**CAT**

\*\*PICO RT 7 WK 2

**Scenario:**

A patient presents to the medicine floor with acute necrotizing pancreatitis (ANP). As acute pancreatitis is associated with high morbidity and mortality with most deaths occurring in patients with acute necrotizing pancreatitis, the team discusses whether or not the patient would benefit from prophylactic use of antibiotics to minimize morbidity and mortality.

**Search Question**: Clearly state the question (including outcomes or criteria to be tracked)

**Is antibiotic prophylaxis beneficial in reducing morbidity and mortality in patients with acute necrotizing pancreatitis?**

**Identify the PICO Elements:**

**P =** patients with acute necrotizing pancreatitis

**I =** antibiotic prophylaxis

**C** **=** no prophylaxis

**O** = reduced morbidity and mortality

**PICO search terms:**

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| **P** | **I** | **C** | **O** |
| Patients with acute necrotizing pancreatitis | Antibiotic prophylaxis | No antibiotic use | Reduced morbidity and mortality |
| Acute necrotizing pancreatitis | Administration of prophylactic antibiotics | Lack of antibiotic prophylaxis | Sepsis and mortality reduction |
| Pancreatic necrosis | Prophylactic parenteral antibiotics | No prophylaxis | Decreased mortality |
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**Search tools and strategy used:**

Databases used: Science Direct, PubMed, Google Scholar

Terms used: antibiotic prophylaxis for acute necrotizing pancreatitis, antibiotic use for patients with acute necrotizing pancreatitis, acute necrotizing pancreatitis and prophylaxis

Articles returned:

* Science Direct: +last 10 years
  + antibiotic prophylaxis for acute necrotizing pancreatitis – 1,459 results
  + antibiotic use for patients with acute necrotizing pancreatitis – 3,916 results
  + acute necrotizing pancreatitis and prophylaxis – 1,790 results
* PubMed: +last 15 tears
  + antibiotic prophylaxis for acute necrotizing pancreatitis – 420 results
  + antibiotic use for patients with acute necrotizing pancreatitis – 1,103 results
  + acute necrotizing pancreatitis and prophylaxis – 1,538 results
* Google Scholar: +last 15 years
  + antibiotic prophylaxis for acute necrotizing pancreatitis – 11,300 results
  + antibiotic use for patients with acute necrotizing pancreatitis – 21,100 results
  + acute necrotizing pancreatitis and prophylaxis – 26,300 results

**How I narrowed down my chosen articles:**

I narrowed my choices to a few selected articles based on the type of study done, namely meta-analysis, systematic review and randomized controlled trials to ensure a high level of evidence. I chose articles that directly answered my PICO question and compared the use of antibiotic prophylaxis with no prophylaxis OR administration of antibiotics as a treatment as opposed to a prophylactic measure. I chose articles which measured certain outcomes including infected pancreatic necrosis (IPN), non-pancreatic infections (NPN), mortality, sepsis and surgical intervention.

**Chosen articles:**

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| **Article 1:**  Prophylactic Antibiotic Administration Reduces Sepsis and Mortality in Acute Necrotizing Pancreatitis: A Meta-Analysis  Sharma, Virender Kumar; Howden, Colin W.\* |
| Link: https://journals.lww.com/pancreasjournal/Fulltext/2001/01000/Prophylactic\_Antibiotic\_Administration\_Reduces.5.aspx |
| Abstract:  Severe acute pancreatitis is frequently complicated by local and systemic infections resulting in substantial morbidity, mortality, and health care costs. Antibiotic prophylaxis may prevent some infections. We searched for randomized, controlled trials comparing antibiotic prophylaxis with no prophylaxis in patients with acute necrotizing pancreatitis (ANP). Only trials that used antibiotics that reach minimum inhibitory concentration (MIC) in necrotic pancreatic tissue were included. We calculated relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) for individual trials and pooled data. Antibiotic prophylaxis significantly reduced sepsis by 21.1% (NNT = 5) and mortality by 12.3% (NNT = 8) compared with no prophylaxis. There was also a nonsignificant trend toward a decrease in local pancreatic infections (ARR = 12%; NNT = 8). Antibiotic prophylaxis decreases sepsis and mortality in patients with ANP. All patients with ANP should be given prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue. |
| Type of study:  Meta-analysis of randomized controlled trials |
| Main Points:   * MEDLINE database search of randomized controlled trials comparing the use of antibiotic prophylaxis with no prophylaxis in patients with ANP * Relative risk reduction, absolute risk reduction and number needed to treat were calculated * Breslow-Day test for homogeneity done to ensure appropriate pooling * Overall rates of pancreatic infection, sepsis and mortality were calculated * 6 randomized controlled trials were identified overall but only 3 included as these focused on patients with acute necrotizing pancreatitis * 2 included patients with severe ANP without pancreatic necrosis on CT and one compared prophylaxis with 2 different antibiotics * 84 patients received antibiotic prophylaxis, 76 control patients did not. Both groups received standard care for pancreatitis – supportive treatment * 1 trial found significant reduction in sepsis in the antibiotic prophylaxis group and 1 trial found significant reduction in mortality in the prophylaxis group * Results – revealed significant improvement in sepsis and mortality in patients with ANP receiving antibiotic prophylaxis with a trend toward reduction in pancreatic infection * Limitations – combining results of different trials, minor variation in inclusion criteria, different antibiotics used for prophylaxis and different protocols used to diagnose pancreatic infection |
| Why I chose it:  I chose this article because it’s a meta-analysis of randomized controlled trials directly answering my PICO question. It analyzed articles comparing the use of antibiotic prophylaxis to no prophylaxis in patients with acute necrotizing pancreatitis. This article clearly listed its limitations at the end of the conclusion which gives it credibility. |

