



SEPSIS :

des nouveaux-nés aux vieillards... tous concernés !

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FOR RESEARCH, FOR HEALTH,
FOR OUR FUTURE

Institut Pasteur 



World Health Organization





SEPSIS

29 mai 2017

SOIXANTE-DIXIÈME ASSEMBLÉE MONDIALE DE LA SANTÉ

Amélioration de la prévention, du diagnostic et de la
prise en charge clinique de l'état septique






The NEW ENGLAND
JOURNAL of MEDICINE

August 3, 2017
Vol. 377: pp 414-417

Recognizing Sepsis as a Global Health Priority —
A WHO Resolution

Konrad Reinhart, M.D., Ron Daniels, M.D., Niranjana Kissoon, M.D., Flavia R. Machado,
Raymond D. Schachter, L.L.B., and Simon Finfer, M.D.

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Every 3-4 seconds someone dies of sepsis. Sepsis occurs when the body's response to an infection damages its own organs and tissues.

Sepsis
a global burden

~ **27 000 000**
people per year develop sepsis

~ **8 000 000**
people per year die




Global Sepsis Alliance

WORLD SEPSIS DAY
September 13



stop sepsis
save lives



African Sepsis Alliance

Every patient in Africa has a right to survive sepsis. Sign the Kampala Declaration

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- 1/ HISTORIQUE**
- 2/ DÉFINITIONS**
- 3/ ÉPIDEMIOLOGIE**
- 4/ MICROBIOLOGIE**
- 5/ DARK VADOR**
- 6/ ALTÉRATION IMMUNOLOGIQUE**
- 7/ DIAGNOSTIC**
- 8/ THÉRAPIES**

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				SEPSIS Puerperal fever		
1519 Lucrece Borgia	1687 Lully	1774 Louis XV	1865 Semmelweis		1868 Rossini	1875 Bizet
						
1883 Manet	1894 Hertz	1894 Mahler	1920 Alexander I of Greece	1926 Rudolph Valentino	2004 Christopher Reeve	
				Celebrities who died of sepsis		
2005 Rainier III	2005 Jean-Paul II	2011 Socrates	2016 M. Ali			
Miss Agnès Souret (18 yrs) - 1 st Miss France (1920) Died of septicemia at the age of 26						

1718



EDWARD STROTHER
(1675 – 1737)

Puerperal fever

Criticon Februm :
OR, A
Critical ESSAY
ON
FEVERS;

WITH THE
DIAGNOSTICKS and METHODS
of CURE, in all the different Species
of them.

To which is prefix'd,
A Large INTRODUCTION concerning
the USE and ABUSE of the *Mathematicks* in
PHYSICK, and the BASIS on which *Indi-*
cations are founded: Where also the *Essodia*
Medicorum is annex'd.

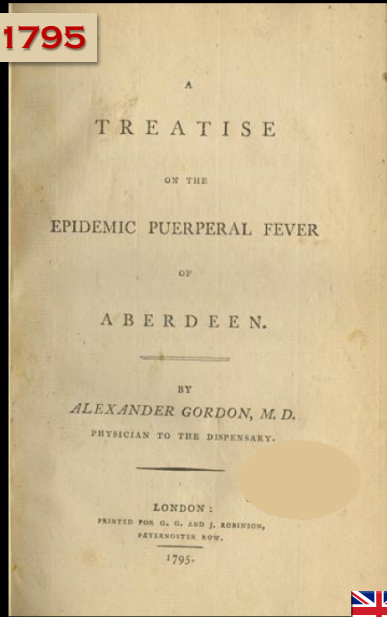
By EDWARD STROTHER, M. D.
A. Coll. Christi. Cantab. & Coll. Med. Lond. Reg.

The Second Edition, carefully Revis'd and Corrected,
with Additions, and a large Index.


LONDON,
Printed for CHARLES RIVINGTON, at the Bible
and Crown in St. Paul's Church-yard. 1718.

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1795





A
TREATISE
ON THE
EPIDEMIC PUERPERAL FEVER
OF
A B E R D E E N.
BY
ALEXANDER GORDON, M. D.
PHYSICIAN TO THE DISPENSARY.
LONDON:
PRINTED FOR G. G. AND J. ROBINSON,
PATERNOSTER ROW.
1795.

ALEXANDER GORDON 
(1752 1799)


It's contagious!


"It is a disagreeable declaration for me to mention, that myself was the means of carrying the infection to a great number of women"


HYGIENE 

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1837




PIERRE A. PIORYY 
(1794 –1879)



TRAITÉ
DE DIAGNOSTIC
DE SÉMÉIOLOGIE.
P.-A. PIORYY,
DEUXIÈME ÉDITION.
Bruxelles,
SOCIÉTÉ TYPOGRAPHIQUE BELGE,
1837.

Septicemia

... From Greek Σήψις, putrefaction
et αίμα, blood

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1843



OLIVER HOLMES
(1809 – 1894)



HYGIENE



1854




CHARLES D. MEIGS
(1792-1869)




"Doctors are gentlemen,
and gentlemen's hands
are clean."

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1847





IGNAZ SEMMELWEIS
(1818 –1865)



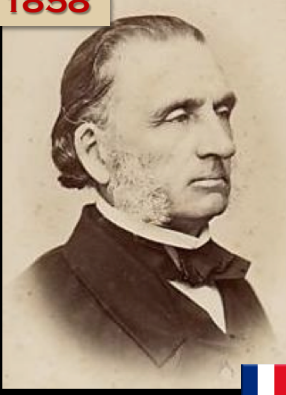
Ausicht des allgemeinen Krankenhauses. Vue de l'Hôpital Général à Vienne.

He succeeded, by antiseptic methods (calcium hypochlorite), in reducing the mortality due to puerperal septicemia from 16% to 0.85%



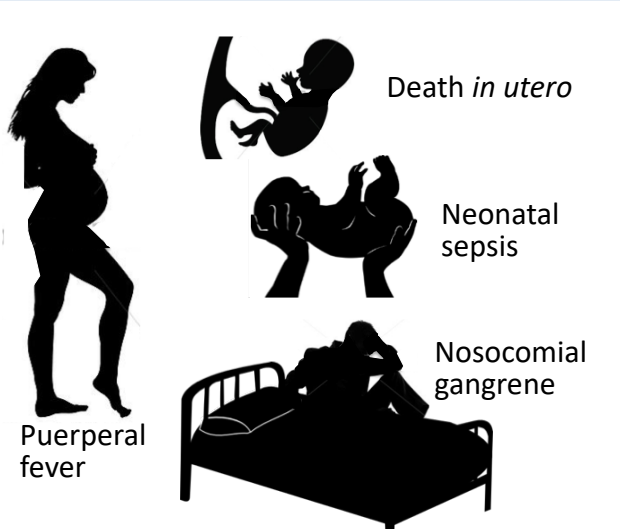
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1858



ARMAND TROUSSEAU
(1801 – 1867)

→ There is no specific diseases




Puerperal fever

Death *in utero*

Neonatal sepsis

Nosocomial gangrene

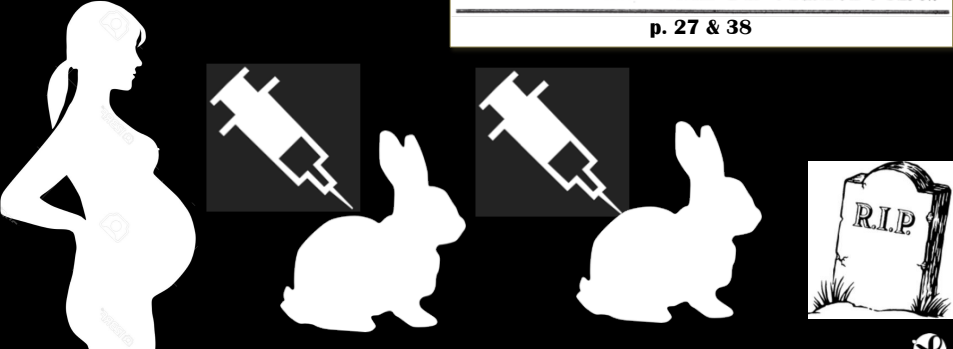
1869



VICTOR FELTZ
(1835-1893)

LÉON COZE
(1819-1896)

→ The blood contains deadly bacteria



1^{re} SÉRIE. — 20^e ANNÉE. N° 2. — 10 FÉVRIER 1869. 2^e SÉRIE. — 9^e ANNÉE.

GAZETTE MÉDICALE DE STRASBOURG.

p. 27 & 38

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1879



LOUIS PASTEUR
(1822 – 1895)



Lochia & blood
Pus from uterus

CONFIRMED

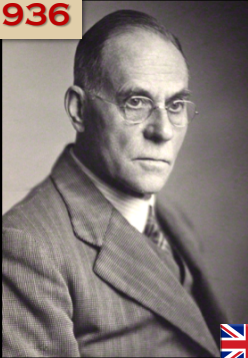


He suggested the use of boric acid to wash the genital tract




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1936




LEONARD COLEBROOK
(1883 -1967)




1935

Sulfamidochrysoïdine, patented under the name **Prontosil**,



GERHARD DOMAGK
(1895 – 1964)

Nobel Prize
Medicine or
Physiology
1939



Lancet 1: 1279-1286


**TREATMENT OF
HUMAN PUERPERAL INFECTIONS, AND
OF EXPERIMENTAL INFECTIONS IN
MICE, WITH PRONTOSIL***

By **LEONARD COLEBROOK, M.B., B.S. Lond.**
MEMBER OF THE SCIENTIFIC STAFF, MEDICAL RESEARCH COUNCIL

MÉAVE KENNY, M.R.C.S. Eng., M.C.O.G.
RESIDENT MEDICAL OFFICER, ISOLATION BLOCK, QUEEN CHARLOTTE'S HOSPITAL, LONDON

AND THE MEMBERS OF THE
HONORARY STAFF OF QUEEN CHARLOTTE'S HOSPITAL

The very first use of antibiotics in humans



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2/ DÉFINITIONS

AAEIP

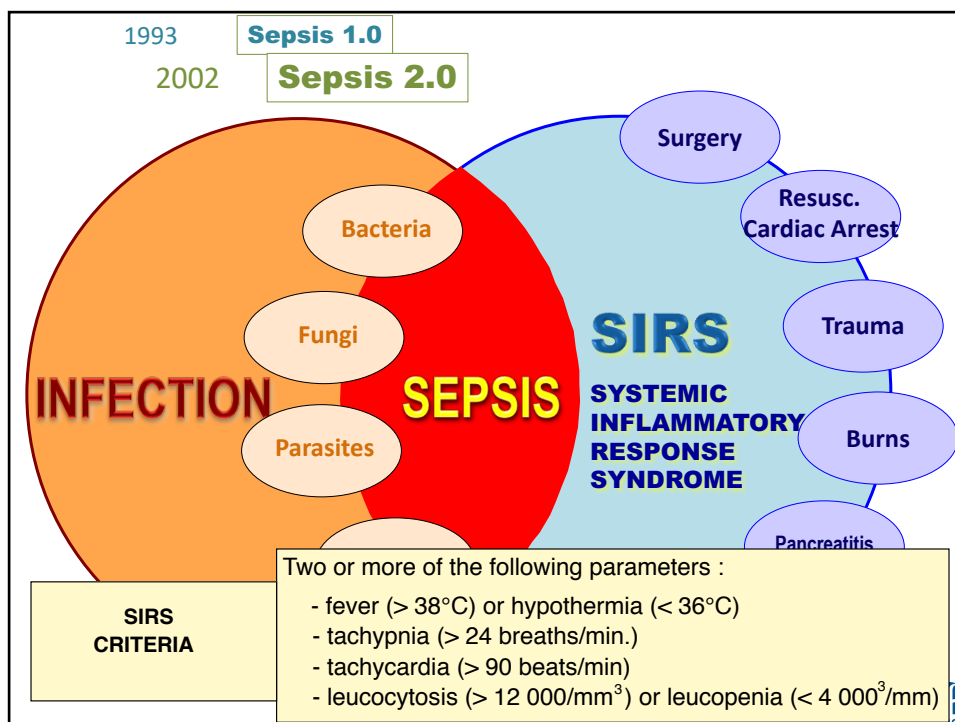
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1993 **Sepsis 1.0**
2002 **Sepsis 2.0**
2016 **Sepsis 3.0**

~~SIRS~~
SEPSIS
~~SEVERE SEPSIS~~
SEPTIC SHOCK

Clinical criteria of sepsis

- Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection

Clinical criteria of septic shock

- Sepsis AND
- Vasopressors required to maintain MAP ≥ 65 mm Hg despite adequate fluid resuscitation,
- Serum lactate ≥ 2 mmol/L

Singer M et al. *The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)*. **JAMA**. 2016 Feb 23; 315: 801-10.

Shankar-Hari M et al. *Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)*. **JAMA**. 2016 Feb 23; 315: 775-87.

Seymour CW et al. *Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)*. **JAMA**. 2016 Feb 23; 315: 762-74


Screening for patients likely to have sepsis


Sepsis-3.0 introduces qSOFA as a tool for identifying patients at risk of sepsis

Quick SOFA


(Sepsis-related Organ Failure Assessment score)

Mnemonic: HAT






quick Sepsis-Related Organ Failure Assessment (q-SOFA)

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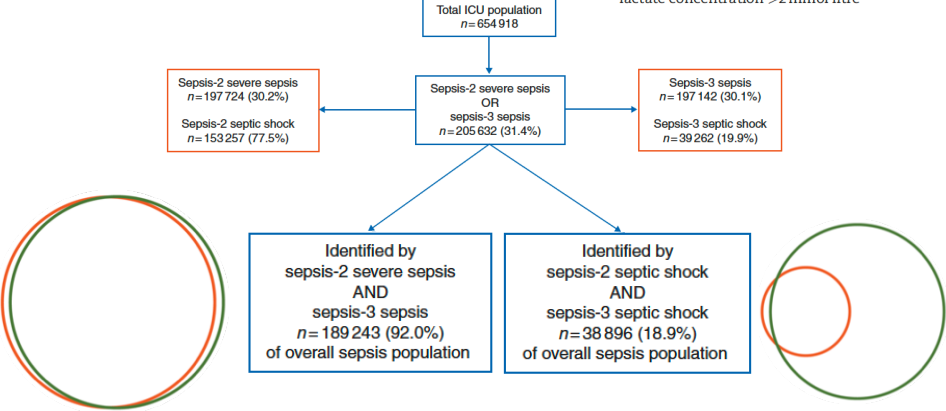
British Journal of Anaesthesia, 119 (4): 626–36 (2017)
Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database
 M. Shankar-Hari^{1,2,3,*}, D. A. Harrison³, G. D. Rubenfeld⁴ and K. Rowan³



SEPTIC SHOCK

Sepsis-2
Infection AND SIRS positive AND (cardiovascular SOFA ≥ 1 OR serum lactate concentration ≥ 4 mmol litre⁻¹)

Sepsis-3
Infection AND cardiovascular SOFA ≥ 2 AND serum lactate concentration > 2 mmol litre⁻¹



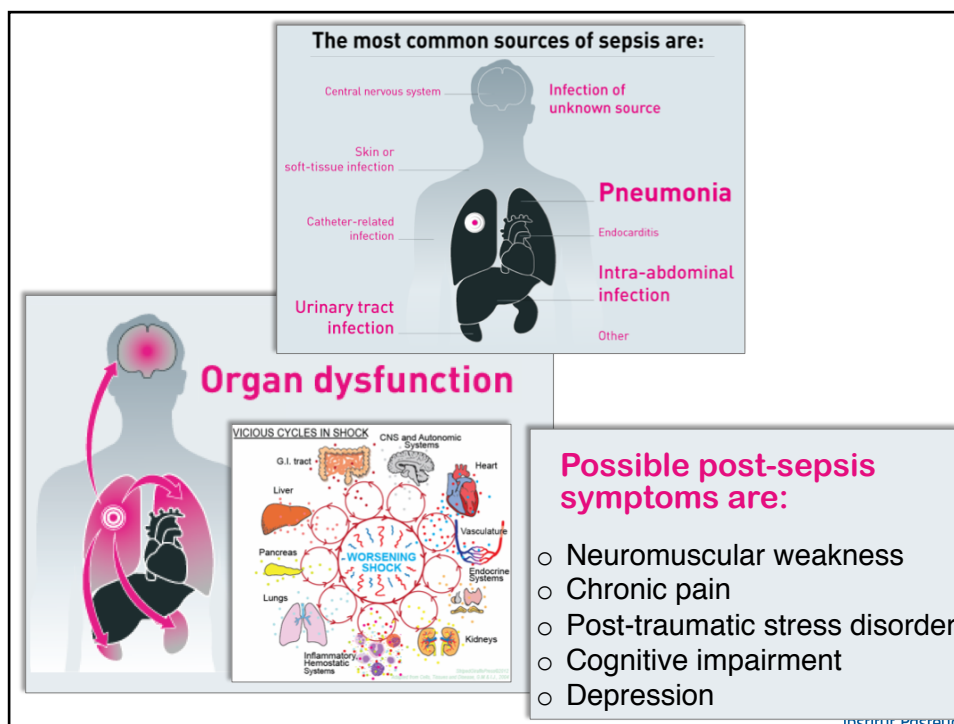
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graph TD
    A[Total ICU population n=654 918] --> B[Sepsis-2 severe sepsis OR sepsis-3 sepsis n=205 632 31.4%]
    B --> C[Sepsis-2 severe sepsis n=197 724 30.2%]
    B --> D[Sepsis-2 septic shock n=153 257 23.4%]
    B --> E[Sepsis-3 sepsis n=197 142 30.1%]
    B --> F[Sepsis-3 septic shock n=39 262 5.9%]
    C --> G[Identified by sepsis-2 severe sepsis AND sepsis-3 sepsis n=189 243 28.9%]
    D --> G
    E --> H[Identified by sepsis-2 septic shock AND sepsis-3 septic shock n=38 896 5.9%]
    F --> H
    
