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Randomized Controlled Trials of Antibiotic Prophylaxis in Severe Acute Pancreatitis: Relationship between Methodological Quality and Outcome

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Key Words
Pancreatitis · Antibiotic prophylaxis · Methodology, quality of · Meta-analysis · Necrotizing pancreatitis · Necrosis

Abstract
Aim: To evaluate the methodological quality of randomized controlled trials (RCTs) of systemic antibiotic prophylaxis in severe acute pancreatitis in relation to outcome. Methods: The MEDLINE, EMBASE and Cochrane databases were searched for RCTs that studied the effectiveness of systemic antibiotic prophylaxis in severe acute pancreatitis. A meta-analysis was performed with a random effects model. Methodological quality was quantified by a previously published scoring system (range 0–17 points). Results: Six studies, with a total of 397 participants, obtained a methodological score of at least 5 points and were included. Systemic antibiotic prophylaxis had no significant effect on infection of pancreatic necrosis (absolute risk reduction (ARR) 0.055; 95% CI –0.084 to 0.194) and mortality (ARR 0.058, 95% CI –0.017 to 0.134). Spearman correlation showed an inverse association between methodological quality and ARR for mortality (correlation coefficient –0.841, p = 0.036). Conclusions: The inverse relationship between methodological quality and impact of antibiotic prophylaxis on mortality emphasizes the importance of high-quality RCTs. At present, adequate evidence for the routine use of antibiotic prophylaxis in severe acute pancreatitis is lacking.

Introduction
Acute pancreatitis has an uncomplicated course in the majority of patients. However, approximately one fifth of patients will develop severe acute pancreatitis [1]. The majority of patients with severe acute pancreatitis suffer from complications, with an overall mortality of up to 30% [2]. Mortality is largely related to multi-organ failure early after the onset of pancreatitis and secondary infection of pancreatic necrosis by enteric bacteria during a second hit of the systemic inflammatory response syndrome [1, 2]. Systemic antibiotic prophylaxis has been
suggested as a strategy to prevent infection of pancreatic necrosis and consequently reduce mortality. Several randomized controlled trials (RCTs) have been performed to evaluate the efficacy of this strategy.

Although the results of these trials are conflicting, various guidelines [3, 4] and meta-analyses [5, 6] advocate the use of antibiotic prophylaxis in severe acute pancreatitis. However, these recommendations were published before the results of the first placebo-controlled RCT became available, which failed to demonstrate a beneficial effect of systemic antibiotic prophylaxis [7]. Nevertheless, two recent meta-analyses both including this trial still came to conflicting results [8, 9] at present, there is no international consensus on the use of antibiotic prophylaxis in severe acute pancreatitis.

One of the main reasons for the lack of consensus is the frequently criticized methodological quality of the published RCTs [10]. The quality of these trials has never been systematically assessed. Recently, a scoring system was published that provides a quantitative measure of the methodological quality of RCTs [11]. We aimed to evaluate the evidence for routine administration of systemic antibiotic prophylaxis in patients with severe acute pancreatitis through both assessment of the methodological quality of the published RCTs and subsequent meta-analysis.

**Methods**

The MEDLINE, EMBASE and Cochrane databases were searched for studies on intravenous antibiotic prophylaxis published since 1990 using the search strategy shown in figure 1. Studies which compared the effectiveness of different antibiotic regimes or the effectiveness of different administration routes were excluded. There were no language restrictions, non-English manuscripts were translated.

Studies on selective decontamination of the digestive tract (SDD) were not included in the present analysis as they focus on a different prophylactic mechanism. SDD aims at preventing bacterial translocation from the gut prior to infection, whereas systemic antibiotic prophylaxis aims to diminish potential hematogenous spread of bacteria after translocation has occurred and/or to treat infection of (peri-)pancreatic necrosis.

The methodological quality of the retrieved RCTs was assessed using the previously published scoring system, which was adapted to the situation in severe acute pancreatitis in accordance with the revised CONSORT statement [12]. The following items were added to the scoring system: antibiotic intervention, method of feeding and participant flow. Three main items (population, intervention and participant flow), subdivided into eight criteria were scored. Zero, one or two points were given for each of the eight criteria (table 1).

Since the participant flow item is not subdivided into further criteria, a third point could be obtained for participant flow in order to weigh the items more equally in the final score. As a result, the maximum score for study quality was 17 points (table 1).

