Acute pancreatitis is due to gallstones or excessive alcohol intake in over 90% of cases. Ten percent to 20% of patients with acute pancreatitis progress to develop severe disease with peripancreatic or intrapancreatic necrosis. Mortality rates are higher with necrotizing (17%) than interstitial (3%) pancreatitis. Infected necrosis develops in the second to third week after symptom onset in approximately 33% of patients with necrotizing pancreatitis. However, with improvement in the management of these patients in the critical care setting, newer studies report lower infection rates (12–25%). If infected necrosis develops, mortality increases to 25–30%, a rate unchanged for several decades. Bacteria are able to access the necrotic pancreatic tissue via translocation from the colon. Lymphogenous and hematogenous spread are additional possible pathways for pancreatic tissue inoculation.

Severe pancreatitis is defined as necrosis involving at least 30% of the pancreas as visualized by contrast-enhanced computed tomography (CT), with greater involvement indicating greater severity of necrosis. C-reactive protein (CRP) values are also used as part of study inclusion criteria. While a CRP level greater than 120 mg/L correlates with pancreatic necrosis, the test should be done at least 36 hours after admission. Amylase or lipase values are not predictive of necrosis. The most common organisms found in infected pancreatic necrosis are bacteria naturally found in the gastrointestinal tract, including Escherichia coli and enterococci. Antibiotics should cover the typical pathogens implicated in pancreatic necrosis.

**OBJECTIVE:** To review studies of antibiotic prophylaxis in acute necrotizing pancreatitis published in the last decade and update recommendations.

**DATA SOURCES:** A search of PubMed (1998–July 2009) was conducted using the terms necrotizing pancreatitis, antibiotics, prophylaxis, and treatment. Clinical studies, meta-analyses, and review articles published in English were included. Additional references were obtained from article bibliographies. Randomized trials published before 1998 were included if indicated.

**STUDY SELECTION AND DATA EXTRACTION:** Relevant studies or meta-analyses on antibiotic prophylaxis since our previous review in 1998 were evaluated; older data were included if still relevant.

**DATA SYNTHESIS:** Since our previous review, 4 more randomized trials, including 2 double-blind trials, have been conducted. The blinded studies found no significant difference in mortality with antibiotic prophylaxis compared with placebo, while the unblinded studies found a significant decrease in infections. Given these disparate results, available guidelines and meta-analyses provide different conclusions, usually based on exclusion or inclusion of a single trial. Based on all available data, antibiotic prophylaxis should not be used in patients with necrotizing pancreatitis. Instead, a more measured, on-demand use of antibiotics is preferred. Antibiotics should be added if signs and symptoms of infection are present (eg, fever, leukocytosis, positive results of cultures). Given improvements in intensive care and nutritional support, recent trials have found a lower incidence of infected necrotizing pancreatitis than before. Therefore, future trials are likely to need higher numbers of patients.

**CONCLUSIONS:** Use of antibiotic prophylaxis for patients with necrotizing pancreatitis is not indicated, based on 2 blinded trials. Instead, on-demand use of antibiotics appears to be appropriate. Given progress in intensive care and the high crossover rate in studies, the need for antibiotic prophylaxis may continue to be debated for decades.

**KEY WORDS:** antibiotics, necrotizing pancreatitis, prophylaxis.


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Author information provided at the end of the text.
The discussion regarding the use of antibiotics to prevent infected necrosis in the setting of severe acute pancreati-
tis has continued for more than 30 years. Antibiotic prophy-
laxis in this setting is continued over several weeks rather
than being limited to 1 or 2 days. Most studies have com-
pared prophylaxis upon diagnosis of necrosis to starting an-
tibiotics empirically (or on demand) after infection is suspect-
ed or documented. We first reviewed this topic in 19989 and
now present an update including data from the last decade.

At the time of the previous review, second- or third-gen-
eration cephalosporins, ureidopenicillins, imipenem, and
trimethoprim/sulfamethoxazole were considered potential
first-line treatment, with metronidazole and clindamycin as
alternative agents with adequate pancreatic tissue penetra-
tion.9 Recent data have shown that ciprofloxacin, piperacillin/
tazobactam, moxifloxacin, and ceftazidime also produce ade-
quate pancreatic tissue concentrations.10-13 However, it is still
unclear whether the ratio of serum to pancreatic tissue con-
centration is of importance, as infections occur in necrotic
pancreatic and peripancreatic fat, while antibiotic concentra-
tions are often measured in nonnecrotic pancreatic tissue.4