```

ICU mortality:
 Sepsis.2 = 21,8%
 Sepsis.3 = 22.4%

— Sepsis-2 septic shock
 — Sepsis-3 sepsis

ICU mortality:
 Sepsis.2 = 25.6%
 Sepsis.3 = 46.7%



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3/ ÉPIDÉMIOLOGIE

A A E I P

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The New York Times

Thursday, July 11, 2012

ABOUT NEW YORK

An Infection, Unnoticed, Turns Unstoppable



For a moment, an emergency room doctor stepped away from the scrum of people working on Rory Staunton, 12, and spoke to his parents. "Your son is seriously ill," the doctor said.

"How seriously?" Rory's mother, Orlaith Staunton, asked.

The doctor paused.

"Gravely ill," he said.

How could that be?

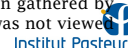
Two days earlier, diving for a basketball at his school gym, Rory had cut his arm. He arrived at his pediatrician's office the next day, Thursday, March 29, vomiting, feverish and with pain in his leg. He was sent to the emergency room at NYU Langone Medical

Center. The doctors agreed: He was suffering from an upset stomach and dehydration. He was given fluids, told to take Tylenol, and sent home.

Partially camouflaged by ordinary childhood woes, Rory's condition was, in fact, already dire. Bacteria had gotten into his blood, probably through the cut on his arm. He was sliding into a septic crisis, **an avalanche of immune response to infection** from which he would not escape. On April 1, three nights after he was sent home from the emergency room, he died in the intensive care unit. The cause was **severe septic shock** brought on by the infection, hospital records say.

Because sepsis, a leading cause of death in hospitals, can at first look like less serious ailments, a campaign to aggressively identify it for early treatment has been undertaken by a consortium of 55 hospitals in the New York region, including NYU Langone.

Yet nowhere along Rory's journey, from boy with a bellyache on Thursday to gravely ill boy on Friday night, did anyone act on strong indications that he might be fighting for his life. Critical information gathered by his family doctor and during his first visit to NYU Langone was not used, was not at hand or was not viewed **as important when decisions were made about his care, records show.**



Mirror UPDATED 12:17, 13 FEB 2018

Mum-of-two died from sepsis on family holiday two days after complaining of sore throat

Her children were waiting for her to join the pool, but tragically the 43-year-old recovered.

Echo 23rd February

Mother died of sepsis after a miscarriage

Kirsty Hough Reporter

itv 7 February 2018 at 3:36pm

Family's heartbreak after death of Sheffield dad from sepsis just two weeks after Christmas

Mirror

"Please can we amputate all your limbs?" Devastating question doctors had to ask mum as she came round from nine-week coma

After developing sepsis following a kidney infection, Kim Smith fell into nine-week coma - when she came around she faced one question: "Please can we amputate all your limbs?"

The Sydney Morning Herald

Young mum's death after giving birth by c-section was avoidable, coroner finds

February 26, 2018 **Global Sepsis Alliance**

Thomas - Taken by Sepsis Within 24 Hours

Before we lost our precious son Thomas, we had a very limited amount of knowledge about sepsis.

BBC NEWS

Sepsis death in The Archers all too familiar, says charity

© 26 February 2018



Nic Grundy is married to Will and has three young children in The Archers

The death of a young mother from sepsis in BBC radio drama The Archers on Friday has prompted an outpouring of shock and emotion.

The character of Nic Grundy developed sepsis, or blood poisoning, after accidentally cutting her arm on a rusty nail and died only days later.

She leaves behind a husband and three children (plus a stepson) in the long-running radio soap.

HOW DID NIC DEVELOP SEPSIS AND HOW COULD HER LIFE HAVE BEEN SAVED?

What is sepsis?

SEPSIS, OR BLOOD POISONING, OCCURS WHEN THE BODY OVER-REACTS TO AN INFECTION AND ATTACKS ITS OWN ORGANS AND TISSUES

THERE ARE 250,000 CASES OF SEPSIS IN THE UK EVERY YEAR.

How did Nic develop it?

NIC CONTRACTED SEPSIS FROM A BADLY INFECTED CUT IN HER ARM

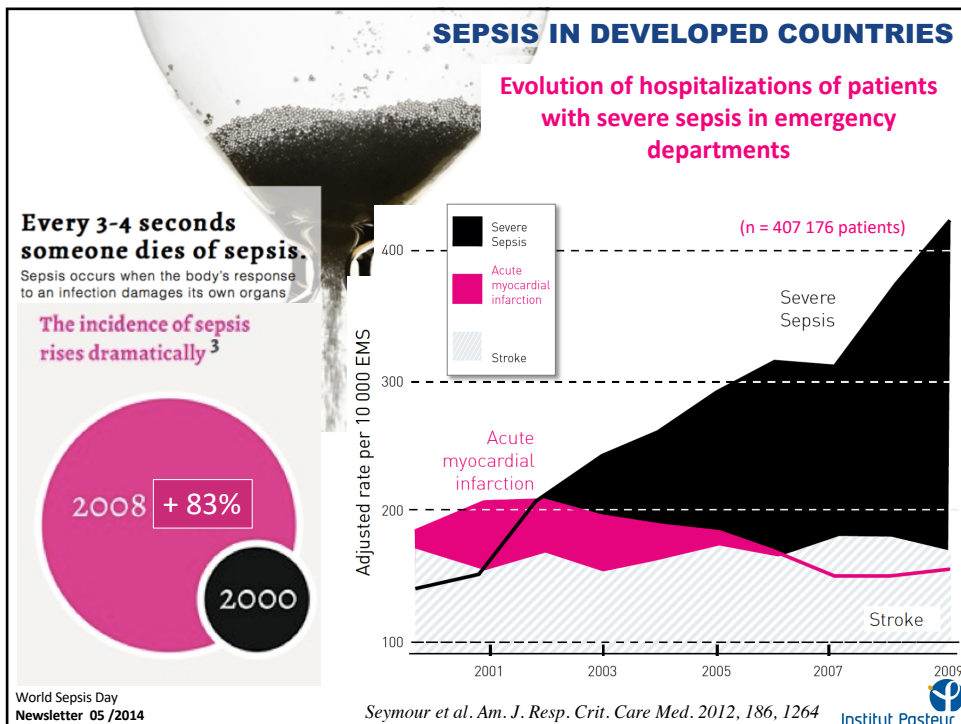
