Assessment of Prophylactic Carbapenem Antibiotics Administration for Severe Acute Pancreatitis: An Updated Systematic Review and Meta-Analysis

Daxin Guo^a Wei Dai^b Jingyi Shen^b Mengting Zhang^b Yetan Shi^b Ke Jiang^b
Luyong Guo^c

^aDepartment of Gastroenterology, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China;

^bThe Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China; ^cThe Emergency Department, Zhuji People's Hospital, Shaoxing, China

Keywords

Severe acute pancreatitis · Infected pancreatitis · Pancreatic necrosis · Prophylaxis · Carbapenem antibiotics · Meta-analysis

Abstract

Background: The effectiveness of prophylactic antibiotics in severe acute pancreatitis (SAP) remains a debatable issue. This meta-analysis aimed to determine the efficacy of prophylactic carbapenem antibiotics in SAP. **Methods:** This meta-analysis of prophylactic carbapenem antibiotics for SAP was conducted in PubMed, EMBASE, Web of Science, MEDLINE, and Cochrane Library up to February 2021. The related bibliographies were manually searched. The primary outcomes involved infected pancreatic or peripancreatic necrosis, mortality, complications, infections, and organ failure. **Results:** Seven articles comprised 5 randomized controlled trials and 2 retrospective observational studies, including 3,864 SAP participants. Prophylactic carbapenem antibiotics in SAP were associated with a statistically significant reduction in the incidence of infections (odds ratio [OR]: 0.27; $p = 0.03$) and complications (OR: 0.48; $p = 0.009$). Nevertheless, no statistically significant difference was demonstrated in

the incidence of infected pancreatic or peripancreatic necrosis (OR: 0.74; $p = 0.24$), mortality (OR: 0.69; $p = 0.17$), extrapancreatic infection (OR: 0.64, $p = 0.54$), pulmonary infection (OR: 1.23; $p = 0.69$), blood infection (OR: 0.60; $p = 0.35$), urinary tract infection (OR: 0.97; $p = 0.97$), pancreatic pseudocyst (OR: 0.59; $p = 0.28$), fluid collection (OR: 0.91; $p = 0.76$), organ failure (OR: 0.63; $p = 0.19$), acute respiratory distress syndrome (OR: 0.80; $p = 0.61$), surgical intervention (OR: 0.97; $p = 0.93$), dialysis (OR: 2.34; $p = 0.57$), use of respirator or ventilator (OR: 1.90; $p = 0.40$), intensive care unit treatment (OR: 2.97; $p = 0.18$), and additional antibiotics (OR: 0.59; $p = 0.28$) between the experimental and control groups. **Conclusions:** It is not recommended to administer routine prophylactic carbapenem antibiotics in SAP.

© 2022 S. Karger AG, Basel

Introduction

Acute pancreatitis (AP) is one of the most prevalent gastrointestinal disorders requiring hospitalization [1]. Furthermore, approximately a fifth of AP patients experi-

Daxin Guo and Wei Dai contributed equally to this work.

ence severe acute pancreatitis (SAP) with a mortality rate of around 20% [2] and even as high as 36–50% with persistent organ failure [3]. Infected pancreatic necrosis is the major contributor to persistent morbidity and late mortality in SAP [4–6]. As a consequence, it is critical to combat pancreatic infection. According to current guidelines, antibiotics that easily penetrate the pancreas [7–11], such as carbapenems and quinolones, are generally recommended in confirmed infected pancreatic necrosis.

However, the question about whether to use prophylactic antibiotics in SAP is controversial. In the past, some guidelines recommended prophylactic antibiotics [12–15], but guidelines now generally do not [7–10, 16]. Meanwhile, meta-analysis put forward different views on whether to employ prophylactic antibiotics in SAP. A meta-analysis revealed that prophylactic antibiotics did not reduce the incidence of pancreatic infection necrosis or mortality in SAP, and thus were not recommended [17]. However, a recent meta-analysis that included 6 randomized controlled trials (RCTs) reached a different conclusion [18].

Although controversial, the clinical use of prophylactic antibiotics in SAP has become widespread, with a use rate of 41–88% [19]. However, excessive and irrational use of prophylactic antibiotics increases resistance rates. For instance, Gram-negative bacteria's resistance to carbapenem antibiotics has become a global issue, and the morbidity and mortality after infection by carbapenem-resistant bacteria are generally higher than those of other susceptible pathogens [20]. According to the above, whether to use prophylactic carbapenem antibiotics in SAP warrants further exploration, and thus we attempt to evaluate the effect of prophylactic carbapenem antibiotics in SAP.

