SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

Gruppo di studio SIAARTI
Infezioni e Sepsi in Terapia Intensiva
SIAARTI
PRO VITA CONTRA DOLOREM SEMPER

MODENA MICU INTENSIVE CARE UNIT 2

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Immunoglobuline: chimere o realtà ?

slides and discussion
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Disclosures

POTENTIAL CONFLICT OF INTEREST
Unrestricted grants, lectures, advisory boards, etc.

Astra Zeneca
Baxter
Biotest
Eli-Lilly
CSL-Behring
Kedrion
MSD
Novartis
NovoNordisk
Orion Pharma
Pfizer
Thermofisher

I trust
in PHYSIOLOGY & EBM,
but the latter is more ‘voluble’,
particularly in these days

Adjunctive & Immune Therapies in Sepsis:

No, of course….

SPECIFIC ADJUNCTIVE THERAPIES & SSC GUIDELINES

	2004	2008	2012	2016
STEROIDS	shocked	refractory shock	refractory shock	refractory shock
TIGHT GLYCEMIC CONTROL (<150 mg/dl)				
rhAPC				
ANTITHROMBIN				
IMMUNOGLOBULINS	pediatric	pediatric		
BLOOD PURIFICATION	Not mentioned	Not mentioned	Not mentioned	
SELENIUM	Not mentioned	Not mentioned		

Adjunctive Therapies in Sepsis: Yes or No ?

No, of course….But

ARE ALL THE PATIENTS WITH SEPTIC SHOCK SIMILAR ?

PREDISPOSITION:	Pre-existing illness, genetic polymorphisms	Difficult Patient
INSULT:	Site of infection, type of infection, virulence and sensitivity of infecting pathogens;	Difficult Micro-organisms Or Site
RESPONSE	SIRS, other signs of sepsis, activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR)	Difficult Immune Inflammatory Response
ORGAN DYSFUNCTION	Time and number of failing organs	

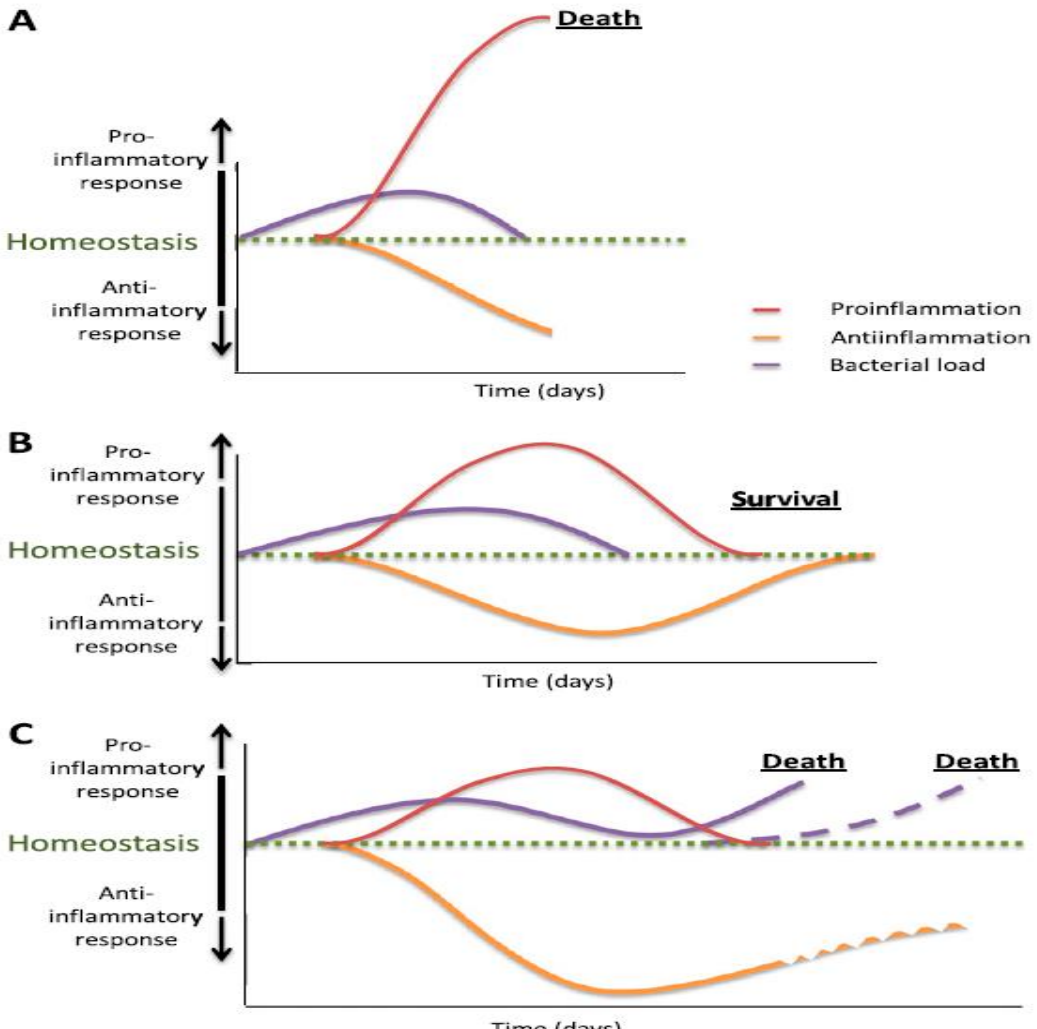
INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

Immunotherapy for the Adjunctive Treatment of Sepsis: From Immunosuppression to Immunostimulation
Time for a Paradigm Change?
Am J Respir Crit Care Med Vol 187, Iss. 12, pp 1287–1293, Jun 15, 2013

The inflammatory-immune response may vary and depends on

@ Microorganism(s) load and virulence

@ Host genetic factors and comorbidities



Healthy young adult with bacteremia by N. Meningitides/S. Pyogen/ S. Pneumonia:

Overwhelming proinflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure

Healthy young adult with CAP responsive to Abx :

adequate proinflammatory re-sponse, combined with an adequate non-sustained antiinflammatory response to pre-vent tissue damage

Patient with breakthrough infection after first sepsis :