SHE WAS SORTING THROUGH A BOX OF JOE'S FLOOD-DAMAGED BELONGINGS

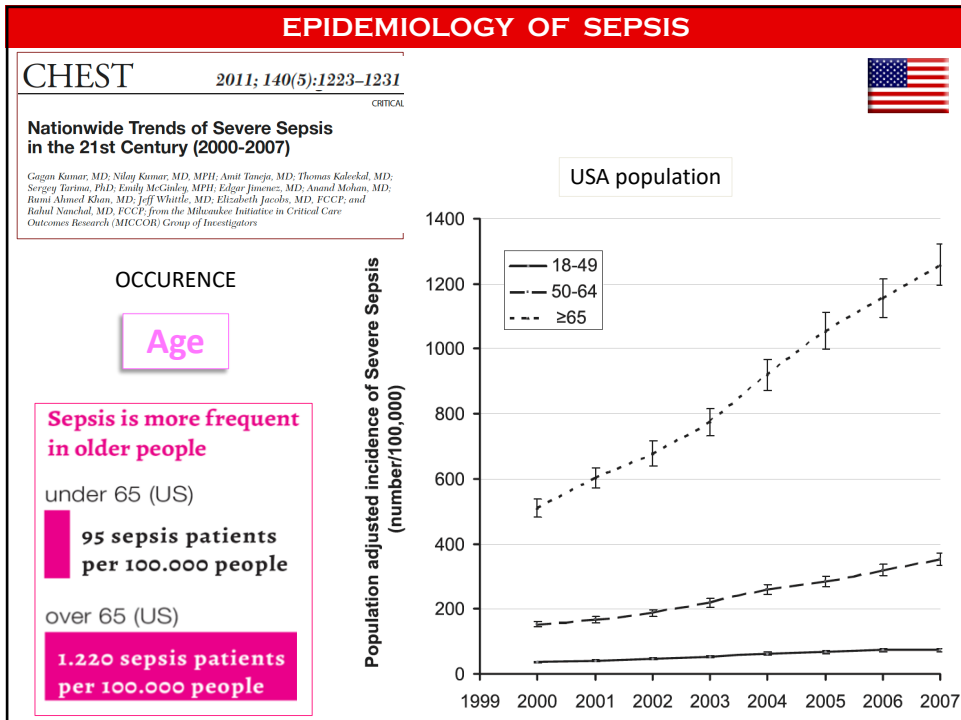
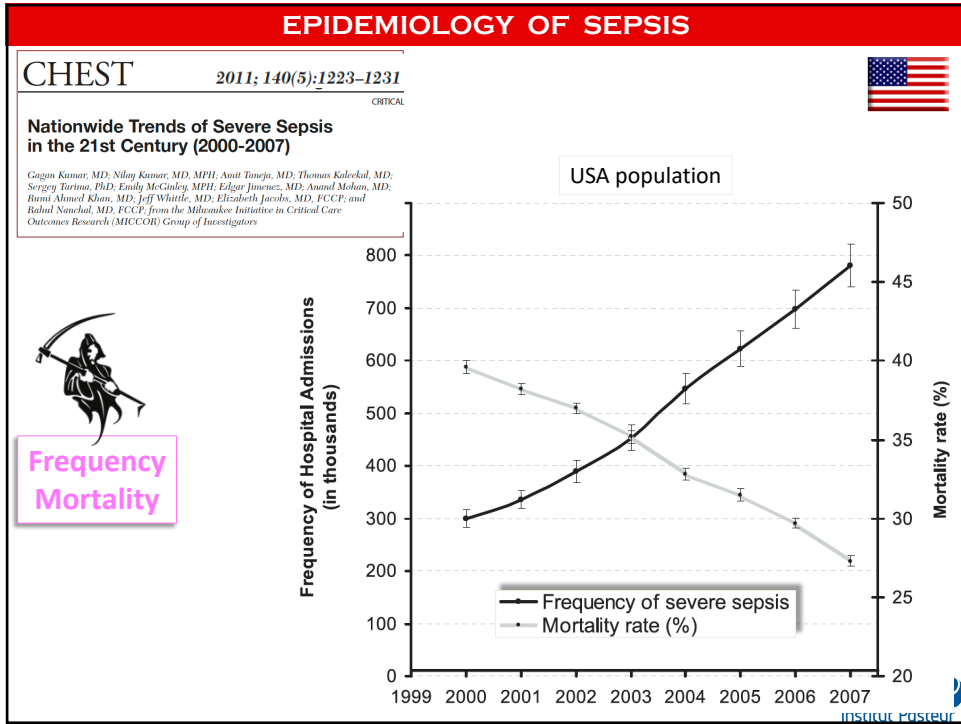
How could Nic's life have been saved?

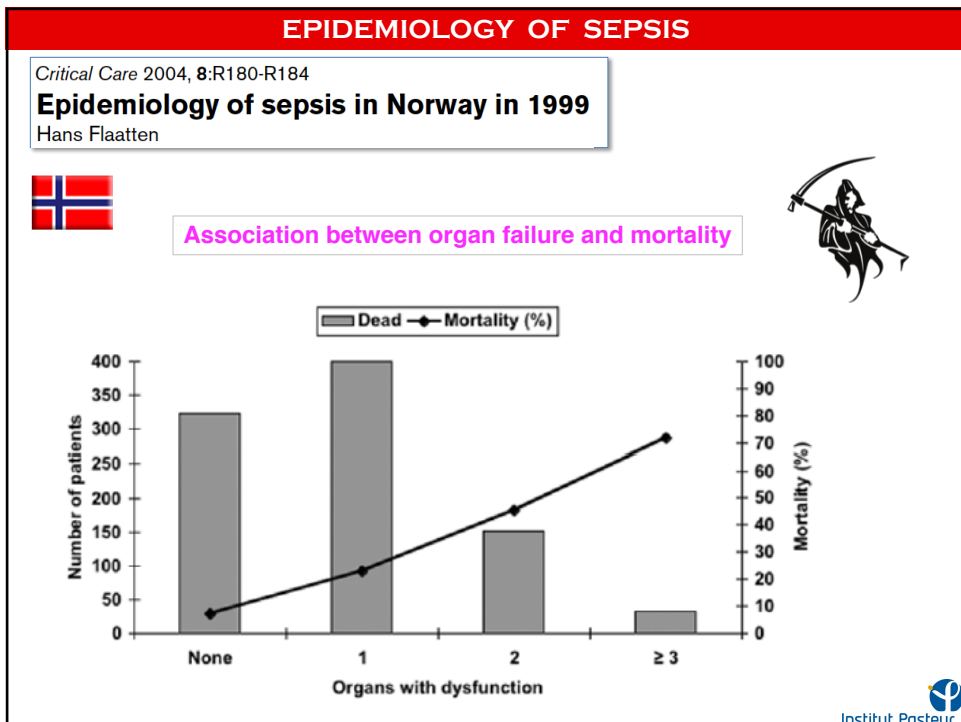
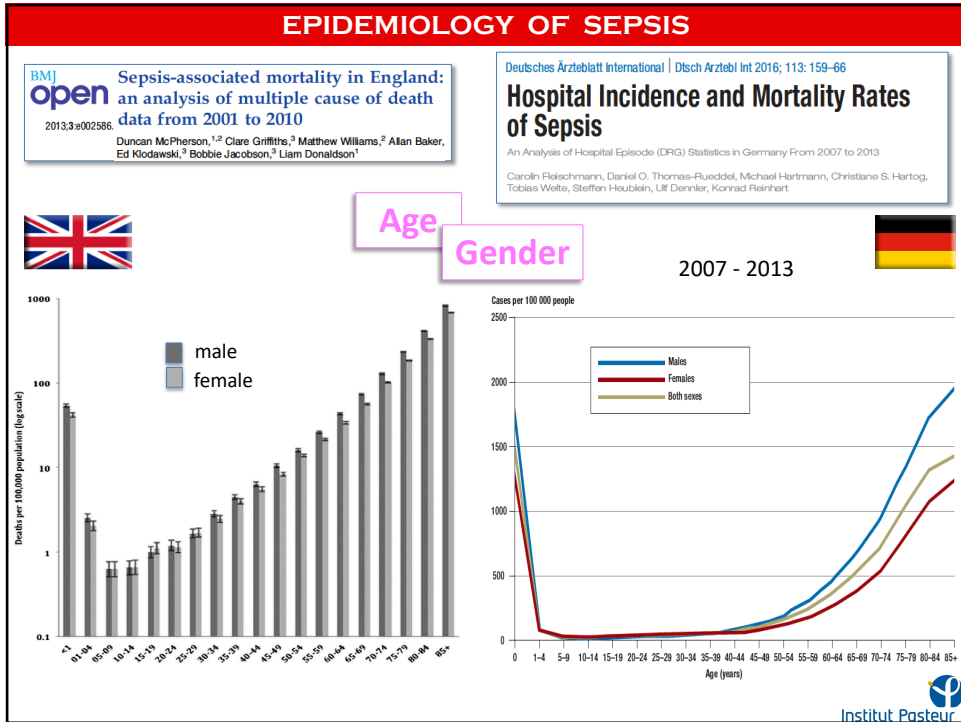
IF NIC HAD MADE IT TO HOSPITAL EARLIER, SHE COULD HAVE SURVIVED. THESE ARE THE WARNING SIGNS:

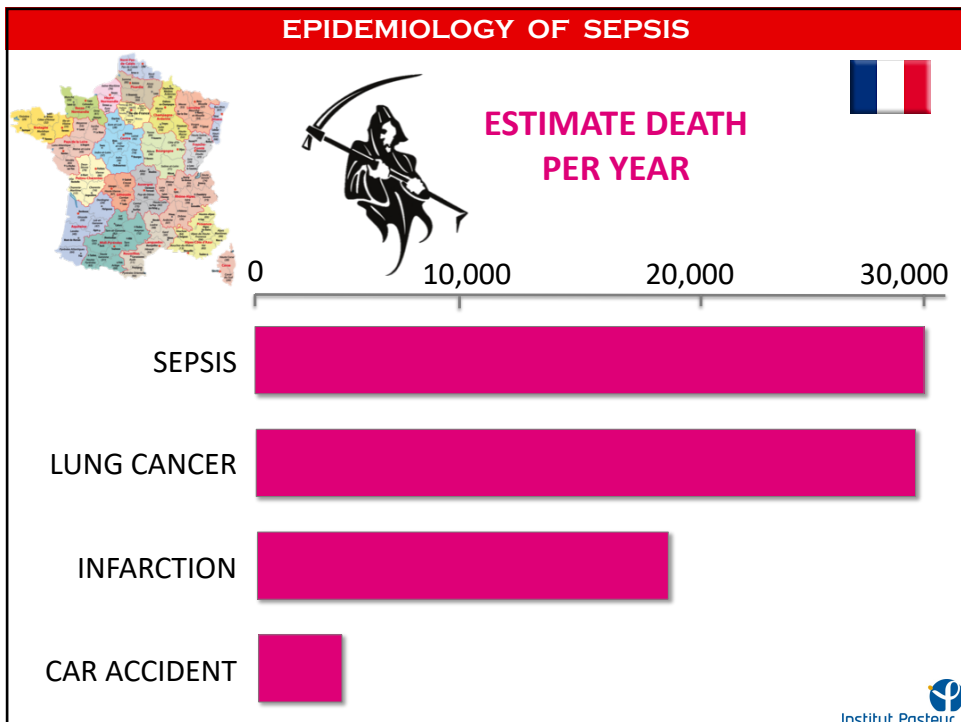
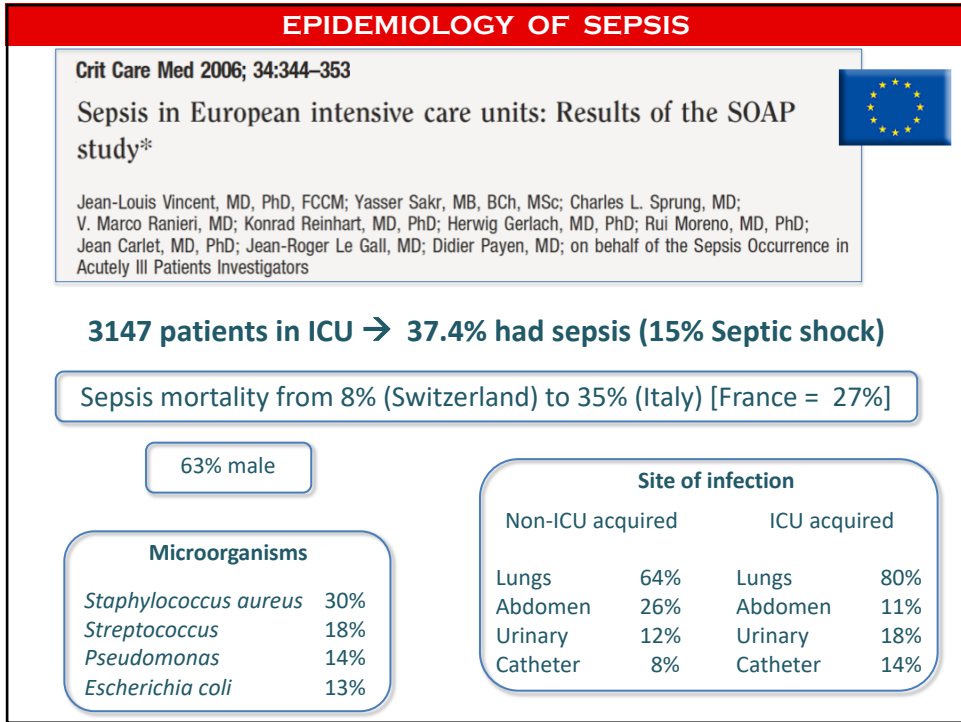
- SLURRED SPEECH OR CONFUSION
- EXTREME SHIVERING OR MUSCLE PAIN
- PASSING NO URINE IN A DAY
- SEVERE BREATHLESSNESS
- IT FEELS LIKE YOU'RE GOING TO DIE
- SKIN MOTTLED OR DISCOLOURED

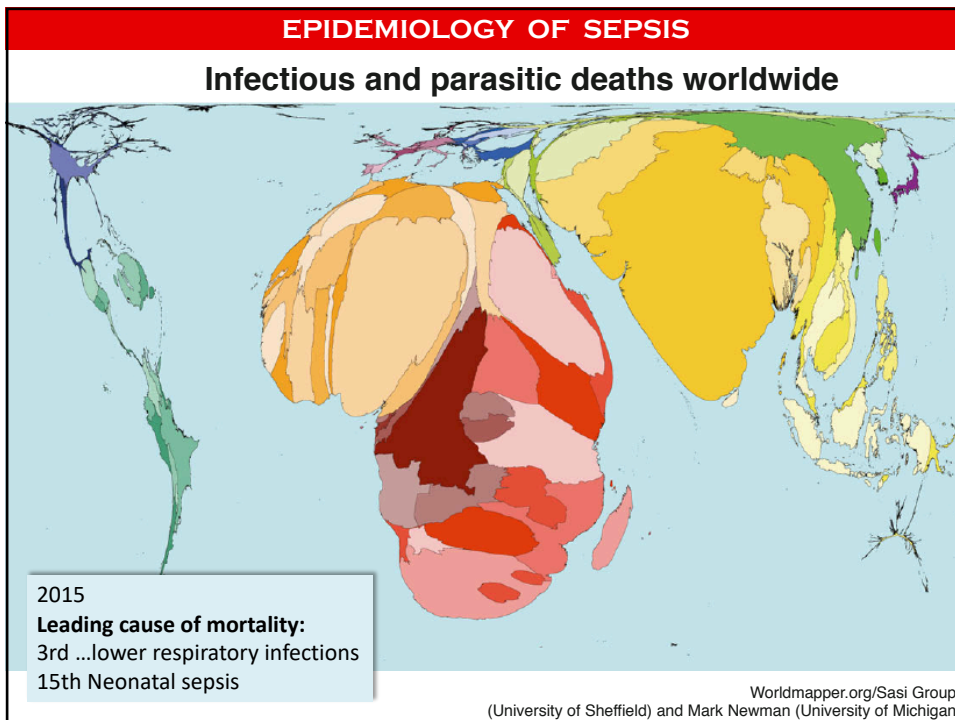
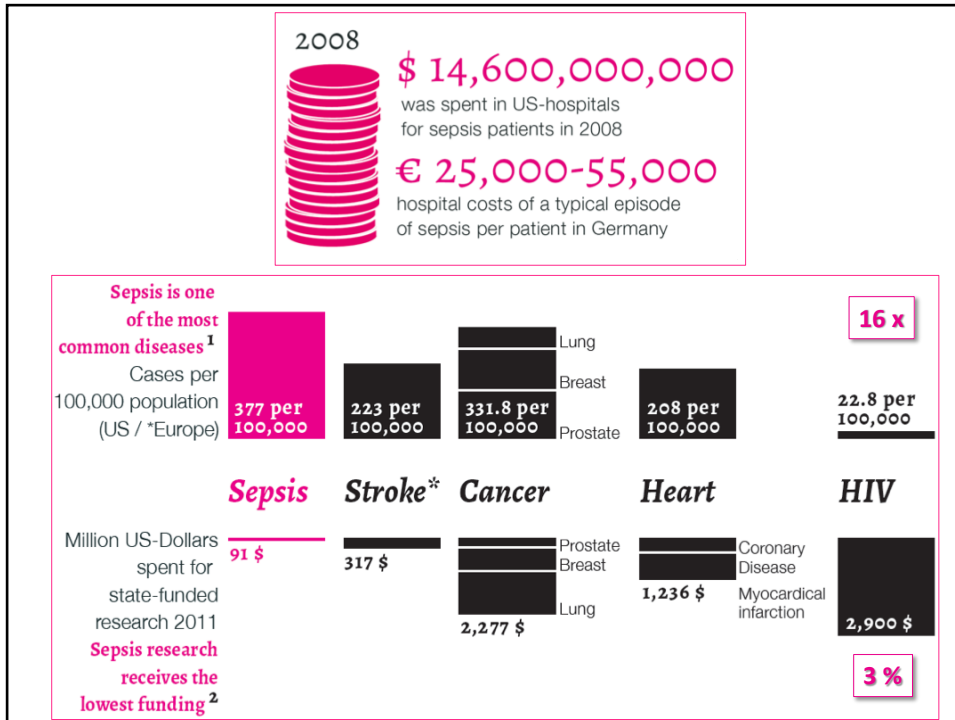


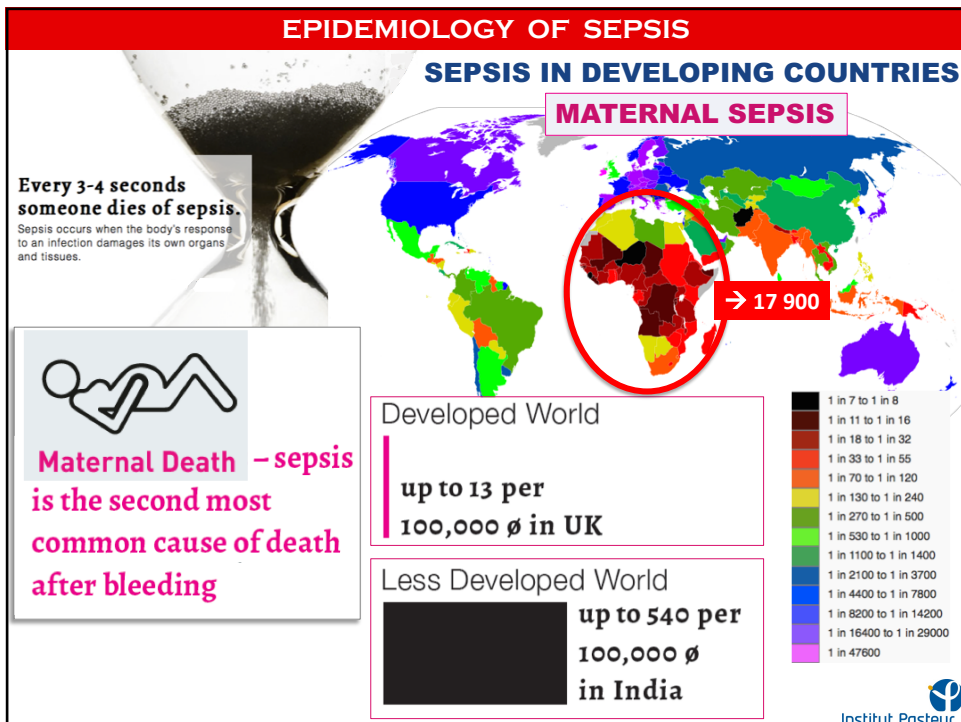
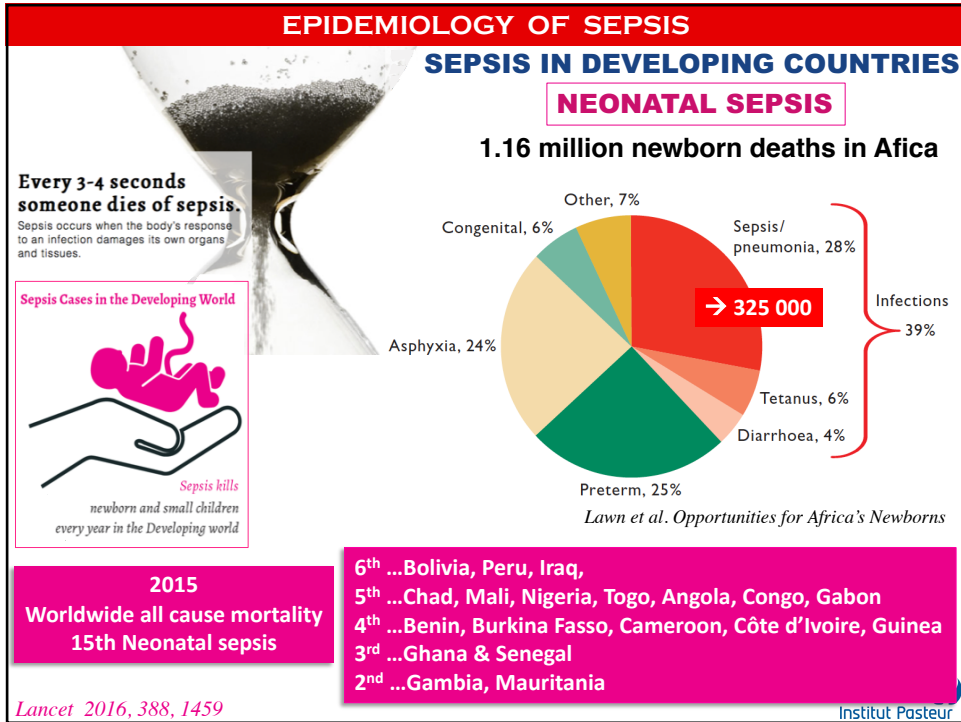












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4/ MICROBIOLOGIE








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MICROBIOLOGY



Bacteriological identity of infecting agents

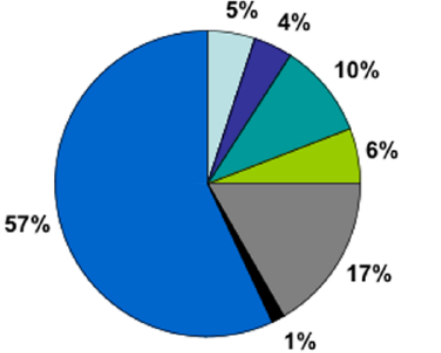


Critical Care 2004, 8:R180-R184

Epidemiology of sepsis in Norway in 1999

Hans Flaatten

- Meningococcus
- Candida species
- Streptococci
- Staph. epidermidis
- Staph. aureus
- Hemophilus
- Gram neg rods



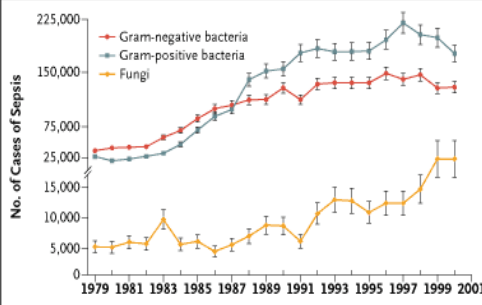
Agent	Percentage
Gram neg rods	57%
Staph. aureus	17%
Streptococci	10%
Staph. epidermidis	6%
Candida species	4%
Meningococcus	5%
Hemophilus	1%

The NEW ENGLAND JOURNAL of MEDICINE

2003;348:1546-54. ORIGINAL ARTICLE

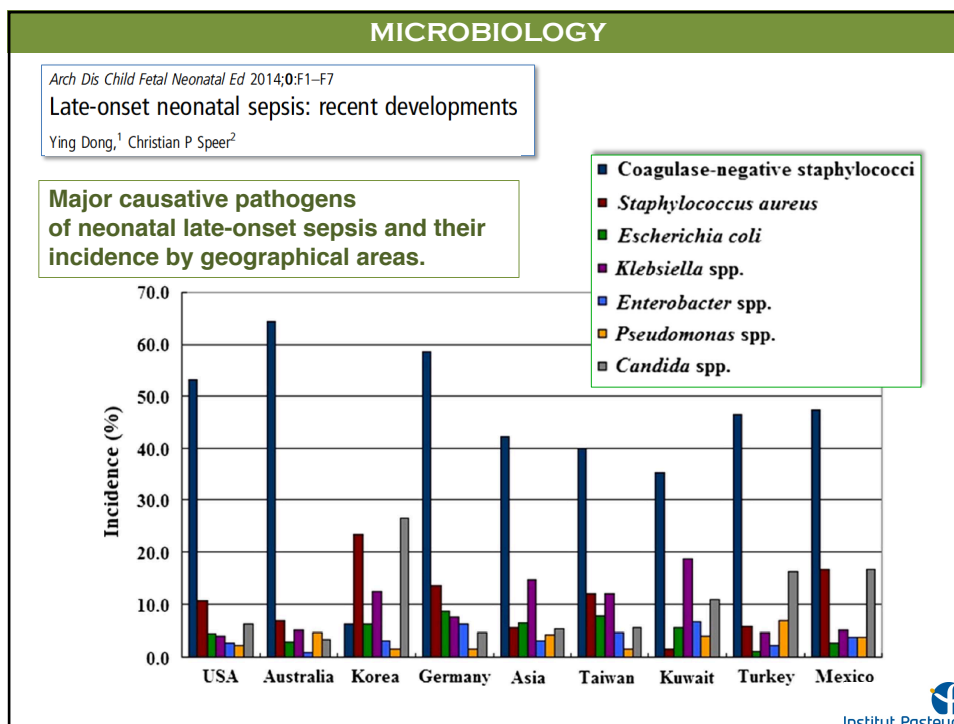
The Epidemiology of Sepsis in the United States from 1979 through 2000

Greg S. Martin, M.D., David M. Mannino, M.D., Stephanie Eaton, M.D., and Marc Moss, M.D.




Year	Gram-negative bacteria	Gram-positive bacteria	Fungi
1979	~25,000	~25,000	~5,000
1985	~50,000	~40,000	~5,000
1991	~100,000	~100,000	~5,000
1997	~150,000	~150,000	~10,000
2000	~150,000	~150,000	~25,000

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MICROBIOLOGY



VIRULENCE

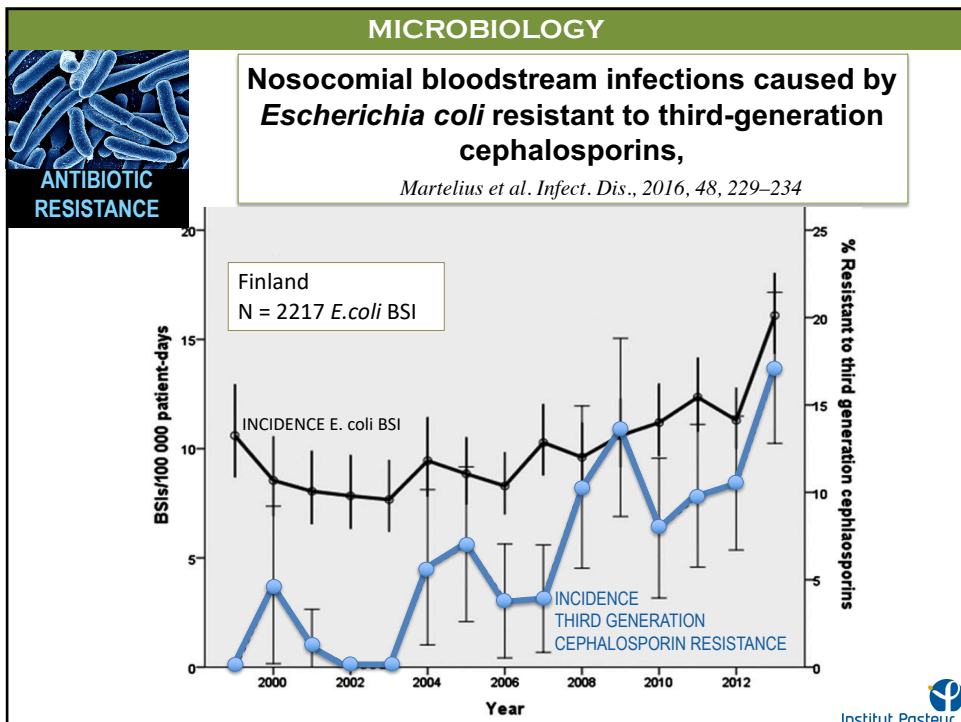
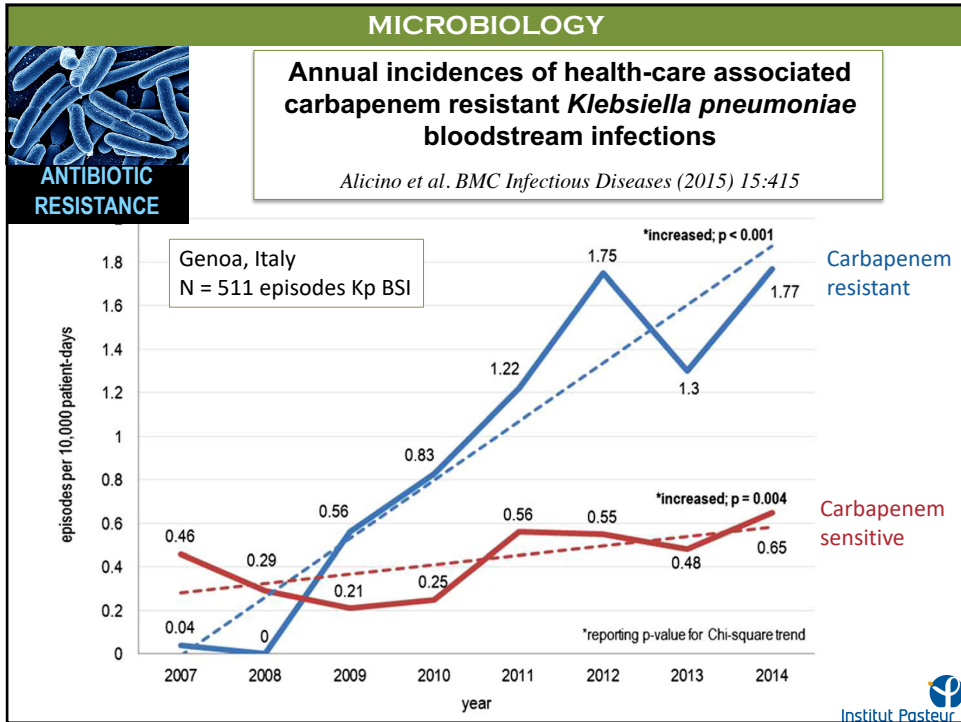
Virulence 6:1, 93-100; January 2015.
Impact of virulence genes on sepsis severity and survival in *Escherichia coli* bacteremia
M Mora-Rillo^{1,*}, N Fernández-Romero², C Navarro-San Francisco¹, J Díez-Sebastián³, M P Romero-Gómez², F Arnalich Fernández¹, J R Arribas López¹, and J Mingorance²

120 adult patients with *E. coli* bacteremia

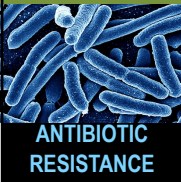
Multivariate analysis for sepsis severity showed that the presence of **cytotoxic necrotizing factor-1** gene (*cnf*) increased the **risk of severe illness** by **6.75 x** (95% confidence interval [CI] 1.79–24.71) and **β -lactamase** gene (*bla_{TEM}*) by **2.59 x** (95% CI 1.04–6.43)

The presence of **ferric yersiniabactin uptake receptor** gene (*fyuA*) was associated to increased **mortality** (OR 8.05, 95% CI 1.37–47.12) while the presence of **P fimbriae** genes had a **protective role** (OR 0.094, 95% CI 0.018–0.494).


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MICROBIOLOGY



ANTIBIOTIC RESISTANCE






2015, 10(12): e0144710

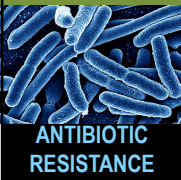
Comparison of Outcomes among Adult Patients with Nosocomial Bacteremia Caused by Methicillin-Susceptible and Methicillin-Resistant *Staphylococcus aureus*: A Retrospective Cohort Study

Jann-Tay Wang¹, Le-Yin Hsu², Tsai-Ling Lauderdale³, Wen-Chien Fan⁴, Fu-Der Wang^{4,5*}

	METHICILLIN SENSITIVE <i>S. aureus</i>	COMMUNITY ACQUIRED METHICILLIN RESISTANT <i>S. aureus</i>	HEALTHCARE ASSOCIATED METHICILLIN RESISTANT <i>S. aureus</i>
<div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> Taipei, Taiwan N = 353 patients 238 <i>S. aureus</i> BSI </div>			
MORTALITY	23.3 %	30.5 %	47.5 %

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MICROBIOLOGY

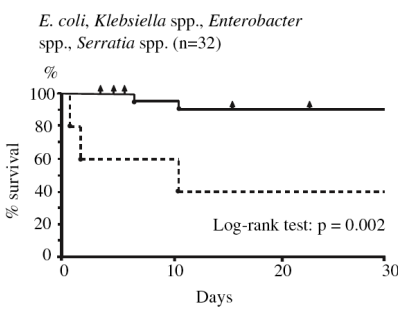


ANTIBIOTIC RESISTANCE

— Antibiotic-susceptible

⋯ Antibiotic-resistant

E. coli, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. (n=32)

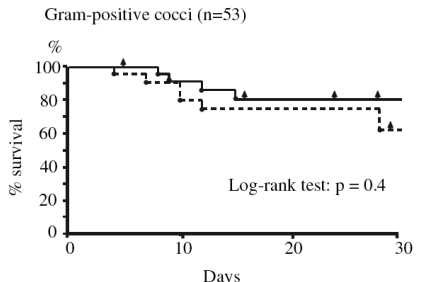


Log-rank test: p = 0.002

Thirty-day mortality of nosocomial systemic bacterial infections according to antibiotic susceptibility in an 800-bed teaching hospital in France