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| **Article 2:**  Early prophylactic antibiotics administration for acute necrotizing pancreatitis: a meta-analysis of randomized controlled trials  Tomohiko Ukai · Satoru Shikata · Machiko Inoue · Yoshinori Noguchi · Hisato Igarashi · Shuji Isaji · Toshihiko Mayumi · Masahiro Yoshida · Yousuke C. Takemura |
| Link:  <https://onlinelibrary-wiley-com.york.ezproxy.cuny.edu/doi/pdfdirect/10.1002/jhbp.221> |
| Abstract:  Background The effectiveness of prophylactic antibiotics use for acute necrotizing pancreatitis has been explored and a number of systematic reviews have been published with conflicting results. The timing of antibiotics administration can be fundamental to their effectiveness, but thus far no re- views have focused on the timing of administration. Methods A systematic review of randomized controlled tri- als (RCTs) of prophylactic antibiotics for acute necrotizing pancreatitis was conducted using MEDLINE (PubMed), CINAHL and Japana Centra Revuo Medicina. Trials in which antibiotics were administered within 72 h after onset of symp- toms or 48 h after admission were included. Our primary out- comes were the mortality rate and the incidence of infected pancreatic necrosis, and secondary outcomes were the inci- dence of non-pancreatic infection and the incidence of surgi- cal intervention.  Results The search revealed six RCTs with a total of 397 pa- tients. The mortality rates were significantly different for those taking antibiotics (7.4%), and controls (14.4%) (odds ra- tio [OR], 0.48; 95% confidence interval [CI], 0.25–0.94). Also, early prophylactic antibiotics use was associated with reduced incidence of infected pancreatic necrosis (antibiotics 16.3%, controls 25.1%; OR, 0.55; 95% CI, 0.33–0.92). Conclusion Early use of prophylactic antibiotics for acute necrotizing pancreatitis is associated with reduced mortality and lower incidence of infected pancreatic necrosis. |
| Type of study:  Systematic review and meta-analysis of randomized controlled trials |
| Main points:   * MEDLINE (PubMed), CINAHL and JAPANA Centra Revuo Medicina used to conduct systematic review of prophylactic antibiotic use for acute necrotizing pancreatitis * Primary outcomes – mortality rate and incidence of infected pancreatic necrosis * Secondary outcomes – incidence of non-pancreatic infection and incidence of surgical intervention * 6 randomized controlled trials identified, total of 397 patients * Antibiotic prophylaxis was also found to be associated with a reduction in incidence of infected pancreatic necrosis * Infected pancreatic necrosis – 564 patients in 9 trials comparing prophylactic antibiotics with no prophylaxis on IPN. Prophylaxis treatment found to have significant effects on reduction of IPN * Mortality – antibiotics were not associated with a significant reduction in mortality * Nonpancreatic infection – 8 studies reported in patients with NPN, antibiotic prophylaxis was not found to be significant in reducing NPN |
| Why I chose this article:  I chose this article because it is a systematic review/meta-analysis of RCTs which is a high level of evidence. It directly answered my PICO question with focused primary and secondary outcomes measured. |

