

# Us et Abus des Antibiotiques: l'exemple de la Pancréatite Aiguë

Th Dugernier  
Soins Intensifs  
Clinique St Pierre - Ottignies



Initial attack → SIRS → MSOF

Pancreatic infection → SIRS → MSOF

1 Week

2 Weeks

3 Weeks

4 Weeks

n Weeks

Antibioprophylaxis

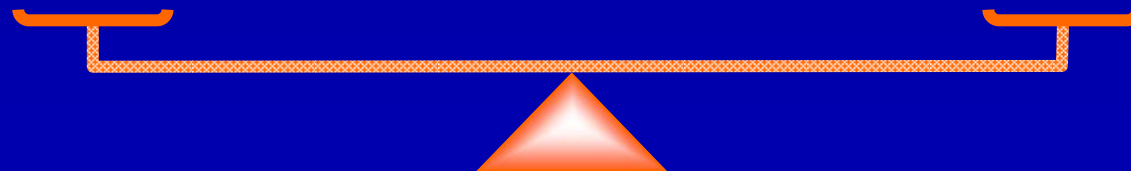
Antibiotic Therapy

Policy

“Antibiotics from admission  
to discharge”

Policy

“Zero Antibiotics”

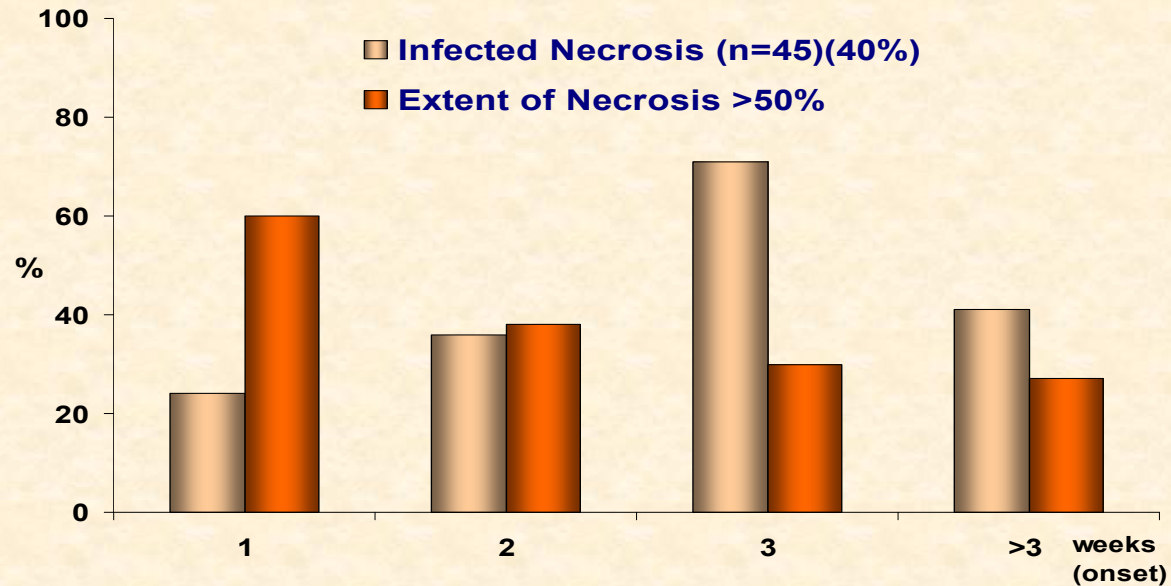


## Cause of Death in Acute Necrotizing Pancreatitis (n=106)

	Survivors (n=96)	Non-survivors (n=10)	Univariate (p)	Multivariate (p)
Extent of necrosis >50%	29	9	<0.001	0.51
BMI (kg/m <sup>2</sup> )	25 (5.2)	33.5 (7)	<0.01	0.28
Infection of necrotic pancreas	26	8	<0.01	0.016
Pre-existing co-morbidity	24	7	<0.01	0.62
Apache II score during the first week of illness	9.4 (4.2)	13.6 (4.7)	<0.05	0.8
Ranson score	3.4 (2.1)	6.4 (1.6)	<0.05	0.2

- **Mortality: 9%**
  - **Sterile necrosis : 3%**
  - **Infected necrosis : 24%**
- **Delay after onset : 91 (15-209) days**
- **Cause of death : infected necrosis in 70%**