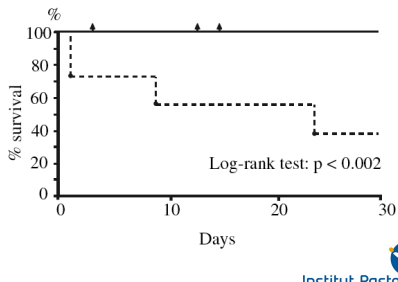
Guillemot et al. *Clin. Microbiol. Infect.* 2005, 11, 502

Gram-positive cocci (n=53)




Log-rank test: p = 0.4


Other Gram-negative bacilli (n=17)



Log-rank test: p < 0.002

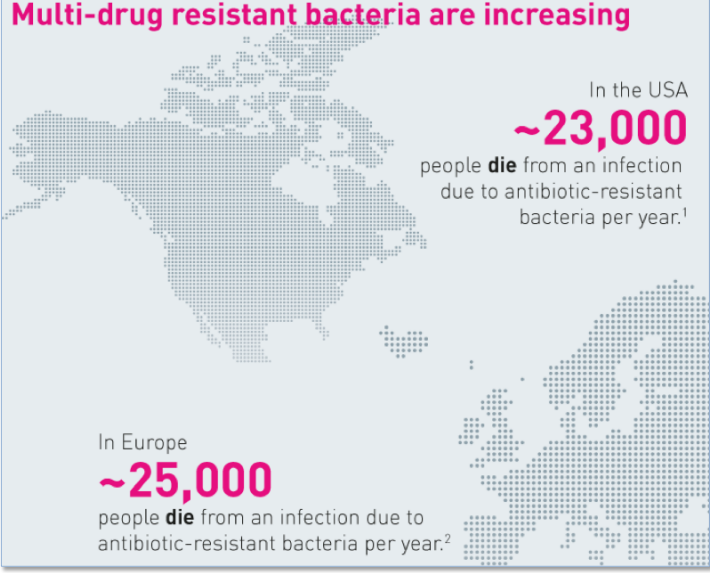
Institut Pasteur 

MICROBIOLOGY




**ANTIBIOTIC
RESISTANCE**

Multi-drug resistant bacteria are increasing




In the USA
~23,000
people **die** from an infection
due to antibiotic-resistant
bacteria per year.¹

In Europe
~25,000
people **die** from an infection due to
antibiotic-resistant bacteria per year.²



WAAAR
World Alliance Against Antibiotic
Resistance



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MICROBIOLOGY



**ANTIBIOTIC
RESISTANCE**

"Unless the many concerned players act urgently in a coordinated way, the world is moving towards a post-antibiotic era in which common infections and minor injuries, which were treated for decades, could kill again"

Dr Keiji Fukuda,
Assistant Director-General of WHO,

April 30, 2014





**SEPSIS : des nouveaux-nés
aux vieillards... tous concernés !**

5/ DARK VADOR



FOR RESEARCH, FOR HEALTH,
FOR OUR FUTURE



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**THE DARK
SIDE OF
THE
IMMUNE
SYSTEM**

CYTOKINE STORM



"Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

SIR WILLIAM OSLER
(1849 – 1919)



An excess of cytokines leads to organ failure

DR. HOUSE



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CYTOKINES HALF ANGEL // HALF DEVIL

Escher
Institut Pasteur

CYTOKINE STORM

Klimt

CONTRIBUTION of CYTOKINES TO MORBIDITY AND MORTALITY

- Tumor necrosis factor (TNF)
- Interleukin-1 (IL-1), IL-12, IL-15, IL-17A, IL-18, IL-27, IL-33
- Interféron-gamma (IFN γ) ; IFN β
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Leukemia Inhibitory factor (LIF)
- Macrophage migration inhibitory factor (MIF)
- High mobility group box-1 (HMGB-1)
- Some chemokines:
CXCL8 (IL-8), CCL5, ligands of CCR1 CXCR1 & 2 ; & CCR4
- Vascular endothelial growth factor (VEGF)

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Into the eye of the cytokine storm.
Tisoncik et al. *Microb.Mol. Biol. Rev.* 2012, 76, 16

CYTOKINE STORM

Journal of Medical Virology 75:185–194 (2005)

An Interferon- γ -Related Cytokine Storm in SARS Patients

Kao-Jean Huang,¹ Ih-Jen Su,^{2,3} Michel Theron,¹ Yi-Chun Wu,² Shu-Kuan Lai,² Ching-Chuan Liu,¹ and Huan-Yao Lei^{1,6}

Respiratory Physiology & Neurobiology 175 (2011) 185–187

Three fatal cases of pandemic 2009 influenza A virus infection in Shenzhen are associated with cytokine storm

Xiao-Wen Cheng^{a,1}, Juan Lu^{b,c,1}, Chun-Li Wu^a, Li-Na Yi^{c,d}, Xu Xie^a, Xiang-Dong Shi^d, Shi-Song Fang^a, Hong Zan^f, Hsiang-fu Kung^{c,e}, Ming-Lian

The Journal of Infectious Diseases 2012;206:1085–25

Host Cytokine Storm Is Associated With Disease Severity of Severe Fever With Thrombocytopenia Syndrome

Yulan Sun,^{1,2} Cong Jin,^{1,4} Faxian Zhan,^{2,4} Xianjun Wang,^{4,5} Mifang Liang,¹ Quanfu Zhang,¹ Shujuan Ding,⁴ Xuhua Guan,¹ Xixiang Hua,² Chuan Li,¹ Jing Du,¹ Qin Wang,¹ Shuo Zhang,¹ Yanping Zhang,¹ Shiwen Wang,¹ Anjiang Xu,¹ Zhenqiang Bi,⁴ and Dexin Li¹

The NEW ENGLAND JOURNAL of MEDICINE

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Suntharalingam et al. 2006, Vol. 355, p. 1018

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CYTOKINE STORM

Shock and multiple organ dysfunction after self-administration of *Salmonella* endotoxin

Taveira da Silva et al. *N. Engl. J. Med.* 1993, 328, 1457


1 mg LPS (15 μ g/k, i.e. 3750 X dose given to human volunteers)








Hours after LPS injection	LPS	Serum concentration (pg/ml)			
		TNF ELISA	TNF Bioassay	IL-6	IL-8
3.6	nd	14 630	9157	nd	nd
6.8	38	147	17	263 510	16 410
11.5	< 5	nd	nd	51 910	3 190

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Detection of circulating cytokines in human sepsis

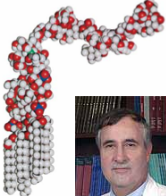

CYTOKINE STORM



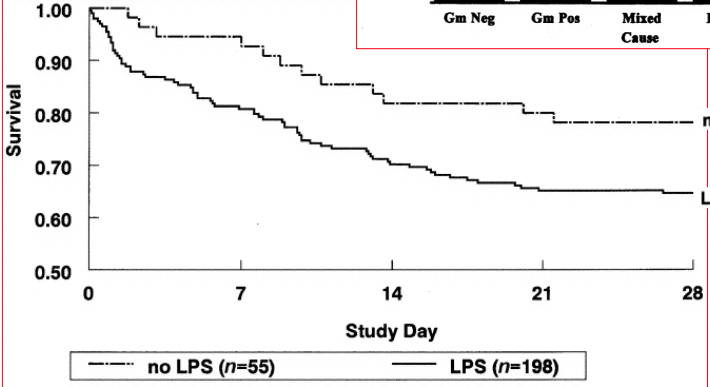
	TNF	1986	Waage et al. <i>Scand. J. Immunol.</i> 24, 739
	IL-1	1988	Girardin et al. <i>N. Engl. J. Med.</i> 319, 397
	IL-6	1989	Waage et al. <i>J. Exp. Med.</i> 169, 33 Hack et al. <i>Blood</i> 74, 1704
	IL-8	1992	Hack et al. <i>Infect. Immun.</i> 60, 2835 Friedland et al. <i>Infect. Immun.</i> 60, 2402
