

bio·sepsis

σήψις

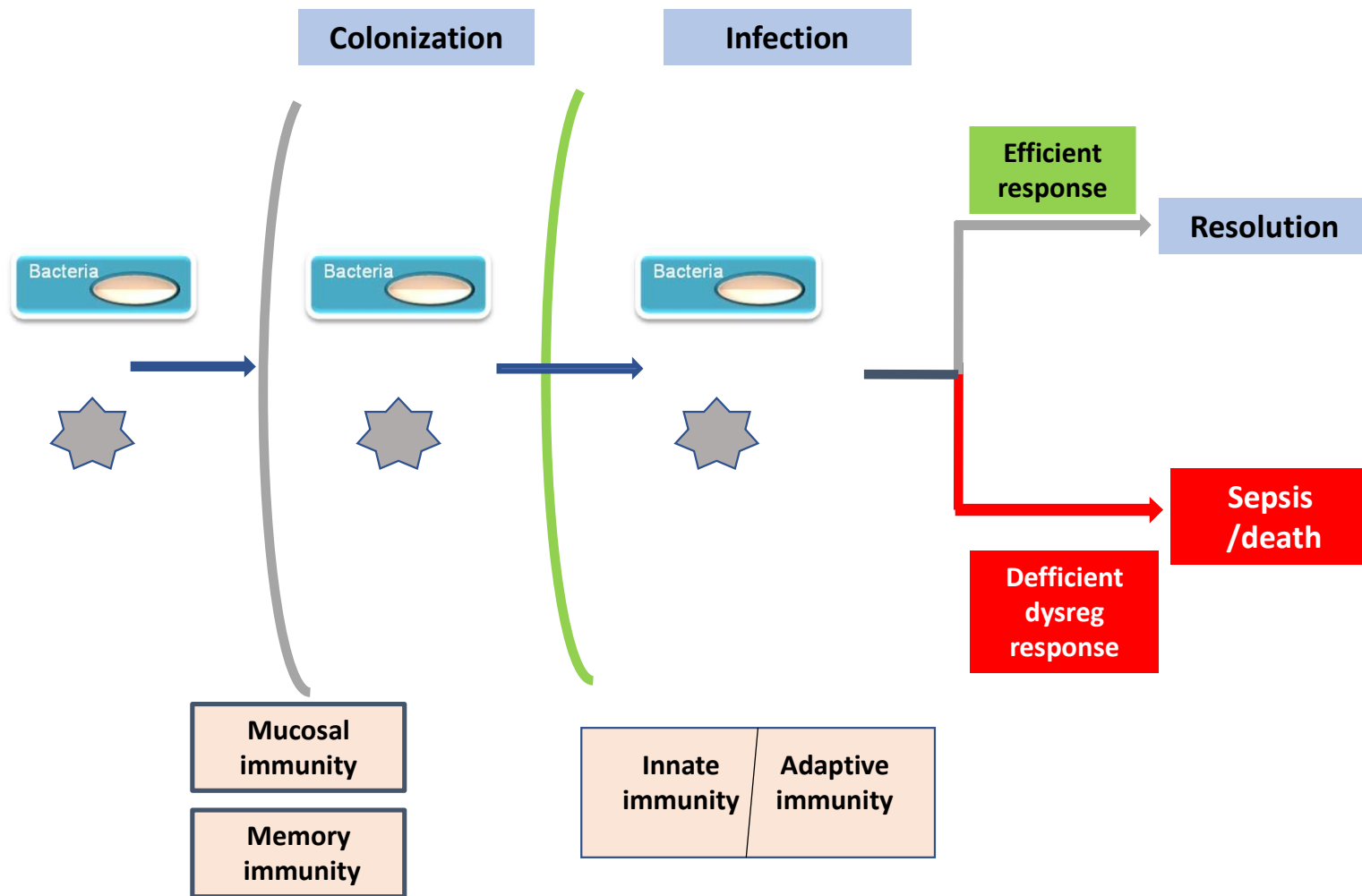


Jesus F Bermejo-Martin, MD PhD

wiseGEEK

egis
European Group on
Immunology of Sepsis

IBSA
Instituto de Investigación
Biomédica de Salamanca



JAMA The Journal of the
American Medical Association

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February 23, 2016, Vol 315, No. 8 >

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Special Communication | February 23, 2016
CARING FOR THE CRITICALLY ILL PATIENT

**The Third International Consensus Definitions for
Sepsis and Septic Shock (Sepsis-3)** FREE



“Sepsis should be defined as life-threatening organ dysfunction caused by a **dysregulated host response to infection**”

JAMA The Journal of the
American Medical Association

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Special Communication | February 23, 2016
CARING FOR THE CRITICALLY ILL PATIENT

**The Third International Consensus Definitions for
Sepsis and Septic Shock (Sepsis-3)** FREE



Organ dysfunction can be identified as
**an acute change in total SOFA score
≥2 points** consequent to the infection.

A SOFA score ≥ 2 reflects an **overall
mortality risk** of approximately **10%**

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ /FIO ₂ , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

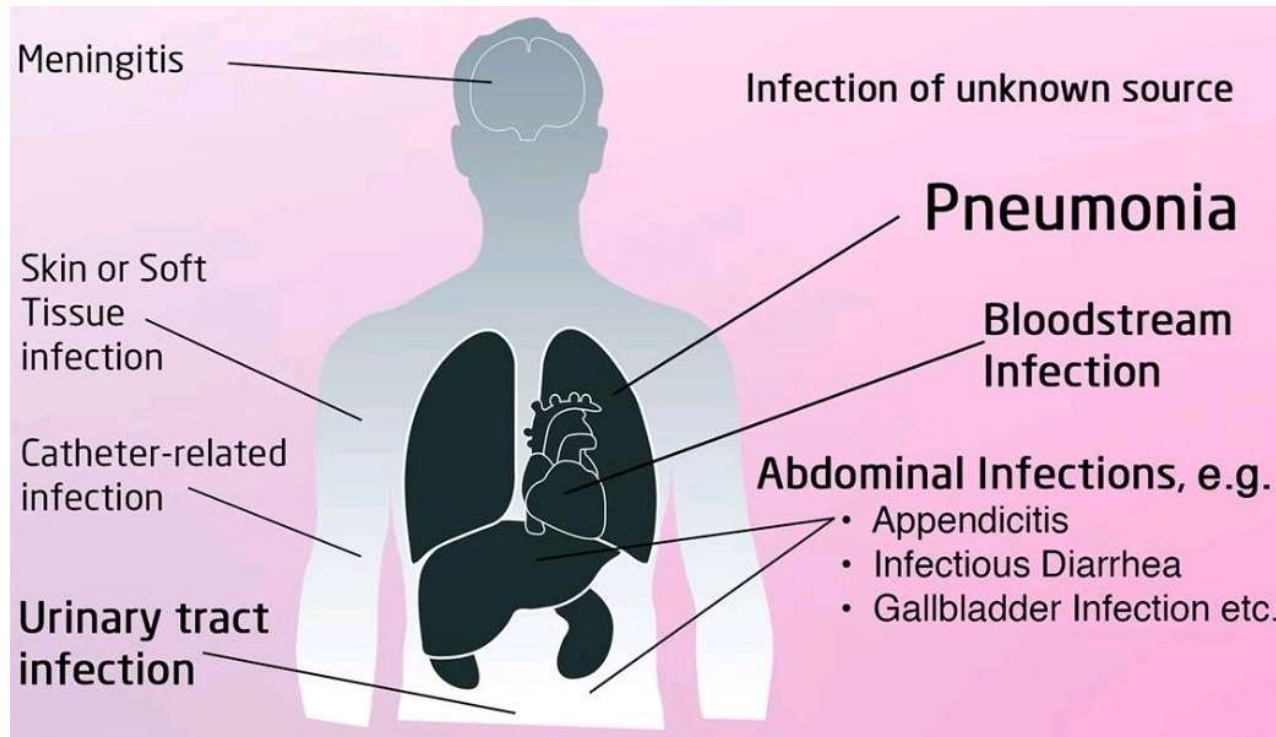
Abbreviations: FIO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

^a Adapted from Vincent et al.²⁷

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Infecciones más frecuentes causantes de sepsis



Global
Sepsis
Alliance

**Cualquier patógeno puede causar sepsis:
(Bacterias, Virus, Hongos)**

Impact of sepsis in the world



47 – 50 x 10⁶ cases /year



11 x 10⁶ deaths



1 out of 5 deaths is associated with sepsis



Severe consequences in survivors

THE LANCET



Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study.

Rudd KE, et al. Lancet. 2020 Jan 18;395(10219):200-211.



World Health
Organization

17 - 05 - 2017

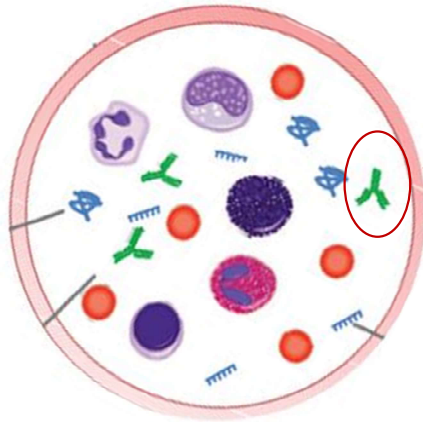


Recognizing Sepsis as a Global Health Priority — A WHO Resolution

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



The NEW ENGLAND
JOURNAL of MEDICINE



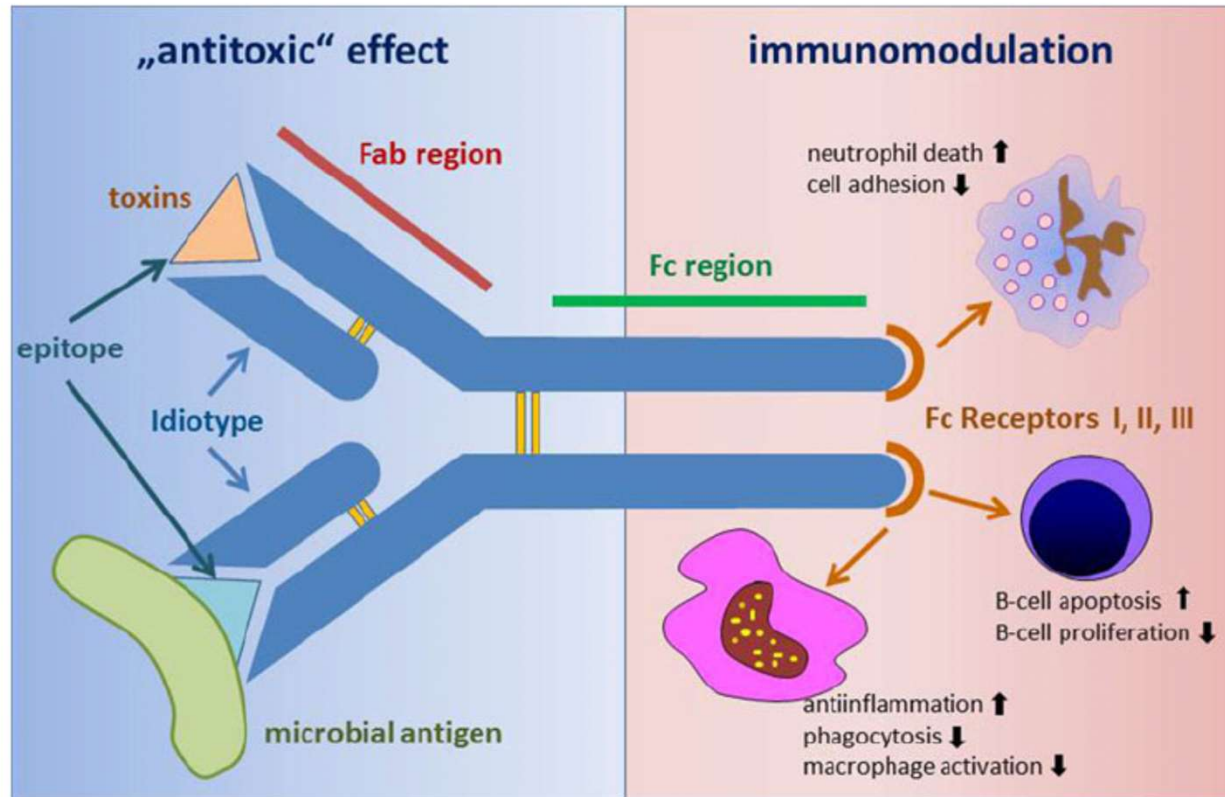
Igs levels

**Frequent
finding in CAP
and sepsis**

Circulating microparticles carry oxidation-specific epitopes and are recognized by natural IgM antibodies^{1S}

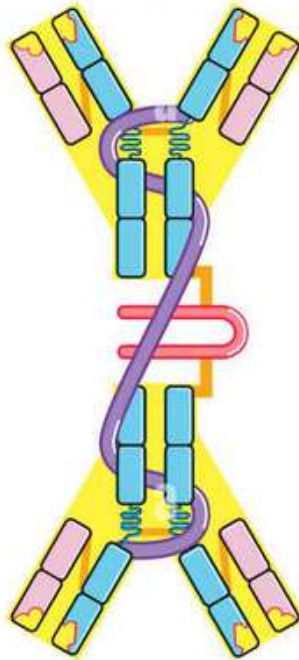
- Important role for natural **IgM** in the **clearance of Oxidation-specific epitopes**
- **Neutralization** of their **proinflammatory properties**.