# Infected Pancreatic Necrosis : Incidence and Impact on Outcome

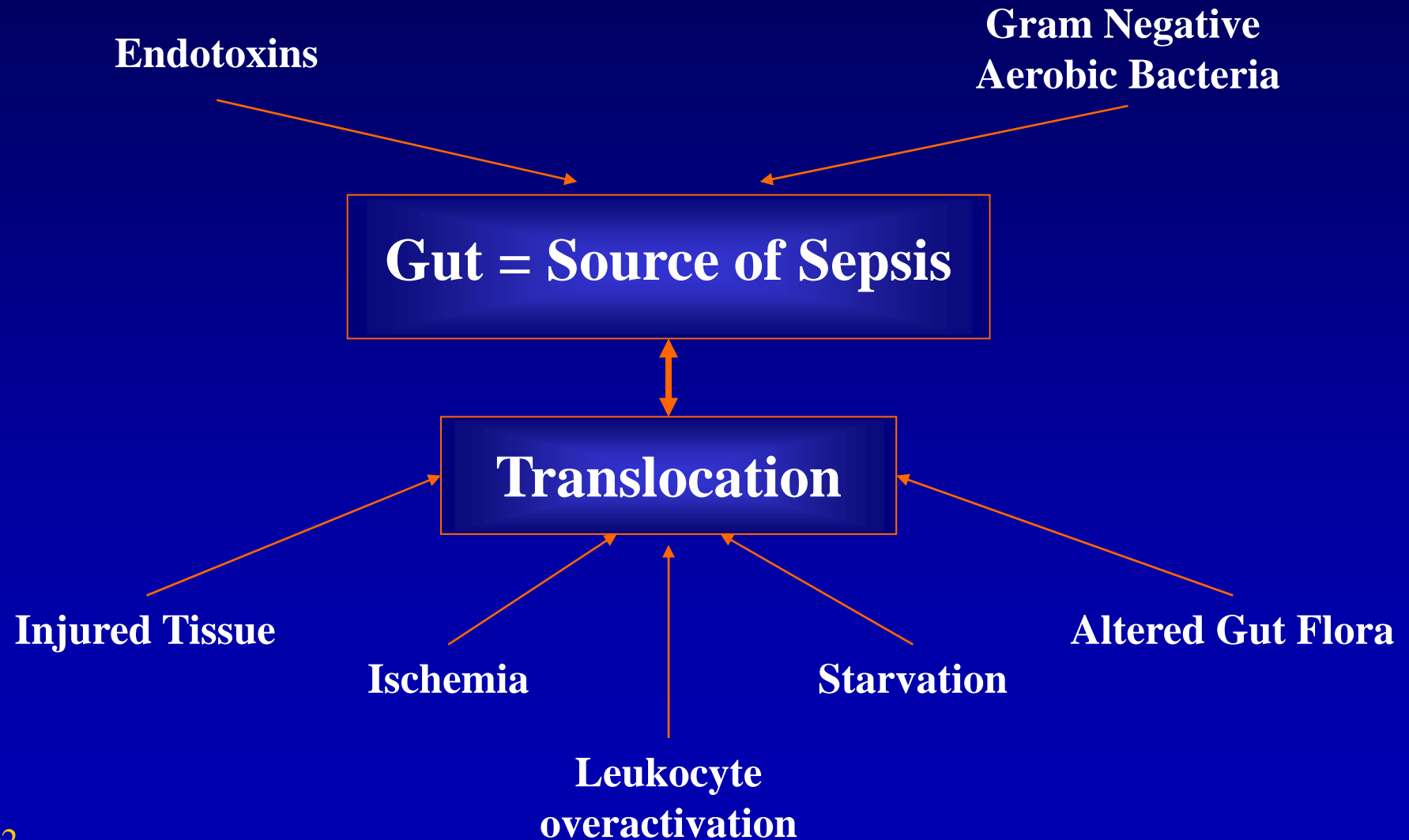


	Weeks				All Pts
	1	2	3	>3	
No Patients	21	22	14	57	114
No Deaths (Infected)	5 (100%)	4 (50%)	5 (50%)	3 (14%)	17 (38%)
No Deaths (Sterile)	2 (13%)	-	-	4 (11%)	6 (9%)

