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Rethinking Carbapenems: A Pharmacokinetic Approach for Antimicrobial Selection in Infected Necrotizing Pancreatitis

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Abstract

Objective: To provide an overview of pathophysiological changes to the pancreas during infected necrotizing pancreatitis (INP), optimal drug properties needed to penetrate the pancreas, human and animal studies supporting the use of antimicrobials, and carbapenem-sparing strategies in INP. **Data Sources:** A literature analysis of PubMed/MEDLINE was performed (from 1960 to September 2020) using the following key terms: *infected necrotizing pancreatitis, necrotizing acute pancreatitis*, and *infected pancreatitis antimicrobial concentration*. Individual antimicrobials were investigated with these search terms. **Study Selection and Data Extraction:** All relevant studies describing the management of INP, and human and animal pharmacokinetic (PK) data supporting antimicrobial use in the pancreas were reviewed for possible inclusion regardless of sample size or study design. **Data Synthesis:** Piperacillin/tazobactam and cefepime achieve adequate pancreatic tissue concentrations in INP studies. A majority of the literature supporting carbapenem use in INP involves imipenem, and meropenem Monte Carlo simulations suggest that standard dosing regimens of meropenem may not achieve PK targets to eradicate *Pseudomonas aeruginosa*. **Relevance to Patient Care and Clinical Practice:** Carbapenems are often utilized for INP treatment based on guideline recommendations. This review discusses PK data, the history of carbapenem use in INP, and the pathophysiology of pancreatitis to suggest carbapenem-sparing strategies and provides stewardship tactics such as when to start antimicrobials, which empirical antimicrobial to use, and when to discontinue antimicrobials in the INP setting. **Conclusions:** Noncarbapenem antipseudomonals, such as piperacillin/tazobactam and cefepime, are appropriate carbapenem-sparing options in INP, based on PK data, spectrum of activity, and risk of collateral damage.

Keywords

infectious diseases, gastroenterology, β-lactams, pancreatitis, antibiotic resistance

Introduction

Acute pancreatitis affects between 4.9 and 73.4 per 100 000 people worldwide.[1] Gallstones and heavy alcohol consumption are the most common inciting etiologies, and clinical severity is based on degree of organ failure.[2,3] Most cases are managed conservatively without procedural intervention or antimicrobials, and up to 20% to 30% of acute pancreatitis cases are considered severe.[4] Those with severe acute pancreatitis can develop necrotic lesions that are at an increased risk for infection.[4] Necrotic pancreatitis is associated with increased rates of organ failure, and infected necrotizing pancreatitis (INP) is associated with mortality rates estimated from 19.8% to 35.2%.[5]

Management of severe necrotizing pancreatitis depends on whether the necrotic tissue is infected or sterile. Clinicians rely on clinical picture, onset of illness, and imaging to determine if infection is present. However, as many as 62% of patients with severe pancreatitis meets systemic inflammatory response syndrome (SIRS) criteria within 24 hours

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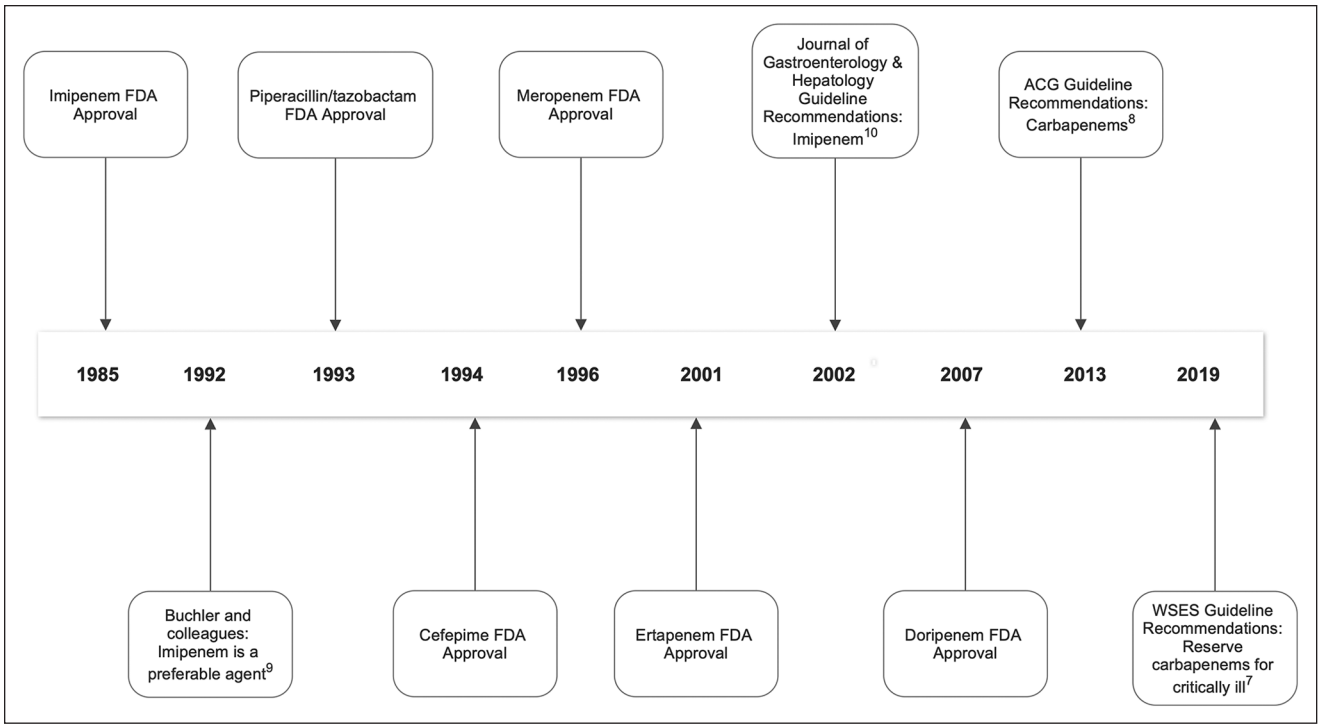