**Clinical Trials**

Based on literature available by 1998, we concluded
that antibiotic prophylaxis was appropriate to prevent in-
fec tious complications and decrease mortality in patients
with acute necrotizing pancreatitis (ANP) involving greater
than 30% of the pancreas.9 The current review is based on
Search terms included necrotizing pancreatitis, antibiotics,
prophylaxis, and treatment. Clinical studies, meta-analyses,
and review articles published in English were included. Of
the literature previously reviewed, several trials have re-
mained pertinent within the discussion of antibiotic prophy-
laxis in patients with ANP and warrant a brief reevalua-
tion.6,14,15 Table 1 summarizes all trials reviewed.6,7,14-17

Three trials previously reviewed are still relevant be-
cause they showed decreased mortality or infection rate with
prophylaxis compared with empiric (on-demand) use.6,14,15
Sainio et al.15 randomized 60 patients with severe ANP to re-
cieve prophylaxis with cefuroxime 1.5 g intravenously every
8 hours or antibiotics only when infection had been verified.
Diagnosis was based on contrast CT results and CRP levels
greater than 120 mg/L. Infectious complications were signifi-
cantly lower with cefuroxime prophylaxis (p = 0.01), but
only the rate of urinary tract infection was significantly lower
(p = 0.007) when infections were evaluated separately. Mor-
tality was lower in the prophylaxis group, with 1 death com-
pared with 7 in the as-needed group (p = 0.028). While bene-
fit was demonstrated with cefuroxime therapy, the authors
highlighted that antibiotic therapy was altered in 20 of 30 pa-

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**Table 1. Randomized Trials of Antibiotic Prophylaxis in Acute Necrotizing Pancreatitis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Intervention</th>
<th>N</th>
<th>&gt;30% Necrosis</th>
<th>Infected Necrosis, n</th>
<th>Mortality, n</th>
<th>Additional Antibiotics, n</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli (1993)14</td>
<td>R</td>
<td>imipenem 0.5 g every 8 h</td>
<td>41</td>
<td>41</td>
<td>5</td>
<td>3</td>
<td>NR</td>
<td>p &lt; 0.01 pancreatic infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medical treatment only</td>
<td>33</td>
<td>33</td>
<td>10</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sainio (1995)15</td>
<td>R</td>
<td>cefuroxime 1.5 g every 8 h antibiotics as needed</td>
<td>30</td>
<td>NR</td>
<td>9</td>
<td>1</td>
<td>20</td>
<td>p = 0.03 if death as reported initially</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>12</td>
<td>7*</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delcenserie (1996)6</td>
<td>R</td>
<td>cefazidime + amikacin + metronidazole</td>
<td>11</td>
<td>NR</td>
<td>0</td>
<td>1</td>
<td>NR</td>
<td>p &lt; 0.03 for severe sepsis which included nonpancreatic infections in 4 additional pts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medical treatment only</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordback (2001)18</td>
<td>R</td>
<td>imipenem 1g every 8 h if for necrosectomy</td>
<td>25</td>
<td>17</td>
<td>2*</td>
<td>2</td>
<td>6</td>
<td>main outcome was need for surgery: 2 T vs 5 C; p = 0.003 for infected necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33</td>
<td>20</td>
<td>14</td>
<td>5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drellinger (2007)4</td>
<td>R, DB, PC</td>
<td>meropenem placebo</td>
<td>50</td>
<td>26</td>
<td>9</td>
<td>10</td>
<td>25</td>
<td>treatment did not delay infection onset; no change in need for surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>31</td>
<td>6</td>
<td>9</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Isenmann (2004)7</td>
<td>R, DB, PC</td>
<td>ciprofloxacin + metronidazole placebo</td>
<td>58</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>16</td>
<td>no difference with treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Røkke (2007)17</td>
<td>R</td>
<td>imipenem early antibiotics as needed</td>
<td>36</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>outcomes not well defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

C = control arm; DB = double blind; NR = not reported; PC = placebo-controlled; R = randomized; T = treatment arm.

*a*Two early deaths included in error; if these are removed, difference was not significant.

*b*Infection was assumed based on clinical parameters in 2 patients receiving imipenem and 14 patients in the control group. Only 3 patients (study allocation not listed) had positive cultures from needle aspiration.

*9*Nine additional patients given as-needed imipenem.
The use of prophylactic treatment led to a significant decrease in pancreatic necrosis compared with no treatment. The use of prophylactic treatment led to a significant decrease in pancreatic necrosis, 12.2% of patients receiving antibiotics versus 30.3% of control patients (p < 0.01). The data from this evaluation have been criticized for lack of blinding, no data presented for nonstudy antibiotic use, not controlling for the need of surgery, and a higher number of patients with greater than 50% necrosis of the pancreas in the treatment group, which may have biased the study in favor of antibiotic use.

