ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Management of severe acute pancreatitis

The Fourth Annual Scientific Meeting in Hepatogastroenterology
Theodor Bilharz Research Institute,
14 th February 2010

Philippe RUSZNIEWSKI

Pôle des Maladies de l'Appareil Digestif
Gastroentérologie-Pancréatologie,
Hôpital Beaujon, Université Paris VII, Clichy

PMAD
PÔLE DES MALADIES DE L'APPAREIL DIGESTIF

How to define the severity of acute pancreatitis ?

- The patient
- Bioclinical scores (Ranson, Imrie , Apache,…)
- Organ failure scores (SOFA, ODIN,…)
- Independent biological markers (CRP, IL6, TAP,…)
- CTscan

How to define the severity of acute pancreatitis ?

- The patient
  - age > 80 y, BMI >30, chronic respiratory failure, other organ deficiencies

- Bioclinical scores
  - Ranson, Imrie
  - Specific and easy to calculate
  - 48th h, well-known severity criteria
  - Low individual value except NPV

- APACHE, SAPS
  - non specific, good NPV

How to define the severity of acute pancreatitis ?

- Organ failure scores (SOFA, ODIN, KNAUSS…)
  - hemodynamic, respiratory, neurological and renal criteria
  - Allow continuous evaluation
  - non specific

- Independent biological markers
  - CRP < 150 mg/l, NPV 94%
  - Elastase, TAP, IL8 ???

How to define the severity of acute pancreatitis ?

- Morphological criteria (Balthazar)

Pancreatic and peri-pancreatic inflammation

- Grade A : normal pancreas (0pt)
- Grade B : focal or diffuse pancreatic enlargment (1pt)
- Grade C : heterogeneous pancreas and peripancreatic fat densification (2 pts)
- Grade D : one peripancreatic fluid collections (3 pts)
- Grade E : Multiple fluid collections or gas in one collection (4 pts)