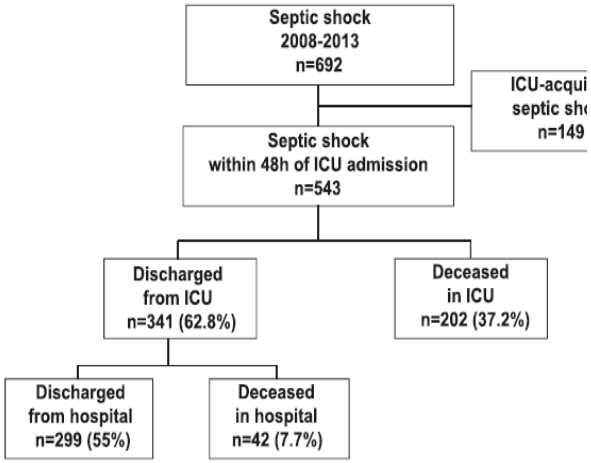
Proinflammatory response combined with a pronounced or sustained anti inflammatory state with persisting bacterial or secondary (opportunistic) infections

Annals of Intensive Care (2015) 5:16

Timing and causes of death in septic shock

Fabrice Daviaud[1,2], David Grimaldi[1,2,3], Agnès Dechartres[2,4], Julien Charpentier[1], Guillaume Geri[1,2], Nathalie Marin[1], Jean-Daniel Chiche[1,2,3], Alain Cariou[1,2], Jean-Paul Mira[1,2,3] and Frédéric P...[1,2,3]*

SEPTIC SHOCK
Timing of Death



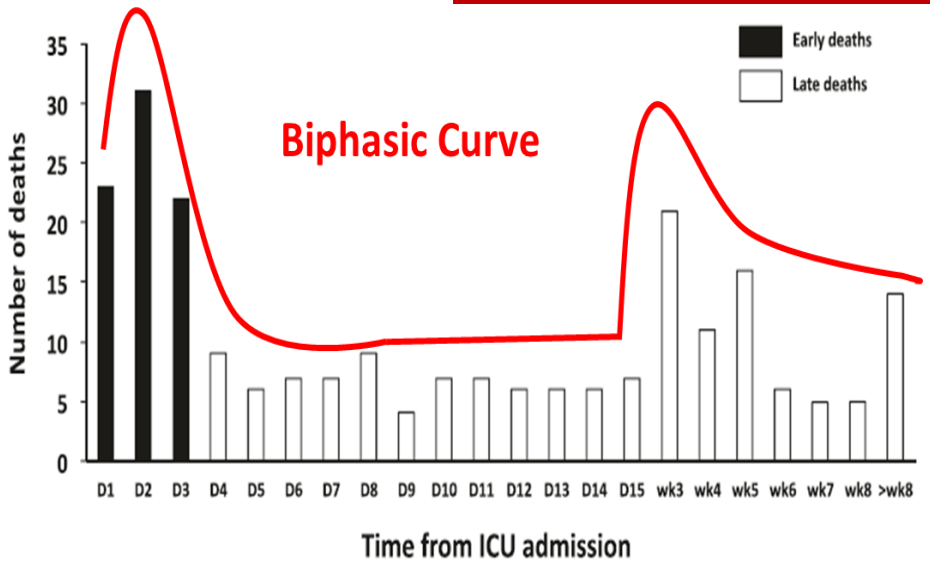
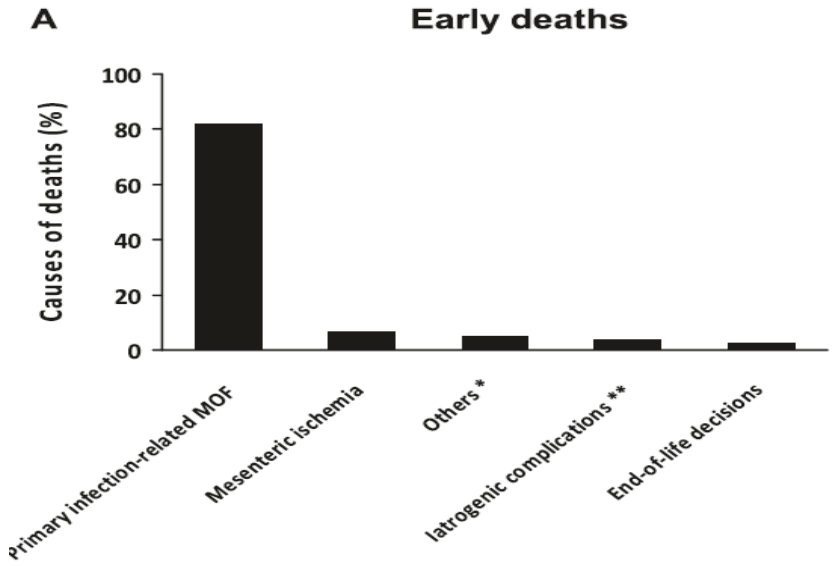
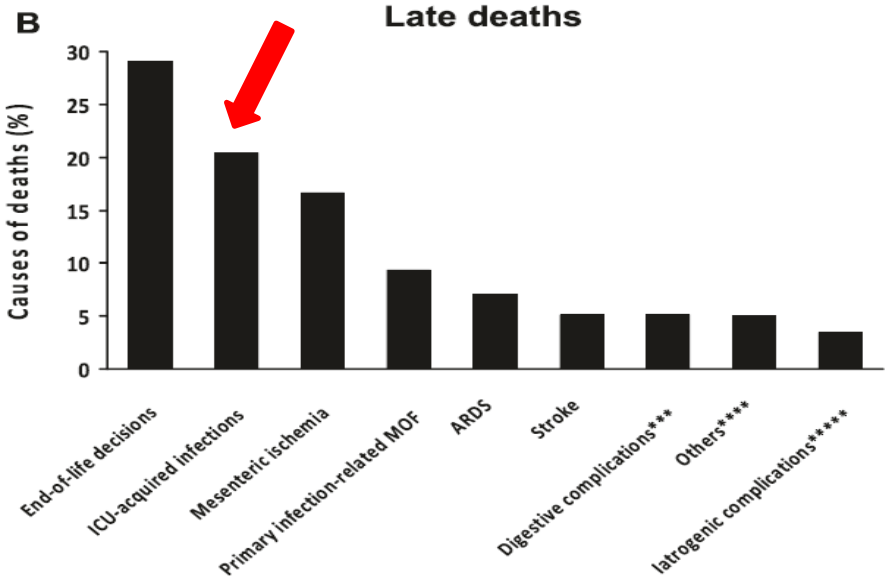


Fig. 2 Distribution of deaths according to time from ICU admission. Numbers of deaths are represented per day during the first 2 weeks and per week thereafter. Early (≤3 days) and late (>3 days) deaths occurred in 78 (32 %) and 166 (68 %) patients, respectively