Delcenserie et al. examined the use of ceftazidime, amikacin, and metronidazole for 10 days versus no therapy in 23 patients with severe alcohol-induced acute pancreatitis with CT-demonstrated fluid collection. Degree of necrosis was not a criterion for inclusion. All patients received parenteral nutrition. Severe sepsis episodes were lower in the antibiotic group (7 vs 0; p < 0.03). Three patients in the control group had infected necrosis versus none in the treatment group. The study has been criticized due to small sample size, an insufficient number of patients with pancreatic necrosis, no data presented on nonstudy antibiotic use, and the diagnostic criteria used for enrollment (eg, fluid collection shown on CT).

Several studies have been conducted since 1998. In 2001, Nordback et al. examined early versus delayed treatment for ANP in patients with CRP greater than 150 mg/L or CT-visualized necrosis. Patients were randomized to receive imipenem 1 g intravenously every 8 hours (n = 25) or placebo (n = 33). Patients receiving placebo were started on imipenem only when an indication for necrosectomy was met. Necrosectomy was indicated in 8% of patients in the treatment group versus 42% of those in the placebo group (p = 0.003), with 8% versus 36%, respectively, ultimately requiring surgery (p = 0.04). The authors concluded that early treatment reduced the need for surgery and major organ complications in patients with ANP. Unfortunately, 32% of treatment and 39% of control patients had less than 30% necrosis at study entry and 42% of patients in the control group needed to receive imipenem. In addition, 9 of 14 patients given delayed imipenem avoided surgery by the use of antibiotics alone and 6 of the 7 patients who required surgery died, possibly due to an unnecessary delay in performing the surgery.

An unblinded, randomized trial examining imipenem 500 mg intravenously every 8 hours for 5–7 days (n = 36) versus no antibiotic (n = 37) unless infection was diagnosed was published in 2007. The investigators fell short of the desired enrollment of 160 patients, enrolling only 73 patients. Twenty-three percent of patients had greater than 30% CT-documented necrosis. The antibiotic group showed a significant decrease in complications, although what these complications entailed was not defined (12 vs 22 for treatment and control groups, respectively; p = 0.03). The incidence of infections was significantly decreased with imipenem compared with delayed antibiotic treatment (5 vs 16, respectively; p = 0.009). However, all infections in the control group were diagnosed in the first 2 weeks after enrollment compared with none in the imipenem group. Based on the study protocol, it is assumed that patients did not receive any imipenem after the first week postenrollment. Many of the control patients diagnosed as infected did not have culture-proven infections but were diagnosed based on “clinical, laboratory, and X-ray findings.” The authors did not provide information on specific infection sites but reported peripancreatic infections in 7 control patients compared with 3 patients treated with imipenem. All 16 patients in the control group were treated with antibiotics other than imipenem. Although these data may appear to support early prophylactic antibiotic use with imipenem, concerns of lower-than-needed sample size, lack of detailed information on complications, and one third of the patients enrolled not having any CT-shown evidence of necrosis, limit the study’s applicability.

Recent randomized controlled trials provide the first data on prophylactic antibiotic use in ANP to come from double-blind studies. The findings of these trials however, complicate assessment of prophylactic antibiotics further.

Isenmann et al. selected patients with CRP greater than 150 mg/L and/or CT-defined pancreatic necrosis. Patients enrolled received ciprofloxacin 400 mg intravenously twice daily plus metronidazole 500 mg intravenously twice daily or placebo for at least 14 and up to 21 days, starting within 72 hours of symptom onset. Although initial recruitment was planned for 200 patients, only 114 were evaluated after enrollment was halted due to an interim analysis that showed no benefit to therapy. Overall, 58 patients entered the treatment arm (37 with CT-documented necrosis, 13 with >30% necrosis) and 56 were given placebo (33 with CT-documented necrosis, 11 with >30% necrosis). Patients remained in the study until “infectious complications, multiple organ failure sepsis, or systemic inflammatory response syndrome occurred.” Open antibiotic use was required in 16 of 58 (28%) patients in the treatment arm a median of 11.5 days after enrollment and in 26 of 56 (46%) patients receiving placebo a median of 5 days after enrollment (p = 0.04). Most of the infections that required open treatment were extrapancreatic infections such as pneumonia or urinary tract infections.
infection. Thirteen central line infections were reported in the study (8 in the treatment group vs 5 in the placebo group), but the percent of extrapancreatic infections overall was similar at 22% and 23%, respectively.

