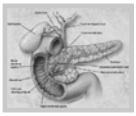
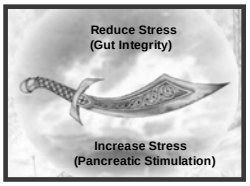
Are Probiotics Safe to Use in Acute Pancreatitis :

What Does the Evidence Show?





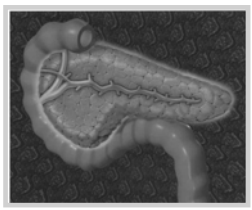
Stephen A. McClave, MD
Professor of Medicine
University of Louisville School of Medicine
Louisville, Kentucky

General Management

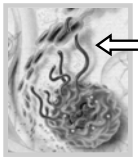
- Wide range of clinical severity
  - Mild self-limited process most common
  - Catastrophic disease, severe complications less frequent
- Initial supportive management regardless of severity
  - IV fluid volume resuscitation
  - Analgesia
  - Correct electrolytes
- Determine disease severity (necrosis, MOF key issues)
  - Ranson's Criteria (≥3)
  - APACHE II score (≥8)
  - Atlanta Classification
  - CRP levels (>150)
  - Balthazar CT grade (>5)

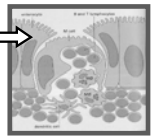
General Management

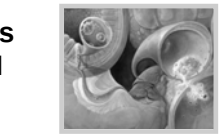
- Seek etiology, rule out gallstone pancreatitis (timing of ERCP?)
- Monitor and manage complications
  - Shock
  - MOF
  - Ascites
  - Sepsis
  - Pseudocyst
- Primary therapy:
  - Obtain enteral access
  - Initiate enteral feeds
  - Add Probiotics??

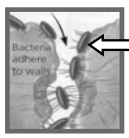


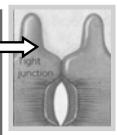
Physiologic Benefits from Providing EN











- Maintain gut integrity (Less bacterial challenge, endotoxemia)
- Set tone for systemic immunity (Innate, acquired responses)
- Attenuate stress response, disease severity (CRP, glucose, TAC)
- Faster resolution of disease process (Duration SIRS, Nutrit Rx, LOS)

Outcome Benefits from Providing EN

- Infection ↓ by 57% [1,3] (EN vs PN, p=0.002)
- Hospital LOS ↓ by 3.94 Days [1,3] (EN vs PN, p=0.0001)
- Organ Failure (MOFS) ↓ by 56% [1,3] (EN vs PN, p<0.05)

- Need for Surg Intervention ↓ by 63% [2,3] (EN vs PN, p<0.05)
- Mortality ↓ by 60% [1,3] (EN vs PN, p<0.05)

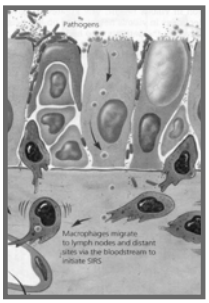
[1] McClave (JPEN 2006;30:143) [2] Marik (BMJ 2004;328:1407)
[3] Jafri, Galandiuk, McClave (DDW 2008 Abstract)

Role of Probiotics

Effect of Comensal Bacteria

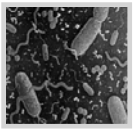
- Pseudomonas Aeruginosa
  - Worst org for gut sepsis
  - Most rapid severe defect
- Bact orgs after shock induce
  - gut cytokine release (TNF, IL-6)
  - Bact OG pathogenic orgs
  - exaggerates response
- Can restoring comensal bacteria reduce this effect in pancreatitis?

Alverdy (CCM 2003;31:598)



Role of Probiotics

Effect of Comensal Bacteria



- **Olah 2002 Pancreatitis Study (Lactobacillus)**

	EN live (n=22)	EN heat-killed (n=23)	
Infected necrosis/abscess	4.5%	30.4%	p=0.023
Hosp LOS	13.7d	21.4d	p=NS

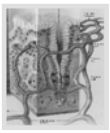
- **Olah 2007 Pancreatitis Study (Four Lactobacillus strains)**

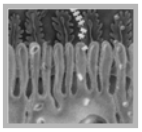
	EN+probios (n=33)	EN alone (n=29)	
SIRS and MOF	24.2%	48.3%	p<0.05
Complicated cases	27.3%	51.7%	p<0.05

Brit J Surg 2002;89:1103 Hepatogastroent 2007;54:590-594

Probiotics Cause Death !

