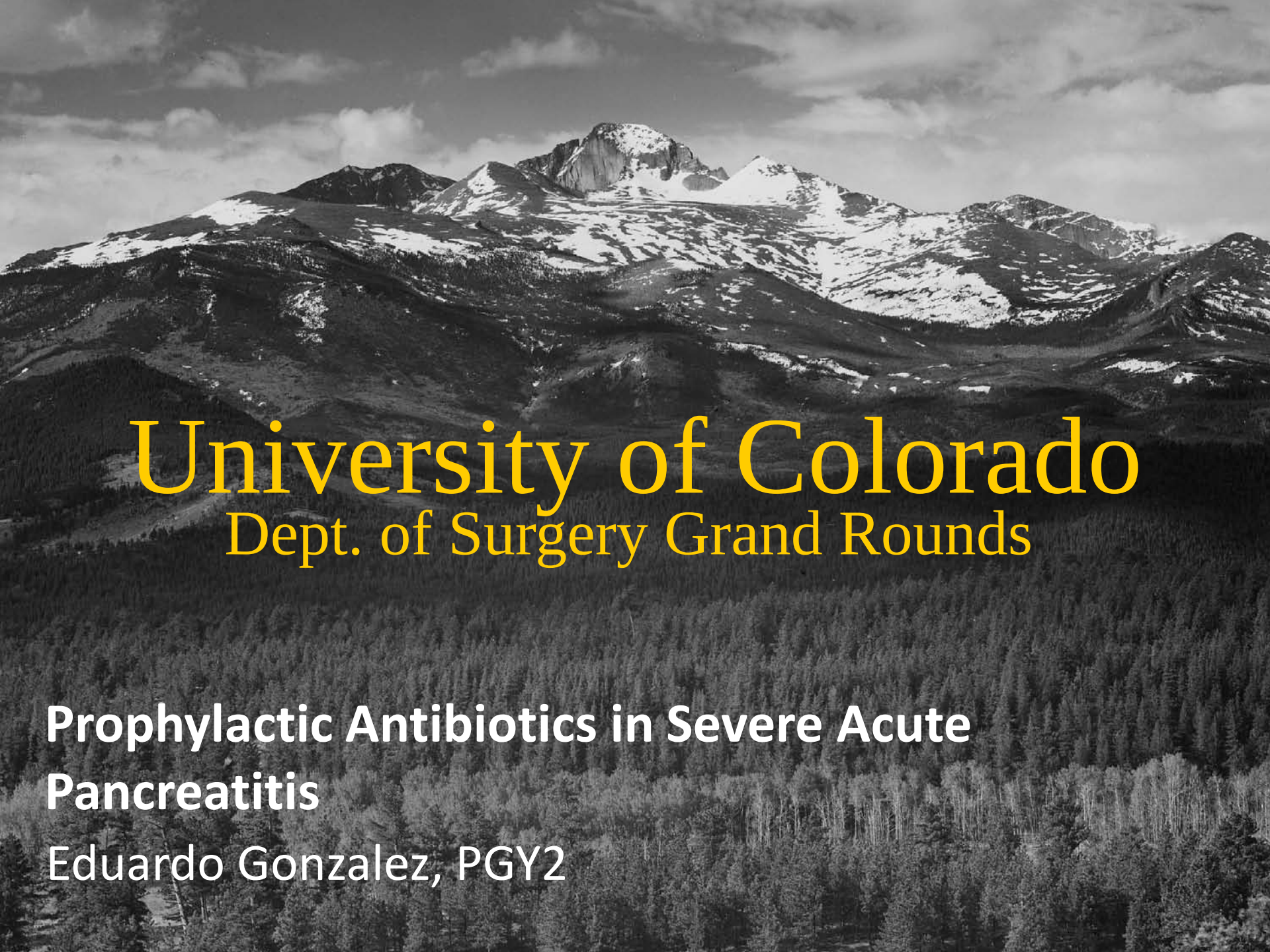
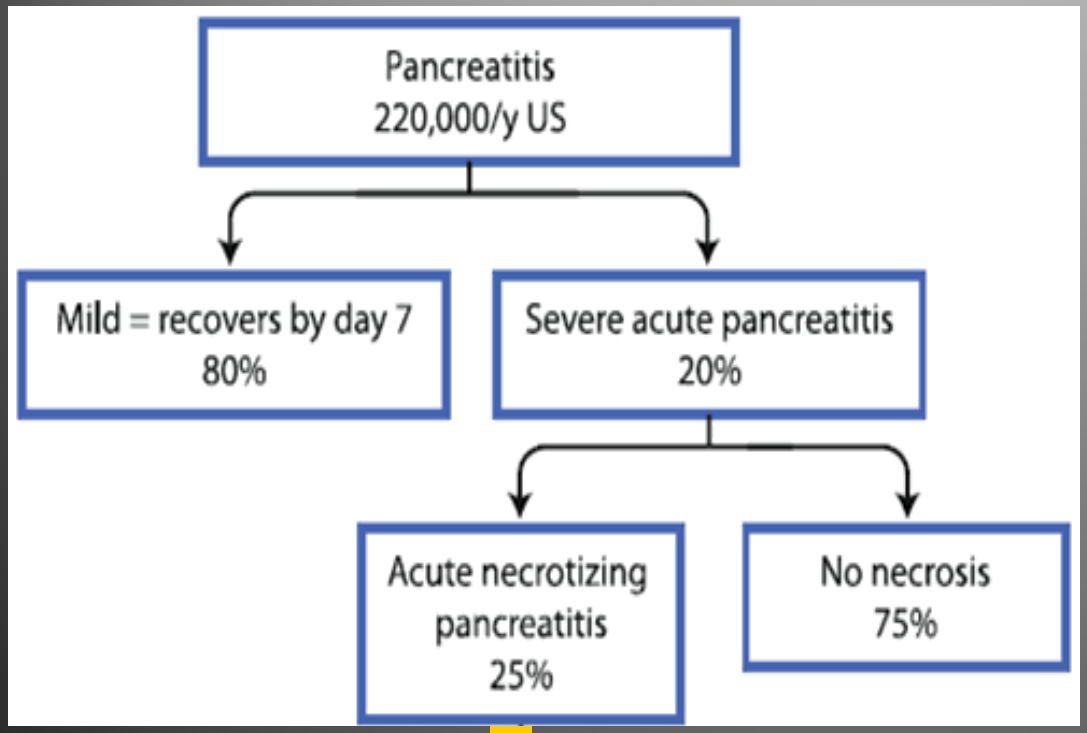