Figure 1. Timeline of carbapenem recommendations in infected necrotizing pancreatitis.

of hospitalization, which can make antimicrobial decision-making difficult.[6] Current guidelines such as the American College of Gastroenterology (ACG) and World Society Journal of Emergency Surgery (WSES) support the use of carbapenems for INP based on spectrum of activity as well as their ability to penetrate pancreatic tissue.[7,8] These recommendations date back to the 1990s when favorable findings with imipenem were noted prior to Food and Drug Administration (FDA) approval of piperacillin/tazobactam or cefepime (Figure 1).[9] These findings were based on a scoring system that ranked antimicrobials on spectrum of activity and tissue penetration in acute and chronic pancreatitis patients (few of whom had necrotic pancreatitis). The recommendation was further supported when imipenem was studied for prophylaxis in severe acute pancreatitis; this practice is no longer recommended, and other antipseudomonal β-lactams were not evaluated in these studies.[10] Other carbapenems were incorporated into guideline recommendations for treatment of INP despite lack of substantial clinical evidence for carbapenems and emerging pharmacokinetic (PK) data for other β-lactams.[7,8,11]

Without the ability to obtain culture data, patients are often given weeks of therapy without a definitive diagnosis of an infection. Carbapenem use increases selective pressure and risk of developing carbapenem-resistant *Enterobacterales* (CRE) infections, and CRE was responsible for up to 1100 deaths and $130 million of health care expenditures in 2017.[12,13] As expected, carbapenem use in INP leads to higher rates of multidrug-resistant organisms (MDROs), and presence of an MDRO in INP is an independent predictor of mortality.[14,15]

The loss of clinical equipoise has placed carbapenems as the standard of care in INP. The purpose of this review is to highlight the pathophysiology and medical management of INP and to evaluate PK data to guide clinicians in carbapenem sparing strategies.

Methods

A literature search using PubMed and MEDLINE databases was conducted from 1960 to September 2020. Search terms included *infected necrotizing pancreatitis, necrotizing acute pancreatitis*, and *infected pancreatitis antimicrobial concentration*. Individual antimicrobials, including ampicillin, piperacillin/tazobactam, cefazolin, cefotaxime, ceftriaxone, cefepime, meropenem, ertapenem, imipenem, ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, vancomycin, metronidazole, gentamicin, and tobramycin, were also searched with the aforementioned search terms. Titles and abstracts of studies in the English language describing the management of INP and the human and animal PK data supporting antimicrobial use in the pancreas were included for review regardless of sample size or study design. References of included articles were also reviewed. The final literature search was conducted on September 30, 2020. Studies focusing on clinical outcomes with prophylactic antimicrobials

Table 1. Acute Pancreatitis Principles and Definitions.

Acute pancreatitis phases				
	Early: ≤7 days		Late: >7 days	
Severity				
Mild: no organ failure or local/systemic complications	Moderate: organ failure <48 hours or local/systemic complications without persistent organ failure		Severe: organ failure >48 hours	
Types of acute pancreatitis				
Manifestation	Definition	Onset	Intervention?	Infection Likely?
Interstitial edematous pancreatitis				
Acute peripancreatic fluid collections	Purely fluid contents that spontaneously resolve within first few weeks of onset	<4 Weeks	No	No
Pancreatic pseudocysts	Fluid collections that are surrounded by a smooth and uniform wall	≥4 Weeks	May require endoscopic drainage depending on size	No
Acute necrotizing pancreatitis				
Acute necrotic collection/ postnecrotic pancreatic fluid collection	Poorly organized, nonliquefied components with no wall	<4 Weeks	Typically not amenable to drainage because of lack of wall	Possible, correlate with clinical picture and onset of illness
Walled off pancreatic necrosis	Necrotic collections that mature to develop a thick wall	≥4 Weeks	Endoscopic necrosectomy preferred	Possible, correlate with clinical picture

for acute pancreatitis were excluded. Because of lack of clinical data, PK data were primarily evaluated.