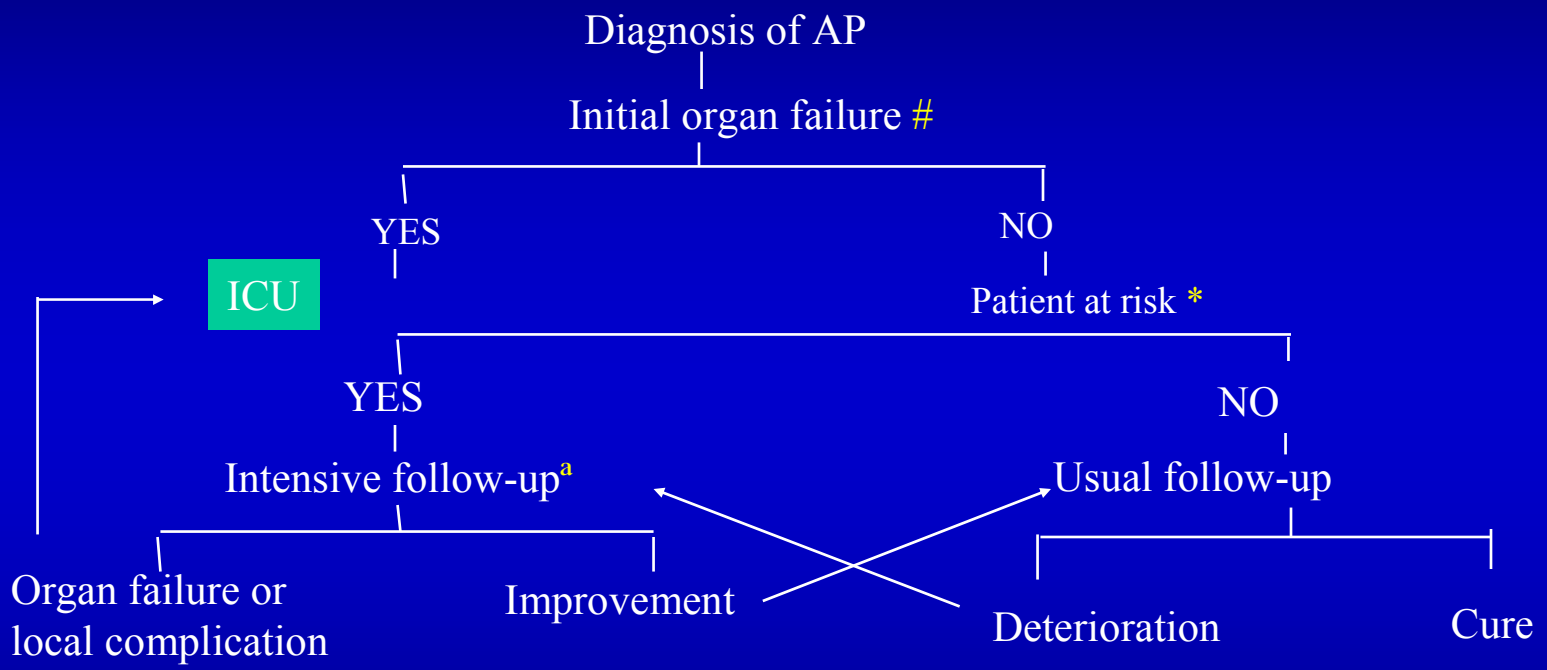
Pancreatic necrosis

No necrosis (0pt)
Necrosis < 30 % (2pts)
Necrosis 30-50 % (4pts)
Necrosis > 50 % (6pts)

TOTAL

Severity index	Morbidity %	Mortality %
» **≤ 3**	**8**	**3**
» **4 - 6**	**35**	**6**
» **7 - 10**	**92**	**17**

How to define the severity of acute pancreatitis ?



Defined as creatinin >170, SBP < 90
PaO2 < 60mmHg, Glasgow <13, Plat < 80G/l

* Patient associated conditions , CRP >150mg/l
Ranson or Imrie > 3, Balthazar score ≥ 4

[a] clinical parameters several times per day ; biological : creatinin, SpO2, blood count daily
CRP twice a week ; CTscan: every 10- 15 days

Specific resuscitation measures

Artificial nutrition : for whom, when and how ?

Which antibiotics in curative situation ?

Should prophylactic antibiotherapy be given ?

- Analgesia

  acetaminophen

  morphin and agonists if necessary

Aspirin and NSAIDs contra-indicated

side effects (kidney, hemostasis,…)

IV Lidocain not recommended

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

Pathophysiogical treatments

No convincing evidence for :

- Gastric antisecretory drugs
- Pancreatic enzymes
- Atropin, acetazolamide
- Isoproterenol
- Glucagon
- Somatostatin or octreotide
- Aprotinin
- Gabexate
- Anti-cytokines or PAF antagonists
- ....

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis

C D Johnson, A N Kingsnorth, C W Imrie, M J McMahon, J P Neoptolemos, C McKay, S K C Toh, P Skaife, P C Leeder, P Wilson, M Larvin, L D Curtis, for the UK Acute Pancreatitis Study Group

Hypothesis : Anti PAF administered within 72 first hours reduces the frequency of systemic (organ failure) or local complications

Gut 2001;48:62

Complications	*Placebo group*	*Lexipafant group*
Organ failure		
On admission	59 (43%)	67 (45%)
Day 3	46 (33%)	40 (27%)
Day 7	36 (26%)	29 (20%)
Overall	80/138 (58%)	85/148 (57%)
Local complications		
Pseudocyst	19 (14%)	8 (5%)[a]
Necrosis	29 (21%)	23 (16%)
Abscess	6 (4%)	5 (3%)
Overall	41/138 (30%)	30/148 (20%)[b]
Systemic sepsis	13/138 (9%)	4/148 (3%)[c]
Deaths		
All attributable deaths	21/136 (15%)	14/147 (10%)
Attributable deaths in patients treated ≤48 h	17/95 (18%)	8/104 (8%)[d]

[a]Fisher's exact test, p=0.025.
[b]χ^2_1=3.41, p=0.065.
[c]Fisher's exact test, p=0.023.
[d]Fisher's exact test, p=0.034.