IMMUNOGLOBULINS

CLINICAL EVIDENCES

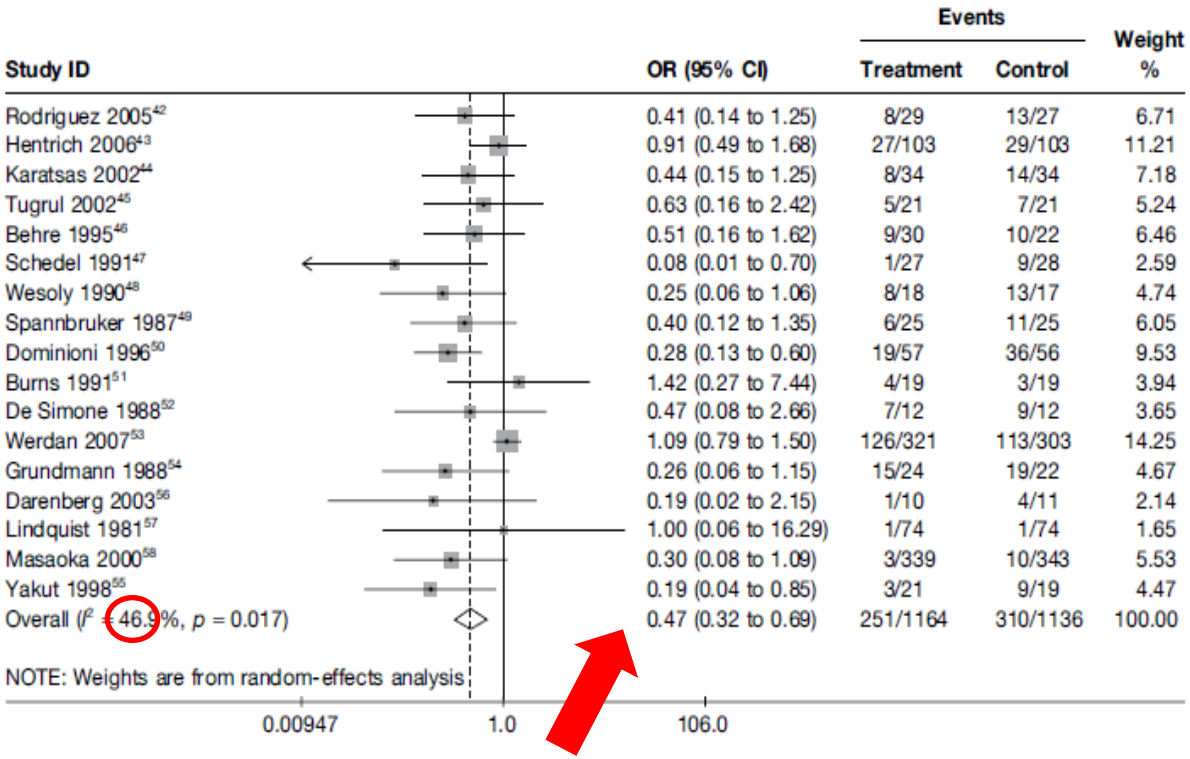


FIGURE 9 Forest plot for random-effects model using inverse variance weights – IVIG and IVIGAM versus control.

- design: RCT
- setting: critical-care setting
- participants: adult patients with severe sepsis or septic shock
- intervention: any standard polyclonal IVIG or immunoglobulin (IgM)-enriched polyclonal IVIG (IVIGAM) compared with no intervention, placebo or another standard polyclonal IVIG or IVIGAM preparation
- outcome measures: all-cause mortality, all-cause mortality reported by subgroup and adverse events.

17 RCT

Heterogeneity:
- Type of Ig
- Type of control (Albumin)
- Dose and duration
- Quality of the study
- Setting (ICU vs No ICU)

Meta-analysis indicate that Ig therapy may reduce mortality of adult patients with severe sepsis or septic shock. Indeed, the low quality of the RCTs analyzed and the high heterogeneity in the study characteristics hinder significantly the reliability of the results observed.

Soares et al. Health Technology Assessment 2010
Alejandra et al. Cochrane Database Syst Rev. 2013
Busani et al. Minerva Anestesiol 2016

Ig and GUIDELINES

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

J. IMMUNOGLOBULINS

1. **We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).**

@ Most IVIg studies are small and some have a high risk of bias

@ The statistical information that comes from the high-quality trials does not support a beneficial effect of polyclonal IVIg.

@ Subgroup effects between IgM-enriched and non-enriched formulations reveal significant heterogeneity.

@ The low certainty of evidence led to the grading as a weak recommendation.

IMMUNOGLOBULINS

Oda et al. Journal of Intensive Care 2014, 2:55
http://www.jintensivecare.com/content/2/1/55

JOURNAL OF INTENSIVE CARE

GUIDELINE Open Access

The Japanese guidelines for the management of sepsis

Shigeto Oda[1*], Mayuki Aibiki[2], Toshiaki Ikeda[3], Hitoshi Imaizumi[4], Shigeatsu Endo[5], Ryoichi Ochiai[6], Joji Kotani[7],

Immunoglobulin

CQ1: What is the indication for immunoglobulin administration in septic patients?

A1: Currently, there is insufficient evidence suggesting that immunoglobulin administration improves the prognosis of adult patients with sepsis (2B). However, with a reduced duration of mechanical ventilation and improvement in ICU survival, administration of immunoglobulin may be considered (2C).

CQ2: When should immunoglobulin be administered?

A2: Immunoglobulin administration may be considered in the early stage of sepsis (2C).

CQ3: What should be the dose and duration of immunoglobulin administration?

A3: A total immunoglobulin dose of ≥0.2 g/kg should be administered for ≥3 days (2C).

CQ4: What should be given particular attention in the selection of immunoglobulin preparation?

A4: Use of a complete-molecular-type preparation is suggested (2C).