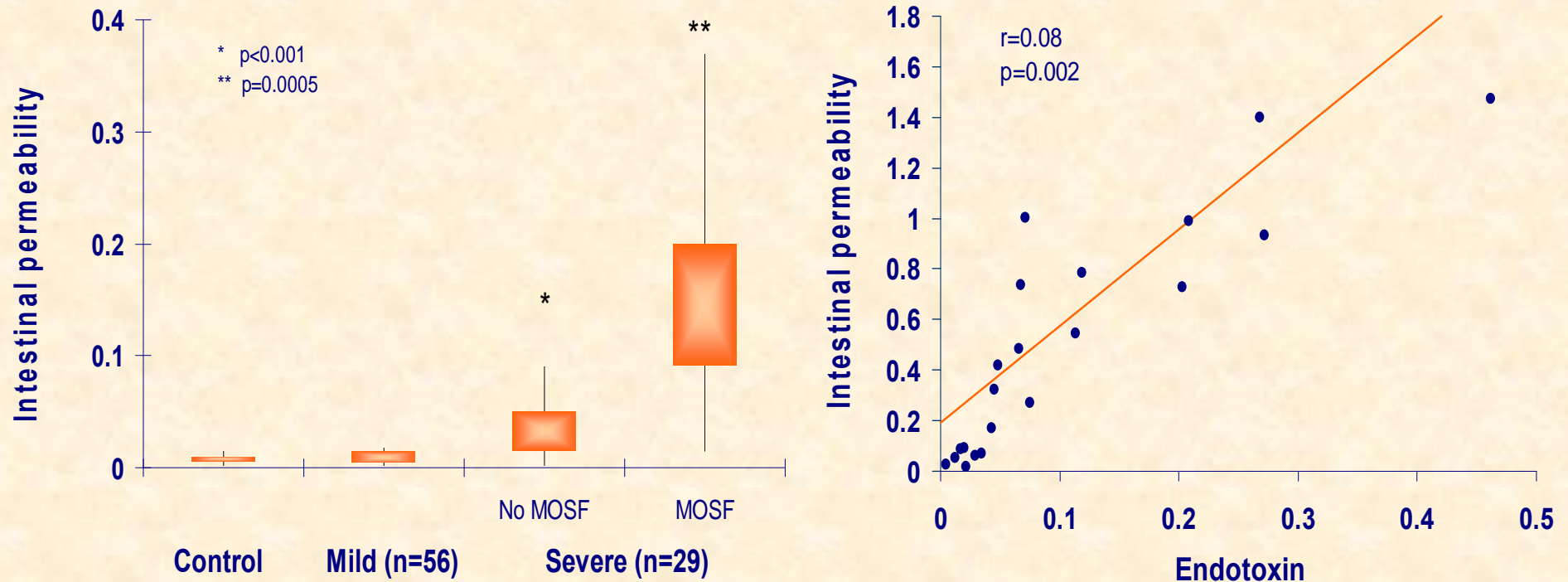


# Pathophysiologic Mechanisms Underlying Pancreatic Infection

## Role of the Gut Barrier



# Intestinal Permeability in Acute Pancreatitis : Correlation with Endotoxemia and Organ Failure



# Persistent Early Organ Failure beyond 48h is Associated with Fatal Outcome

## The Major Impact of the Individual Systemic Host Response

- Persistent EOF and pancreatic infection are the major determinants of outcome
- Persistent EOF is the major determinant of the development of infected necrosis (OR:12.25,95%CI 2.19-68.51)

Lytras D, et al. Pancreas 2008;36:249-54

Rau B, et al. Clin Gastroenterol Hepatol 2005;3:159-66

Büchler M; et al. Ann Surg 2000;232:614-26

### Persistent EOF is “ALL” :

- a “red flag” for infection
- cause and consequence
- prognostic factor and marker

The individual systemic host response plays the central role,  
morphologic factors and time elapsed after onset  
are of less importance