In the subgroup of patients with documented necrosis, the difference for open use of antibiotics was not significant (37% [n =37] treatment group vs 57% [n =33] placebo group; p = NS) at a median of 14 versus 9 days after enrollment, respectively. Specific antibiotics were at the discretion of the physician, but the recommended regimen was imipenem and vancomycin. The investigators did not report how many patients received the preferred regimen. The rates of infected pancreatic necrosis and mortality were similar between the treatment and placebo arms at 12% versus 9% and 5% versus 7%, respectively (p = NS). Whether the antibiotic choice (quinolone/metronidazole combination) and a high baseline quinolone resistance rate may have contributed to the findings of this study is unclear. In addition, the small number of patients with documented necrosis greater than 30%, the large number of patients in both groups who needed open antibiotic use, and the halting of the study before the recruiting target was reached limit the conclusion strength from this study.18,22

The most recent randomized, double-blind, controlled trial compared meropenem 1 g intravenously every 8 hours with placebo in 100 patients (50 in each group) within 5 days of symptom onset.4 Patients with contrast-enhanced CT-scan documented greater than or equal to 30% necrosis of the pancreas were eligible. If a contrast-enhanced CT was judged by the investigator to not be indicated, a non-contrast scan showing multiple peripancreatic fluid collections and pancreatic edema along with either CRP greater than 120 mg/L or multiple organ dysfunction was deemed to meet criteria for inclusion. The investigators wanted to enroll 240 patients but, due to slow enrollment and funding issues, completed enrollment of only 100 patients. Of these 100 patients, 52% in the meropenem group and 62% in the placebo group had greater than 30% necrosis of the pancreas, higher rates than the other blinded trial. Rates of pancreatic or peripancreatic infections were similar between groups, with 23% in the treatment group and 15% in the placebo group (p = NS).4 Alternative antibiotic therapy use, mortality, need for surgery, and rates of adverse events were also similar between the groups. The weaknesses of this trial are that it was underpowered due to slow enrollment and 54% of the placebo group and 50% of the treatment group required additional nonstudy antibiotics a median of 14 and 17 days, respectively, after study entry. Nonetheless, the timing of as-needed antibiotics was much later than in the previous blinded trial. In addition, patients were enrolled without greater than 30% necrosis of the pancreas. Despite these criticisms, the trial was randomized and double-blind, which provides a stronger design for controlling confounders. In addition, the investigators controlled for the type of nutritional support for patients in both groups.

Meta-Analyses

Seven meta-analyses have been published on prophylactic antibiotic use in necrotizing pancreatitis.20,23-29 Table 2 provides a summary of these analyses. The first analysis, published in 1998, supported a conclusion that prophylactic antibiotics of various drug classes improve mortality outcomes.23 This analysis included studies from the 1970s that used ampicillin in patients at low risk for infection. These studies showed no benefit of treatment, possibly due to inadequate pancreatic concentrations of the drug and the popul-
tion of low-risk patients. Therefore, these studies are no longer considered adequate for further evaluation. The mortality benefit found was associated with the trial by Sainio et al., and the benefit disappears if this trial is removed from the analysis.

A 2001 meta-analysis included only 3 studies, of which have been reviewed above, in addition to a study published in German that was translated by the meta-analysis authors to English. The German study evaluated ofloxacin and metronidazole compared with placebo, according to the meta-analysis report. The authors concluded that antibiotic prophylaxis significantly reduced sepsis and mortality. The mortality benefit found was again due to inclusion of the Sainio et al. trial, which, upon reanalysis, showed no mortality benefit. The decrease in sepsis was mainly due to the Pedezzoli et al. trial and, as previously discussed, more patients in the treatment group had severe necrosis, potentially favoring treatment. The German study found no difference for any outcome. The authors recommended that all patients with ANP should receive prophylaxis with antibiotics that have proven pancreatic penetration, such as imipenem. No tests for publication bias were conducted.

The 2006 meta-analysis included 6 studies with 329 patients, the same 3 studies of the 2001 meta-analysis listed above, and studies by Nordback et al., and a study published only in abstract form. The abstract appears to be the only study limited to patients with greater than 30% pancreatic necrosis. Unfortunately, it included only 35 patients and it has yet to be published as a full article. Patients received a combination of ciprofloxacin and metronidazole or meropenem for 10 days in the prophylaxis group or the same antibiotics only when indicated in the therapeutic group. The reason for using meropenem over the combination regimen was not listed. Based on the short abstract description, it appears to be a retrospective outcome review instead of a randomized study. The diagnosis of necrosis could have been based on CT scan findings or autopsy. It is unclear whether the authors may have meant a pancreatic aspiration biopsy instead of autopsy. No significant differences between prophylaxis or on-demand treatment for infectious complications, infectious necrosis, length of stay, abscess formation, surgical treatment, or mortality were found in this study. The meta-analysis authors conducted heterogeneity and publication bias evaluations, contacted authors for missing information, provided a complete description for excluding studies, and evaluated the quality of the included trials. The only statistically significant benefit of antibiotic prophylaxis when the studies are combined was a shorter length of hospital stay (5.64 days less; p = 0.04). When the study by Dellinger et al. was included, the meta-analysis conclusions were the same for length of stay, but a statistically significant decrease in nonpancreatic infection was reported in patients receiving prophylaxis (p = 0.01).