	IL-10	1994	Marchand et al. <i>Lancet</i> 343, 707
	IL-1Ra	1994	Rogy et al. <i>J. Am Coll Surg.</i> 178, 132
	TGFβ	1996	Marie et al. <i>Ann. Intern. Med.</i> 125, 520

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Circulating LPS in patients with severe sepsis

Opal et al. (1999)
J. Infect. Dis. 180, 1584

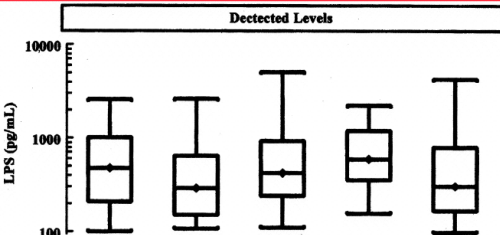


Survival

Study Day

no LPS (n=55) LPS (n=198)

Detected Levels

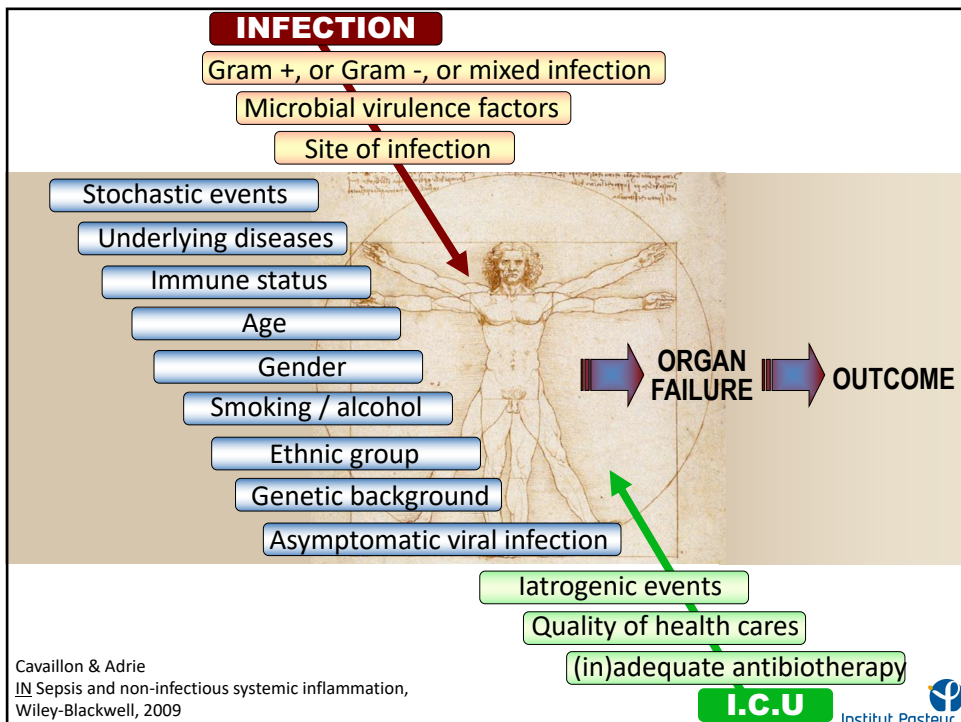
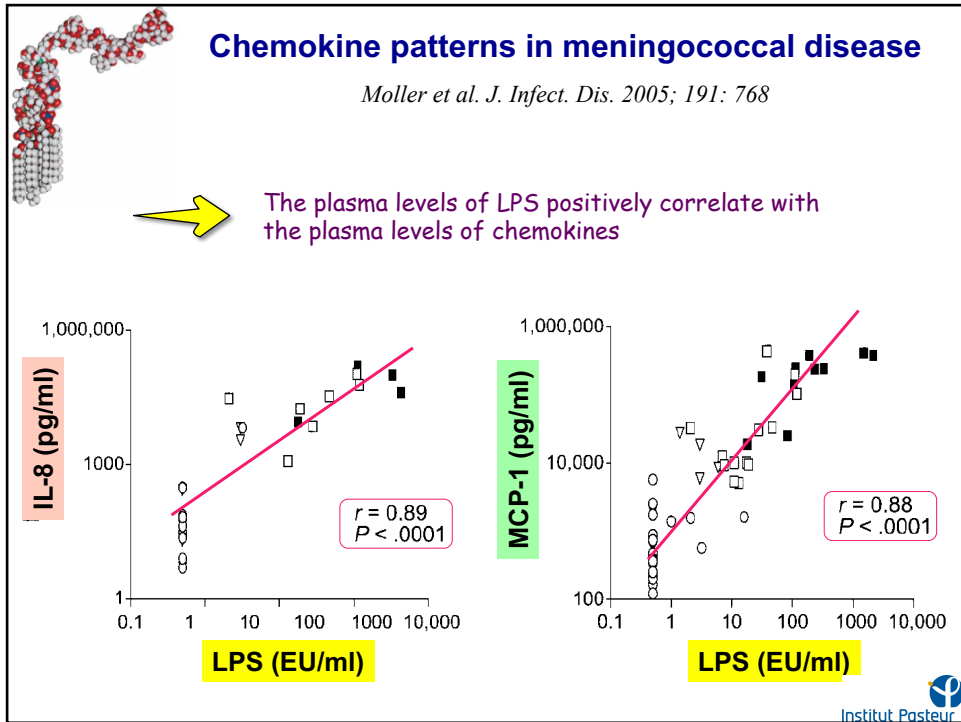


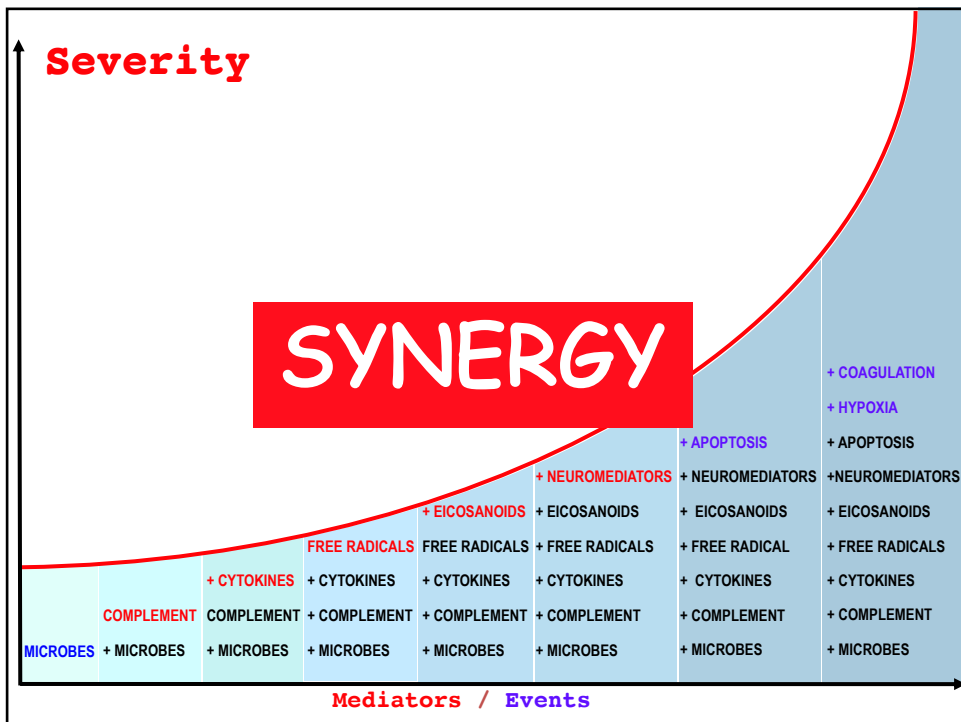
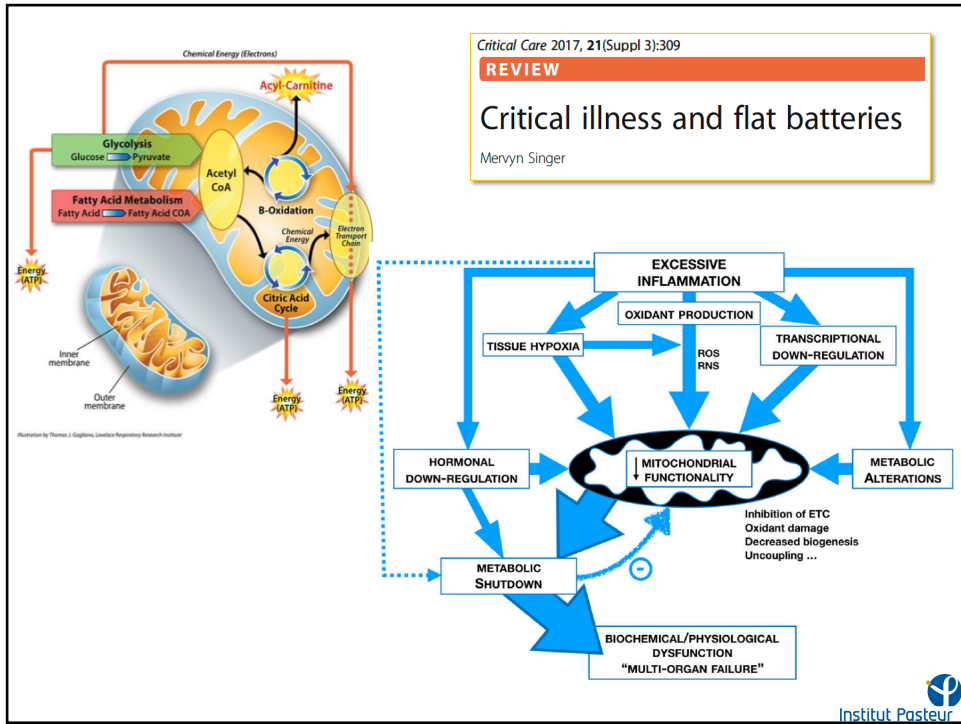
LPS (pg/mL)

Percent Undetectable

Gm Neg	Gm Pos	Mixed Cause	Fungal	Unknown
28.8%	15.0%	19.8%	27.8%	18.8%

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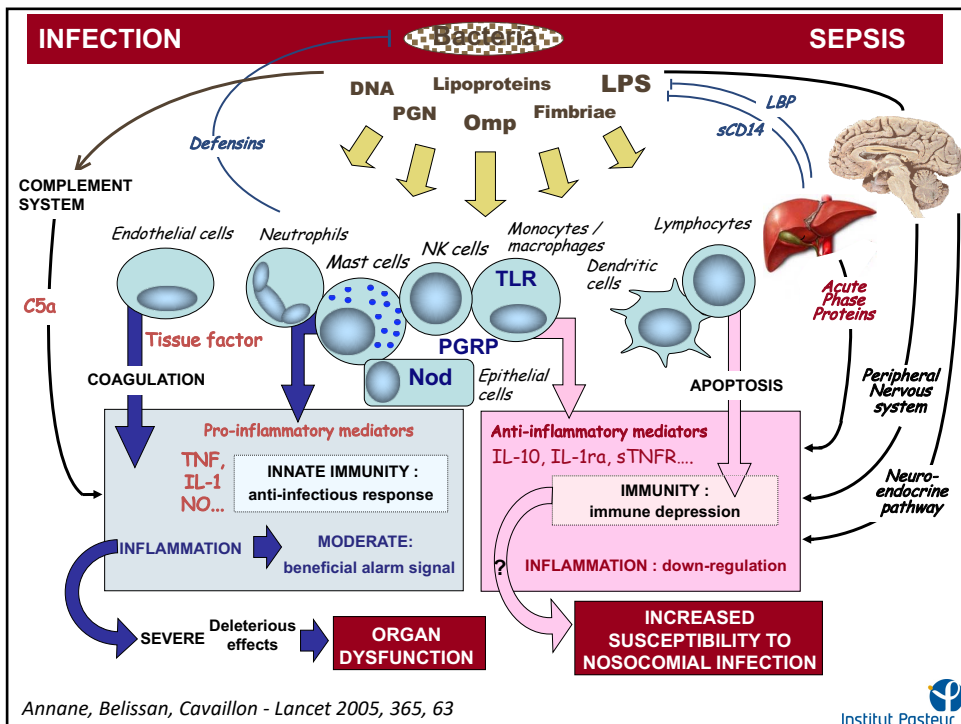
6/ ALTÉRATION IMMUNITAIRE

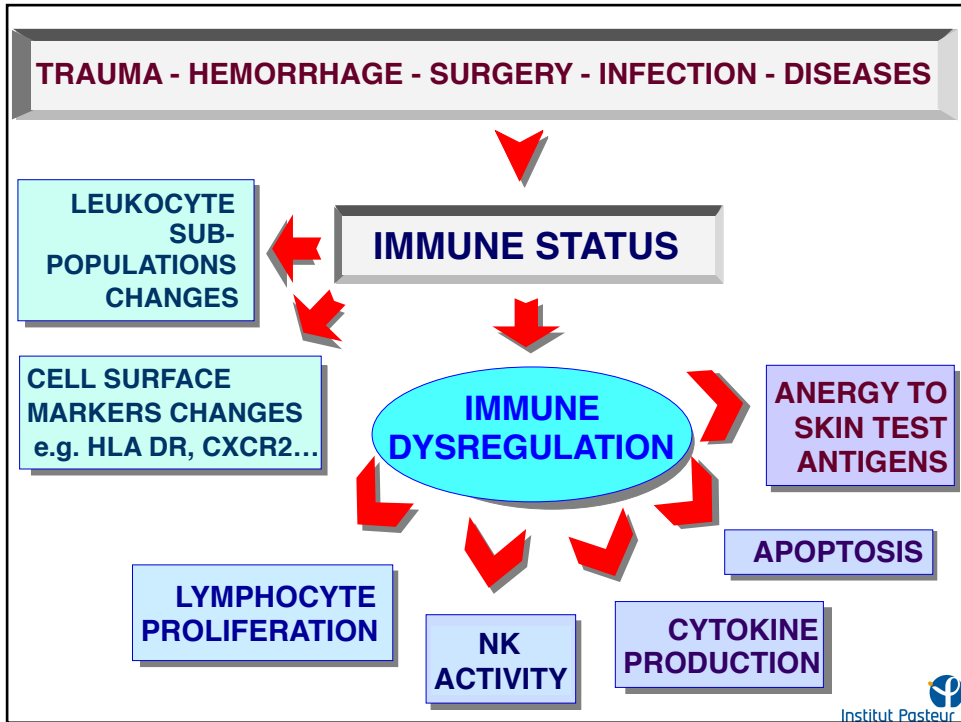





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Sepsis : a new hypothesis for pathogenesis of the disease process

Bone et al. Chest 1997, 112, 235

SIRS
Systemic Inflammatory Response Syndrome

~~Predominates~~

Organ Dysfunction Cardiovascular compromise shock

CARS
Compensatory Anti-inflammatory Response Syndrome

~~Predominates~~

Suppression of the immune system

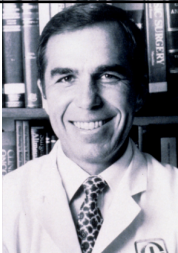
Thromb Haemost 2009; 101: 36-47

Review Article

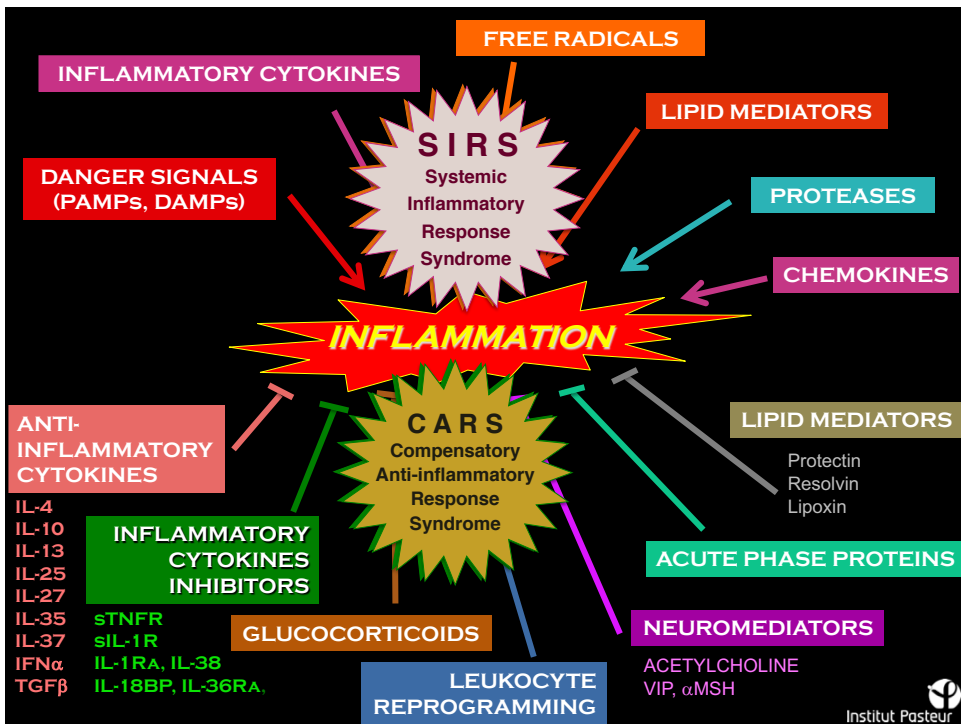
Compensatory anti-inflammatory response syndrome

Minou Adib-Conquy; Jean-Marc Cavallion
Unité Cytokines & Inflammation, Institut Pasteur, Paris, France

CARS may be considered as an **adapted** compartmentalized response with the aim to silence some acute pro-inflammatory genes, and to maintain the possible expression of certain genes involved in the anti-infectious process.



Roger BONE
(1941-1997)



THE TWO WAVES CONCEPT

J. Endotoxin Res. 2001, 7, 85

17th Immunodepression in sepsis and SIRS assessed by *ex vivo* cytokine production is not a generalized phenomenon: a review

Jean-Marc Cavaillon, Minou Adib-Conquy, Isabelle Cloëz-Tayarani, Catherine Fitting

Systemic Inflammatory Response syndrome (SIRS)

Enhanced *ex vivo* cytokine production

Enhanced NF-κB expression in nucleus of
- alveolar macrophages
- lung neutrophils
- liver cells

SIRS IN TISSUES

Time

Reduced *ex vivo* cytokine production

Reduced NF-κB expression in nucleus of peripheral blood mononuclear cells of sepsis and trauma patients

Compensatory anti-inflammatory Response syndrome (CARS)

CARS IN HEMATOPOIETIC COMPARTMENTS

CONCEPT OF COMPARTMENTALIZATION

We postulate that SIRS and CARS should not be opposed, but most probably occur concomitantly in different compartments: SIRS predominates within the inflamed tissues while blood leukocytes show hyporeactivity.

LYMPHOPENIA

Observed for all lymphocyte subsets

Normal Values (age-matched)

Septic shock Patients H0

Septic Shock Patients H48

Nbr of cells / μ l

CD4+ CD8+ B NK

Venet et al. Shock. 2010 34, 358-63.

Observed for all lymphocyte subsets but not Treg	Cells/mL	Healthy volunteers	Septic patients
Total lymphocytes		3113 \pm 739	1239 \pm 237
CD3 ⁺ T lymphocytes		1352 \pm 86	626 \pm 58
CD4 ⁺ T lymphocytes		836 \pm 49	428 \pm 74
CD4 ⁺ CD25 ⁺ (Treg)		173 \pm 13	168 \pm 32
CD4 ⁺ CD25 ⁻		663 \pm 41	260 \pm 44
$\gamma\delta$ T lymphocytes		56 \pm 9	16 \pm 4
Others (including B, CD8 ⁺ , NK)		1761	613

Monneret et al Mol Med 2008;14, 64

APOPTOSIS **Sepsis induces apoptosis of B, CD4+ T lymphocytes and dendritic cells**

Hotchkiss et al. J. Immunol. 2001, 166, 6952
N. Engl. J. Med. 2003, 348, 138

Human spleen

B cell (CD20)

TRAUMA (A) SEPTIC (C)

CD4 T cell

TRAUMA (A) SEPTIC (C)

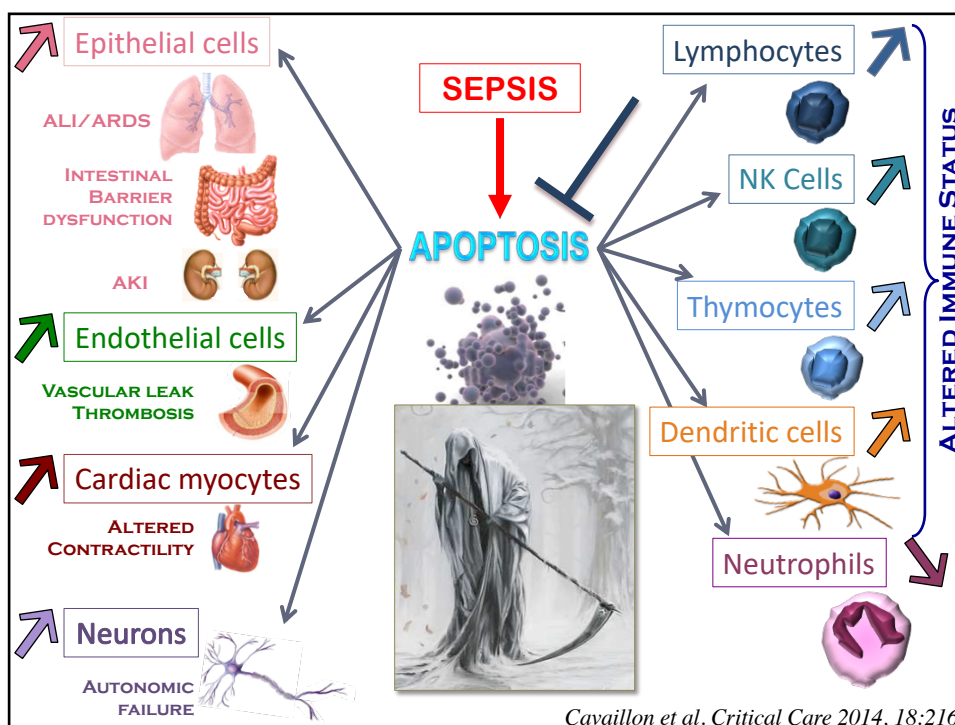
Follicular dendritic cells

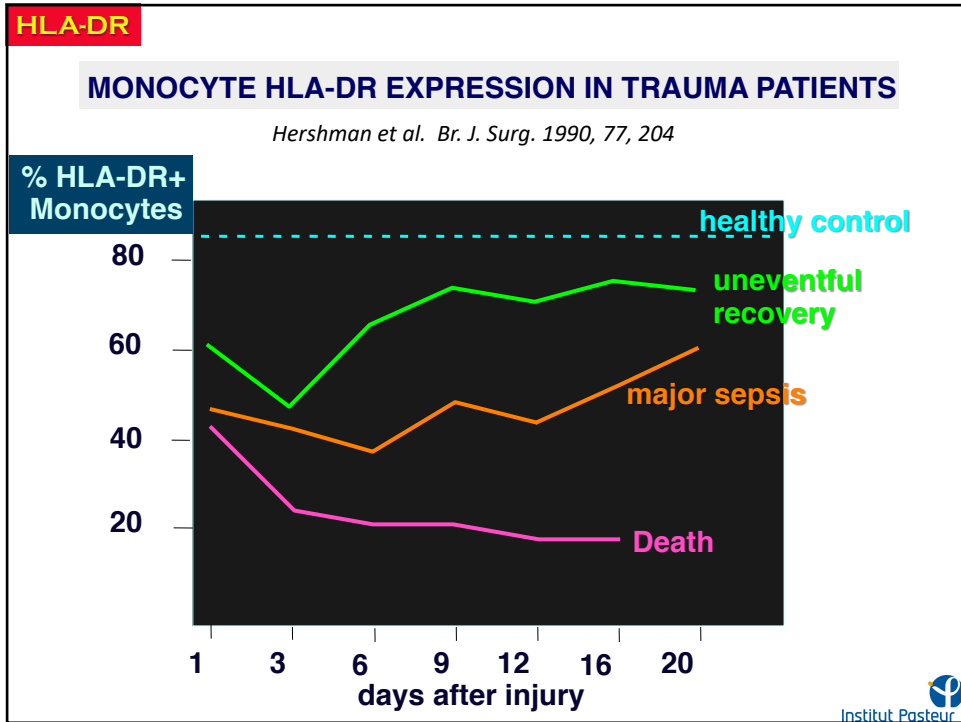
TRAUMA (A) SEPTIC (B)

Active Caspase 9

TRAUMA (A) SEPTIC (B)

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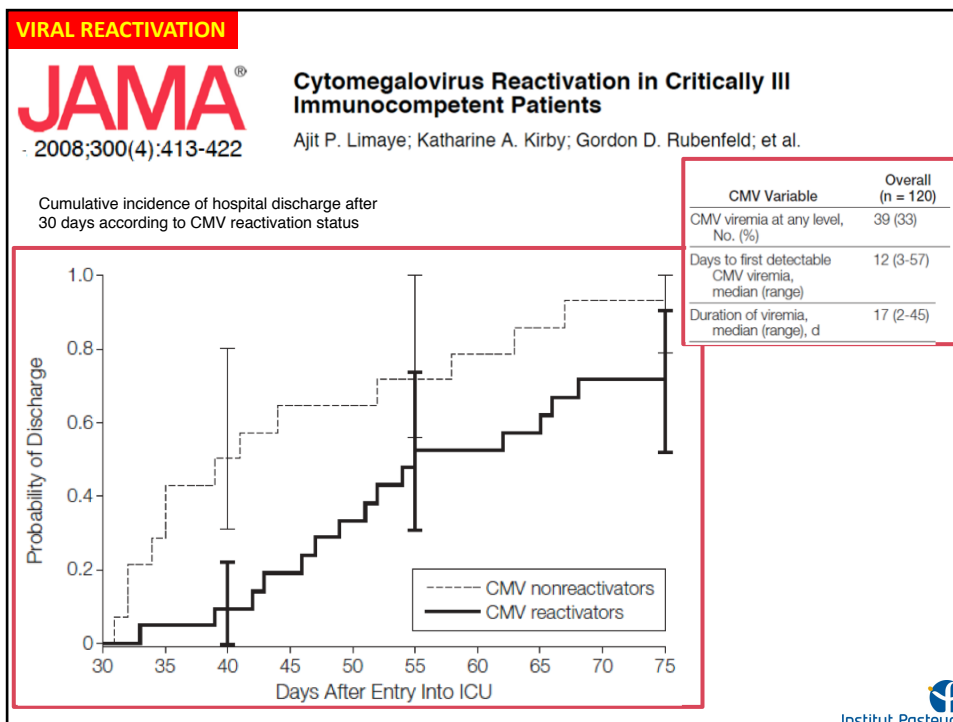




ALTERED EX VIVO CYTOKINE PRODUCTION IN SEPSIS AND SIRS

<p>MONOCYTES</p> <p>LPS → TNFα, IL-1α, IL-1β, IL-6</p>	<p>Dysregulation of in vitro cytokine production by monocytes during sepsis</p> <p><i>Muñoz et al. J. Clin. Invest. 1991, 88: 1747</i></p>