Dutch Multi-Center Trial of Probiotics in SAP





(* $p \leq 0.05$) († $p = 0.08$)	Probiotic (n=152)	Controls (n=144)
MOF	22%	10% *
Surgical Intervention	18%	10% *
ICU LOS	6.6d	3.0d †
Septic Complications	30%	28%
Bowel Ischemia	6% (9 pts)	0% *
Mortality	16%	6% *

(6 out of 9 pts with ischemic bowel on pressor agents)

Besselink (Lancet 2008;371:651)

Probiotics in Severe AP

Comparison of the Three Studies

	Olah 2002 [1] (n=45)	Olah 2007 [2] (n=82)	Besselink 2008 [3] (n=296)
APACHE II Scores	9.15	11.0	8.5
Imrie Scores	2.6	3.0	3.35
CRP (mg/dl)	197.0	203.5	269.0
% EtOH Etiology	64.5%	61.0%	18.5%
% Necrosis	44.5%	61.0%	27.0%
Age (yrs)	45.3	46.7	59.7

[1]Brit J Surg 2002;89:1103 [2]Hepatogastro 2007;54:590 [3]Lancet 2008;371:651

Probiotics in Severe AP

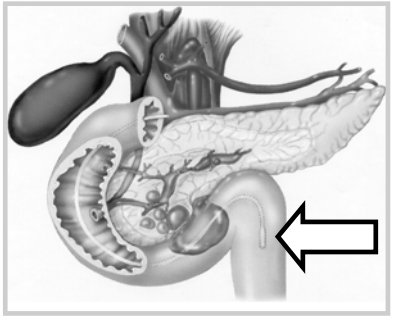
Comparison of the Three Studies

	Olah 2002[1]	Olah 2007[2]	Besselink 2008[3]
Centers	Single	Single	Multicenter (n=15)
Formula	Nutrison Fiber	Nutrison Fiber	Nutrison Multifiber
Prebiotic	Oat Fiber	Beta glucan, inulin, pectin, starch	Cornstarch, maltodextran
Organisms	L. Planitarium	L. Plantarum L. Pediacoccus L. Leuconostoc L. Paracasei	L. Acidophilus L. Casei L. Salivarius L. Lactis B. Bifidum B. Lactis
Dose	10^9	10^{10} x 4	10^{10} x 6
Duration Rx	1 week	1 week	4 weeks

[1]Brit J Surg 2002;89:1103 [2]Hepatogastro 2007;54:590 [3]Lancet 2008;371:651

Probiotics in Acute Pancreatitis:

Where Do We Stand?



Increased Mortality with Probiotics in Severe Acute Pancreatitis: What Next?

Louis M.A. Akkermans

University Medical Center Utrecht
The Netherlands

and

Dutch Acute Pancreatitis Study Group

CNW, New Orleans
Februari 1 2009

Universitair Medisch Centrum Utrecht

The Netherlands

Inhabitants:

>16 million

Surface:

41.528 km²

"the ideal referral area for a multicentre RCT"

Dutch Pancreatitis Study Group

- 22 hospitals, including all university medical centres
- Surgeons, gastroenterologists, radiologists, etc.
- Aim: to improve treatment of acute pancreatitis (AP) through a combination of consultation, centralisation and multicenter research

IAP

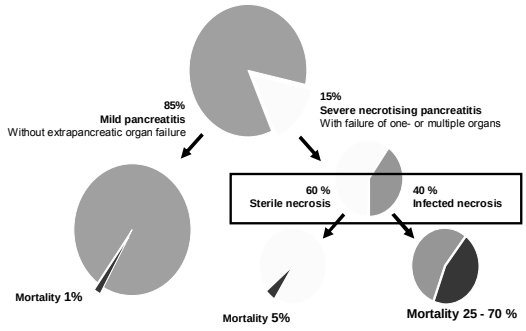
E-P-C EUROPEAN PANCREATIC CLUB

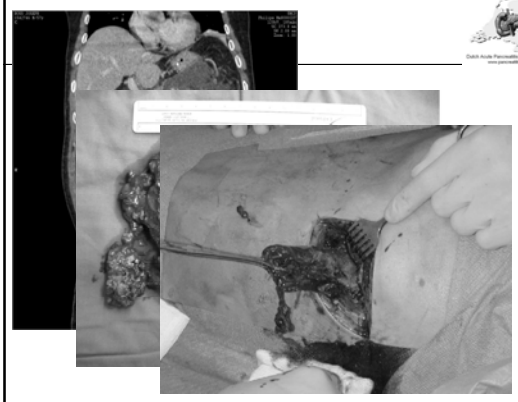
Acute Pancreatitis a deadly and relatively rare disease

- Incidence is rising with 5% per year (50% in 10 yrs)
- *35 patiënts/ hospital/ year, 5- 10 severe cases*
- *5% mortality overall*[1]
- ***11-18% mortality "predicted severe"*** [1]
- *80% mortality caused by infections*

Banks, Am J Gastroenterol 2006

Clinical course





Mechanism for infection: bacterial translocation

1. Intestinal lumen: small bowel bacterial overgrowth
2. Mucosal barrier failure: increased permeability
3. Immune system: dysregulation pro- and anti-imflammatory balance

Infections in Acute Pancreatitis: prophylaxis?