The 2007 meta-analysis included 10 trials from 1993 to 2004 and appears to have analyzed the largest number of patients and trials. Unfortunately, there are problems with several of the trials analyzed. The largest trial, which contributed 156 patients and favored treatment, was an uncontrolled evaluation of continuous regional arterial infusion of imipenem and/or a protease inhibitor (ie, gabexate mesilate). This study should have been excluded, as the route of medication administration is not standard, the study was uncontrolled, and it may have biased the results in favor of treatment. In addition, several of the trials included in the analysis did not provide information on the need for surgical interventions or incidence of sepsis and about half involved antibiotics other than imipenem. Three of the trials included duration of therapy or compared 2 different antibiotic regimens. These trials were not designed to compare prophylaxis versus delayed antibiotic treatment and should have been excluded. The authors concluded that prophylaxis significantly decreases the incidence of both infected pancreatic necrosis (RR 0.57; p = 0.0005) and mortality (RR 0.76; p = 0.032) and that all patients with proven or anticipated necrosis should receive antibiotics.

The 3 analyses published in 2008 selected randomized controlled trials of patients with ANP through 2007. The trials included in these meta-analyses were the same, except that only one excluded the study available in abstract form previously listed with the 2001 meta-analysis. Hart et al. excluded the study by Røkke et al. because the authors allowed the use of CRP levels to evaluate necrosis. The meta-analysis was reported using odds ratio instead of RR used by the other 2 meta-analyses. In addition, the analysis by Bai et al. assumed heterogeneity of studies and used a random-effects model before pooling the data and checked for publication bias; whereas, Xu et al. tested for heterogeneity and, not finding any, used a fixed-effects model. Hart et al. reported using both fixed and random models. Conclusions presented by the authors of these meta-analyses vary with regard to rates of infected pancreatic necrosis but are similar regarding mortality. Bai et al. reported a relative risk for necrosis infection of 0.81 (p = NS), Hart et al. reported an odds ratio of 0.72 (p = NS), while Xu et al. gave a relative risk of 0.69 (p = 0.02), favoring antibiotic prophylaxis. All 3 analyses reported no mortality benefit. Two of the analyses reported significant decreases in length of hospital stay (RR 5.64, p
However, only 3 of the studies included in the meta-analyses evaluated the hospital stay variable. A significant reduction of infection when imipenem was used (p = 0.009) compared with no reduction with other antibiotics (p = NS) was also reported by Xu et al.

Limitations within the available meta-analyses include small sample sizes even when multiple studies are combined, differences in entry criteria, confounding due to variations in adjuvant therapies, and inherent differences in nutritional support and surgical interventions offered at varying study sites. Newer data show benefit with enteral nutrition compared with parenteral nutrition. Also, no distinction between early- and late-phase death is presented in the current literature to help differentiate between deaths resulting from infected ANP versus other causes. The differing conclusions reached by all 7 meta-analyses highlight the fact that inclusion or exclusion of a single study can affect conclusions.

Antibiotic Selection

Head-to-head comparisons of prophylactic antimicrobials are sparse. Bassi et al. compared pefloxacin 400 mg intravenously twice daily with imipenem 500 mg intravenously 3 times daily for 2 weeks in 60 patients with necrosis involving greater than or equal to 50% of the pancreas. The investigators were not able to achieve the target of 100 patients due to the strict necrosis criterion. While mortality and rates of extrapancreatic infection did not vary between groups, the incidence of pancreatic infection was lower with imipenem (3 of 30; 10%) versus pefloxacin (10 of 30; 34%; p = 0.034). However, 3 of the infections in the pefloxacin group were documented in the second week of treatment and, after surgery, patients continued to receive the drug until the 14 days were complete. Seven of the 10 patients also had extrapancreatic infections; however, infecting organisms or additional treatment for these was not reported. All 3 infections in the imipenem group developed during the fourth week of hospitalization. These infections were caused by methicillin-resistant Staphylococcus aureus in 2 of the patients and therefore were not covered by imipenem.

The use of meropenem 500 mg intravenously 3 times daily versus imipenem 500 mg intravenously 4 times daily was evaluated in 176 patients with necrotizing pancreatitis. This study showed no significant difference between the treatment arms with regard to rates of pancreatic infection, extrapancreatic infection, or clinical outcome. No data were presented on the use of nonstudy antibiotics other than 3 cases that required treatment with oxacillin for catheter-related sepsis.