Methods

Search Strategy and Eligible Studies

This meta-analysis was systematically conducted to identify articles on the prophylactic use of carbapenem antibiotics for SAP retrieved from PubMed, EMBASE, Web of Science, MEDLINE, and Cochrane Library up to February 2021. Pancreatitis or AP or hemorrhagic pancreatitis or necrotizing pancreatitis, or alcoholic pancreatitis were used as search terms in conjunction with (carbapenems or doripenem or ertapenem or invanz or imipenem or meropenem). These terms were adjusted to conform to specified requirements of various databases. Additionally, bibliographies of relevant reviews and meta-analyses were manually retrieved to ensure the integrity of search session. The primary outcome measures for the meta-analysis included infected pancreatic or peripancreatic necrosis, mortality, complications, infections, and organ failure.

Selection and Exclusion Criteria

Articles were included if they met the following criteria: (a) study design: observational studies or RCTs; (b) participants: SAP patients; (c) intervention: prophylactic carbapenem antibiotics; (d) control: no antibiotics, including placebo; and (e) outcome measures: infected pancreatic necrosis or mortality. The exclusion criteria were as follows: (a) studies using alternative antibiotics; (b) studies comparing 2 antibiotics, such as meropenem versus imipenem; (c) studies comparing antibiotic use duration; (d) studies investigating the efficacy of antibiotics in SAP treatment; (e) articles not published in English; and (f) the full text is unavailable. If there are duplicate publications from the same trial, the most recent article will be used. This meta-analysis was conducted in accordance with the PRISMA 2020 statement: an updated guideline for reporting systematic reviews [21].

Data Extraction and Quality Assessment

Two researchers independently retrieved and extracted data from included articles on the author, year, country, diagnostic criteria, the number of patients, interventions, administration time, antibiotic use duration, and study design. We also extracted primary outcomes including but not limited to infected pancreatic or peripancreatic necrosis, mortality, complications, infections, and organ failure. Furthermore, the quality assessment was conducted in line with the Cochrane Collaboration's tool [22] and Newcastle-Ottawa Quality Assessment Scale [23]. Consensus and discussion were used to resolve any discrepancies.

Statistical Analysis

Statistical analysis was performed using Revman version 5.3 (the Cochrane Collaboration). SAP outcomes were quantified using odds ratios (OR) and 95% confidence interval (95% CI). The χ^2 test and I^2 test were employed to quantify heterogeneity [24]. A fixed-effects model was utilized, while $I^2 \leq 50\%$ or else a random-effects model was implemented. If $OR < 1$, the prophylactic antibiotic was beneficial to the study outcomes; otherwise, if $OR > 1$, the prophylactic antibiotic was a risk factor for the study outcomes. All statistics were performed using a 2-sided test, and $p < 0.05$ was considered statistically significant.

Results

Eligible Studies

The PRISMA checklist for our meta-analysis is given in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000520892). The flowchart of search strategy is outlined in Figure 1. The search in 5 databases and relevant bibliographies yielded 1,330 initially included articles. After excluding duplicated articles, the remaining articles were filtered according to their titles and abstracts. Following additional full-text retrieval, 7 articles fulfilled the inclusion criteria and were selected [25–31].

Fig. 1. Flow diagram of selection.

Table 1. Characteristics of included clinical trials in the meta-analysis

Author	Country	Diagnostic criteria for SAP	Patients, <i>n</i>		Interventions		Time of administration	Duration of antibiotic use, days	Study design
			experimental	control	experimental	control			
Dellinger et al. [25]	North America and Europe	CT or Balthazar grade E with either CRP >120 mg/L or MOD score >2	50	50	Meropenem	Placebo	Within 120 h of symptoms onset	7–21	RCT
Ho and Frey [26]	America	CT	75	50	Imipenem-cilastatin	No antibiotic	NR	28	Retrospective observational study
Nakaharai et al. [27]	Japan	Prognostic factor score ≥3	2,493	861	Imipenem-cilastatin, meropenem, doripenem, biapenem, and panipenem	No antibiotic	NR	NR	Retrospective observational study
Nordback et al. [28]	Finland	CT and CRP >150 mg/L	25	33	Imipenem-cilastatin	No antibiotic	Within 48 h of admission	NR	RCT
Poropat et al. [29]	Croatia	APACHE II score ≥8	49	49	Imipenem-cilastatin	Placebo	Within 72 h of symptoms onset	7–21	RCT
Rokke et al. [30]	Norway	CT and CRP >120 mg/L (within 24 h) or CRP >200 mg/L (within 48 h)	36	37	Imipenem-cilastatin	No antibiotic	Within 72 h of symptoms onset	5–7	RCT
Xue et al. [31]	China	CT	29	27	Imipenem-cilastatin	No antibiotic	Within 72 h of symptoms onset	7–14	RCT

SAP, severe acute pancreatitis; CT, computerized tomography; CRP, C-reactive protein; MOD, multiple organ dysfunction; APACHE II, Acute Physiology and Chronic Health Evaluation II; RCT; randomized controlled trial; NR, not reported.