University of Colorado
Dept. of Surgery Grand Rounds

Prophylactic Antibiotics in Severe Acute Pancreatitis

Eduardo Gonzalez, PGY2

Mortality from Acute Pancreatitis



SAP [1]

- **>30% necrosis**
- **SBP<90, sCr>2.0, PaO2<60**
- **>500ml GI blood loss**
- **abscess, or pseudocyst.**

30% mortality[2]

2–3 weeks after presentation

Infection is most common cause of death in necrotizing pancreatitis (NP)

1.Bradley et al. *Ann Chir 1993;*47:537–541 **2.**Widdison et al. *Br J Surg 1993;*80:148–154.

Infection in Necrotizing Pancreatitis

Bacterial contamination present, in ANP surgical specimens with no abscess[1]

→ 24% at 7d from presentation
→ 74% at >14d from presentation

Infection in ANP correlates with degree of necrosis

E. coli, Klebsiella, Enterococcus, Pseudomonas
75% specimens monomicrobial

Approaches to decrease infection in ANP:

→ enteral feeding
→ CT-guided aspiration
→ antibiotics
→ necrosectomy

Banks et al, *Am J Gastroenterol*. 2006;101(10):2379

Horvath et al. *Surg Endosc*. 2001;15(10):1221.

Berger et al, *Gastroenterology*. 1986;91(2):433

Jacobson et al. Clin Gastroenterol Hepatol. 2007;5(8):946.

Role of Antibiotics in SAP

RCT's 1970s (**Craig** et al, Ann Intern Med. 1975; **Howes** et al, J Surg Res. 1975, **Finch** et al, Ann Surg. 1976)
mild pancreatitis, ampicillin, no significant effect on mortality.

Pederzoli P. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitiswith imipenem.
Surg Gynecol Obstet 1993

Sainio V, Early antibiotic treatment in acute necrotizing pancreatitis.
Lancet 1995

Schwarz M, Ergebnisse einer kontrollierten **Dtsch Med Wochenschr 1997**

Nordback, Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis—a single-center randomized study. **J Gastrointest Surg. 2001**

Isenmann R, Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis – a **placebo controlled, double-blind trial**.
Gastroenterology 2004

Dellinger EP, Early antibiotic treatment for severe acute necrotizing pancreatitis: **randomized, double-blind, placebo-controlled** study. **Ann Surg 2007**

Røkke O, Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. **Scand J Gastroenterol 2007**

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Villatoro E, Mulla M, Larvin M.
Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Pederzoli P, Bassi C, Vesentini S, Campedelli A.

A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitiswith imipenem.

Surg Gynecol Obstet 1993;176:480–3.

