## APPENDIX

## I. PROTOCOL

Population: Acute pancreatitis cases.

Acute Necrotizing Pancreatitis: Acute pancreatitis cases with >30% necrosis and/or serum CRP >100 mg/dL in abdominal CT.

**Intervention and Comparison:** Carbapenem prophylaxis (imipenem, meropenem, doripenem, ertapenem) and placebo or standard therapy without antibiotic therapy.

#### Outcome

Mortality: In-hospital mortality.

*Surgical intervention*: Cases with pancreatitis complications who underwent surgical intervention.

*Peri-pancreatic infection*: Infection with microbiological evidence in peripancreatic tissue (in samples taken by surgery or fine needle aspiration).

Non-pancreatic infections: Non-pancreatic infection proven by microbiological culture.

#### Types of Trials Included: Randomized control trials.

#### **Inclusion Criteria**

- Full-text or abstract available, English-written articles.
- Articles published up to December 2022.
- Articles including the intervention (carbapenems)-comparison (placebo or standard therapy) groups in acute pancreatitis cases.

#### **Exclusion Criteria**

• Articles comparing carbapenems with other antibiotic groups in acute pancreatitis.

#### **Review process**

The systematic review was conducted in accordance with the PRISMA guidelines. Three reviewers searched the literature and retrieved all publications that met the inclusion criteria.

Each publication was evaluated for methodological quality using the Cochrane Collaboration's risk assessment tool for risk of bias for RCTs.

Literature Search Databases: PUBMED database.

#### Literature Search Keywords

- Pancrea\* and carbapenem
- Pancrea\* and imipenem
- Pancrea\* and meropenem
- Pancrea\* and ertapenem
- Pancrea\* and doripenem

**Data Analysis and Recording:** Cases characteristics (necrotizing or non-necrotizing pancreatitis), treatment regimens (Type of carbapenems, duration, starting time), outcomes (mortality, surgical intervention, peri-pancreatic or non-pancreatic infections and their definitions), follow-up periods were controlled and recorded.

**Bias Assessment for Studies:** Bias assessment for RCTs was made according to version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), 22 August 2019.

# II. CHARACTERISTICS AND OUTCOMES OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW AND META-ANALYSIS

Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet. 1993;176(5):480-3.

Methods	Randomized controlled trial Multicenter study <i>Allocation method:</i> Casual number table (pre-printed random tables) <i>Blinding:</i> Open	
Including criteria	Acute pancreatitis cases	
Excluding criteria	Not stated	
Number of total cases	74 patients	
Intervention	41 patients received medical treatment with prophylactic antibiotics (imipenem 0.5 g every 8 hours for 14 days	
Control	33 patients received medical treatment without prophylactic antibiotics	
Outcomes	<ul> <li>Mortality</li> <li>Surgery</li> <li>Peripancreatic infections</li> <li>Non-pancreatic infections</li> <li>Adverse events</li> </ul>	
Follow-up duration	Not stated	
Bias	Authors' judgement         Reason for judgement	
Random sequence generation	Low risk	Casual number table
Allocation concealment	Unclear risk Not available	
Blinding of participants and personnel	Unclear risk Not available	
Blinding of outcome	Unclear risk Not available	
Incomplete outcome data	Low risk There were post-randomization dropouts	
Selective reporting	Low risk Outcome results, including adverse events, were reported	
Other bias	Low risk	No other risk of bias

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):113-8; discussion 118-20. [CrossRef]

Methods	Randomized controlled trial
	Monocenter study
	Allocation method: Not stated
	Blinding: Open
Including criteria	Patients with severe acute pancreatitis and pancreatic necrosis
	(Severity based on CRP concentration > 150 mg/L and computerized
	tomography [CT])
Excluding criteria	- Patients who had already been started on antibiotics
	- Patients admitted directly to the intensive care unit (ICU) with
	multiorgan failure

	- Patients suspected to have a reaction to study drugs	
Number of total cases	58 patients	
Intervention	25 patients received medical treatment with prophylactic antibiotics (Imipenem 1g every 8 hours; therapy duration was not stated)	
Control	33 patients received medical treatment without prophylactic antibiotics	
Outcomes	<ul> <li>Mortality</li> <li>ICU or hospital stay</li> <li>Adverse event</li> </ul>	
Follow-up duration	Not stated	
Bias	Authors' judgement         Reason for judgement	
Random sequence generation	Unclear risk	Not available
Allocation concealment	Unclear risk Not available	
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available
Incomplete outcome data	High risk	There were post-randomization dropouts (32 cases)
Selective reporting	High risk	Adverse events were not reported
Other bias	Low risk	No other risk of bias