## Controlled Trials of Antibiotic Prophylaxis in Severe Acute Pancreatitis

		Blinded	Patients (n)	Antibiotics	Pancreatic infection	Non pancreatic infection	Surgery	Mortality
Pederzoli, et al.	(1993)	No	74	Imipenem	↓ (30%)	↓ (48%)	≡	≡
Sainio, et al.	(1995)	No	30	Cefuroxime	= (40%)	↓ ↓	↓	↓
Deleenserie, et al.	(1996)	No	23	Ceftazidime Amikacin Metronidazole	↓ (36%)	? (22%)	?	≡
Schwarz, et al.	(1997)	No	26	Ofloxacin Metronidazole	= (53%)	? ?	?	≡
Nordbaek, et al.	(2001)	No	58	Imipenem	= (42%)	? ?	≡	≡
Isenmann, et al.	(2004)	“Double”	76	Ciprofloxacin Metronidazole	= (14%)	↓ (4%)	≡	≡
Dellinger, et al.	(2007)	“Double”	100	Meropenem	= (12%)	= (48%)	≡	≡
Rokke, et al.	(2007)	No	73	Imipenem	= (19%)	↓ (4%)	≡	≡
Garcia-Barrosa, et al.	(2008)	“Double”	41	Ciprofloxacin	= (42%)	= (42%)	=	=
Luiten, et al.	(1995)	No	102	Ceftazidime + SDD	↓ (38%)	? ?	↓	↓

## Meta-Analyses on the Prophylactic Use of Antibiotics in Acute Pancreatitis (2006-2009)

Authors	Time of publication	Number of included trials	Total number of patients	Prophylactic effect of antibiotics
Xiong, et al. Med Princ Pract	Feb 2006	6	338	Nonsignificant
Heinrich, et al. Ann Surg	Feb 2006	6	390	Significant
Mazaki, et al. Br J Surg	June 2006	6	329	Nonsignificant
Villatoro, et al. Cochrane Database	Oct 2006	5	294	Significant
Dambrauskas, et al. Medicina	April 2007	10	1279	Significant
de Vries, et al. Pancreatology	Sept 2007	6	397	Nonsignificant
Bai, et al. Am J Gastroenterol	Oct 2007	7	467	Nonsignificant
Xu, et al. Scand J Gastroenerol	Oct 2008	8	540	Significant
Hart, et al. South Med J	Nov 2008	7	429	Nonsignificant
Mazaki, et al. Ann Surg	Dec 2008	7	429	Nonsignificant
Jafri, et al. Am J Surg	Feb 2009	8	502	Nonsignificant

# Prophylactic Antibiotics for Predicted Severe Acute Pancreatitis

## Recovery of resistant bacteria

Antibiotic group	18/23	(78%)*
Placebo group	6/28	(21%)*

\*p<0.0001

# Severe Acute Pancreatitis : Pancreatic infection

## Bacterial strains in pancreatic infection

Type	(%)
Escherichia coli	29
Staphylococcus aureus	15
Klebsiella species	11
Pseudomonas species	10
Streptococcus faecalis	10
Proteus species	6
Enterobacter species	4
Staphylococcus epidermidis	2
Other streptococci	2
Citrobacter species	1
Different anaerobes	10

Adjusted for polymicrobial infections of 26 %

# Acute necrotizing pancreatitis : a treatment strategy based on the status of infection and antibiotic prophylaxis (n=86)

Bacteriologic findings in patients with infected necrosis (n=29) ( 34%)

Germ	Number of positive cultures (n=47) (% of all positive cultures)
<i>Staphylococcus spp.</i>	17 (36%)
<i>Candida</i>	8 (17%)
<i>Enterococcus</i>	6 (13%)
<i>Escherichia coli</i>	5 (11%)
<i>Klebsiella spp.</i>	4 (9%)
<i>Streptococcus spp.</i>	3 (6%)
<i>Pseudomonas aeruginosa</i>	2 (4%)
<i>Morganella morgani</i>	1 (2%)
<i>Bacteroides fragilis</i>	1 (2%)

**Gram positive bacteria in 55% of patients**  
**Fungal infection in 29% of patients**



## Early Prophylactic Meropenem for Acute Necrotizing Pancreatitis

	Treatment Group			
	Meropenem (n=50)		Placebo (n=50)	
	n	%	n	%
<b>Primary cause of pancreatitis</b>				
Biliary	22	44	12	24
Alcohol	18	36	26	52
Other	10	20	12	24
<b>% necrosis by contrast-enhanced CT</b>				
< 30%	15	30	10	20
≥ 30%	26	52	31	62
Not recorded	9	18	9	18
<b>Interval, symptom onset to first dose of study drug</b>	<b>4.0 days</b>	<b>2-7</b>	4.3 days	2-9
<b>Interval, symptom onset to nutritional support</b>			1.8 days	
<b>Duration of administration</b>	8.5 days	1-21	9 days	1-21
<b>Ranson score</b>	4.5	1-8	3.8	0-8
<b>APACHE II</b>	12.7	2-30	11.5	0-39
<b>MOD score &gt;2</b>	<b>11</b>	<b>22</b>	11	22

