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Review article

Infection increases mortality in necrotizing pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Objectives: To assess the influence of infection on mortality in necrotizing pancreatitis.
Methods: Eligible prospective and retrospective studies were identified through manual and electronic searches (August 2015). The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). Meta-analyses were performed with subgroup, sensitivity, and meta-regression analyses to evaluate sources of heterogeneity.
Results: We included 71 studies (n = 6970 patients). Thirty-seven (52%) studies used a prospective design and 25 scored ≥5 points on the NOS suggesting a low risk of bias. Forty studies were descriptive and 31 studies evaluated invasive interventions. In total, 801 of 2842 patients (28%) with infected necroses and 537 of 4128 patients (13%) with sterile necroses died with an odds ratio [OR] of 2.57 (95% confidence interval [CI], 2.00–3.31) based on all studies and 2.02 (95%CI, 1.61–2.53) in the studies with the lowest bias risk. The OR for prospective studies was 2.96 (95%CI, 2.51–3.50). In sensitivity analyses excluding studies evaluating invasive interventions, the OR was 3.30 (95%CI, 2.81–3.88). Patients with infected necrosis and organ failure had a mortality of 35.2% while concomitant sterile necrosis and organ failure was associated with a mortality of 19.8%. If the patients had infected necrosis without organ failure the mortality was 1.4%.
Conclusions: Patients with necrotizing pancreatitis are more than twice as likely to die if the necrosis becomes infected. Both organ failure and infected necrosis increase mortality in necrotizing pancreatitis.

1. Introduction

Infection in pancreatic necrosis is a major concern in the late phase of acute pancreatitis [1,2]. It is unknown whether the infection per se increases the risk of death [3–6]. Diagnosing infected pancreatic necrosis can be challenging. Currently there is no international consensus. Different diagnostic strategies are used. The recommended methods include contrast enhanced computed tomography (CT) and culturing from fine needle aspiration. When infected necrosis is present, current guidelines recommend minimally invasive intervention when the necrosis is encapsulated to a walled-off necrosis after 3–4 weeks.

Two reviews have previously evaluated prognosis of patients with acute pancreatitis [7,8]. One review included a meta-analysis of *P* values evaluating the influence of infected necrosis on mortality in patients who underwent open surgery [7]. The review included 11 observational studies and found that infection had no effect on mortality. The second review included 14 observational studies of patients with acute pancreatitis and found that those with both organ failure and infected necrosis had increased mortality [8]. There are no systematic reviews evaluating if infection increases mortality in patients with necrotizing pancreatitis. Numerous studies may provide data to allow such an assessment. We therefore conducted this systematic review with meta-analysis of all available clinical studies.

2. Methods

2.1. Study identification

We conducted this review based on a registered protocol (PROSPERO 2015:CRD42015017601). We included clinical studies regardless of their design, publication status, year of publication,

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blinding, or language. Studies evaluating secondary infections developed after interventions, chronic pancreatitis, or pancreatic pseudocysts were excluded. In case a study was reported in more than one publication, we extracted data from the publication with the largest number of patients and the longest duration of follow-up.

Eligible studies were identified through electronic searches in Medline, Embase, The Cochrane Library, and Web of Science. The last update was August 2015. The search strategy included the following terms ((necroti* pancreatitis) OR ("walled-off pancreatic necrosis")) AND infection AND (study OR trial)). We also scanned reference lists from original articles and reviews.

The primary outcome measure was mortality. Secondary outcomes measures were organ failure, multiple organ failure, and admission to an intensive care unit.

The included patients had necrotizing pancreatitis as defined by non-enhancement of pancreatic parenchyma on contrast enhanced CT or intraoperative findings of necrotic tissue. Pancreatic collections were defined according to the revised Atlanta classification [9]. In studies published before the revised classifications, we included pancreatic abscess, necroma, and organized necrosis as synonymous with walled-off pancreatic necrosis. Infected necrosis should be proven by either Gram staining or culturing. If patients were categorized as having infected necrosis by the presence of gas on CT-scan or clinical suspicion, and no information on culturing was provided, the studies were excluded.