Gut 2001;48:62

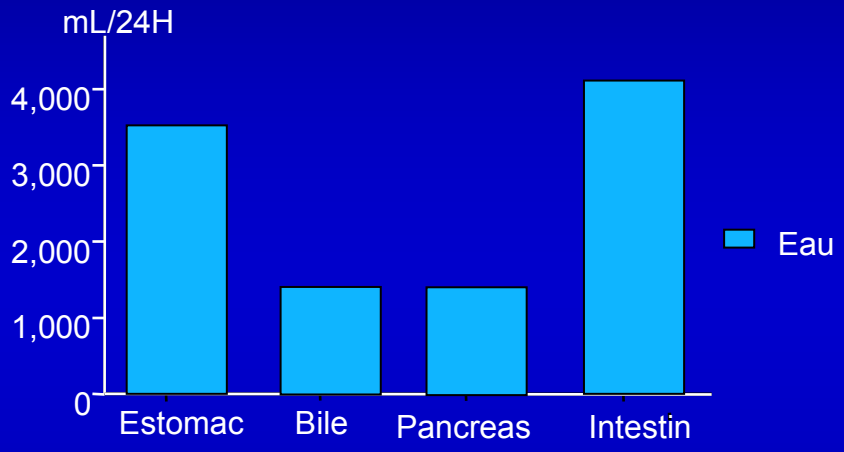
Management principles

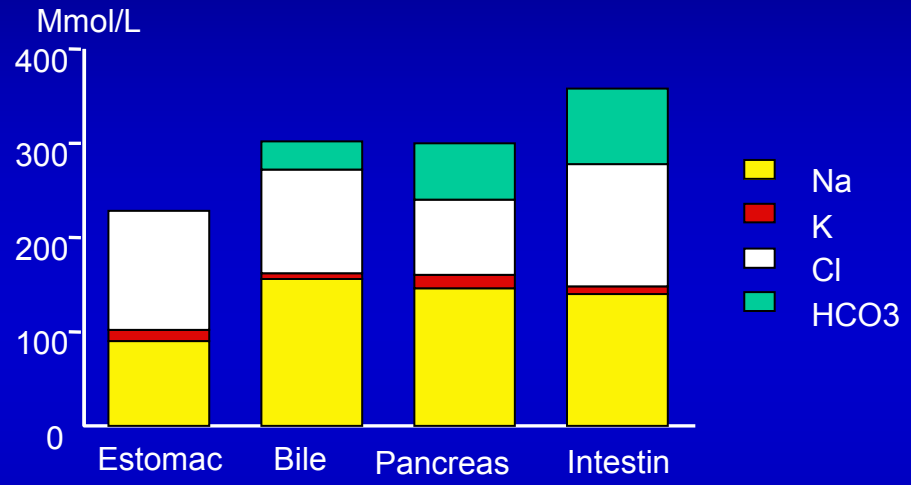
- Volemia
- Renal failure
- Sepsis and septic shock
- Acute respiratory failure
- Coagulation failure
- Neurological deficiency