Table 2. Analysis of SAP outcomes

Carbapenems versus no antibiotic	Studies, <i>n</i>	OR	95% CI	<i>p</i> value	Heterogeneity (<i>I</i> ²), %	Model
Infected pancreatic or peripancreatic necrosis	6	0.74	0.44, 1.23	0.24	0	FE
Mortality	6	0.69	0.41, 1.16	0.17	0	FE
Surgical intervention	4	0.97	0.53, 1.79	0.93	0	FE
Pancreatic pseudocyst	3	0.59	0.23, 1.55	0.28	0	FE
Additional antibiotics	3	0.59	0.23, 1.54	0.28	58	RE
Dialysis	3	2.34	0.12, 45.21	0.57	89	RE
Use of respirator or ventilator	3	1.90	0.43, 8.29	0.40	83	RE
ICU treatment	2	2.97	0.61, 14.39	0.18	85	RE
ARDS	2	0.80	0.33, 1.91	0.61	0	FE
Organ failure	2	0.63	0.32, 1.24	0.19	0	FE
Complications	3	0.48	0.28, 0.84	0.009	0	FE
Fluid collections	2	0.91	0.50, 1.65	0.76	0	FE
Infections	3	0.27	0.08, 0.87	0.03	78	RE
Extrapancreatic infections	3	0.64	0.15, 2.75	0.54	70	RE
Pulmonary infection	2	1.23	0.44, 3.44	0.69	0	FE
Blood infection	2	0.60	0.20, 1.76	0.35	0	FE
UTI	2	0.97	0.30, 3.16	0.97	28	FE

SAP, severe acute pancreatitis; CI, confidence interval; OR, odds ratio; FE, fixed-effects model; RE, random-effects models; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; UTI, urinary tract infection.

Study Characteristics and Quality

Table 1 and online supplementary Table 2 summarize the baseline characteristics of the studies. The 7 articles comprised 5 RCTs [25, 28–31] and 2 retrospective observational studies [26, 27], including 3,864 SAP participants divided into experimental (2,757 participants) and control (1,107 participants) groups. SAP patients were diagnosed using computerized tomography (CT) or any of the following: Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 8 , multiple organ dysfunction score > 2 , C-reactive protein > 120 mg/L, or prognostic factor score ≥ 3 . Five [25, 26, 28, 30, 31] of these 7 studies included imaging findings on CT scans as part of their criteria for diagnosing SAP, whereas 2 studies [27, 29] defined SAP using the prognostic factor score or APACHE II score. Imipenem was used in 5 studies [26, 28–31], and meropenem was used in 1 study [25]. Another study [27] used various types of carbapenem antibiotics. In 3 trials [29–31], antibiotics were started after 72 h of symptom onset. Two trials [25, 28] started 48 h and 120 h after symptoms onset, respectively, while another 2 trials [26, 27] did not specify a start time.

Online supplementary Table 3 presents the quality assessment of studies. Two high-quality retrospective observational studies had a Newcastle-Ottawa Scale score > 6 , and the risk of bias of RCTs was assessed.

Infected Pancreatic or Peripancreatic Necrosis

Six trials involving 510 patients compared the impact of prophylactic carbapenem antibiotic use versus no antibiotics on preventing infected pancreatic or peripancreatic necrosis, which occurred in 33 of 264 patients (12.5%) in the experimental group and 39 of 246 patients (15.9%) in the control group (Table 2). The prophylactic use of carbapenem antibiotics was not associated with a statistically significant reduction in the incidence of infected pancreatic or peripancreatic necrosis (OR: 0.74, 95% CI: 0.44–1.23; $p = 0.24$), and no heterogeneity was observed ($I^2 = 0$).

Mortality

Six trials reported related data of mortality. Of 510 patients, 29 of 264 patients (11.0%) in the experimental group and 38 of 246 patients (15.4%) in the control group died (Table 2). No statistically significant difference was observed between the 2 groups (OR: 0.69, 95% CI: 0.41–1.16; $p = 0.17$), indicating that prophylactic carbapenem antibiotics were not linked to a significantly decreased risk of mortality, and no heterogeneity was observed ($I^2 = 0$).

Other Noninfectious Complications

Other noninfectious complications include local and systemic complications. Local complications include

pancreatic pseudocyst, pancreatic or peripancreatic fluid collection, lung disease, and kidney disease, whereas systemic complications include diabetes mellitus. Three trials provided data on the incidence of complications (Table 2). Complications occurred in 38 of 110 patients (34.5%) in the experimental group and 60 of 119 patients (50.4%) in the control group. The prophylactic use of antibiotics was correlated with a statistically significant reduction in the incidence of complications (OR: 0.48, 95% CI: 0.28–0.84; $p = 0.009$), and no heterogeneity was observed ($I^2 = 0$). Prophylaxis of antibiotics reduced the incidence of total complications but did not significantly affect pseudocyst, pancreatic or peripancreatic fluid collection, and acute respiratory distress syndrome (ARDS).