- Infectious complications are responsible for 80% of mortality in acute pancreatitis
- Mortality of patients with infections: 30%
- A preventive strategy is highly needed
- Two options:
  1. ***Antibiotics***
  2. ***Probiotics***

Option 1: antibiotics

- The prophylactic use of antibiotics has long been controversial disadvantages: (multi-)resistance, high costs
- Methodology of the randomised controlled trials has been frequently criticized
- Two large double-blind, placebo-controlled trials and several meta-analyses: ***no effect of antibiotics!***

Option 2: probiotics?

Hypothesis: probiotics reduce bacterial translocation by:

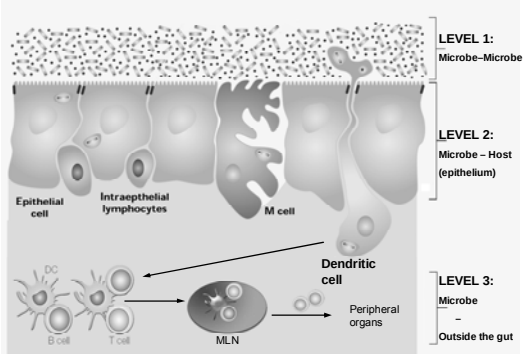
1. *preventing bacterial overgrowth*
2. *reinforcing the mucosal barrier function*
3. *regulating the systemic immune system*

Probiotics: Current evidence?

- Promising results in 12 placebo-controlled trials in surgical conditions
- Several good quality RCTs: pancreatic resections, liver transplantations; significant reduction of infectious complications[1-3]
- Negative effects of probiotics: none!

[1]Rayes et al, *Transplantation* 2002
[2]Rayes et al, *Ann Surg* 2007
[3]Sugawara et al, *Ann Surg* 2006

3 Levels of Probiotic Action



Selection of Probiotics *(Ecologic 641)*

Microbe - microbe

- *Lactobacillus acidophilus*
- *Lactobacillus salivarius*

Immunomodulation

- *Lactobacillus casei*
- *Bifidobacterium bifidus*
- *Bifidobacterium infantis*

Microbe - host

- *Lactococcus lactis*

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial

Marc GH Besselink,
Hjalmar C van Santvoort, Erik Buskens, Marja A Boermeester, Harry van Goor, Harro M Timmerman, Vincent B Nieuwenhuijs, Thomas L Bollen, Bert van Ramshorst, Ben JM Witteman, Camiel Rosman, Rutger J Ploeg, Menno A Brink, Alexander FM Schaapherder, Cornelis HC Dejong, Peter J Wahab, Cees JHM van Laarhoven, Erwin van der Harst, Casper HJ van Eijck, Miguel A Cuesta, Louis MA Akkermans, Hein G Gooszen and the members of the

Dutch Acute Pancreatitis Study Group

Lancet Februari 14, 2008 371;651-9

Methods I

- Randomised, double-blind, placebo-controlled multicenter trial
  - *all 8 Dutch university medical centers*
  - *7 major teaching hospitals*
- 298 patients with predicted severe acute pancreatitis
  - *APACHE II score ≥8,or*
  - *Imrie score ≥3, or*
  - *CRP >150 mg/L*
- Within 72 hours after onset of symptoms a multispecies probiotic preparation or placebo was administered enterally twice daily for 28 days with the continuously running fibre-enriched tube feeding

Methods II

- **Primary endpoint**: the composite of infectious complications during admission and a 90-day follow-up
  - *Infected pancreatic necrosis*
  - *Bacteraemia*
  - *Pneumonia*
  - *Urosepsis*
  - *Infected ascites*
- **Secondary endpoints** included mortality and adverse events

