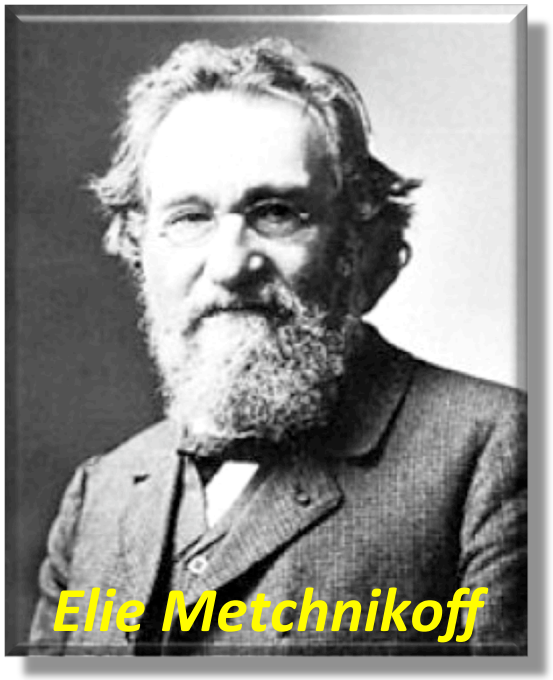
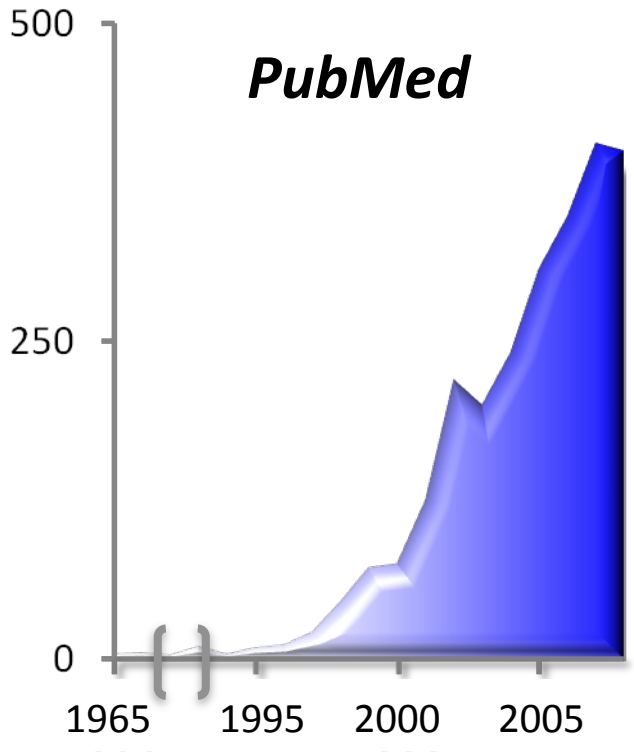
Modifications thérapeutiques du microbiote en Réanimation

Journées Francophones de Nutrition,
Reims, 09-12-2011

Probiotiques





« Les probiotiques sont des microorganismes viables qui lorsqu'ils sont ingérés en quantité suffisante ont un effet bénéfique sur la santé »

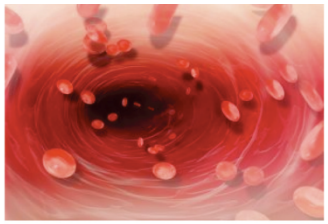
Probiotic	A live microbial food ingredient which is beneficial to health
Prebiotic	A non-digestible food ingredient which beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon having the potential to improve host health
Synbiotic	A mixture of probiotics and prebiotics which beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, and thus improving host health and wellbeing

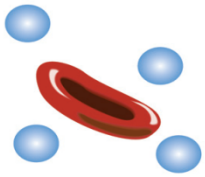
Medical condition	Class(es) of probiotic
Lactose maldigestion	LAB and *Streptococcus salivarius* subsp. *thermophilus*
Gastroenteritis	
Acute diarrhea	LAB, *Bifidobacterium* species, or *Saccharomyces boulardii*
Antibiotic-associated diarrhea	LAB or *S. boulardii*
Traveler's diarrhea	LAB
Allergies	LAB
Clostridium difficile–induced colitis	LAB
Dental caries	LAB
Intestinal inflammation in children with cystic fibrosis	LAB
Respiratory infection in children	LAB
Nasal colonization with pathogens	LAB
Inflammatory bowel disease or irritable bowel syndrome	LAB and *Bifidobacterium* species, *S. boulardii* and drug, *S. boulardii* alone, or LAB alone

Effets des probiotiques

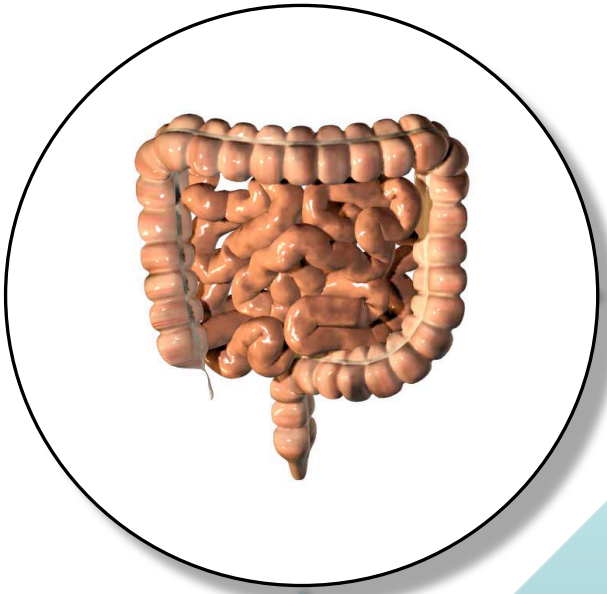
Effets moléculaires	*Effets cliniques*
Effets immunologiques	**Effets digestifs**
Stimulation production IgA	Prévention/réduction diarrhées
Réduction production IgE	Prévention/réduction diarrhées postantibiotiques
Stimulation production NO	Prévention/Traitement des poussées de MICI
Modulation synthèse et profil cytokinique	Réduction symptômes colon irritable
Stimulation production peptides antimicrobiens	
Stimulation macrophages	
Stimulation cellules NK	
Modulation différentiation Thelpers (Th1/Th2)	
Induction tolérance orale	
Effets non-immunologiques	**Effets dermatologiques**
Exclusion compétitive des bactéries pathogènes, prévention de l'adhérence, modification pH local	Réduction de l'atopie
Diminution production toxiques microbiens	Modification de la flore vaginale
Stimulation production mucine	
Amélioration de la barrière intestinale	
Production nutriments	
Production antioxydants	
Modulation apoptose	
Réduction mutagénicité	
Stimulation croissance et régénération épithéliale	
Modulation métabolisme des acides gras	

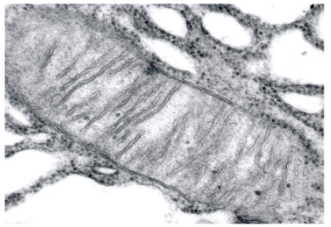
Choc, Troubles circulatoires





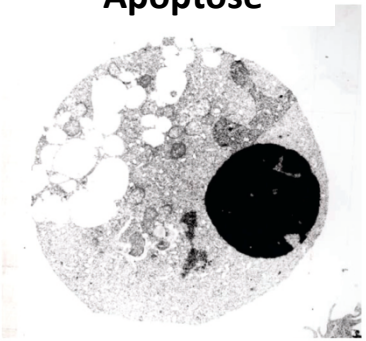
Cytokines pro-inflammatoires





Cytopathie, Acidose

Apoptose



Monoxyde d' azote NO

Peroxynitrite ONOO

Déséquilibre de la flore, colonisation par bactéries pathogènes

Hyperperméabilité digestive, TB ?

Lysozyme-Modified Probiotic Components Protect Rats against Polymicrobial Sepsis: Role of Macrophages and Cathelicidin-Related Innate Immunity[1]

Heng-Fu Bu,*† Xiao Wang,*† Ya-Qin Zhu,*‡ Roxanne Y. Williams,* Wei Hsueh,† Xiaotian Zheng,† Ranna A. Rozenfeld,‡ Xiu-Li Zuo,† and Xiao-Di Tan[2]*†‡

The Journal of Immunology

The Journal of TRAUMA® *Injury, Infection, and Critical Care*

Pretreatment With Pro- and Synbiotics Reduces Peritonitis-Induced Acute Lung Injury in Rats

Demet Tok, MD, Ozer Ilkgul, MD, Stig Bengmark, MD, PhD, Hasan Aydede, MD, Yamac Erhan, MD, Fatma Taneli, MD, Cevval Ulman, MD, Seda Vatansever, MD, Can Kose, MD, and Gulay Ok, MD

Clinical Nutrition (2005) 24, 211–219

ELSEVIER

Clinical Nutrition

http://intl.elsevierhealth.com/journals/clnu

ORIGINAL ARTICLE

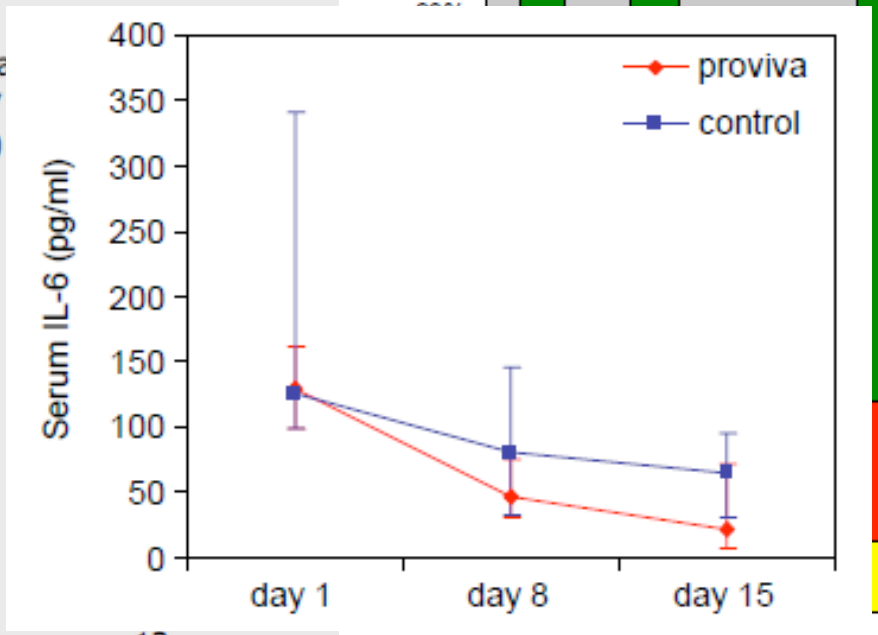
A prospective randomised trial of probiotics in critically ill patients

Clare E. McNaught, Nicholas P. Woodcock, Alexander D.G. Anderson, John MacFie*

Department of Surgery, Combined Gastroenterology Research Group, Scarborough Hospital, Woodlands Drive, Scarborough, North Yorkshire YO12 6QL, UK