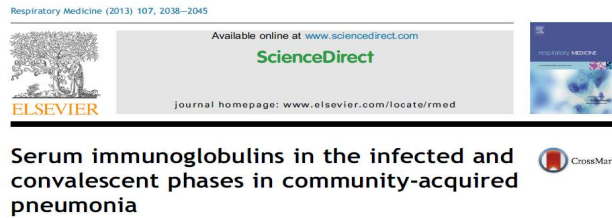
Toussaint S, Gerlach H.
 Curr Infect Dis Rep. 2012 Oct;14(5):522-9.

secretory
IgA



Mucosal immunity

de la Torre MC
et al



Venet F
et al



Taccone FS
et al



Hypo-
gammaglobulinemia



Ig levels below
normality

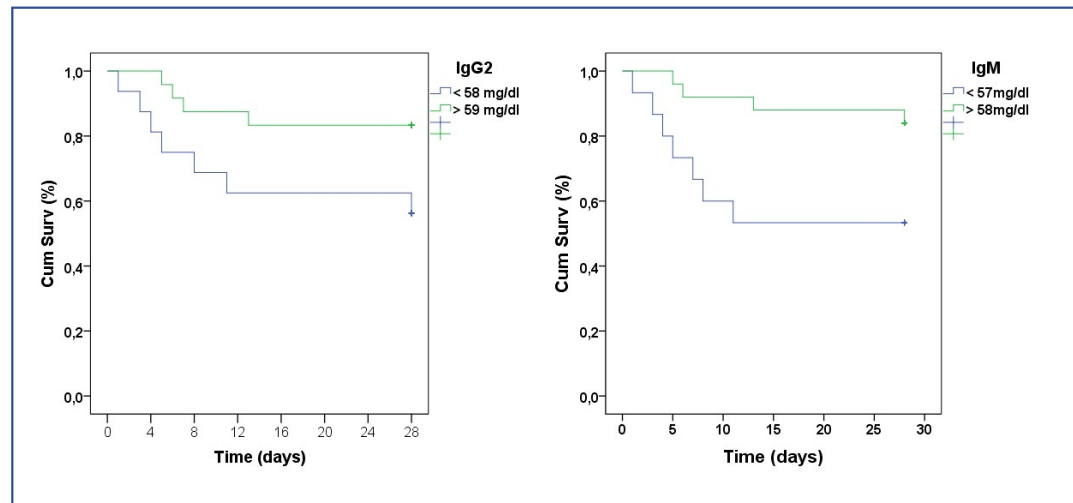


Short communication

IgM levels in plasma predict outcome in severe pandemic influenza

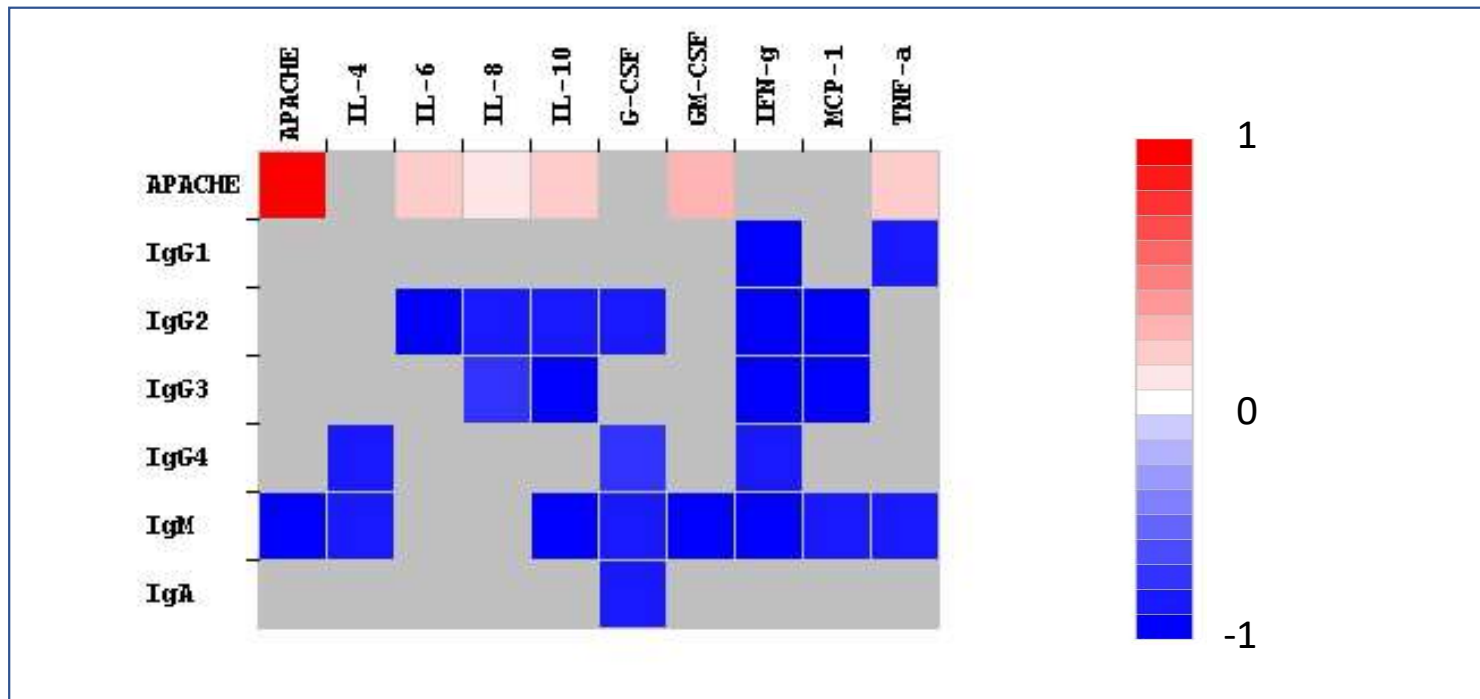


Justel M et al



Short communication

IgM levels in plasma predict outcome in severe pandemic influenza

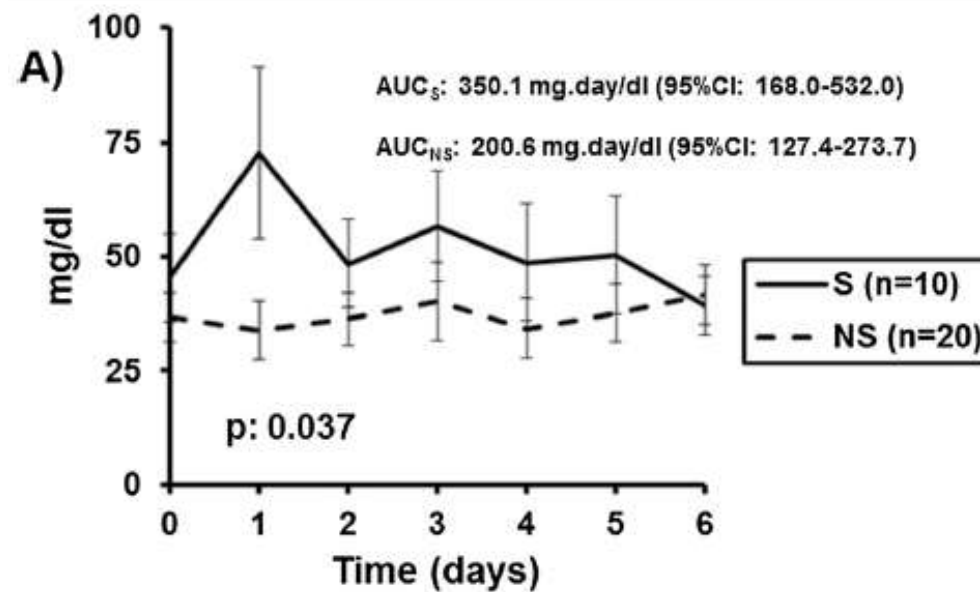


Inverse correlation between Igs and cytokine levels

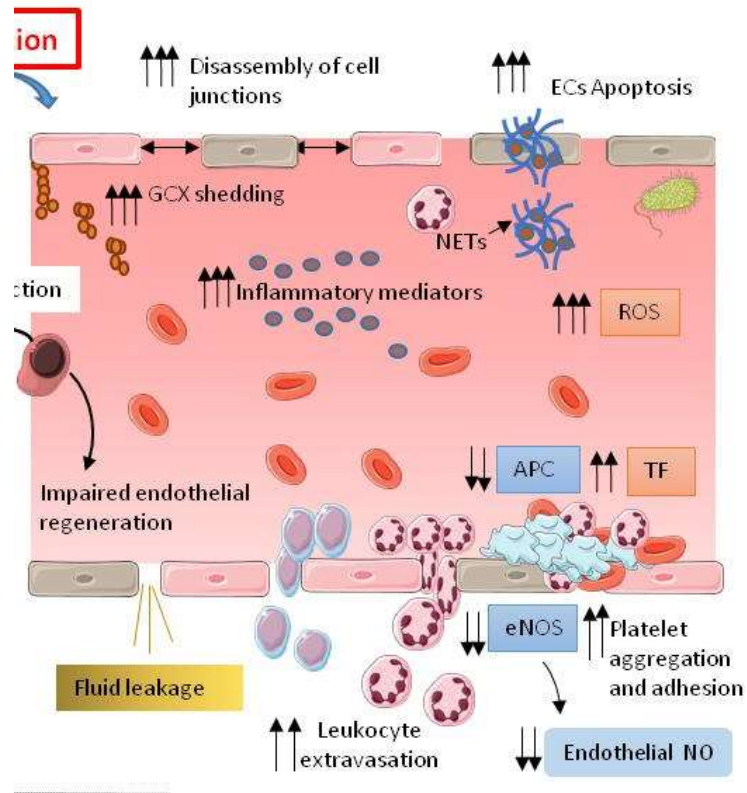
RESEARCH

Open Access

Kinetics of circulating immunoglobulin M in sepsis: relationship with final outcome



C. Sepsis: acute-on-chronic endothelial dysfunction



Review

Shared Features of Endothelial Dysfunction between Sepsis and Its Preceding Risk Factors (Aging and Chronic Disease)