RCT
74 patients with SAP and PN proven on CT.
6 Italian centers.
Imipenem 500mg iv q8 for 14 days

33 patients - intensive medical treatment with no prophylactic antibiotics.
41 patients - intensive medical treatment with prophylactic antibiotics

Pancreatic sepsis detected by (percutaneous CT or ultrasound-guided needle aspiration and intraoperative samples). The incidence of pancreatic sepsis was much less in treated patients (12.2 vs. 30.3%, p < 0.01).

Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis – a **placebo controlled, double-blind trial**. **Gastroenterology 2004**;126:997–1004.

RCT, Randomized, placebo-controlled, double-blind trial

76 patients with severe AP and PN on CT
Ciprofloxacin 400mg iv bd, and Metronidazole 500mg iv bd, 21d treatment

41 patients - supportive treatment and prophylactic antibiotics
-15 patients with clinical deterioration, switch in antibiotics

35 patients – supportive treatment and placebo.
- 20 patients with clinical deterioration, switch in antibiotics

Study medication was given for 3–23 days (med 12 days)

Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis – a **placebo controlled, double-blind trial**. **Gastroenterology 2004**;126:997–1004.

Infected PN → CIP/MET 12% Vs. 9% Placebo (*p* 0.585).
Mortality → 5% CIP/MET Vs. 7% Placebo

Underpowered for oratlity, no reported secondary – outcomes shock, and renal insufficiency, need for resection

Dellinger EP, Tellado JM, Soto NE, Ashles SW, Barie PS, Dugernier T, et al.
Early antibiotic treatment for severe acute necrotizing pancreatitis:
randomized, double-blind, placebo-controlled study.
Ann Surg 2007;245:674–83.

RCT, placebo-controlled, double-blind.

100 patients with severe AP and proven pancreatic necrosis on CT,
Multicenter (US and Europe)
Meropenem 1g q8h, recommended 14 (range 7 – 21)

50 patients - supportive treatment and meropenem
50 – received supportive treatment and placebo.

31 patients treatment group, and 32 in placebo,
received the study drug for less than 14 days.

Dellinger EP, Tellado JM, Soto NE, Ashles SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: **randomized, double-blind, placebo-controlled** study. **Ann Surg 2007**;245:674–83.

Pancreatic or peripancreatic infections → Meropenem 18% Vs. 12% Placebo (*p=0.40*)
Mortality → Meropenem 20% Vs. 18% Placebo (*p*=0.799).
Surgical intervention → Meropenem 26% Vs. 20% (*p*=0.476).

>50% patients on each arm interrupted antibiotics or received non-study antibiotics

Table 1. Characteristics of RCTs Included in the Meta-Analysis

Author (Ref.)	Year	Setting	Total No.	Blinding	Risk of Bias	Dosage and Duration
Pederzoli (9)	1993	Multicenter	74	Single	High	Imipenem 0.5 g IV 8 hourly
Sainio (22)	1995	Single center	60	Single	High	Cefuroxime 1.5 g IV 8 hourly
Schwarz (23)	1997	Single center	26	Single	High	Ofloxacin 0.2 g b.i.d. IV & metronidazole 0.5 g b.i.d. IV
Nordback (10)	2001	Single center	39	Single	High	Imipenem 1 g IV 8 hourly
Isenmann (11)	2004	Multicenter	76	Double	Low	Ciprofloxacin 0.4 g b.i.d. IV & metronidazole 0.5 g b.i.d. IV
Dellinger (24)	2007	Multicenter	100	Double	Low	Meropenem 0.5 g IV 8 hourly
Rokke (25)	2007	Multicenter	73	No	High	Imipenem 0.5 g IV 8 hourly

IV = intravenous.

Jacobson et al. Clin Gastroenterol Hepatol. 2010;5(8):946.

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Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Mortality *p=0.07*

Analysis 1.1. Comparison 1 Antibiotics versus control, Outcome 1 Mortality.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

Comparison: 1 Antibiotics versus control

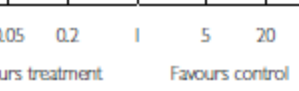
Outcome: 1 Mortality

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pederzoli 1993	3/41	4/33		15.1 %	0.60 [0.15, 2.51]
Sainio 1995	1/30	7/30		23.9 %	0.14 [0.02, 1.09]
Schwarz 1997	0/13	2/13		8.5 %	0.20 [0.01, 3.80]
Nordback 2001	2/25	5/33		14.7 %	0.53 [0.11, 2.50]
Isenmann 2004	3/41	4/35		14.7 %	0.64 [0.15, 2.67]
Dellinger 2007	6/41	5/41		17.1 %	1.20 [0.40, 3.62]
Rkke 2007	2/12	2/16		5.9 %	1.33 [0.22, 8.16]
Total (95% CI)	**203**	**201**		**100.0 %**	**0.60 [0.34, 1.05]**

