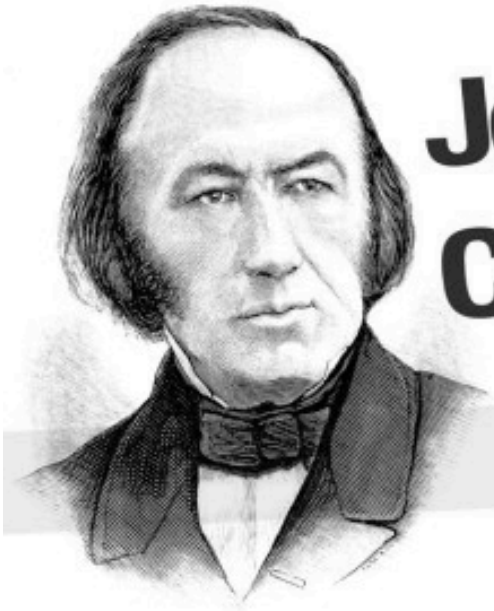
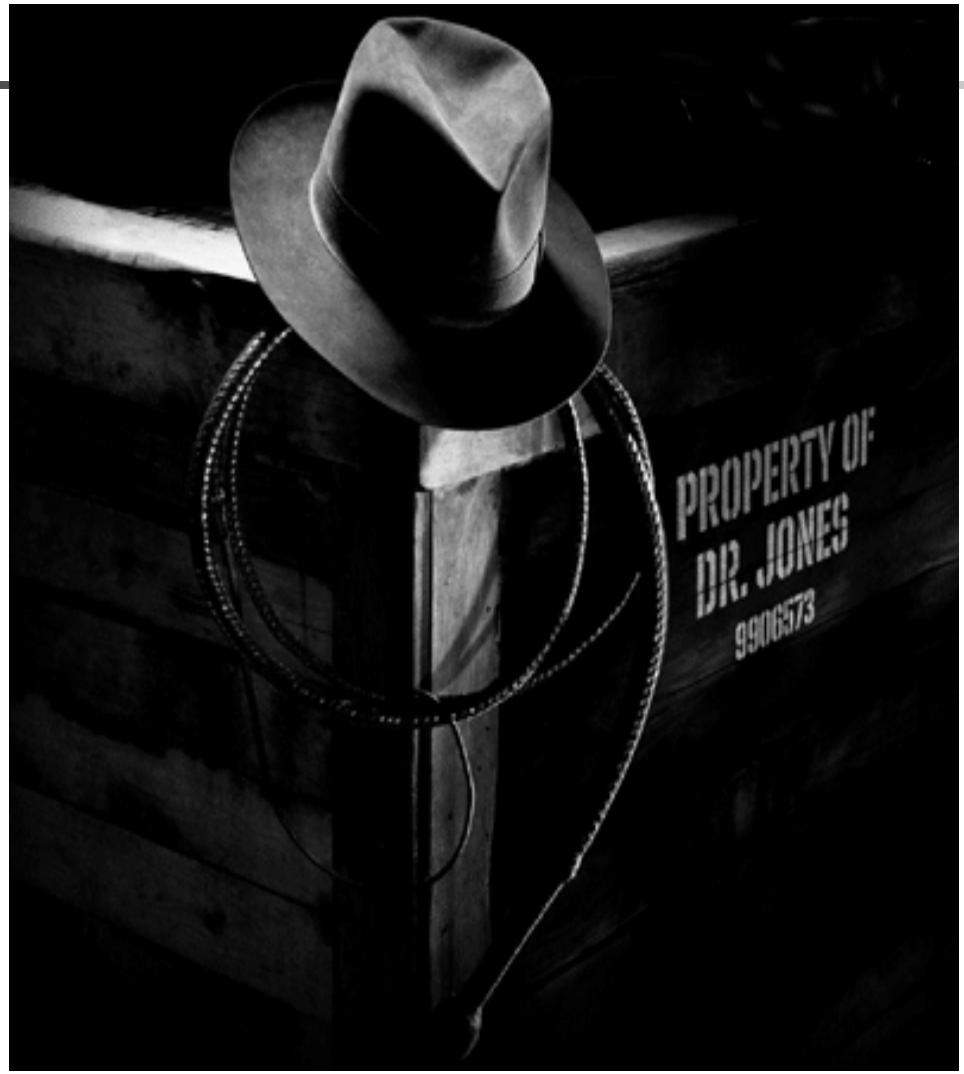


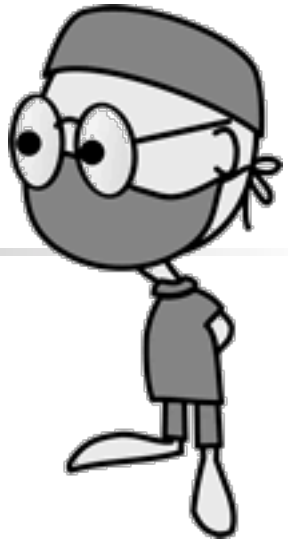
Journée de l'Hôpital Claude Bernard

Nouvelles stratégies de prise en charge

Traitements non antibiotiques des infections graves

B. Guery (Lille)





1991….

TREATMENT OF GRAM-NEGATIVE BACTEREMIA AND SEPTIC SHOCK WITH HA-1A HUMAN MONOCLONAL ANTIBODY AGAINST ENDOTOXIN

A Randomized, Double-Blind, Placebo-Controlled Trial

ELIZABETH J. ZIEGLER, M.D., CHARLES J. FISHER, JR., M.D., CHARLES L. SPRUNG, M.D., RICHARD C. STRAUBE, M.D., JERALD C. SADOFF, M.D., GARRETT E. FOULKE, M.D., CORNELIS H. WORTEL, M.D., MITCHELL P. FINK, M.D., R. PHILLIP DELLINGER, M.D., NELSON N.H. TENG, M.D., PH.D., I. ELAINE ALLEN, PH.D., HARVEY J. BERGER, M.D., GENELL L. KNATTERUD, PH.D., ALBERT F. LOBUGLIO, M.D., CRAIG R. SMITH, M.D., AND THE HA-1A SEPSIS STUDY GROUP*

Placebo n=92
HA-1A n=105

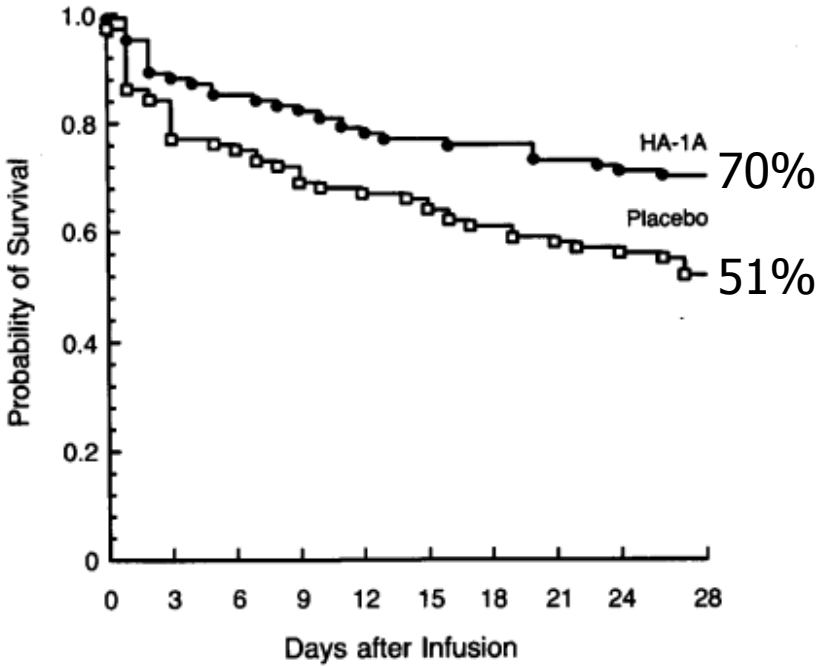


Figure 1. Probability of Survival in Patients with Gram-Negative Bacteremia.

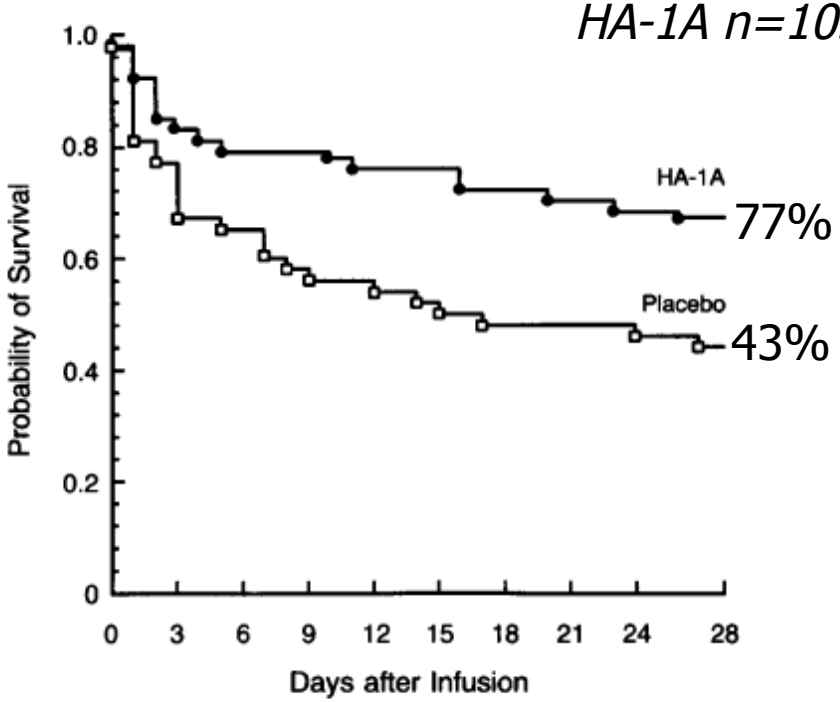


Figure 2. Probability of Survival in Patients with Gram-Negative Bacteremia and Shock at Entry.

N Engl J Med 1991; 324:429-36

Treatment of Septic Shock with Human Monoclonal Antibody HA-1A

A Randomized, Double-Blind, Placebo-Controlled Trial

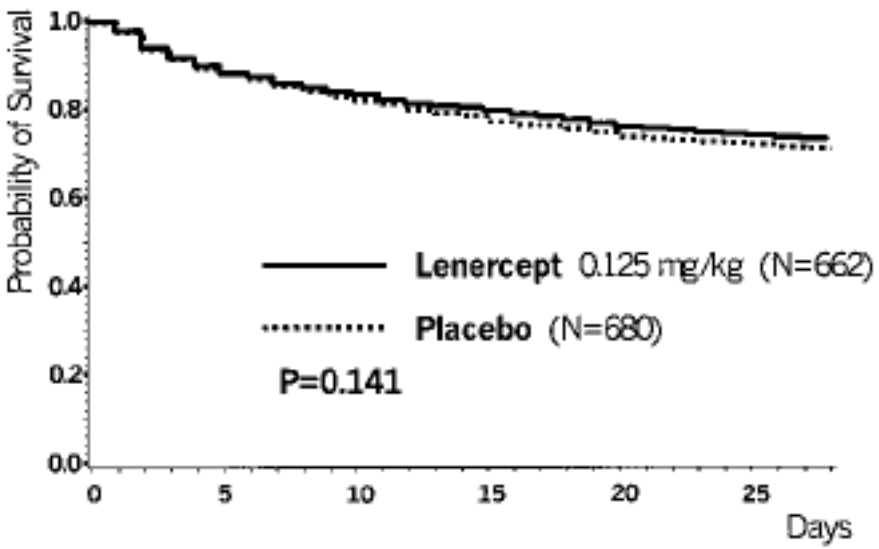
Richard V. McCloskey, MD; Richard C. Straube, MD; Corazon Sanders, PhD; Susan M. Smith, RN; Craig R. Smith, MD; and the CHESS Trial Study Group

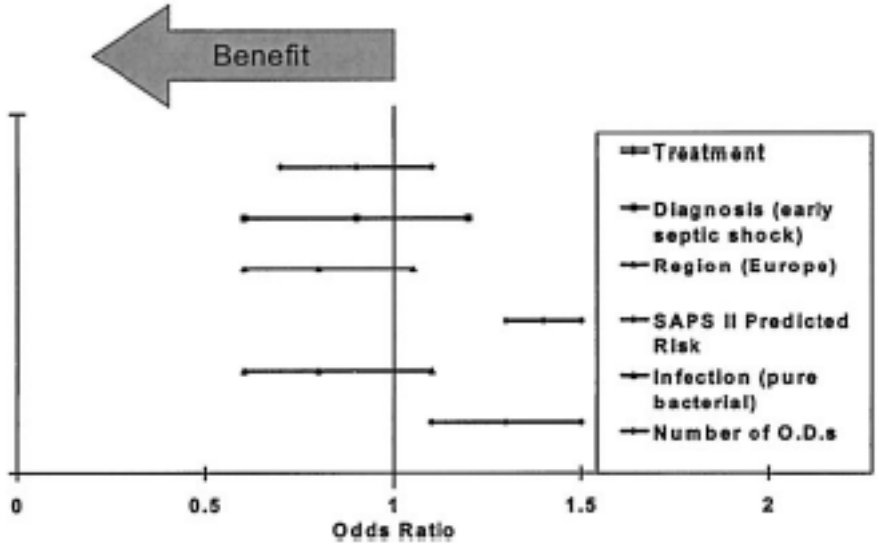
« We **stopped** the trial at the first interim analysis because the **all-cause mortality rate** for patients treated with HA-1A who did not have Gram-negative bacteremia (42%; 244 of **577**) **exceeded** that of the patients given placebo (38%; 230 of **608**) by an amount greater than that in the prespecified safety stopping rule (F = 0.09; Fisher one-tailed exact test). »

Ann Intern Med. 1994; 121:1-5.

Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: A randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients

Edward Abraham, MD; Pierre-François Laterre, MD; Jorge Garbino, MD; Susan Pingleton, MD; Thomas Butler, MD; Thierry Dugernier, MD; Benjamin Margolis, MD; Kenneth Kudsk, MD; Werner Zimmerli, MD; Paula Anderson, MD; Marc Reynaert, MD; Daniel Lew, MD; Werner Lesslauer, MD, PRPN; Sharon Passe; Philip Cooper, PhD; Alex Burdeska, PhD; Marlene Modi, PhD; Anton Leighton, MD; Miklos Salgo, MD; Philippe Van der Auwera, MD; for the Lenercept Study Group





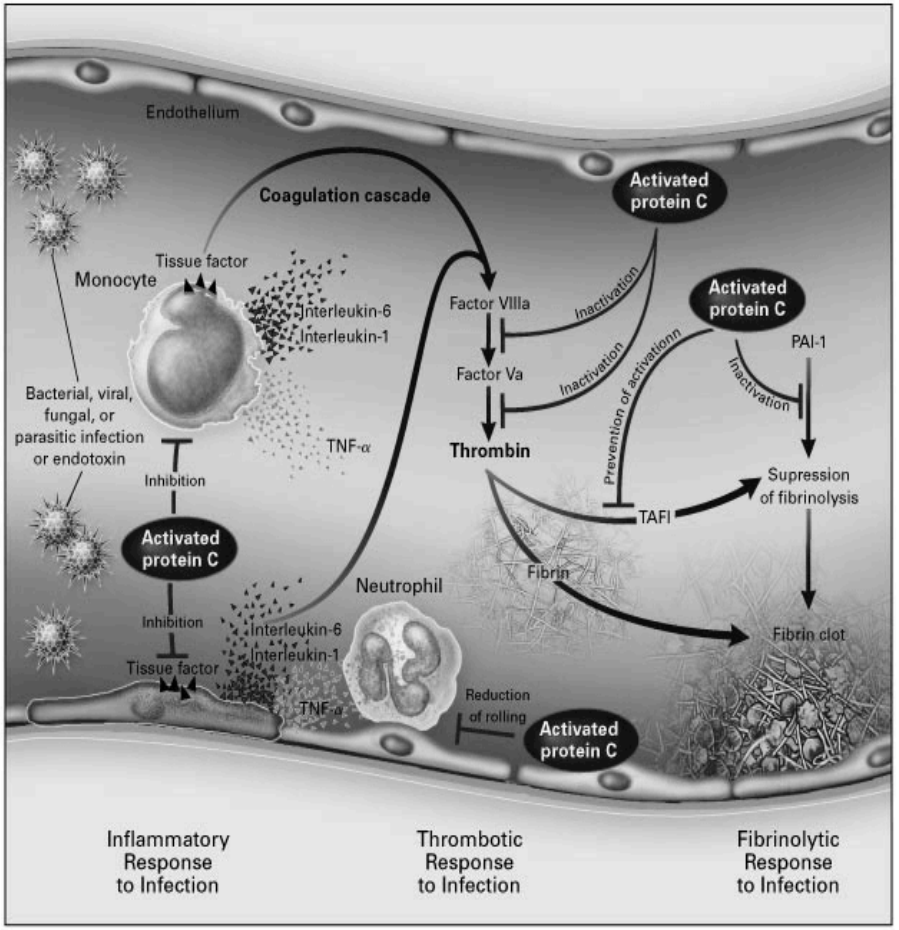
"Lenercept had no significant effect on mortality in the study population"

Crit Care Med 2001 Vol. 29, No. 3

2001….

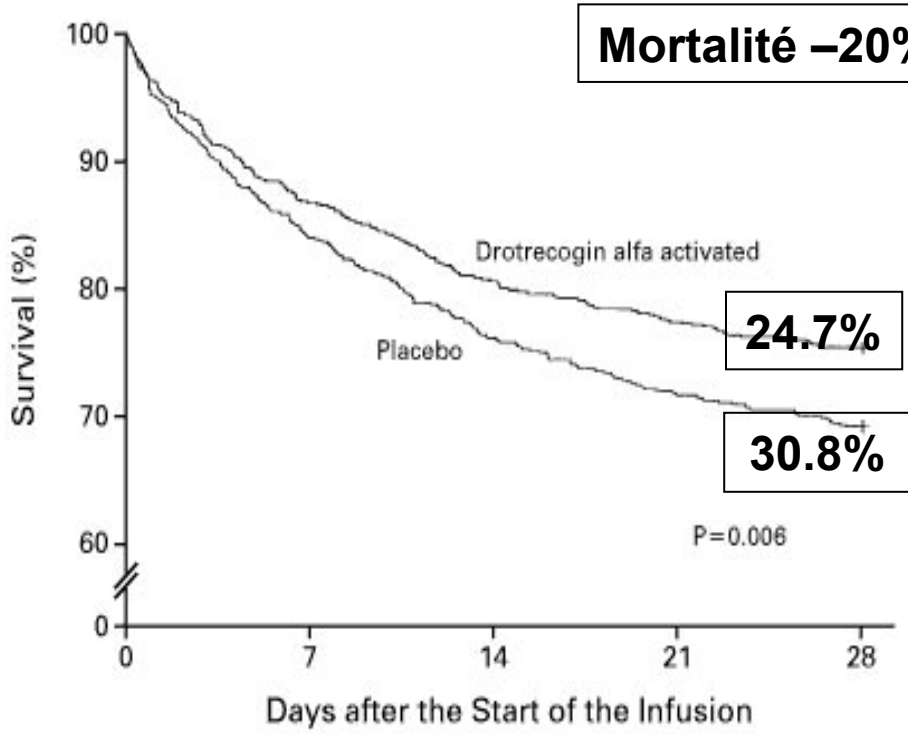
EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*



NEJM 2001

Mortalité –20%



No. at Risk					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

NEJM 2001

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2011
EMA/856472/2011
Press Office

Press release

Xigris (drotrecogin alfa (activated)) to be withdrawn due to lack of efficacy

PROWESS-SHOCK study shows no gain in 28-day survival of septic shock patients


U.S. Department of Health & Human Services www.hhs.gov

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Drugs

Home > Drugs > Drug Safety and Availability

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- Importing Prescription Drugs
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors

FDA Drug Safety Communication: Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit

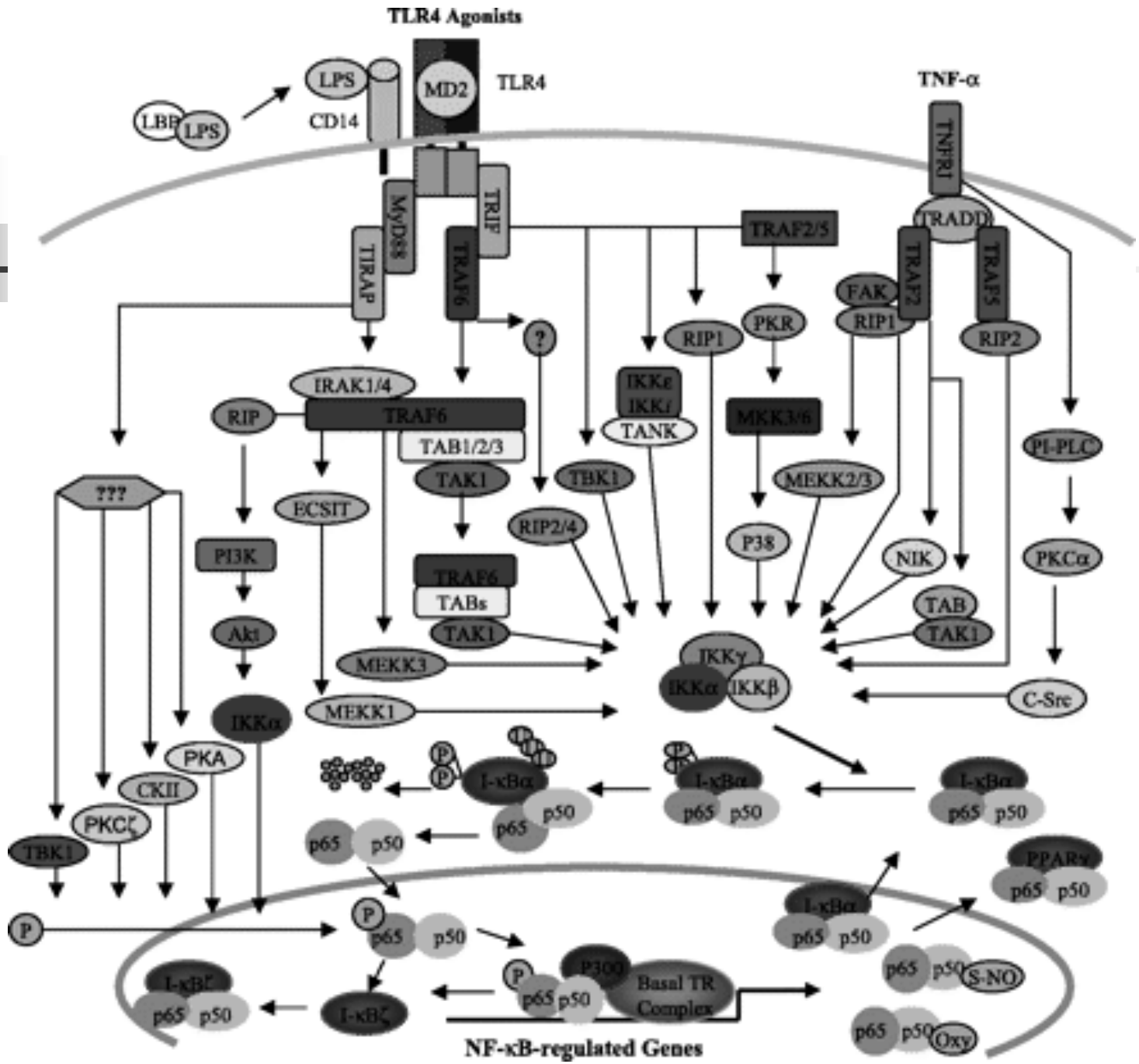
Safety Announcement

[10-25-2011] The U.S. Food and Drug Administration (FDA) is informing healthcare professionals and the public that on October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris [drotrecogin alfa (activated)]. In a recent study, Xigris failed to show a survival benefit for patients with severe sepsis and septic shock.

Xigris treatment should not be started in new patients. Xigris treatment should be stopped in patients being treated with Xigris.

All remaining Xigris product should be returned to the supplier from whom it was purchased.

LPS → TNF → Pas bon…..


TLR4 Agonists
LPS
LBP
LPS
CD14
MD2
TLR4
TNF-α
TNFRI
TRADD
TRAF2
TRAF5
MyD88
TRIF
TIRAP
TRAF6
TRAF2/5
FAK
RIP1
RIP2
PKR
?
RIP1
IRAK1/4
RIP
TRAF6
TAB1/2/3
TAK1
IKKε
IKKi
TANK
MKK3/6
PI-PLC
???
ECSIT
TBK1
MEKK2/3
RIP2/4
P38
NIK
PI3K
TRAF6
TABs
TAK1
TAB
TAK1
PKCα
Akt
MEKK3
IKKγ
IKKα
IKKβ
C-Src
MEKK1
IKKα
PKA
CKII
PKCζ
TBK1
I-κBα
p65
p50
P
PPARγ
I-κBζ
P300
Basal TR
Complex
S-NO
Oxy
NF-κB-regulated Genes

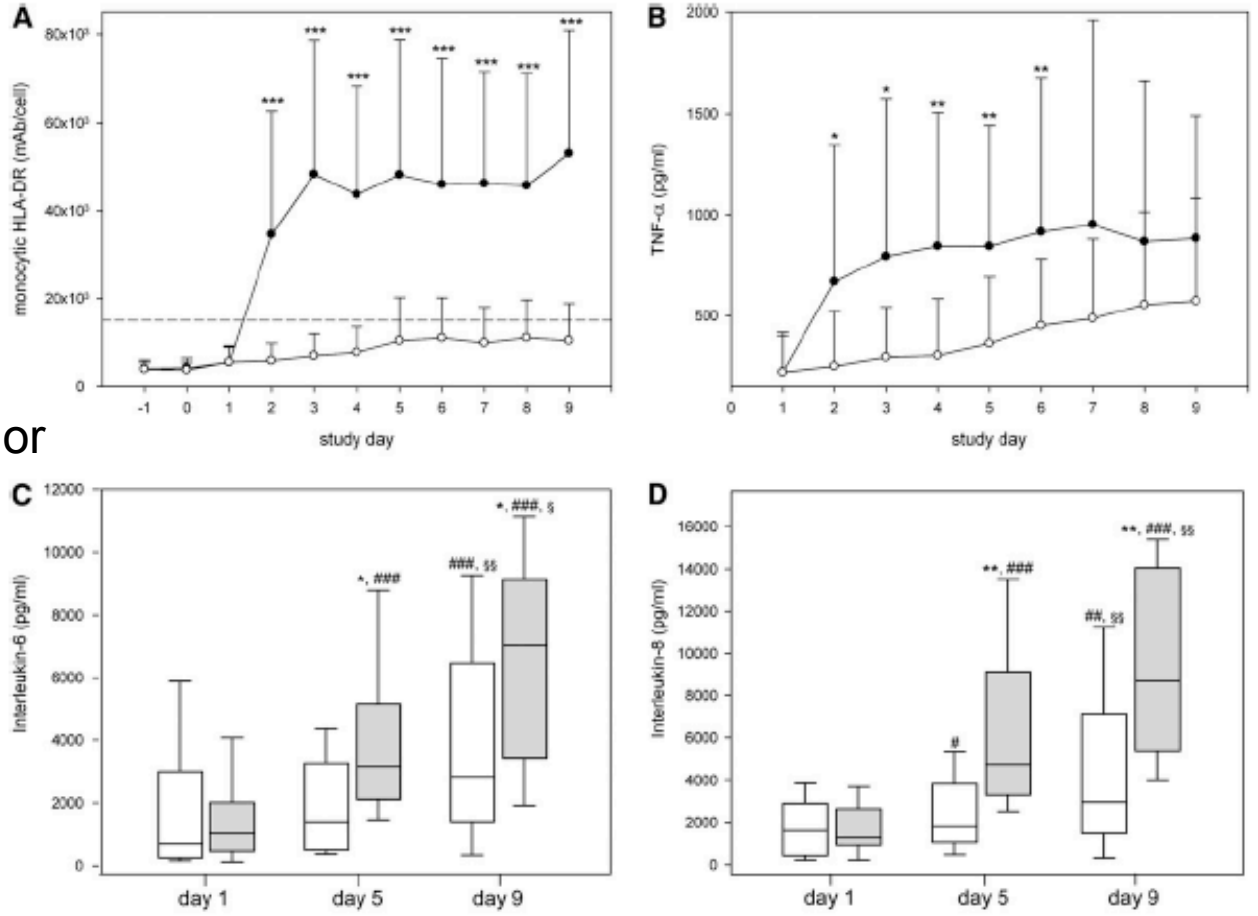
"My approach is nontraditional, but from a uniquely Western perspective."

Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

Christian Meisel[1*], Joerg C. Schefold[2*], Rene Pschowski[2], Tycho Baumann[1], Katrin Hetzger[1], Jan Gregor[3], Steffen Weber-Carstens[4], Dietrich Hasper[2], Didier Keh[4], Heidrun Zuckermann[3], Petra Reinke[2,5], and Hans-Dieter Volk[1,5]

19 patients/group
GM-CSF (4 **m**g/kg/d) or placebo for
8 days.



Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

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Christian Meisel[1]*, Joerg C. Schefold[2]*, Rene Pschowski[2], Tycho Baumann[1], Katrin Hetzger[1], Jan Gregor[3], Steffen Weber-Carstens[4], Dietrich Hasper[2], Didier Keh[4], Heidrun Zuckermann[3], Petra Reinke[2,5], and Hans-Dieter Volk[1,5]

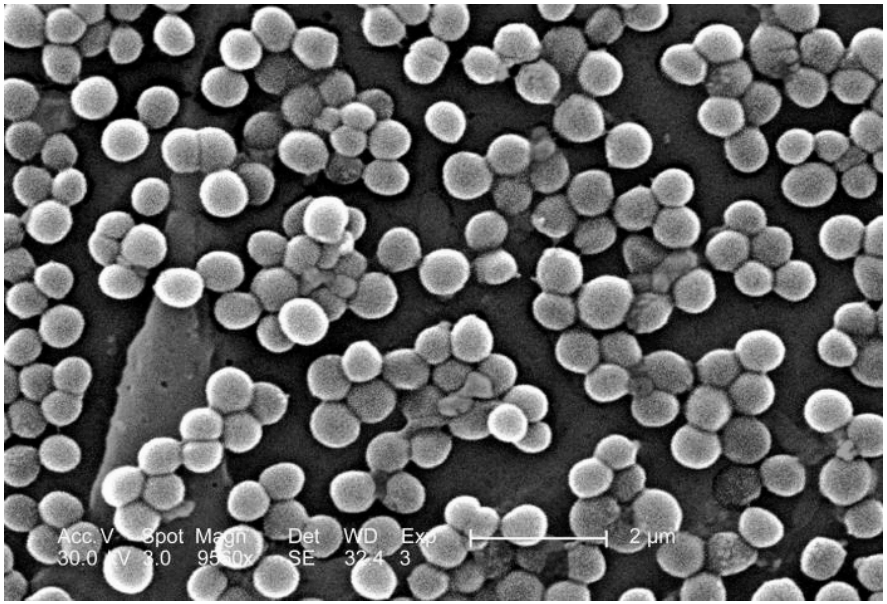
Characteristics	GM-CSF Group ($n = 19$)	Placebo Group ($n = 19$)	P Value
Time on ventilator, Days 1–9, hours	147.9 ± 102.8	207.2 ± 57.5	0.037*
APACHE-II			
Study Day 1	21.3 ± 6.1	22.5 ± 6.6	NS*
Study Day 9	16.7 ± 5.9	20.8 ± 7.4	(0.06)*
Days 1 vs. 9	$P = 0.02$*	NS*	—

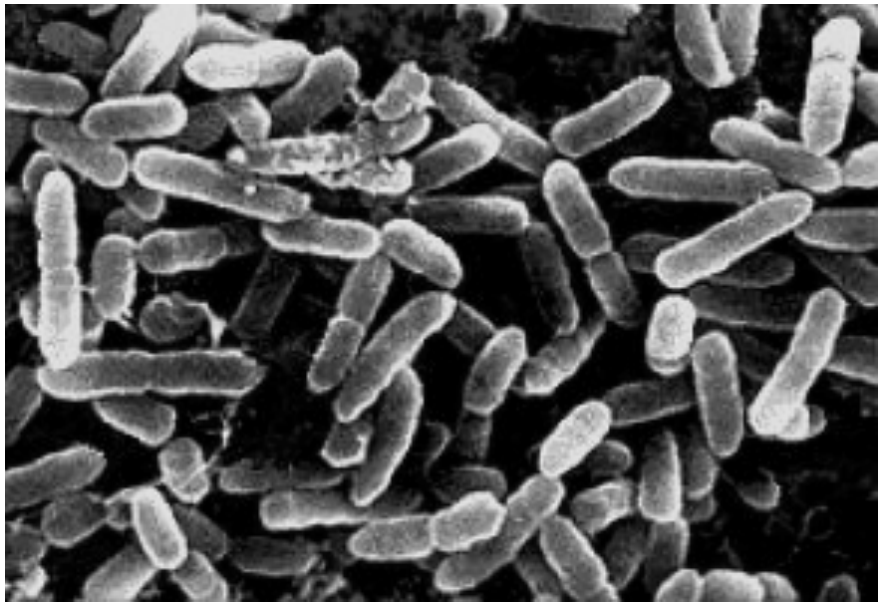
Am J Respir Crit Care Med Vol 180. pp 640–648, 2009

Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock

Dianne P. Stephens, MD; Jane H. Thomas, BN, Grad Dip PH; Alisa Higgins, BPhysio (Hon), MPH; Michael Bailey, BSc (Hons), MSc (Stats), PhD; Nicholas M. Anstey, MB, BS, FRACP, PhD; Bart J. Currie, MBBS, FRACP, DTM&H; Allen C. Cheng, MBBS, FRACP, PhD

Conclusion: **G-CSF does not improve outcomes in patients with septic shock, excluding melioidosis. Increased hepatic dysfunction and higher peak troponin levels in patients receiving G-CSF have not been reported in previous clinical trials and warrant further investigation. (Crit Care Med 2008; 36:448–454)**

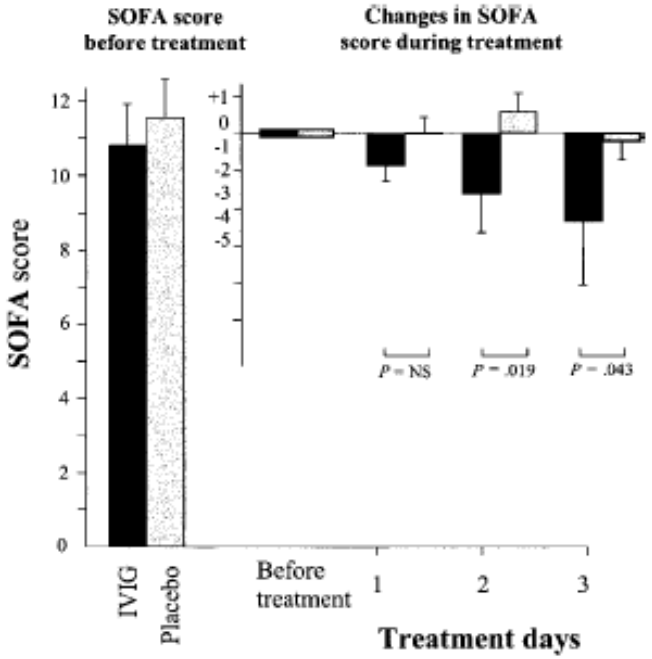

Acc.V Spot Magn Det WD Exp
30.0 kV 3.0 9560x SE 32.4 3
2 µm



Intravenous Immunoglobulin G Therapy in Streptococcal Toxic Shock Syndrome: A European Randomized, Double-Blind, Placebo-Controlled Trial

Jessica Darenberg,[1] Nahla Ihendyane,[1] Jan Sjölin,[3] Ewa Aufwerber,[2] Sven Haidl,[4] Per Follin,[5] Jan Andersson,[1] Anna Norrby-Teglund,[1] and the StreptIg Study Group[a]

- 21 patients
- Etude prospective randomisée double aveugle



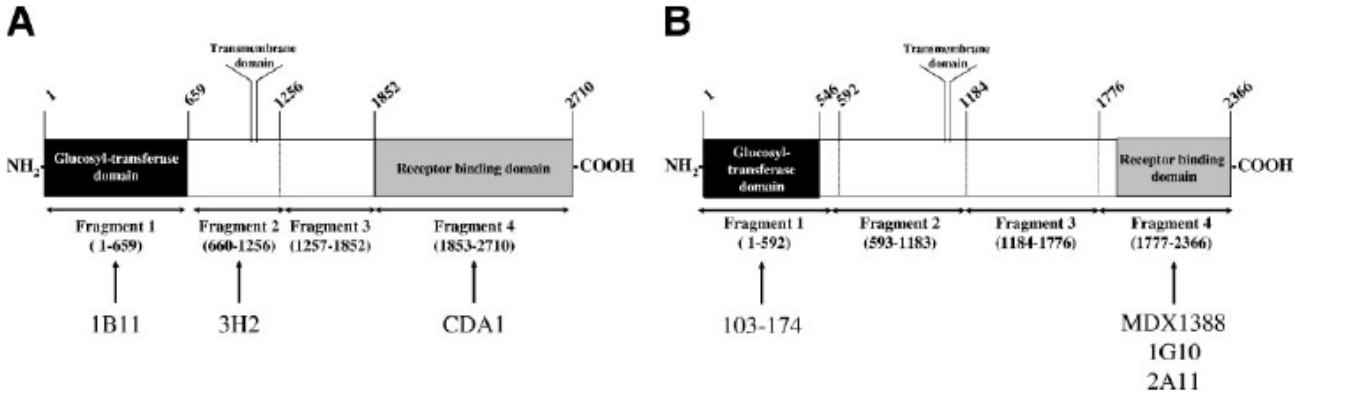
End point	All included patients		Patients with GAS only	
	IVIG group (n = 10)	Placebo group (n = 11)	IVIG group (n = 8)	Placebo group (n = 10)
Primary: mortality day 28, no. (%) of patients	1 (10)	4 (36)	1 (12.5)	3 (30)

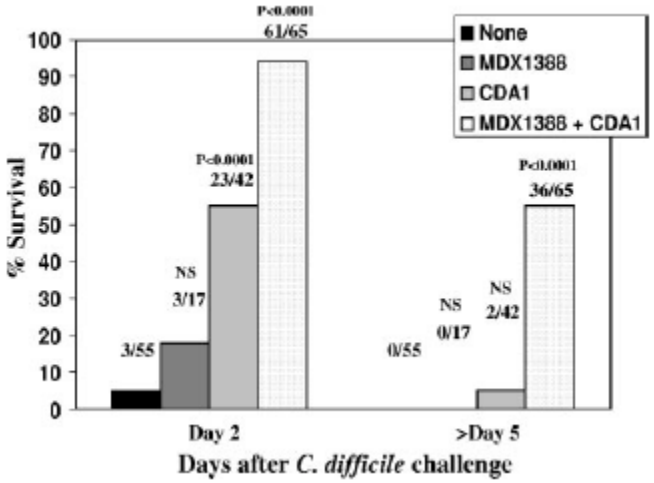
NS

CID 2003:37 (1 August)

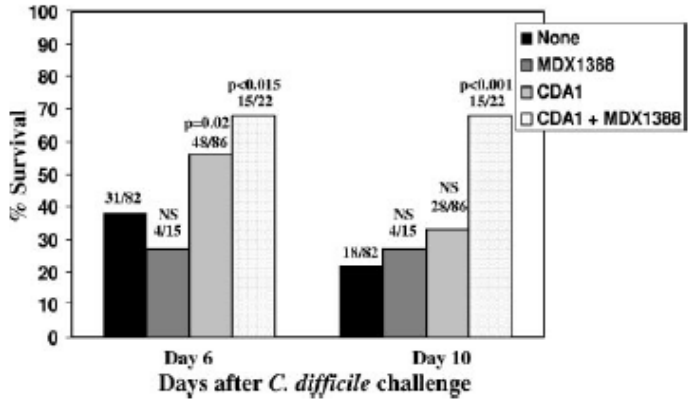
Human Monoclonal Antibodies Directed against Toxins A and B Prevent *Clostridium difficile*-Induced Mortality in Hamsters[▽]

Gregory J. Babcock,[1]† Teresa J. Broering,[1]† Hector J. Hernandez,[1]† Robert B. Mandell,[1] Katherine Donahue,[1] Naomi Boatright,[1] Anne M. Stack,[3] Israel Lowy,[2] Robert Graziano,[2] Deborah Molrine,[1] Donna M. Ambrosino,[1] and William D. Thomas, Jr.[1]*





Primary challenge



Relapse

Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

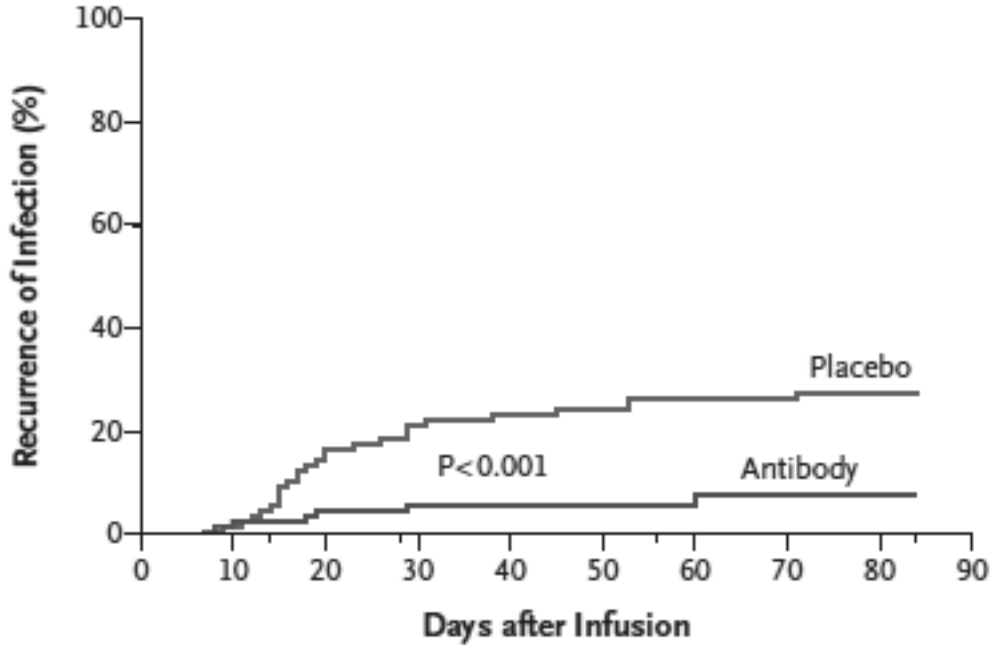
Israel Lowy, M.D., Ph.D., Deborah C. Molrine, M.D., M.P.H., Brett A. Leav, M.D., Barbra M. Blair, M.D., Roger Baxter, M.D., Dale N. Gerding, M.D., Geoffrey Nichol, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Leney, Ph.D., Susan Sloan, Ph.D., Catherine A. Hay, Ph.D., and Donna M. Ambrosino, M.D.

Table 1. **Demographic and Clinical Characteristics of the Patients at Baseline.***

Characteristic	Monoclonal Antibody (N=101)	Placebo (N=99)	P Value
Mean age — yr	63	64	0.62
Female sex — no. (%)	61 (60)	71 (72)	0.10
Antibiotic treatment for CDI — no. (%)			
Metronidazole	71 (70)	77 (78)	0.26
Vancomycin§	30 (30)	22 (22)	0.26
CDI severity			
Severe disease at enrollment — no. (%)¶	44 (44)	36 (36)	0.32
Mean no. of unformed stools per day			
At screening	8.2	6.5	0.008
At infusion	7.9	6.3	0.01
More than one previous episode of CDI — no. (%)‖	29 (29)	32 (33)	0.64
Presence of BI/NAP1/027 strain — no. (%)**	25 (32)	19 (26)	0.38

Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

Israel Lowy, M.D., Ph.D., Deborah C. Molrine, M.D., M.P.H., Brett A. Leav, M.D., Barbra M. Blair, M.D., Roger Baxter, M.D., Dale N. Gerding, M.D., Geoffrey Nichol, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Leney, Ph.D., Susan Sloan, Ph.D., Catherine A. Hay, Ph.D., and Donna M. Ambrosino, M.D.



No. at Risk				
Antibody	101	93	89	85
Placebo	99	77	66	62

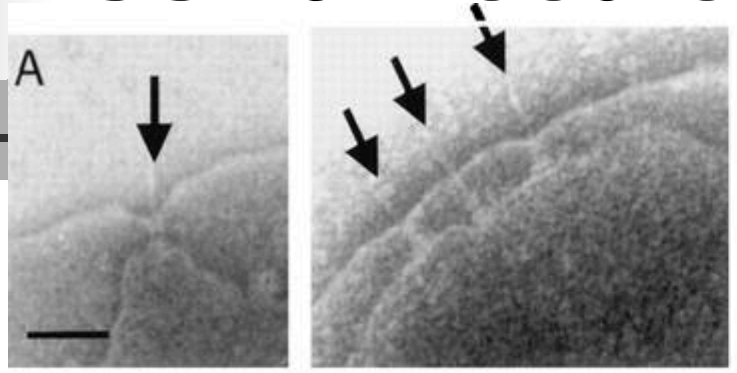
Figure 1. Time to Recurrence of *Clostridium difficile* Infection (CDI).