2.2. Data extraction

Two authors (M.W. and S.N.) independently extracted data. Disagreements were resolved through discussion before analyses. In case of disagreement, a third author (L.L.G.) acted as ombudsman. The following data were extracted: Patient characteristics (aetiology, alcohol consumption, smoking, age, gender, proportion with Gram-negative, Gram-positive, fungal, and polymicrobial infections); disease severity score (Ranson and APACHE (Acute Physiology and Chronic Health Evaluation) II); type of treatment (antibiotic prophylaxis, conservative/supportive management only, minimally invasive interventions, and open surgery); trial design (including study period and country of origin); outcomes (mortality, organ failure, and admission to the intensive care unit).

Conservative management was defined as supportive treatment only i.e. treatment with fluids, nutrition, and antibiotics. Minimally invasive treatment was defined as percutaneous drainage, video-assisted retroperitoneal debridement, and/or endoscopic transmural drainage and debridement.

2.3. Bias control

Bias control was assessed using the Newcastle-Ottawa Scale (NOS) [10]. For each study a quality score was calculated based on the selection of patients in the infected and sterile groups (maximum 4 points), the comparability of the infected and sterile groups (maximum 2 points), and the ascertainment of the outcome of interest (maximum 3 points). A lower score represented a greater risk of bias. We defined studies with at least five points as 'high quality' of bias control.

2.4. Statistical analysis

We combined the results of the included studies in random-effects and fixed-effects meta-analyses. We reported the results of the random-effects models, due to the expected clinical heterogeneity for all analyses and the fixed-effect models only if the conclusions of the two models differed. The results are reported as odds ratio (OR) with 95% confidence intervals (CI) and the I^2 statistic as a measure of heterogeneity. We defined I^2 values as unimportant (I^2 < 30%), moderate (I^2 30–50%), substantial (I^2 51–75%), or considerable (I^2 > 75%). We tested the risk of publication bias and other small study effects in regression analysis (Harbord's test). Subgroup and sensitivity analyses were performed to compare the studies with the lowest and highest risk of bias (based on the NOS score). In sensitivity analyses studies in which all patients underwent invasive interventions and studies using antibiotic prophylaxis were excluded. Studies published before the first Atlanta Classification were also excluded in sensitivity analyses. To distinguish between older studies using early necrosectomy and later studies using delayed interventions, we performed subgroup analysis of studies before 1997 and from 1997. We conducted random-effects meta-regression analysis to evaluate the influence of the following predictors: intervention (proportion of patients undergoing invasive interventions, including minimally invasive and open surgery), aetiology (proportion with pancreatitis due to

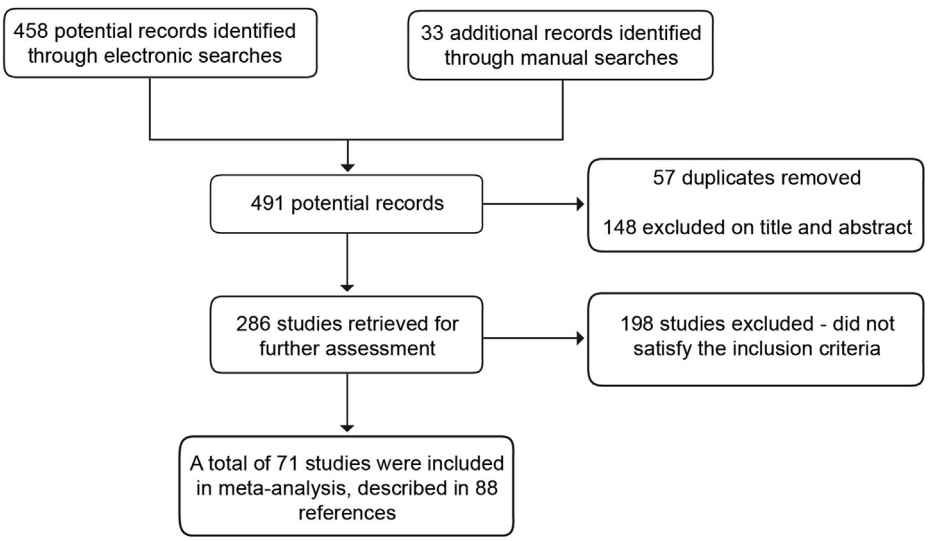

Fig. 1. Flow diagram of the study selection process.

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