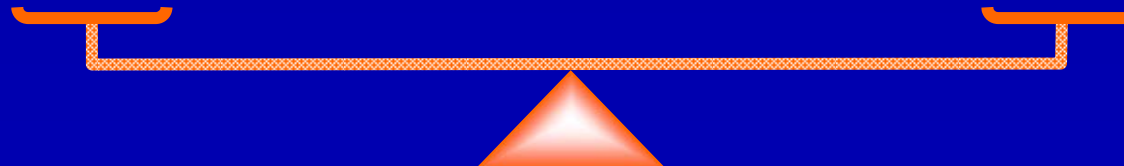
# Antibiotic Prophylaxis in Severe Acute Pancreatitis

## PRO

- Infected pancreatic necrosis = major impact on outcome
- No specific therapy to lessen the volume of necrosis
- No reliable means to decrease pancreatic infection
- Results of experimental studies
  - Pathophysiology
  - Pharmacodynamic data
  - Antibioprophylaxis

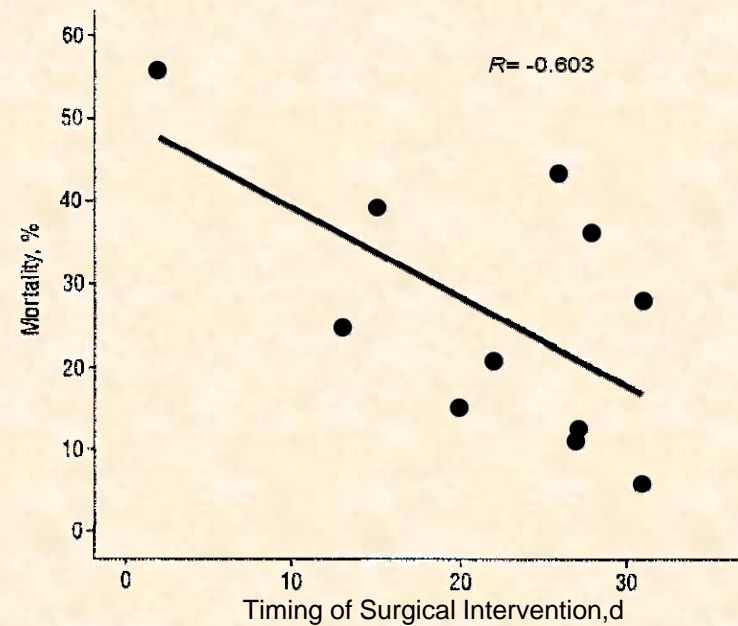
## CONTRA

- Cost
- Ecological risk
- Human studies : inconsistent results
- The 2 controlled studies showed no benefits
- Methodological flaws
  - Small number of patients
  - Not stratified by etiology/severity/early vs late death
  - Investigators not blinded in most studies
  - No standardized indication for surgery
  - No pharmacodynamic data
  - No microbiological data
  - Uncertain microbiological diagnosis
  - Inadequate type/dosage/timing of antibiotics
  - High crossover rate
  - No standardized nutritional support
  - Impact of extra-pancreatic infection



# Association between Timing of Surgery and Outcome in Severe Acute Pancreatitis

	Design	No. of patients	Patients with Pancreatic infection %	Delay before surgery, day	Mortality %
Mier, et al. (1997)	Randomized controlled	25	60	2	56
Fernandez-del Castillo, et al. (1998)	Retrospective	64	56	31	6
Branum, et al. (1998)	Retrospective	50	84	27	12
Farkas, et al. (1998)	Retrospective	203	100	20	15
Büchler, et al. (2000)	Prospective	28	96	22	21
Ashley, et al. (2001)	Retrospective	36	92	27	11
Beattie, et al. (2002)	Retrospective	54	68	26	43
Götzinger, et al. (2003)	Prospective	250	74	15	39
Connor, et al. (2005)	Prospective	88	77	31	28
Rau, et al. (2005)	Retrospective/Prospective	285	49	13	25
Besselink, et al. (2007)	Retrospective	53	83	28	36
Total, median		54	77	26	25