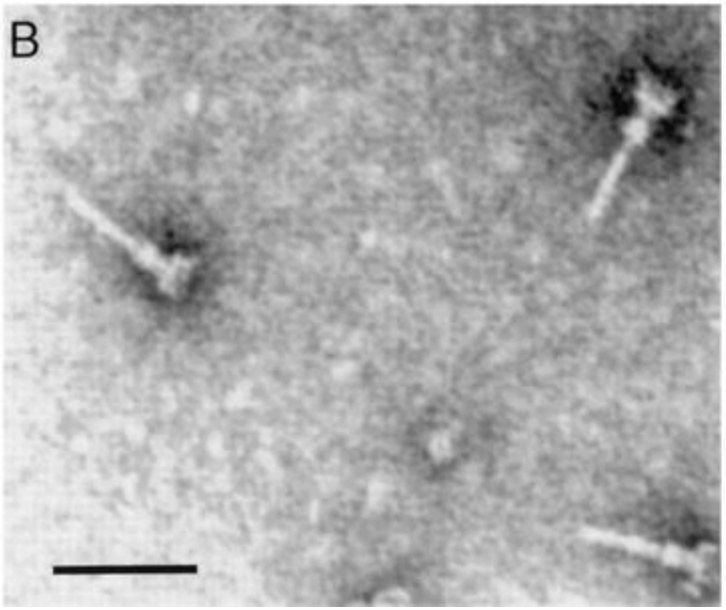
Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

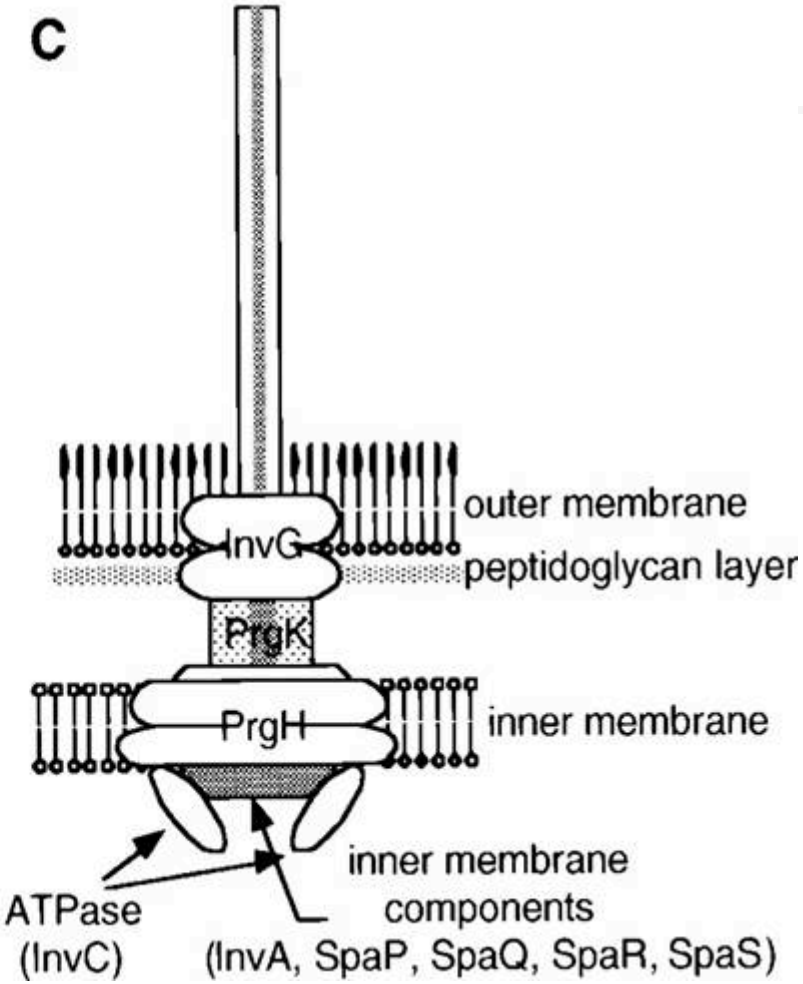
Israel Lowy, M.D., Ph.D., Deborah C. Molrine, M.D., M.P.H., Brett A. Leav, M.D., Barbra M. Blair, M.D., Roger Baxter, M.D., Dale N. Gerding, M.D., Geoffrey Nichol, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Leney, Ph.D., Susan Sloan, Ph.D., Catherine A. Hay, Ph.D., and Donna M. Ambrosino, M.D.

- The combined administration of CDA1 and CDB1 human monoclonal antibodies in addition to antibiotics significantly reduced the recurrence of *C. difficile* infection.

TTSS: a needle

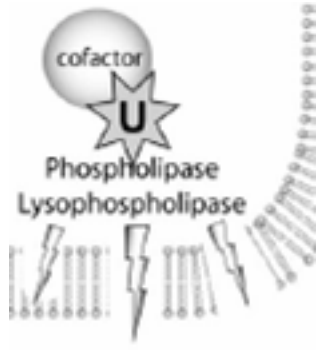






Kubori et al. Science 1998

Surmortalité et SST III

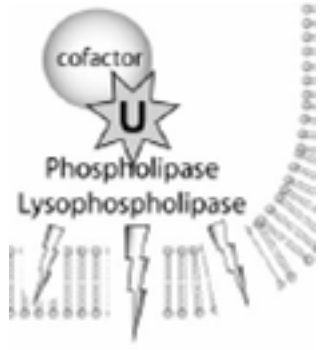


	Infection aiguë	Infection chronique
SSTT [+]	89%	41%

	SSTT [+]	SSTT [-]
Mortalité	21%	3%

	RR décès
PcrV seule	7,4
PcrV + toxine(s)	8,7

(Roy Burman et al, J Infect Dis. 2001)



35 patients ventilés
Pneumonie à *P.aeruginosa*

Production de Protéines
Issues du système de sécrétion
de type III

\+
27/35

\-
8/35

22 Sévère
(81%)

5 Modérées
(19%)

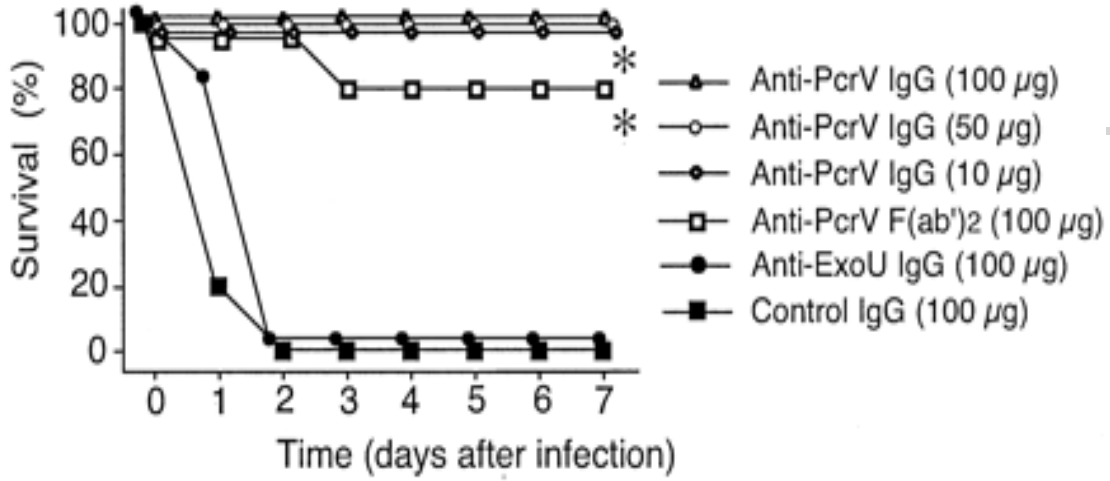
3 Sévères
(38%)

5 Modérées
(62%)

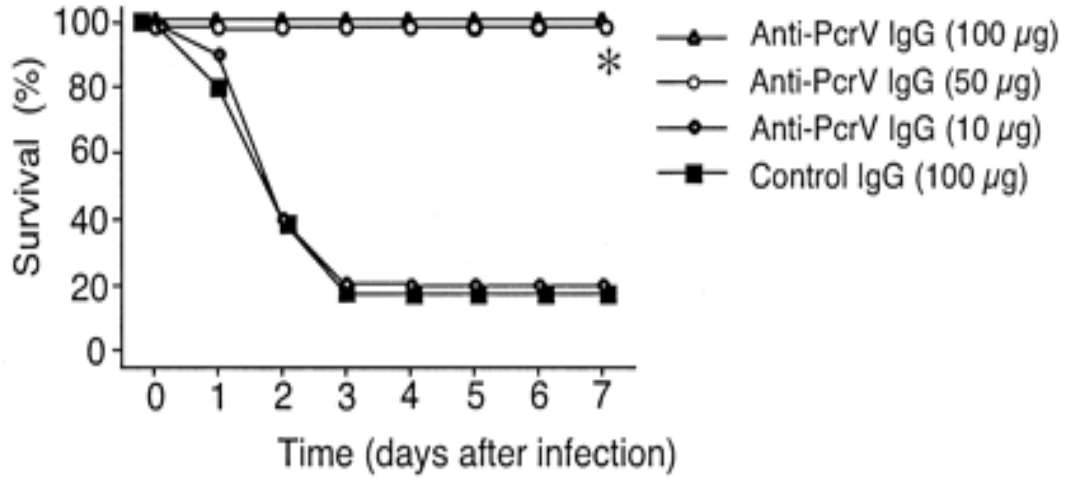
ExoU : 10/35 (29%) associée à 90% de formes sévères

Hauser et al, Crit Care Med 2002

a. Intravenous treatment 1 h after infection



b. Intravenous treatment 4 h after infection

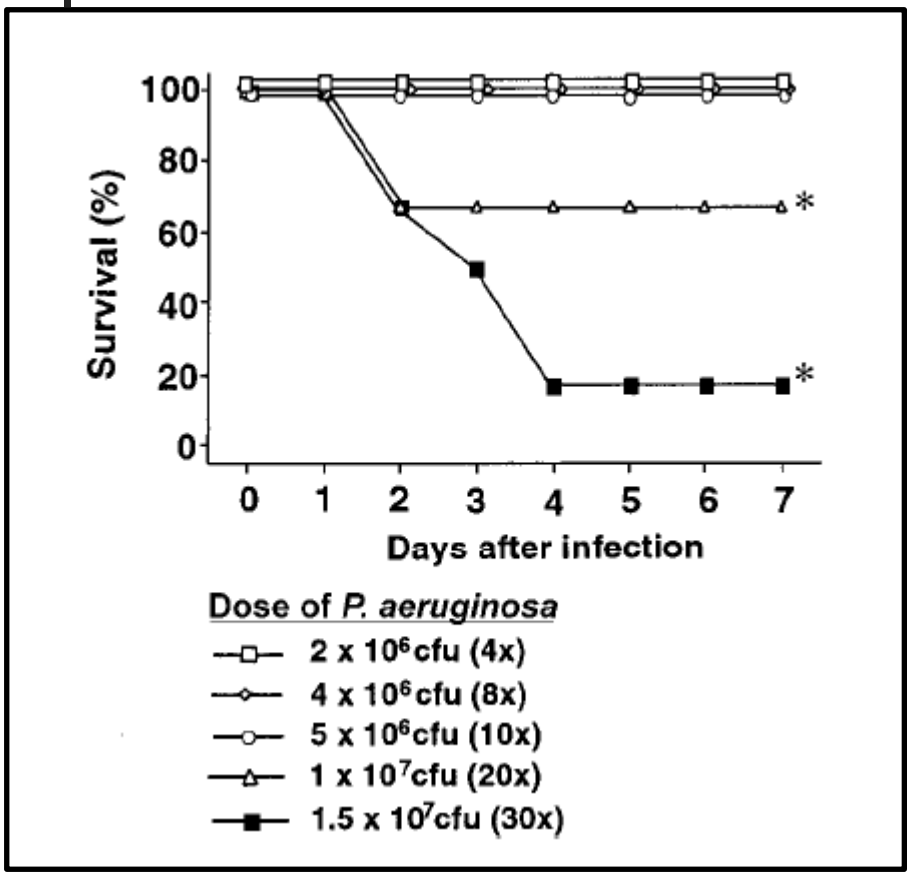


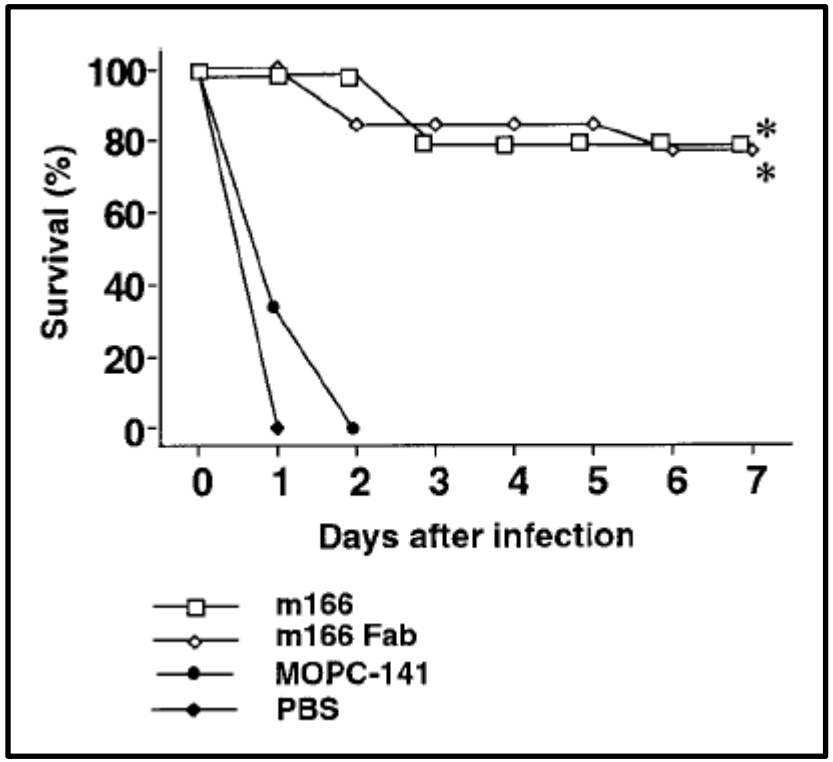
Shime et al, J Immunol 2001

Generation and Characterization of a Protective Monoclonal Antibody to *Pseudomonas aeruginosa* PcrV