<p>NEUTROPHILS</p> <p>LPS → IL-8, IL-1Ra</p>	<p>Reduced ex vivo interleukin-8 production by neutrophils in septic and nonseptic systemic inflammatory response syndrome</p> <p><i>Marie et al. Blood 1998, 91: 3439</i></p> <p>Interleukin-1 receptor antagonist production during infectious and noninfectious systemic inflammatory response syndrome</p> <p><i>Marie et al. Crit Care Med 2000; 28: 2277</i></p>
<p>LYMPHOCYTES</p> <p>Con.A → IL-2, IL-5, IL-10</p>	<p>Ex vivo T-lymphocyte derived cytokine production in SIRS patients is influenced by experimental procedures</p> <p><i>Muret et al. Shock 2000, 13, 169</i></p>
<p>NK CELLS</p> <p>PAMPs + IL-15 + IL-18 → GM-CSF, IFNγ</p>	<p>NK cell tolerance to TLR agonists mediated by regulatory T-cells after polymicrobial sepsis.</p> <p><i>Souza-Fonseca-Guimaraes et al. J Immunol. 2012; 188: 5850-8</i></p> <p>Toll-like receptors expression and interferon-γ production by NK cells in human sepsis</p> <p><i>Souza-Fonseca-Guimaraes et al. Crit. Care 2012, 16 :R206</i></p>

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7/ DIAGNOSTIC

A
A
E I P

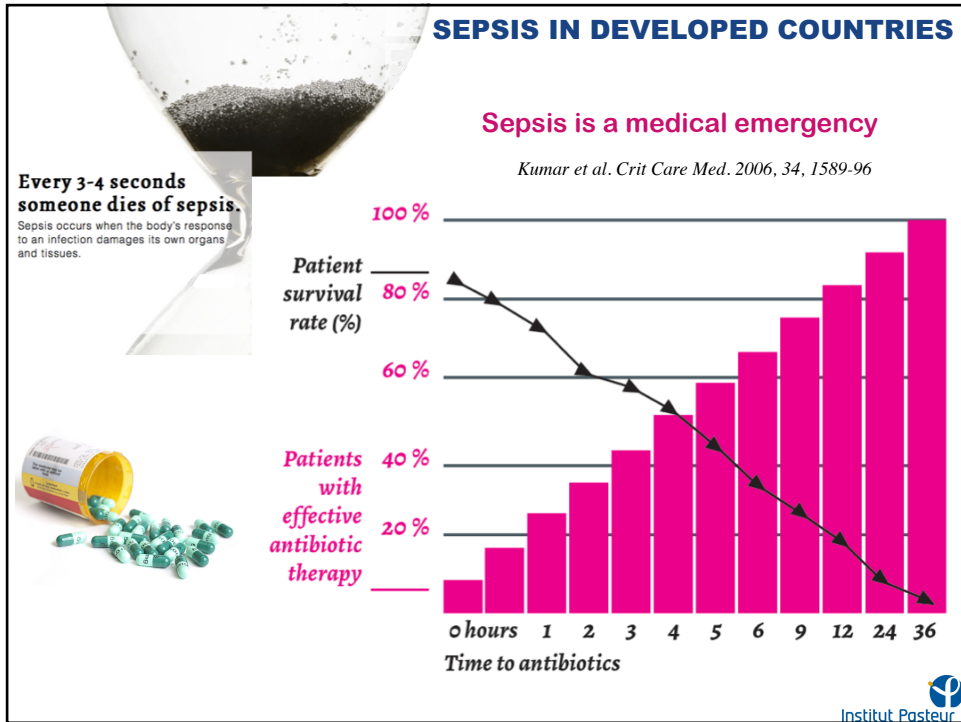
AGENCE
UNIVERSITAIRE
DE LA FRANCOPHONIE

Réseau International
Instituts Pasteur

Direction de
l'Enseignement
Institut Pasteur

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FOR OUR FUTURE

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Main biomarkers of interest in sepsis

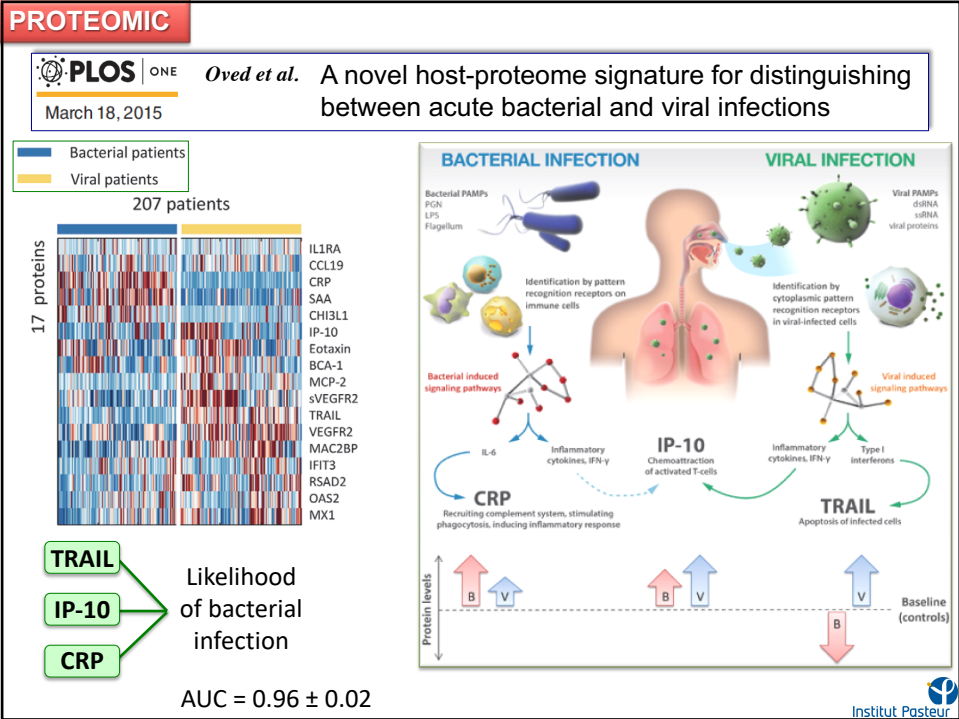
<p>Acute phase proteins</p> <ul style="list-style-type: none"> C-reactive protein Serum amyloid A LPS Binding protein Pentraxin 3 Procalcitonin 	<p>Hormones</p> <ul style="list-style-type: none"> Leptin Testosterone/oestradiol Vasopressin/copeptin Natriuretic peptides 	<p>Enzymes</p> <ul style="list-style-type: none"> Elastase Metalloproteinase Dipeptidylpeptidase Phospholipase A2 YKL-40 Granzyme A
<p>Tissue injury biomarkers</p> <ul style="list-style-type: none"> Lactate Hyaluronan Pancreatic stone protein Heat shock proteins 	<p>Apoptosis-related biomarkers</p> <ul style="list-style-type: none"> Fas and FasL CK18 	<p>Coagulation biomarkers</p> <ul style="list-style-type: none"> Antithrombin Protein C Thrombomodulin Plasminogen activator inhibitor von Willebrand factor
<p>Alarmins (DAMPs)</p> <ul style="list-style-type: none"> DNA HMGB-1 S100A8/9 Galectin-3 	<p>Soluble receptors</p> <ul style="list-style-type: none"> Soluble CD14 Soluble MD2 Soluble ST2 Soluble TREM-1 Soluble TNF R Soluble IL-2R (sCD25) Soluble CD163 Soluble decoy receptor 3 Soluble urokinase-type plasminogen activator receptor 	<p>Cell-surface biomarkers</p> <ul style="list-style-type: none"> HLA-DR TLR4 CD14 CD25 CD40 CD48 CD64 CD69 CD80 TREM1 CX3CR1
<p>Cytokines</p> <ul style="list-style-type: none"> Interleukin-1 Interleukin-1 receptor antagonist Interleukin-6 Interleukin-10 Interleukin-13 Interleukin-18 Interleukin-27 Tumor necrosis factor Macrophage migration inhibitory factor 	<p>Vascular endothelial biomarkers</p> <ul style="list-style-type: none"> Soluble ICAM1 Soluble E-selectin Soluble L-selectin Soluble VCAM-1 Soluble-ELAM-1 Angiopoietin Vascular endothelial growth factor Endothelin Endocan Adrenomedullin Heparin-binding protein Growth arrest-specific 6 	<p>Miscellaneous</p> <ul style="list-style-type: none"> Fibronectin Selenium Morphine Gelsolin Osteopontin C3a
<p>Chemokines</p> <ul style="list-style-type: none"> Interleukin-8 (CXCL8) IP-10 (CXCL10) Monocyte chemoattractant factor-1 (CCL2) Macrophage inflammatory protein-1α/β (CCL3; CCL4) RANTES (CCL5) 		

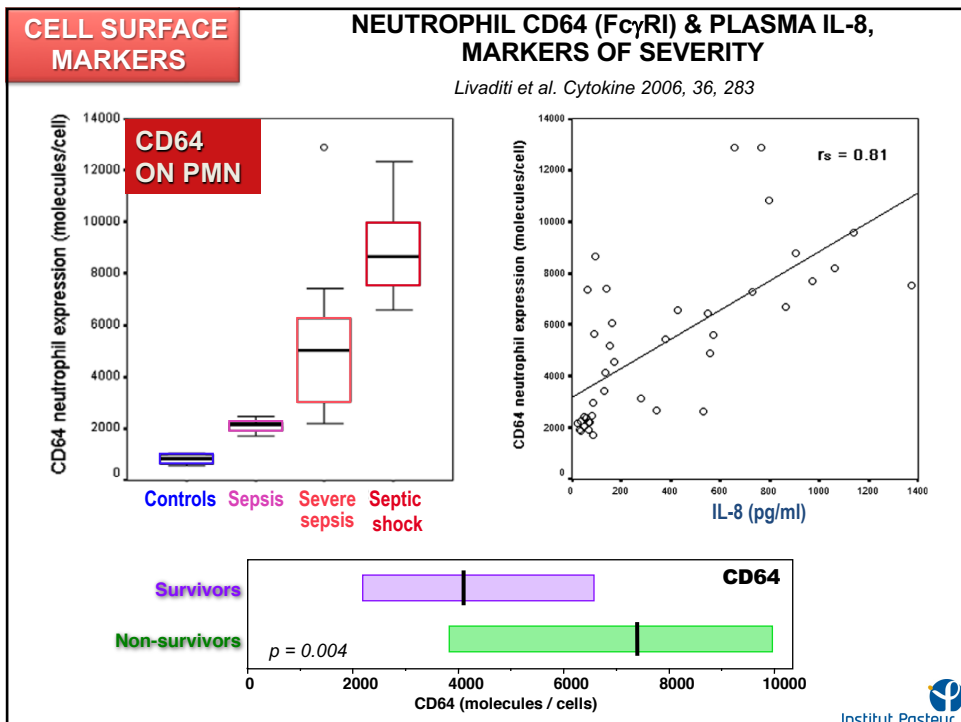
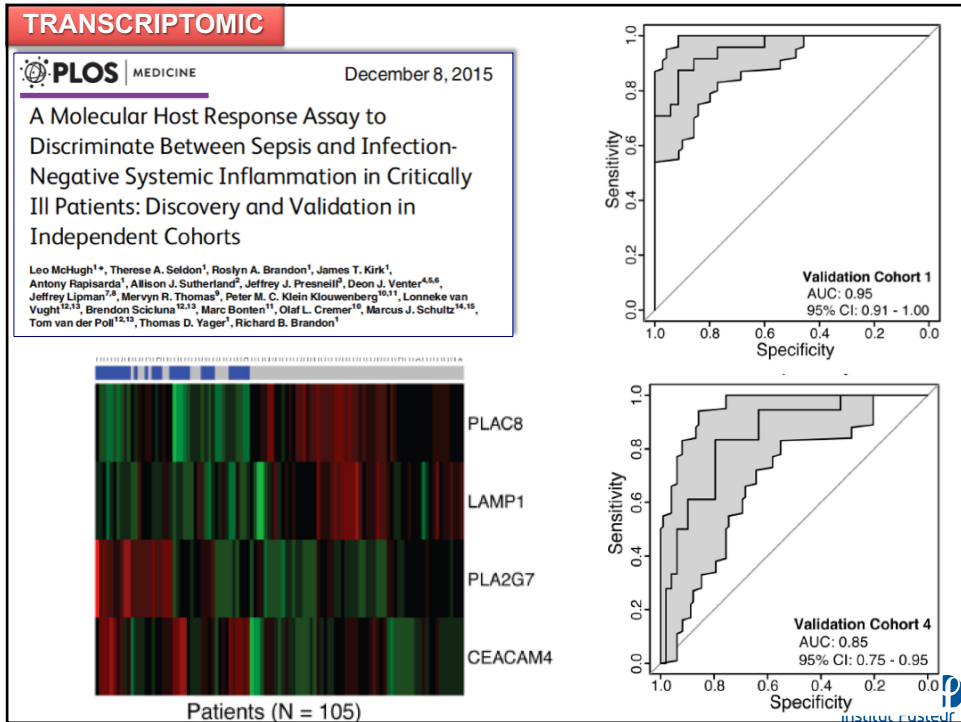
Parlato & Cavaillon, Methods in Molecular Biology, 2015, 1237, 149-211

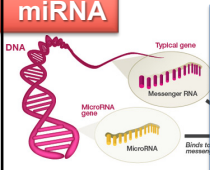
Combined biomarkers for sepsis diagnosis

IL-6 + CRP	Messer et al. <i>J Pediatr.</i> 1996,129:574–580
IL-6 + PMN count	Strait <i>Pediatrics</i> 1999, 104:1321–1326
IL-6 + IL-10	Kellum et al. <i>Arch Intern Med</i> 2007, 167:1655–1663
IL-10 + HLA DR expression	Strohmeier et al. <i>Cytometry (B)</i> 2003, 53, 54
IL-8 + GM-CSF	Fischer et al. <i>Intensive Care Med</i> 2002, 28:1324–1331
IL-8 + sCD25 + CRP	Santana Reyes et al. <i>Acta Paediatr</i> 2003, 92:221–227
CRP + sICAM-1 + sE-selectin	Edgar et al. <i>BMC Pediatr</i> 2010,10:22
CRP + temperature	Povoa et al. <i>Clin Microbiol Infect</i> 2005, 11:101–108