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

Hypovolemia and extracellular dehydration

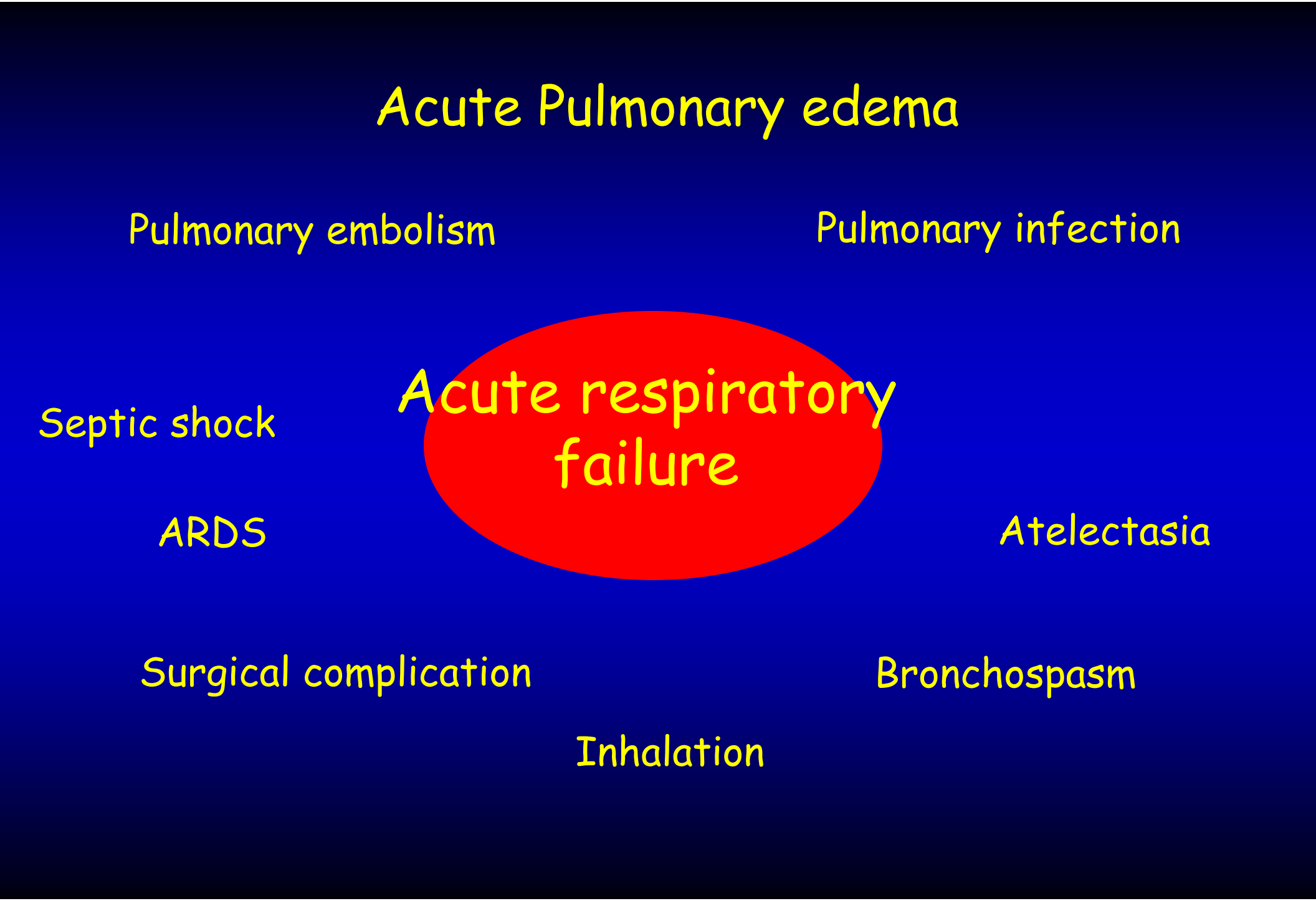
fluids and electrolytes



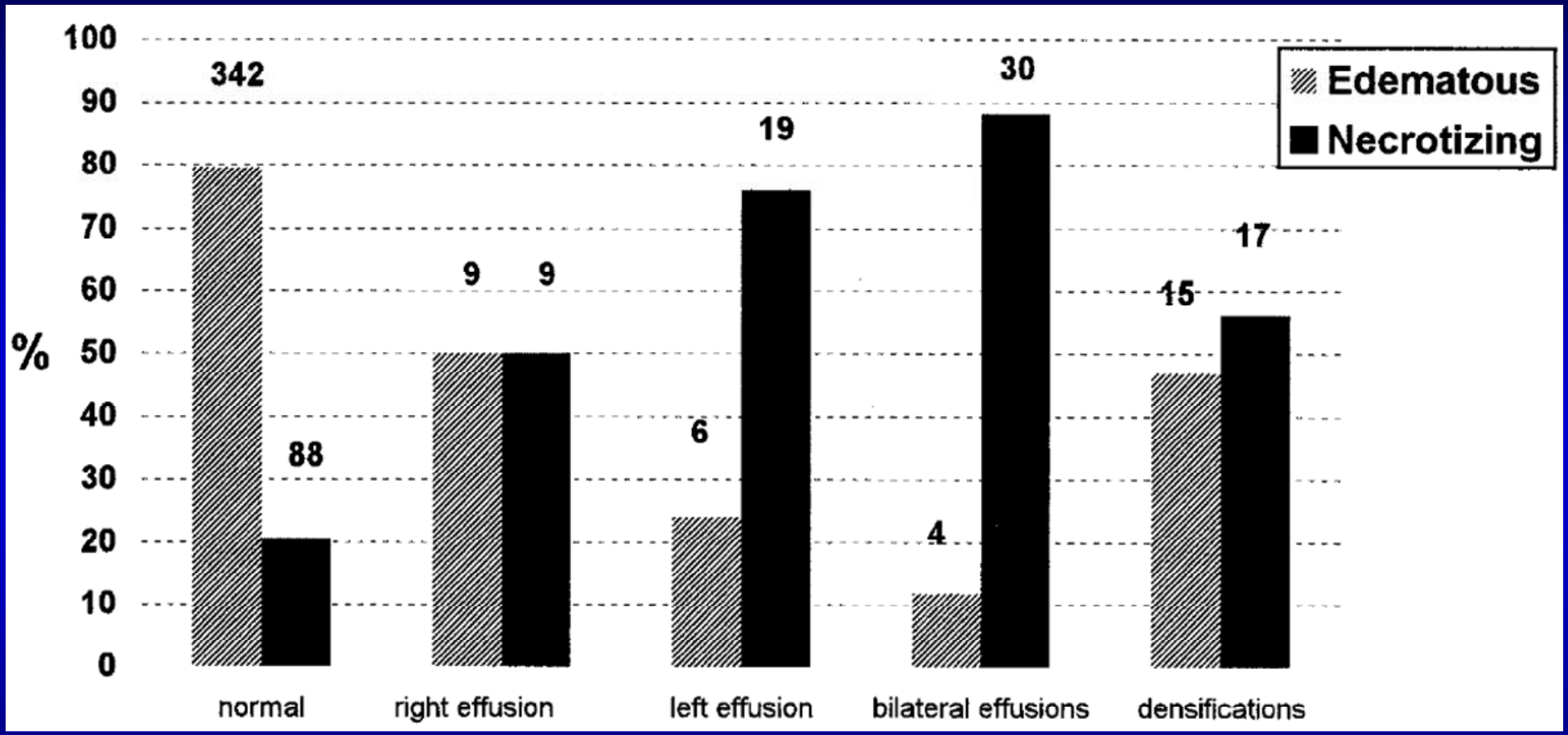


High volume requirements : 10,000 mL within 48 hours
Functional renal failure and hypovolemic shock

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92


Acute Pulmonary edema
Pulmonary embolism
Pulmonary infection
Septic shock
Acute respiratory failure
ARDS
Atelectasia
Surgical complication
Bronchospasm
Inhalation

Pleural effusion



58 (36 %) pleural effusion
75 (46 %) abnormal lungs

Talamini, Am J Surg, 1999

ARDS

Incidence poorly known

Hypoxia not correlated with severity of AP

Alterations of capillary membrane even if normal PaO_2

Most frequent within the first week

Symptomatic treatment

Octreotide ?

Paran H. Dig Dis Sci 2000;45:2247-51

Specific resuscitation measures

Artificial nutrition : for whom, when and how ?

Which antibiotics in curative situation ?

Should prophylactic antibiotherapy be given ?

Nutrition ?

Digestive rest = no oral intake

Total parenteral nutrition