Timing and Duration of Prophylactic Therapy

Most trials have enrolled patients with documented necrotizing pancreatitis prior to entry. Manes et al., however, randomized 215 patients into a meropenem treatment group to begin therapy at the time of acute pancreatitis diagnosis, with antibiotic withdrawal after a negative CT for pancreatic necrosis, or to delayed meropenem treatment after CT confirmation of necrosis. The CT scan was performed at least 48 hours after symptom onset. Of the 108 patients enrolled in the early treatment arm, only 30 continued therapy (50% with <30% necrosis) and 29 of 107 patients in the delayed therapy arm initiated therapy (48% with <30% necrosis). The final study results are based on the 59 patients who continued or started therapy. Early initiation of antibiotic therapy versus delayed therapy was associated with significant decreases in extrapancreatic infection (5 vs 13, respectively; p < 0.03), incidence of surgery (4 vs 11; p < 0.05), and hospitalization days (18 vs 30; p = 0.01). The most common extrapancreatic infections were pulmonary and urinary tract for both groups. The timing for these infections was not specified but was listed as similar between the groups. The incidence of pancreatic infection was not significantly different between the groups (4 early vs 9 delayed treatment). Three of the 4 infections in the early treatment group developed during the second week of disease compared with 4 of 9 in the delayed treatment group. All patients received parenteral nutrition, which is not considered optimal nutrition therapy. In addition, at least half of the patients had less than 30% pancreatic necrosis, and none of them developed an infection.

The duration of antibiotic prophylaxis was evaluated in 92 patients receiving imipenem 500 mg 4 times a day for 14 days, with either discontinuation at that point or continuation as long as systemic complications of the disease were present. The 2 groups varied only on duration of therapy, 14.8 versus 19.7 days, and rates of both pancreatic and extrapancreatic infection were similar.

Complications from Antibiotic Use

Concern exists that increased use of prophylactic antibiotics in patients with ANP may increase the incidence of gram-positive bacteria such as staphylococci. This shift was demonstrated in a small study comparing patients receiving imipenem with a historical control group of patients not given prophylaxis. A significant drop in the incidence of gram-negative pathogens (56% in the control group vs 26% in the antibiotic group; p = 0.005) was reported, compared with an increase in gram-positive in-
volvement (23% in control patients vs 52% in treatment patients; \( p = 0.009 \)) with the administration of prophylactic imipenem. In this cohort, gram-positive organisms in the treatment group consisted mainly of enterococci (10 of 30 isolates) and \textit{S. epidermidis} (10 of 30 isolates). No significant increase in \( \beta \)-lactam resistance or fungal infection was evident. A randomized study reported predominance of gram-positive infections, although most of these were \textit{S. epidermidis} isolated from central lines.\textsuperscript{7}

Another concern with the use of prophylactic antibiotics is the potential for increased bacterial resistance. As previously stated, no significant increases in resistance to \( \beta \)-lactams were seen in patients receiving imipenem prophylaxis, despite change in pathogen type, compared with the control group.\textsuperscript{36} Several studies have addressed the issue of infection with resistant organisms.\textsuperscript{7,32,35,37} Isenmann et al.\textsuperscript{7} reviewed isolates from patients receiving prophylactic ciprofloxacin and metronidazole or placebo. They found that 18 of the 23 treatment isolates and 6 of the 28 placebo isolates (\( p < 0.0001 \)) were resistant to ciprofloxacin. However, quinolone resistance is increasingly common. Three studies have reported a 21–30% imipenem resistance rate among gram-negative pathogens isolated from patients who received at least 14 days of imipenem.\textsuperscript{32,35,37} In one study, the presence of resistance was correlated with a negative outcome.\textsuperscript{37}

Clinical evidence is unclear regarding fungal infection rates in patients receiving prophylactic antibiotics. In one report, 24% of infected pancreatic necrosis cases within a university hospital cohort were due to fungal pathogens, representing an increase from a historical fungal infection rate of 10%; however, no distinction between primary and secondary infection was provided.\textsuperscript{37} A retrospective review of 62 patients with necrotizing pancreatitis found no cases of primary fungal infection and only an 11% secondary infection rate; however, imipenem use for these patients was low at 27%.\textsuperscript{38} A review of 4 randomized trials of prophylactic antibiotic use containing data on the incidence of fungal infection found no statistically significant difference in fungal infection rate between patients receiving antibiotics (4.9%) and control patients (6.7%).\textsuperscript{8} A review of 46 patients who received prophylaxis or treatment with antibiotics for an average of 20 days found an overall incidence of \textit{Candida} infections of 37%, which increased to 50% if patients given prophylactic fluconazole were excluded.\textsuperscript{39}

Guidelines

Current guidelines reflect the conflicting data regarding antibiotic use in ANP reviewed above. In 2002, the International Association of Pancreatology put forth guidelines for the management of acute pancreatitis.\textsuperscript{40} These guidelines gave a Grade A recommendation (eg, strong evidence from a meta-analysis or at least 1 randomized trial) to the use of prophylactic broad-spectrum antibiotics in order to reduce the incidence of infection in CT-defined cases of necrotizing pancreatitis, but do caution that mortality may not be improved. No specific antibacterial agent was recommended, but the Association’s conclusions were based on data from studies of imipenem, cefuroxime, and the combination of ceftazidime, amikacin, and metronidazole.\textsuperscript{6,14-17} No blinded study was included, since those were published after 2002.\textsuperscript{47} These guidelines were revisited in 2004\textsuperscript{48} by a consensus conference and resulted in the recommendation against antibiotic or antifungal prophylaxis (Grade B, based on moderate quality evidence) due to newer data that included the Isenmann et al.\textsuperscript{7} blinded study.