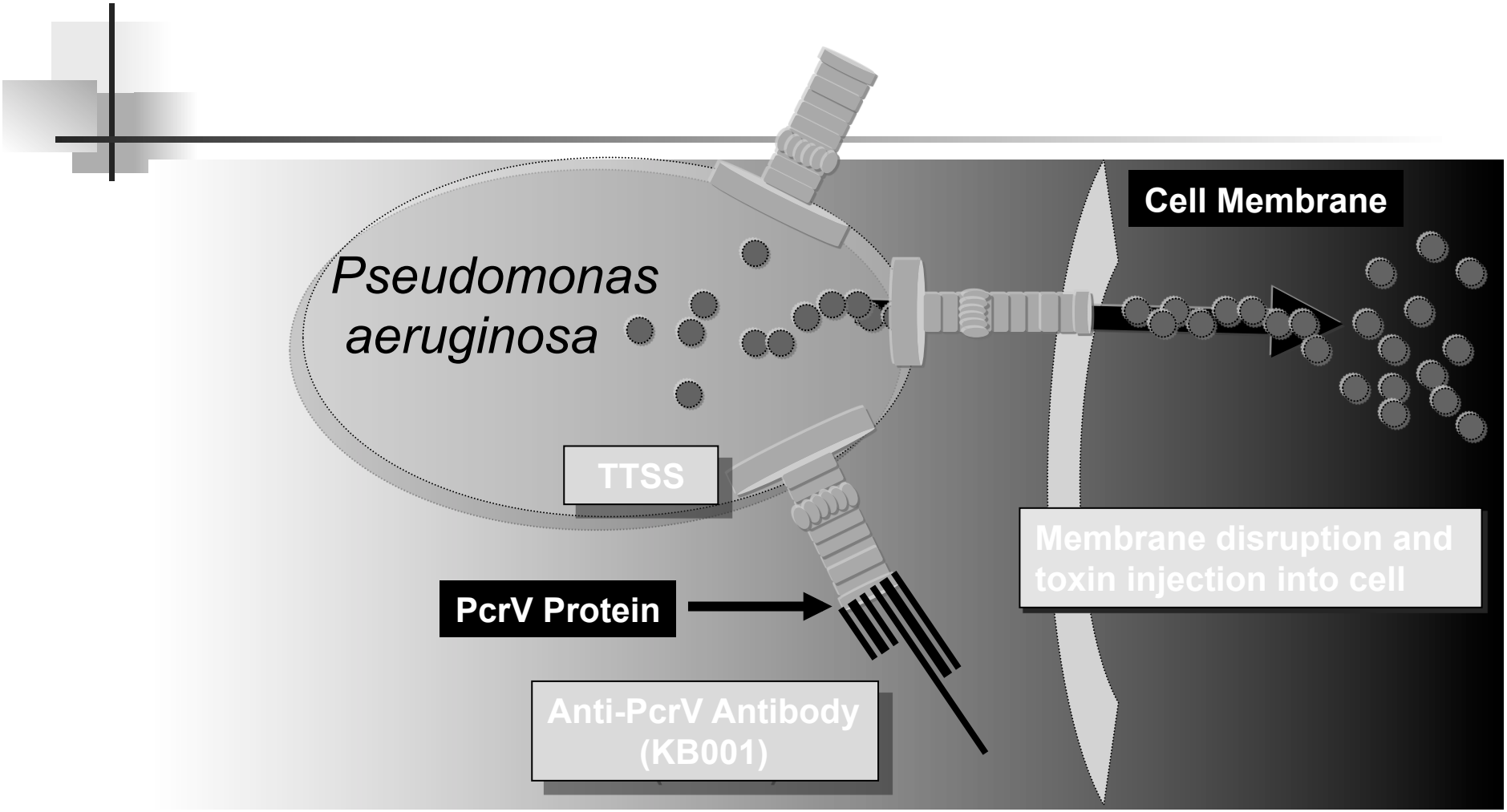
Dara W. Frank,[1] Amy Vallis,[1]
Jeanine P. Wiener-Kronish,[2,3,4] Arup Roy-Burman,[2,5]
Edward G. Spack,[6] Brian P. Mullaney,[2,a]
Mehdi Megdoud,[2] James D. Marks,[2] Robert Fritz,[1]
and Teiji Sawa[2]

[1]*Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, Milwaukee; Departments of* [2]*Anesthesia and Perioperative Care and* [3]*Medicine,* [4]*Cardiovascular Research Institute, and* [5]*Division of Critical Care Medicine of the Department of Pediatrics, University of California, San Francisco, and* [6]*InterMune, Brisbane, California*





JID 2002;186 (1 July)


Cell Membrane
Pseudomonas aeruginosa
TTSS
Membrane disruption and toxin injection into cell
PcrV Protein
Anti-PcrV Antibody (KB001)

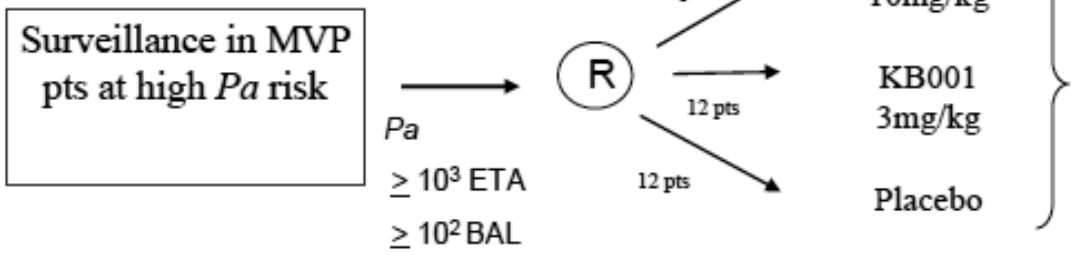
Pharmacokinetics and Safety Profile of the Human Anti-*Pseudomonas aeruginosa* Serotype O11 Immunoglobulin M Monoclonal Antibody KBPA-101 in Healthy Volunteers[▽]

Hedvika Lazar,[1]* Michael P. Horn,[1]† Adrian W. Zuercher,[1]‡ Martin A. Imboden,[1]§ Peter Durrer,[2] Michael Seiberling,[3] Rolf Pokorny,[3] Christophe Hammer,[1] and Alois B. Lang[1]¶

"Overall, the human monoclonal antibody KBPA-101 was well tolerated over the entire dose range in healthy volunteers, and no serious adverse events have been reported."

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3442–3446

KB001 Trial



Number developed Pa VAP during surveillance	46
Number received KB001	39
Number with Pa infection on Day 0-1	4
Number evaluable	35

Endpoints

Day 1-3

- Change vs. placebo
  - *Pa* burden
  - Bact diversity
  - Inflammation
  - Lung function

Day 28

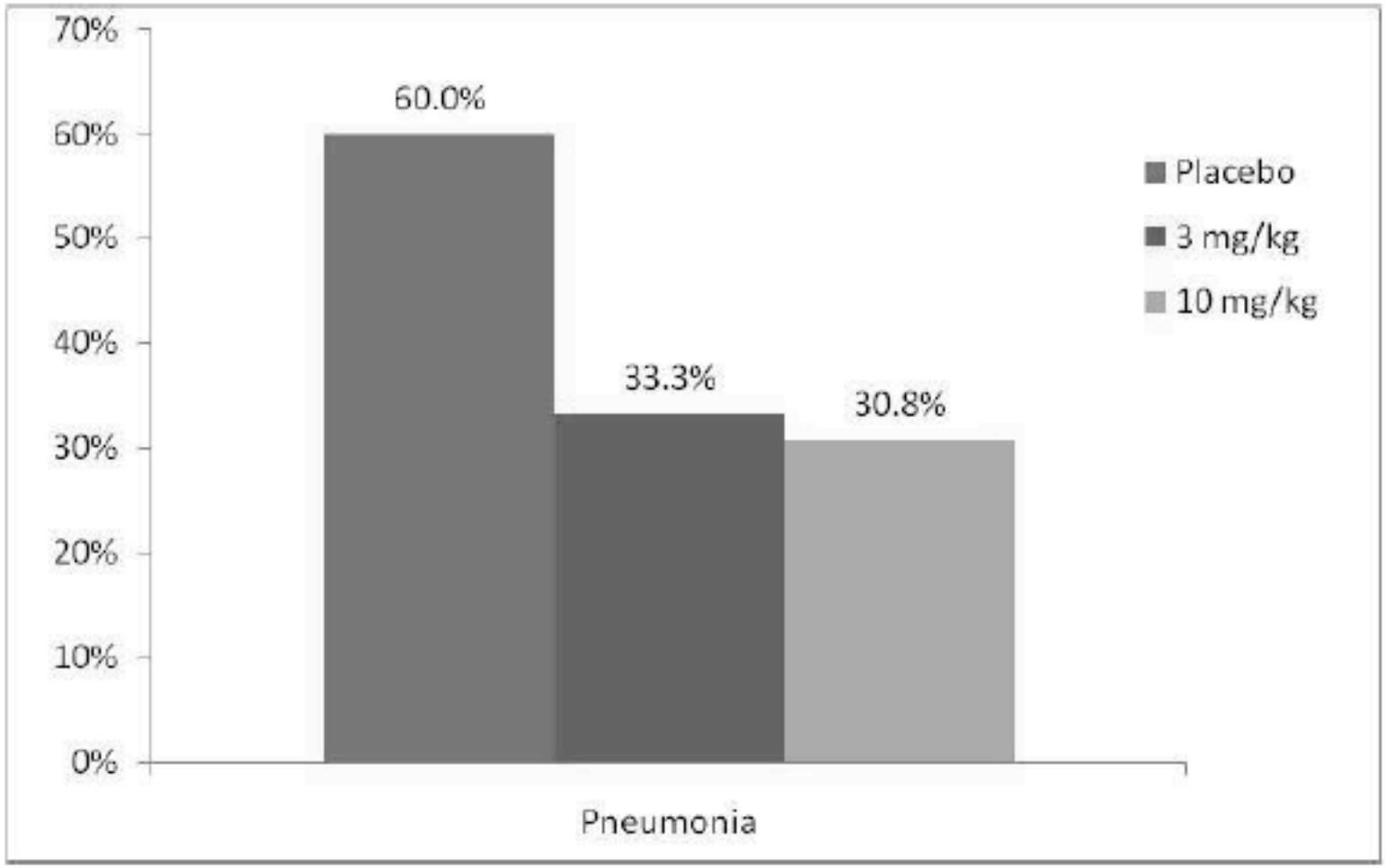
- Frequency
  - *Pa* VAP/sepsis
  - *Pa* relapse
- Time to VAP
- Clinical and MV endpts
- Pharmacokinetics
- KB001 airway penetration
- Immunogenicity

Chastre et al ATS 2010

Safety Population (N=39)	Placebo (N=12)	3 mg/kg (N=13)	10 mg/kg (N=14)
Male, n (%)	10 (83%)	8 (62%)	8 (57%)
Age, mean	66	62	61
Days on MV, median	15	7	16
Antibiotics in past 14 days, n (%)	11 (92%)	12 (92%)	13 (93%)
Trauma, n (%)	1 (8%)	2 (15%)	1 (7%)
Surgery, n (%)	6 (50%)	11 (85%)	7 (50%)
Coma, n (%)	3 (25%)	2 (15%)	2 (14%)
Organ transplant, n (%)	1 (8%)	6 (46%)	1 (7%)
COPD, n (%)	5 (42%)	5 (39%)	2 (14%)
Tracheostomy at baseline, n (%)	4 (33%)	4 (31%)	9 (64%)

Chastre et al ATS 2010

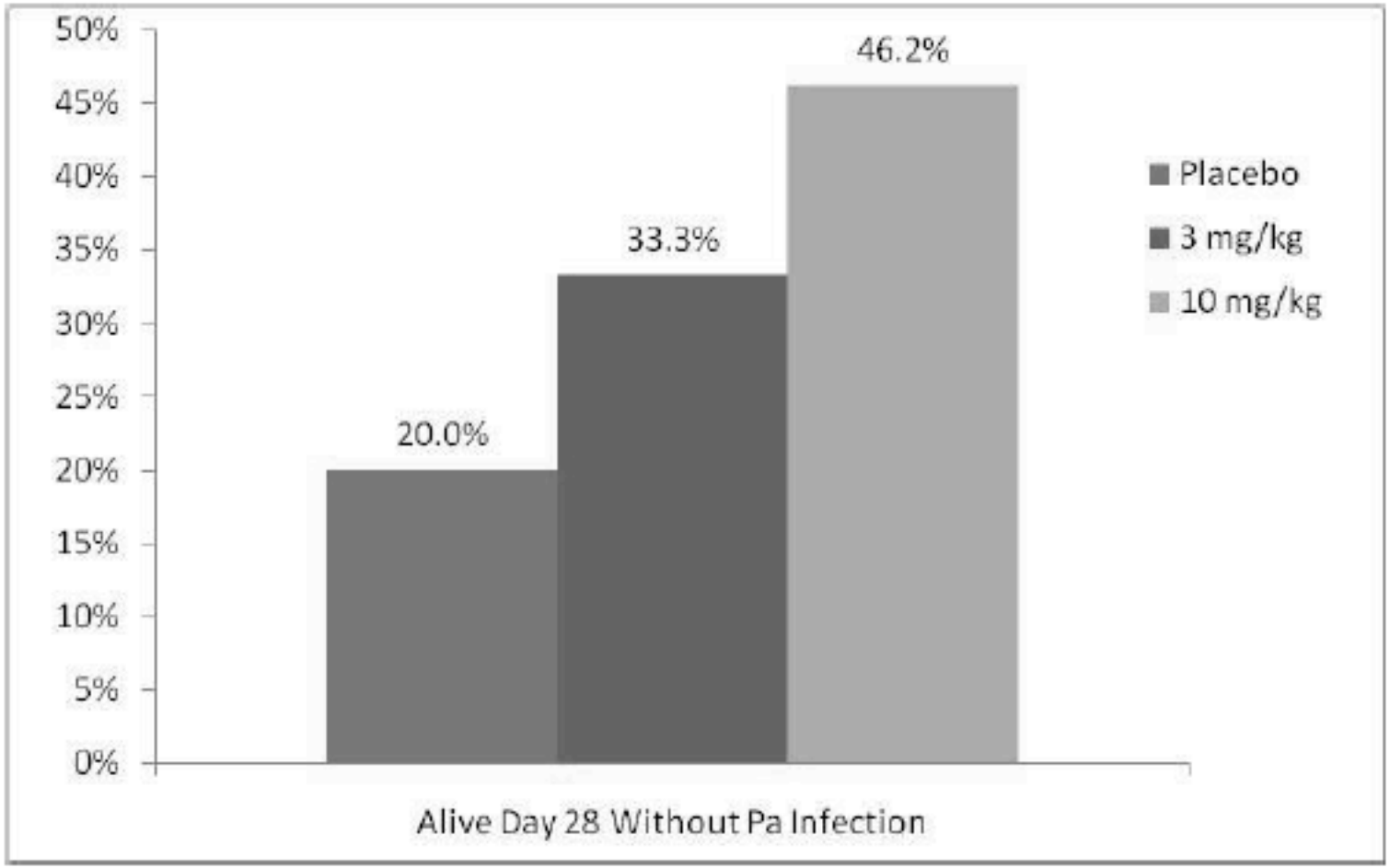
Decreased Incidence of Pneumonia



Evaluable Population

Chastre et al ATS 2010

Increased *Pa* Event Free Survival



Evaluable Population

Excluding subjects with Pa UTI

Chastre et al ATS 2010

A Phase I/II Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose Escalation Study of KB001 in Cystic Fibrosis Patients Infected with *Pseudomonas aeruginosa*

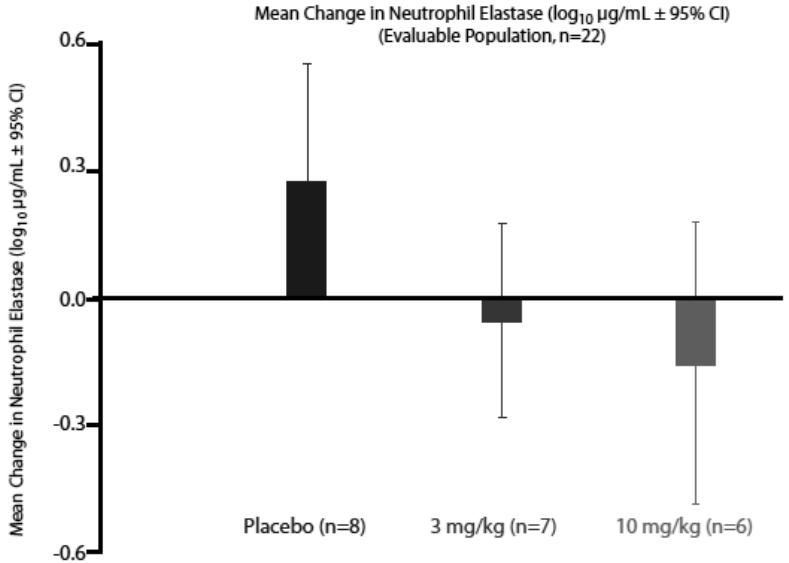
Milla, Carlos E; Accurso, Frank J.; Chmiel, James F.; McCoy, Karen S.; Billings, Joanne L; Atkinson, Jeffrey J; Clancy, John P; Liou, Theodore G; Acton, James D; Lynch, Susan V; Slusher, Nicole A; Burns, Jane L.; Mayer-Hamblett, Nicole; Harris, Kirk J; Patel, Rajesh; Tremblay, Thomas M; Parli, Teresa J.