Early enteral feeding

Initial management

- Nasogastric tube for aspiration (vomiting)
- No oral intake (pain and digestive intolerance)
- Mild forms : gradual refeeding after 48 hours without pain (lipase < 3 N)

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

Initial management

- Severe AP : early enteral nutrition with a nasojejunal or nasogastric (++) tube (from the 48th hour)
- Jejunostomy only if surgery for another reason
- Enteral route >> parenteral route (tolerance, cost, lower morbidity and at least equivalent efficacy)
- TPN if enteral nutrition not tolerated

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

EN vs TPN in severe AP

Al-Omran M et al. The Cochrane Library, Issue 3, 2004

Meta-analysis
104 studies
5 randomized
2 analyzed (exclusive enteral or parenteral feeding, endoscopic tube placement)

Kalfarentzos BJS 1997
McClave JPEN 1997

Although less complications are observed with EN, data are insufficient to conclude.
Further studies…..

EN vs TPN in severe AP

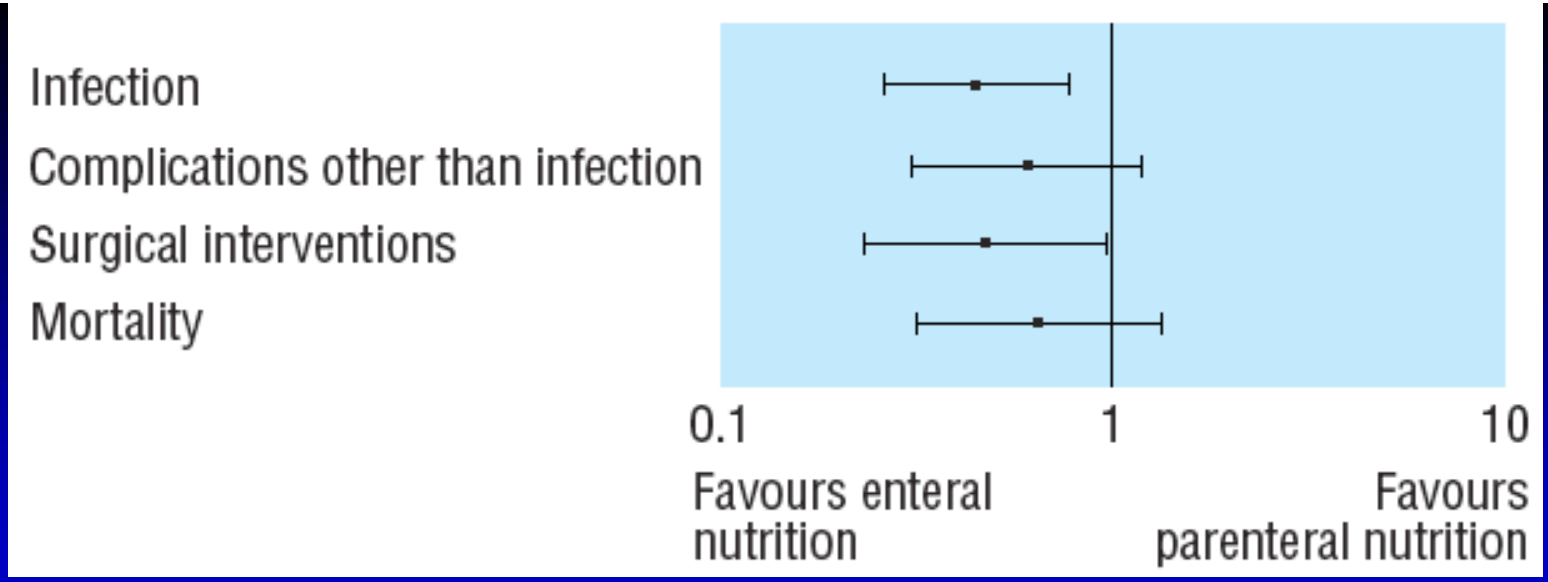
Marik PE et Zaloga GP. BMJ 2004; 328:1407