Hejtmankova S, Cech P, Hoskovec D, Kostka R, Leffler J, Kasalicky M, et al. Antibiotic prophylaxis in severe acute pancreatitis: Randomized multicenter prospective study with meropenem. Gastroenterology. 2003:124(4):A85. [CrossRef]

2003,124(4).A03. [CI055KCI]		
Methods	Randomized controlled trial Multicenter study <i>Allocation Method:</i> Not stated <i>Blinding:</i> Open	
Including criteria	Patients with severe acute pancreatitis	
Excluding criteria	<ul> <li>&lt; 18 years of age</li> <li>More than 48 hours from the onset of symptoms</li> <li>Pancreatitis following surgery or endoscopic retrograde cholangiopancreatography (ERCP)</li> <li>Infectious complications</li> <li>Already receiving antibiotics for the previous two weeks</li> </ul>	
Number of total cases	41	
Intervention	21 participants received medical treatment with prophylactic antibiotics (Meropenem 0.5 g every 8 hours for 10 days)	
Control	20 participants received medical treatment without antibiotics	
Outcomes	<ul><li>Mortality</li><li>Surgery</li><li>Peripancreatic infection stay</li></ul>	
Follow-up duration	???	
Bias	Authors' judgement	Reason for judgement
Random sequence generation	Unclear risk	Not available
Allocation concealment	Unclear risk	Not available
Blinding of participants and personnel	Unclear risk	Not available
Blinding of outcome	Unclear risk	Not available

Incomplete outcome data	Unclear risk	Not available
Selective reporting	Low risk	Outcome results, including adverse events, were reported
Other bias	Low risk	No other risk of bias

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Manes G, Uomo I, Menchise A, R pancreatitis: a controlled randomiz	abitti PG, Ferrara EC, Uomo G. Timin ed study with meropenem. Am J Gast	ng of antibiotic prophylaxis in acute troenterol. 2006;101(6):1348-53.	
[CrossRef]			
	Randomized controlled trial		
Methods	Multicenter study		
	Allocation method: Computer-gen	erated list	
	Blinding: Open		
Including oritoria	- Patients older than 18 years	- Patients older than 18 years	
Including criteria	- Diagnosis of AP, admission within 48 hours of onset of symptoms		
	- Referred patients		
Excluding criteria	- Immunocompromised patients		
Encluding criteria	- Patients with underlying chronic	pancreatitis	
Number of total cases	59		
Intervention	30 participants received medical therapy with prophylactic antibiotic (500 g every 8 hours for at least 14 days)		
Control	29 participants received medical therapy without prophylactic antibiotic		
Outcomes	<ul> <li>Mortality</li> <li>Surgery</li> <li>Peripancreatic infection</li> <li>Non-pancreatic infection</li> <li>Multiorgan failure</li> <li>Systemic complications (acute renal failure, acute respiratory distress syndrome, pleuropericardial effusion, diabetic ketoacidosis, hypocalcemia, cardiac arrhythmia, gastrointestinal bleeding)</li> <li>Local complications (portal/mesenteric, thrombosis, pancreatic fistula, pseudocysts, pancreatic ascites)</li> <li>Hospitalization days</li> </ul>		
	<ul> <li>Local complications (portal/mese pseudocysts, pancreatic ascites)</li> <li>Hospitalization days</li> </ul>	nteric, thrombosis, pancreatic fistula,	
Follow-up duration	<ul> <li>Local complications (portal/mese pseudocysts, pancreatic ascites)</li> <li>-Hospitalization days</li> <li>Not Stated</li> </ul>	nteric, thrombosis, pancreatic fistula,	
Follow-up duration Bias	<ul> <li>Local complications (portal/mese pseudocysts, pancreatic ascites)</li> <li>-Hospitalization days</li> <li>Not Stated</li> <li>Authors' judgement</li> </ul>	Reason for judgement	
Follow-up duration Bias Random sequence generation	<ul> <li>Local complications (portal/mese pseudocysts, pancreatic ascites)</li> <li>-Hospitalization days</li> <li>Not Stated</li> <li>Authors' judgement</li> <li>Low risk</li> </ul>	Reason for judgement         Computer generated list	
Follow-up duration Bias Random sequence generation Allocation concealment	nypocarcenna, cardiac armythinna,         - Local complications (portal/mese pseudocysts, pancreatic ascites)         -Hospitalization days         Not Stated         Authors' judgement         Low risk         Unclear risk	Reason for judgement         Computer generated list         Not available	
Follow-up duration Bias Random sequence generation Allocation concealment Blinding of participants and personnel	nypocarcenna, cardiac armythinia,         - Local complications (portal/mese pseudocysts, pancreatic ascites)         -Hospitalization days         Not Stated         Authors' judgement         Low risk         Unclear risk         Unclear risk	Reason for judgement         Computer generated list         Not available	
Follow-up duration Bias Random sequence generation Allocation concealment Blinding of participants and personnel Blinding of outcome	nypocarcenna, cardiac armythinna,         - Local complications (portal/mese pseudocysts, pancreatic ascites)         -Hospitalization days         Not Stated         Authors' judgement         Low risk         Unclear risk         Unclear risk         Unclear risk	Reason for judgement         Computer generated list         Not available         Not available         Not available	
Follow-up durationBiasRandom sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcomeIncomplete outcome data	hypocacenna, cardiac armythina,         - Local complications (portal/mese pseudocysts, pancreatic ascites)         -Hospitalization days         Not Stated         Authors' judgement         Low risk         Unclear risk         Unclear risk         Low risk         Low risk	Reason for judgement         Computer generated list         Not available         Not available         There were no post-randomization dropouts	
Follow-up durationBiasRandom sequence generationAllocation concealmentBlinding of participants and personnelBlinding of outcomeIncomplete outcome dataSelective reporting	nypocarcenna, cardiac armythinia,         - Local complications (portal/mese pseudocysts, pancreatic ascites)         -Hospitalization days         Not Stated         Authors' judgement         Low risk         Unclear risk         Unclear risk         Low risk         High risk	Reason for judgement         Computer generated list         Not available         Not available         There were no post-randomization dropouts         Adverse events were not reported.	