Pathophysiology of Acute Pancreatitis

Pancreatitis is characterized by inflammation and acinar cell destruction with release of proteolytic enzymes that cause cell autodigestion and blood vessel damage. Severe acute pancreatitis is characterized by organ failure greater than 48 hours, and clinical manifestations include fever, acute respiratory distress syndrome, pleural effusions, renal failure, and metabolic abnormalities.[5,14]

The revised Atlanta classification is used to standardize diagnosis and management of acute pancreatitis. Imaging findings are categorized as interstitial edematous pancreatitis or necrotizing pancreatitis (Table 1).[3]

Necrotizing pancreatitis is classified as lack of flow of contrast in the pancreas on imaging. Generally, greater than 50% necrosis is considered significant. In the first 4 weeks, this is called a postnecrotic pancreatic fluid collection (PNPFC) or acute necrotic collection. After approximately 4 weeks, if the necrotic collections are not resorbed, the necrotic collection can mature and develop a thick wall, termed walled-off pancreatic necrosis (WOPN). Both PNPFCs and WOPNs can become infected via direct translocation from the gastrointestinal tract or hematogenous spread in the setting of impaired host defenses (Table 1).[16] Timing of infection in necrotizing pancreatitis is variable and typically occurs at 3 to 4 weeks but can happen as early as 7 days.[17] This is clinically suspected if there is clinical deterioration or gas in the necrotic area on imaging.

During the early stages of acute pancreatitis, interstitial edema produces an environment that many antimicrobials are able to penetrate well.[18] Decreased capillary blood flow is observed and can decrease antimicrobial penetration, although it is of unclear clinical relevance.[19] As acute pancreatitis progresses to its later stages that are more commonly associated with INP, interstitial edema resolves and increased presence of necrotic tissue leads to decreased antimicrobial penetration.

Guideline Recommended Treatment

Uncertainty surrounds INP treatment, including when to start antimicrobials, which antimicrobials to use, and duration of therapy. The ACG Guideline on the Management of Acute Pancreatitis suggests that infected necrosis should be suspected in patients who deteriorate or fail to improve after 7 to 10 days of hospitalization.[8] ACG recommends either computed tomography–guided fine needle aspiration for cultures or the empirical use of antimicrobials without culture data. In common practice, the latter approach is used because the diagnostic yield of aspiration is low and there is a risk of introducing infection during the procedure.[6] ACG recommends carbapenems or fluoroquinolones with metronidazole as empirical therapy. The WSES Guidelines for the Management of Severe Acute Pancreatitis recommend ureidopenicillins (such as piperacillin) and third-generation cephalosporins because of their intermediate penetration into pancreatic tissue.[6] WSES specifies that although fluoroquinolones and carbapenems have adequate tissue penetration, fluoroquinolones should be avoided due to high rates of

resistance and should be used only in patients with β-lactam allergies. They further comment that carbapenems should be reserved for very critically ill patients because of increased rates of CRE infections but do not define which patients meet this criterion.

Duration of antimicrobial therapy is also an area without clear recommendations. The Surgical Infection Society guidelines recommend repeat imaging studies while on therapy and, if clinical examination improves, to discontinue antimicrobial therapy.[20] Treatment of INP before a wall has formed is challenging, and often, antimicrobials are trialed first. In practice, antimicrobials are often continued for several days after clinical improvement or after improvement in laboratory results.

Ideal Antimicrobial Characteristics

Spectrum of Activity

A retrospective review representing approximately 1100 cases of pancreatic infections (both monomicrobial and polymicrobial) found that the most common organisms isolated were *Escherichia coli* (35%), *Klebsiella pneumoniae* (24%), *Enterococcus* spp (24%), *Staphylococcus* spp (14%), and *Pseudomonas* spp (11%).[21] Some studies suggest that gram-positive organisms are more commonly isolated in INP when the infection is developed postoperatively.[22] A study assessing adverse outcomes associated with INP recovered extended-spectrum β-lactamase (ESBL) organisms in 3.19% of patients.[23] Therefore, empirical coverage of ESBLs should only be considered if a patient has risk factors for resistance.

Pharmacokinetic Properties

An important factor when considering the ability of antimicrobials to reach the site of action in INP is the volume of distribution (V_d). Agents with a large V_d (>42 L) are lipophilic and penetrate tissues well with lower concentrations of antimicrobial in the serum. Agents with a smaller V_d are hydrophilic and are associated with lower tissue levels and higher serum levels. Lipophilic agents with a large V_d are preferable from a PK perspective for the treatment of INP.

The ability of an antimicrobial to work optimally is also dependent on its pH. Pancreatic juice pH is approximately 8, and antimicrobials need to be pharmacologically active in alkaline environments.[24] Weak acids are favored in this environment, so that ion trapping of antimicrobials can occur, which creates higher concentrations of antimicrobials in pancreatic juice and tissue.