Received 1 August 2003; accepted 23 August 2004

	Probiotic group	Control group
No. of patients	52	51
M:F ratio	33:19	25:26
Median age	71 yea	
Interquartile range	65–77	
Range	28–90	
Diagnoses		
Post-op GI	14	
Post-op vascular	10	
Post-op trauma	3	
Post-op other	2	
Medical	21	
Trauma	0	
Other	2	
APACHE II scores		
Median	12	12
Interquartile range	9–16	8–17

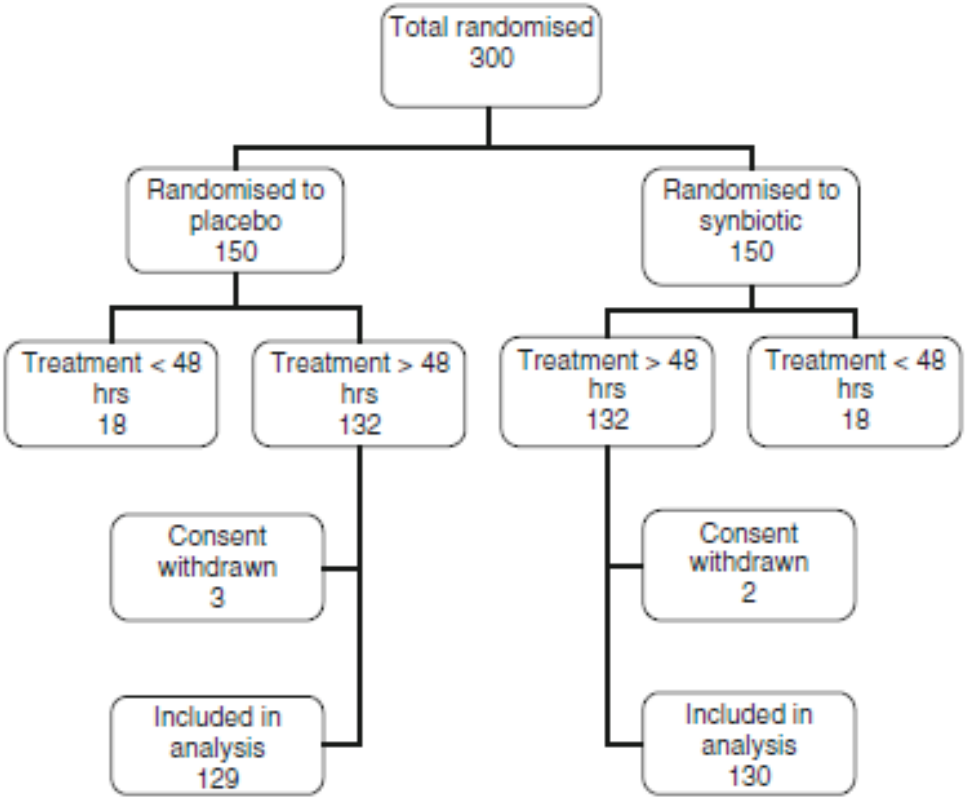


Intensive Care Med
DOI 10.1007/s00134-008-1368-1

ORIGINAL

David J. W. Knight
Dale Gardiner
Amanda Banks
Susan E. Snape
Vivienne C. Weston
Stig Bengmark
Keith J. Girling

Effect of synbiotic therapy on the incidence of ventilator associated pneumonia in critically ill patients: a randomised, double-blind, placebo-controlled trial



Variable	Synbiotic	Placebo	*P*	Relative risk (95% Confidence Interval)
Number of patients	130	129		
VAP (% of total)	12 (9)	17 (13)	0.42	0.70 (0.35–1.41)
Polymicrobial VAP	3	5		
Individual pathogens				
Enterobacteriaceae	6	7		
Pseudomonas aeruginosa		1		
MRSA		1		
Haemophilus influenzae		1		
Acinetobacter baumannii	3	1		
Stenotrophomonas maltophilia		1		
VAP episodes per 1,000 ventilator days	13	14.6	0.91	0.89 (0.42–1.87)
Number of ventilator days, median (IQR)	5 (2–9)	5 (3–11)	0.82	

Oral probiotic and prevention of Pseudomonas aeruginosa infections: a randomized, double-blind, placebo-controlled pilot study in ICU-patients

Critical Care 2008, **12**:R69 doi:10.1186/cc6907

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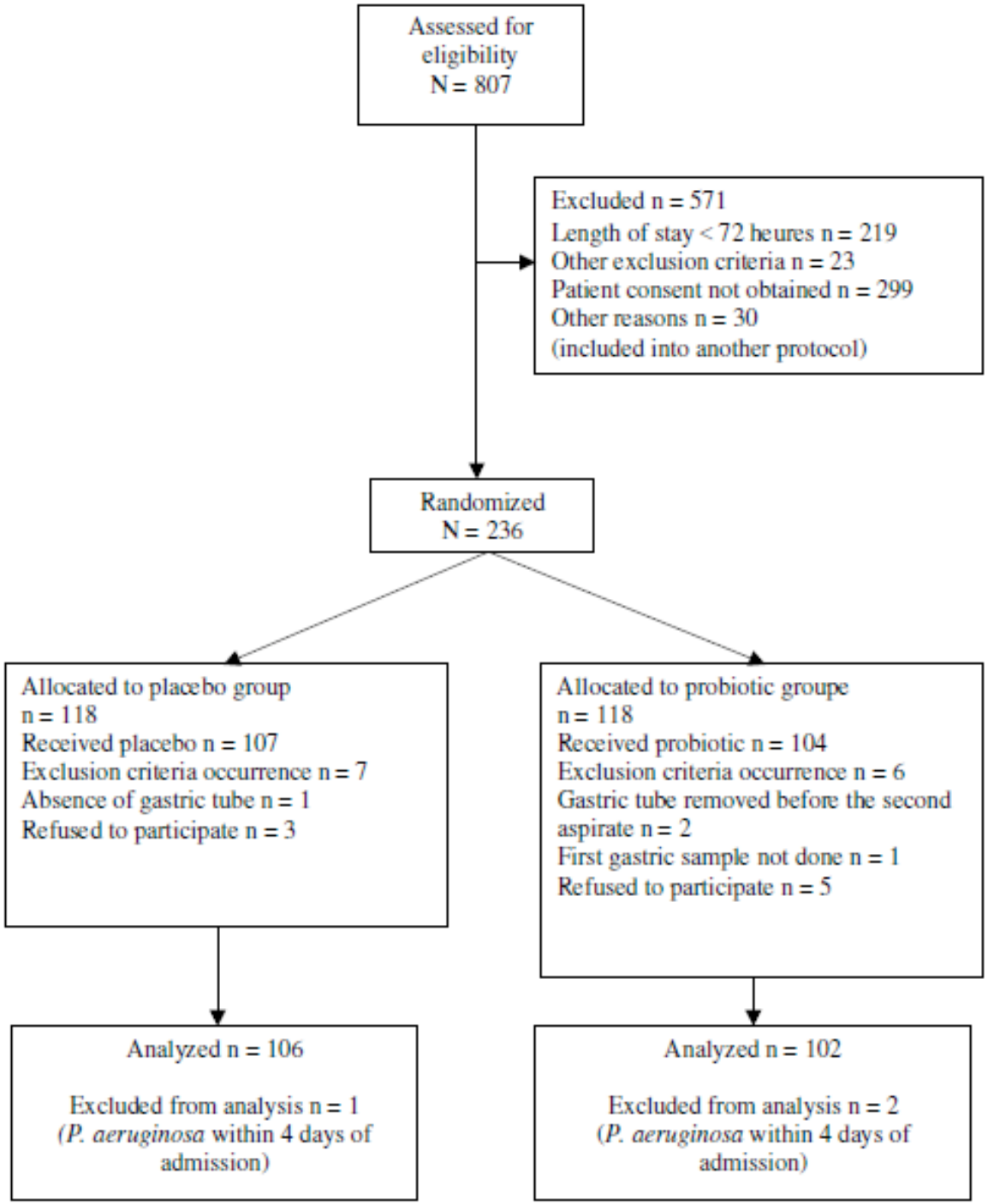
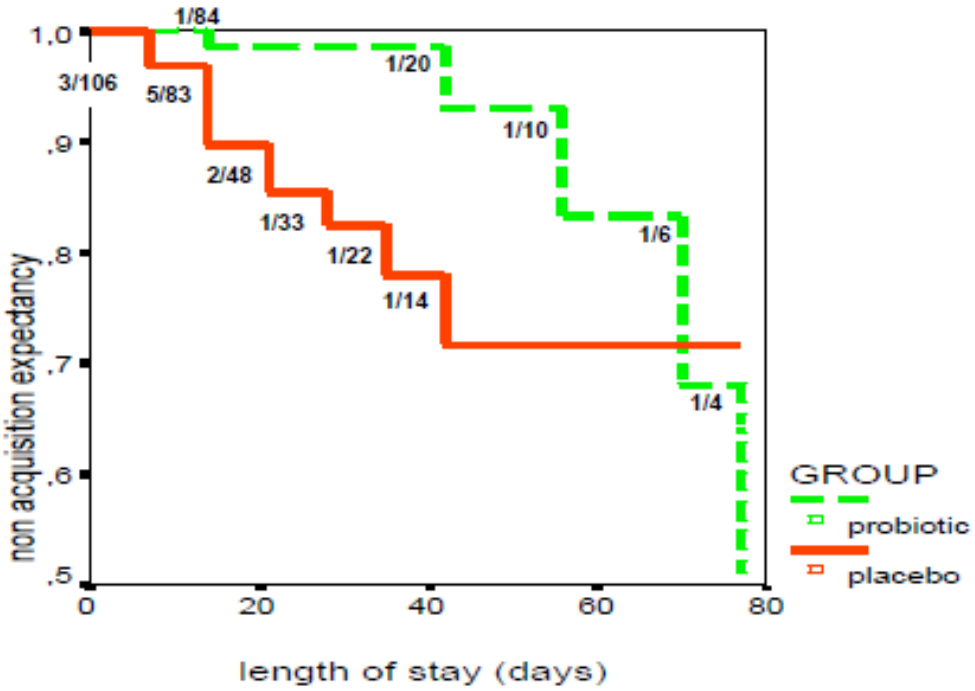

Assessed for eligibility N = 807
Excluded n = 571
Length of stay < 72 heures n = 219
Other exclusion criteria n = 23
Patient consent not obtained n = 299
Other reasons n = 30
(included into another protocol)
Randomized N = 236
Allocated to placebo group n = 118
Received placebo n = 107
Exclusion criteria occurrence n = 7
Absence of gastric tube n = 1
Refused to participate n = 3
Allocated to probiotic groupe n = 118
Received probiotic n = 104
Exclusion criteria occurrence n = 6
Gastric tube removed before the second aspirate n = 2
First gastric sample not done n = 1
Refused to participate n = 5
Analyzed n = 106
Excluded from analysis n = 1
(P. aeruginosa within 4 days of admission)
Analyzed n = 102
Excluded from analysis n = 2
(P. aeruginosa within 4 days of admission)