Results I: Baseline characteristics

Randomisation succesful

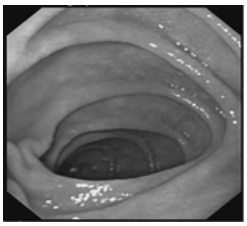
	Probiotics (N=152)	Placebo (N=144)
[illegible]pancreatitis		
	8·6 (±4·4)	8·4 (±4·5)
	3·3 (±1·7)	3·4 (±1·6)
C-reactive protein (on admission)	268 (±127)	270 (±122)
SOFA (on admission)	[illegible] (±2·0)	1·9 (±1·6)
MODS (on admission)	[illegible]	[illegible] (±1·5)
Organ failure prior to randomisation§	[illegible]	[illegible]
Multi-organ failure prior to randomisation	5 (3·3%)	[illegible]
Endoscopic sphincterotomy	48 (32%)	[illegible]
Interval first symptoms to admission (days)	0 (0-3)	0 (0-3)
Interval admission to first dose (days)	2 (0-4)	2 (0-3)
Interval admission to enteral nutrition (days)	2 (0-7)	2 (0-7)

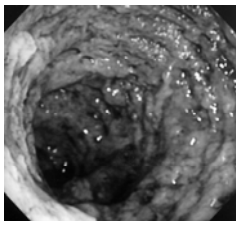
Results II

	Probiotics (N=152)	Placebo (N=144)	p value
Primary endpoint			
Any infectious complication*	46 (30%)	41 (28%)	0·80
Infected necrosis	21 (14%)	14 (10%)	0·29
Bacteraemia	33 (22%)	22 (15%)	0·18
Pneumonia	24 (16%)	16 (11%)	0·31
Urosepsis	1 (0·7%)	2 (1%)	0·61
Infected ascites	4 (3%)	0 (0%)	0·12
Secondary endpoint			
Bowel ischaemia	9 (6%)	0 (0%)	0·004
Mortality	24 (16%)	9 (6%)	0·01

Besselink, Lancet 2008

Normal and ischemic small bowel

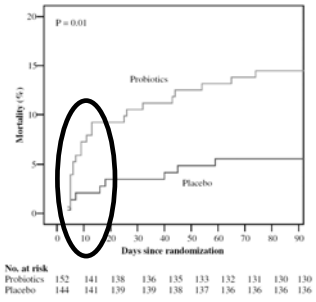




Results III: Bowel ischaemia

- 9 cases of bowel ischaemia, 8 died, survivor: 22yr old male
- Detected during operation and/or autopsy in 7 hospitals (4 university and 3 teaching hospitals)
- Organ failure: median 2 days after admission (range 1-6)
- Occurrence: median 5 days after admission (range 3-12)
- Death: median 6 days after admission (range 4-125)
- In 8 of the 9 patients (including the survivor) the small bowel was involved

Probiotics: mortality first 14 days



Besselink, Lancet 2008

Overwhelming media attention

www.sciencemag.org SCIENCE VOL 319 1 FEBRUARY 2008

CLINICAL TRIALS

Deaths Prompt a Review of Experimental Probiotic Therapy

1632

Vragen van het lid **Kant** (SP) aan de minister van Volksgezondheid, Welzijn en sport over *de probiotica-trial.* (Ingezonden 12 februari 2008)

Conclusion

- In patients with predicted severe acute pancreatitis, probiotic prophylaxis did not reduce the risk of infectious complications
- Probiotic prophylaxis was associated with an over two-fold increased mortality and should therefore not be administered in this category of patients

Follow-up studies

What is the effect of the probiotic preparation on:

intestinal permeability,

enterocyte damage, and

bacterial translocation

- Prospective study in 141 patients with predicted severe acute pancreatitis in 14 hospitals randomised in the PROPATRIA study

- 24h urine was collected 24-48h and 72h after onset of probiotic/placebo treatment

Besselink, 2008

Follow-up studies

In urine collected 24-48 hrs after start probiotics (n=141) determined:

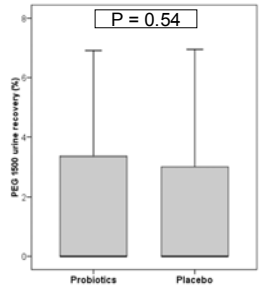
- ***Intestinal permeability*** = *excretion of orally adminstered **PEG** macromolecules (PolyEthylene Glycol)*
- ***Enterocyte damage*** = *excretion of **IFABP** (Intestinal Fatty Acid Binding Protein, located solely in small bowel)*
- ***Bacterial translocation*** = *NOx (NO-metabolites) concentration*

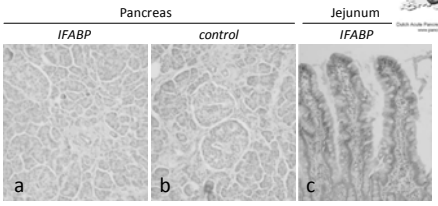
Besselink, 2008

Probiotics and Intestinal permeability

PEG was higher in patients who developed:

Organ failure (P<0.0001)
Bacteremia (P=0.001)
Died (P=0.009)





Frozen sections of pancreas (a, b) and jejunum (c) were incubated with a monoclonal anti-human IFABP antibody (a and c) or with buffer (b) and processed for immunohistochemistry.