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| **Article 3:**  Meta-analysis of prophylactic parenteral antibiotic use in acute necrotizing pancreatitis  Žilvinas Dambrauskas1, 2, Antanas Gulbinas1, 2, Juozas Pundzius1, Giedrius Barauskas1 |
| Link:  <https://pubmed.ncbi.nlm.nih.gov/17485956/> |
| Abstract:  **Background:**Acute pancreatitis is a potentially serious condition. It carries an overall mortality rate of 10-15%. Infectious complications account for approximately 80% of deaths from acute pancreatitis, and the question arises whether or not prophylactic antibiotics are useful in the prevention of these complications. Therefore, we performed an evidence-based analysis to assess the effect of available prophylactic antimicrobial treatment on the development of infected necrosis and sepsis, need for surgery, and mortality.  **Methods:**A comprehensive PubMed search was performed evaluating the value of prophylactic administration of parenteral antibiotics in patients with acute necrotizing pancreatitis. Only articles published in English language between January 1990 and May 2006 were included. The search strategy initially generated 692 articles related to antibiotics in the treatment of acute pancreatitis. This number was reduced to 97 publications related to clinical trials on the same topic. Finally, 10 randomized clinical trials concerning prophylactic parenteral antibiotics in patients with acute necrotizing pancreatitis were identified. We have performed a meta-analysis using the random-effects model to assess the impact of prophylactic antibiotics on development of infected pancreatic necrosis and sepsis, need for surgery, and overall mortality.  **Results:**Patients with necrotizing acute pancreatitis should receive effective antibiotic prophylaxis (i.e., carbapenems intravenously) to decrease the risk of infected necrosis and sepsis and need of surgery.  **Conclusions:**While providing new insights into key aspects of antibiotic prophylaxis, this evidence-based analysis highlights the need for further clinical trials regarding the indications for antibiotic prophylaxis. |
| Type of study:  Meta-analysis |
| Main points:   * PubMed search performed evaluating parenteral administration of antibiotics in patients with acute necrotizing pancreatitis * 692 articles identified, 10 randomized clinical trials included in the study. * Random-effects model used to assess the effect of prophylactic antibiotics on potential development of infected pancreatic necrosis and sepsis, need for surgery and mortality. * Only series with CT-proven pancreatic necrosis were included in the meta-analysis * Overall, 1,279 patients included in the meta-analysis. 641 received prophylactic antibiotics and 638 were the control group. * Primary outcomes – infected necrosis, mortality * Secondary outcomes – need for surgery, incidence of sepsis * Infected necrosis – 324 patients experienced infected necrosis, 113 in prophylactic group and 211 in control group. Antibiotic prophylaxis was associated with reduction in risk of occurrence of infected necrosis * Mortality – 209 patients died, 88 in prophylactic group and 121 in control group. Antibiotic prophylaxis was associated with significant reduction in mortality rate. * Need for surgery – 167 patients had surgery, 59 in prophylactic group and 108 in control group. Tx with antibiotics was associated with reduced need to go to surgery * Sepsis – 307 patients were septic, 90 in prophylactic group and 217 in the control group. Antibiotics were associated with reduced incidence of sepsis. * Antibiotic prophylaxis was found to be superior compared to no prophylaxis or antibiotic treatment but not done prophylactically. * Patients should receive antibiotics prophylactically, namely carbapenems. |
| Why I chose this article:  This article is a meta-analysis and directly answers my PICO question. Its primary and secondary outcomes measured what I was looking to measure. This article broke down the numbers of patients in each group and each primary/secondary outcome very clearly, listing the number of patients in the prophylactic and control group and their outcomes. 1,279 patients were including in this meta-analysis which is a nice sample size and gives credibility to its results. I also like that this article compared antibiotic prophylaxis to antibiotic treatment, both have use of antibiotics but one is prophylactic and one is not. |

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| **Article 4:**  Prophylactic antibiotics reduce pancreatic necrosis in acute necrotizing pancreatitis: a meta-analysis of randomized trials  Linhua Yao, Xiayue Huang, Yuqin Li, Ruihua Shi, Guoxin Zhang |
| Link:  https://www.karger.com/Article/Pdf/318780 |
| Abstract:  ***Background and Aim:*** The use of prophylactic antibiotics to prevent infection and reduce mortality in patients with acute necrotizing pancreatitis (ANP) remains controversial. The aim of this study is to perform a systematic review of the data from randomized controlled trials to compare prophy- lactic antibiotic treatment of patients with ANP versus pla- cebo. ***Methods:*** A computerized literature search was con- ducted using Medline, PubMed, EMBase and Cochrane Cen- tral Register of Controlled Trials (CENTRAL) for relevant articles published in English from January 1990 to March 2010. MeSH terms and keywords used to identify articles in- cluded ‘antibiotic’, ‘pancreatitis’, and ‘randomized’. Outcome measures were infected pancreatic necrosis (IPN), mortality, nonpancreatic infection (NPN) and need for surgical inter- vention. ***Results:*** Nine trials involving 564 patients were in- cluded. Analysis suggested that IPN was significantly re- duced by treatment with antibiotics (RR 0.73, 95% CI 0.54– 0.98, p = 0.04). Mortality (p = 0.1), NPN (p = 0.07), and need for surgical intervention (p = 0.17) were not significantly re- duced by antibiotic treatment. Subsequent subgroup analysis confirmed that antibiotics were statistically superior to controls in reducing of infected necrosis (p = 0.003) and also mortality (p = 0.02) in single-blinded randomized controlled trials. ***Conclusion:*** Prophylactic antibiotic treatment reduced occurrence of IPN, but did not affect mortality, NPN, or surgi- cal intervention in patients with ANP. |
| Type of study:  Meta-analysis of randomized trials |
| Main points:   * Computerized literature search conducted using Medline, PubMed, EMBase and Cochrane Central Register of Controlled Trials * 9 trials identified including 564 patients * Trials from single-blinded, double-blinded, single-center and multi-center studies were included. Different antibiotics were used and tested * Fixed-effects and random-effects were used to pool data according to heterogeneity * Infected pancreatic necrosis - results showed that antibiotic prophylaxis was found to significantly reduce rate of infected pancreatic necrosis (IPN) and results with different antibiotic agents didn’t differ * Mortality – antibiotics weren’t found to significantly reduce mortality, only when using cephalosporins was mortality somewhat effected * Nonpancreatic infection – antibiotics weren’t found to significant reduce nonpancreatic infection * Surgical interventions – antibiotics weren’t found to reduce the need for surgical intervention |
| Why I chose this article:  This article is a meta-analysis of randomized trials which is a high level of evidence. It directly answered my PICO question and measured primary and secondary outcomes. 9 trials were included in this study which is more than many other meta-analyses I saw, lending to its credibility. |