Ideal PK studies include humans with INP and are reported in units that can be extrapolated to patient care. PK data evaluating patients with malignancies, chronic pancreatitis, or healthy pancreatic tissue are not reflective of the same inflammatory changes observed in INP; some studies suggest that if there are sufficient PK data in healthy tissue, it should be correlated to necrotic tissue, but this remains controversial.[24] Pancreatic juice typically achieves higher antimicrobial concentrations than necrotic tissue and even enhances antimicrobial activity, but tissue data are preferable because they most accurately represent the site of infection.[25] However, pancreatic juice can serve as a vehicle for antimicrobial delivery to necrotic tissue and is often studied to justify the use of antimicrobials in INP as a surrogate for necrotic tissue.[25] Many PK tissue studies use tissue homogenates (expressed in milligram per kilogram concentrations), but these results are ambiguous compared with results reported in microgram per milliliter, which can be directly compared to the interaction of an antimicrobial and a minimum inhibitory concentration (MIC). Whole tissue homogenate concentrations are only an estimate of unbound drug and cannot be directly correlated with MICs.[26] Therefore, human INP studies with tissue concentrations expressed in microgram per milliliter are preferred.

Clinicians must critically evaluate the way in which pancreatic necrotic tissue and juice concentrations are presented and consider antimicrobial-specific PK/pharmacodynamic (PD) indices. Many studies opt to report the tissue to serum ratio or conclude that an antimicrobial with the highest concentration is the most optimal. Tissue to serum ratios may be misleading if serum concentrations are low; this may correlate with a high ratio but does not address if the concentration in the tissue is high enough to adequately eradicate an organism. Additionally, neither of these principles is useful if the clinician does not take into account each antimicrobial's PK/PD indices. For example, β-lactams perform optimally when the free drug concentration is greater than the MIC for a specified percentage of the dosing interval (%fT > MIC). Therefore, concentration of the antimicrobial in the tissue matters, but half-life is also of great importance. Peak concentrations and tissue to serum ratios do not account for the duration of time the antimicrobial concentration is above the MIC. On the contrary, aminoglycosides perform best under a peak/MIC index where high concentrations are essential. Therefore, peak concentrations are helpful in determining the utility of an aminoglycoside.

Collateral Damage

As previously mentioned, myriad MDROs have been observed in the treatment of INP and are identified as independent risk factors for mortality in INP.[14,23] Approaches to mitigate the risk of MDRO development include appropriate antimicrobial selection and duration.

Antimicrobials by Class

Aminoglycosides

Buchler et al[9] evaluated antimicrobial concentrations in 89 adult patients with primarily chronic pancreatitis and pancreatic carcinoma, 8 of whom had INP. Tobramycin pancreatic tissue concentrations 120 minutes after intravenous administration of 80 mg (lower than standard adult dose of 3 to 5 mg/kg) were 0.4 mg/kg (Table 2).[9] Bassi et al[25] also found that gentamicin 80 mg administered to 12 INP patients resulted in levels of 0.15 to 0.5 mg/kg. As previously mentioned, the utility of tissue homogenate concentrations is low, but these data suggest that aminoglycosides are unlikely to achieve appropriate peak to MIC ratios (approximately 8 to 10). This is further supported by the highly hydrophilic nature of aminoglycosides.

Carbapenems

Despite lower V_d values, data support the use of carbapenems in INP (Table 2). The recommendation is based primarily on literature with the use of imipenem. Imipenem was also evaluated in the aforementioned Buchler et al[9] study, and imipenem was found to have pancreatic tissue concentrations of 6 mg/kg, which was second only to piperacillin.[9] Imipenem concentrations were found to be much lower in a study evaluating solely acute necrotizing pancreatitis patients (0.19-3.35 mg/kg).[25] Although this tissue homogenate data are difficult to interpret, meropenem has more recently been the subject of PK studies that are more directly applicable to clinical care. A Monte Carlo simulation was performed on pancreatic juice concentrations after a single dose of meropenem 500 mg in 10 patients with endoscopic nasopancreatic drainage for biliary or pancreatic disease.[34] Most patients had pancreatic cancer (60%), and only 20% had a diagnosis of acute pancreatitis. A dose of 500 mg every 8 hours had a greater than 90% rate of achieving probability of target attainment (PTA) for *Enterobacterales*, with an MIC $\leq$0.125 μg/mL, and 1000 mg every 8 hours was needed for MICs $\leq$0.25 μg/mL. Of concern, the above regimen had a 41.3% rate of achieving PTA for *P aeruginosa* isolates. None of the studied regimens (all of which were intermittent) were able to achieve greater than 90% PTA for *P aeruginosa* isolates. Another study suggests that 500 mg doses of meropenem in 30-minute intermittent infusion every 8 hours in patients with an average serum creatinine of 1.43 mg/dL are not sufficient for *Enterobacterales* with MICs $\geq$0.5 μg/mL.[35]

Although carbapenems remain an option from a spectrum of activity and PK perspective, the risk of MDRO production cannot be understated. Increasing the risk for MDROs outweighs the benefit of empirically providing activity for the low rates of ESBL organisms that are observed in INP.[23] The risk of carbapenem-associated resistance is time dependent, and the largest risk of resistance occurs within 8 to 15 days of carbapenem therapy and is associated with an odds ratio (OR) of 70.1 (14.9-421.0).[55] Clinicians are forced to consider more expensive and toxic regimens when carbapenems and other β-lactams are eliminated from their armamentarium.