The 2006 guidelines from the American College of Gastroenterology (ACG) recommend, at a grade III level of evidence, that prophylactic antibiotics not be used to prevent pancreatic infection in patients with necrotizing pancreatitis.\textsuperscript{3} A grade III recommendation was defined as being based on data from well-designed trials without randomization.

The American Gastroenterological Association Institute currently recommends that if prophylactic antibiotics are being considered, they should be used only in patients with pancreatic necrosis involving greater than 30% of the gland as imaged by CT and for no longer than 14 days.\textsuperscript{41} However, the authors of the guidelines, and others, state that it is reasonable to use antibiotics only as indicated rather than as prophylaxis, based on current data.\textsuperscript{41-43}

Discussion

While newer data on the subject of prophylactic antibiotic use come from studies with more robust designs, we are still without a definite answer regarding the use of prophylactic antibiotics in ANP. One of the most common confounders in the current studies is the inclusion of patients who would be considered at low risk for infected ANP (eg, those with <30% necrosis).\textsuperscript{22,44} In addition, in many studies, including 2 double-blind trials, at least half of the patients in the control group required antibiotics, leading to high crossover rates.\textsuperscript{1,4,7,18,25,43} Given that many patients with necrotizing pancreatitis will require antibiotic therapy, several authors advocate an on-demand, or empiric, use of antibiotics for the management of infectious complications instead of starting antibiotics within 2 or 3 days of diagnosis, regardless of clinical status or degree of necrosis.\textsuperscript{4,7,41,43} One author stated that cost savings can be realized by on-demand antibiotic use.\textsuperscript{8} While no trial has explored the cost-effectiveness of antibiotics in ANP, one study reported the cost of prophylaxis to be twice that of on-demand antibiotics.\textsuperscript{37} The use of broad-spectrum antibiotics for several weeks and the potential impact on resistance patterns, development of fungal infections, \textit{Clostridium difficile} colitis, and other adverse effects need to also be considered.\textsuperscript{21,44}
Given the available data, we conclude that providing antibiotic prophylaxis to all patients with defined pancreatic necrosis involving greater than 30% of the pancreas does not appear to be warranted. A more measured on-demand use of antibiotics in this population only when necrosis is accompanied by signs of possible infection appears to be indicated and corresponds to more sound clinical antibiotic use. Several signs and symptoms of infection, such as fever or leukocytosis, combined with positive cultures from sterile sites or from pancreatic needle aspiration, and hemodynamic instability or organ failure would need to be present. Fever or leukocytosis alone should not be used as indications for antibiotics, as these are usually present in patients with pancreatitis without infection. Patients considered to be at low risk for infectious necrotizing pancreatitis likewise should be monitored for possible infections but should not receive prophylaxis. Common practices to decrease extrapancreatic nosocomial complications such as central line- or urinary catheter-related infections should be applied to all of these patients, regardless of degree of necrosis, to further improve outcomes.

If empiric antibiotic treatment is used, imipenem would be recommended as the agent of choice. This recommendation is based on data from trials showing imipenem’s effectiveness and superiority to pefloxacin. Meropenem has been shown to be equivalent to imipenem and represents a possible treatment choice according to formulary considerations. There are no data on the use of doripenem. Evidence of increased ciprofloxacin resistance would favor the use of a carbapenem over a fluoroquinolone. Empiric therapy should be continued until culture sensitivities are available (usually about 3 days) and treatment should be streamlined to the narrowest-spectrum, most cost-effective agent. If no cultures are positive and the patient is stable, serious consideration should be given to stopping empiric antibiotic therapy to avoid superinfections or other complications instead of continuing therapy for several weeks. In some centers, imipenem empiric use may not be warranted if the rate of gram-negative resistance is low and a third-generation cephalosporin (eg, ceftriaxone, cefotaxime) may provide adequate empiric coverage; nonetheless, these antibiotics have not been specifically studied for use in ANP and would not cover enterococci or anaerobes. The inclusion of empiric vancomycin for all patients does not appear to be warranted at this time. We recommend against the use of antifungal coverage, as data have yet to support the need for initial coverage against these pathogens.