Extrapancreatic Infections

The extrapancreatic infection involved pneumonia, sepsis, urinary infection, and other sites. Three trials provided data on the incidence of infections, with 35 of 160 patients (21.9%) in the experimental group and 66 of 136 patients (48.5%) in the control group (Table 2). There was a significant reduction in infections associated with prophylactic carbapenem antibiotics use (OR: 0.27, 95% CI: 0.08–0.87; $p = 0.03$), whereas heterogeneity was high ($I^2 = 78\%$). Although the overall infection rate had declined, extrapancreatic infection, pulmonary infection, blood infection, and urinary tract infection (UTI) demonstrated no significant difference between the 2 groups.

Other Indicators

Prophylaxis of antibiotics did not reduce the incidence of organ failure, intervention, and intensive care unit (ICU) treatment (Table 2). The intervention included additional antibiotics, surgical interventions, and instrument interventions, such as dialysis machines and respirators or ventilators.

Discussion

Although prophylactic carbapenem antibiotics have been widely used clinically in SAP, their effect in SAP has been controversial, with different conclusions generated from evidence-based studies. As a result, this meta-analysis was conducted to determine the effect of prophylactic carbapenem antibiotics in SAP. The main finding of our study was that compared with no antibiotics, prophylactic carbapenem antibiotics significantly reduced the incidence of general infections and complications but revealed no significant difference across the subgroup anal-

ysis. In infection-related subgroup analysis, prophylactic carbapenem antibiotics had no significance in reducing infected pancreatic or peripancreatic necrosis, extrapancreatic infection, pulmonary infection, blood infection, and UTI. Similarly, across subgroup analysis of other noninfectious complications, the incidence of mortality, organ failure, ARDS, pancreatic pseudocyst, and fluid collection was not significantly reduced. In addition, prophylactic carbapenem antibiotics did not reduce the incidence of interventions (ICU treatment, additional antibiotic use, surgical interventions, and instrument interventions).

In SAP, pancreatic or peripancreatic necrosis is initially aseptic and can progress to infected necrosis if infected with intestinal bacteria [32]. Intestinal bacteria translocation is caused by intestinal barrier dysfunction, immune suppression, and bacterial disorder in combination [33, 34]. In this process, intestinal ischemia and ischemia-reperfusion damage the intestinal barrier and alter intestinal flora due to microcirculation disturbance, inflammatory mediators, apoptosis, and a decline in enteral nutrition [35–37]. Because *Escherichia coli* and *Klebsiella pneumoniae* were the most common pathogens in pancreatic infections [5, 38–41], carbapenem antibiotics may be effective against pancreatic infection. Nevertheless, our results are consistent with previous findings, which indicated that in infection-related subgroup analysis, prophylactic carbapenem antibiotics did not decrease the incidence of infected pancreatic or peripancreatic necrosis [42–44]. Numerous factors could account for our findings. Originally, pathogen spectrum changes may affect the antimicrobial effectiveness of carbapenem antibiotics. Although Gram-negative bacteria remained dominant in pancreatic infection, the proportion of Gram-positive bacteria increased notably [45]. Also, an increase in multiresistant bacteria was observed over the disease course [46, 47]. Marstrand-Joergensen et al. [48] discovered that carbapenem-resistant bacteria were responsible for 33% of pancreatic infections. Furthermore, prophylactic carbapenem antibiotics may be a dangerous factor for infected pancreatic necrosis. Lee et al. [46] confirmed that carbapenem antibiotics could cause intestinal flora changes and considered carbapenem antibiotics a significant source of bacterial infections of infected pancreatic necrosis. Nevertheless, Xu and Cai [49] found that antibiotic prophylaxis timing is essential; early prophylactic antibiotics could decrease the incidence of infected pancreatic necrosis. The result of Xu and Cai [49] is consistent with a recent meta-analysis that focuses on the onset time of prophylactic antibiotics use in acute necrotizing

pancreatitis [18]. Meanwhile, Japanese guidelines for managing AP recommend that using prophylactic antibiotics within 72 h of onset in SAP may improve prognosis [15]. Regrettably, our study was limited in assessing the timing of prophylactic use of carbapenem antibiotics due to the lack of access to original source data. As a consequence, additional RCTs are required to resolve this issue.

Additionally, our meta-analysis revealed that prophylactic carbapenem antibiotic use had no significant effect on the incidence of extrapancreatic infection in the lungs, urethra, or blood. One possible explanation is that compensatory anti-inflammatory response syndrome (CARS) leads to immune deficiency or suppression, predisposing to secondary infections [50]. This is because CARS and systemic inflammatory response syndrome (SIRS) compound and worsen as the disease progresses, leading to mixed antagonistic response syndromes, which eventually cause low inflammation levels and develop severe immunosuppression [45]. Sharma et al. [51] revealed that gene expression reduction of human leukocyte antigen-DR associated with CARS causes immunosuppression resulting in gut bacteria translocation. Additionally, extrapancreatic infection bacteria vary depending on infection site. Hematogenous spread is a significant cause of extrapancreatic infection [52]. Tian et al. [53] found that bloodstream and biliary tract infections were mainly Gram-positive bacteria, and UTIs were mainly fungi. Therefore, carbapenem antibiotics may not play an excellent preventive effect for different infection types. Consequently, it is recommended to select appropriate antibiotics after culturing from the extrapancreatic infection site with patients who suspected clinical symptoms of infection.