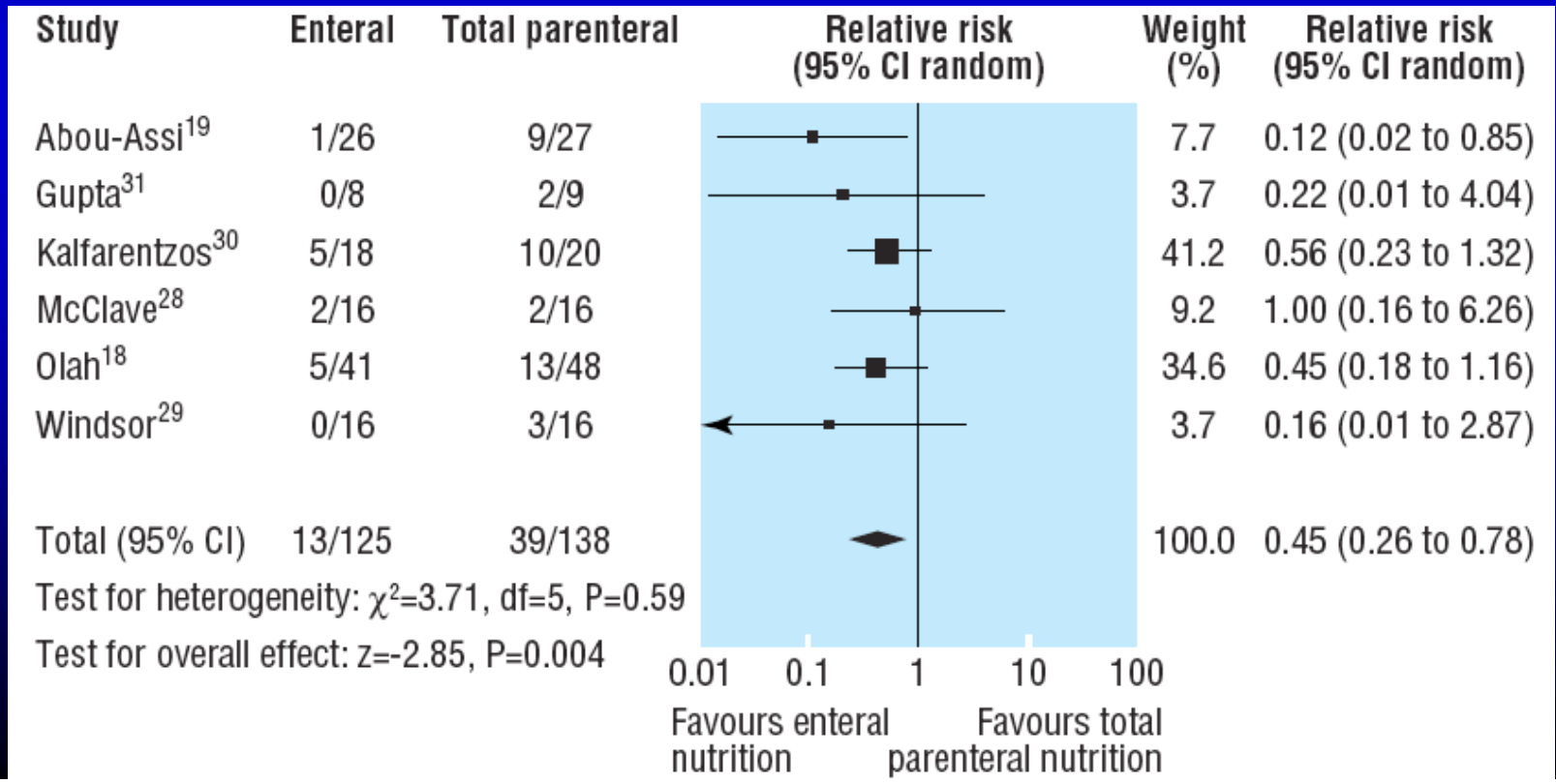
Meta-analysis
117 studies
12 randomized
6 analyzed