1/84
1,0
3/106
5/83
1/20
1/10
.9
2/48
1/33
1/6
.8
1/22
1/14
.7
1/4
.6
.5
non acquisition expectancy
0
20
40
60
80
length of stay (days)
GROUP
probiotic
placebo

OR: 3.46

Clinical Nutrition (2007) 26, 182–192

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REVIEW

The use of pre- pro- and synbiotics in adult intensive care unit patients: Systematic review

Peter J. Watkinson[a,*], Vicki S. Barber[a], Paul Dark[b], J. Duncan Young[a]

[a]*Intensive Care Society Trials Group, Kadoorie Centre, Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK*
[b]*Hope Hospital, University of Manchester, UK*

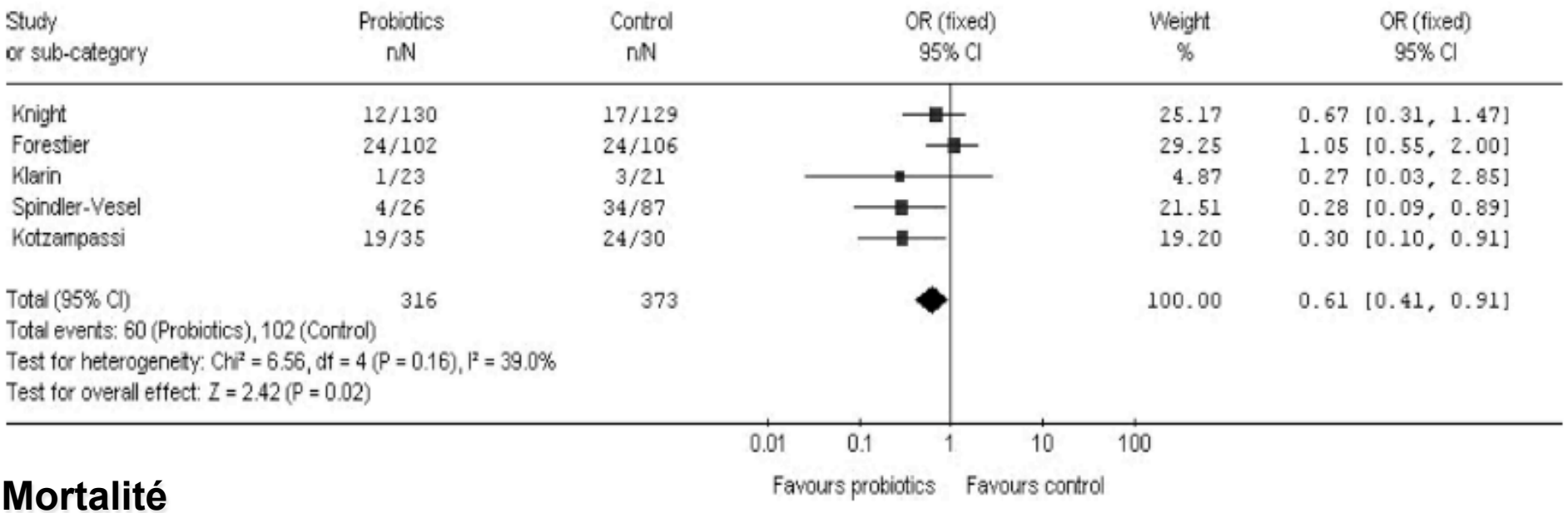
Received 22 June 2006; accepted 29 July 2006

Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials*

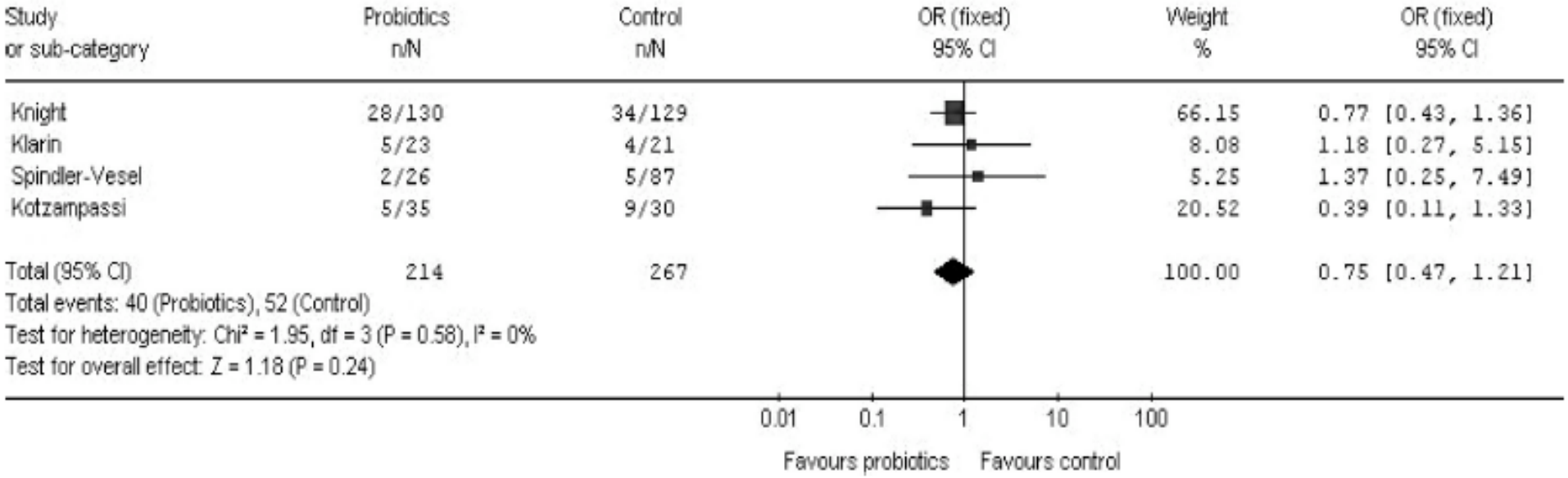
Ilias I. Siempos, MD; Theodora K. Ntaidou, MD; Matthew E. Falagas, MD, MSc, DSc

Crit Care Med 2010

PAVM



Mortalité



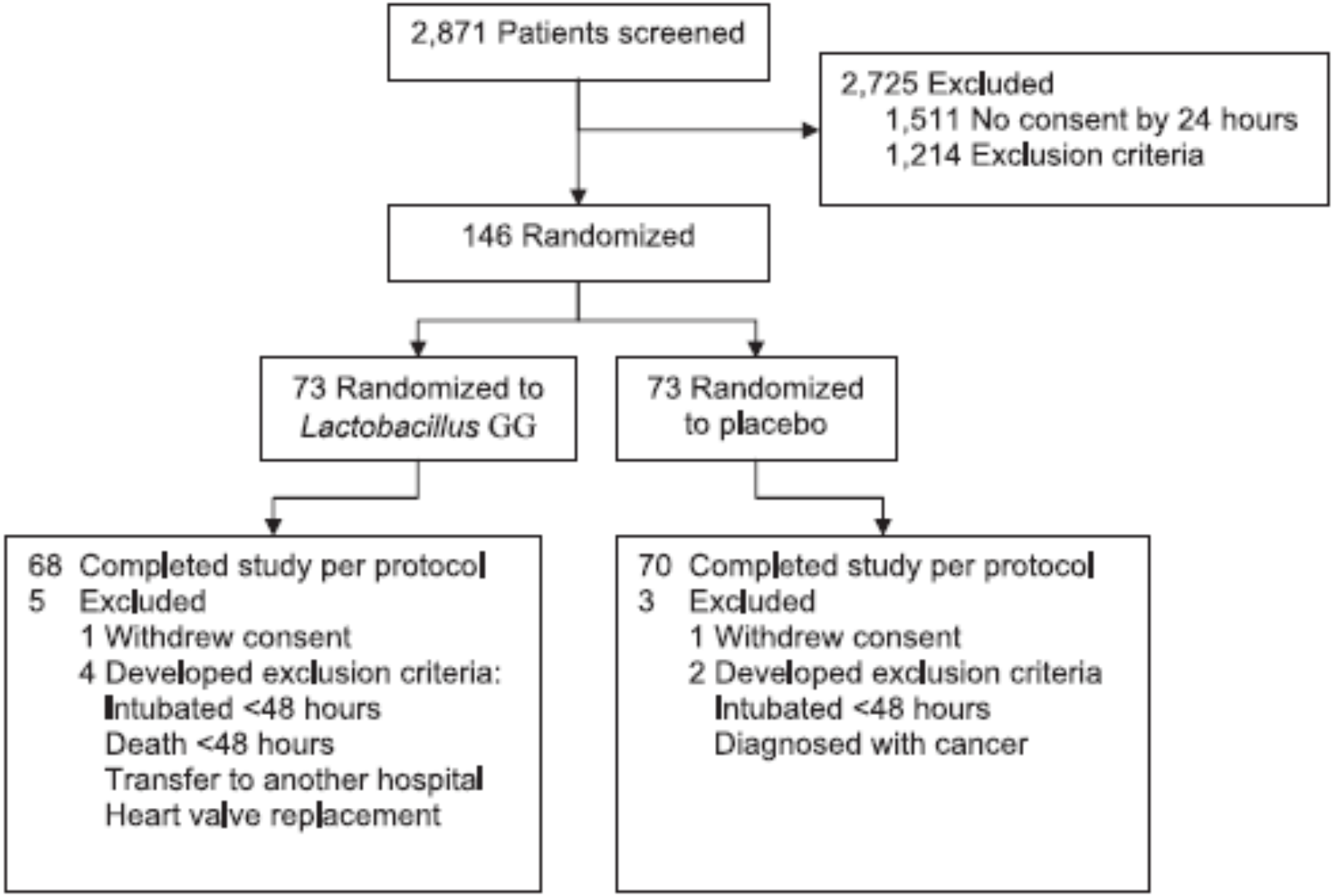
Probiotic Prophylaxis of Ventilator-associated Pneumonia