Prevention, Diagnosis, Therapy and Follow-up Care of Sepsis February 15th 2010

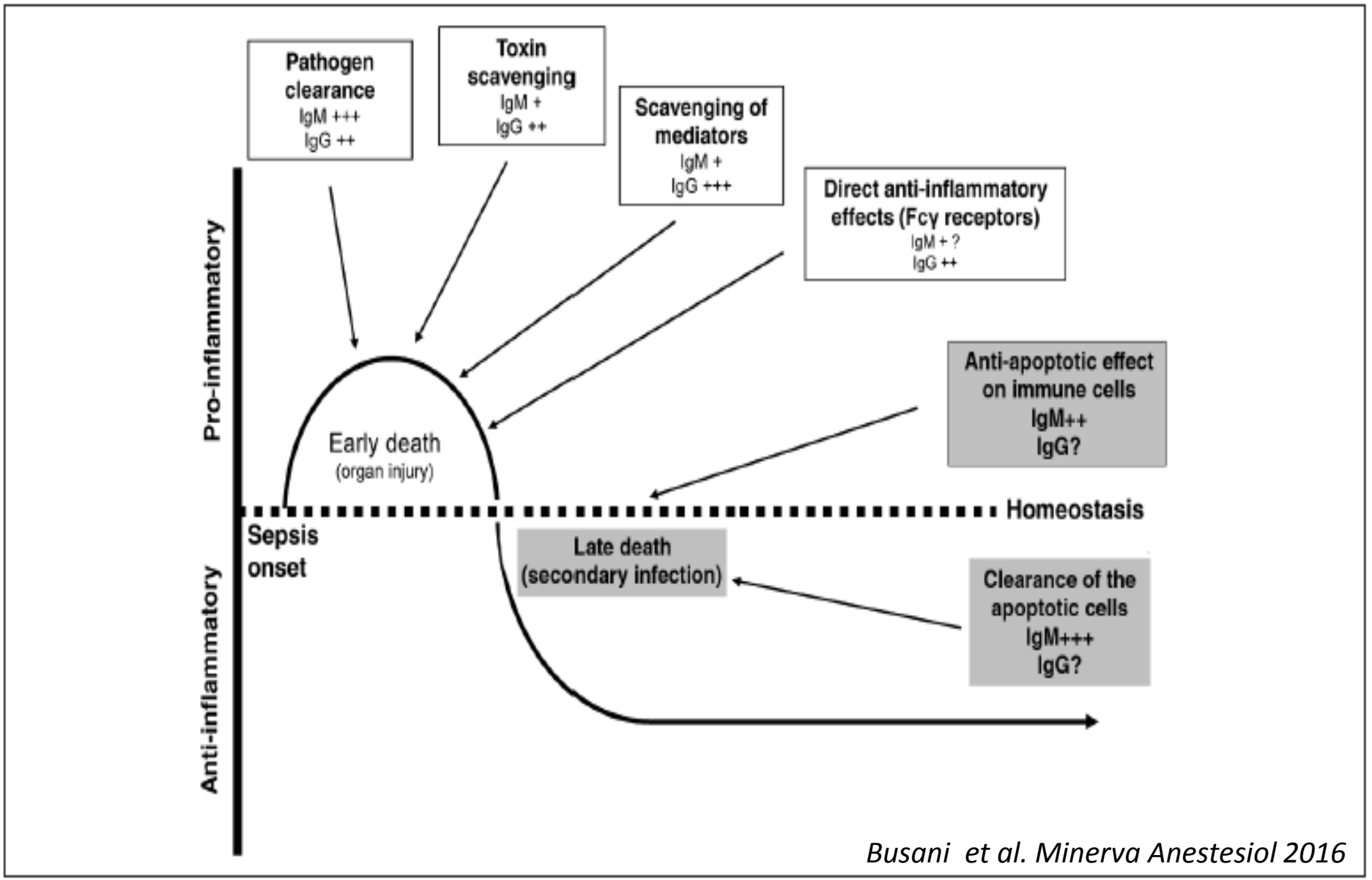
1st revision of S-2k guidelines of the German Sepsis Society (*Deutsche Sepsis-Gesellschaft e.V. (DSG)*) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (*Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)*)

- The use of ivIgGAM may be ***considered*** for treatment of adult patients with severe sepsis or septic shock.

→ **Recommendation level C** (evidence level Ia for [322])

Comment: *The experts in the field are not in agreement about this recommendation. The recommendation rests on a meta-analysis from the year 2007 [322]. However, a further meta-analysis published in 2007 in the same volume of Crit Care Med [323], which employed a different trial quality evaluation methodology and produced different results, recommends that a high-quality, adequately powered and transparently presented study be conducted in order to determine the significance of I.V. immunoglobulin therapy.*

Ig: HOW IT WORKS ?



Busani et al. Minerva Anestesiol 2016

Figure 1.—Possible mechanism of action of Ig in the proinflammatory and immunosuppressive phases of sepsis.

IMMUNE DYSFUNCTION

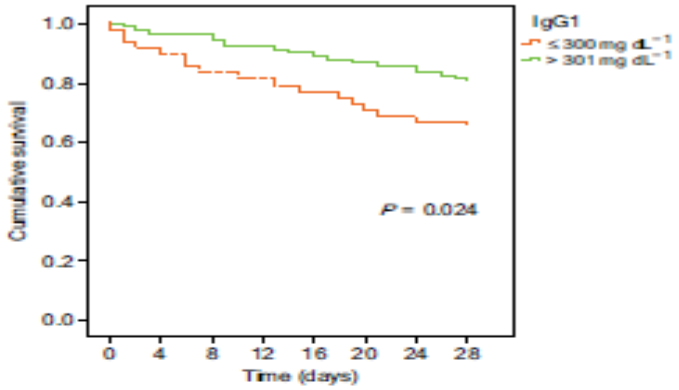
1. 172 severe sepsis and septic shock patients
2. Ig at sepsis diagnosis

Original Article | Journal of INTERNAL MEDICINE

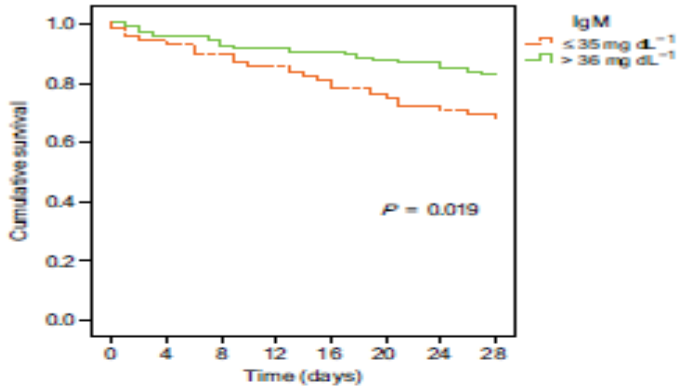
doi: 10.1111/joim.12265

Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis

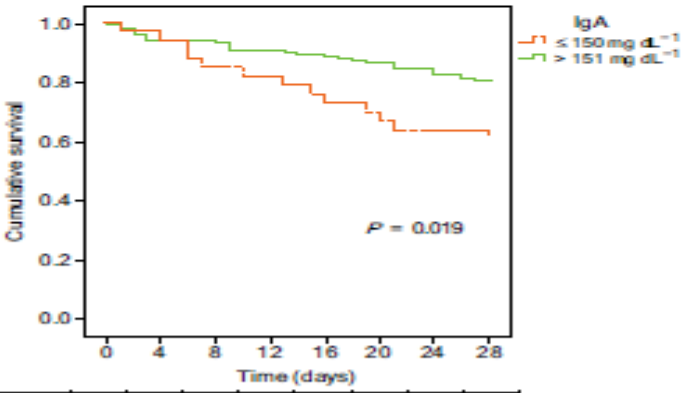
J. F. Bermejo-Martín[1,*], A. Rodriguez-Fernandez[2,*], R. Herrán-Monge[3], D. Andaluz-Ojeda[1,4], A. Muriel-Bombín[3], P. Merino[3], M. M. García-García[3], R. Citores[4], F. Gandía[4], R. Almansa[1], J. Blanco[3,5] & for the GRECIA Group (Grupo de Estudios y Análisis en Cuidados Intensivos)[†]



