancreatitis between 2007 and March 2017 at the tertiary referral center Klinikum rechts der Isar der Technischen Universität München. We screened our administrative diagnosis database for patients with pancreatitis (International Classification of Diseases (ICD)-10 code K85 and K86). Candida infection of pancreatic necrosis requires confirmation by microbiology. So only patients with necrotising pancreatitis requiring invasive treatment (percutaneous and/or transgastric/transduodenal drainage, surgical/percutaneous and/or endoscopic necrosectomy) in the late phase of pancreatitis (>10 d after onset of symptoms) were included in the study. Necrotising pancreatitis was classified according to the revised Atlanta classification [6]. We identified 136 patients that met the inclusion criteria. Patients with microbiological evidence of Candida species in blood samples or in pancreatic walled-off necrosis formed the study group, those without were assigned to the control group. Only microbiology specimen obtained at first intervention of the walled-off necrosis were included to distinguish infection from colonisation. For Candida resistance profiles EUCAST breakpoints were used. Patients with suspected or proven invasive candidiasis were initially treated with an Echinocandin until susceptibility testing was available. The study was approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, project number 5726/13). Written consent was specifically waived by the approving institutional review board.

Statistical analysis was performed using IBM SPSS Statistics 22 (SPSS Inc, Chicago, Illinois, USA). Samples were checked for normal distribution using the Shapiro-Wilk test. Variables were not normally distributed. Accordingly, descriptive data are presented as median, range and interquartile range (IQR). Risk ratios are displayed as odds ratio (OR) with 95% confidence interval (CI). To compare qualitative parameters, chi-square test was used and in small samples (expected frequency of test variable less than 5) Fisher's exact test was used. For the analysis of quantitative parameters, Mann-Whitney-U test was employed. All statistical tests were two-sided with a level of significance (p-value) of 5%. A multivariate logistic regression model was used to identify risk factors for Candida infection of pancreatic necrosis. Factors with a p-value below 0.1 in univariate analysis or a high probability according to our data or the literature were included in multivariate regression analysis.

3. Results

In total, 136 patients with necrotising pancreatitis requiring intervention were treated at our institution, 54 had proven Candida infected necrosis and 7 developed candidemia (Fig. 1 and Table 1). No patient was under immunosuppressive therapy.

Most patients (84.6% - 115/136) were treated with at least two different interventions (percutaneous, endoscopic and/or surgical). In 18.5% (10/54) Candida species were cultured in specimen obtained by two different treatment modalities. In both, necrotic specimen and blood cultures, *Candida albicans* was the most frequently isolated Candida species (Table 2). In general, *Candida albicans* was also the most frequently isolated pathogen in pancreatic necrosis after *Enterococcus faecium*.

In all patients (7/7) who developed candidemia there was evidence of Candida infection or colonisation of different organ systems. In 66.7% (4/6) the same Candida species was identified in the

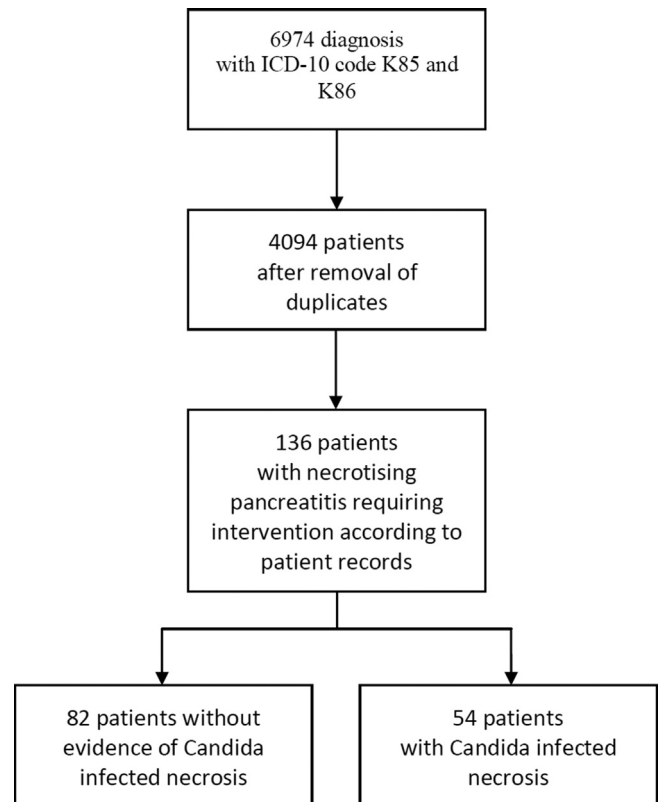


Fig. 1. Flow chart of patient selection.

necrosis and in the blood culture. More than 1 *Candida* species in pancreatic necrosis was cultured in 18.5% (10/54) of the patients.

Patients with *Candida* infected pancreatic necrosis had a significantly higher in hospital mortality comparing to patients without *Candida* infection (Table 1). Patients with candidemia had the highest in hospital mortality (57.1% (4/7) versus 20.2% (26/129), $p=0.042$). In multivariate logistic regression analysis gender, alcohol and nicotine abuse were analysed for their impact on *Candida* infections of pancreatic necrosis (Table 3). Fungal infection of pancreatic necrosis was found more often in patients with a post-ERCP pancreatitis (OR 4.32, CI 1.01–18.36, $p=0.048$) and less frequent in men (OR 0.32, CI 0.13–0.78, $p=0.013$).

4. Discussion

Contrary to intra-abdominal infections in general, fungal infections of pancreatic necrosis are very common [14]. In older studies the rate of primary infection of pancreatic necrosis with *Candida* species ranges from 0–40% [15–18]. However, in these older studies surgical necrosectomy was the standard treatment. More conservative and less invasive treatment of necrotising pancreatitis resulted in a decrease in overall mortality from almost 40%–11% [7,16]. As hospitalisation is a risk factor for candidiasis, this more conservative management with preferably late interventions might explain the high rate of primary candidiasis of pancreatic necrosis in our study population [13]. And as it is associated with an excess of morbidity and mortality, *Candida* infection of pancreatic necrosis is a relevant problem. These patients not only required more interventions and a longer treatment in hospital but also had a significantly increased mortality [14].

Whether colonisation with *Candida* species is of pathologic relevance or a concomitant feature in critically ill patients is an

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