Carbapenem antibiotics did not affect the incidence of acute peripancreatic effusion or pancreatic pseudocyst. The acute peripancreatic fluid collection develops in the early stage of pancreatitis and may progress into pancreatic pseudocyst after 4 weeks [3]. Pancreatic pseudocyst refers specifically to the fluid collection in the peripancreatic tissues due to pancreatic duct disruptions and extravasation of pancreatic secretions [3, 54]. Acute peripancreatic fluid collection and pancreatic pseudocyst are rarely infected and can self-regress [55]. Thus, carbapenem antibiotics are ineffective in treating aseptic complications.

Subgroup analysis of other noninfectious complications presented that carbapenem antibiotics were ineffective in preventing the occurrence of organ failure. Nordback et al. [28] reached similar conclusions in their RCT. They concluded that it is difficult to distinguish between organ failures caused by infections and

those caused by cytokine storms. A possible reason may be associated with organ failure progression. In the initial phase of AP, the precipitating inappropriate release and activation of trypsinogen to trypsin within the acini activates other digestive enzymes, the kinin system, and the complement cascade, leading to pancreatic parenchymal autodigestion [2]. When the pancreas is injured, inflammatory cells and cytokines are activated, resulting in local and systemic inflammation [50]. However, excessive activation causes SIRS [50], which develops into early primary organ failure, whereas sepsis induced by infected pancreatic necrosis develops late secondary organ failure [56]. The research by Marstrand-Joergensen further confirmed that extrapancreatic and pancreatic infections were independent risk factors of organ failure [48]. However, because carbapenem antibiotics were ineffective at controlling SIRS and reducing the incidence of infected pancreatic necrosis, organ failure risk factors cannot be effectively improved. Moreover, ARDS is a type of organ failure, and carbapenem antibiotics did not reduce ARDS incidence. This may be because SIRS is the central link of ARDS [57]. All cytokines, including tumor necrosis factor- α , interleukin (IL)-1, and IL-6, participated in the SIRS process. IL-6 complexed with a soluble interleukin-6 receptor to activate signal transducer and activator of transcription 3 in the pancreas. Persistent signal transducer and activator of transcription 3 activation resulted in elevated CXCL1 levels that mediated granulocyte infiltration into the lung, promoting ARDS [58]. High mobility group protein 1, as a pro-inflammatory mediator released by necrotic acinar cells, amplifies the inflammatory cascade. High mobility group protein 1 induced thoracic injury through nuclear translocation of nuclear factor kappa-B [59]. Prophylactic antibiotics can combat infection, but it is impossible to intervene in the inflammatory storm caused by SIRS on pulmonary vascular epithelial cells, alveolar epithelial cells, and lung-gas-blood barrier, resulting in increased pulmonary vascular permeability and eventually ARDS [57, 60, 61].

Organ failure and infection of pancreatic necrosis are determinants of mortality in AP patients [62, 63]. However, because the 2 risk factors, organ failure and infected pancreatic necrosis, cannot be effectively controlled during prophylactic carbapenem antibiotic use, the incidence of mortality cannot be reduced. Villatoro et al. [64] believed that prophylactic antibiotics could reduce the incidence of mortality by preventing nonpancreatic infections. Nevertheless, our study found no significant reduc-

tion in the incidence of nonpancreatic infections, which may be due to the promoting role of CARS in the infection.

Regarding intervention, our findings indicate that preventive carbapenem antibiotics did not reduce the incidence of ICU treatment, additional antibiotic use, surgical interventions, and instrument interventions. Previous meta-analyses have yielded similar results. Jafri et al. [65] and Hart et al. [66] discovered no difference in the incidence of surgical intervention with prophylactic antibiotics in SAP. However, Rokke et al. [30] believed that early imipenem could delay the onset of infection and thus delay the onset of surgical intervention, suggesting the need for RCTs to examine the potential benefit of prophylactic carbapenem antibiotics on surgical intervention timing.

With the use of prophylactic antibiotics, there is an increasing concern about the development of antibiotic resistance. Prophylactic antibiotics in SAP may develop multiresistant bacterial and fungal infections [67]. Xue et al. [31] found that fungal infection was associated with prophylactic carbapenem antibiotics. Furthermore, much attention should be paid to some side effects, such as anemia and abdominal pain. Nakaharai et al. [27] suggested that routine prophylactic carbapenem antibiotic administration in SAP increased the risk of *Clostridium difficile*-associated diarrhea. To gain more vital evidence on these clinical questions, additional RCTs investigating in this regard should be designed. Moreover, whether the results of prophylactic carbapenem antibiotics differ according to the etiology of pancreatitis is unclear. In acute biliary pancreatitis, positive bacterial bile cultures were frequent [68]. Thus, prophylactic carbapenem antibiotics might be beneficial in those acute biliary pancreatitis patients. Nevertheless, it is regrettable that due to insufficient relevant information in the original studies, we cannot perform subgroup analysis according to the etiology. Further studies are certainly required.