PCT + mid-regional-proadrenomedullin	Angeletti et al. <i>Clin Chem Lab Med</i> 2013, 51:1059–1067
PCT + sTREM-1 + CD64	Gibot et al. <i>Am J Respir Crit Care Med</i> 2012, 186:65–71
PCT + C3a	Selberg et al. <i>Crit Care Med</i> 2000, 28:2793–2798
PSP + (sCD25 or PCT)	Llewelyn et al <i>Crit Care</i> 2013, 17:R60
suPAR, sTREM-1, MIF, CRP, and PCT	Kofoed et al. <i>Crit Care</i> 2007, 11:R38
IL-1Ra + protein C + gelatinase-associated lipocalin	Shapiro et al <i>Crit Care Med</i> 2009, 37:96–104

Parlato & Cavaillon, Methods in Molecular Biology, 2015, 1237, 149-211







miRNA

October 2009 | Volume 4 | Issue 10 | e7405

MicroRNA Fingerprints Identify *miR-150* as a Plasma Prognostic Marker in Patients with Sepsis

Catalin Vasilescu^{1*}, Simona Rossi^{2*}, Masayoshi Shimizu², Stefan Tudor¹, Angelo Veronese², Manuela Ferracin³, Milena S. Nicoloso², Elisa Barbarotto², Monica Popa¹, Oana Stanculea¹, Michael H. Fernandez⁴, Dan Tulbure⁵, Carlos E. Bueso-Ramos⁴, Massimo Negrini³, George A. Calin^{2*}

Biochemical and Biophysical Research Communications 2010; 394: 184-8

Serum miR-146a and miR-223 as potential new biomarkers for sepsis

Jia-feng Wang^{a,1}, Man-li Yu^{b,1}, Guang Yu^{c,1}, Jin-jun Bian^a, Xiao-ming Deng^a, Xiao-jian Wan Ke-ming Zhu^{a,*}

J Trauma Acute Care Surg. 2012;73: 850–854

Four serum microRNAs identified as diagnostic biomarkers of sepsis

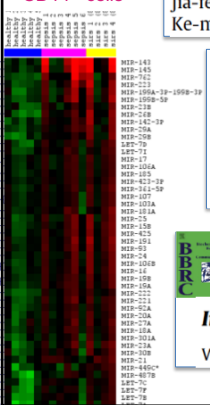
Hui-juan Wang, Peng-jun Zhang, Wei-jun Chen, Dan Feng, Yan-hong Jia, and Li-xin Xie, Beijing, China


Biochemical and Biophysical Research Communications 2009; 380: 437-41

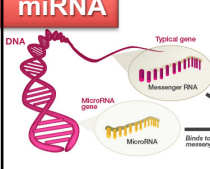
In vivo profile of the human leukocyte microRNA response to endotoxemia

Wolfgang M. Schmidt^{a,b,*}, Alexander O. Spiel^a, Bernd Jilma^a, Michael Wolzt^a, Markus Müller^a

miRNA from CD14+ cells





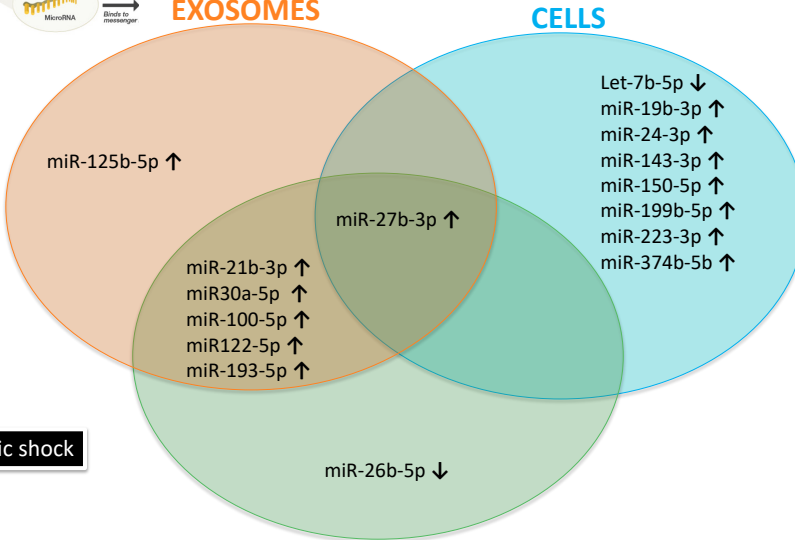


miRNA

Cellular and extracellular miRNAs are blood compartment-specific in sepsis

Reithmair et al. *J. Cell. Mol. Med.* 2017, 21, 2403


EXOSOMES

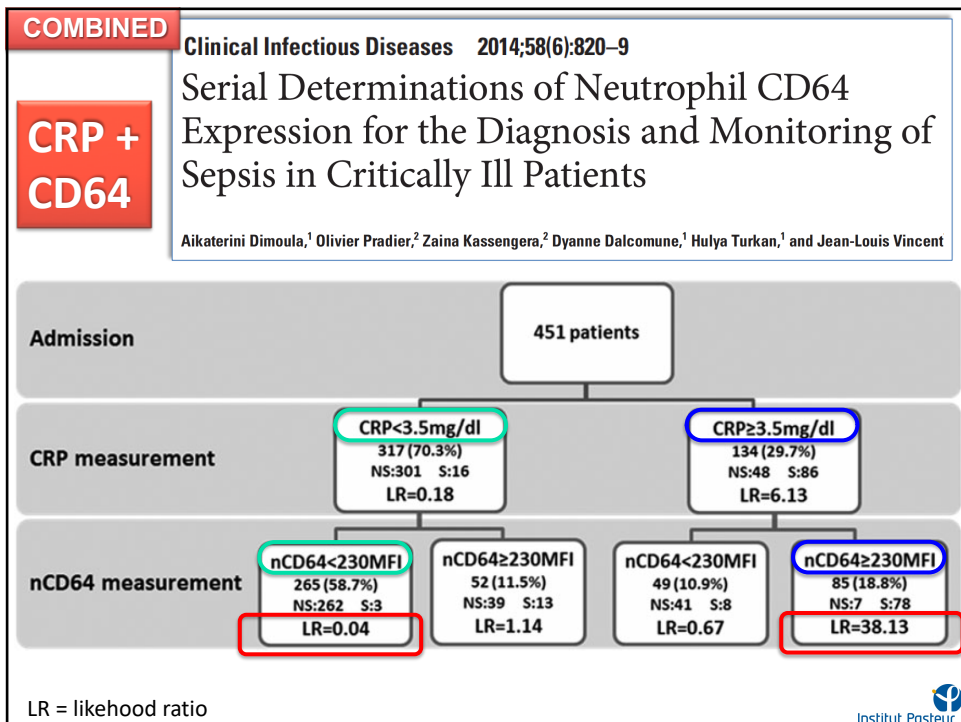
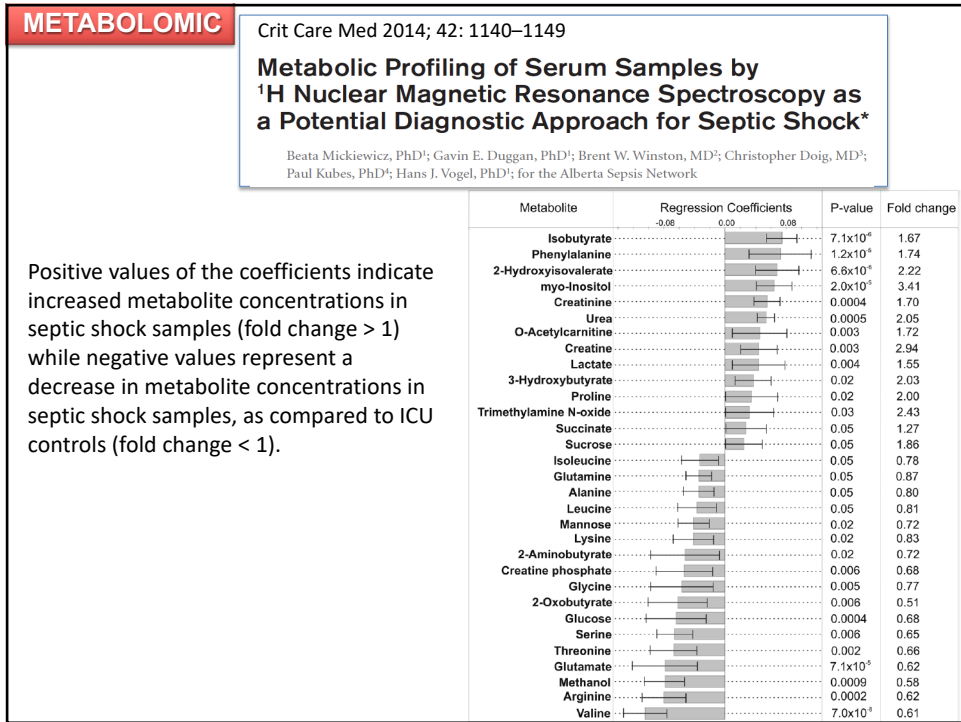


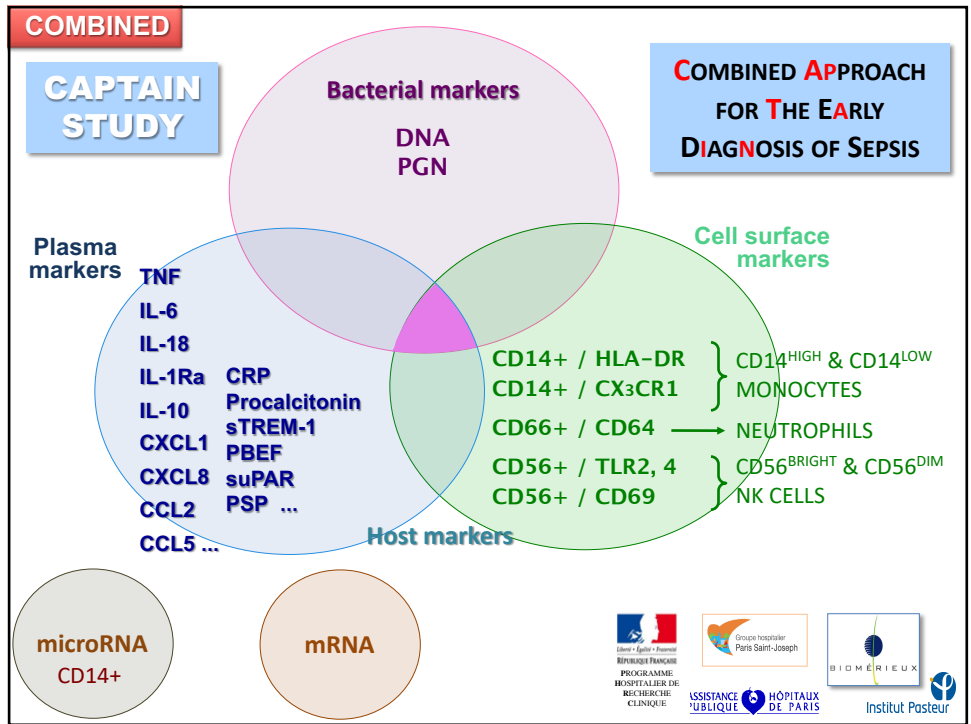
CELLS

Septic shock

SERUM







BACTERIAL DNAemia

Clinical Microbiology Reviews[®] April 2018 Volume 31 Issue 2 e00089-17

Emerging Technologies for Molecular Diagnosis of Sepsis
Mridu Sinha,^a Julieta Jupe,^b Hannah Mack,^a Todd P. Coleman,^{a,f} Shelley M. Lawrence,^{c,d,g,h} Stephanie I. Fraley

Blood Culture : 24 – 48 h

Bacterial DNA

Polymerase chain reaction (PCR)
+ mass spectrometry
+ Universal digital high-resolution melt (*U-dHRM*)

Loop-mediated isothermal amplification (LAMP Technology)

40 studies
% SENSITIVITY : 68.8% [range : 25.6 – 95.2]
% SPECIFICITY : 85.2% [range : 50 – 98.7]

Logos: SeptiTest, Molzym, Iridica, Abbott, SIRS Lab, PLoS one

June 2012 | Volume 7 | Issue 6 | e38916

DNAemia Detection by Multiplex PCR and Biomarkers for Infection in Systemic Inflammatory Response Syndrome Patients
Catherine Fitting¹, Marianna Parlato¹, Minou Adib-Conquy¹, Nathalie Memain², François Philippart², Benoit Misset², Mehran Monchi³, Jean-Marc Cavallion^{1*}, Christophe Adrie²



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aux vieillards... tous concernés !**

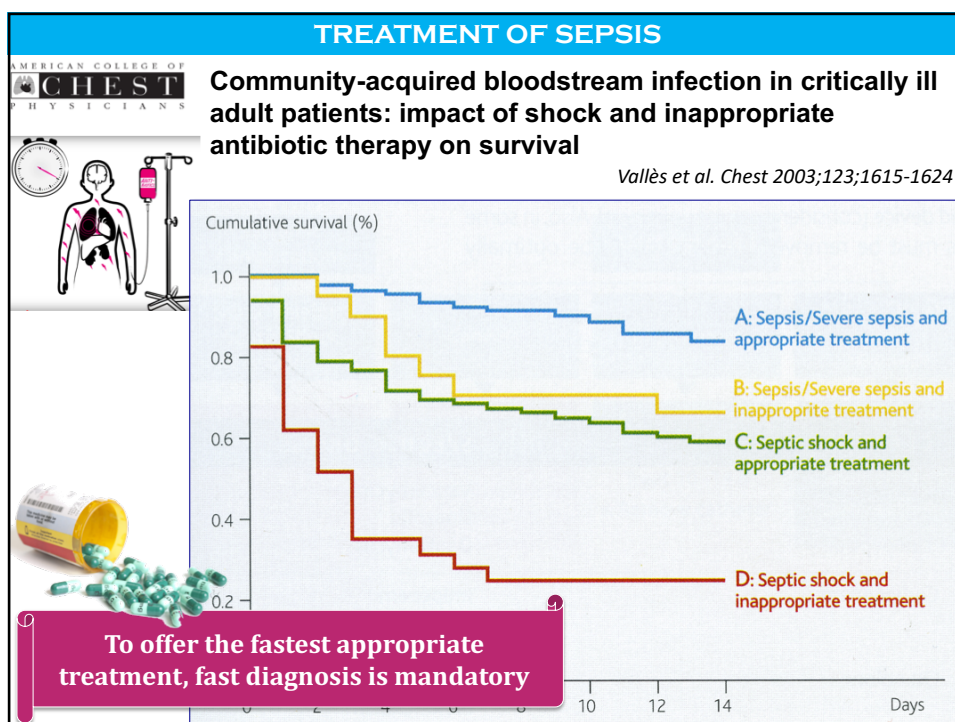
8/ THÉRAPIES






FOR RESEARCH, FOR HEALTH,
FOR OUR FUTURE


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TREATMENT OF SEPSIS


In the field of sepsis during the last three decades, thousands of mice have been saved with new therapeutic ways targeting inflammation... No humans

Why mice are not a good model?




SIRS

Systemic Inflammatory Response Syndrome



CARS



Homo sapiens



Mus musculus





SEPSIS

Septembre 2017
Vol. 59 • N° 231


Association des Anciens Élèves de l'Institut Pasteur

NOUVELLES THÉRAPIES DU SEPSIS : L'ÉCHEC DES MODÈLES ANIMAUX

Jean-Marc CAVAILLON¹
Institut Pasteur

TREATMENT OF SEPSIS


Crit Care Med 2008; 36:1311–1322
 Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail?
 Gustavo A. Ospina-Tascón, MD; Gustavo Luiz Büchele, MD; Jean-Louis Vincent, MD, PhD





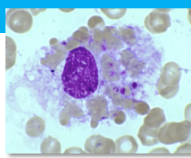
1987 - 2006

72 STUDIES
54 535 patients

- 55 NO EFFECT**