Røkke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LØ, et al. Early treatment of severe pancreatitis		
with imipenem: a prospective randomized clinical trial. Scand J Gastroenterol. 2007;42(6):771-6. [CrossRef]		
Mathada	Randomized controlled trial	
Methods Multicenter study		

	Allocation method: Computer-based randomization without		
	stratification		
	Blinding: Open		
<b>.</b>	- Patients with severe acute pancreatitis		
Including criteria	- Necrosis on CT and CRP>120 firs	st 24 hours or CRP>200 first 48 hours	
	- Duration of symptoms of less than	172 hours and	
	- Age below 18 years - Ongoing antibiotic treatment - Previous episodes of acute pancreatitis		
Excluding criteria	- Post-ERCP pancreatitis		
_	- Concomitant bacterial infection su	ch as cholangitis or cholecystitis	
	- Allergy to imipenem		
	- Pregnancy		
Number of total cases	73		
Intervention	36 patients received early antibiotic	treatment with imipenem (0.5 g,	
Control	27 notion to modify thereas	wwithout antibiotics	
	37 patients received medical therap	y without antibiotics	
	- Mortality		
	- Surgery		
Outcomes	- Non-nancreatic infection		
	- Organ failure		
	- ICU and hospital stay		
	- Adverse events		
Follow-up duration	1 month		
Bias	Authors' judgement	Reason for judgement	
Random sequence generation	Low risk	Computer-based randomization	
Allocation concealment	Unclear risk	Not available	
Blinding of participants and personnel	High risk	Unblinded	
Blinding of outcome	High risk	Unblinded	
Incomplete outcome data	Low risk	There were no post-randomization dropouts	
Selective reporting	High risk	Adverse events were not reported.	
Other bias	Low risk	No other risk of bias	

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 [CrossRef]

	Randomized controlled trial
Methods	Multicenter study
	Allocation method: Computer-based randomization
	Blinding: Double-blind
	- Patients with 30% necrosis of the pancreas confirmed by contrast-
Including criteria	enhanced CT or who had non-contrast scans with extensive or multiple
	peripancreatic fluid collections of either CRP > 120 mg/L or multiple
	organ dysfunction (MOD)>2
	- Patients within 120 hours of the onset of symptoms
	- Patients diagnosed with a concurrent pancreatic or peripancreatic
	infection
Excluding criteria	- Patients received an investigational drug 30 days before enrollment
	- Antimicrobial therapy for 48 hours before randomization
	- Patients who had an allergy to beta-lactam antimicrobial agents

	<ul> <li>Patients who received or were likely to require probenecid</li> <li>Progressing underlying disease, neutropenia, or cirrhosis</li> <li>Pregnant or lactating females</li> </ul>		
Number of total cases	100		
Intervention	50 participants received medical treatment with meropenem (1g every 8 hours, for 2-21 days)		
Control	50 received medical treatment without	50 received medical treatment without antibiotic	
Outcomes	<ul> <li>Mortality</li> <li>Surgery</li> <li>Peripancreatic infection.</li> <li>Non-pancreatic infection</li> <li>Adverse events</li> </ul>		
Follow-up duration	42 days		
Bias	Authors' judgement	Reason for judgement	
Random sequence generation	Low risk	Computer-based randomization	
Allocation concealment	Low risk	Random numbers	
Blinding of participants and personnel	Low risk	Double-blind	
Blinding of outcome	Low risk	Double-blind	
Incomplete outcome data	Low risk	There were no post- randomization dropouts	
Selective reporting	Low risk	Outcomes including adverse events were reported	
Other bias	Low risk	No other risk of bias	