Three researchers independently reviewed all studies (A.C.d.V., M.G.H.B., C.I.B.v.d.K.). In case of discrepant judgments a consensus reading followed. In order to include only studies of sufficient methodological quality in further analysis, in accordance with the study by van Nieuwenhoven et al. [11], a cutoff methodological score of 5 points was used.

Subsequently, meta-analysis of the trials was performed with a random effects model, thereby modeling the inter-study variance to estimate the overall effect of systemic antibiotic prophylaxis in severe acute pancreatitis.

The relation between the methodological quality of the studies and reported outcomes on infection of pancreatic necrosis and mortality was evaluated with a Spearman correlation coefficient, accounting for within-study variances. Significance was taken at \( p < 0.05 \).
Results

From 256 articles screened (fig. 1), 8 RCTs fulfilled the inclusion criteria [7, 13–19]. Two Czech trials were translated into English [17, 18]. The study of Nordback et al. [20] was excluded as antibiotic prophylaxis was used in both arms of the study.

Methodological Quality

The methodological quality score varied from 2 points for Spicak et al. [17] to 15 points for Isenmann et al. [7] and Dellinger et al. [19] (table 2). Both Czech trials [17, 18] scored less than 5 points and were consequently excluded (table 3).

Patient Characteristics

According to the methodological quality assessment, only Isenmann et al. [7] randomized patients into highly comparable groups. In most studies various baseline characteristics were not reported. Pederzoli et al. [14] included significantly more patients with more than 50% pancreatic necrosis in the antibiotic group.

Blinding

The studies of Isenmann et al. [7] and Dellinger et al. [19] were the only ones with a double-blind placebo-controlled design. Delcenserie et al. [13] and Schwarz et al. [16] did not clearly define the difference between ‘antibiotic prophylaxis’ and ‘antibiotics on demand’, possibly introducing bias.

Method of Feeding

The association of enteral feeding with a significantly lower incidence of infections has clearly been demonstrated [21]. Three studies [7, 15, 16], including the placebo-controlled trial from Isenmann et al. [7], did not state the method of feeding.

Participant Flow

Isenmann et al. [7] and Dellinger et al. [19] described the participant flow explicitly; the other trials did not mention the loss to follow-up and whether an intention-to-treat analysis was performed.

Meta-Analysis

The 6 RCTs with a methodological quality score of at least 5 points were included in the meta-analysis [7, 13–16, 19]. In total, 203 patients received antibiotic prophylaxis; 194 patients were included in the control group. For the individual studies the absolute risk reduction (ARR)

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Consecutive eligible consenting patients or random series</td>
</tr>
<tr>
<td>1</td>
<td>Attempt made to enroll as such, with failure due to reasons explicitly outlined</td>
</tr>
<tr>
<td>0</td>
<td>Selected patients (not consecutive or random) or not described</td>
</tr>
<tr>
<td>2</td>
<td>Groups comparable on ≥7 characteristics</td>
</tr>
<tr>
<td>1</td>
<td>Groups comparable on 4–6 characteristics</td>
</tr>
<tr>
<td>0</td>
<td>Groups comparable on ≤3 characteristics</td>
</tr>
<tr>
<td></td>
<td>Age (mean differs by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Sex (proportion of men in each group differs by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Ranson score (median differs by &lt;1 point)</td>
</tr>
<tr>
<td></td>
<td>Mean maximum C-reactive protein in first 48 h (mean differs by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Pancreatic necrosis presence (proportion of patients differs by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>&gt;30% pancreatic necrosis (proportion of patients differs by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Etiology (mean proportions differ by &lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Time (in days) between inclusion and onset of symptoms (mean differs by &lt;10%)</td>
</tr>
</tbody>
</table>

Table 1. Criteria for assessment of methodological quality
for infection of pancreatic necrosis ranged from –0.077 to 0.333 and the relative risk reduction (RRR) from –46.2 to 87.8%. For mortality the ARR ranged from –0.02 to 0.2, the RRR from –10.5 to 80%. There was no overall significant reduction in infection of pancreatic necrosis, ARR 0.055 (95% confidence interval (CI) –0.084 to 0.194) and mortality, ARR 0.058 (95% CI –0.194 to 0.154; table 4; fig. 2, 3).