It is worth noting that the meta-analysis found a significant reduction in the total incidence of infections and complications, but no statistical significance was found for the subgroup analysis of infections and other noninfectious complications. Primarily, the included studies were heterogeneous in terms of outcome definitions and infection site; thus, care must be taken when comparing different results. For instance, in Rokke's study, CT or ultrasound-guided fine-needle aspiration for bacteriological analysis was not part of the protocol [30]. However, in other studies, CT or ultrasound-guided fine-needle

aspiration of the pancreas or its peripancreatic collection is considered a diagnostic criterion for infection [25, 26, 28, 29]. Second, heterogeneity also existed between prophylactic carbapenem antibiotic administrations, as treatment duration, follow-up duration, and time of administration were different. Additionally, the number of articles included in this study was limited so that the results could happen by chance.

The present systematic analysis had several limitations that should be considered. First, the included studies had differences in the etiology and diagnostic criteria for SAP, introducing selection bias. For example, only 2 articles used the Ranson score as one of the criteria for SAP severity stratification, and such difference may have contributed to the heterogeneity. Second, because 2 of the studies were cohort studies, we could not control some confounding factors such as demographic characteristics and disease severity. Third, the included studies were heterogeneous regarding study design, treatment duration, follow-up duration, time of administration, and outcome definitions, making it difficult to provide a more comprehensive interpretation of results. Additionally, some subgroup analyses used a limited sample size, which might reduce the power of statistical analysis. However, we systematically conducted a meta-analysis on prophylactic carbapenem antibiotics in SAP for various indicators, including the incidence of pancreatic pseudocyst, fluid collection, and organ failure, which have never been highlighted in previous meta-analyses. This research systematically studied the effect of prophylactic carbapenem antibiotics on SAP to guide clinical medication.

Conclusion

In conclusion, although our report tentatively suggests that prophylactic carbapenem antibiotics may be beneficial in reducing infections and complications, they have no significant effect on reducing the incidence of infections and other noninfectious complications in the subgroup, such as mortality, infected pancreatic or peripancreatic necrosis, and organ failure. There is currently insufficient evidence to support the benefit of routine prophylactic carbapenem antibiotic administration in SAP. Consequently, routine prophylactic carbapenem antibiotics administration is not recommended for SAP. In addition, more sizeable well-designed RCTs and additional research are required.

Statement of Ethics

Our study was a meta-analysis and was therefore exempt from ethical approval.

Conflict of Interest Statement

The authors declare no competing interests.

Funding Sources

The study received no fund support.

Author Contributions

Each author contributed significantly to concept and development of the present paper. L.G. and D.G. designed the research process. J.S. and W.D. searched the database for corresponding articles and extracted useful information from the articles above. M.Z. and Y.S. used statistical software for analysis. K.J. drafted the meta-analysis. All authors had read and approved the manuscript and ensured that this was the case.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

- 1 Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology*. 2019;156(1):254–72.e11.
- 2 Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: a review. *JAMA*. 2021;325(4):382–90.
- 3 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis – 2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–11.
- 4 Brown A. Prophylactic antibiotic use in severe acute pancreatitis: hemlock, help, or hype? *Gastroenterology*. 2004;126(4):1195–8.
- 5 Schmidt PN, Roug S, Hansen EF, Knudsen JD, Novovic S. Spectrum of microorganisms in infected walled-off pancreatic necrosis – impact on organ failure and mortality. *Pancreatol*. 2014;14(6):444–9.
- 6 Baltatzis M, Jegatheeswaran S, O'Reilly DA, Siriwardena AK. Antibiotic use in acute pancreatitis: global overview of compliance with international guidelines. *Pancreatol*. 2016;16(2):189–93.
- 7 Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379–400.
- 8 Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):140016–5.
- 9 Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol*. 2013;13(4 Suppl 2):e1–15.
- 10 Italian Association for the Study of the Pancreas (AISP); Pezzilli R, Zerbi A, Campa D, Capurso G, Golfieri R, et al. Consensus guidelines on severe acute pancreatitis. *Dig Liver Dis*. 2015;47(7):532–43.
- 11 Leppaniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg*. 2019;14:27.
- 12 Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, et al. Guidelines for the management of acute pancreatitis. *J Gastroenterol Hepatol*. 2002;17(Suppl):S15–39.
- 13 Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, et al. IAP guidelines for the surgical management of acute pancreatitis. *Pancreatol*. 2002;2(6):565–73.
- 14 Yousaf M, McCallion K, Diamond T. Management of severe acute pancreatitis. *Br J Surg*. 2003;90(4):407–20.
- 15 Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, et al. Japanese guidelines for the management of acute pancreatitis: Japanese guidelines 2015. *J Hepatobiliary Pancreat Sci*. 2015;22(6):405–32.
- 16 Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. *Gastroenterology*. 2018;154(4):1096–101.
- 17 Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010;2010(5):CD002941.
- 18 Ukai T, Shikata S, Inoue M, Noguchi Y, Igarashi H, Isaji S, et al. Early prophylactic antibiotics administration for acute necrotizing pancreatitis: a meta-analysis of randomized controlled trials. *J Hepatobiliary Pancreat Sci*. 2015;22(4):316–21.
- 19 Barrie J, Jamdar S, Smith N, McPherson SJ, Siriwardena AK, O'Reilly DA. Mis-use of antibiotics in acute pancreatitis: insights from the United Kingdom's National Confidential Enquiry into patient outcome and death (NCEPOD) survey of acute pancreatitis. *Pancreatol*. 2018;18(7):721–6.
- 20 Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. *Clin Infect Dis*. 2019;69(Suppl 7):S521–8.
- 21 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- 22 Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- 23 Lo CK, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014;14:45.
- 24 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–60.
- 25 Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Ann Surg*. 2007;245(5):674–83.
- 26 Ho HS, Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. *Arch Surg*. 1997;132(5):487–3; discussion 92–3.
- 27 Nakaharai K, Morita K, Jo T, Matsui H, Fushimi K, Yasunaga H. Early prophylactic antibiotics for severe acute pancreatitis: a population-based cohort study using a nationwide database in Japan. *J Infect Chemother*. 2018;24(9):753–8.