Piperacillin/Tazobactam

When Buchler et al[9] performed their study, they also ranked antimicrobials into categories of low concentrations, antimicrobials with pancreatic tissue concentrations to inhibit some but not all of the bacteria in INP, and antimicrobials with high bactericidal activity against most INP organisms.[9] Of interest, piperacillin without its β-lactamase inhibitor was studied and had the highest tissue concentrations of any antimicrobial studied, including carbapenems (20.3 mg/kg; Table 2). Piperacillin was subsequently placed into the category of achieving high concentrations but not having adequate activity. Piperacillin without a β-lactamase inhibitor eliminates anaerobic activity and significantly reduces activity against β-lactamase–producing gram-negative organisms. This study set the precedent for the recommendation of carbapenems in INP but did not study both components of piperacillin/tazobactam nor did it provide a way to clinically interpret the concentrations of the antimicrobials studied besides recommending agents with the highest tissue homogenate concentration.

Concentrations of piperacillin/tazobactam 4500 mg intermittent infusion every 8 hours have since been studied in patients with acute necrotizing pancreatitis. One study evaluated patients after they received 3 consecutive doses of piperacillin/tazobactam 4500 mg infused over 30 minutes, and the average necrotic tissue concentration was 120 mg/kg (SD = $\pm$34), which is notably higher than that in previous studies measuring piperacillin and other carbapenem concentrations.[24] This study was performed after multiple doses and only studied patients with known INP, which suggests that the findings may be more reliable than other studies performed in a more heterogeneous population that received only 1 dose of an antimicrobial. For reference, piperacillin and tazobactam intestinal mucosal tissue concentrations are 64.6 to 67.8 mg/kg and 9.11 to 22.7 mg/kg, respectively, 61 to 90 minutes after a 30-minute 4500-mg infusion.[56] Additionally, piperacillin/tazobactam was evaluated in a Monte Carlo simulation for the treatment of prostatitis. Patients with prostatic hypertrophy undergoing transurethral resection of the prostate procedure achieved concentrations of 130.2 mg/kg of piperacillin and 15.4 mg/kg of tazobactam.[57] The authors concluded that piperacillin/tazobactam dosed at 4500 mg over 30 minutes every 8 hours had a 90% rate of achieving PTA (50%fT > MIC) in *Enterobacterales*. If the aforementioned intra-abdominal and prostatic concentrations are sufficient evidence to place

Table 2. Pharmacokinetic Data for Antimicrobials in Infected Necrotizing Pancreatitis.

Antimicrobial	Volume of distribution	pH	Patient population	Pancreatic juice concentration	Necrotic tissue concentration
Aminoglycosides[9,25,27,28]					
Gentamicin	+	3-5.5	Human INP	—	2 Hours: 0.15-0.5 mg/kg
Tobramycin	+		Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 0.4 mg/kg
Carbapenems[9,18,25,29-34,35]					
Ertapenem	+	7.5	Human pancreatic carcinoma, chronic pancreatitis, etc	—	3 Hours: 3.85 mg/kg 5 Hours: 3.3 mg/kg 8 Hours: 0.9 mg/kg
Imipenem	+	6.5-8.5	Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 6 mg/kg
			Human INP	—	2 Hours: 1.4 mg/kg 2.5 Hours: 3.35 mg/kg 5 Hours: 0.19 mg/kg
			Human pancreatic transplant	1.5 Hours: 1.7 μg/mL	—
Meropenem	+	7.3-8.3	Human pancreatic malignancy	1 Hour: 2.08 μg/mL	—
			Human hepato-biliary-pancreatic surgery	1 Hour: 2.12 μg/mL	—
			Animal INP model	—	6 Hours: 6.56 μg/mL 48 Hours: 5.52 μg/mL
Noncarbapenem β-lactams[9,11,18,24,36-45]					
Ampicillin	+	8-10	Pancreatic disease fluid concentrations in ERCP	Undetectable	—
			Animal chronic pancreatic fistula	4 Hours: 0.8 μg/mL	—
Cefepime	+	4-6	Animal INP model	—	1 Hour: 22.34 μg/mL 3 Hours: 2.26 μg/mL
			Human pancreatic tissue	—	3 Hours: 10.7 μg/mL
			Animal INP model	—	6 Hours: 11.75 μg/mL 48 Hours: 9.43 μg/mL
			Animal acute pancreatitis model	—	0.5 Hours: 75 mg/kg
Cefotaxime	++	5-7.5	Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 9.1 mg/kg
Ceftriaxone	+	6.7	Human duodenopancreatectomy	2 Hours: 2.1 mg/kg	2 Hours: 6.0 mg/kg
Piperacillin/ tazobactam	+	5.5-6.8	Human acute/chronic pancreatitis, carcinoma	—	2 Hours, piperacillin only: 20.3 mg/kg
			Human INP	—	0.5 Hours: 120 mg/kg
Fluoroquinolones[9,46-51]					
Ciprofloxacin	+++	3.5-4.6	Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 0.9 mg/kg
			Human allograft pancreatic juice	4 Hours: 0.5 μg/mL	
Moxifloxacin	+++	4.1-4.6	Human chronic pancreatitis and pancreatic carcinoma	—	4 Hours: 3.1 mg/kg
Ofloxacin	+++	2-9	Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 1.7 mg/kg
			Human allograft pancreatic juice	4 Hours: 2.7 μg/mL	—
			Acute necrotizing acute pancreatitis model	—	1.5 Hours: 0.5 mg/kg
Nitroimidazoles[9,25,52]					
Metronidazole	++	5.8	Human acute/chronic pancreatitis, carcinoma	—	2 Hours: 3.5 mg/kg
			Human INP	—	2 Hours: 8.48 mg/kg
Glycopeptides[53,54]					
Vancomycin	++	2.5 -4.5	Human necrotizing pancreatitis undergoing necrosectomy	—	At steady state, time unknown: 5.84 μg/mL