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| **Article 5:**  Prophylactic Antibiotic Treatment in Patients with Predicted Severe Acute Pancreatitis: a placebo-controlled, double-blind trial  Rainer Isenmann, Michael Runzi, Martina Kron, Haral Goebell, Hans G. Berger |
| Link:  https://www.gastrojournal.org/article/S0016-5085(03)02150-4/fulltext |
| Abstract:  Math Eq Antibiotic prophylaxis in necrotizing pancreatitis remains controversial. Until now, there have been no double-blind studies dealing with this topic. Math Eq A total sample size of 200 patients was calculated to demonstrate with a power of 90% that antibiotic prophylaxis reduces the proportion of patients with infected pancreatic necrosis from 40% placebo (PLA) to 20% ciprofloxacin/metronidazole (CIP/MET). One hundred fourteen patients with acute pancreatitis in combination with a serum C-reactive protein exceeding 150 mg/L and/or necrosis on contrast-enhanced CT scan were enrolled and received either intravenous CIP (2 × 400 mg/day) + MET (2 × 500 mg/day) or PLA. Study medication was discontinued and switched to open antibiotic treatment when infectious complications, multiple organ failure sepsis, or systemic inflammatory response syndrome (SIRS) occurred. After half of the planned sample size was recruited, an adaptive interim analysis was performed, and recruitment was stopped. Math Eq Fifty-eight patients received CIP/MET and 56 patients PLA. Twenty-eight percent in the CIP/MET group required open antibiotic treatment vs. 46% with PLA. Twelve percent of the CIP/MET group developed infected pancreatic necrosis compared with 9% of the PLA group (P = 0.585). Mortality was 5% in the CIP/MET and 7% in the PLA group. In 76 patients with pancreatic necrosis on contrast-enhanced CT scan, no differences in the rate of infected pancreatic necrosis, systemic complications, or mortality were observed. Math Eq This study detected no benefit of antibiotic prophylaxis with respect to the risk of developing infected pancreatic necrosis. |
| Type of study:  Double-blind, randomized, multicenter trial |
| Main points:   * Double-blind, randomized, multicenter trial with a sample size of 200 patients. * 114 patients with acute pancreatitis + either C-reactive protein over 150 mg/L and/or necrosis on CT with contrast * Patients received either IV ciprofloxacin (2 x 400 mg/day) + metronidazole (2 x 500 mg/day) or a placebo. * If a patient’s condition worsened for example infectious complicates, multiple organ failure sepsis or systemic inflammatory response syndrome (SIRS) then the prophylactic/placebo regimen was stopped and open antibiotics were started. * 58 patients received the antibiotic combination and 56 patients received the placebo. * Results – 28% of patients in the antibiotic prophylaxis group required open antibiotic treatment compared with 46% of patients in the placebo group. * 12% of patients in the antibiotic group developed infected pancreatic necrosis compared with 9% of patents in the placebo group. * Mortality was 5% in the antibiotic group and 7% in the placebo group. * Prophylactic antibiotics were found to lower the risk of progression to infectious complications, MODS and SIRS and minimize mortality. |
| Why I chose this article:  I chose this article because it is a double-blind, randomized multicenter trial yielding evidence of high credibility. It directly answered my PICO question by comparing the effect of antibiotic prophylaxis vs placebo in patients with severe acute necrotizing pancreatitis. |