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. [CrossRef]

	Randomized controlled trial
Methods	Multicenter study
	Allocation method: Computer-derived random number sequence
	Blinding: Open
Including outonic	- Patients older than 18 years
	- Patients with 30% or more necrosis of the pancreas, as proven by
Including criteria	contrast-enhanced computerized tomography (CECT),
	- Patients within 72 hours after the onset of the symptoms
	-Concurrent sepsis or (peri)pancreatic infection caused by a second
	disease
	-Direct transfer to the ICU due to multiple organ failure
	-Recurrent or ERCP, or traumatic or operative pancreatitis
Excluding criteria	-Pregnancy, malignancy or immunodeficiency
	-History of allergy to imipenem-cilastatin
	-History of antibiotic administration within 48 hours before enrollment
	-Possible death within 48 hours after enrollment.
Number of total cases	56
Intervention	29 participants received medical therapy with the antibiotic Imipenem
	(0.5 g every 8 hours, for 7-14 days)
Control	27 participants received medical therapy without antibiotic
	- Mortality
	- Surgery
Outcomes	- Peri-pancreatic infection
	- Non-pancreatic infection
	- Adverse events

Follow-up duration	Not stated			
Bias	Authors' judgement	Reason for judgement		
Random sequence generation	Low risk	Computer-derived random number sequence		
Allocation concealment	Unclear risk	Not available		
Blinding of participants and personnel	Unclear risk	Not available		
Blinding of outcome	Unclear risk	No available		
Incomplete outcome data	High risk	There were post-randomization dropouts		
Selective reporting	Low risk	Outcomes, including adverse events, were reported		
Other bias	Low risk	No other risk of bias		

Poropat G, Goričanec K, Lacković A, Kresović A, Lončarić A, Marušić M. Systematic review with trial sequential analysis of prophylactic antibiotics for acute pancreatitis. antibiotics (Basel). 2022;11(9):1191. [CrossRef]

	Randomized controlled trial								
	Multicenter study								
Methods	Allocation method: Computer-gene	erated random							
	number sequence								
	Blinding: Double-blind								
	- Patients older than 18 years								
Including criteria	- First episode of AP and a calculated acute physiology and chronic								
	near evaluation if (APACHE II) score of $\geq 8$ , regardless of ethology								
	- Patients presented at the hospital within 72 hours of symptoms onset.								
	- Active and documented infection	at admission							
	- Concomitant antibiotic treatment	or antibiotic treatment present within							
	72 hours before enrollment								
	- AP diagnosed at surgery								
Excluding criteria	- Active malignancy								
	- Known immune deficiency								
	- Chronic pancreatitis								
	- Pregnant and breastfeeding women								
	- Patients unwilling to participate								
Number of total cases	98								
Intervention	Patients received prophylactic antib	viotics (500g, every 8 hours)							
Control	Patients received placebo								
	- Mortality								
	- Surgery								
Outcomes	- Peripancreatic infection								
	- Non-pancreatic infection								
	- Serious adverse events								
Follow-up duration	Not Stated								
Bias	Authors' judgement	Reason for judgement							
Random sequence generation	Low risk Computer-based randomization								
Allocation concealment	Low risk	Random numbers							
Blinding of participants and personnel	Low risk	Double-blind							

Blinding of outcome	Low risk	Double-blind		
Incomplete outcome data	Low risk	There were no post-randomization dropouts		
Selective reporting	Low risk	Outcomes, including adverse events, were reported.		
Other bias	Low risk	No other risk of bias		

# **III. RESULTS OF THE META-ANALYSIS**

PICO 1: Does the use of prophylactic carbapenem reduce the risk of mortality in acute