Pa BURDEN: MEDIAN LOG $_{10}$ CFU/gm				
	Evaluable Population N=22	Placebo (N=8)	3 mg/kg (N=7)	10 mg/kg (N=7)
Mucoid	Day 0 Baseline (BL)	6.6	8.2	7.5
	Change from BL to Day 14	0	0	-0.1
	Change from BL to Day 28	0.8	0	-0.4
	Change from BL to Day 56	0.3	-0.3	-0.4
Non Mucoid	Day 0 (BL)	6.8	7.9	6.3
	Change from BL to Day 14	0	-0.3	0
	Change from BL to Day 28	-0.4	0.6	0
	Change from BL to Day 56	0	0.1	0
Total	Day 0 (BL)	8.0	8.3	7.7
	Change from BL to Day 14	-0.5	-0.2	-0.1
	Change from BL to Day 28	-0.3	0.2	-0.2
	Change from BL to Day 56	0.2	0	-0.4

A Phase I/II Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose Escalation Study of KB001 in Cystic Fibrosis Patients Infected with *Pseudomonas aeruginosa*

Milla, Carlos E; Accurso, Frank J.; Chmiel, James F.; McCoy, Karen S.; Billings, Joanne L; Atkinson, Jeffrey J; Clancy, John P; Liou, Theodore G; Acton, James D; Lynch, Susan V; Slusher, Nicole A; Burns, Jane L.; Mayer-Hamblett, Nicole; Harris, Kirk J; Patel, Rajesh; Tremblay, Thomas M; Parli, Teresa J.

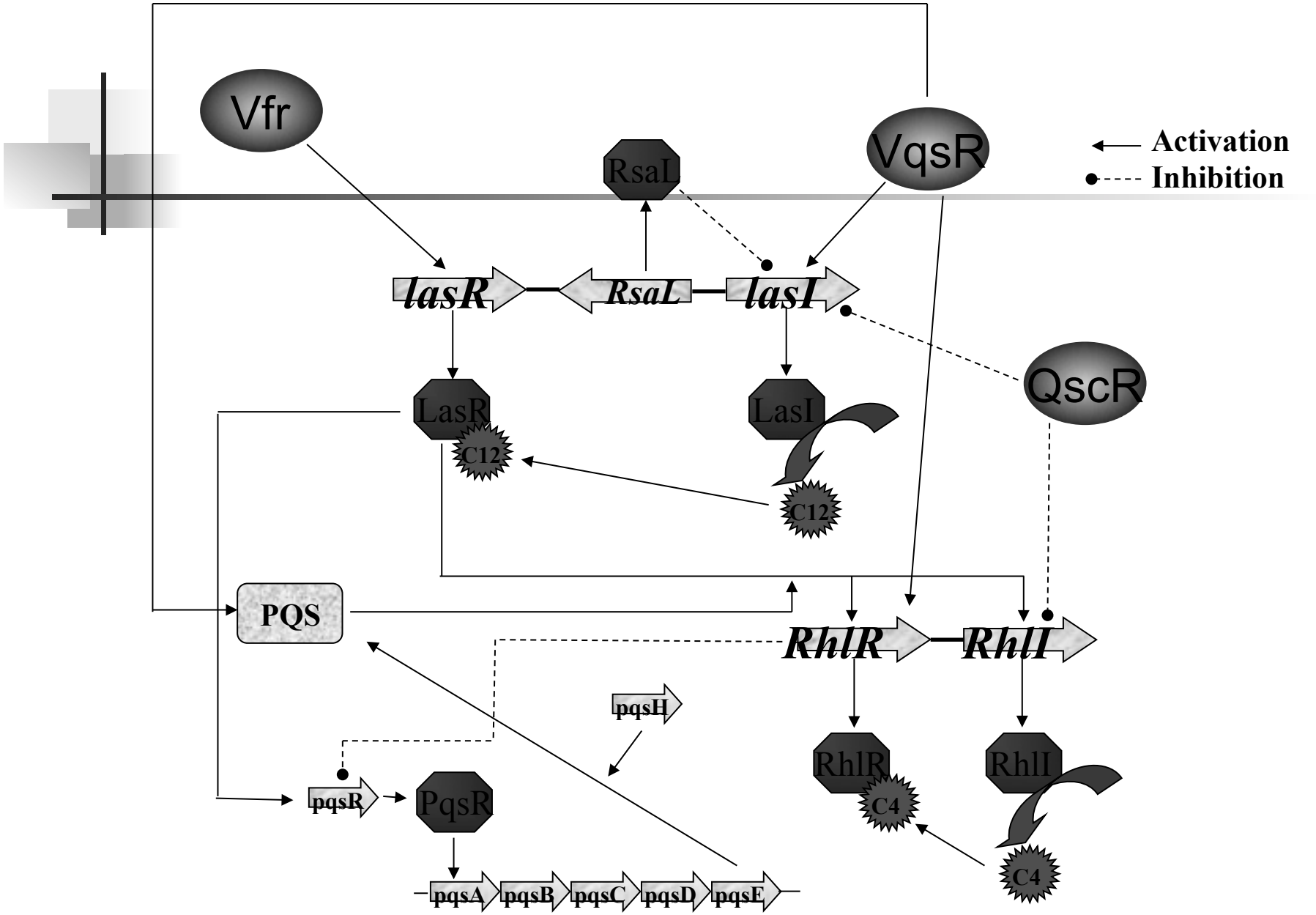
IMPACT ON FREE ELASTASE



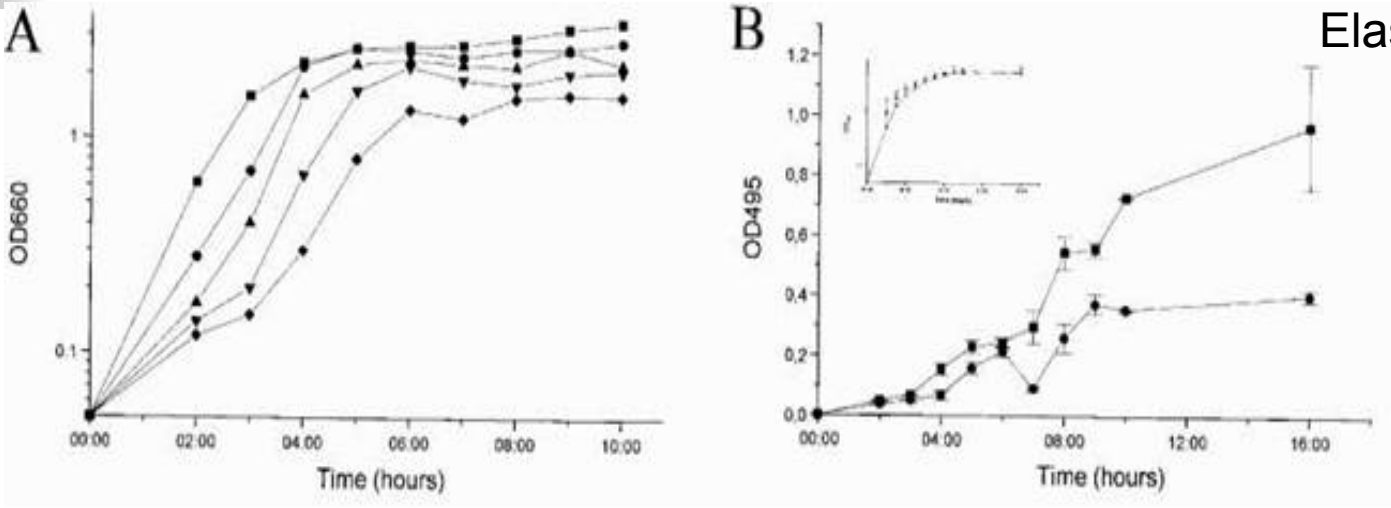
CHANGE IN SPUTUM INFLAMMATORY CELLS & CYTOKINES

Log_{10} Change from Baseline to Day 28 in Patient Sputum (Median)

Evaluable Population N=22	Placebo (N=8)	3 mg/kg (N=7)	10 mg/kg (N=7)
Neutrophils	0.25	-0.03	-0.38
IL-8	0.19	-0.08	-0.25
Neutrophil Elastase	0.29	-0.01	-0.23
Myeloperoxidase	0.18	0.06	-0.26
Macrophages	0.29	-0.22	-0.47
IL-1 beta	0.25	0.03	-0.24
TNF alpha	0.09	0	-0.05

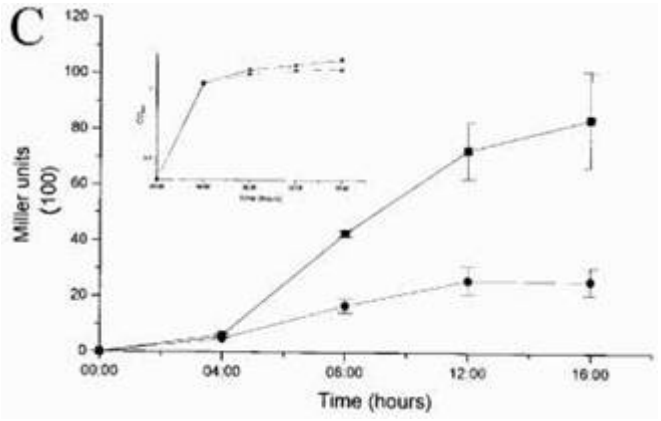

Vfr
VqsR
RsaL
Activation
Inhibition
lasR
RsaL
lasI
QscR
LasR
C12
LasI
C12
PQS
RhlR
RhlI
pqsH
pqsR
PqsR
RhlR
RhlI
C4
C4
pqsA
pqsB
pqsC
pqsD
pqsE

QS Inhibition with macrolides



Elastase

Not bactericidal
Not bacteriostatic



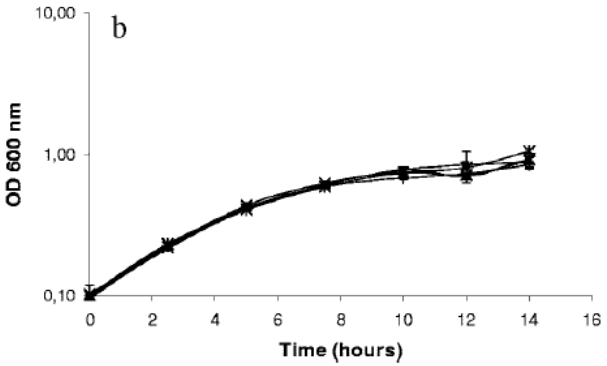
Rhamnolipid

QS Inhibition

Tateda K et al. AAC 2001

Azithromycin Blocks Quorum Sensing and Alginate Polymer Formation and Increases the Sensitivity to Serum and Stationary-Growth-Phase Killing of *Pseudomonas aeruginosa* and Attenuates Chronic *P. aeruginosa* Lung Infection in *Cftr*$^{-/-}$ Mice$^{\nabla}$

Nadine Hoffmann,[1]* Baoleri Lee,[1] Morten Hentzer,[2] Thomas Bovbjerg Rasmussen,[2] Zhijun Song,[1] Helle Krogh Johansen,[1] Michael Givskov,[2] and Niels Høiby[1]



no AZM (control)
2 g/ml AZM
4 g/ml AZM
8 g/ml AZM
12 g/ml AZM

TABLE 1. Effect of AZM on virulence factor production by *P. aeruginosa* over 24 h of culture

Virulence factor	AZM concn (μg/ml)	Activity per cell[a]	% of control
Elastase	0 (control)	0.075 ± 0.007	100
	2	0.058 ± 0.008	77
	4	0.034 ± 0.009	45
	8	0.038 ± 0.010	51
Chitinase	0 (control)	188 ± 11	100
	2	124 ± 18	66
	4	29 ± 9	15
	8	18 ± 10	10
Pyocyanin	0 (control)	0.044 ± 0.004	100
	2	0.019 ± 0.005	43
	4	0.014 ± 0.003	32
	8	0.007 ± 0.002	16
Alginate	0 (control)	612 ± 37.5	100
	2	383 ± 38.9	63
	4	340 ± 62.5	56
	8	320 ± 9,8	52

[a] Values are means ± standard deviations for three replicates. The specific activities are A_{495}/OD_{600} for elastase, U/OD_{600} for chitinase, A_{520}/OD_{600} for pyocyanin, and $\mu g/ml/OD_{600}$ for alginate.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2007, p. 3677–3687

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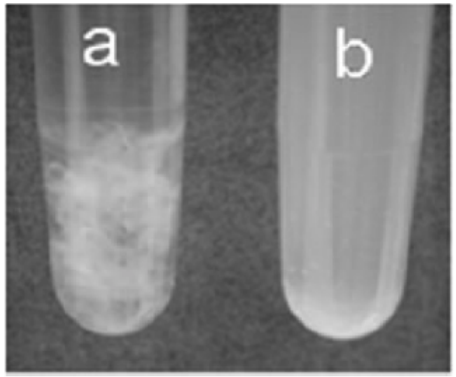
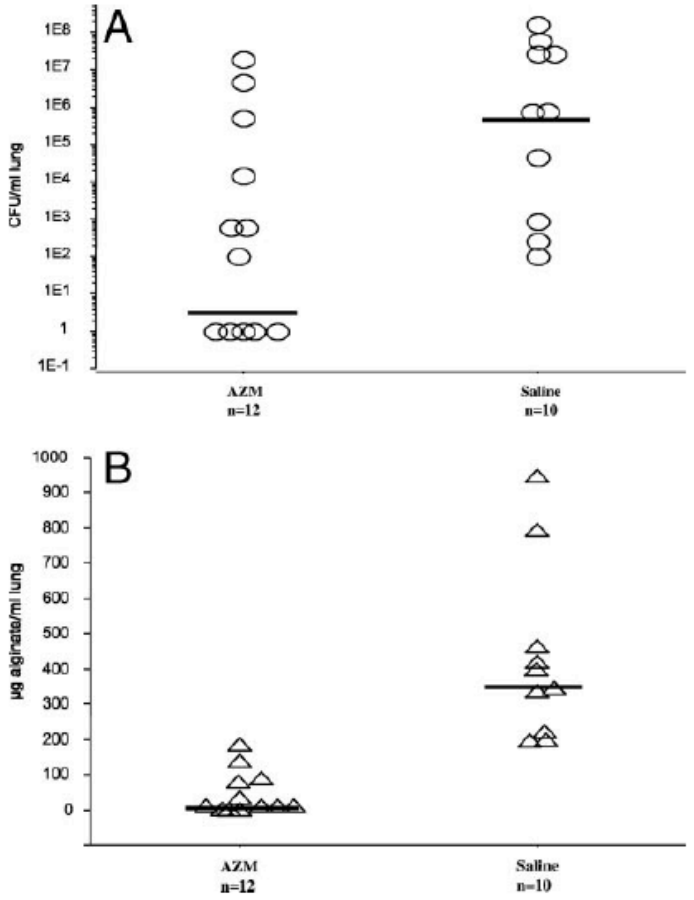


FIG. 3. Alcohol precipitation of alginate from liquid ox bouillon cultures of *P. aeruginosa* NH57388A after 24 h of incubation at 37°C. The precipitation of high-weight polymers of alginate in untreated cultures (a) versus that in cultures treated with 12 μg AZM/ml (b) was negative.