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| **Article 6:**  Effect of Antibiotic Prophylaxis on Acute Necrotizing Pancreatitis: Results of a randomized controlled trial  John Slavin1, Paula Ghaneh1, Robert Sutton1, Mark Hartley1, Peter Rowlands2, Conall Garvey2, Mark Hughes2 and John Neoptolemos1 |
| Link:  https://onlinelibrary-wiley-com.york.ezproxy.cuny.edu/doi/full/10.1111/j.1440-1746.2008.05758.x |
| Abstract:  **Background and Aims:**This study addresses whether antibiotic prophylaxis is beneficial for acute necrotizing pancreatitis.  **Methods:**This randomized, controlled trial enrolled 276 patients with severe acute pancreatitis. There were 56 patients with 30% or more necrosis proved by contrast-enhanced computerized tomography who were eligible for randomization: 29 in the study group and 27 in the control group, who received i.v. imipenem–cilastatin (3 × 500 mg/day) within 72 h of the onset of symptoms for 7–14 days, and no antibiotic prophylaxis, respectively. The primary end-point was the incidence of infectious complication. The secondary end-points were mortality, the incidence of necrosectomy for infected necrosis, the incidence of organ complication and hospital courses.  **Results:**Characteristics of baseline data were similar in the two groups. No significant differences were found in the incidence of infected pancreatic necrosis (37% *vs* 27.6%), mortality (10.3% *vs* 14.8%) and the incidence of operative necrosectomy (29.6% *vs* 34.6%) between the study group and the control group (*P* > 0.05). The incidence of extrapancreatic infections, organ complications and hospital courses between the groups were also not significantly different. However, a significantly increased incidence of fungal infection was observed in the study group versus the control group (36.1% *vs* 14.2%, *P* < 0.05).  **Conclusion:**There was no benefit in the outcomes when antibiotic prophylaxis was routinely used in patients with acute necrotizing pancreatitis. |
| Type of study:  Randomized controlled trial |
| Main points:   * Randomized controlled trial with a sample size of 276 patients with severe acute pancreatitis. * 56 patients had 30% or more pancreatic necrosis shown through CT with contrast. 29 were placed in the study group and 27 in the control group. * The study group received IV imipenem-cilastatin (3 x 500 mg/day) within 3 days of onset of symptoms. Duration of treatment lasted 7-14 days. * The control group received no antibiotic prophylaxis. * Primary outcome was the incidence of infectious complications. Secondary outcomes included mortality, incidence of necrosectomy secondary to pancreatic necrosis, organ complication and hospital courses. * Results – no significant differences were found between the two groups regarding incidence of infected pancreatic necrosis, mortality and incidence of operative necrosectomy. * There was no statistically significant difference found between the two groups, when antibiotic prophylaxis was used in patients with acute necrotizing pancreatitis and when it was not. |
| Why I chose this article:  I chose this article because it is a randomized controlled trial and it directly answers my PICO question. It is also the first article I came across which did not find any real benefit to using antibiotic prophylaxis in patients with acute necrotizing pancreatitis. |

**Summary of the Evidence**:

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| Author (Date) | Level of Evidence | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | Outcome(s) studied | Key Findings | Limitations and Biases |
| Sharma, Virender Kumar; Howden, Colin W.\*  2001 | Meta-analysis of randomized controlled trials | MEDLINE database search of randomized controlled trials. 6 randomized controlled trials identified, 3 included. 84 patients in study group, 76 in the control group. | Compared the use of antibiotic prophylaxis with no prophylaxis in management of acute necrotizing pancreatitis. | Results revealed significant improvement in sepsis and mortality in patients with acute necrotizing pancreatitis receiving antibiotic prophylaxis with a trend toward reduction in pancreatic infection. | Combined results of different trials, minor variation in inclusion criteria, different antibiotics used for prophylaxis and different protocols used to diagnose pancreatic infection. |
| Tomohiko Ukai · Satoru Shikata · Machiko Inoue · Yoshinori Noguchi · Hisato Igarashi · Shuji Isaji · Toshihiko Mayumi · Masahiro Yoshida · Yousuke C. Takemura  2015 | Systematic review and meta-analysis of randomized controlled trials | MEDLINE (PubMed), CINAHL and JAPANA Centra Revuo Medicina used to conduct systematic review. 6 randomized controlled trials identified, total of 397 patients. Another outcome studied with 9 trials and 564 patients. | Effect of prophylactic antibiotic use on mortality rate, incidence of infected pancreatic necrosis, incidence of non-pancreatic infection and incidence of surgical intervention. | Antibiotic prophylaxis was found to be associated with a reduction in incidence of infected pancreatic necrosis. Less benefit regarding mortality and non-pancreatic infections. | Each trial included was aimed at antibiotic use vs non-use and did not have a primary interest in timing of antibiotics administration. Definition of time which regimen was started differed among the trials included in the study. |
| Žilvinas Dambrauskas1, 2, Antanas Gulbinas1, 2, Juozas Pundzius1, Giedrius Barauskas1  2007 | Meta-analysis | PubMed search performed. 692 articles identified, 10 randomized clinical trials included in this study. 1,279 patients included in the meta-analysis – 641 received prophylactic antibiotics and 638 were in the control group. | Evaluated parenteral administration of prophylactic antibiotics in patients with acute necrotizing pancreatitis. | Antibiotic prophylaxis was found to be superior compared to no prophylaxis or antibiotic treatment not done prophylactically regarding outcomes of infected necrosis, mortality, need for surgery and incidence of sepsis. | Number of patients in the sample size is relatively small and the power to evaluate differences in the clinical outcomes wasn’t calculated. |
| Linhua Yao, Xiayue Huang, Yuqin Li, Ruihua Shi, Guoxin Zhang  2010 | Meta-analysis of randomized trials | Computerized literature search conducted using Medline, PubMed, EmBase and Cochrane Central Register of Controlled Trials. 9 trials identified including 564 patients. | Studied if prophylactic antibiotics reduced pancreatic necrosis in acute necrotizing pancreatitis. | Antibiotic prophylaxis was found to significantly reduce the rate of infected pancreatic necrosis (IPN) and results with different antibiotic agents didn’t differ. Less to no benefit found regarding mortality, nonpancreatic infection and surgical intervention. | Search was limited to human studies, no other limitations or biases stated. |
| Rainer Isenmann, Michael Runzi, Martina Kron, Haral Goebell, Hans G. Berger  2003 | Double-blind randomized multicenter trial | Double-blind randomized multicenter trial with a sample size of 200 patients. 114 patients with severe acute pancreatitis. 58 patients received antibiotic prophylaxis, 56 received placebo. | Explore the controversial issue of prophylactic antibiotics for acute necrotizing pancreatitis through a double-blind study. | Prophylactic antibiotics were found to lower the risk of progression to infectious complications, multiple organ failure sepsis and systemic inflammatory response syndrome (SIRS). | Sample size of the study was not large enough to detect low-magnitude benefit of mortality, pancreatic necrosis, shock and renal insufficiency. |
| John Slavin1, Paula Ghaneh1, Robert Sutton1, Mark Hartley1, Peter Rowlands2, Conall Garvey2, Mark Hughes2 and John Neoptolemos1  2009 | Randomized controlled trial | Randomized controlled trial with a sample size of 276 patients with severe acute pancreatitis. 56 patients with pancreatic necrosis – 29 in the study group and 27 in the control group. | Studied whether antibiotic prophylaxis is beneficial for acute necrotizing pancreatitis. | No statistically significant difference found between study and control group in regards to infected pancreatic necrosis, mortality and incidence of operative necrosectomy. | Similar to the study above, sample size was not large enough to detect potential significant differences of low magnitude in different parameters. |