Abbreviations: INP, infected necrotizing pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

piperacillin/tazobactam as a viable option for severe intra-abdominal infections and prostatitis, then it is reasonable to extrapolate that the milligram per kilogram concentrations in necrotic pancreatic tissue are reliable for the treatment of INP as well.[20,58]

Although piperacillin/tazobactam is associated with development of resistant organisms, the risk and implications are less severe than those associated with carbapenems.[55] Piperacillin/tazobactam has lower rates of resistance development in INP compared with carbapenems, with an OR of 1.5 (0.5-4.3).[55]

Cephalosporins

Few data are available regarding the use of third-generation cephalosporins in INP. Ceftriaxone tissue concentrations 2 hours after a 1-g dose were 6.0 ± 8.6 mg/kg, and cefotaxime tissue concentrations after a 2-g dose have been reported similarly at 9.1 mg/kg (Table 2).[9,44] As discussed, these tissue concentrations are difficult to apply to clinical practice, but ceftriaxone concentrations at 2 hours indicate that it would likely meet PK parameters given its long half-life of 5 to 9 hours.[35] Ceftriaxone and cefotaxime tissue to serum ratios at 2 hours are 0.11 to 0.15 and 0.32, respectively. Again, tissue to serum ratios are not clinically relevant for treatment of INP. If ceftriaxone concentrations are able to stay above the MIC for 60% to 70% of the dosing interval, then it should adequately eradicate the organism from a PK perspective regardless of the ratio of ceftriaxone in tissue to serum.

Cefepime is a broad-spectrum fourth-generation cephalosporin that was FDA approved after many INP PK studies were conducted and has, thus, not been addressed in guideline recommendations. To our knowledge, only 1 human study and several animal and PK analyses have been performed on cefepime pancreatic concentrations. Cefepime tissue concentrations were evaluated at a dose of 2000 mg over 30 minutes in 9 patients with pancreatic pseudocysts (some from INP).[41] Mean pancreatic tissue and pseudocyst concentrations were 10.7 and 6.3 μg/mL, respectively. These levels are comparable to cefepime concentrations observed in the appendix and gallbladder (and cefepime is commonly used to treat these types of intra-abdominal infections) and are sufficient to treat lower MICs such as 2 μg/mL.[59] Cefepime was also studied in animal models with simulated INP and peak cefepime concentrations between 22.34 and 75 mg/kg, and 6-hour levels were 11.75 mg/kg.[11,18,40] It appears that higher doses and longer infusion times may be necessary to achieve PK/PD targets for an MIC of 8 μg/mL.

Third- and fourth-generation cephalosporins differ in their rates of collateral damage. Third-generation cephalosporins are associated with increased rates of vancomycin-resistant *Enterococci* (VRE), ESBLs, and *Clostridioides difficile* infections (CDIs).[60] Third-generation cephalosporins were found to be the antimicrobial class most highly associated with CDIs (OR = 3.20; 95% CI = 1.80-5.71).[61] Cefepime is associated with a lower risk (OR = 2.14; 95% CI = 1.30-3.52) of CDI and is not found to be a risk factor for the development of VRE.

Fluoroquinolones

The original recommendation for fluoroquinolones in INP is based on ofloxacin data, which is not commonly prescribed. Ofloxacin was found to have concentrations of 1.7 mg/kg after a dose of 200 mg.[9] These findings were confirmed in multiple studies and suggest that fluoroquinolones have adequate penetration into pancreatic tissue.[47,51] Ciprofloxacin tissue concentrations after a 200-mg intravenous dose in patients with chronic pancreatitis, carcinoma, and INP were 0.9 mg/kg 120 minutes after administration (Table 2).[9] Ciprofloxacin achieved a peak tissue concentration of 0.5 mg/mL after administration of ciprofloxacin 500 mg orally once in pancreatic transplant juice.[51] These data are difficult to interpret for several reasons, including the following: lower doses of intravenous ciprofloxacin were administered than what is used for treatment; the pancreatic transplant population studied oral ciprofloxacin; and the reported units in both studies are not standard. Ciprofloxacin operates under an area under the curve (AUC)/MIC PK/PD index. An optimal AUC/MIC between 125 and 250 is preferred for severe infections.[62] Rates of increasing MICs and Clinical and Laboratory Standards Institute changes in break points make this AUC/MIC target increasingly difficult to reach, especially in the setting of penetrating necrotic tissue. Despite historical data supporting fluoroquinolone use in INP, it appears that these data are primarily in an uncommonly used fluoroquinolone, ofloxacin. With continued increase in resistance trends noted with fluoroquinolones, they are likely an inappropriate treatment option in the INP setting.