Methodological Quality in Relation to Study Outcome

The Spearman correlation coefficient showed no significant relationship between the methodological qual-
ity of the trials and the reported risk of infected pancreatic necrosis (table 5). With the Spearman correlation coefficient, an inverse significant relationship between methodological score and the ARR (correlation coefficient $-0.841$, $p = 0.036$) and RRR for mortality (correlation coefficient $-0.948$, $p = 0.004$) was demonstrated (table 5; fig. 4).

### Table 4. Absolute (ARR) and relative risk reductions (RRR) of infected pancreatic necrosis and mortality

<table>
<thead>
<tr>
<th></th>
<th>AB group</th>
<th>Control group</th>
<th>ARR</th>
<th>95% CI</th>
<th>RRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infected pancreatic necrosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pederzoli et al. [14]</td>
<td>5/41</td>
<td>10/33</td>
<td>0.181</td>
<td>$-0.031$ ; $0.393$</td>
<td>0.576</td>
<td>(57.6%)  ; $-0.072$ ; $0.832$</td>
</tr>
<tr>
<td>Sainio et al. [15]</td>
<td>9/30*</td>
<td>12/30</td>
<td>0.1</td>
<td>$-0.175$ ; $0.375$</td>
<td>0.240</td>
<td>(24.0%) ; $-0.502$ ; $0.615$</td>
</tr>
<tr>
<td>Delcenserie et al. [13]</td>
<td>0/11</td>
<td>4/12*</td>
<td>0.333</td>
<td>$-0.064$ ; $0.731$</td>
<td>0.878</td>
<td>(87.8%) ; $-1.008$ ; $0.993$</td>
</tr>
<tr>
<td>Schwarz et al. [16]</td>
<td>8/13</td>
<td>7/13</td>
<td>$-0.077$</td>
<td>$-0.534$ ; $0.380$</td>
<td>$-0.133$</td>
<td>(–13.3%) ; $-1.159$ ; $0.405$</td>
</tr>
<tr>
<td>Isenmann et al. [7]</td>
<td>7/58</td>
<td>5/56</td>
<td>$-0.031$</td>
<td>$-0.162$ ; $0.099$</td>
<td>$-0.317$</td>
<td>(–31.7%) ; $-2.721$ ; $0.534$</td>
</tr>
<tr>
<td>Dellinger et al. [19]</td>
<td>9/50</td>
<td>6/50</td>
<td>$-0.060$</td>
<td>$-0.200$ ; $0.080$</td>
<td>$-0.462$</td>
<td>(–46.2%) ; $-2.664$ ; $0.417$</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>38/203</td>
<td>44/194</td>
<td>0.055</td>
<td>$-0.084$ ; $0.194$</td>
<td>0.101</td>
<td>(10.1%) ; $-0.430$ ; $0.435$</td>
</tr>
</tbody>
</table>

| **Mortality**            |          |               |        |                  |        |                  |
| Pederzoli et al. [14]   | 3/41     | 4/33          | 0.048  | $-0.113$ ; $0.210$ | 0.370  | (37.0%) ; $-1.361$ ; $0.832$ |
| Sainio et al. [15]      | 1/30     | 7/30          | 0.2    | $-0.005$ ; $0.405$ | 0.800  | (80.0%) ; $-0.074$ ; $0.963$ |
| Delcenserie et al. [13] | 1/11     | 3/12          | 0.159  | $-0.238$ ; $0.556$ | 0.536  | (53.6%) ; $-1.657$ ; $0.919$ |
| Schwarz et al. [16]     | 0/13     | 2/13          | 0.153  | $-0.128$ ; $0.436$ | 0.800  | (80.0%) ; $-2.801$ ; $0.989$ |
| Isenmann et al. [7]     | 3/58     | 4/56          | 0.020  | $-0.086$ ; $0.125$ | 0.249  | (24.9%) ; $-1.895$ ; $0.805$ |
| Dellinger et al. [19]   | 10/50    | 9/50          | $-0.020$ | $-0.194$ ; $0.154$ | $-0.105$ | (–10.5%) ; $-1.428$ ; $0.497$ |
| **Total**               | 18/203   | 29/194        | 0.058  | $-0.017$ ; $0.134$ | 0.301  | (30.1%) ; $-0.403$ ; $0.652$ |

* Pancreatic abscess included.