- 28 Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis – a single-center randomized study. *J Gastrointest Surg*. 2001;5(2):113–20; discussion 8–20.
- 29 Poropat G, Radovan A, Peric M, Mikolasevic I, Giljaca V, Hauser G, et al. Prevention of infectious complications in acute pancreatitis: results of a single-center, randomized, controlled trial. *Pancreas*. 2019;48(8):1056–60.
- 30 Rokke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LO, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. *Scand J Gastroenterol*. 2007;42(6):771–6.
- 31 Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: results of a randomized controlled trial. *J Gastroenterol Hepatol*. 2009;24(5):736–42.
- 32 Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. *JAMA*. 2004;291(23):2865–8.
- 33 Balzan S, de Almeida Quadros C, de Cleve R, Zilberstein B, Ceconello I. Bacterial translocation: overview of mechanisms and clinical impact. *J Gastroenterol Hepatol*. 2007;22(4):464–71.
- 34 Liu J, Huang L, Luo M, Xia X. Bacterial translocation in acute pancreatitis. *Crit Rev Microbiol*. 2019;45(5–6):539–47.
- 35 Zhang XP, Zhang J, Song QL, Chen HQ. Mechanism of acute pancreatitis complicated with injury of intestinal mucosa barrier. *J Zhejiang Univ Sci B*. 2007;8(12):888–95.
- 36 Cen ME, Wang F, Su Y, Zhang WJ, Sun B, Wang G. Gastrointestinal microecology: a crucial and potential target in acute pancreatitis. *Apoptosis*. 2018;23(7–8):377–87.
- 37 Landahl P, Ansari D, Andersson R. Severe acute pancreatitis: gut barrier failure, systemic inflammatory response, acute lung injury, and the role of the mesenteric lymph. *Surg Infect*. 2015;16(6):651–6.
- 38 Moka P, Goswami P, Kapil A, Xess I, Sreenivas V, Saraya A. Impact of antibiotic-resistant bacterial and fungal infections in outcome of acute pancreatitis. *Pancreas*. 2018;47(4):489–94.
- 39 Jain S, Mahapatra SJ, Gupta S, Shalimar, Garg PK. Infected pancreatic necrosis due to multidrug-resistant organisms and persistent organ failure predict mortality in acute pancreatitis. *Clin Transl Gastroenterol*. 2018;9(10):190.
- 40 Mowbray NG, Ben-Ismael B, Hammada M, Shingler G, Al-Sarireh B. The microbiology of infected pancreatic necrosis. *Hepatobiliary Pancreat Dis Int*. 2018;17(5):456–60.
- 41 Lu JD, Cao F, Ding YX, Wu YD, Guo YL, Li F. Timing, distribution, and microbiology of infectious complications after necrotizing pancreatitis. *World J Gastroenterol*. 2019;25(34):5162–73.
- 42 Wittau M, Mayer B, Scheele J, Henne-Bruns D, Dellinger EP, Isenmann R. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol*. 2011;46(3):261–70.
- 43 Bai Y, Gao J, Zou DW, Li ZS. Antibiotics prophylaxis in acute necrotizing pancreatitis: an update. *Am J Gastroenterol*. 2010;105(3):705–7.
- 44 Bai Y, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2008;103(1):104–10.
- 45 Fan N, Hu Y, Shen H, Liu S, Zhao G, Sun L, et al. Compositional and drug-resistance profiling of pathogens in patients with severe acute pancreatitis: a retrospective study. *BMC Gastroenterol*. 2020;20(1):405.
- 46 Lee HS, Lee SK, Park DH, Lee SS, Seo DW, Kim MH, et al. Emergence of multidrug resistant infection in patients with severe acute pancreatitis. *Pancreatol*. 2014;14(6):450–3.
- 47 Wurstle S, Hapfelmeier A, Wohrl C, Dichtl K, Lahmer T, Rasch S, et al. Changes in pathogen spectrum and antimicrobial resistance development in the time-course of acute necrotizing pancreatitis. *J Gastroenterol Hepatol*. 2019;34(12):2096–103.