#### pancreatitis cases?

P: Acute pancreatitis cases

I: Carbapenem

**C:** Placebo or standard therapy

**O:** In-hospital mortality

Figure 1a. Forest plot for mortality in all studies

	Carbape	enem	Conti	rol		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEF			
Dellinger et al., 2007	10	50	9	50	21.6%	1.11 [0.49, 2.50]	_ <b>_</b> _				
Manes et al.2006	3	30	3	29	7.3%	0.97 [0.21, 4.41]					
Nordback et al.,2001	2	25	5	33	10.3%	0.53 [0.11, 2.50]		•••			
Pederzoli et al.,1993	3	41	4	33	10.6%	0.60 [0.15, 2.51]		• •••			
Poropat et al.2019	7	49	8	49	19.2%	0.88 [0.34, 2.23]		<b></b>			
Røkke et al.2007	3	36	4	37	9.4%	0.77 [0.19, 3.20]					
Spicak J et al. ,2003	4	20	5	21	11.7%	0.84 [0.26, 2.69]		•••			
Xue et al.,2009	3	29	4	27	9.9%	0.70 [0.17, 2.84]		• •••			
Total (95% CI)		280		279	100.0%	0.84 [0.55, 1.27]	•				
Total events	35		42								
Heterogeneity: $Chi^2 = 1$	.13, df =	7 (P = 0)	).99); I <sup>2</sup> =	= 0%							
Test for overall effect: Z	L = 0.84 (I	P = 0.40	0)				Crabapenem Control	00			
Risk of bias legend         (A) Allocation concealment (selection bias)         (B) Blinding of participants and personnel (performance bias)         (C) Blinding of outcome assessment (detection bias)         (D) Incomplete outcome data (attrition bias)         (E) Selective reporting (reporting bias)         (F) Other bias											

Figure 1b. Forest plot for mortality in studies only included acute necrotizing pancreatitis

	Carbape	enem	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG
5.1.1 Mortality								
Dellinger et al., 2007	10	50	9	50	34.3%	1.11 [0.49, 2.50]		
Nordback et al.,2001	2	25	5	33	16.4%	0.53 [0.11, 2.50]		<b>e e</b> <del>e</del>
Røkke et al.2007	3	36	4	37	15.0%	0.77 [0.19, 3.20]		• •••••
Spicak J et al. ,2003	4	20	5	21	18.6%	0.84 [0.26, 2.69]		<b>+ +</b>
Xue et al.,2009	3	29	4	27	15.8%	0.70 [0.17, 2.84]		
Subtotal (95% CI)		160		168	100.0%	0.85 [0.51, 1.43]	•	
Total events	22		27					
Heterogeneity: $Chi^2 = 0$	.87, df =	4 (P = 0)	).93); I <sup>2</sup> :	= 0%				
Test for overall effect: Z	2 = 0.62 (I	P = 0.54	4)					
Total (95% CI)		160		168	100.0%	0.85 [0.51, 1.43]	•	
Total events	22		27					
Heterogeneity: $Chi^2 = 0$	.87, df =	4 (P = 0)	).93); I <sup>2</sup> :	= 0%				4
Test for overall effect: Z	2 = 0.62 (F	P = 0.54	4)				Carbapenem Control	,
Test for subgroup differ	rences: No	t applic	able				carbapenent control	
Risk of bias legend								
(A) Random sequence g	generation	(selection	on bias)					
(B) Allocation concealme	ent (selecti	on bias)	)					
(C) Blinding of participa	nts and pe	ersonnel	(perforn	nance b	ias)			
(D) Blinding of outcome	assessme	nt (dete	ction bia	s)				
(E) Incomplete outcome	data (attri	ition bia	s)					
(F) Selective reporting (r	reporting b	oias)						
( <b>G</b> ) Other bias								

Figure 1c. Forest plot for mortality in studies compared imipenem and placebo/standard therapy

	Imiper	nem	Cont	rol		Risk Ratio	Risk Ratio	<b>Risk of Bias</b>
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEF
Nordback et al.,2001	2	25	5	33	17.4%	0.53 [0.11, 2.50]		•••
Pederzoli et al.,1993	3	41	4	33	17.9%	0.60 [0.15, 2.51]		• • • •
Poropat et al.2019	7	49	8	49	32.2%	0.88 [0.34, 2.23]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Røkke et al.2007	3	36	4	37	15.9%	0.77 [0.19, 3.20]		
Xue et al.,2009	3	29	4	27	16.7%	0.70 [0.17, 2.84]		• •••
Total (95% CI)		180		179	100.0%	0.72 [0.41, 1.27]	•	
Total events	18		25					
Heterogeneity: $Chi^2 = 0$	.39, df =	4 (P =	0.98); I <sup>2</sup>	= 0%				
Test for overall effect: Z	= 1.13 (	P = 0.2	26)				Imipenem Control	
Risk of bias legend								
(A) Allocation concealme	ent (select	tion bia	s)					
(B) Blinding of participar	nts and p	ersonne	el (perfor	mance	bias)			
(C) Blinding of outcome	assessme	ent (det	ection bia	as)				
(D) Incomplete outcome	data (att	rition b	ias)					
(E) Selective reporting (r	eporting	bias)						
(F) Other bias	-							

Figure 1d. Forest plot for mortality in high-quality studies



Figure 1f. Funnel plot for mortality studies



# **PICO 2:** Does the use of prophylactic carbapenem reduce the risk of surgical intervention in acute pancreatitis cases?

- P: Acute pancreatitis cases
- I: Carbapenem
- C: Placebo or standard therapy
- **O:** Surgical intervention

Figure 2a. Forest plot for surgical intervention in all studies.