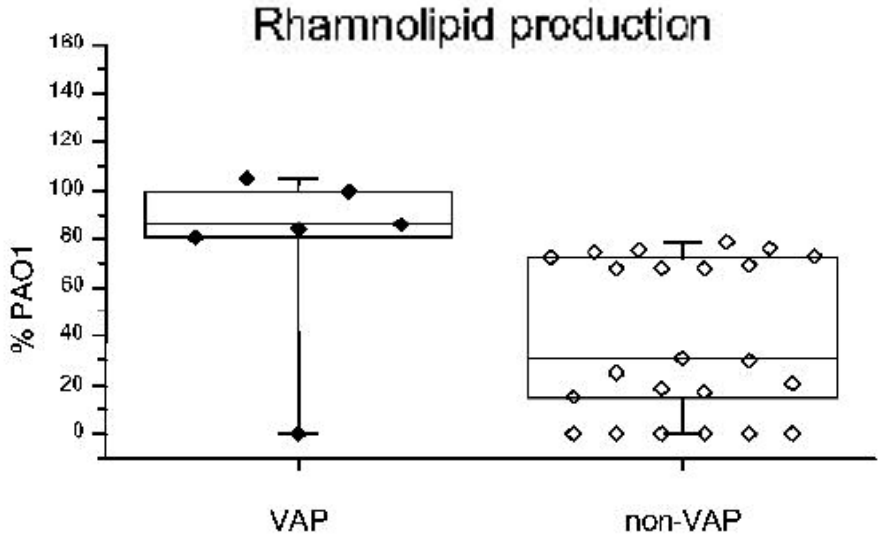
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2007, p. 3677–3687

Quorum-sensing dependent virulence during *Pseudomonas aeruginosa* colonization and pneumonia in mechanically ventilated patients.

Thilo Köhler[1,2], Raphael Guanella[3], Jean Carlet[4], and Christian van Delden[1,2]

320 P. aeruginosa isolates and tracheal aspirates from 29 patients, six developed VAP (20%).

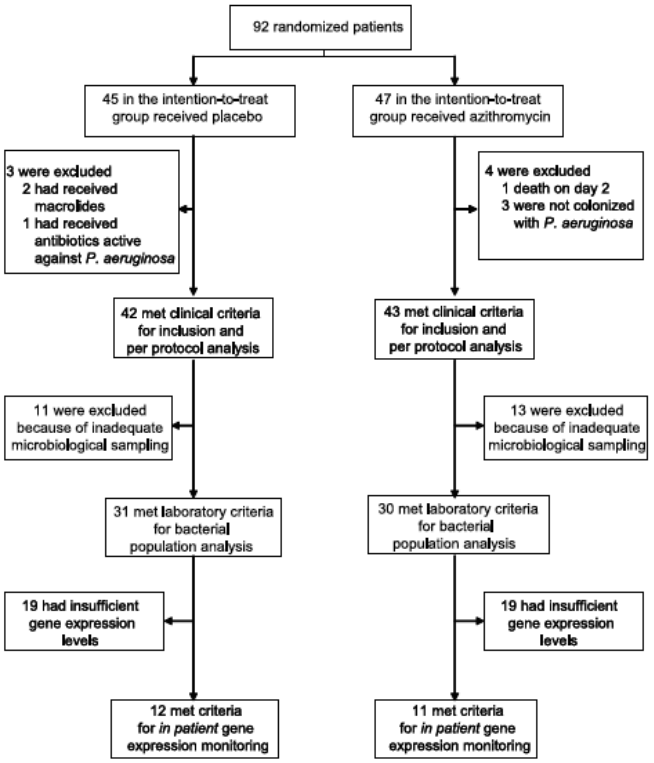
- 7 patients colonized by QS-proficient isolates
  - 57% developed VAP as compared to
- 22 patients colonized by QS-deficient isolates
  - 9% developed VAP (p = 0.018).



Thorax. 2010 Aug;65(8):703-1

Quorum Sensing Inhibition Selects for Virulence and Cooperation in *Pseudomonas aeruginosa*

Thilo Köhler[1], Gabriel G. Perron[2], Angus Buckling[2], Christian van Delden[1]*



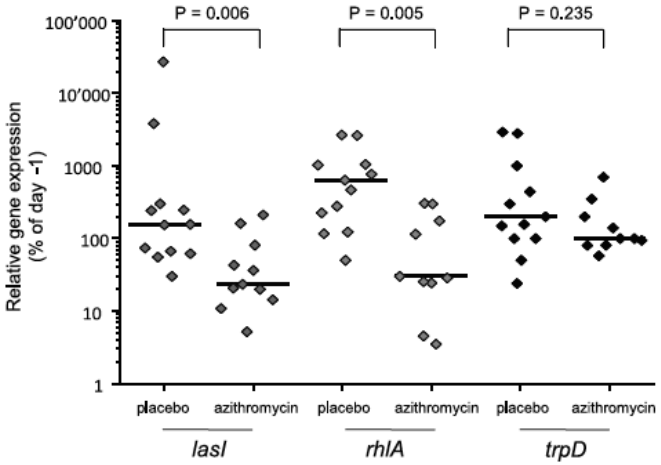
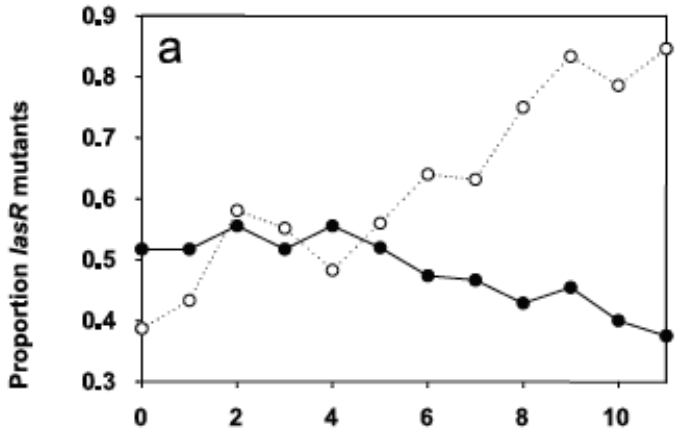


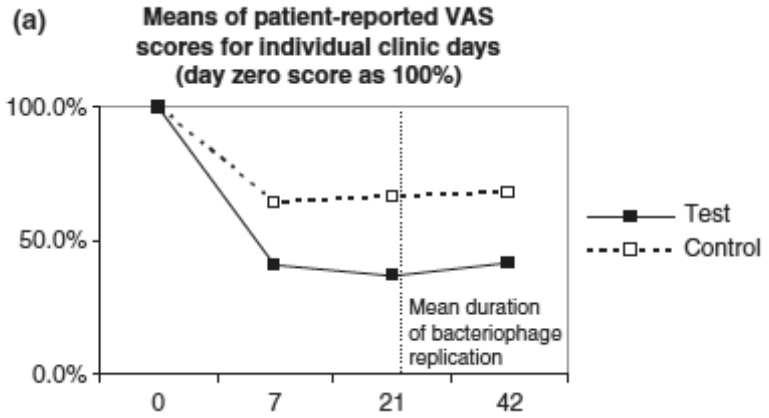
Figure 2. *In patient* QS-inhibition in azithromycin-treated patients.

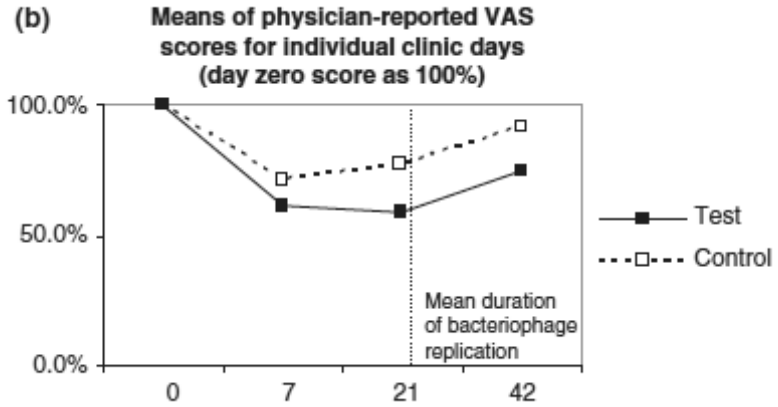


A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy

Wright, A.*, Hawkins, C.H.†, Änggård, E.E.† & Harper, D.R.†

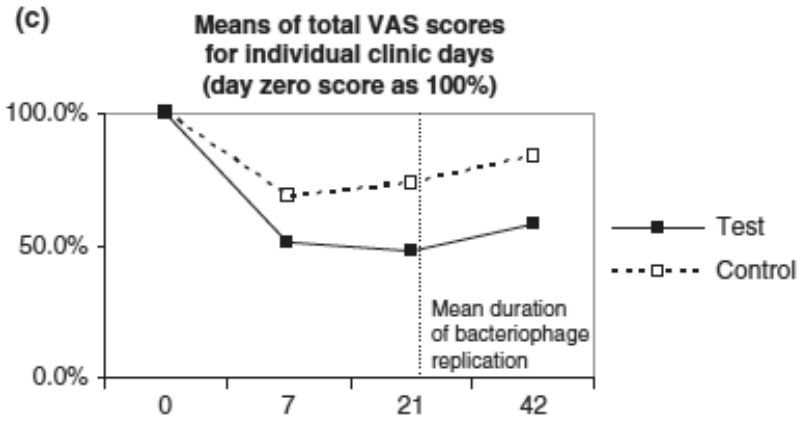
Visual Analogue Scale (VAS)





- Physician
erythema/inflammation,
ulceration/granulation/polyps,
discharge quantity,
discharge type and odour

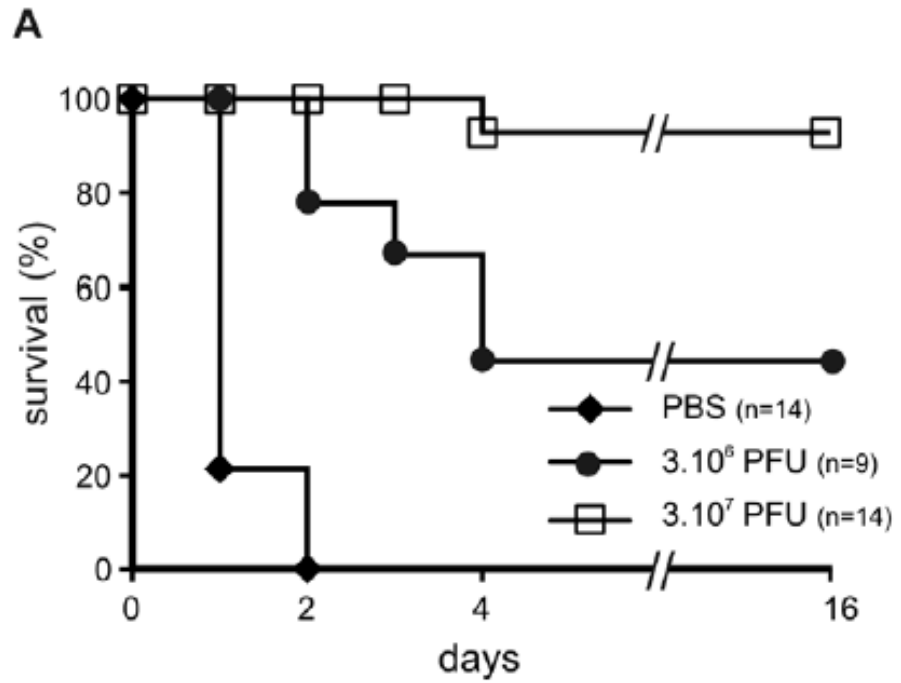
- Patients
Discomfort, itchiness, wetness, smell



Clin. Otolaryngol. 2009, **34**, 349–357

Pulmonary Bacteriophage Therapy on *Pseudomonas aeruginosa* Cystic Fibrosis Strains: First Steps Towards Treatment and Prevention

Eric Morello[1], Emilie Saussereau[1], Damien Maura[1], Michel Huerre[2], Lhousseine Touqui[3,4], Laurent Debarbieux[1]*