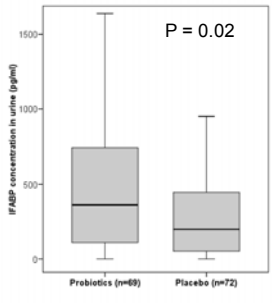
In collaboration with Prof. W. Buurman, Maastricht

IFAPB is a marker for intestinal enterocyte damage and is solely located in the small bowel and not in the pancreas.

Probiotics and Enterocyte damage

IFABP concentration in urine were higher in patients who developed:

Bacteremia (P=0.03)
Infected necrosis (P=0.01)
Organ failure (P=0.008)

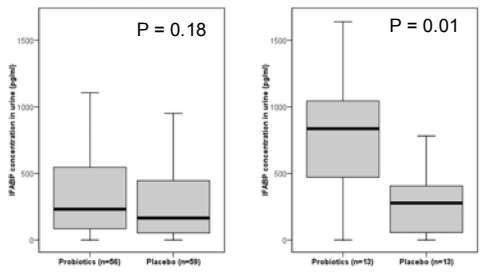


Besselink, 2008

Enterocyte damage

Subgroups +/- organ failure

Without organ failure | **With organ failure**



Besselink, 2008

Probiotics and bacterial translocation

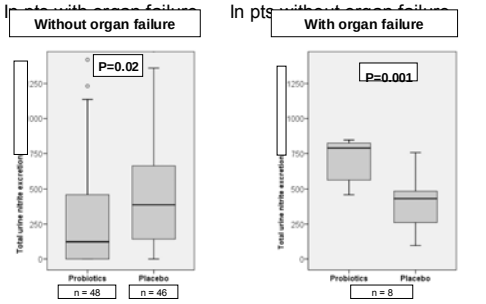
- Nitric oxide (NO) is a documented marker of bacterial translocation in acute pancreatitis
- NO is produced by a variety of cells, in particular endothelial cells, macrophages and platelets
- NO production is a primary reaction to bacteria and is a key mediator of multiple organ failure and sepsis
- Because NO is an unstable molecule, NO-metabolites (NOx) in urine are generally accepted as a reflection of NO production

P = 0.99

Besselink, 2008

Bacterial translocation and probiotics (NOx)

Subgroups +/- organ failure



Take home messages

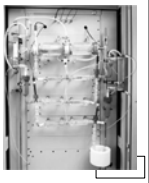
Possible effects of the probiotic product used in PROPATRIA:

1. **PEG excretion was significantly enhanced in AP (intestinal permeability ↑), but there was no difference between placebo and probiotics.(no probiotic effect)**
2. **Decrease of NOx excretion in patients without organ failure (positive probiotic effect)**
3. **Increase of NOx excretion in patients with organ failure (negative probiotic effect)**
4. **No effect on IFABP excretion in patients without organ failure**
5. **Deteriorating effect on smal bowel integrity (IFABP ↑) in patients with organ failure (negative probiotic effect)**
6. **Probiotics should not be used in patients with organ failure**

Ongoing research

- **Very early compared with normal start of enteral nutrition in patients with predicted severe acute pancreatitis: PYTHON-trial**

- **Role of enteral feeding, fibers and diferent probiotics in a gastrointestinal model (TIM-1)**
- **Effects of fermentation products** (lactate, SCFA, pH) **from TIM-model in cell lines** (Caco-2) **and animal models**



Future research

Urine samples from PROPATRIA patients: Metabolomics

- **Are there treatment-induced differences?**
- **Are the metabolic alterations host or microbiota-derived?**
- **Can we correlate specific alterations in microbiota-derived metabolites to specific members of the gastro-intestinal microbiota (i.e. the probiotics applied or the endogenous microbiota)?**

Faeces

Microbiology (qPCR probiotics, FISH, Array)

DNA

Genetic risk factors (including polymorphisms innate immunity)

Blood samples

- Chemokine and cytokine profiling

Acknowledgements

Dutch Acute Pancreatitis Study Group

SenterNovem