≤300 mg dL⁻¹	48	43	40	39	37	32	34	31
>301 mg dL⁻¹	124	119	117	114	110	108	104	100



≤35 mg dL⁻¹	67	63	61	58	53	51	48	45
>36 mg dL⁻¹	104	99	96	95	94	91	88	85



≤150 mg dL⁻¹	33	31	28	27	24	22	21	19
>151 mg dL⁻¹	138	131	129	126	123	120	116	110

Fig. 1 *Kaplan–Meier curves showing the impact of immunoglobulin levels on survival. Number of surviving (censored) patients over time is shown at the bottom of each graph.*

IMMUNE DYSFUNCTION
Ig and Free light Chains

Can Concurrent Abnormalities in Free Light Chains and Immunoglobulin Concentrations Identify a Target Population for Immunoglobulin Trials in Sepsis?

Crit Care Med 2017;

Manu Shankar-Hari, PhD, MSc, FRCA, FFICM[1,2]; Mervyn Singer, MD, FRCP, FFICM[3]; Jo Spencer, PhD[1]

@ Light chains κ and λ (immunoglobulin constituents) circulate independently in blood as free light chains.

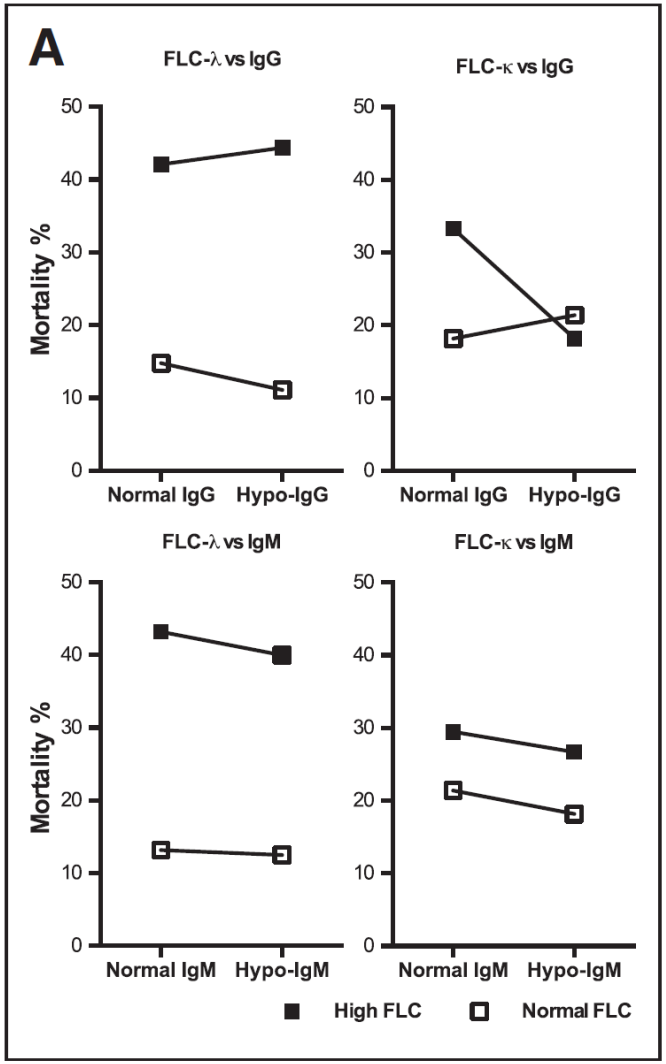
@ Hp: Could abnormalities in free light chain and immunoglobulin levels identify a high risk of death sepsis ?

@ 101 patients with sepsis (74% survived) on ICU days 1, 3, and 7: Serum total free light chain, immunoglobulin G, A, and M

@ **On ICU day 1, high free light chain λ and κ were seen in 46.5% and 75.3%**

@ **On ICU day 1, low immunoglobulin levels were observed in 45.5%.**

@ **Higher mortality only in patients with high FLCλ, irrespective of their hypo-IgG or hypo-IgM status**



Why IgM preparation ?