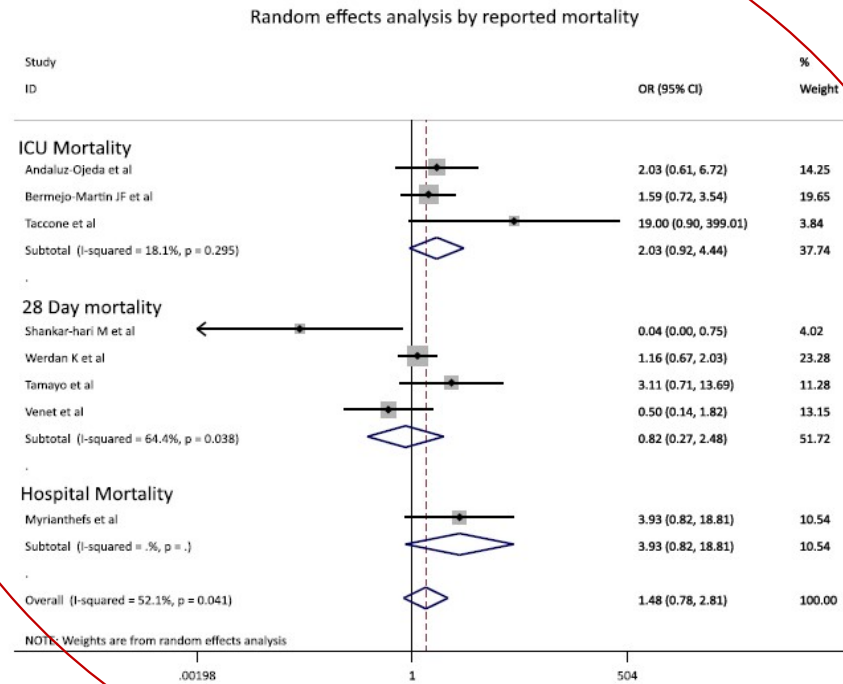
Jesus F. Bermejo-Martín ^{1,2,*}, Marta Martín-Fernández ^{1,2,*}, Cristina López-Mestanza ¹, Patricia Duque ³ and Raquel Almansa ^{1,2}



Manu Shankar-Hari
Nicholas Culshaw
Benjamin Post
Eduardo Tamayo
David Andaluz-Ojeda
Jesús F. Bermejo-Martín
Sebastian Dietz
Karl Werdan
Richard Beale
Jo Spencer
Mervyn Singer

Endogenous IgG hypogammaglobulinaemia in critically ill adults with sepsis: systematic review and meta-analysis

**Controversial
influence of
hypogamma on
prognosis...**



RESEARCH

Open Access



Higher levels of IgA and IgG at sepsis onset are associated with higher mortality: results from the Albumin Italian Outcome Sepsis (ALBIOS) trial

Laura Alagna^{1†}, Jennifer M. T. A. Meessen^{2†}, Giacomo Bellani^{3,4}, Daniela Albiero³, Pietro Caironi^{5,6}, Irene Principale⁵, Luigi Vivona⁷, Giacomo Grasselli^{7,8}, Francesca Motta², Nicolò M. Agnelli², Vieri Parrir Stefano Romagnoli^{10,11}, Roberto Keim¹², Francesca Di Marzo Capozzi¹³, Fabio S. Taccone¹⁴, Walter Ta Barbara Bottazzi¹⁵, Alessandra Bandera^{1,7}, Andrea Cortegiani^{16,17} and Roberto Latini^{2*}

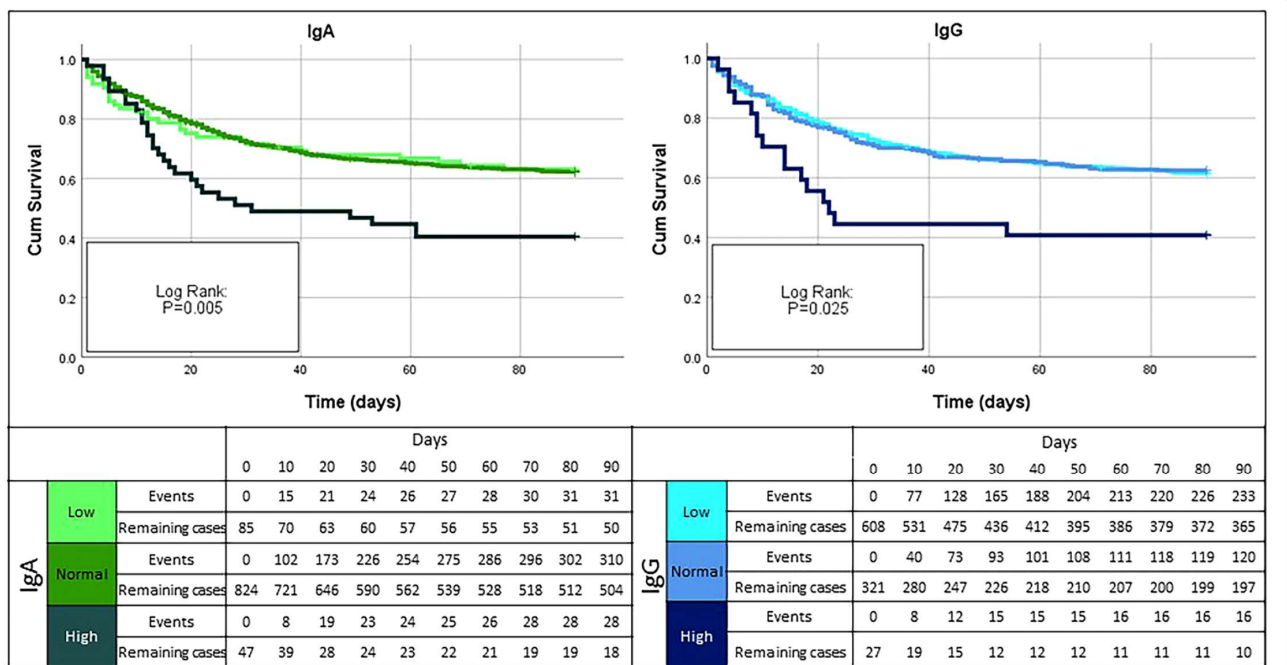
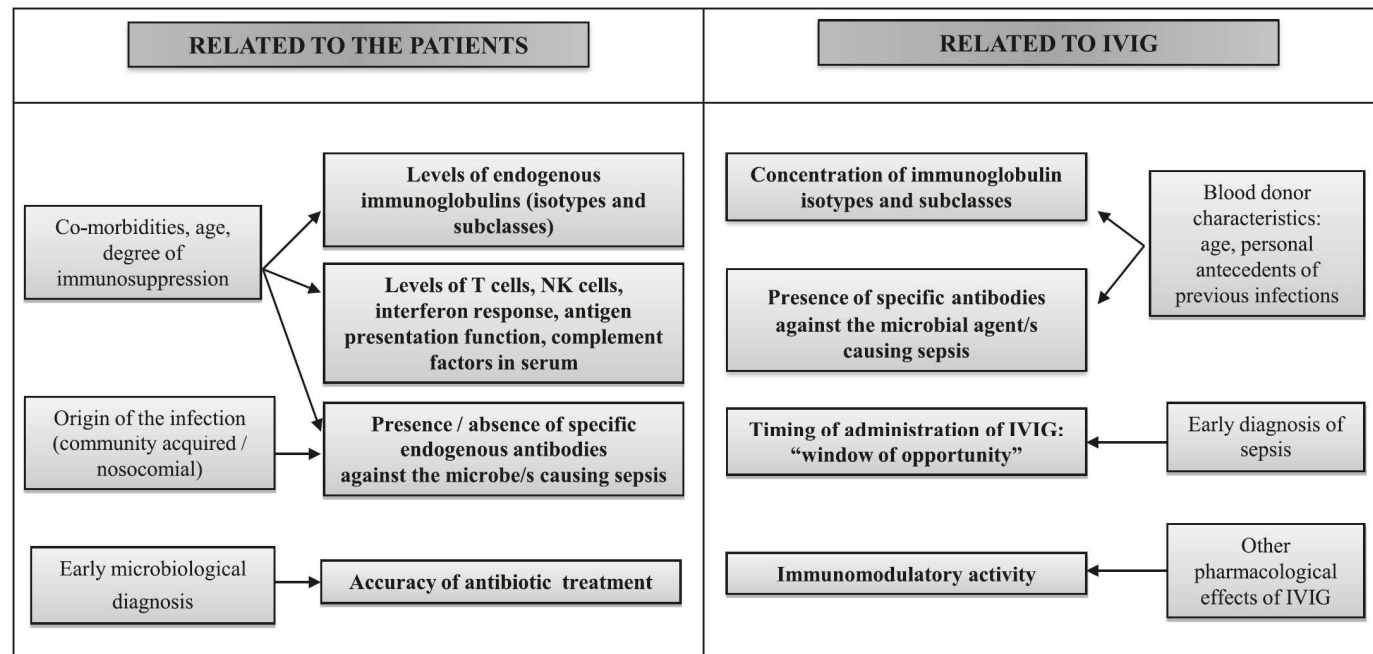


Fig. 2 Kaplan–Meier analysis for IgA and IgG-groups and 90-day mortality

The original sins of clinical trials with intravenous immunoglobulins in sepsis

Raquel Almansa¹, Eduardo Tamayo¹, David Andaluz-Ojeda¹, Leonor Nogales¹, Jesús Blanco^{2,3}, Jose Maria Eiros¹, Jose Ignacio Gomez-Herreras¹ and Jesus F Bermejo-Martin^{1*}

FACTORS TO TAKE INTO ACCOUNT IN CLINICAL TRIALS WITH IVIG IN SEPSIS





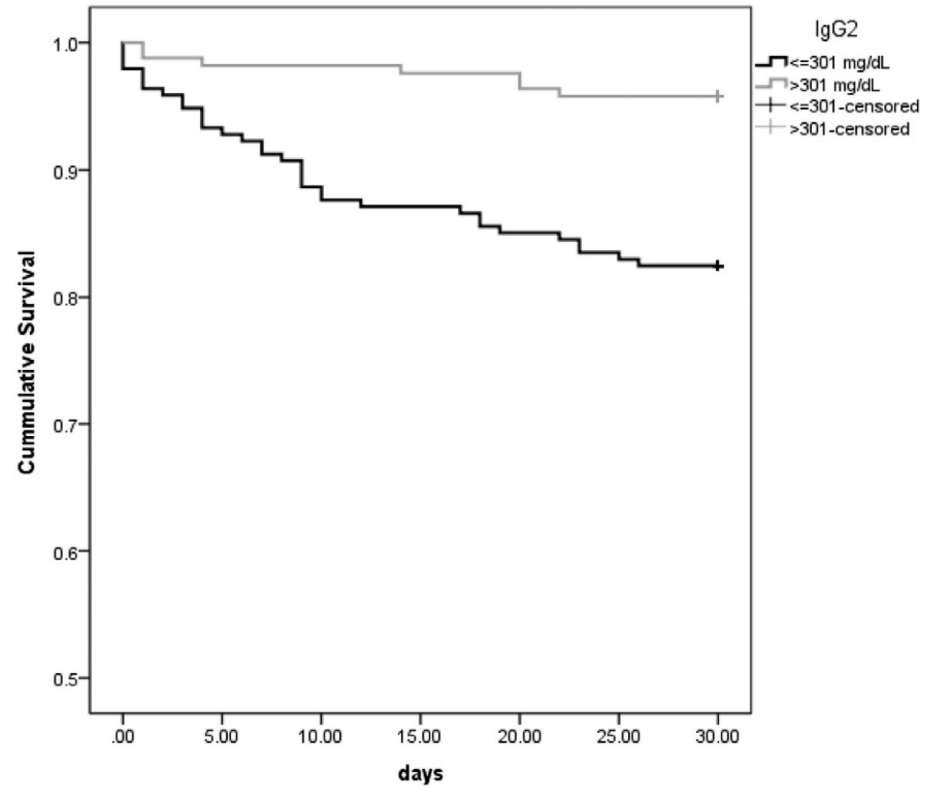
Do isotypes matter?