- *Kalfarentzos BJS 1997*
- *McClave JPEN 1997*
- *Windsor Gut 1998* (not considered by Al-Omran)
- *Abou-Assi Am J Gastroenterol 2002*
- *Olah Nutrition 2002*
- *Gupta Pancreatology 2003*

Lower incidence of infections, surgical interventions and LoS with enteral nutrition

Risk of infection





…Although information is limited in terms of study numbers and methodological quality, available evidence does not support the use of TPN in patients with severe AP. This conclusion is based on the wide spectrum of clinical and experimental arguments, as well as on pathophysiology of acute pancreatitis.

Enteral nutrition should be preferred route of nutritional support

Marik PE et Zaloga GP. BMJ 2004; 328:1407

Recommendation 9. We recommend that enteral nutrition be used in preference to parenteral nutrition in patients with SAP. Enteral nutrition should be initiated after initial resuscitation. The jejunal route should be used if possible (level 1a evidence, grade A recommendation).

Critical Care Medicine 2004,32;2524

Recommendation 10. We recommend parenteral nutrition only be used when attempts at enteral nutrition have failed after a 5- to 7-day trial (level 5 evidence, grade D recommendation).

Critical Care Medicine 2004,32;2524

EN in current practice…

- 500 mL (25 -30 mL/H) reaching 2000/2500 mL in 48 hours (100 mL/H)
- 2,000 Kcal/j (1 Kcal/mL)
- semi-elementary with low lipid concentration
- 40 g proteins /L (5.9 g nitrogen/L)
- 75% glucid energetic supply
- 9 % lipid energetic supply

Eatock FC. Am J Gastroenterol 2005;100:432-439

Specific resuscitation measures

Artificial nutrition : for whom, when and how ?

Which antibiotics in curative situation ?

Should prophylactic antibiotherapy be given ?

Infection of necrosis in 40-70 % of the cases

Renner et al. Dig Dis Sci. 1985;30:1005-18

Infection site

pancreatic parenchyma
peri-pancreatic
fluid collection

Gerzof et al. Gastroenterology. 1987;93:1315

Digestive pathogens (gram negative bacteria)

Beger et al. World J Surg. 1985;9:972
Gastroenterology. 1986;91:433

Route of contamination

- systemic
- lymphatic
- biliary
- translocation

Runkel et al. Curr Surg. 1990;47:460
J Surg Res. 1991;51:18
Medich et al. Am J Surg. 1993;165:46
Deitch et al. Am J Surg. 1990;159:79
Widdison et al. Gut. 1994;35:1306

Infected necrosis = surgery

Radiological or
endoscopic drainage could be considered
as alternatives

Antibiotics and pancreas

Clinical and experimental data

↓

3 groups of AB according to penetration in necrosis

Group A : low concentration < MIC
Aminosides, aminopenicillins, CG1

Group B : variable individual concentration
Mezlocillin, piperacillin, CG 3 (cefotaxime)

Group C : high concentration > MIC

Imipenem, fluoroquinolones, cefoperazone, imidazoles, fluconazole

Antibiotics are justified if :

- Infection proven
- Septic shock
- Cholangitis
- Nosocomial infection

- Antibioprophylaxia if invasive procedures

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

SFAR expert conference on probabilist antibiotics

Patients not treated with antibiotics

- Imipenem (1g X 3/j)

or

- Ciprofloxacin (400mgX3/j) or Ofloxacin (400 mgX2/j)

or Cefotaxime (2 g X 3/j)

+ Imidazole (metronidazole 500 mg X 3/j)

Aminosides not useful

Treatment thereafter adapted to antibiogram

Montravers P.Antibiothérapie probabiliste des états septiques graves. Conférence d'experts SFAR. Paris: Elsevier; 2004:195-200.