Fluoroquinolones have multiple FDA black box warnings, such as tendon rupture, neurotoxicity, and increased risk of ruptures and tears in the aorta. Additionally, fluoroquinolones are associated with high rates of CDIs (OR = 1.66; 95% CI = 1.17-2.35) and resistance development during INP treatment (OR = 1.9; 95% CI = 0.2-15.6).[55,61]

Metronidazole

Metronidazole is often paired with cephalosporins and fluoroquinolones to provide gram-negative anaerobic coverage. Metronidazole's small molecular weight, weak base, and extensive tissue distribution are favorable for achieving adequate INP concentrations.[25]

Metronidazole achieved tissue concentrations of 3.5 mg/kg after a dose of 500 mg intravenously in various types of

pancreatitis and pancreatic carcinoma (Table 2).[9] Higher concentrations were observed in a study primarily evaluating INP patients; metronidazole tissue concentrations were 4.45 to 8.48 mg/kg.[25,52]

Resistance to metronidazole usually occurs as a result of selective pressure but is not commonly encountered in clinical practice. Metronidazole is an appropriate option in the treatment of INP.

Relevance to Patient Care and Clinical Practice

Need for Antimicrobials

Little guidance is available for prespecified criteria for antimicrobial management; the authors provide their recommendations based on expert opinion for consideration (Figure 2). Onset of symptoms and presentation should coincide with the typical onset of INP, which can be considered 7 to 10 days after onset of acute pancreatitis symptoms.[8,17] The risk of INP increases as the disease advances; therefore, clinical suspicion should increase as hospitalization progresses. Diagnosis should coincide with acute decompensation or lack of improvement with supportive care; prior to initiation of antimicrobials, imaging should be obtained to evaluate for gas and necrosis. CT imaging with air bubbles suggests INP with a sensitivity of 56% and specificity of 97%.[63] The risk of infection is highest when greater than 50% necrosis is observed on imaging, but infection can still occur with necrosis of 30% to 50%.[64] Other etiologies for decompensation should be evaluated if occurring prior to 7 to 10 days of symptoms.

Choice of Empirical Antimicrobial

Although *Enterobacterales* are most commonly isolated in INP, the authors believe that empiric antipseudomonal coverage is often warranted based on duration of hospitalization and severity of illness. β-Lactams are preferred over aminoglycosides and fluoroquinolones to mitigate poor tissue penetration and collateral damage, respectively. Piperacillin/tazobactam has been shown in human studies to achieve adequate INP tissue concentrations when administered as an intermittent infusion, whereas cefepime has data from INP animal studies and human studies in non-INP patients to support its use. Therefore, piperacillin/tazobactam is an appropriate empirical first-line option, and cefepime is a reasonable second-line option. Most INP literature for carbapenem use discusses imipenem, and meropenem Monte Carlo simulations suggest that standard dosing regimens may not achieve PK targets to eradicate *P aeruginosa*. Although this can be managed with appropriate dosing strategies, it raises the question of why carbapenems have consistently been deemed standard of care. A retrospective cohort study evaluating risk factors for MDROs in severe acute pancreatitis found a trend toward initial carbapenem use and higher rates of MDROs (66% vs 41%; $P = 0.112$).[14] Acute pancreatitis infections caused by MDROs is an independent predictor of mortality (OR = 8.4; 95% CI = 3.1-22.5).[13] Carbapenems should be reserved for patients with known history of colonization or infection with ESBL organisms, facilities with greater than 20% ESBL rates, or patients who continue to show signs of unresolved infection and are not candidates for source control after 10 to 14 days of therapy (Figure 2).

Duration of Therapy

Trends toward increased duration of therapy leading to risk of MDROs in INP have been noted (24.2 ± 21.7 days vs 16.8 ± 15.4 days; $P = 0.255$).[22] Additionally, length of antimicrobial therapy increases the risk for development of invasive candidiasis.[65] Guidelines offer no recommendation regarding duration of therapy. Given a lack of supporting evidence, the authors recommend evaluating patients after 10 to 14 days of therapy and consider antimicrobial time-out in patients with no further signs of infection. Discontinuation of antimicrobials can coincide with repeat imaging to determine if there are necrotic areas that can be drained and also to consider aspiration to determine organisms and antimicrobial susceptibilities. Patients who still exhibit signs of infection at 10 to 14 days should be reimaged and evaluated for necrosectomy; antimicrobial discontinuation can be considered 24 to 48 hours after source control is achieved. Once patients are able to be discharged from their hospitalization, consideration should be taken if patients require further antimicrobials. In select instances, clinicians should consider the risks and benefits of placing a central line for outpatient use versus use of oral agents. Oral fluoroquinolone use has been studied in various degrees of pancreatic dysfunction, but no study has evaluated these agents in INP specifically, so data must be interpreted cautiously.[47,49]

Dosing Strategies

Use of β-lactams in critically ill patients in tissue that is difficult to penetrate warrants dose optimization. In a Monte Carlo simulation of meropenem, no intermittent dosing regimen was able to achieve PTA for *P aeruginosa*, which highlights the need to consider extended infusions of β-lactams for INP.[34] Both higher doses and extended dosing intervals are necessary to ensure adequate concentrations in necrotic tissue (Figure 2).