- 48 Marstrand-Joergensen MR, Bertilsson S, Kalaitzakis E. Extrapneumonic infections are common in acute pancreatitis and they are related to organ failure: a population-based study. *Eur J Gastroenterol Hepatol*. 2020;32(10):1293–300.
- 49 Xu T, Cai Q. Prophylactic antibiotic treatment in acute necrotizing pancreatitis: results from a meta-analysis. *Scand J Gastroenterol*. 2008;43(10):1249–58.
- 50 Kylanpaa ML, Repo H, Puolakkainen PA. Inflammation and immunosuppression in severe acute pancreatitis. *World J Gastroenterol*. 2010;16(23):2867–72.
- 51 Sharma D, Jakkampudi A, Reddy R, Reddy PB, Patil A, Murthy HVV, et al. Association of systemic inflammatory and anti-inflammatory responses with adverse outcomes in acute pancreatitis: preliminary results of an ongoing study. *Dig Dis Sci*. 2017;62(12):3468–78.
- 52 Foitzik T, Fernández-del Castillo C, Ferraro MJ, Mithöfer K, Rattner DW, Warshaw AL. Pathogenesis and prevention of early pancreatic infection in experimental acute necrotizing pancreatitis. *Ann Surg*. 1995;222(2):179–85.
- 53 Tian H, Chen L, Wu X, Li F, Ma Y, Cai Y, et al. Infectious complications in severe acute pancreatitis: pathogens, drug resistance, and status of nosocomial infection in a University-affiliated Teaching Hospital. *Dig Dis Sci*. 2020;65(7):2079–88.
- 54 Habashi S, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol*. 2009;15(1):38–47.
- 55 Hines OJ, Pandol SJ. Management of severe acute pancreatitis. *BMJ*. 2019;367:l6227.
- 56 Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. *Gastroenterology*. 2019;156(7):2008–23.
- 57 Ge P, Luo Y, Okoye CS, Chen H, Liu J, Zhang G, et al. Intestinal barrier damage, systemic inflammatory response syndrome, and acute lung injury: a troublesome trio for acute pancreatitis. *Biomed Pharmacother*. 2020;132:110770.
- 58 Zhang H, Neuhofer P, Song L, Rabe B, Lesina M, Kurkowski MU, et al. IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality. *J Clin Invest*. 2013;123(3):1019–31.
- 59 Luan ZG, Zhang XJ, Yin XH, Ma XC, Zhang H, Zhang C, et al. Downregulation of HMGB1 protects against the development of acute lung injury after severe acute pancreatitis. *Immunobiology*. 2013;218(10):1261–70.
- 60 Zhang W, Zhang M, Kuang Z, Huang Z, Gao L, Zhu J. The risk factors for acute respiratory distress syndrome in patients with severe acute pancreatitis: a retrospective analysis. *Medicine*. 2021;100(2):e23982.
- 61 Stevens JP, Law A, Giannakoulis J. Acute respiratory distress syndrome. *JAMA*. 2018;319(7):732.
- 62 Sternby H, Bolado F, Canaval-Zuleta HJ, Marra-Lopez C, Hernando-Alonso AI, DelVal-Antonana A, et al. Determinants of severity in acute pancreatitis: a Nation-Wide Multicenter Prospective Cohort Study. *Ann Surg*. 2019;270(2):348–55.
- 63 Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*. 2010;139(3):813–20.
- 64 Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2006;(4):CD002941.
- 65 Jafri NS, Mahid SS, Idstein SR, Hornung CA, Galandiuk S. Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis. *Am J Surg*. 2009;197(6):806–13.
- 66 Hart PA, Bechtold ML, Marshall JB, Choudhary A, Puli SR, Roy PK. Prophylactic antibiotics in necrotizing pancreatitis: a meta-analysis. *South Med J*. 2008;101(11):1126–31.
- 67 Mourad MM, Evans R, Kalidindi V, Navaratnam R, Dvorkin L, Bramhall SR. Prophylactic antibiotics in acute pancreatitis: endless debate. *Ann R Coll Surg Engl*. 2017;99(2):107–12.
- 68 De Waele B, Van Nieuwenhove Y, Lauwers S, Delvaux G. Biliary tract infection in patients with acute biliary pancreatitis. *Surg Infect*. 2003;4(3):241–6.