IgG2 as an independent risk factor for mortality in patients with community-acquired pneumonia[☆]



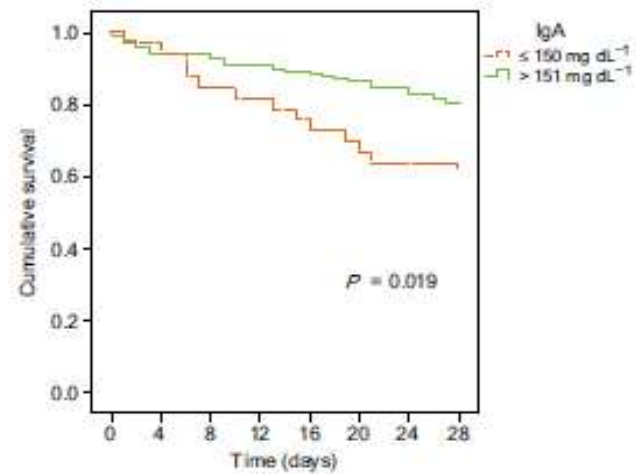
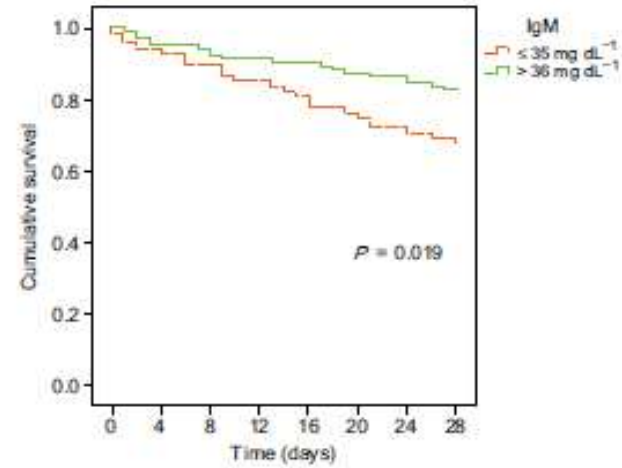
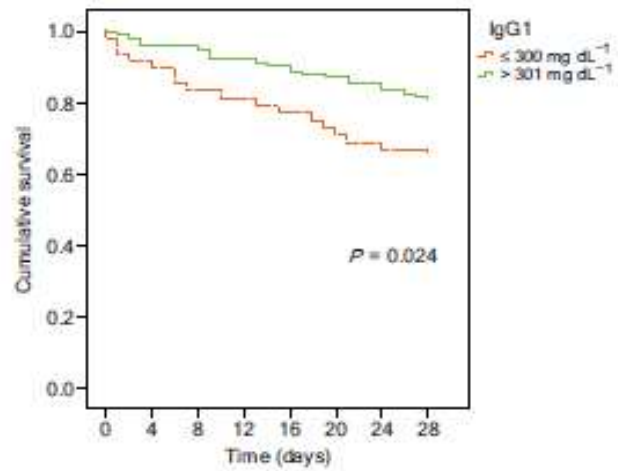
Mari C. de la Torre^{a,*}, Elisabet Palomera^b, Mateu Serra-Prat^b, Estel Güell^a, Joan Carles Yébenes^a, Jesús F. Bermejo-Martín^{c,1}, Jordi Almirall^{a,d,e,1}



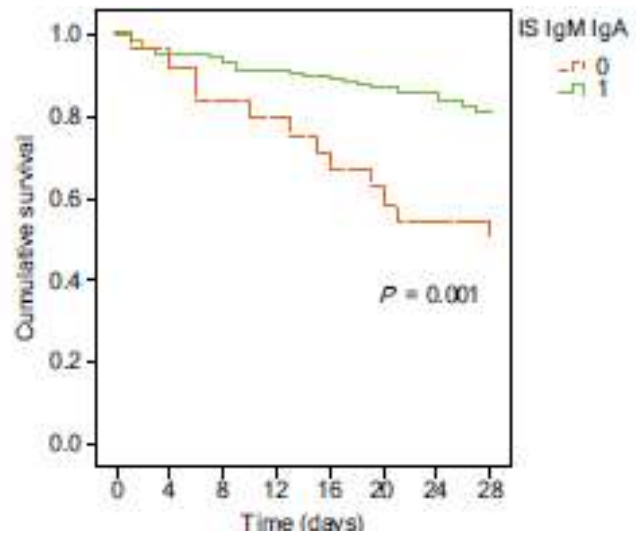
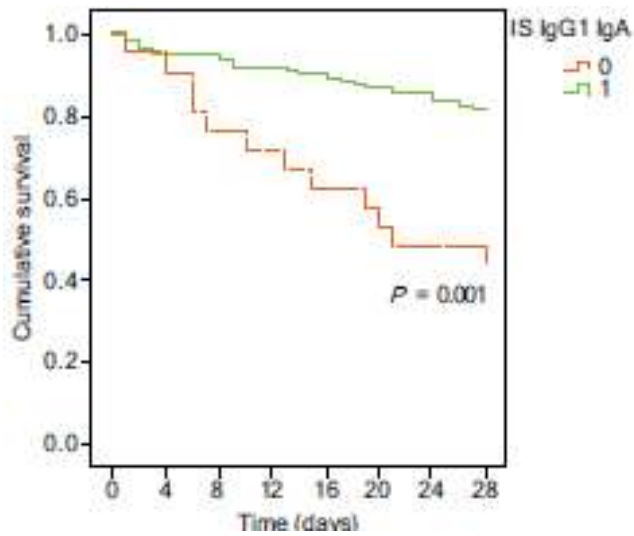
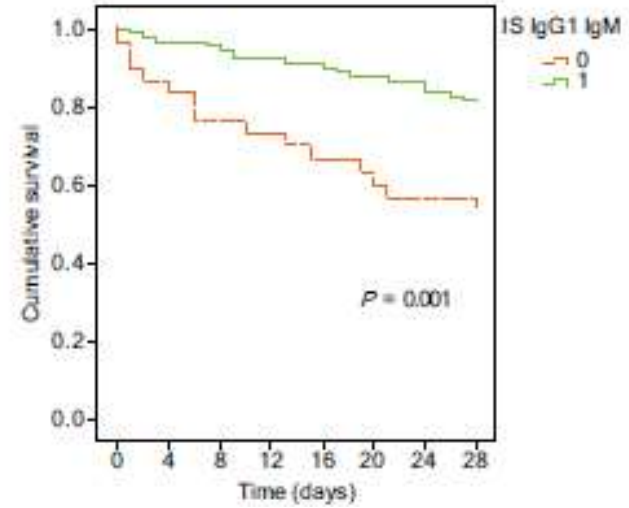
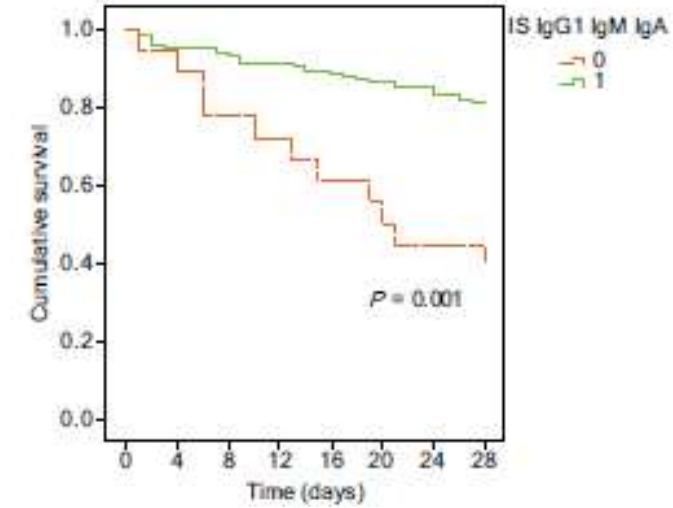


Is there any synergy
between
immunoglobulin isotypes?

Influence of individual immunoglobulin isotypes on survival in sepsis



Synergistic association between IgG IgA IgM...



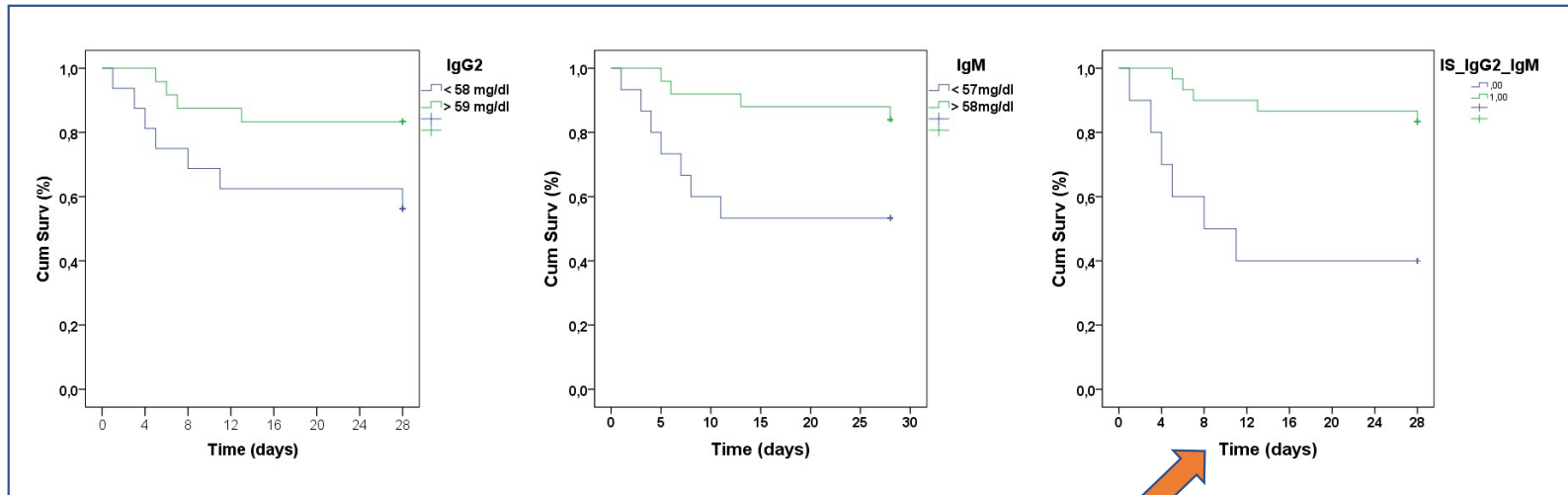


Short communication

IgM levels in plasma predict outcome in severe pandemic influenza



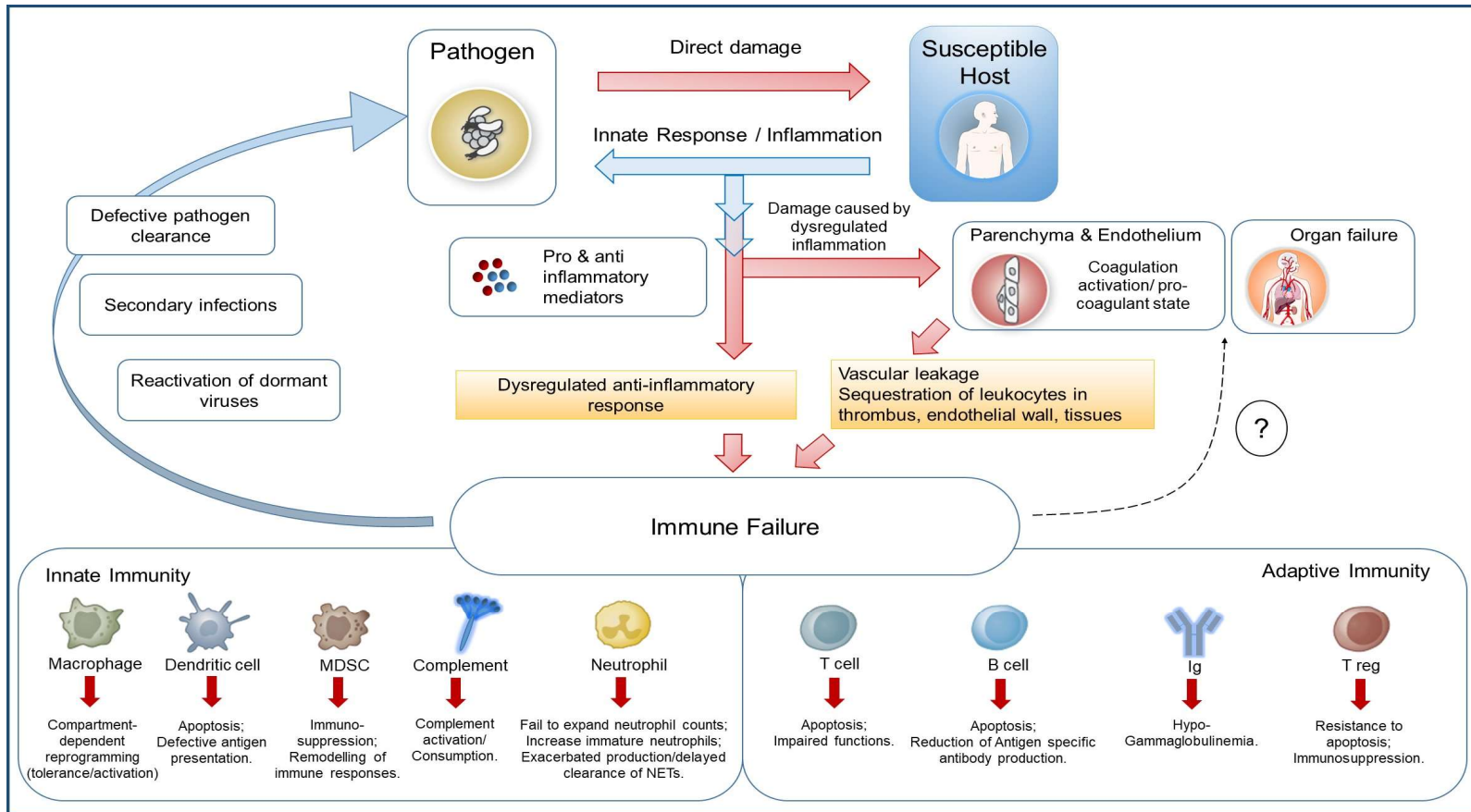
Justel M et al



Combined score IgG2 + IgM



What is the influence of
other immunity actors?