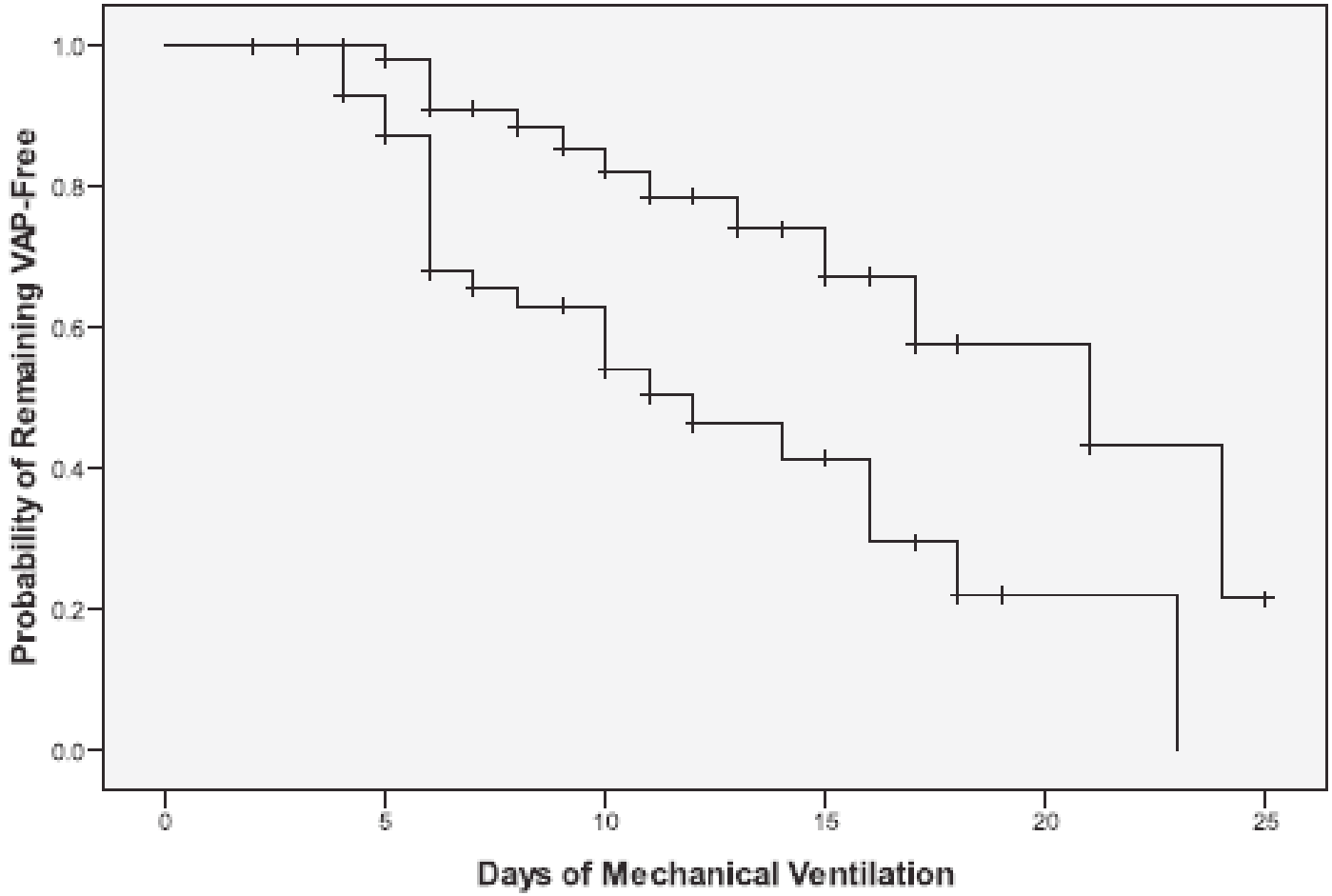
A Blinded, Randomized, Controlled Trial

Lee E. Morrow[1], Marin H. Kollef[2], and Thomas B. Casale[3]

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Creighton University School of Medicine, Omaha, Nebraska; [2]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University in St. Louis, School of Medicine, St. Louis, Missouri; and [3]Department of Allergy and Immunology, Creighton University School of Medicine, Omaha, Nebraska

AJRCCM 2010


2,871 Patients screened
2,725 Excluded
1,511 No consent by 24 hours
1,214 Exclusion criteria
146 Randomized
73 Randomized to *Lactobacillus* GG
73 Randomized to placebo
68 Completed study per protocol
5 Excluded
1 Withdrew consent
4 Developed exclusion criteria:
Intubated <48 hours
Death <48 hours
Transfer to another hospital
Heart valve replacement
70 Completed study per protocol
3 Excluded
1 Withdrew consent
2 Developed exclusion criteria
Intubated <48 hours
Diagnosed with cancer


Probability of Remaining VAP-Free
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Days of Mechanical Ventilation

	Placebo ($n = 70$)	*Lactobacillus* GG ($N = 68$)	*P* Value
Death	15 (21.4%)	12 (17.6%)	0.47
Clostridium difficile diarrhea	13 (18.6%)	4 (5.8%)	0.02
Days of *Clostridium difficile* diarrhea, mean ± SD*	13.2 ± 7.4	9.8 ± 4.9	0.39
ICU-associated diarrhea	44 (62.9%)	42 (61.8%)	0.81
Days of ICU-associated diarrhea, mean ± SD†	5.9 ± 3.8	4.1 ± 3.7	0.03
Total antibiotic-days, mean ± SD	16.3 ± 14.4	13.3 ± 10.4	0.16
Prescribed for VAP	8.6 ± 10.3	5.6 ± 7.8	0.05
Prescribed for *Clostridium difficile*	2.1 ± 4.8	0.5 ± 2.3	0.02
Hospital length of stay in days, mean ± SD	21.7 ± 17.4	21.4 ± 14.9	0.90
ICU length of stay in days, mean ± SD	14.6 ± 11.6	14.8 ± 11.8	0.87
Duration of mechanical ventilation in days, mean ± SD	9.6 ± 7.2	9.5 ± 6.3	0.91
Hospital charges	$416,446 ± 359,701	$350,847 ± 258,087	0.22

Intensive Care Med
DOI 10.1007/s00134-010-1927-0

ORIGINAL

Damien Barraud
Claire Blard
François Hein
Olivier Marçon
Aurélie Cravoisy
Lionel Nace
François Alla
Pierre-Edouard Bollaert
Sébastien Gibot

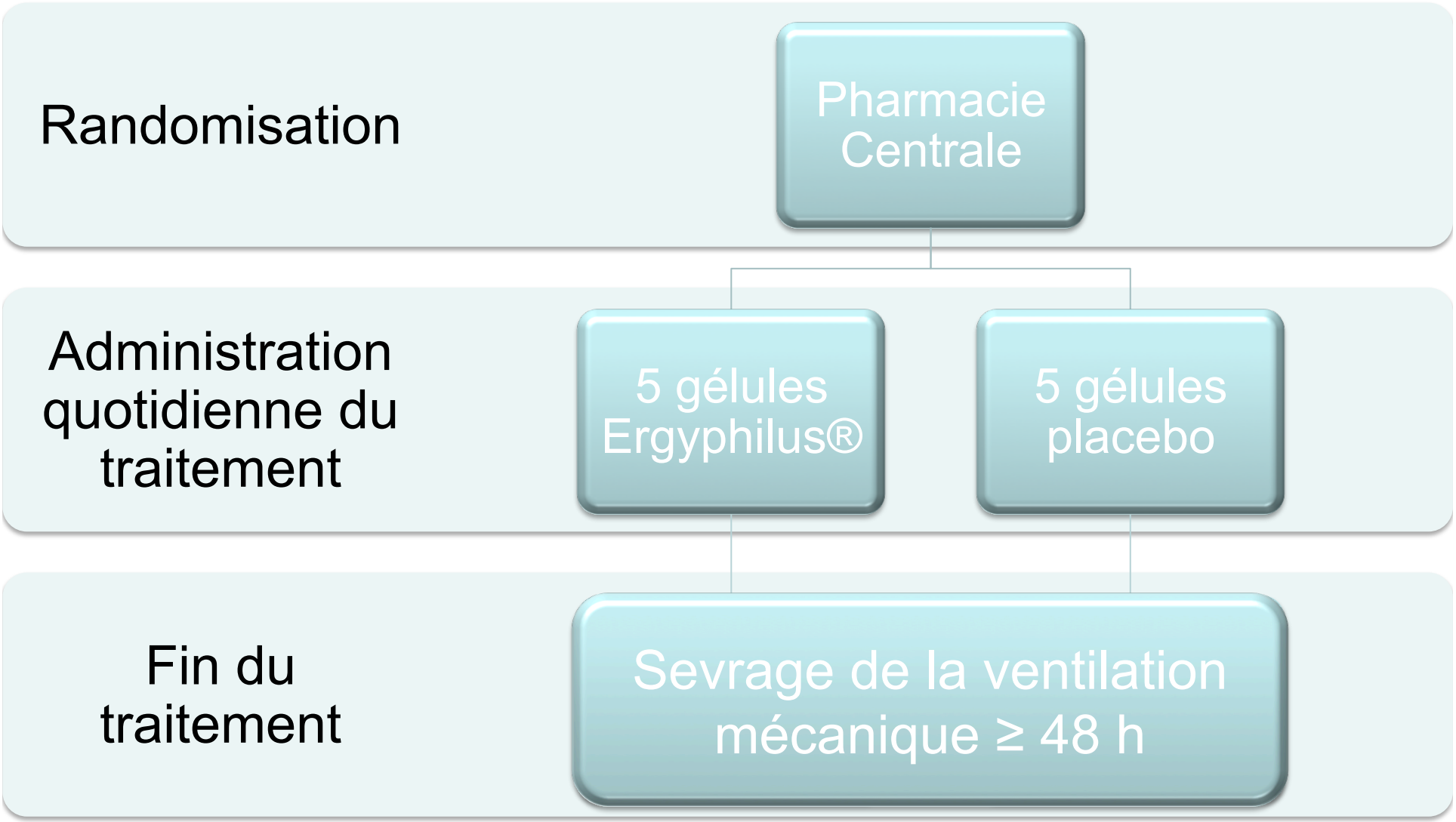
Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial

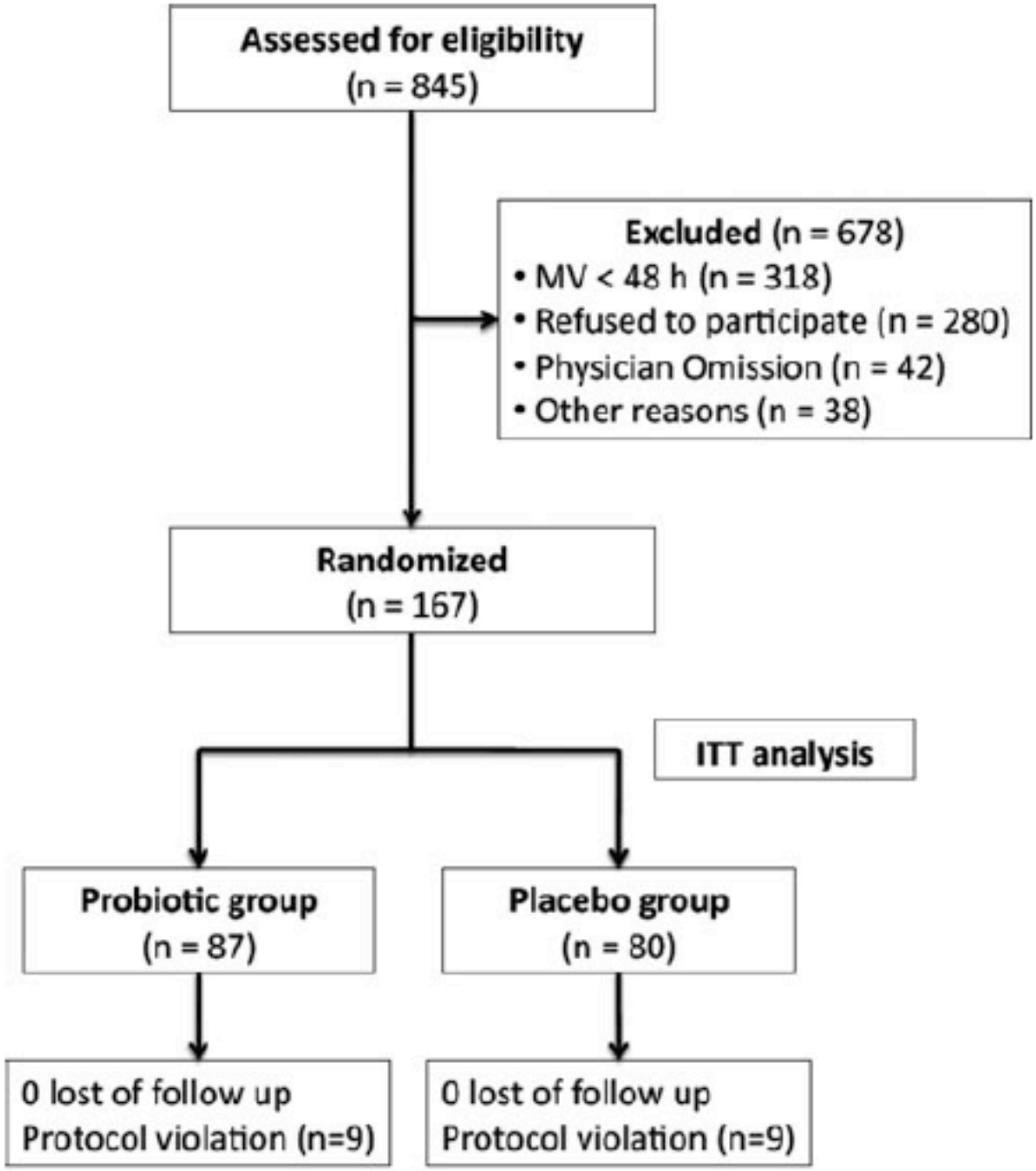
Patients et méthodes

- ***Critères d'inclusion*** : patients majeurs ventilés mécaniquement pour une durée prévisible ≥ 48h

- ***Critères d'exclusion*** :
  - Sujet mineur / Femme enceinte
  - Immunodépression
  - Grêle court
  - Tutelle