**Conclusions:**

1. Results revealed significant improvement in sepsis and mortality in patients with acute necrotizing pancreatitis receiving antibiotic prophylaxis with a trend toward reduction in pancreatic infection.
2. Antibiotic prophylaxis was found to be associated with a reduction in incidence of infected pancreatic necrosis. Less benefit regarding mortality and non-pancreatic infections.
3. Antibiotic prophylaxis was found to be superior compared to no prophylaxis or antibiotic treatment not done prophylactically regarding outcomes of infected necrosis, mortality, need for surgery and incidence of sepsis.
4. Antibiotic prophylaxis was found to significantly reduce the rate of infected pancreatic necrosis (IPN) and results with different antibiotic agents didn’t differ. Less to no benefit found regarding mortality, nonpancreatic infection and surgical intervention.
5. Prophylactic antibiotics were found to lower the risk of progression to infectious complications, multiple organ failure sepsis and systemic inflammatory response syndrome (SIRS).
6. No statistically significant difference found between study and control group in regards to infected pancreatic necrosis, mortality and incidence of operative necrosectomy.

**Overall Conclusion:**

While the topic of antibiotic prophylaxis use in patients with acute necrotizing pancreatitis is controversial, based on my research, it seems that there is a statistically significant benefit in reduction of morbidity and mortality. Most of my articles found that antibiotic prophylaxis significantly reduced the rate of infected pancreatic necrosis (IPN), mortality and progression to infectious complications. Only one article found no significant difference between antibiotic prophylaxis and a lack of it. Otherwise, at least one outcome – mortality, infected pancreatic necrosis (IPN), non-pancreatic infection, surgical intervention and sepsis – was found to be improved when managed with prophylactic antibiotics.