THE LANCET
Infectious Diseases

Current gaps in sepsis immunology: new opportunities for translational research

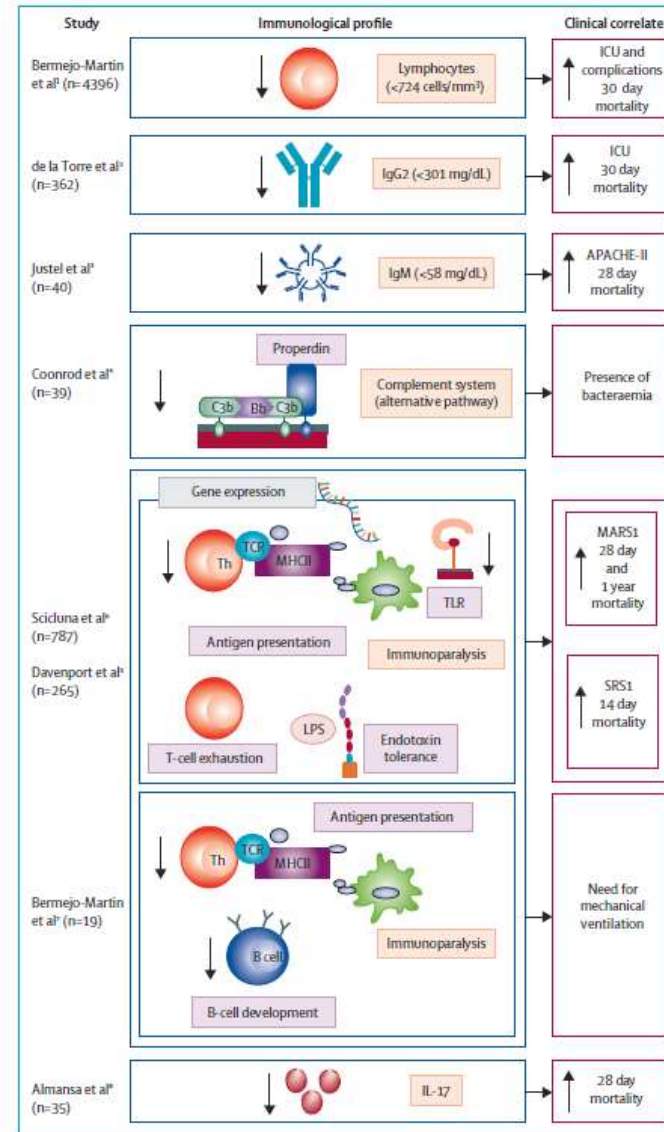
Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki, Martin Sebastian Winkler, Gunnar Lachmann, Paul La Rosée, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Matthijs Kox, Jean-Marc Cavillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Marta Martin-Fernandez, Raquel Almansa, Ignacio Martin-Loeches, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, André Scherag, Christian Meisel, Joerg C Schefold, Jesús F Bermejo-Martin

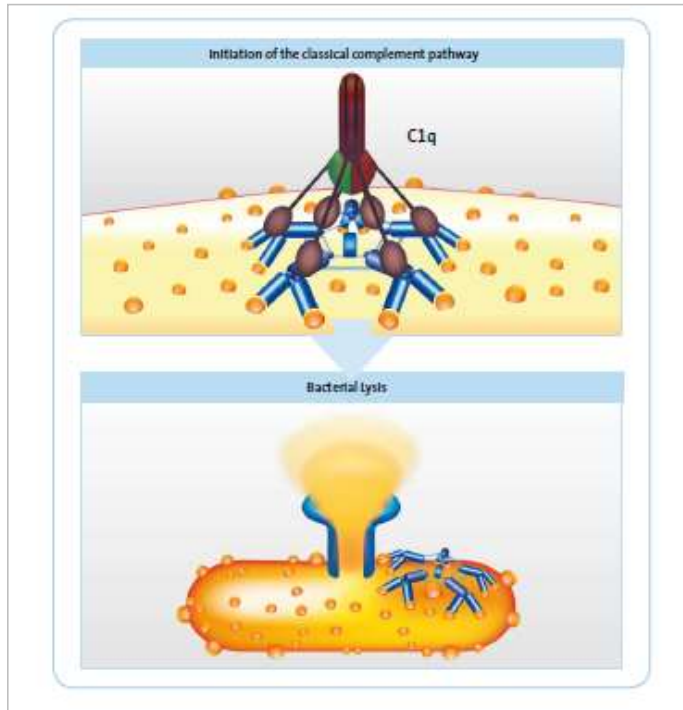
Immunological profiling to assess disease severity and prognosis in CAP

THE LANCET Respiratory Medicine

Bermejo-Martin JF, Almansa R, Martin-Fernandez M, Menendez R, Torres A.

www.thelancet.com/respiratory
Vol 5 December 2017 e36





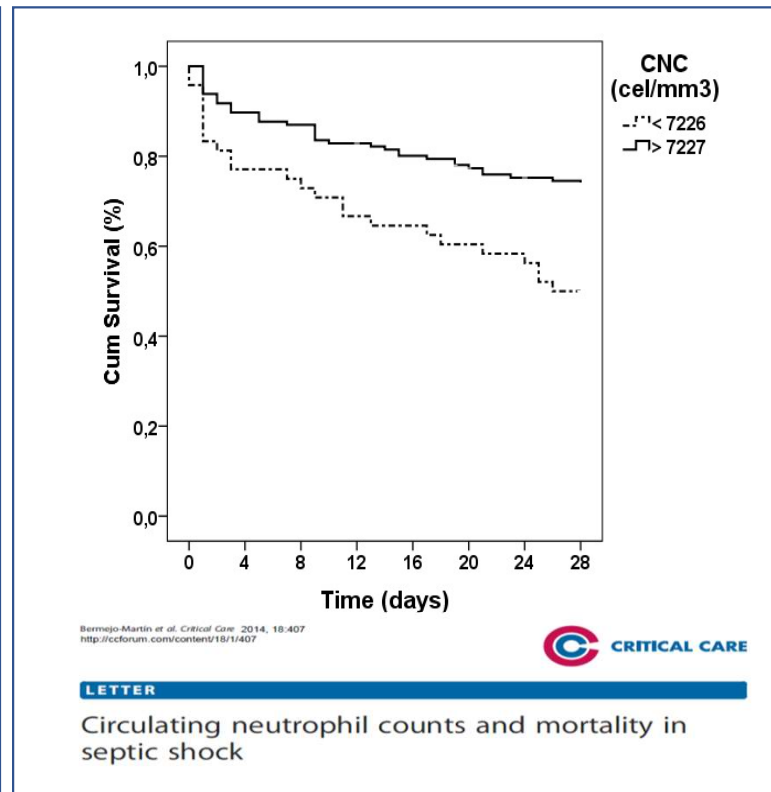
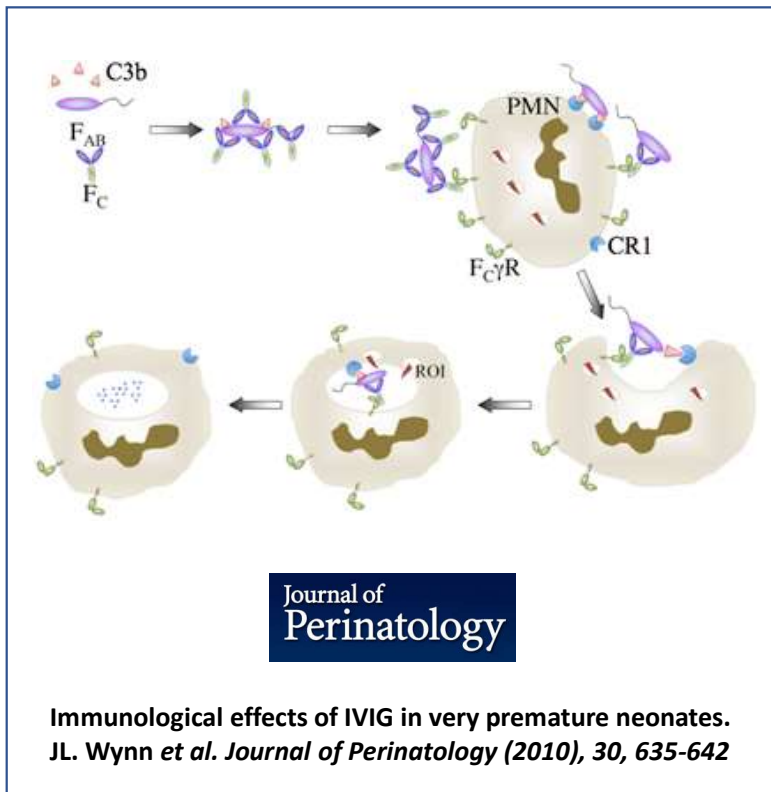
**Immunoglobulins kill bacteria
by activation of the classical
pathway of complement system**



**We need to asses complement
factors levels and function!**

Image from





Immunoglobulins promote bacterial opsonization by neutrophils



We need to assess neutrophil counts!

Is the predictive ability of immunoglobulins different depending on sepsis severity ?



The protective association of endogenous immunoglobulins against sepsis mortality is restricted to patients with moderate organ failure.