# Conservative Management of Infected Pancreatic Necrosis A Falling Myth or a Still Impassable Frontier ?

**“Infected Pancreatic Necrosis = Immediate Surgery”**



**“Conservative Management of Infected Necrosis”**

A subset of stable patients can be successfully managed with long term antibiotics alone. High risk necrosectomy can be avoided or delayed until infected necrosis is “organized”. As an alternative, percutaneous or endoscopic drainage can be applied.

Dubner, et al. Pancreas 1996

Adler, et al. Am J Gastroenterol 2003

Ranush, et al. Dig Surg 2003

Renzi, et al. Pancreas 2005

Sivasankar, et al. Hepatobiliary Pancreat Dis Int 2006

Lie, et al. Pancreas 2007

**Management of infected necrosis depends on**

- Patient's condition
- response to antibiotics
- consistency of necrosis
- local expertise

## Postponing Necrosectomy is Associated with Prolonged Use of Antibiotics and Increased Incidence of Fungal and Antibiotic-resistant Organisms Colonization/Infection

	Time from initial admission to operation			p Value
	Day 1-14 (n=16)	Day 15-29 (n=11)	Day ≥30 (n=26)	
APACHE II score	9 (3-21)	11 (4-19)	9 (2-14)	.57
Infected necrosis, No.(%)	10 (63)	9 (82)	25 (96)	.02
Preoperative multiple organ failure, No.(%)	6 (38)	5 (45)	6 (23)	.35
Antibiotic prophylaxis >30d, No.(%)	0	1 (9)	10 (38)	.04
Median time of antibiotic use (range)	4 (0-11)	17 (0-29)	25 (0-77)	<.001
Broad-spectrum antibiotic use,d	12 (0-38)	28 (0-66)	26 (0-82)	.002
Primary Candida or resistant microorganism, No.(%)	1 (6)	1 (6)	9 (35)	.05
Antibiotic-resistant microorganism during admission, No.(%)	6 (38)	5 (45)	19 (73)	.06

# **Guidelines for the Management of the Critically Ill Patient with Severe Acute Pancreatitis**

**International Consensus Conference – Washington 2004**

**“The use of empirical antimicrobial therapy while awaiting the results of cultures should be based on the rate of clinical deterioration, with deescalation once results are available and cessation of antimicrobials in the absence of proven infection”**

# Source control : Intra-abdominal Infections

➤ « *Operate when condition stabilized* » ??

➤ **Mortality**

- **Surgical control of infection** **13%**
- **Surgical control impossible** **27%**