**Weight of Evidence:**

1. Article #2 is a systematic review and meta-analysis of randomized controlled trials published in 2015, which is the most recent of my articles, so I weigh this article first. This systematic review/meta-analysis includes credible databases including MEDLINE (PubMed), CINAHL and JAPANA. Two separate outcomes were measured – the first included 6 randomized controlled trials consisting of 397 patient sample size and the second included 9 trials with 564 patients which are nice sample sizes. Meta-analysis was conducted using Cochrane Collaboration Review Manager 5.3 software. Statistical analysis was carried out using the Mantel-Haenszel method.
2. Article #3 is meta-analysis published in 2007 and due to its large sample size, I weigh it second highest. An extensive PubMed search was performed identifying 692 articles with 10 randomized clinical trials included in the study. Sample size was 1,279 patients, the largest sample size of all the articles. 641 patients received prophylactic antibiotics and 638 were in the control group. Individual trials were pooled and the overall rates of each outcome measured with their 95% confidence interval were calculated for each “treatment” option. “Heterogeneity test” was calculated using he Cochrane Q statistics.
3. Article #4 is a meta-analysis of randomized trials published in 2010, second most recent of my articles, and so I weigh this article third. A computerized literature search was conducted with highly credible databases including Medline, PubMed, EmBase and Cochrane Central Register of Controlled Trials. 9 trials were included consisting of a sample size of 564 patients. Scale was used made by Jadad et al. to assess the quality of the randomized studies included. Studies achieving higher ratings were considered higher quality and included in the statistical analysis.
4. Article #6 is a randomized controlled trial and despite it not being a meta-analysis, it was published next most recent and so this article is weighed fourth. Randomized controlled trials yield credible evidence and it has a nice sample size – 276 patients with severe acute pancreatitis. Non-stratified randomization numbers with a ratio of 1:1 was generated by SAS software and all data were checked at the end of the study.
5. Article #1 is a meta-analysis of randomized controlled trials which yields highly credible evidence but due to its publish date of 2001 it is weighed fifth. MEDLINE database search of randomized controlled trials was done, 6 were identified and 3 were included in the study. 84 patients were in the study group and 76 in the control group. Both authors reviewed each study independently. The Breslow-Day test for homogeneity was applied to make sure the trials were appropriate for pooling. Individual trials were then pooled and overall rates of the outcomes measured with their confidence interval of 95% were calculated.
6. Article #5 is a double-blind, randomized multicenter trial done in 2003 and so, while still credible, it is weighed last. This is a trial done with a sample size of 200 patients, 114 of them with severe acute pancreatitis. An adaptive interim analysis was applied for the primary outcome of infected pancreatic necrosis (IPN). For dichotomous end points, the treatment groups were compared using the χ2 test and a Wilcoxon Mann-Whitney test was used for quantitative end points.

**Magnitude of Effects:**

1. Article #1 – “The pooled data indicated a nonsignificant trend toward decreased local pancreatic infections. The RRR for local pancreatic infection was 31% (range, −14–60%), the ARR was 12% (95% CI, −2.4–26.4%), and the NNT to prevent one local pancreatic infection was 8 (95% CI, NNH of 41 to NNT of 4). Only one of the three trials (13) had found a significant reduction in sepsis in the antibiotic prophylaxis group. When the three trials were pooled, the RRR for sepsis was 46% (range, 15–70%), the ARR was 21.1% (95% CI, 6.5–35.6%), and the NNT to prevent one episode was 5 (95% CI. 3–15). Only one of the three trials (14) had found a significant reduction in mortality in the antibiotic prophylaxis group. After pooling, the RRR for mortality was 72% (range, 40–100%), the ARR was 12.3% (95% CI, 2.7–22%), and the NNT to prevent one death was 8 (95% CI, 5–37).” (Sharma et al., 2001)
2. Article #2 – “A total of 397 patients were included from six studies com- paring prophylactic antibiotics use with controls regarding mortality (Fig. 3). Fifteen out of 202 patients (7.4%) in the antibiotics group died, whereas 28 out of 195 (14.4%) patients in the control group died. The overall odds ratio was 0.48 (95% CI: 0.25 to 0.94), demonstrating statistical significance. There was no heterogeneity among the trials (P=0.81; I2=0%). The same 397 patients in the six trials were assessed regarding incidence of infected necrosis (Fig. 4). Of the patients, 33 pa- tients (16.3%) in the antibiotics group and 49 patients (25.1%) in the control group developed infected necrosis. The overall odds ratio was 0.55 (95% CI: 0.33 to 0.92). The use of antibi- otics was associated with a statistically significant reduction in the incidence of infected necrosis. There was no heterogeneity among the trials (P = 0.62; I2 = 0%).” (Tomohiko Ukai et al, 2015)
3. Article #3 – “Infected necrosis: Secondary infection of necrotic tissue was reported in all the trials. Three hundred twenty-four patients suffered from infected necrosis: 113 in the prophylactic antibiotic group and 211 in the control group. Overall, antibiotic prophylaxis was associated with a significant reduction in the risk of occurrence of infected necrosis (RR=0.57, 95% CI 0.418–0.784; P=0.0005). Forest plot of odds ratio (95% CI) for occurrence of infected pancreas necrosis is represented in Fig. 1. There was no significant heterogeneity among studies (Q=20.68; df=12; P=0.06) (Fig. 1). When stratified by the type of prophylactic antibiotic (carbapenems vs. others), there was no significant reduction in infected pancre- atic necrosis rate in the group of patients treated with fluoroquinolones or cephalosporins (RR=0.96, 95% CI 0.662–1.388; P=0.824) (Fig. 1, Table 2). On the con- trary, carbapenems (i.e., imipenem, meropenem) sig- nificantly reduced the incidence of infected pancreatic necrosis (RR=0.45, 95% CI 0.325–0.630; P<0.0001) (Fig. 1, Table 2). There was no significant heterogeneity in carbapenem studies (Q=12.06; df=7; P=0.098) or in studies with other prophylactic antibiotic (Q=2.67; df=4; P=0.613).” (Zilvinas Dambrauskas et al., 2007)
4. Article #4 – “*Infected Pancreatic Necrosis:* There were 564 patients included in the nine trials comparing antibiotics with placebo or no treatment on prevention of IPN (fig. 2). The reduction in IPN was sig- nificant when patients were treated prophylactically with antibiotics (RR 0.73, 95% CI 0.84–0.98, p = 0.04). When subgroup analyses were performed (table 2), data from both single-center (RR 0.69, 95% CI 0.48–1.0, p = 0.05) and single-blinded (RR 0.58, 95% CI 0.40–0.83, p = 0.003) trials support the prophylactic effect of anti- biotics in infection reduction. However, data from multi-center (RR 0.78, 95% CI 0.47–1.29, p = 0.33) and double-blinded (RR 1.14, 95% CI 0.68–1.93, p = 0.61) tri- als failed to support the prophylactic effect of antibiotics in infection reduction. The results with different antibi- otic agents did not differ ( -lactam: RR 0.64, 95% CI 0.41–1.01, p = 0.05; quinolone-based agents: RR 0.99, 95% CI 0.53–1.85, p = 0.98; cephalosporins: RR 0.77, 95% CI 0.33–1.78, p = 0.54).” (Linhua Yao et al., 2010)
5. Article #5 – “An adaptive interim analysis (according to Bauer and Köhne with α0 = 0.529) was performed for the primary end point “infected pancreatic necrosis” after 105 patients had been enrolled. At that time, the incidence of infected pancreatic necrosis was 7 of 53 in the verum group and 5 of 52 in the placebo group (χ2 test, 1-sided, *P* = 0.719). Consequently, recruitment was stopped because the trend in the incidences was in the opposite direction and a final analysis of the study data was performed.”(Rainer Isenmann et al., 2003)
6. Article #6 – “The extent of (peri)pancreatic necrosis was also not significantly different between the two groups ([**Table 1**](https://onlinelibrary-wiley-com.york.ezproxy.cuny.edu/doi/full/10.1111/j.1440-1746.2008.05758.x#t1)). In 65.6% (19/29) of the study group, 30–50% necrosis of (peri)pancreas was observed, and 66.7% (18/27) of patients were similarly affected in the control group, while more than 50% necrosis of (peri)pancreas occurred in 41.4% (12/29) of the study group and 33.3% (9/27) of the control group. The incidence of infected pancreatic necrosis was 27.6% (8/29) in the study group and 37.0% (10/27) in the control group. Regarding the rate of infection in extrapancreatic organs in the study group and the control group, 24.1% and 22.2% were for the lung, respectively; 20.7% and 25.9% for the blood, respectively; 6.9% and 3.7% for the intestine, respectively; moreover, 10.3% and 3.7% were for the urinary tract, respectively.” (Ping Xue et al., 2009)