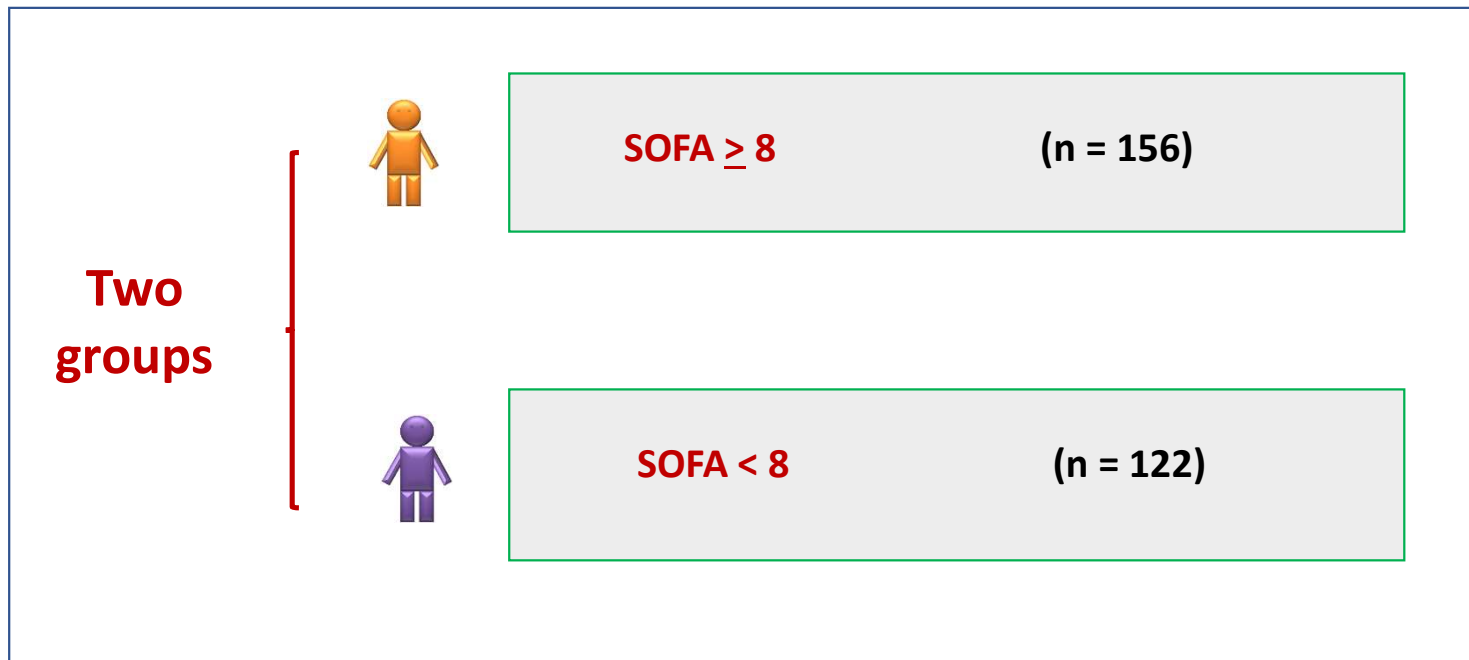
GRECIA

ABISS - EDUSEPSIS

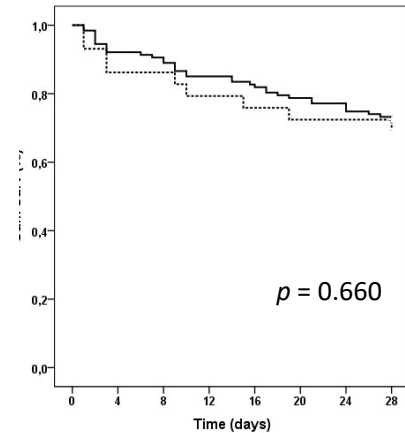
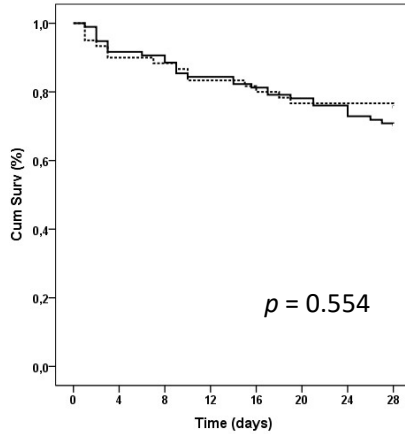
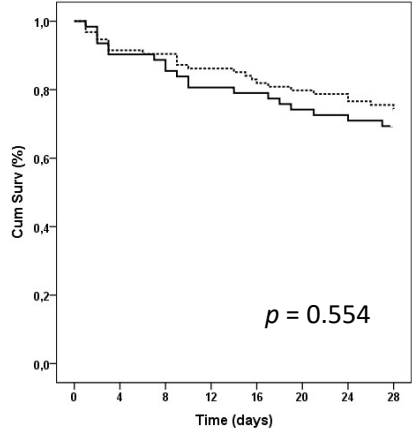
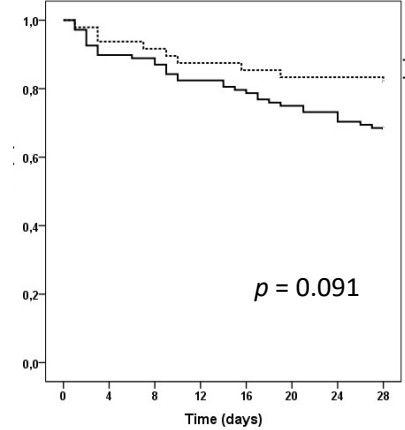
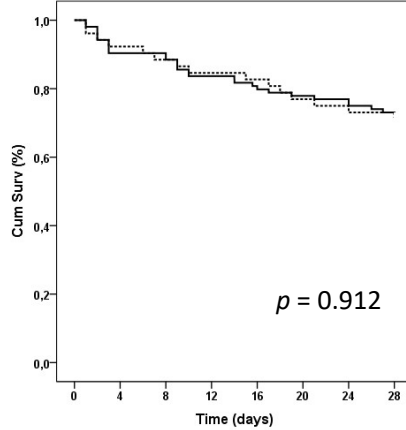
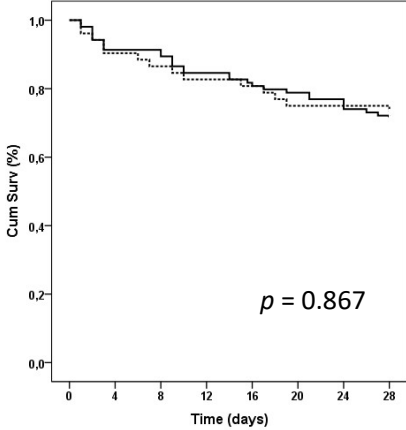
Ignacio Martin-Loeches, Arturo Muriel-Bombín, Ricard Ferrer, Antonio Artigas, Jordi Sole-Violan, Leonardo Lorente, David Andaluz-Ojeda, Adriele Prina-Mello, Ruben Herrán-Monge, Borja Suberviola, Ana Rodriguez-Fernandez, Pedro Merino, Ana M Loza, Pablo Garcia-Olivares, Eduardo Anton, Eduardo Tamayo, Wysali Trapiello, Jesús Blanco, Jesús F Bermejo-Martin

Status: response to reviewers

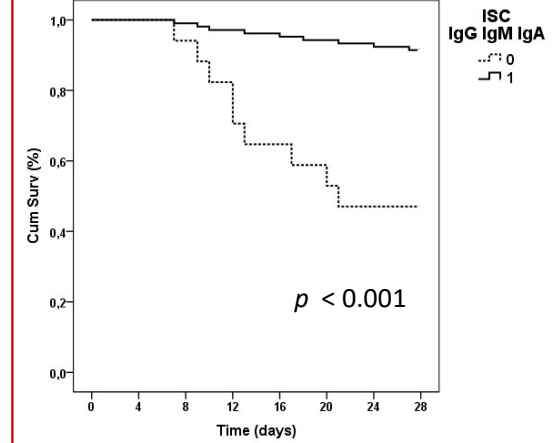
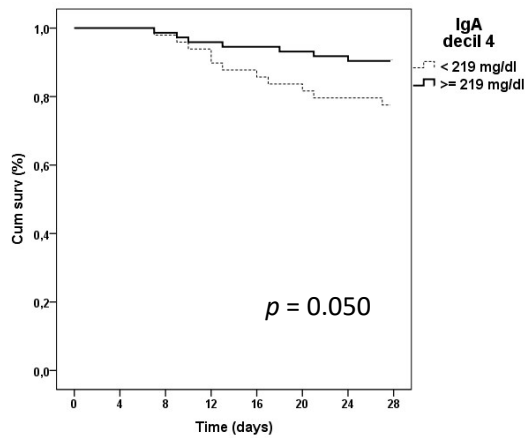
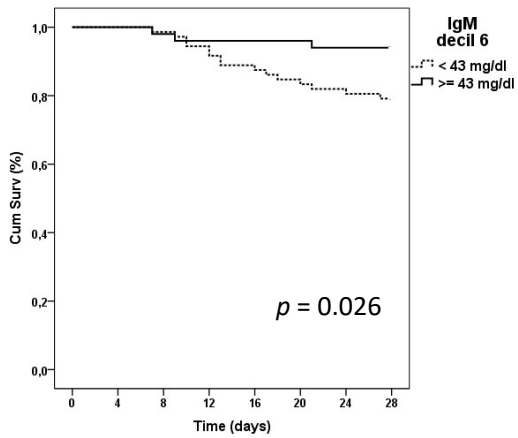
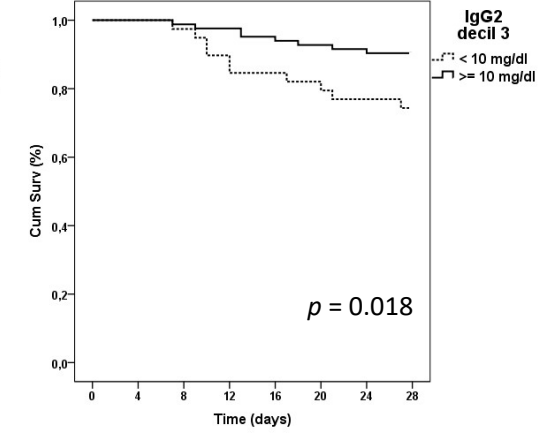
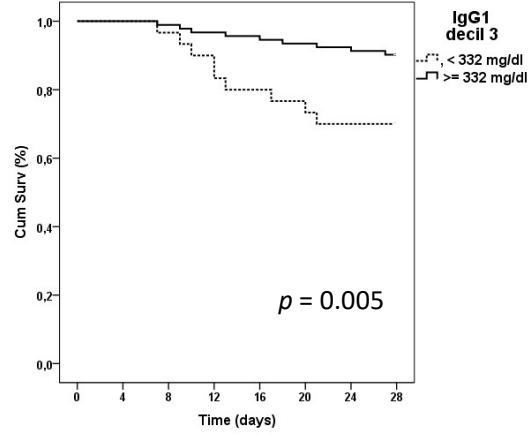
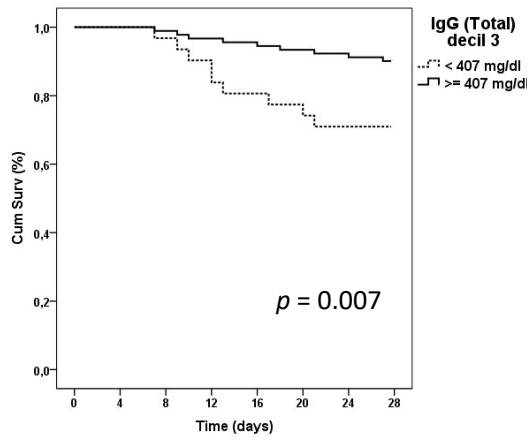
278 patients admitted to the ICU with sepsis



SOFA \geq 8



SOFA < 8





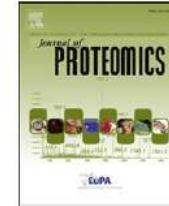
What is the influence of immunoglobulins against specific microbes?