The importance of natural IgM: scavenger, protector and regulator

Michael R. Ehrenstein and Clare A. Notley

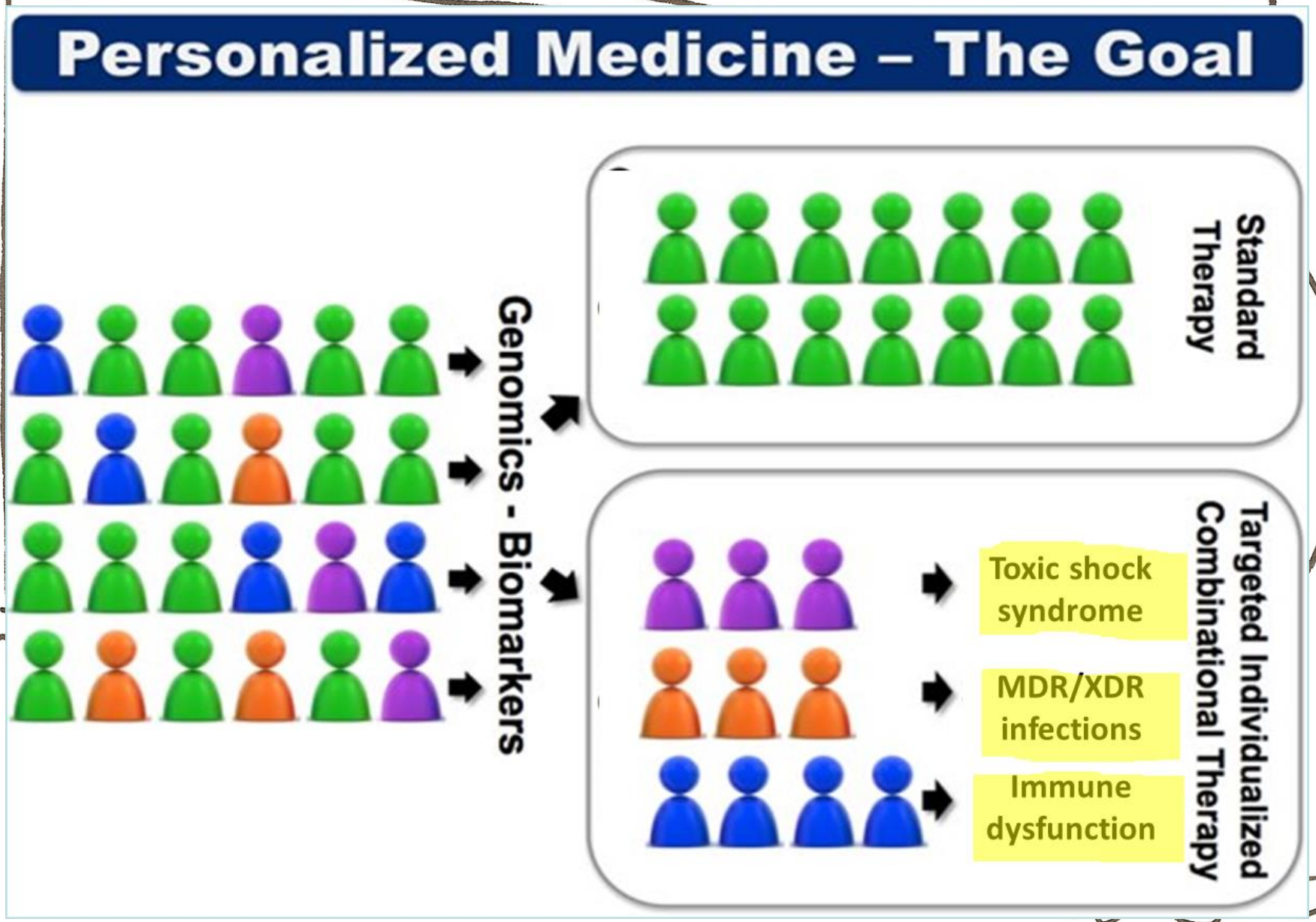
NATURE REVIEWS | IMMUNOLOGY
VOLUME 10 | NOVEMBER 2010 |

@ Natural IgM is the first to appear during ontogeny, the oldest and the only class of antibody present in all vertebrates
@ Immune IgM is the first antibody to be produced during immune response
@ IgM has low affinity but high reactivity to common components of invading microorganisms such as nucleic acids, phospholipids and carbohydrates.
@ IgM participates in diverse pathophysiologies including infection, B cell homeostasis, inflammation, autoimmunity and atherosclerosis.

Humoral immune response: anti-bacterial modes of action		IgM exhibits:
1. Increase of bacterial phagocytosis		100-fold higher phagocytosis-promoting activity compared to IgG [10]
2. Induction of bacterial lysis due to specific activation of complement on bacterial surfaces		1000-fold higher affinity towards C1q (first protein in the classical complement pathway) than IgG [11]
3. Neutralization of toxins		neutralization of antibiotic-induced endotoxin release [12]

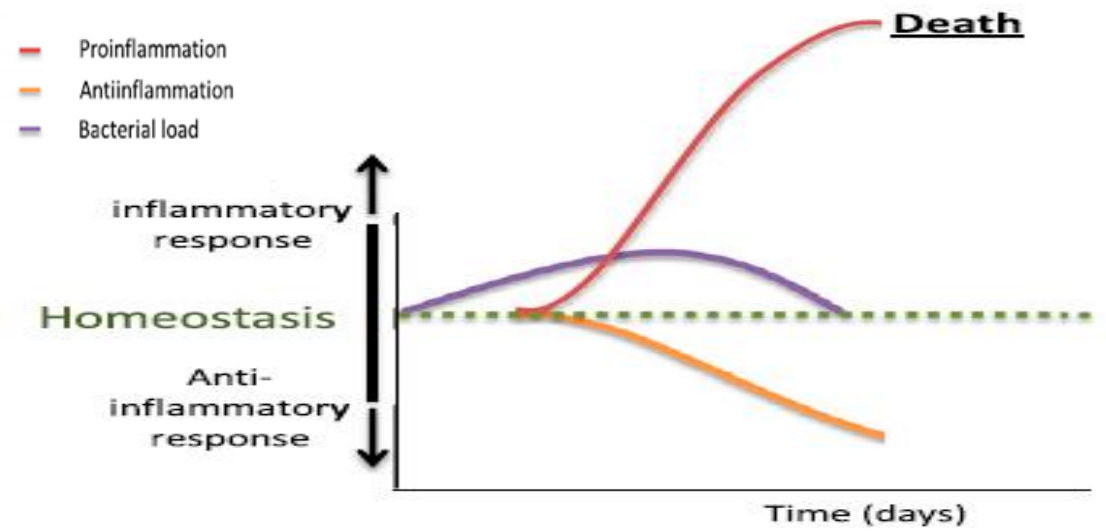
Fig. 1 The role of IgM in the humoral immune response

ARE ALL THE PATIENTS WITH SEPTIC SHOCK SIMILAR ?



Which patients may benefit from Ig therapy?

Pathobiology

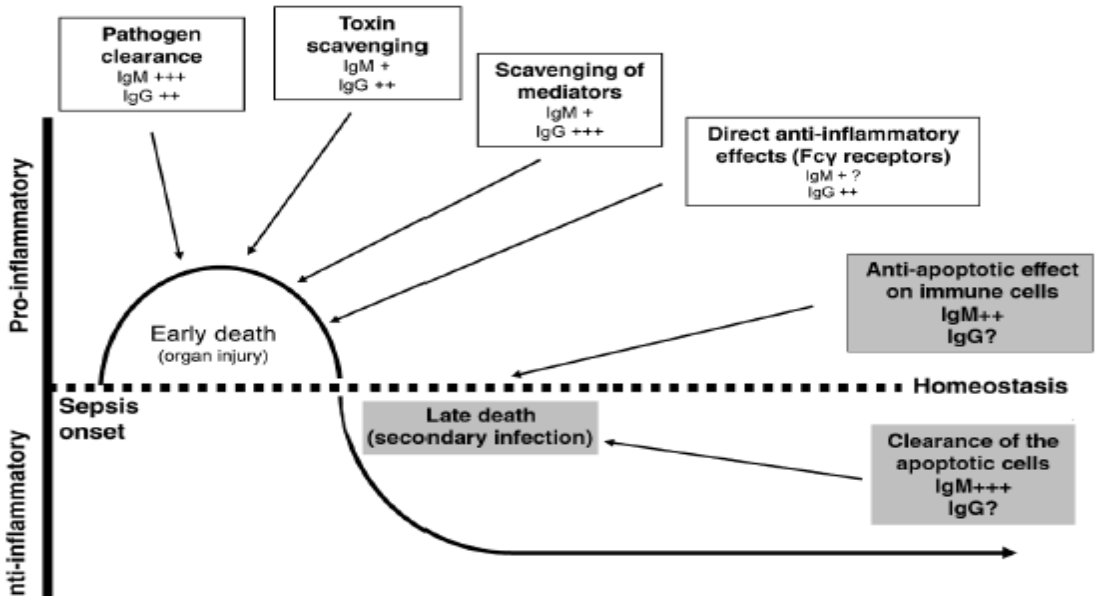


Clinical Scenario

Healthy adult with severe infection by Streptococcus spp: *Overwhelming pro-inflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure*