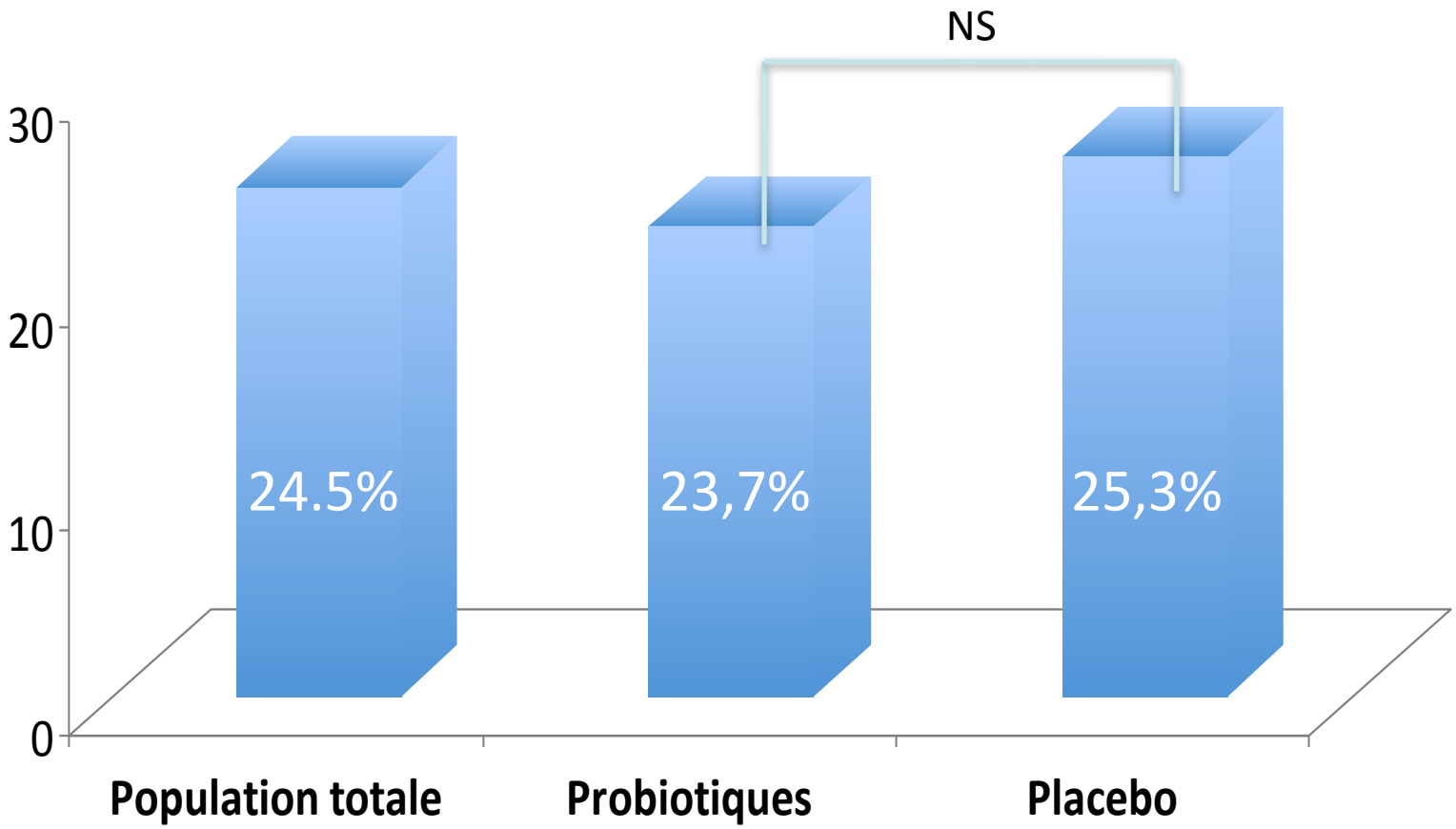
Patients et méthodes

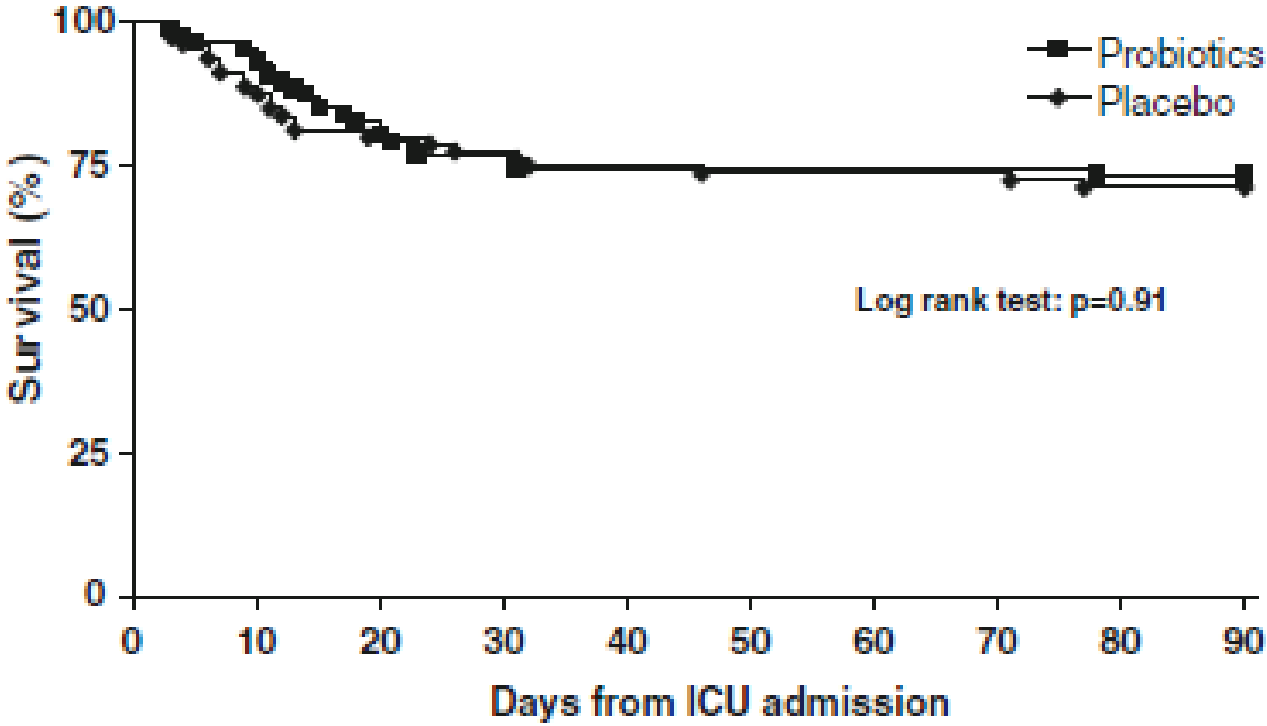


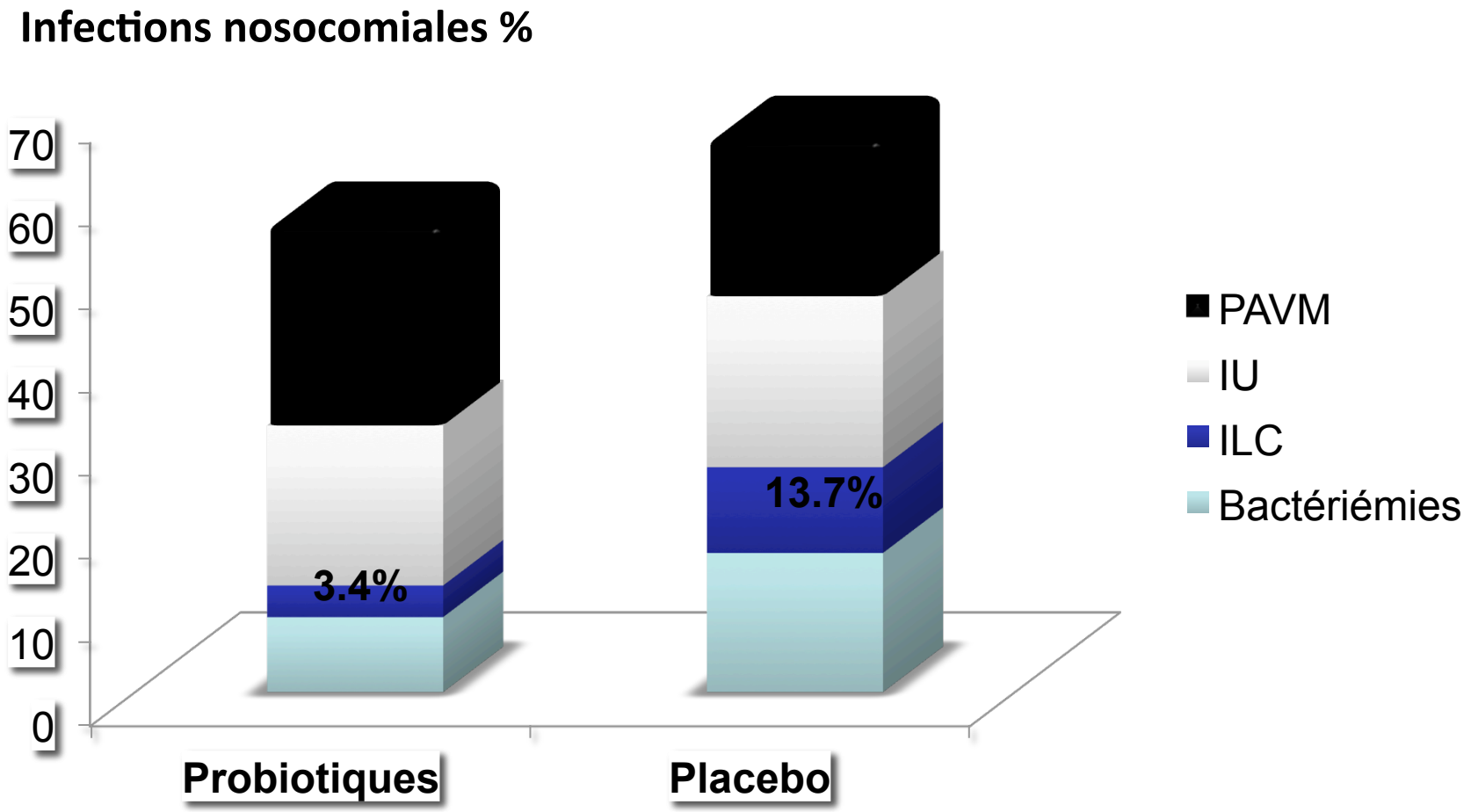

Assessed for eligibility
(n = 845)
Excluded (n = 678)
• MV < 48 h (n = 318)
• Refused to participate (n = 280)
• Physician Omission (n = 42)
• Other reasons (n = 38)
Randomized
(n = 167)
ITT analysis
Probiotic group
(n = 87)
Placebo group
(n = 80)
0 lost of follow up
Protocol violation (n=9)
0 lost of follow up
Protocol violation (n=9)

	Total ($n = 167$)	Probiotics ($n = 87$)	Placebo ($n = 80$)
Age (years)	60.7 ± 15.8	59.1 ± 15.9	61.8 ± 15.5
Sex (male), *n*	68 (41)	33 (38)	35 (44)
McCabe score	0.46 ± 0.53	0.43 ± 0.56	0.48 ± 0.50
BMI (kg/m^2)	27.7 ± 7.6	27.7 ± 7.6	27.6 ± 7.6
SAPS II	59.8 ± 18.5	58.6 ± 17.3	60.5 ± 19.6
SOFA score at admission	9.3 ± 4.6	9.0 ± 4.6	9.7 ± 4.8
Reason for admission, *n*			
Shock	77 (46)	39 (45)	38 (47.5)
Acute respiratory failure	58 (35)	28 (32)	30 (37.5)
Coma	6 (3.5)	4 (4.5)	2 (2.5)
Other	26 (15.5)	16 (18.5)	10 (12.5)
Delay from admission to treatment (days)	2.4 ± 1.8	2.5 ± 1.8	2.3 ± 1.8
Infections and sources, *n*			
Bacteremia	19 (11.4)	9 (10.4)	10 (12.5)
Lung	76 (45.5)	38 (43.7)	38 (47.5)
Urinary tract infection	10 (6)	4 (4.6)	6 (7.5)
Abdomen	4 (2.4)	2 (2.3)	2 (2.5)
Skin and soft tissue	6 (3.6)	3 (3.4)	3 (3.7)
Meningitis	6 (3.6)	4 (4.6)	2 (2.5)
Other	12 (7.2)	7 (8.0)	5 (6.2)
Unknown	7 (4.2)	4 (4.6)	3 (3.7)
Non-infected	27 (16.2)	16 (18.4)	11 (13.8)
Antibiotic treatment			
Before inclusion, *n*	57 (34)	27 (31)	31 (39)
Duration before inclusion (days)	4.0 ± 4.3	4.6 ± 5.4	3.4 ± 2.9
At inclusion, *n*	140 (84)	71 (82)	69 (86)
Biomarkers			
C reactive protein (mg/L)	166 ± 124	168 ± 121	165 ± 128
Procalcitonin (ng/mL)	12.4 ± 13.1	11.0 ± 10.9	13.2 ± 15.3

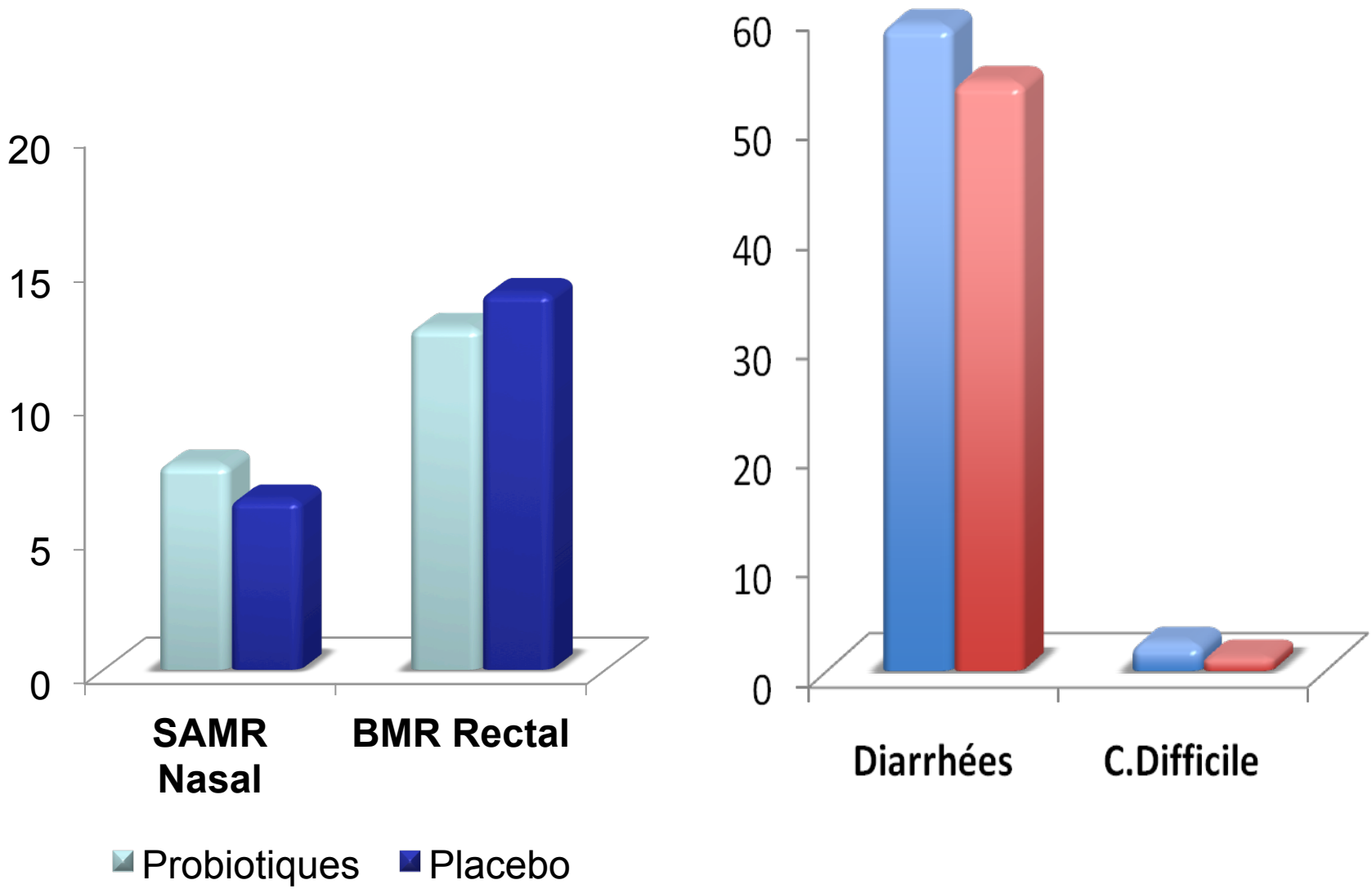
Mortalité J28 (%)