Figure 2b. Forest plot for surgical intervention in studies only included acute necrotizing pancreatitis.

	Carbape	enem	Cont	ol		Risk Ratio	Risk Ratio	Risk of Bias		
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG		
Dellinger et al., 2007	13	50	10	50	31.8%	1.30 [0.63, 2.68]		9999999		
Nordback et al.,2001	2	25	5	33	13.7%	0.53 [0.11, 2.50]		•••		
Røkke et al.2007	3	36	3	37	9.4%	1.03 [0.22, 4.76]	<b>+</b>	$\bullet \bullet $		
Spicak J et al. ,2003	4	20	5	21	15.5%	0.84 [0.26, 2.69]		•••		
Xue et al.,2009	8	29	9	27	29.6%	0.83 [0.37, 1.83]		• •••		
Total (95% CI)		160		168	100.0%	0.96 [0.61, 1.49]	•			
Total events	30		32							
Heterogeneity: $Chi^2 = 1$	.43, df =	4 (P = 0)	).84); I <sup>2</sup> =	= 0%						
Test for overall effect: Z	= 0.19 (F	P = 0.85	5)				Carbapenem Control			
Heterogeneity: Chi <sup>2</sup> = 1.43, df = 4 (P = 0.84); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.19 (P = 0.85)         Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)         (D) Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias										

Figure 2c. Forest plot for surgical intervention in studies compared imipenem and placebo/standard therapy.

	Imiper	nem	Conti	ol		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG			
Nordback et al.,2001	2	25	5	33	15.0%	0.53 [0.11, 2.50]		• • •			
Pederzoli et al.,1993	12	41	11	33	42.4%	0.88 [0.45, 1.73]		• • • •			
Røkke et al.2007	3	36	3	37	10.3%	1.03 [0.22, 4.76]		• • • • • • •			
Xue et al.,2009	8	29	9	27	32.4%	0.83 [0.37, 1.83]					
Total (95% CI)		131		130	100.0%	0.82 [0.52, 1.32]	•				
Total events	25		28			·····					
Heterogeneity: $Chi^2 = 0.43$ , $df = 3$ (P = 0.93); $l^2 = 0\%$											
Test for overall effect: Z	. = 0.81	P = 0.4	12)				Imipenem Control				
Risk of bias legend											
(A) Random sequence g	eneratior	n (select	tion bias)								
(B) Allocation concealme	ent (select	ion bia	s)								
(C) Blinding of participa	nts and p	ersonne	el (perfor	mance	bias)						
(D) Blinding of outcome assessment (detection bias)											
(E) Incomplete outcome data (attrition bias)											
(F) Selective reporting (reporting bias)											
( <b>G</b> ) Other bias											







- **P:** Acute pancreatitis cases
- I: Carbapenem
- **C:** Placebo or standard therapy
- **O:** Peripancreatic infection

Figure 3a. Forest plot for peripancreatic infection in all studies.

	Carbape	enem	Plase	bo		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEF			
Dellinger et al., 2007	9	50	6	50	10.5%	1.50 [0.58, 3.90]		$\mathbf{+}\mathbf{+}\mathbf{+}\mathbf{+}\mathbf{+}\mathbf{+}\mathbf{+}$			
Manes et al.2006	4	30	9	29	16.0%	0.43 [0.15, 1.24]		😛 😛 😑			
Pederzoli et al.,1993	5	41	10	33	19.4%	0.40 [0.15, 1.06]		$\mathbf{e}  \mathbf{e}  $			
Poropat et al.2019	3	49	2	49	3.5%	1.50 [0.26, 8.59]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet$			
Røkke et al.2007	3	36	7	37	12.1%	0.44 [0.12, 1.57]					
Spicak J et al. ,2003	5	20	12	21	20.5%	0.44 [0.19, 1.02]		<b>+ +</b>			
Xue et al.,2009	8	29	10	27	18.1%	0.74 [0.35, 1.61]		• • • •			
Total (95% CI)		255		246	100.0%	0.63 [0.44, 0.91]	$\bullet$				
Total events	37		56								
Heterogeneity: $Chi^2 = 6$	5.64, df =	6 (P = 0)	0.36); I <sup>2</sup>	= 10%				100			
Test for overall effect: 2	Z = 2.44 (	P = 0.0	1)				Carbapenem Plasebo	100			
Risk of bias legend         (A) Allocation concealment (selection bias)         (B) Blinding of participants and personnel (performance bias)         (C) Blinding of outcome assessment (detection bias)         (D) Incomplete outcome data (attrition bias)         (E) Selective reporting (reporting bias)											
(F) Other bias	reporting i	JIA3)									

Figure 3b. Forest plot for peripancreatic infections in studies only included acute necrotizing pancreatitis.