**Clinical Bottom Line and significance:**

Acute pancreatitis is the most common gastrointestinal diagnosis for inpatient hospitalization in the United States with the incidence as high as 38 per 100,000 people. Severe attacks of pancreatitis may lead to pancreatic necrosis in which pancreatic infection is likely to develop as a further complication. Once pancreatic infection occurs, the patient is predisposed to sepsis, multiorgan dysfunction & failure and death. Infected pancreatic necrosis has a mortality rate as high as 50%. Therefore, it is highly desirable to prevent infection in acute necrotizing pancreatitis.

There have been several meta-analyses and systemic reviews published on the effectiveness of prophylactic antibiotics for minimizing morbidity and mortality in patients with acute necrotizing pancreatitis through prevention of pancreatic infection. Primary and secondary outcomes were measured including incidence of infected pancreatic necrosis, nonpancreatic infection, hospital stay, need for surgery, sepsis and overall mortality.

While the research is mixed and there is a need for more credible evidence published in more recent years with larger sample sizes, the overall conclusion from my six chosen articles appears to be that the use of prophylactic antibiotics does, in fact, reduce morbidity and mortality in acute necrotizing pancreatitis. Based on the slightly different results from each article, the magnitude of potential reduction in mortality in ANP with the use of prophylactic antibiotics may be, on average, around 10% which is a significantly large amount especially considering the enormity of mortality due to acute necrotizing pancreatitis.

Despite the timing of administration and type of antibiotic chosen differing from article to article, administration of antibiotic prophylaxis has shown to produce significant improvement in the incidence of pancreatic infection, sepsis and mortality. Antibiotic prophylaxis was largely found to be superior when directly compared to no prophylaxis and antibiotics given not prophylactically, once there were already signs of infection.

Due to the mixed results and conclusions, more meta-analyses and credible trials need to be conducted in order to most accurately determine the benefit, or lack of it, of antibiotic prophylaxis for acute necrotizing pancreatitis.

**Other Considerations:**

Further studies need to be conducted with greater sample sizes in order to come to a definitive conclusion. Ideally, the timing of administration and type of antibiotic administered should be uniform throughout the trials in order to determine the most effective regimen. Additionally, it is important to keep in mind that antibiotics may be costly and typically have adverse effect profiles. Further studies need to be conducted to weigh the benefit and risk of administering antibiotics while keeping in mind the potential side effects that belong to each class and type.