Contents lists available at ScienceDirect

Journal of Proteomics

journal homepage: www.elsevier.com/locate/jprot



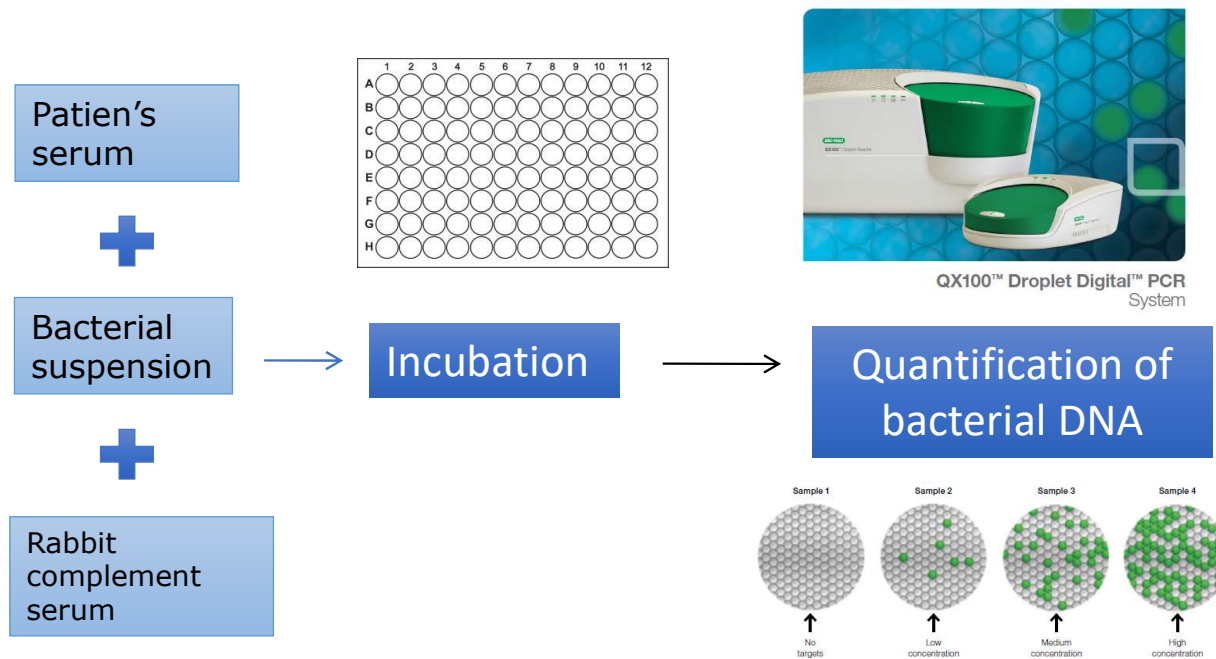
Specific serum IgG at diagnosis of *Staphylococcus aureus* bloodstream invasion is correlated with disease progression



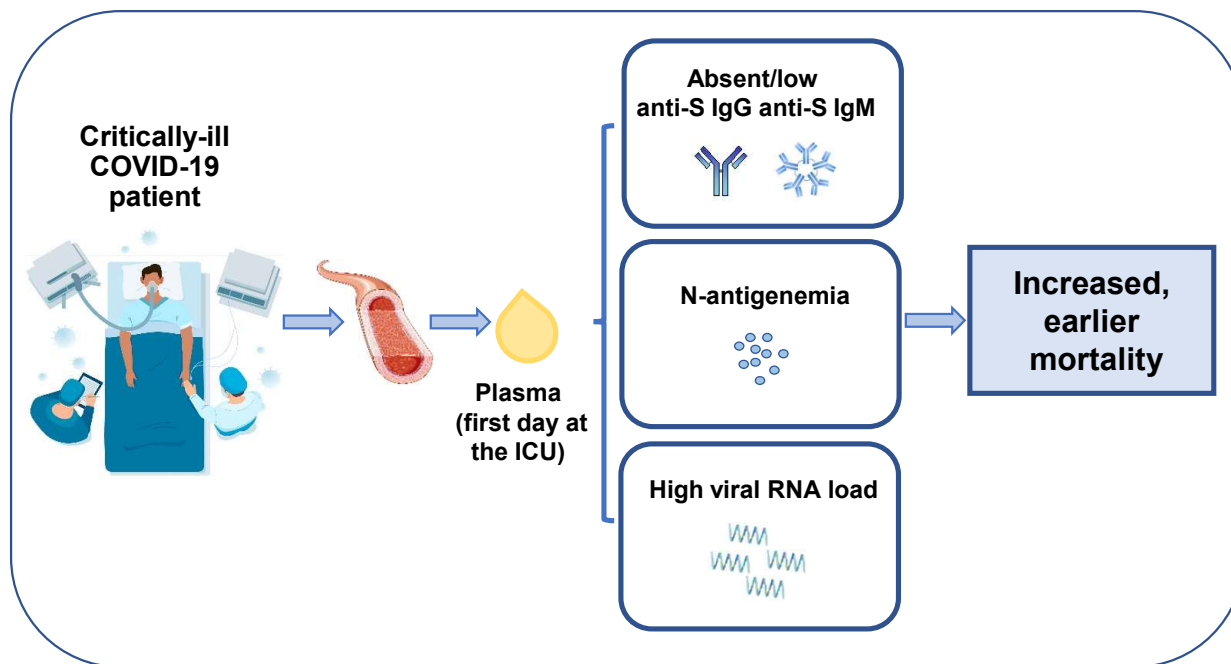
Stenzel A et al:

S. aureus-specific serum IgG levels at diagnosis of S. aureus infection were lower in patients developing sepsis than in patients without sepsis (P<0.05).

Evaluation of the presence of specific neutralizing antibodies

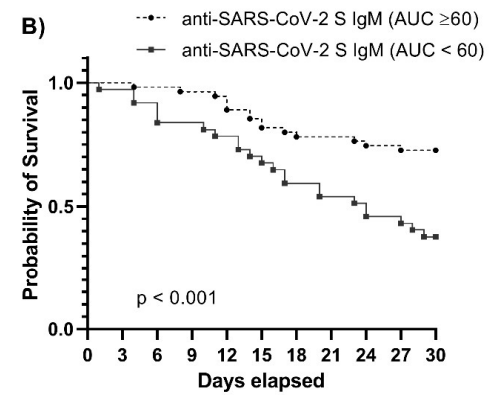
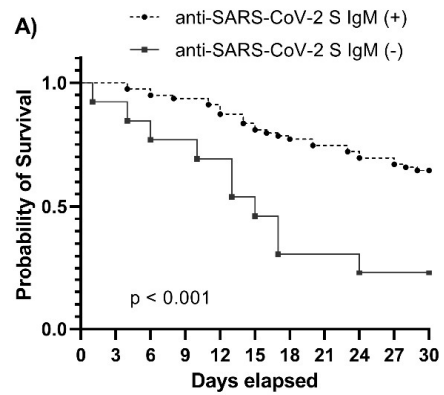


Low anti-SARS-CoV-2 S antibody levels predict increased mortality and dissemination of viral material to blood in critical COVID-19

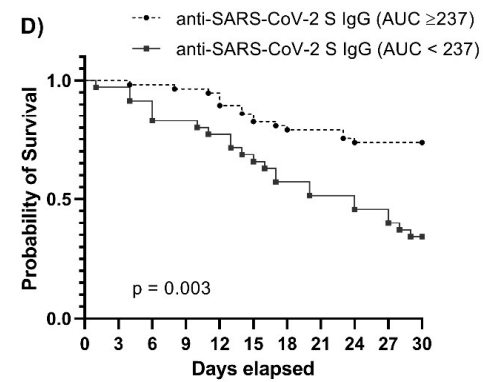
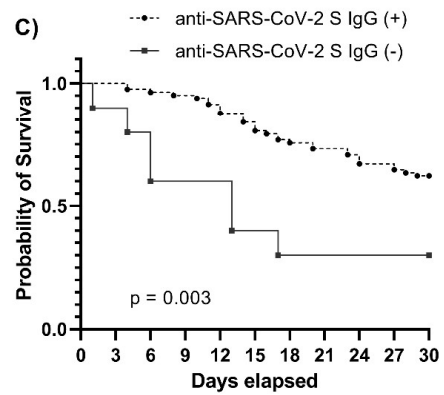


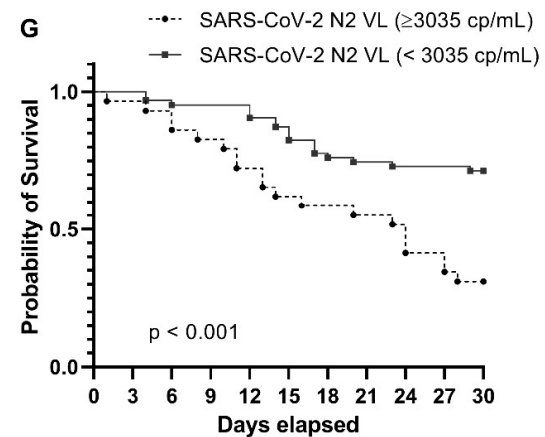
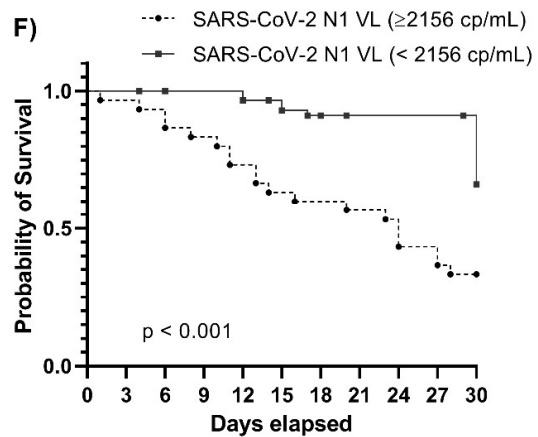
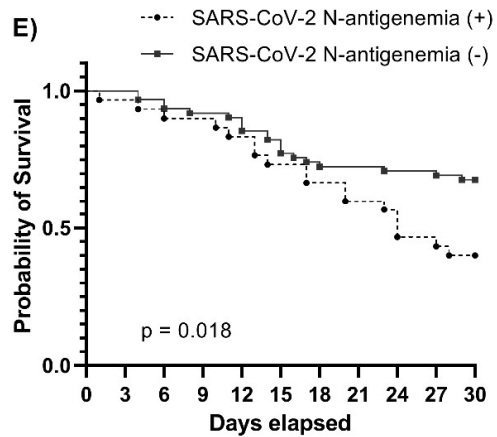
Patient vector created by freepik (www.freepik.com-<https://www.freepik.com/vectors/patient>)
 Blood vessel created by smart servier medical art (<https://smart.servier.com/>)

Anti-S IgM at ICU admission

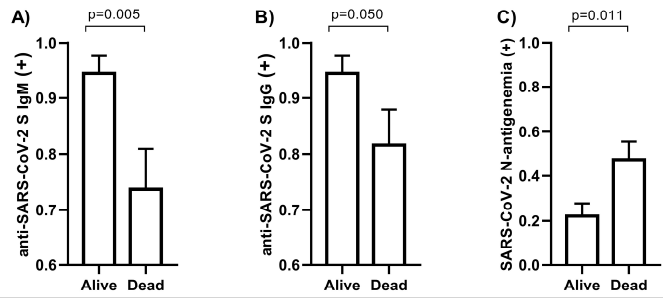


Anti-S IgG at ICU admission

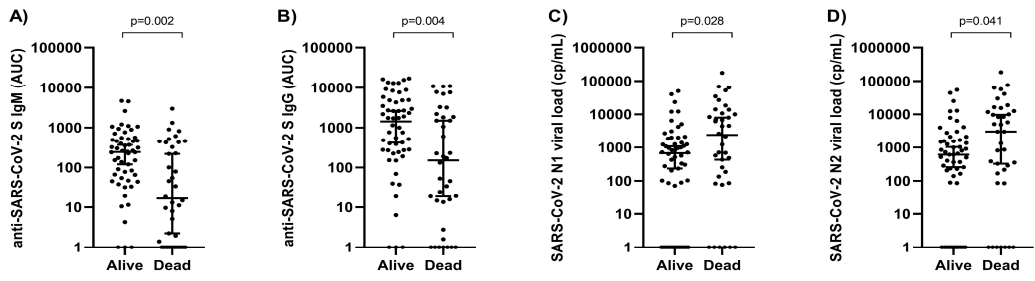




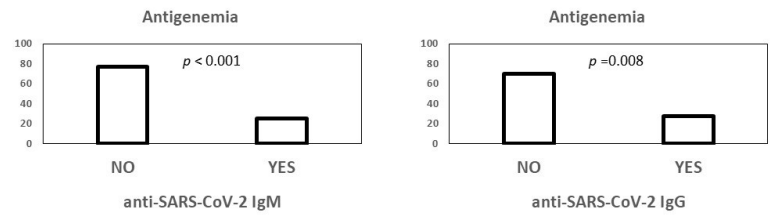
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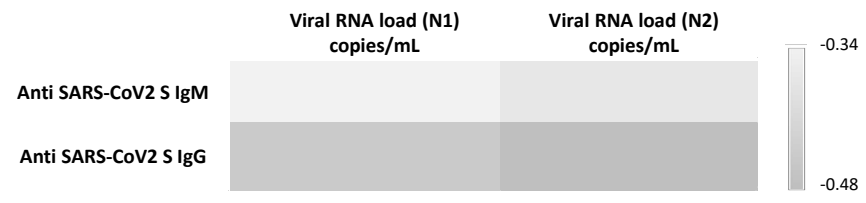
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3



4





What about therapies
replacing Igs?