	Carbape	enem	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG
Dellinger et al., 2007	9	50	6	50	17.2%	1.50 [0.58, 3.90]		
Røkke et al.2007	3	36	7	37	19.7%	0.44 [0.12, 1.57]		• •••••
Spicak J et al. ,2003	5	20	12	21	33.5%	0.44 [0.19, 1.02]		<del>••••</del>
Xue et al.,2009	8	29	10	27	29.6%	0.74 [0.35, 1.61]		• •••
Total (95% CI)		135		135	100.0%	0.71 [0.46, 1.11]	•	
Total events	25		35					
Heterogeneity: Chi <sup>2</sup> = 4	1.17, df =	3 (P =	0.24); I <sup>2</sup>	= 28%				4
Test for overall effect: 2	Z = 1.50 (	P = 0.1	3)				Carbapenem Control	)
Risk of bias legend								
(A) Random sequence	generation	(selecti	on bias)					
(B) Allocation concealme	ent (select	ion bias	)					
(C) Blinding of participa	ints and p	ersonne	l (perforn	nance b	oias)			
(D) Blinding of outcome	assessme	ent (dete	ction bia	s)				
(E) Incomplete outcome	data (attr	ition bia	s)					
(F) Selective reporting (	reporting l	oias)						
( <b>G</b> ) Other bias								

**Figure 3c.** Forest plot for peripancreatic infections in studies compared imipenem and placebo/standard therapy.

	Imipen	em	Contr	ol		Risk Ratio		Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	ABCDEF
Pederzoli et al.,1993	5	41	10	33	36.5%	0.40 [0.15, 1.06]			• •••
Poropat et al.2019	3	49	2	49	6.6%	1.50 [0.26, 8.59]			
Røkke et al.2007	3	36	7	37	22.8%	0.44 [0.12, 1.57]			
Xue et al.,2009	8	29	10	27	34.1%	0.74 [0.35, 1.61]			• •••
Total (95% CI)		155		146	100.0%	0.60 [0.36, 1.00]		•	
Total events	19		29						
Heterogeneity: Chi <sup>2</sup> = 2	.24, df = 3	3 (P = 0	.52); l² =	0%			L 0.01		100
Test for overall effect: Z	:= 1.95 (F	P = 0.05	j)				0.01	Imipenem Control	100
Risk of bias legend									
(A) Allocation conceal	nent (sele	ection b	ias)						
(D) Direction of a solicity of	and a second sec				- hissa)				

(B) Blinding of participants and personnel (performance bias)

(C) Blinding of outcome assessment (detection bias)

(D) Incomplete outcome data (attrition bias) (E) Selective reporting (reporting bias)

(F) Other bias

Figure 3d. Forest plot for peripancreatic infections in high-quality studies.

	Carbape	enem	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG			
Dellinger et al., 2007	9	50	6	50	75.0%	1.50 [0.58, 3.90]		<b></b>			
Poropat et al.2019	3	49	2	49	25.0%	1.50 [0.26, 8.59]		<b></b>			
Total (95% CI)		99		99	100.0%	1.50 [0.65, 3.47]	•				
Total events	12		8								
Heterogeneity: $Chi^2 = 0$	0.00, df =	1 (P = 1)	1.00); I <sup>2</sup>	= 0%				100			
Test for overall effect: 2	Z = 0.95 (	P = 0.3	4)				Carbapenem Control	100			
Risk of bias legend											
(A) Random sequence	generation	(selecti	on bias)								
(B) Allocation concealm	ent (select	ion bias	)								
(C) Blinding of participa	ints and p	ersonne	l (perforr	nance b	oias)						
(D) Blinding of outcome	(D) Blinding of outcome assessment (detection bias)										
(E) Incomplete outcome data (attrition bias)											
(F) Selective reporting (	reporting l	oias)									
( <b>G</b> ) Other bias											

Figure 3e. Funnel plot for peripancreatic infection studies.



#### PICO 4: Does the use of prophylactic carbapenem reduce the risk of non-pancreatic

#### infection in acute pancreatitis cases?

**P:** Acute pancreatitis cases

- I: Carbapenem
- **C:** Placebo or standard therapy
- **O:** Non-pancreatic infection

Figure 4a. Forest plot for non-pancreatic infection in all studies.