### Discussion

This study demonstrates that the study quality of the included RCTs was generally moderate. Interestingly, the effect of antibiotic prophylaxis on mortality seemed smaller in studies of higher methodological quality.

Strikingly, the findings in the study of van Nieuwenhoven et al. [11] regarding the methodological quality of...
the studies on SDD in intensive care patients were similar to ours, i.e. an inverse relationship between methodological quality score and the benefit of antibiotic prophylaxis. An assessment of the methodological quality of studies based on the information in published articles could be influenced by flaws in reporting trials, i.e. something may not be reported although it was correctly performed. Obviously, it is impossible to correct for this factor. In our meta-analysis, trials were weighted regardless of the methodological score. At this moment, there are no guidelines on how to weigh studies of specific methodological quality when combining results in a meta-analysis.

The heterogeneity of studies included in a meta-analysis reduces the reliability in general [22]. Several factors could have influenced the outcome of the present meta-analysis. Firstly, two studies [13, 15] included only patients with alcohol-induced pancreatitis, whereas the other studies included patients regardless of the etiology of pancreatitis. There is controversy, however, about whether the etiology of pancreatitis influences mortality [23–26]. Secondly, it is plausible that inclusion of less ill patients and patients without pancreatic necrosis leads to underestimation of the effect of systemic antibiotics in patients with acute pancreatitis. However, the patients included in the study with the largest effect size of antibiotic prophylaxis on infection [13] had the lowest mean Ranson score of 2.3, predicting mild pancreatitis. Thirdly, only two studies were double-blind, placebo-controlled [7, 19]. In the other studies, the absence of blinding might have led to a higher prescription rate of antibiotics in the control group. The risk of early ‘cross-over’ (use of antibiotics in the control group) demands standardization of antibiotic indications, especially in studies without blinding. Total crossover rates were only reported in the studies by Sainio et al. [15] (77%), Isenmann et al. [7] (46%) and Dellinger et al. [19] (52%). Finally, the antibiotics used in the studies varied (table 3); one study with imipenem [14], one study with meropenem [19], two with cephalosporins [13, 15], and two with a combination of third-generation fluoroquinolones and metronidazole [7, 16]. This makes it difficult to compare the outcome, since it could be influenced by, amongst others, the level of penetration of the antibiotics in (necrotic) pancreatic tissue and the antimicrobial spectrum of the antibiotics [27–30].

Since the use of broad-spectrum antibiotic prophylaxis may lead to bacterial resistance [31], fungal infections [32], selective overgrowth of pathogens leading to, for instance, Clostridium difficile colitis [33] and increased costs [34], the balance between beneficial and harmful effects of antibiotic prophylaxis should clearly be in favor of antibiotics in order to justify their use. The current meta-analysis demonstrated no beneficial effects of antibiotic prophylaxis on the incidence of both infected pancreatic necrosis and mortality. Furthermore, in the RCT from Isenmann et al. [7], patients receiving antibiotic prophylaxis experienced a significant increase in infections with bacteria resistant to the prophylactic antibiotics administered.

Table 5. Association between methodological quality score and risk reduction of infection of pancreatic necrosis and mortality with linear regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR infected necrosis</td>
<td>–0.438</td>
<td>0.385</td>
</tr>
<tr>
<td>RRR infected necrosis</td>
<td>–0.403</td>
<td>0.429</td>
</tr>
<tr>
<td>ARR mortality</td>
<td>–0.841</td>
<td>0.036</td>
</tr>
<tr>
<td>RRR mortality</td>
<td>–0.948</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Fig. 4. Significant relationship between methodological quality scores and risk reduction of mortality. ARR = Absolute risk reduction; RRR = relative risk reduction.
Routine use of antibiotic prophylaxis in severe acute pancreatitis does not prevent infection of pancreatic necrosis and mortality. The generally moderate quality of the studies may have contributed to an overly enthusiastic opinion on the effect of antibiotic prophylaxis in patients with severe acute pancreatitis. At present, opinion-based medicine has taken over, resulting in widespread use of antibiotic prophylaxis in severe acute pancreatitis. The inverse relationship between methodological quality and the impact of antibiotic prophylaxis on mortality emphasizes the importance of high-quality RCTs.

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