Score-based immunoglobulin G therapy of patients with sepsis:
The SBITS study*

Karl Werdan, MD; Günter Pilz, MD; Oskar Bujdoso, MS; Peter Fraunberger, MD; Gertraud Neeser, MD;
Roland Erich Schmieder, MD; Burkhard Viell, PhD; Walter Marget, MD; Margret Seewald, MD;
Peter Walger, MD; Ralph Stuttmann, MD; Norbert Speichermann, MD; Claus Peckelsen, MD;
Volkhard Kurowski, MD; Hans-Heinrich Osterhues, MD; Ljiljana Verner, MD; Roswita Neumann, PhD;
Ursula Müller-Werdan, MD; for the Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group

Crit Care Med. 2007 Dec;35(12):2693-2701



Conclusions:

In patients with score-defined severe sepsis, ivIgG with a total dose of 0.9 g/kg body weight does not reduce mortality.

SBITs

IVIG contained only IgG and....

APACHE II in IVIG group



27.6 + 4.5

APACHE II in placebo group



28.0 + 4.5

**GRECIA
ABISS -
EDUSEPSIS**

APACHE-II score
for the less severe group



18 + 5.6

The highest impact on mortality risk was for ISC IgGAM !

The good news is.....

SOFA < 8



The majority of cases of sepsis !!!

Surviving Sepsis Campaign

“We encourage large multicenter studies to further evaluate the effectiveness of polyclonal immunoglobulins in sepsis”



**OK, large studies.....
but more oriented please...!**

- SOFA score
- Basal levels of IgG, IgA and IgM

Precision Medicine in Sepsis



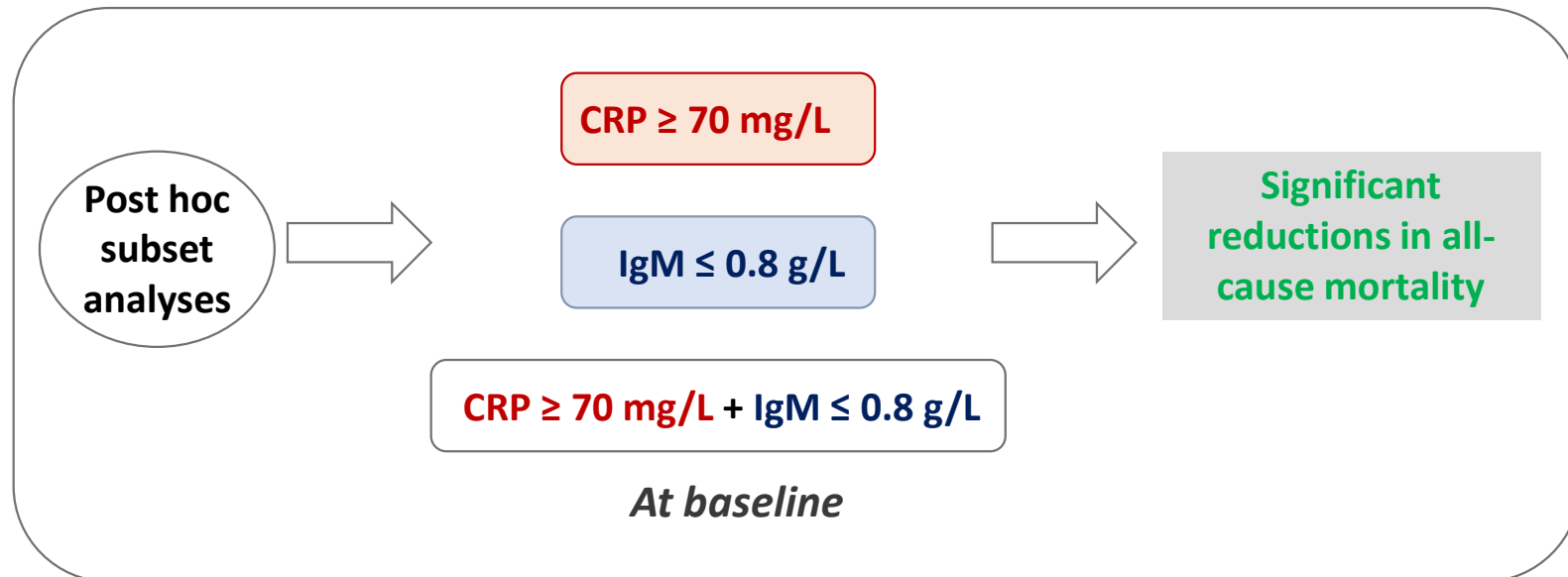
SEVEN-DAY PROFILE PUBLICATION

Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study)



Tobias Welte^{1*}, R. Phillip Dellinger², Henning Ebel³, Miguel Ferrer⁴, Steven M. Opal⁵, Mervyn Singer⁶, Jean-Louis Vincent⁷, Karl Werdan⁸, Ignacio Martin-Loeches^{8,9}, Jordi Almirall¹⁰, Antonio Artigas⁹, Jose Ignacio Ayestarán¹¹, Sebastian Nuding³, Ricard Ferrer¹², Gonzalo Sirgo Rodríguez¹³, Manu Shankar-Hari¹⁴, Francisco Álvarez-Lerma¹⁵, Relmer Riessen¹⁶, Josep-Maria Sirvent¹⁷, Stefan Kluge¹⁸, Kai Zacharowski¹⁹, Juan Bonastre Mora²⁰, Harald Lapp²¹, Gabriele Wöbker²², Ute Achtzehn²³, David Brealey²⁴, Axel Kempa²⁵, Miguel Sánchez García²⁶, Jörg Brederlau²⁷, Matthias Kochanek²⁸, Henrik Peer Reschreiter²⁹, Matthew P. Wise³⁰, Bernd H. Belohradsky³¹, Iris Bobenhausen³², Benjamin Dälken³², Patrick Dubovy³², Patrick Langohr³², Monika Mayer³², Jörg Schüttrumpf³², Andrea Wartenberg-Demand³², Ulrike Wippermann³², Daniele Wolf³² and Antoni Torres³³

Overall, no statistically significant difference in VFDs between trimodulin and placebo



RECOVERY trial finds Regeneron's monoclonal antibody combination reduces deaths for hospitalised COVID-19 patients who have not mounted their own immune response

16 June 2021




COMMENT | VOLUME 21, ISSUE 9, P1201-1202, SEPTEMBER 01, 2021

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Monoclonal antibodies as antibacterial therapies: thinking outside of the box

Marin H Kollef  Kevin D Betthausen

Published: April 21, 2021 • DOI: [https://doi.org/10.1016/S1473-3099\(21\)00062-1](https://doi.org/10.1016/S1473-3099(21)00062-1)  Check for updates


 PlumX Metrics

Table 2. Companies currently pursuing Hu-mAb therapy for bacterial infections caused by ESKAPEE pathogens and *Clostridium difficile*—products and stage of development.

Name	Bacterial Species Targeted	Company	Development Phase
AR301	<i>Staphylococcus aureus</i>	Aridis Pharmaceuticals	Phase 2 Complete Ongoing Phase 3
MEDI4893	<i>Staphylococcus aureus</i>	Medimmune	Phase 2 Complete
MEDI3902	<i>Pseudomonas aeruginosa</i>	Medimmune	Phase 1 Complete Ongoing Phase 2
AR101	<i>Pseudomonas aeruginosa</i>	Aridis Pharmaceuticals	Phase 1 Complete Ongoing Phase 2
514G3	<i>Staphylococcus aureus</i>	XBiotech	Phase 2
ARN-100	<i>Staphylococcus aureus</i>	Arsansis	Phase 2 Halted
PolyCAB	<i>Clostridium difficile</i>	MicroPharm	Phase 1
RG7861	<i>Staphylococcus aureus</i>	Roche	Phase 1
TRL1068	Biofilm—multiple species	Trellis Bioscience	Preclinical Entering Phase 1
AR401-mAb	<i>Acinetobacter baumannii</i>	Aridis Pharmaceuticals	Preclinical
VXD-003	<i>Acinetobacter baumannii</i>	VaxDyn	Preclinical
Cd-ISTAb	<i>Clostridium difficile</i>	Integrated BioTherapeutics	Preclinical
ASN-4	<i>Escherichia coli</i> (ST131)	Arsansis—Outlicensed to BB100	Preclinical
ASN-5	<i>K. pneumoniae</i>	Arsansis—Outlicensed to BB200	Preclinical



Review

Monoclonal Antibodies as an Antibacterial Approach Against Bacterial Pathogens

Daniel V. Zurawski* and Molly K. McLendon

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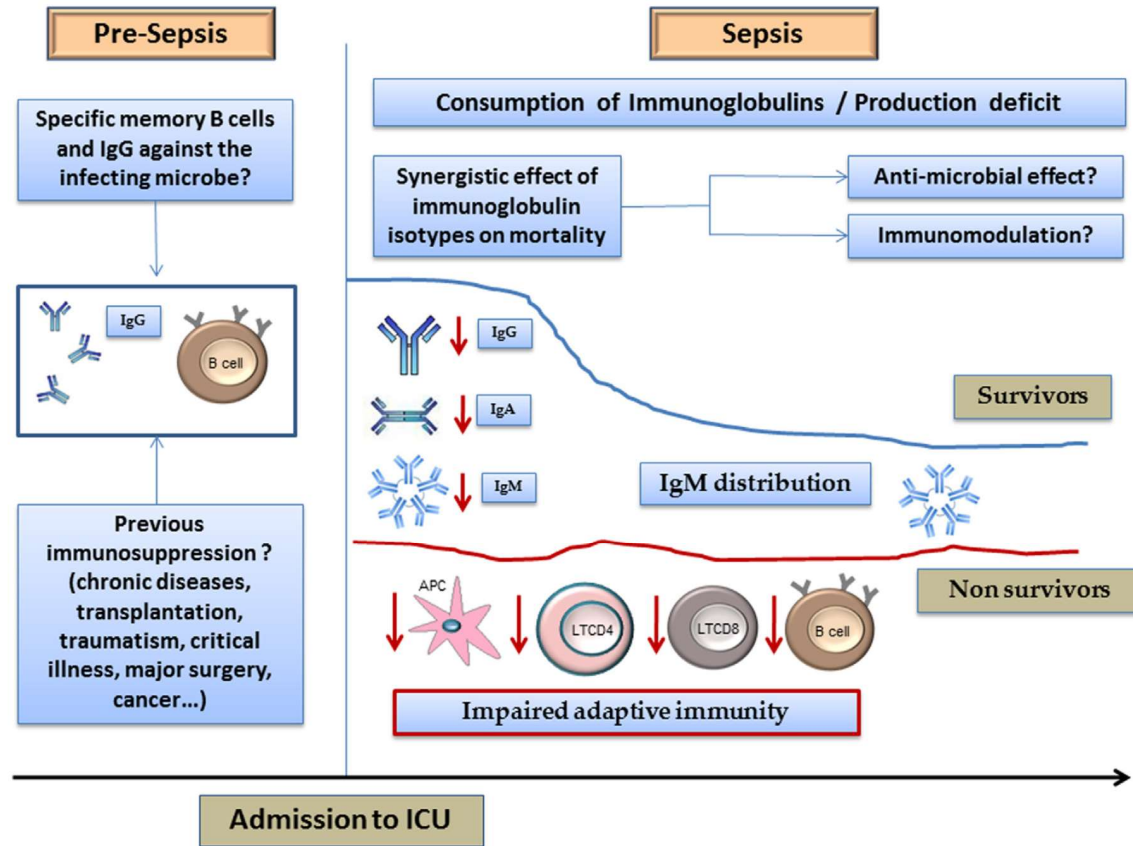


Endogenous immunoglobulins and sepsis: New perspectives for guiding replacement therapies



Jesús F. Bermejo-Martin^a, Evangelos J. Giamarellos-Bourboulis^{b,*}

J.F. Bermejo-Martin, E.J. Giamarellos-Bourboulis / International Journal of Antimicrobial Agents 46 (2015) S25–S28



Conclusions

Immunoglobulin levels may have a different impact on the mortality risk of sepsis patients based on their severity

In patients with moderate organ failure, the simultaneous presence of low levels of IgG, IgA and IgM is a robust predictor of both acute and post-acute mortality

These findings should be taken into account in the design / result analysis of clinical trials with IVIG in sepsis

Profiling levels of specific antibodies / function could be key





Raquel Almansa Nadia García Alicia Ortega

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bio·sepsis

σήψις



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