Conclusion

The balance between adequately identifying and treating INP and acting as a steward can be challenging. There are few human studies of antimicrobial penetration in INP, and

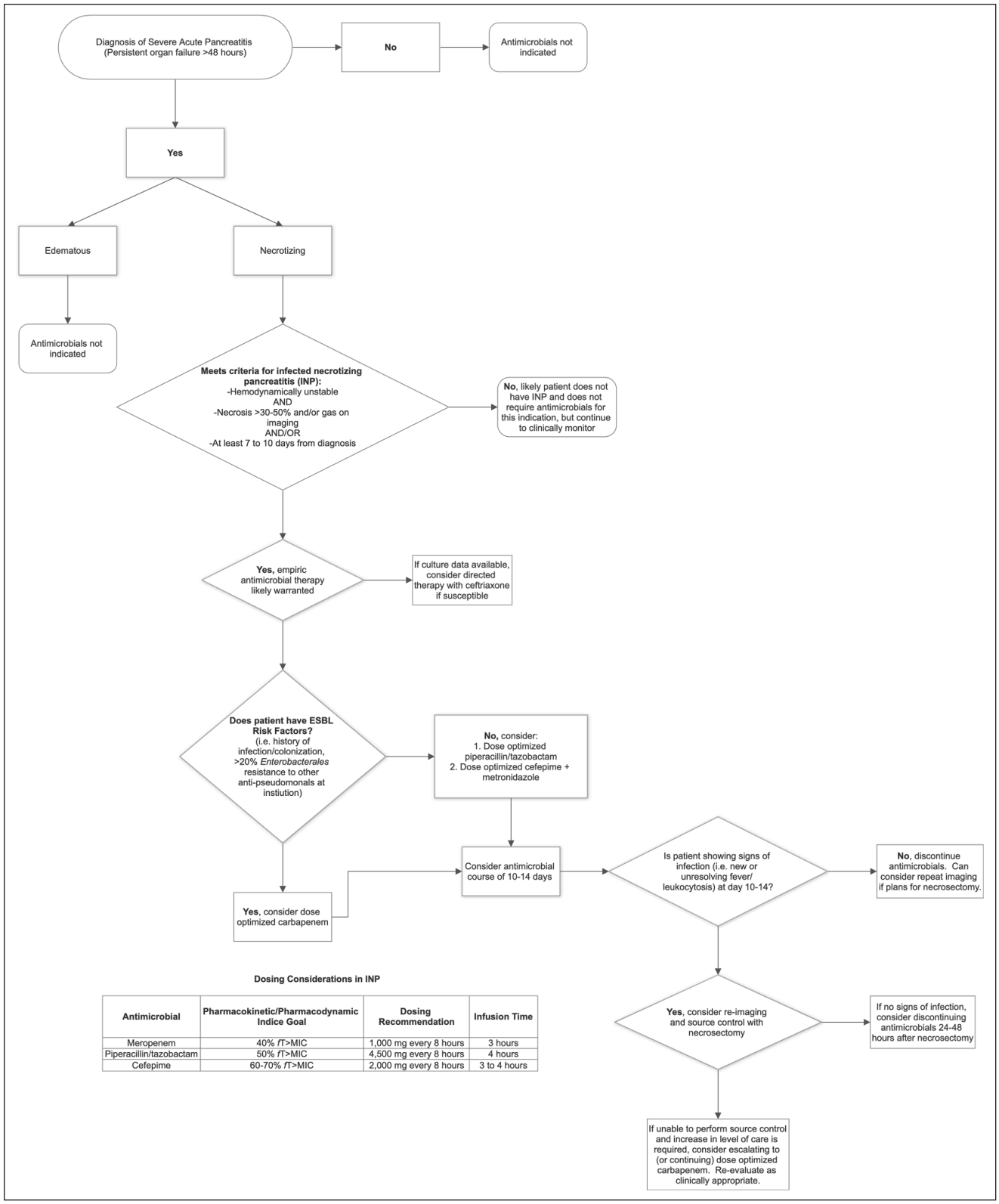

Figure 2. Infected necrotizing pancreatitis treatment algorithm.
Abbreviations: ESBL, extended-spectrum β-lactamase; fT>MIC, free drug concentration greater than minimum inhibitory concentration.

clinicians are forced to make decisions based on studies with varying numbers of patients and heterogeneous disease severity. The choice to adopt carbapenems, primarily meropenem, as a first-line option in INP leads to extended duration of a broad-spectrum antimicrobial that increases risk for development of MDROs. After examining the data, clinicians should consider the use of other β-lactams such as piperacillin/tazobactam or cefepime with dose optimization for empiric therapy. Carbapenems should be reserved for continued clinical worsening or culture data confirming need for extended-spectrum activity. Duration of therapy should be based on clinical status and antimicrobial time out, or discontinuation should be considered in patients with observed clinical improvement. Studies with clinical outcomes instead of concentration- and PK-based outcomes are warranted.

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