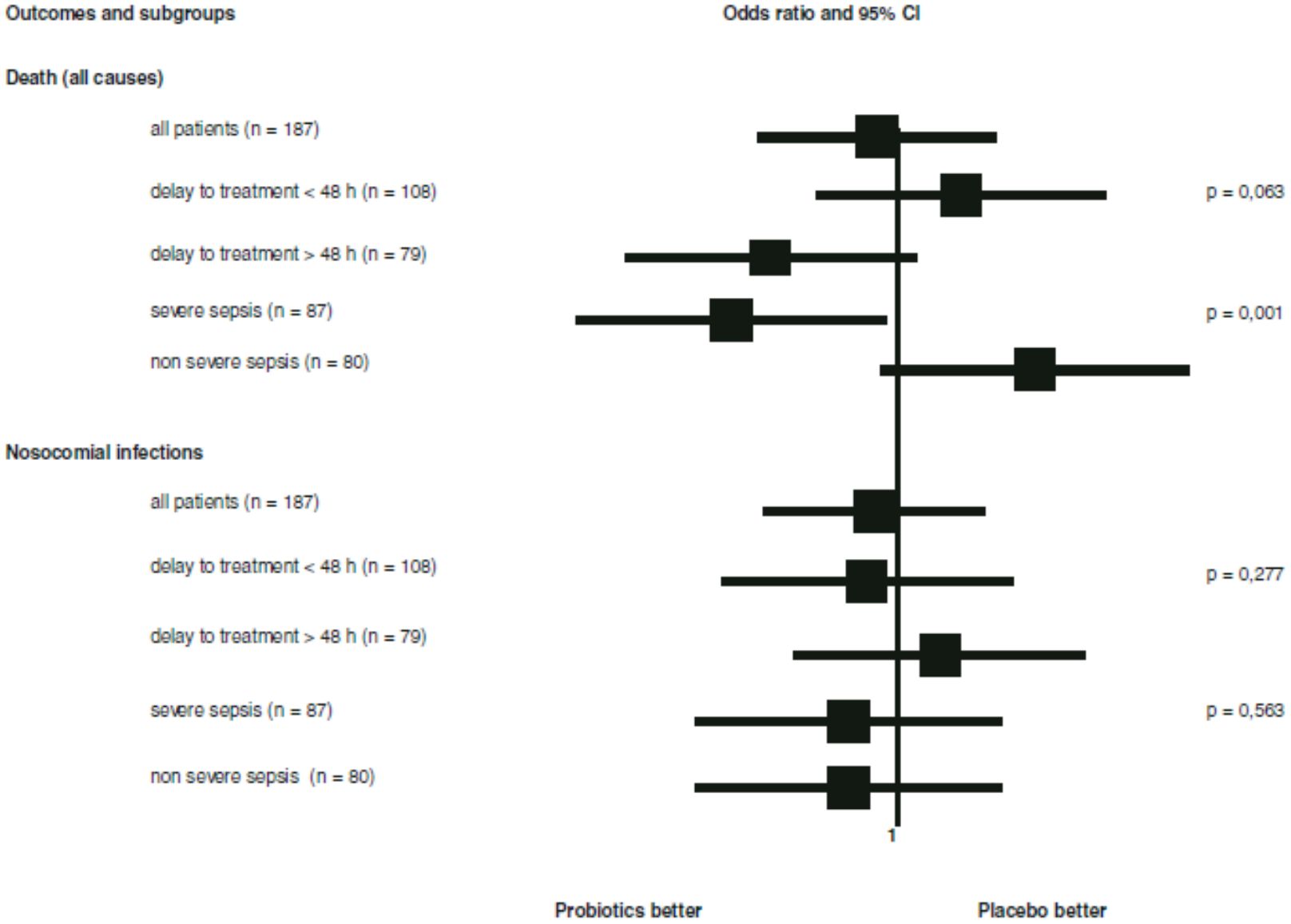


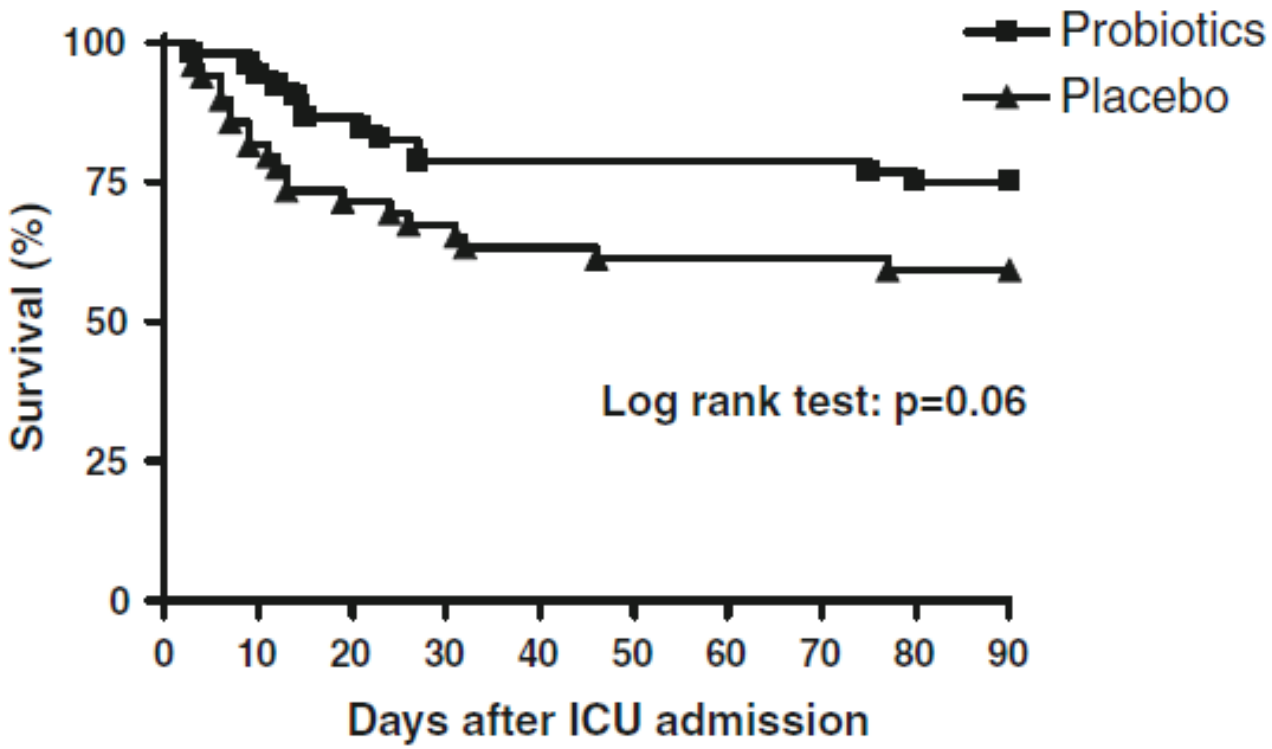

100
75
50
25
0
Survival (%)
0
10
20
30
40
50
60
70
80
90
Days from ICU admission
Probiotics
Placebo
Log rank test: p=0.91


Infections nosocomiales %
70
60
50
40
30
20
10
0
3.4%
13.7%
Probiotiques
Placebo
PAVM
IU
ILC
Bactériémies

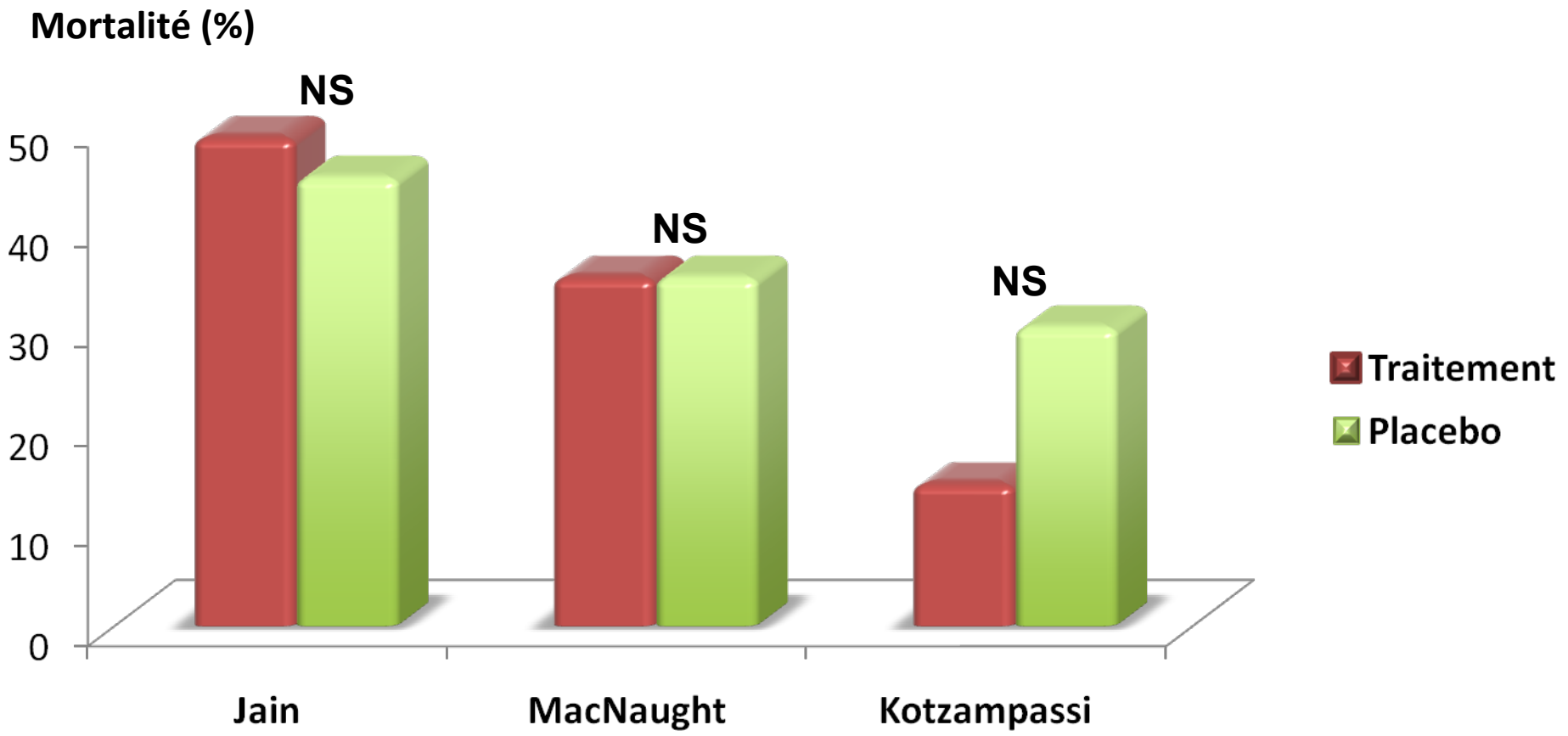
Évènements %


20
15
10
5
0
SAMR Nasal
BMR Rectal
Probiotiques
Placebo
60
50
40
30
20
10
0
Diarrhées
C.Difficile

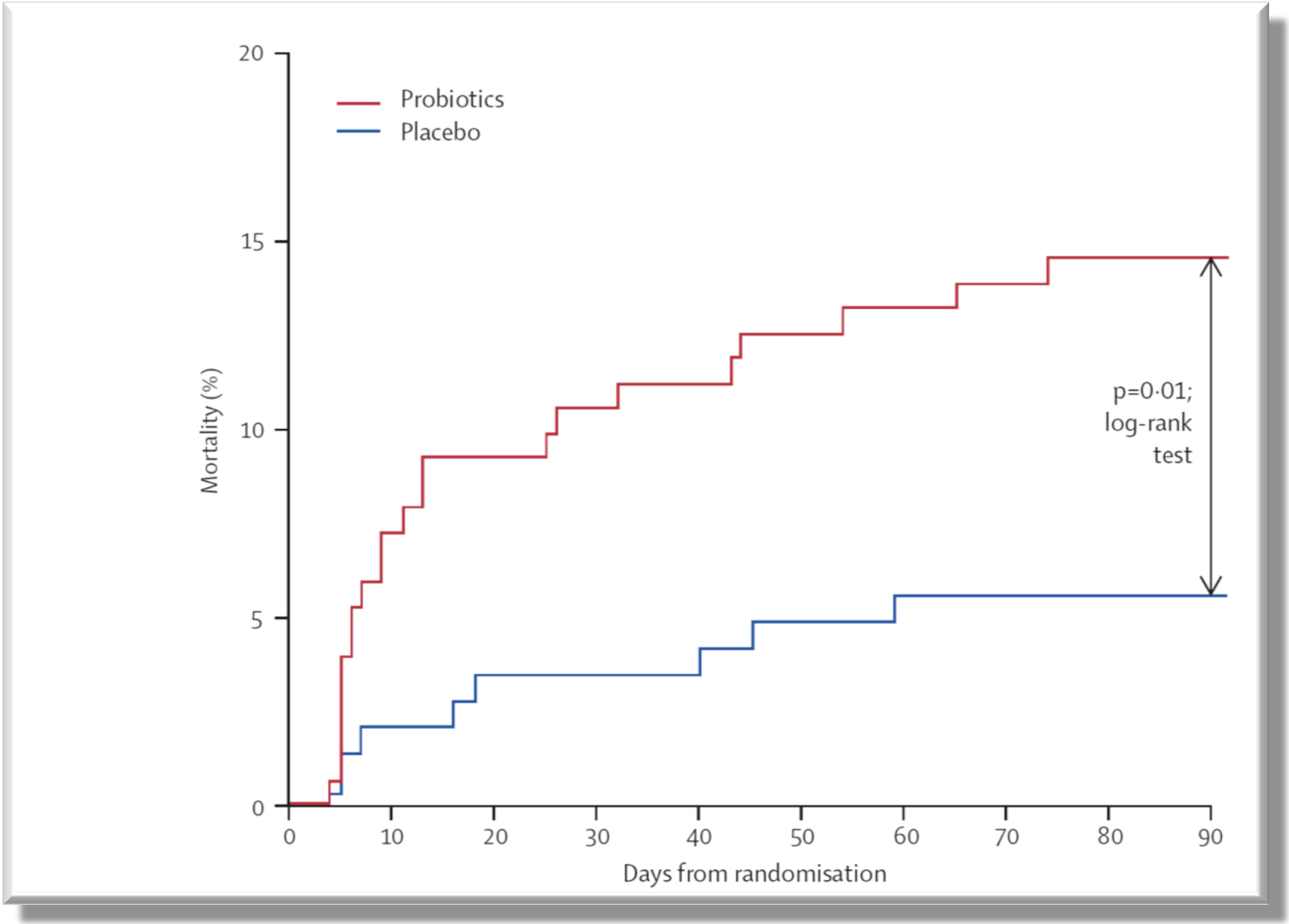

Outcomes and subgroups
Odds ratio and 95% CI
Death (all causes)
all patients (n = 187)
delay to treatment < 48 h (n = 108)
delay to treatment > 48 h (n = 79)
severe sepsis (n = 87)
non severe sepsis (n = 80)
p = 0,063
p = 0,001
Nosocomial infections
all patients (n = 187)
delay to treatment < 48 h (n = 108)
delay to treatment > 48 h (n = 79)
severe sepsis (n = 87)
non severe sepsis (n = 80)
p = 0,277
p = 0,563
1
Probiotics better
Placebo better