Summary

Based on currently available data, use of antibiotic prophylaxis in ANP is not indicated. Large, well-controlled trials including only patients meeting the ACG definition of pancreatic necrosis (involving >30% of the pancreas) with additional information, such as timing of antibiotics and differences in etiology of pancreatitis, are still needed. Unfortunately, slow recruitment; currently low infection rates, which would increase the number of patients needed per group; possible inclusion of patients with less than 30% necrosis; crossover of groups; and blending logistics need to be considered as well. All of these issues may contribute to the continuation of this debate for years to come.

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References

Se incluyeron estudios publicados previo a 1998 fueron también incluídos si se consideraban relevantes. Los estudios no ciegos, sin embargo, documentaron una disminución administrarse profilaxis con antibióticos en comparación con placebo. Los estudios ciegos no encontraron una diferencia significativa en mortalidad al administrarse profilaxis con antibióticos en pacientes con episodios agudos de pancreatitis necrotizante. Se incluyeron estudios clínicos, meta análisis y artículos de revisión publicados en el idioma inglés. Se identificaron artículos adicionales de las bibliografías de éstos. Estudios aleatorios publicados previo a 1998 fueron también incluídos si se consideraba indicado.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se incluyeron estudios relevantes o meta análisis realizados sobre la profilaxis con antibióticos en episodios agudos de pancreatitis necrotizante publicados en la última década, y actualizar las recomendaciones.


Selección de estudios y extracción de datos: Se incluyeron estudios relevantes o meta análisis realizados sobre la profilaxis con antibióticos a partir de la revisión previa realizada por los autores. Se incluyeron datos previos a esta revisión si se consideraban relevantes.

Síntesis de datos: Se identificaron 4 estudios aleatorios, 2 de éstos doble ciego desde la última revisión publicada por los autores. Los estudios ciegos no encontraron una diferencia significativa en mortalidad al administrarse profilaxis con antibióticos en comparación con placebo. Los estudios no ciegos, sin embargo, documentaron una disminución significativa en infecciones. De acuerdo de los datos disponibles, no se recomienda administrar profilaxis con antibióticos en pacientes con episodios agudos de pancreatitis necrotizante. Se prefecte un uso más cauteloso de antibióticos según el cuadro clínico de cada paciente. Los antibióticos deben ser utilizados si hay presencia de signos y síntomas de infección (ej., fiebre, leucocitosis, cultivos positivos). Como resultado de los avances en el soporte nutricional en las unidades de cuidado intensivo, los estudios recientes han revelado una menor incidencia de pancreatitis necrotizante en comparación con el pasado. En el futuro, por...
Antibiotic Prophylaxis in Acute Necrotizing Pancreatitis

CONCLUSIONS: La profilaxis con antibióticos en episodios agudos de pancreatitis necrotizante no está indicada de acuerdo con los 2 estudios ciegos evaluados. El uso de antibióticos según el cuadro clínico en particular parece ser apropiado. Dado el progreso en el manejo de pacientes en las unidades de cuidado intensivo, la necesidad de profilaxis con antibióticos en pacientes con pancreatitis necrotizante aguda continuará siendo sujeto de debate por décadas.

Antibioprophylaxie pour une Pancréatite Aiguë avec Nécrose

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SYNTHÈSE DES DONNÉES: Depuis notre dernière revue, 4 études randomisées additionnelles, incluant 2 études à double insu, ont été effectuées. Aucune différence significative dans la mortalité avec antibioprophylaxie en comparaison au placebo n’a été trouvée dans les études à double insu alors que les études ouvertes ont démontré une diminution des infections. Face à ces résultats divergents, les guides d’utilisation disponibles et les méta-analyses procurent des conclusions différentes, normalement basées sur l’inclusion ou l’exclusion d’une seule étude. Lorsque toutes les données disponibles sont regroupées, l’antibioprophylaxie ne devrait pas être utilisée chez les patients souffrant d’une pancréatite aiguë avec nécrose. Au contraire, l’usage mesuré d’un antibiotique, à la demande, est suggéré. Des antibiotiques devraient être prescrits si des signes et symptômes d’infections sont présents (ie, fièvre, leucocytose, cultures positives). Tenant compte des améliorations observées dans les soins intensifs et l’apport nutritionnel, les études récentes ont démontré une incidence moindre de pancréatite aiguë avec nécrose que précédemment. Par conséquent, les prochaines études nécessiteront la présence d’un nombre plus élevé de patients.

CONCLUSIONS: L’usage d’une antibioprophylaxie pour les patients atteints de pancréatite aiguë avec nécrose n’est pas indiqué en tenant compte des 2 études à double insu. L’usage d’antibiotiques, à la demande, semble plus approprié. Tenant compte du progrès réalisé en soins intensifs et le taux croisé élevé dans les études, l’usage d’une antibioprophylaxie sera probablement encore débattu pour les décennies à venir.

Traducido por Wanda T Maldonado

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