SFAR expert conference on probabilist antibiotics

Patients previously treated with antibiotics

Imipenem (1 gx3/j)

+ Vancomycin (15 mg/kg initial dose)

(then IV for concentration 20 mg/l)

+ Fluconazole 400 mg X 3 /j

Treatment thereafter adapted to antibiogram

Montravers P.Antibiothérapie probabiliste des états septiques graves. Conférence d'experts SFAR. Paris: Elsevier; 2004:195-200.

Specific resuscitation measures

Artificial nutrition : for whom, when and how ?

Which antibiotics in curative situation ?

Should prophylactic antibiotherapy be given ?

Prophylactic antibiotics recommended in case of invasive procedures

Gastroenterol Clin Biol 2001; 25:1S5-1S246
Gastroenterol Clin Biol 2001; 25:177-92

Can infected necrosis be prevented by prophylactic antibiotics ?

Prophylactic Antibiotic Treatment in Patients With Predicted Severe Acute Pancreatitis: A Placebo-Controlled, Double-Blind Trial

RAINER ISENMANN,* MICHAEL RÜNZI,† MARTINA KRON,§ STEFAN KAHL,‖ DIETMAR KRAUS,¶ NORBERT JUNG,# LUDWIG MAIER,** PETER MALFERTHEINER,‖ HARALD GOEBELL,†† HANS G. BEGER,§§ and THE GERMAN ANTIBIOTICS IN SEVERE ACUTE PANCREATITIS (ASAP) STUDY GROUP

Inclusion : abdominal pain + Amylase or lipase X3
Severity : CRP>150 mg/L
or
visible necrosis on CTscan

Inclusion within 72 h after initiation of symptoms

Randomized double-blind vs placebo
Ciprofloxacin 400mgX2 + Metronidazole 500mg X2

Main outcome : reduction in infected necrosis

GASTROENTEROLOGY 2004;126:997–1004

	Ciprofloxacin +Metronidazole (n=41)	Placebo (n=35)
Pancreatic infection	17%	14%
Extrapancreatic infection	29%	34%
Mortality	7%	11%

GASTROENTEROLOGY 2004;126:997–1004

Early Antibiotic Treatment for Severe Acute Necrotizing Pancreatitis

A Randomized, Double-Blind, Placebo-Controlled Study

E. Patchen Dellinger, MD, Jose M. Tellado, MD,† Norberto E. Soto, MD,‡ Stanley W. Ashley, MD,§ Philip S. Barie, MD, MBA,‖ Thierry Dugernier, MD, PhD,¶ Clement W. Imrie, FRCS,# Colin D. Johnson, MChir, FRCS,** Hanns-Peter Knaebel, MD, MBA,†† Pierre-Francois Laterre, MD,‡‡ Enrique Maravi-Poma, MD, PhD,§§ Jorge J. Olsina Kissler, MD, PhD,‖‖ Miguel Sanchez-Garcia, MD, PhD,¶¶ and Stefan Utzolino, MD##*

≥30% necrosis on CTscan
or Baltazar E and CRP > 120 mg/L or MOD score >2
Inclusion within 5 days (120 h) after symptom onset
Meropenem 1gX3/j vs placebo
7-21 days recommendation 14 days
Follow-up at least 35 days
Main objective: reduction of infected necrosis

Ann Surg 2007;245:674-8

TABLE 2. Development and Time to Onset of Pancreatic or Peripancreatic Infection From Symptom Onset

	Treatment Group			
	Meropenem (n = 50)		Placebo (n = 50)	
	n	%	n	%
Patients with pancreatic or peripancreatic infection	9	18	6	12
Patients with resistant pancreatic or peripancreatic infection	4	8	3	6
Mean (range) no. of days to diagnosis of infection	21.3 (5–35)	—	20.8 (11–25)	
Mortality	10	(20 %)	9	(18 %)

Ann Surg 2007;245:674-83

We recommend against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis in light of inconclusive evidence and divided expert opinion

Subsets of patients who benefit from antibiotics may be identified by further investigation.

Level of evidence 2b, Grade B recommendation

Critical Care Medicine 2004,32;2524

We do not recommend the routine use of selective digestive decontamination of the digestive tract in the management of necrotizing pancreatitis.

Further investigation of this promising strategy in severe acute pancreatitis is warranted.

Level of evidence 2b, Grade B recommendation

Critical Care Medicine 2004,32;2524

Conclusions

- Symptomatic treatment according to current ICU recommendations
- No « magic bullet » for pathophysiological treatment
- Early enteral nutrition
- Avoid prophylaxy with antibiotics
- In case of documented infection, wide spectrum antibiotics, then adapted to antibiogram
- Beware of etiological treatment (biliary AP+++)