 - Incl. Anti-LPS ; High dose corticoids ; IL-1Ra ; anti-TNF ; PAF R antagonist ; Anti-thrombin ; high volume hemofiltration ; Rec Tissue Factor Inh. ; Elastase Inh. ;
- 10 POSITIVE IMPACT**
 - High dose IgG Not supported later
 - Steroids Not supported later
 - Act. Protein C Not supported later
 - High Vol. Hemofiltr. Not supported later
- 7 NEGATIVE IMPACT**
 - Incl. TNF-Fcγ & iNOS inhibitor

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TREATMENT OF SEPSIS


HEMOPHAGOCYTOSIS
MACROPHAGE ACTIVATION SYNDROME

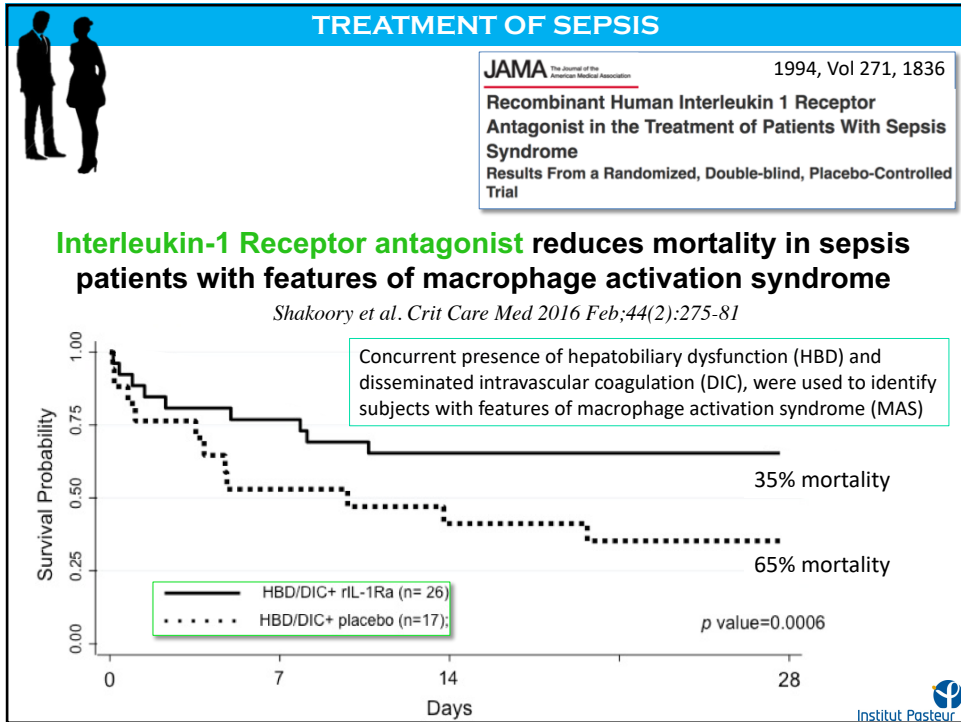
Bone marrow

Raschke and Garcia-Orr
Hemophagocytic Lymphohistiocytosis. A potentially underrecognized association with **systemic inflammatory response syndrome, severe sepsis and septic shock** in adults
Chest 2011, 140, 933-8


→ 60 - 65 %

.... Agressive immunosuppressive therapy should not be delayed.


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BOOSTING THE IMMUNE SYSTEM

IFN γ nature medicine 1997 Jun;3(6):678-81 


Monocyte deactivation in septic patients: restoration by IFN- γ treatment
Döcke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, Volk HD, Kox W.
Am J. Resp. Crit. Care Med. 2009, 180, 640

GM-CSF The Journal of Immunology, 2012, 189: 

Granulocyte-Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression
A Double-Blind, Randomized, Placebo-controlled Multicenter Trial
Christian Meisel^{1*}, Joerg C. Scheffold^{2*}, Rene Pischowski², Tycho Baumann¹, Katrin Hetzger¹, Jan Gregor³, Steffen Weber-Carstens⁴, Dietrich Hasper², Didier Keh⁴, Heidrun Zuckermann³, Petra Reinke^{2,5}, and Hans-Dieter Volk^{1,5}

IL-7 The Journal of Immunology, 2012, 189: 

IL-7 Restores Lymphocyte Functions in Septic Patients
Fabienne Venet^{*,†}, Anne-Perrine Foray^{*}, Astrid Villars-Méchin^{*}, Christophe Malcus, Françoise Poitevin-Later^{*}, Alain Lepape^{*,‡}, and Guillaume Monneret^{*,†}

IL-15 The Journal of Immunology, 2010, 184: 1401. 

IL-15 Prevents Apoptosis, Reverses Innate and Adaptive Immune Dysfunction, and Improves Survival in Sepsis
Shigeaki Inoue^{*}, Jacqueline Unsinger^{*}, Christopher G. Davis^{*}, Jared T. Muenzer, Thomas A. Ferguson[†], Katherine Chang^{*}, Dale F. Osborne^{*}, Andrew T. Clark[‡], Craig M. Coopersmith^{*,§}, Jonathan E. McDunn^{*}, and Richard S. Hotchkiss^{*,§}

BOOSTING THE IMMUNE SYSTEM

NATURE REVIEWS | IMMUNOLOGY 862 | DECEMBER 2013 | VOLUME 13

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

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BOOSTING THE IMMUNE SYSTEM

Cavaillon et al. *Critical Care* 2014, 18:216

REVIEW

Is boosting the immune system in sepsis appropriate?

Jean-Marc Cavaillon^{1*}, Damon Eisen^{2,3} and Djilali Annane⁴

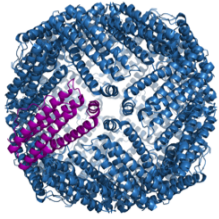
GM-CSF

INTERLEUKIN-7


γ-INTERFERON

While all these cytokines can restore the immune status, all these cytokines possess pro-inflammatory properties that can be deleterious in certain compartments.


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FERRITINE



World Health Organization




International Clinical Trials Registry Platform
Search Portal

A Trial of Validation and Restoration of Immune Dysfunction in Severe Infections and Sepsis (PROVIDE)


Date of registration : 27/10/2017

Primary sponsor : Hellenic Institute for the Study of Sepsis



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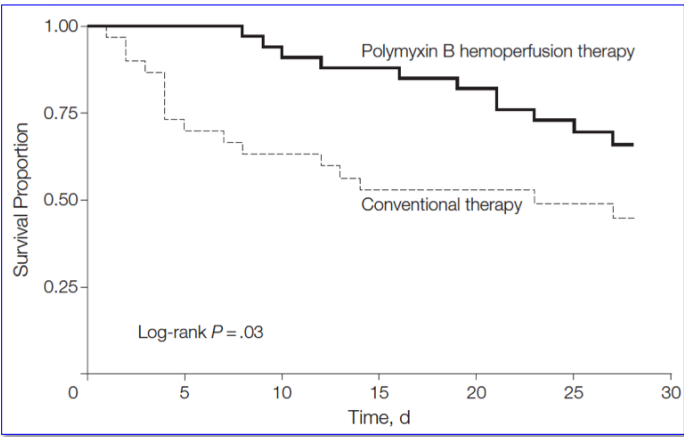
TREATMENT OF SEPSIS



JAMA 2009;301(23):2445-2452

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial

Dinna N. Cruz; Massimo Antonelli; Roberto Fumagalli; et al.




Survival Proportion

Time, d

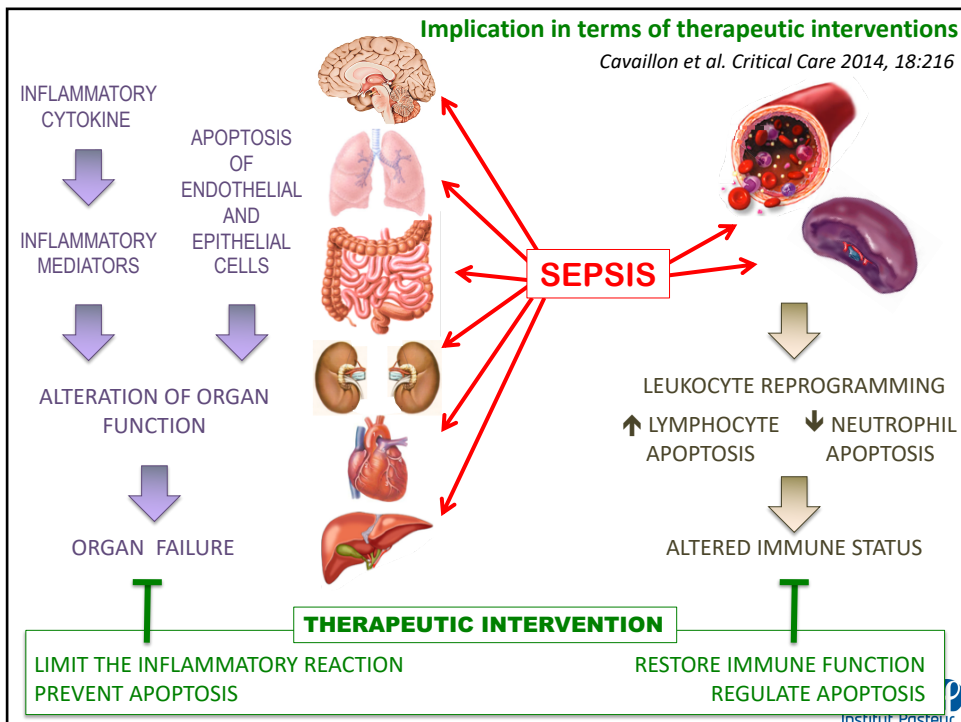
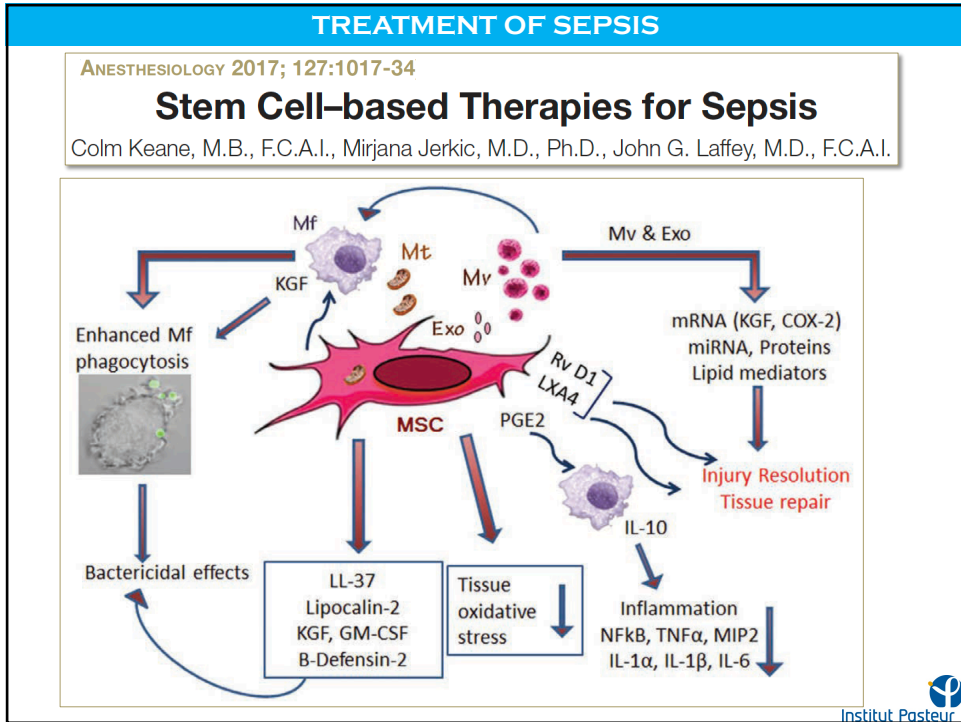
Polymyxin B hemoperfusion therapy

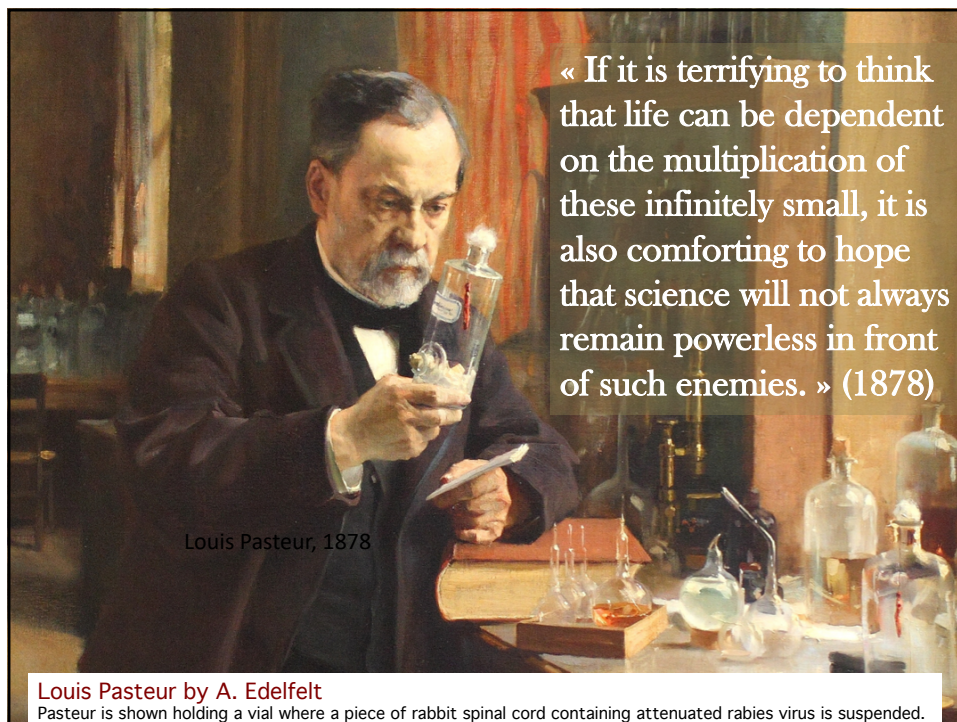
Conventional therapy

Log-rank $P = .03$



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« If it is terrifying to think that life can be dependent on the multiplication of these infinitely small, it is also comforting to hope that science will not always remain powerless in front of such enemies. » (1878)

Louis Pasteur, 1878

Louis Pasteur by A. Edelfelt

Pasteur is shown holding a vial where a piece of rabbit spinal cord containing attenuated rabies virus is suspended.