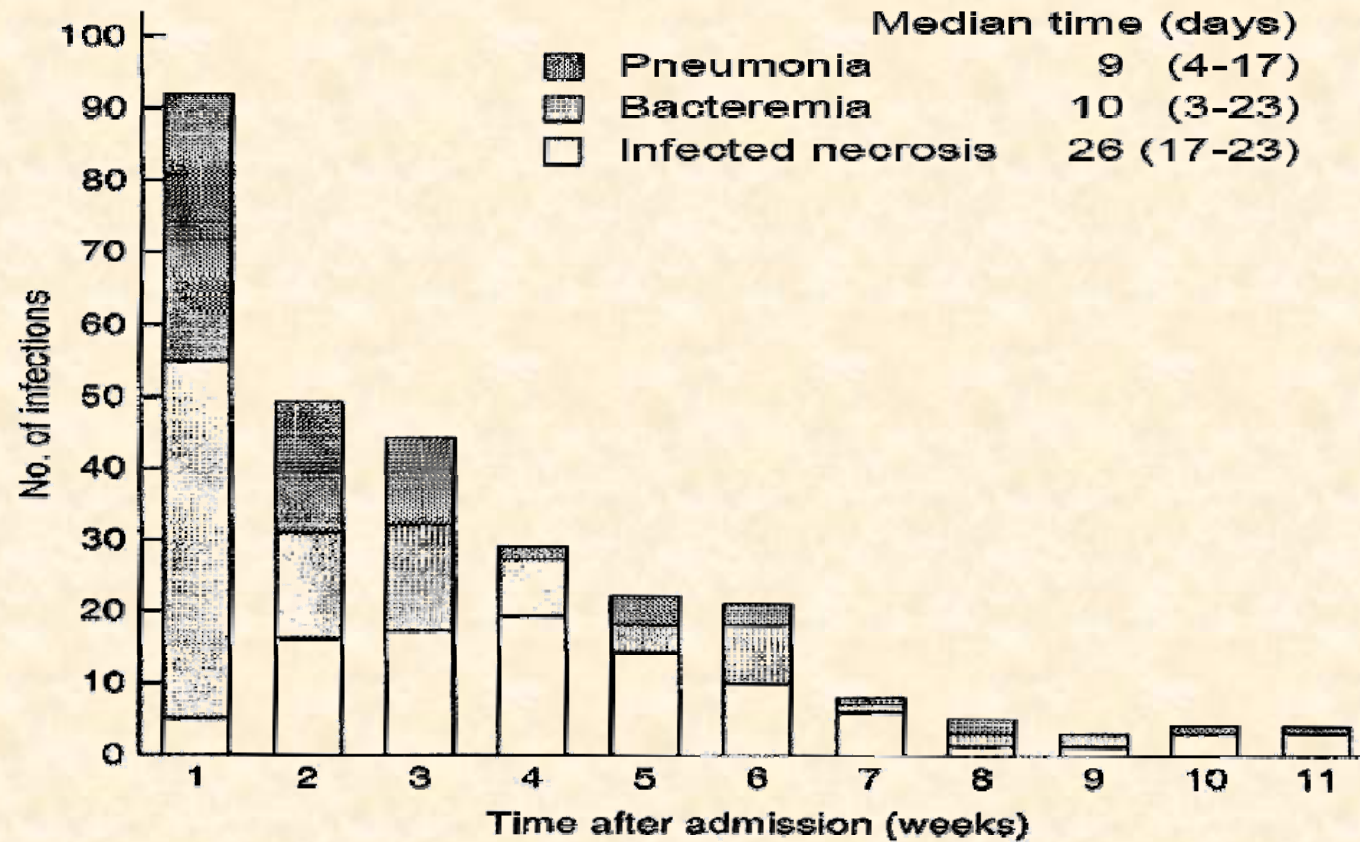
Seiler et al. Surgery 2000;127:178

➤ **Mortality and Antimicrobial adequacy**

- **Inadequate surgery + inadequate antibiotics** **100%**
- **Inadequate surgery + adequate antibiotics** **90%**

Carlet Infection en Reanimation Masson 1986:126-135

## Timing of Extra-pancreatic and Pancreatic Infections in Acute Pancreatitis (n=173)



- 49% of infections were diagnosed within 7 days of admission!
- 18% of infected necrosis were diagnosed within 14 days of admission!

## Impact of Extra-pancreatic and Pancreatic Infections on the Outcome of Acute Pancreatitis (n=731)

Prediction of death	Odds ratio	<i>p</i>
Persistent organ failure	18.02 (8.48-38.27)	<0.001
Bacteremia	3.42 (1.65-7.17)	0.001
Age	1.05 (1.03-1.07)	<0.001

- Previous bacteremia increased the risk of infected necrosis (65% vs 38%, $p=0.002$ )
- Of those who died, 80% had infection: 60% had bacteremia and 50% had infected necrosis
- The mortality rate increased with fungal infections

# Benefits of Early Enteral Nutrition vs TPN in Severe Acute Pancreatitis

## Meta-analysis of the randomized trials

	Relative risk (95% confidence interval)	p Value
Infectious complication	0.47 (0.28-0.77)	<.001
Pancreatic Infections	0.48 (0.26-0.91)	.02
Surgical intervention	0.37 (0.21-0.65)	.001
Death	0.32 (0.11-0.98)	.03
Organ failure	0.67 (0.30-1.52)	.21

# Prevention and Treatment of (peri) Pancreatic Infected Necrosis

## A Multimodal Approach

- **Early Staging**
- **Organ support**
- **Biliary pancreatitis : early sphincterotomy**
- **Early enteral nutrition**
- **Antimicrobial therapy**
- **Timely surgical drainage**
- **Endoscopic / RX guided - percutaneous drainage**

In the treatment of sepsis, early and appropriate antibiotic therapy is more important than any other intervention!!