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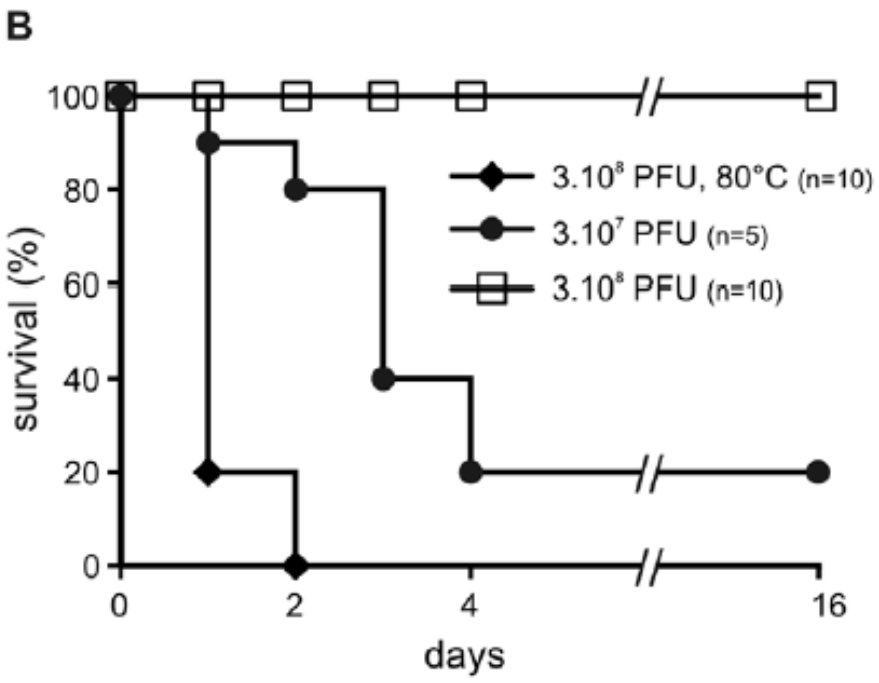
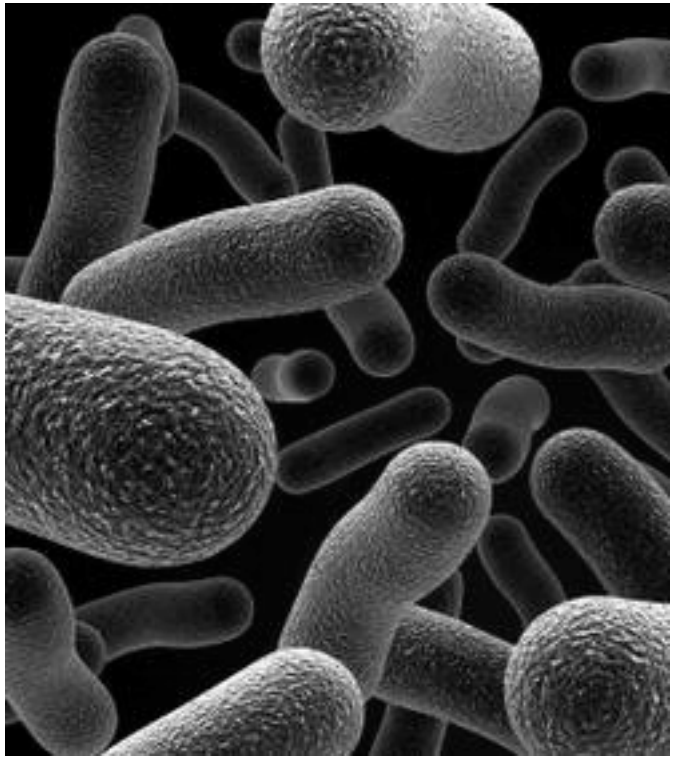
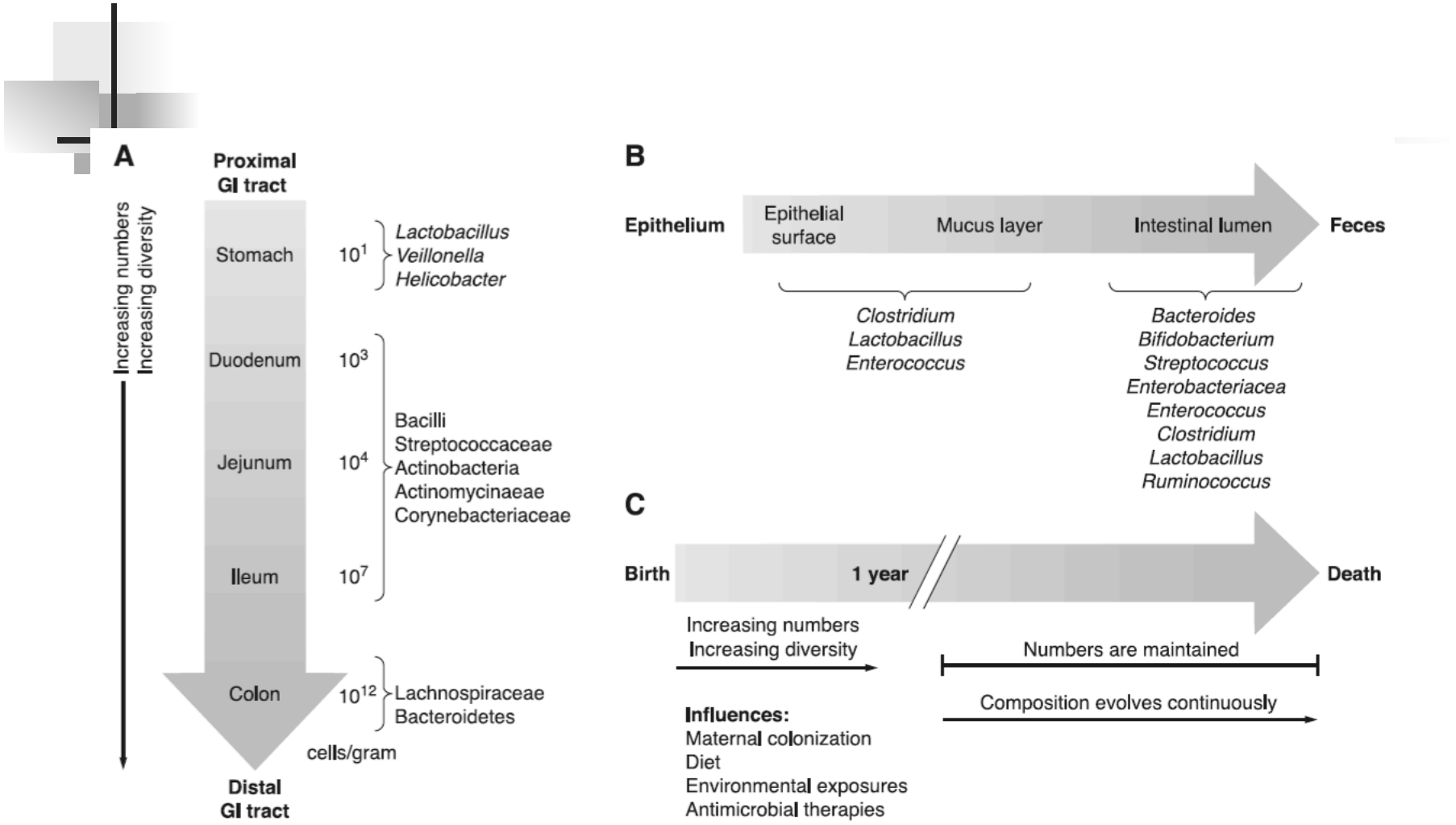


Preventive 4d

PLoS ONE
February 2011 | Volume 6 | Issue 2 | e16963

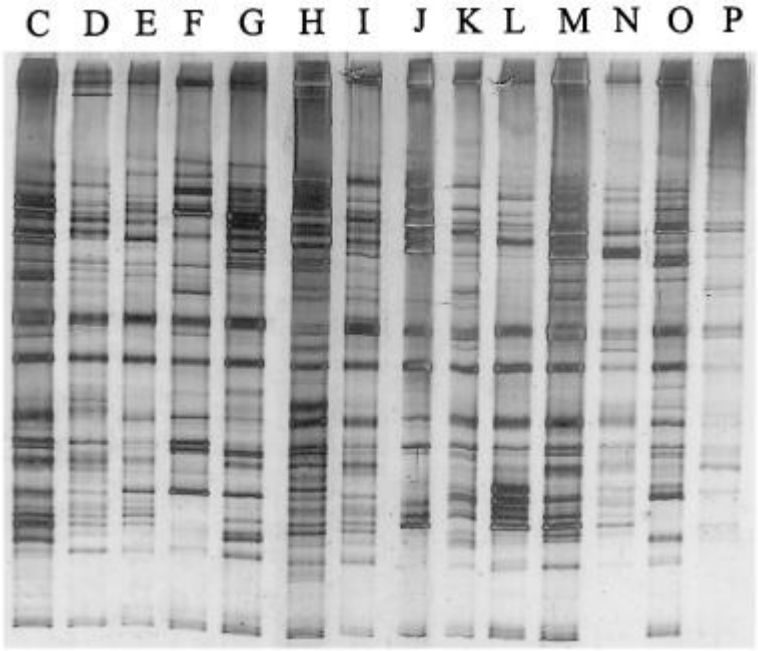
Microbiote





Sekirov, 2010

14 sujets sains



Spécifique de chaque individu

Zoetendal, 1998

Probiotiques

- Terme introduit en 1953 par Werner Kollath
- Par opposition aux antibiotiques
- Ce sont des facteurs microbiens qui stimulent la croissance d'autres microorganismes.
- La nécessité du caractère vivant des souches est ajouté à la définition par Roy Fuller en 1989.

Probiotiques

Alfred Nissle

- Isolement en 1917 d'une souche de *E. coli* à partir de selles d'un soldat qui, lors d'une épidémie de Shigellose, n'a pas développé d'entérocolite.
- Utilisation de sa souche avec succès dans des cas de Salmonellose et Shigellose [Nissle 1959].

Essais contrôlés et diarrhée post-antibiotique

Adulte	D' Souza	2002	BMJ
	Cremonini	2002	Aliment Pharmocol Ther
	Szajewska	2005	Aliment Pharmocol Ther
	Hawrelak	2005	Digestion
Enfant	Szajewska	2006	J Pediatr
	Johnston	2006	CMAJ
	Johnston	2007	Cochrane Database Syst Rev.

⇒Efficacité modérée des probiotiques à prévenir la diarrhée post-ATB

- *S. boulardii* ou *L. rhamnosus* GG chez l' enfant
- *L. casei* DN 114 001 chez la personne âgée
- Pb dans la définition de la diarrhée et de la gravité clinique

Essais contrôlés et colite à *Clostridium difficile*

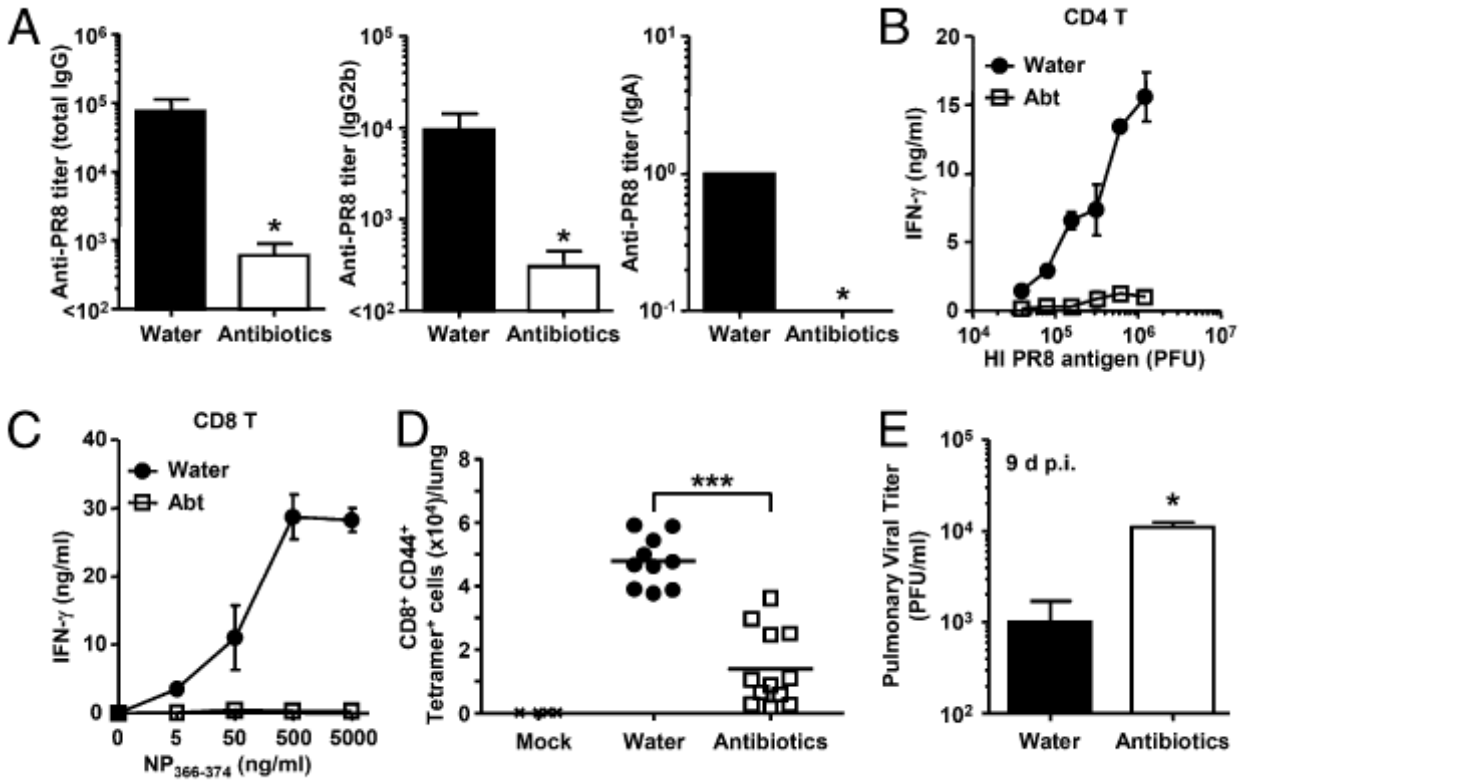
Lewis	2007	Am J Gastroenterol	**Pour**
Dendukuri	2005	CMAJ	**Contre**

Difficulté à discerner prévention et traitement au moment de la colite

Microbiota regulates immune defense against respiratory tract influenza A virus infection

Takeshi Ichinohe[a,b,1], Iris K. Pang[a,1], Yosuke Kumamoto[a], David R. Peaper[c], John H. Ho[a], Thomas S. Murray[c,d], and Akiko Iwasaki[a,2]

Ampicillin (1 g/L), vancomycin (500 mg/L), neomycin sulfate (1 g/L), and metronidazole (1 g/L) in drinking water for 4 wk before PR8 virus infection (10 pfu per mouse).



Proc Natl Acad Sci USA 2011

Greffe de flore.....

Author	Year	Cases (*n*)	Route of instillation		Cured (%)	Ref #
			Upper GI tract	Lower GI tract		
Eiseman	1958	4	1	3	4 (100)	[24]
Bowden	1981	16	1	15	13 (81)	[25]
Schwan	1984	1		1	1 (100)	[40]
Tvede	1989	6		6	6 (100)	[26]
Fløtterød	1991	1	1		1 (100)	[30]
Paterson	1994	7		7	7 (100)	[41]
Lund-Tønnesen	1998	18	1	17	15 (90)	[32]
Gustafsson[a]	1998	13		13	13 (100)	[33]
Persky	2000	1		1	1 (100)	[31]
Faust	2002	6		6	1 (100)	[42]
Aas	2003	16	16		15 (94)	[10]
Jorup-Rönström	2006	5		5	5 (100)	[28]
Nieuwdorp	2008	7	4	3	7 (100)	[34]
Total		100	24	76	89 (89)	

Bakken et al, *Anaerobe 2009*