Probiotics
Placebo
100
75
50
25
0
Survival (%)
Log rank test: p=0.06
0
10
20
30
40
50
60
70
80
90
Days after ICU admission

• Absence d'effet sur la mortalité

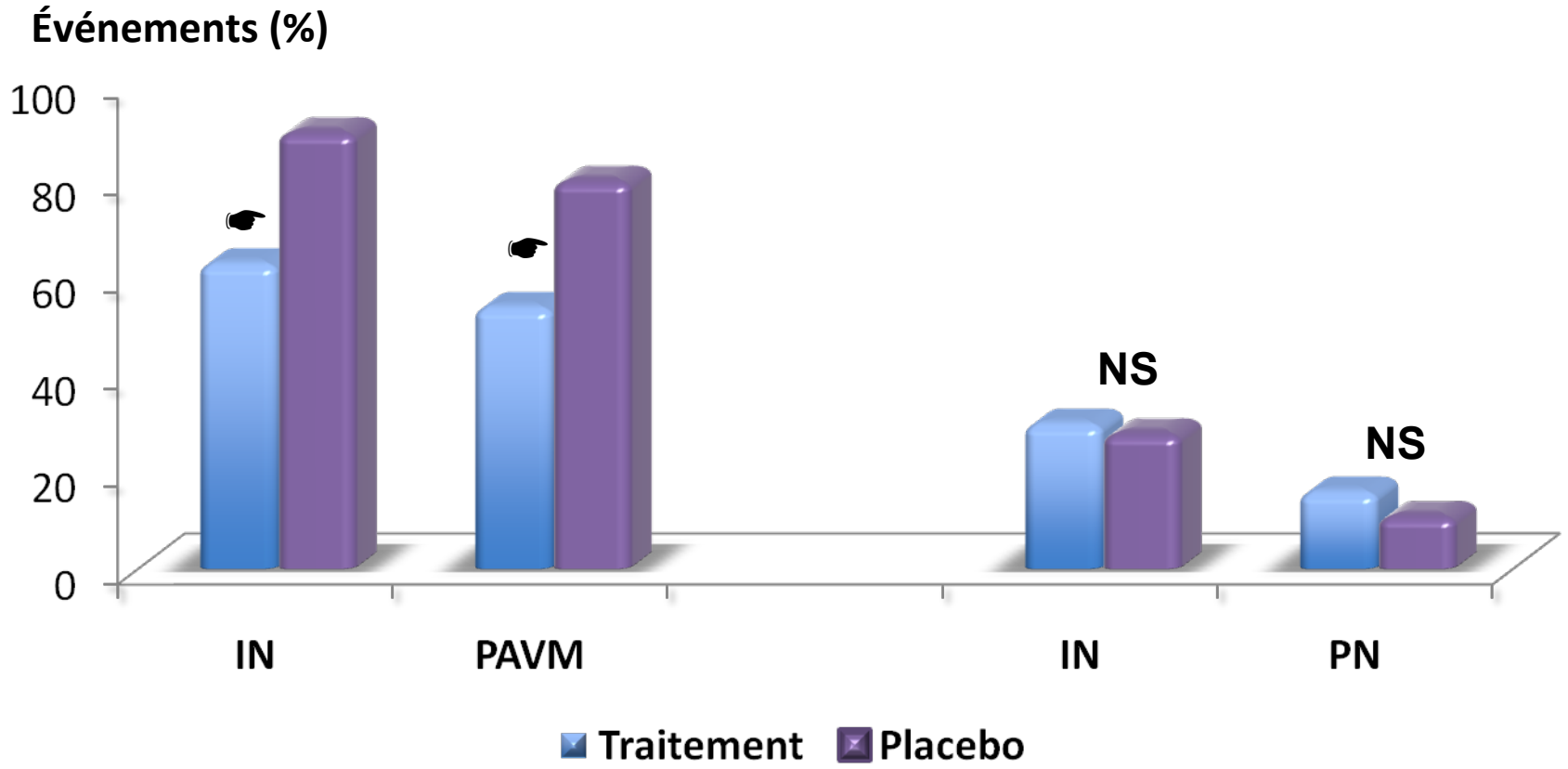


Jain Clin Nutr 2004, MacNaught Clin Nutr 2005, Kotzampassi World J Surg 2006



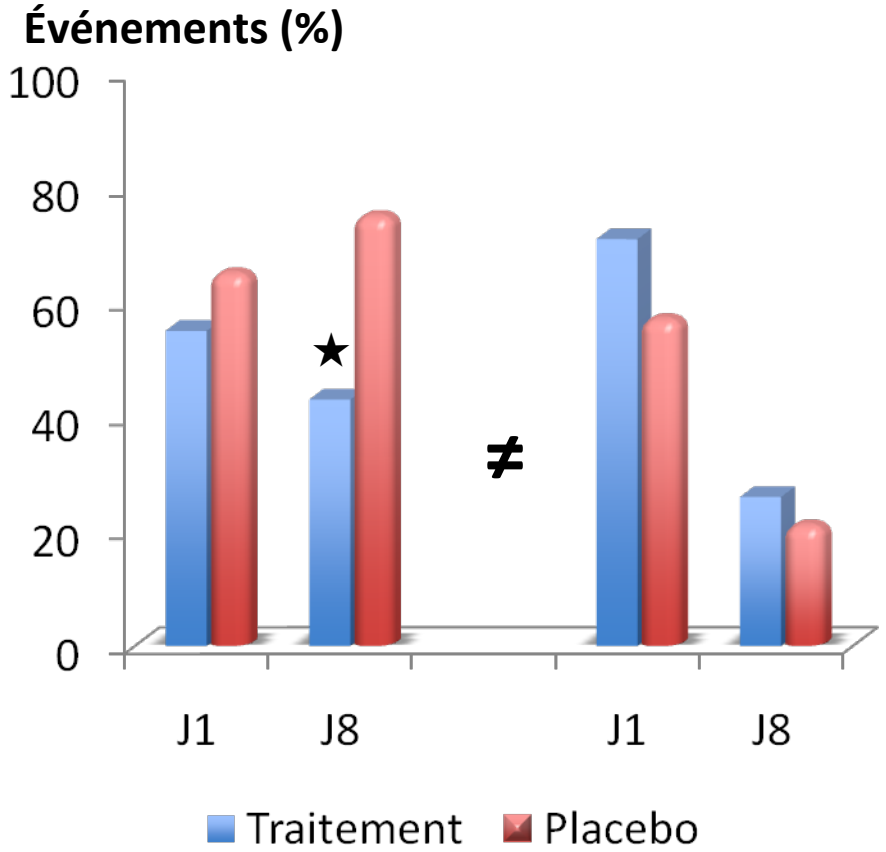
Besselink Lancet 2008

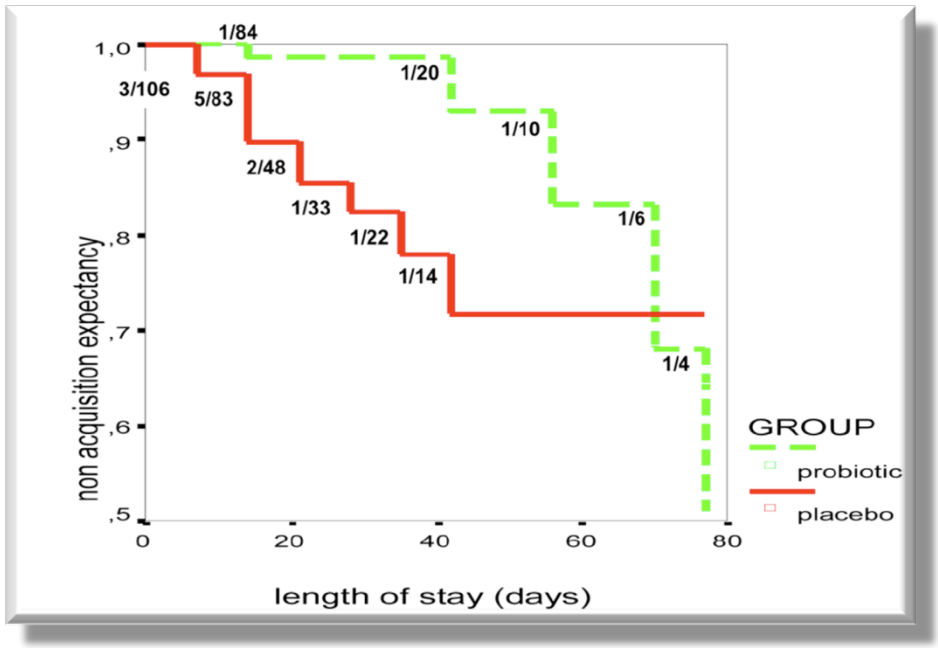
- **Absence d'effet bénéfique sur le critère infections nosocomiales**



Kotzampassi World J Surg 2006 *Besselink Lancet 2008*

- **Absence d'effet bénéfique sur le critère colonisation par des BMR**





- **Absence d'effet indésirable notable…**

  - **EIG**
    - Infections à lactobacilles, saccharomyces,…
    - Ischémie mésentérique
  - ***Facteurs de risque*** :
    - Immunodépression
    - Grêle court

Ishibashi Am J Clin Nutr 2001, Snydman Clin Infect Dis 2008, Besselink Lancet 2008

- ***Limites*** :
  - Analyse intermédiaire
  - Pas de mesure de la colonisation effective du tube digestif par le *Lactobacillus*
  - Rôle des diarrhées *?*

Conclusion

- **Malgré des effets théoriques intéressants, une facilité d'utilisation, un faible coût, et un profil de sécurité satisfaisant, il ne semble pas exister de bénéfice à la prescription routinière de ces produits chez le patient ventilé de réanimation.**

- *Nombreuses questions en suspens* : type de germe, dose optimale à administrer, délai et durée de traitement optimaux…