Total events: 17 (Antibiotics), 29 (Control)

Heterogeneity: $Chi^2 = 4.75$, $df = 6$ ($P = 0.58$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.80$ ($P = 0.072$)



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Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Pancreatic Necrosis *p=0.42*

Analysis 1.2. Comparison 1 Antibiotics versus control, Outcome 2 Infected Pancreatic Necrosis.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

Comparison: 1 Antibiotics versus control

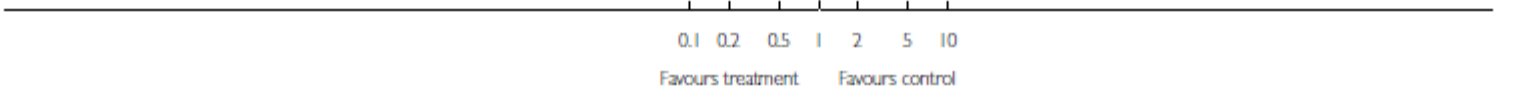
Outcome: 2 Infected Pancreatic Necrosis

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pederzoli 1993	5/41	10/33		14.2 %	0.40 [0.15, 1.06]
Sainio 1995	9/30	12/30		24.3 %	0.75 [0.37, 1.51]
Schwarz 1997	8/13	7/13		26.5 %	1.14 [0.59, 2.22]
Nordback 2001	1/25	6/33		3.6 %	0.22 [0.03, 1.71]
Isenmann 2004	7/41	5/35		12.3 %	1.20 [0.42, 3.43]
Dellinger 2007	8/41	5/41		12.8 %	1.60 [0.57, 4.48]
Rkke 2007	2/12	4/16		6.3 %	0.67 [0.15, 3.06]
Total (95% CI)	**203**	**201**		**100.0 %**	**0.85 [0.57, 1.26]**

Total events: 40 (Antibiotics), 49 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 6.94$, df = 6 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 0.80 (P = 0.42)



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Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Non-pancreatic Infections *p=0.08*

Analysis 1.3. Comparison 1 Antibiotics versus control, Outcome 3 Non-Pancreatic Infections.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

Comparison: 1 Antibiotics versus control

Outcome: 3 Non-Pancreatic Infections

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pederzoli 1993	6/41	16/33		22.4 %	0.30 [0.13, 0.68]
Nordback 2001	4/25	1/33		5.6 %	5.28 [0.63, 44.38]
Isenmann 2004	13/41	17/35		30.7 %	0.65 [0.37, 1.15]
Rkke 2007	2/12	6/16		11.0 %	0.44 [0.11, 1.83]
Dellinger 2007	13/41	17/41		30.2 %	0.76 [0.43, 1.36]
Total (95% CI)	**160**	**158**		**100.0 %**	**0.62 [0.36, 1.06]**

Total events: 38 (Antibiotics), 57 (Control)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 7.61$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 1.73 (P = 0.083)

Cochrane Database Syst Rev 2010

Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.

Fungal Infection *p=0.9*

Analysis 1.5. Comparison 1 Antibiotics versus control, Outcome 5 Fungal Infection.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

Comparison: 1 Antibiotics versus control

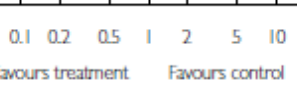
Outcome: 5 Fungal Infection

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pederzoli 1993	0/41	4/33		10.6 %	0.09 [0.01, 1.61]
Sainio 1995	1/30	0/30		8.8 %	3.00 [0.13, 70.83]
Schwarz 1997	3/13	2/13		33.9 %	1.50 [0.30, 7.55]
Nordback 2001	1/25	0/33		8.9 %	3.92 [0.17, 92.43]
Isenmann 2004	1/41	1/35		11.8 %	0.85 [0.06, 13.15]
Dellinger 2007	2/41	1/41		15.9 %	2.00 [0.19, 21.21]
Rkke 2007	0/12	2/16		10.2 %	0.26 [0.01, 4.99]
Total (95% CI)	**203**	**201**		**100.0 %**	**1.06 [0.41, 2.70]**

Total events: 8 (Antibiotics), 10 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.47$, df = 6 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.11 (P = 0.91)



Conclusions on Antibiotics for Severe Acute Pancreatitis

A mortality benefit , p=0.07, reported as a trend, cannot disregard potential clinical benefit

Benefit in non-pancreatic infection can lead to long term mortality benefit and has not been followed

Heterogeneity of the methods and patients in the previous studies make it difficult combine their results

Beta-lactams have yielded the best result vs. FQ/MET

Most antibiotic courses studied have included 14-23 days

No increase in incidence of fungal infection

Reports of increased incidence of bacterial resistance have not been assoc. with antibiotic use.