	Carbapenem Contro		ol	Risk Ratio		Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG		
Dellinger et al., 2007	16	50	24	50	24.7%	0.67 [0.41, 1.10]		<b>444444</b>		
Manes et al.2006	5	30	13	29	13.6%	0.37 [0.15, 0.91]		• • • •		
Pederzoli et al.,1993	6	41	16	33	18.2%	0.30 [0.13, 0.68]		• •••		
Poropat et al.2019	12	49	15	49	15.4%	0.80 [0.42, 1.53]		<b>444444</b>		
Røkke et al.2007	3	36	12	37	12.2%	0.26 [0.08, 0.84]				
Xue et al.,2009	18	29	15	27	16.0%	1.12 [0.72, 1.74]	+	• •••		
Total (95% CI)		235		225	100.0%	0.60 [0.46, 0.78]	•			
Total events	60		95							
Heterogeneity: $Chi^2 = 1$	Heterogeneity: $Chi^2 = 14.27$ , $df = 5$ (P = 0.01); $l^2 = 65\%$									
Test for overall effect: Z	2 = 3.80 (	P = 0.0	001)				Carbapenem Control			
Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)         (D) Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias										

Figure 4b. Forest plot for non-pancreatic infection in studies only included acute necrotizing

pancreatitis.

	Carbapenem Control		Risk Ratio		Risk Ratio	Risk of Bias			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG	
Dellinger et al., 2007	16	50	24	50	46.7%	0.67 [0.41, 1.10]		<b>444444</b>	
Røkke et al.2007	3	36	12	37	23.0%	0.26 [0.08, 0.84]		• • • • • • •	
Xue et al.,2009	18	29	15	27	30.2%	1.12 [0.72, 1.74]	<b>+</b>	• •••	
Total (95% CI)		115		114	100.0%	0.71 [0.51, 0.98]	•		
Total events	37		51						
Heterogeneity: $Chi^2 = 6.99$ , $df = 2$ (P = 0.03); $l^2 = 71\%$									
Test for overall effect: Z = 2.08 (P = 0.04)									
Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)         (D) Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias									

**Figure 4c.** Forest plot for non-pancreatic infection in studies compared imipenem and placebo/standard therapy.

	Imipenem Contro		ol Risk Ratio			Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG
Pederzoli et al.,1993	6	41	16	33	29.5%	0.30 [0.13, 0.68]		• •••
Poropat et al.2019	12	49	15	49	25.0%	0.80 [0.42, 1.53]		<b></b>
Røkke et al.2007	3	36	12	37	19.7%	0.26 [0.08, 0.84]		
Xue et al.,2009	18	29	15	27	25.8%	1.12 [0.72, 1.74]	+	• •••
Total (95% CI)		155		146	100.0%	0.63 [0.45, 0.87]	•	
Total events	39		58					
Heterogeneity: $Chi^2 = 1$	2.36, df	= 3 (P)	= 0.006	; $I^2 = 7$	6%			
Test for overall effect: $Z = 2.79$ (P = 0.005)							Imipenem Control	
Risk of bias legend         (A) Random sequence generation (selection bias)         (B) Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)         (D) Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)         (F) Selective reporting (reporting bias)         (G) Other bias								

Figure 4d. Forest plot for non-pancreatic infections in high-quality studies.

	Carbapenem Con		Cont	Control		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M-H, Fixed, 95% CI	ABCDEFG	
Dellinger et al., 2007	16	50	24	50	61.5%	0.67 [0.41, 1.10]			
Poropat et al.2019	12	49	15	49	38.5%	0.80 [0.42, 1.53]		<b></b>	
Total (95% CI)		99		99	100.0%	0.72 [0.48, 1.07]	•		
Total events	28		39						
Heterogeneity: $Chi^2 = 0$	.19, df =	1 (P = 0)	0.66); I <sup>2</sup>	= 0%				100	
Test for overall effect: 2	Z = 1.65 (	P = 0.1	0)				Carbapenem Control	100	
<u>Risk of bias legend</u>									
(A) Random sequence	generation	(selecti	on bias)						
(B) Allocation concealm	ent (select	ion bias	)						
(C) Blinding of participants and personnel (performance bias)									
(D) Blinding of outcome assessment (detection bias)									
(E) Incomplete outcome data (attrition bias)									
(F) Selective reporting (reporting bias)									
(G) Other bias									

Figure 4e. Funnel plot for non-pancreatic infection studies.



 Table 1. Summary of findings.

			Absolute effect		
Results	Patients (studies)	Relative effect (95% CI)	The risk with placebo or standard therapy	The expected difference in risk with carbapenem therapy (95% CI)	
Mortality	559 (8)	0.85 (0.55-1.27)	150/1000 cases	26 fewer/1000 cases (-83 - +32)	
Surgical intervention	420 (6)	0.81 (0.57-1.17)	234/1000 cases	35 fewer/1000 cases (-114 - +43)	
Peripancreatic infection	501 (7)	0.60 (0.41-0.87)	228/1000 cases	90 fewer/1000 cases (-15823)	
Non-pancreatic infection	460 (6)	0.60 (0.46-0.78)	422/1000 cases	167 fewer/1000 cases (-25282)	