Mode of action

a) Pathogen lysis-phagocytosis
b) Direct Anti-inflammatory



IgM and Menigococcal Infection

Potential role of IgM-enriched immunoglobulin as adjuvant treatment for invasive meningococcal disease

Carlo Tascini[1], Fiorentino Fraganza[2], Francesca Salani[3], Emanuela Sozio[4], Marco Rossi[1], Francesco

Intensive Care Med
DOI 10.1007/s00134-017-4957-z

@ 111 cases of Invasive menigococcal disease (Tuscany region n = 53 cases and Naples n = 58 cases), October 2013 to December 2016
@ 35 patients with IgM (Naples) and 76 without IgM (Naples and Tuscany)
@ Death: 3% (1/35) IgM and 16% (12/76) No IgM
@ Severe complications: 6% (2/35 had amputation of the extremities) IgM and 12% (11/76) No IgM (5/11 amputation of the extremities and 6/11 hearing loss).

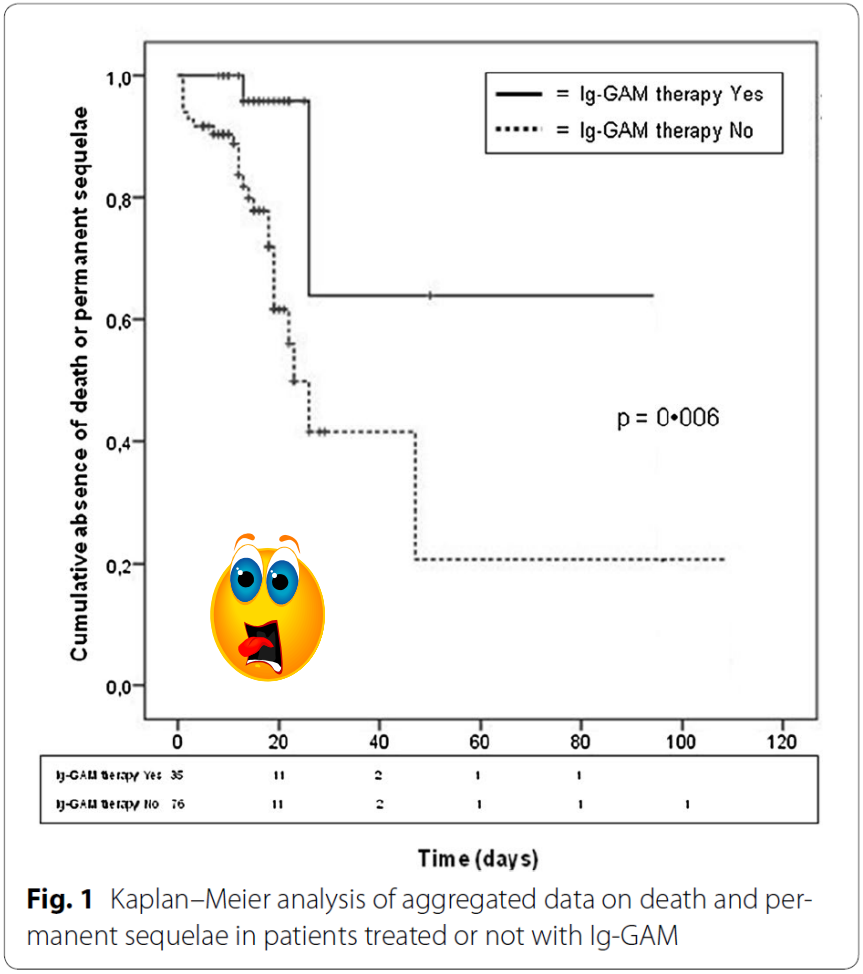


Fig. 1 Kaplan–Meier analysis of aggregated data on death and permanent sequelae in patients treated or not with Ig-GAM

In conclusion, our experience suggests that Ig-GAM adjuvant therapy might have a favourable impact on the overall outcome in patients with IMD. Prospective, randomized clinical trials are therefore warranted.

Severe Pneumonia: CIGMA RCT -Phase II Study

Intensive Care Med (2018) 44:438–448
https://doi.org/10.1007/s00134-018-5143-7

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 Dellinger[2], Henning Ebelt[3], Miguel Ferrer[4], Steven M. Opal[5], Mervyn Singer[6],

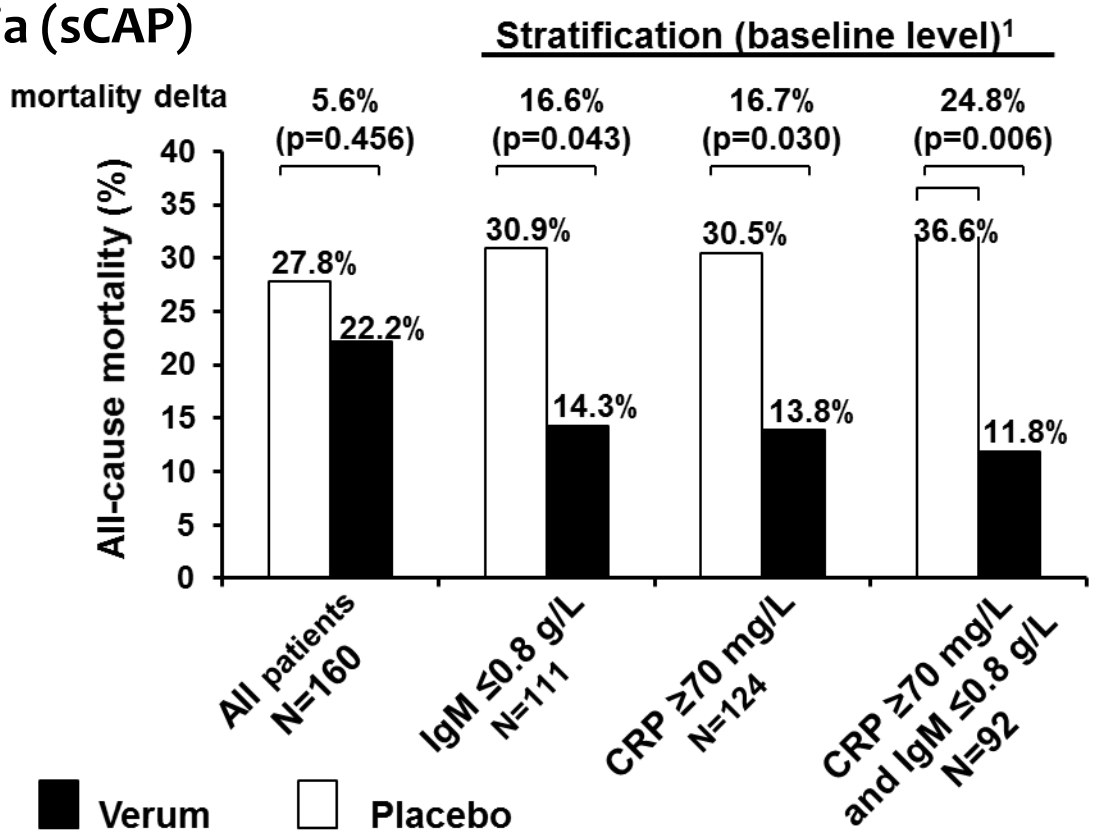
Objectives:

Efficacy and safety of a **novel polyclonal antibody preparation containing high IgM and IgA levels** in addition to IgG (verum) as adjunctive treatment to standard of care in **intubated and mechanically ventilated patients with severe community acquired pneumonia (sCAP)**

Patient number:
160 patients (verum: 81 patients, placebo: 79 patients)

Primary endpoint:
VFDs (mean 11.0 vs. 9.6 days, respectively, p=0.173)

Mortality results:
Pronounced mortality advantage in selected subgroups representing the majority of the study population.



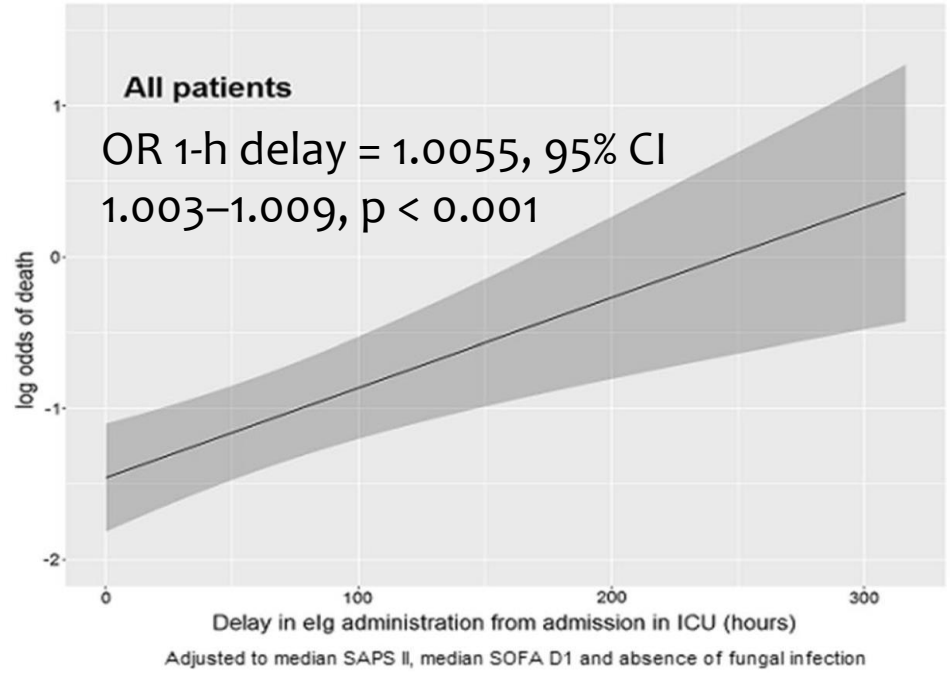
IgM and TIMING

RESEARCH Open Access

Effects of the timing of administration of IgM- and IgA-enriched intravenous polyclonal immunoglobulins on the outcome of septic shock patients

Giorgio Berlot[1*], Claudio Michele Vassallo[2], Nicola Busetto[1], Margarita Nieto Yabar[1], Tatiana Istrati[1],

@ Single center retrospective analysis over 17 years
@ 355 patients with septic shock treated by IgM
@ Overall ICU mortality rate 30%



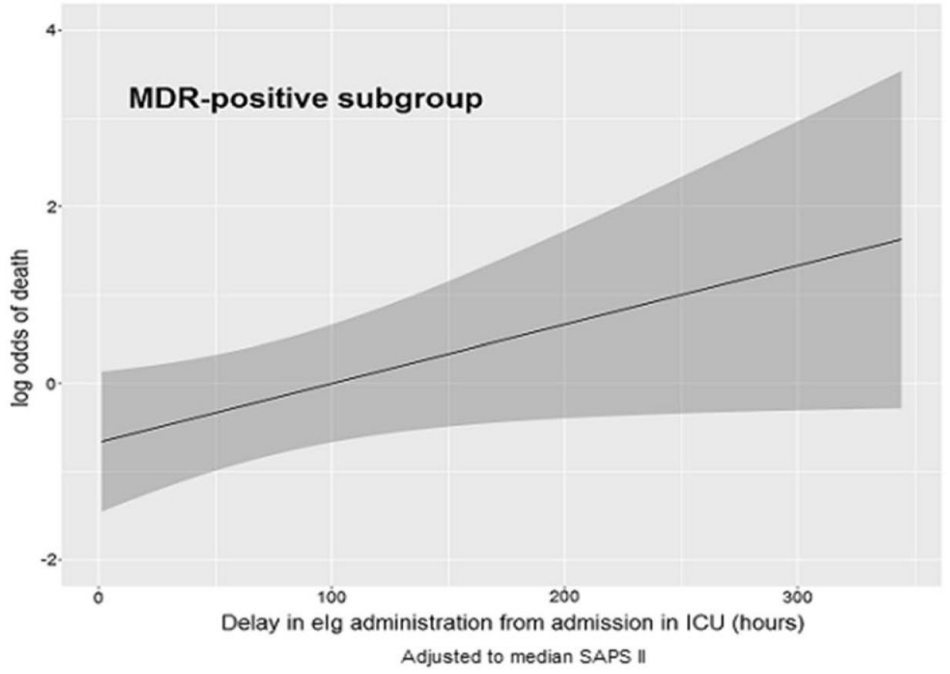
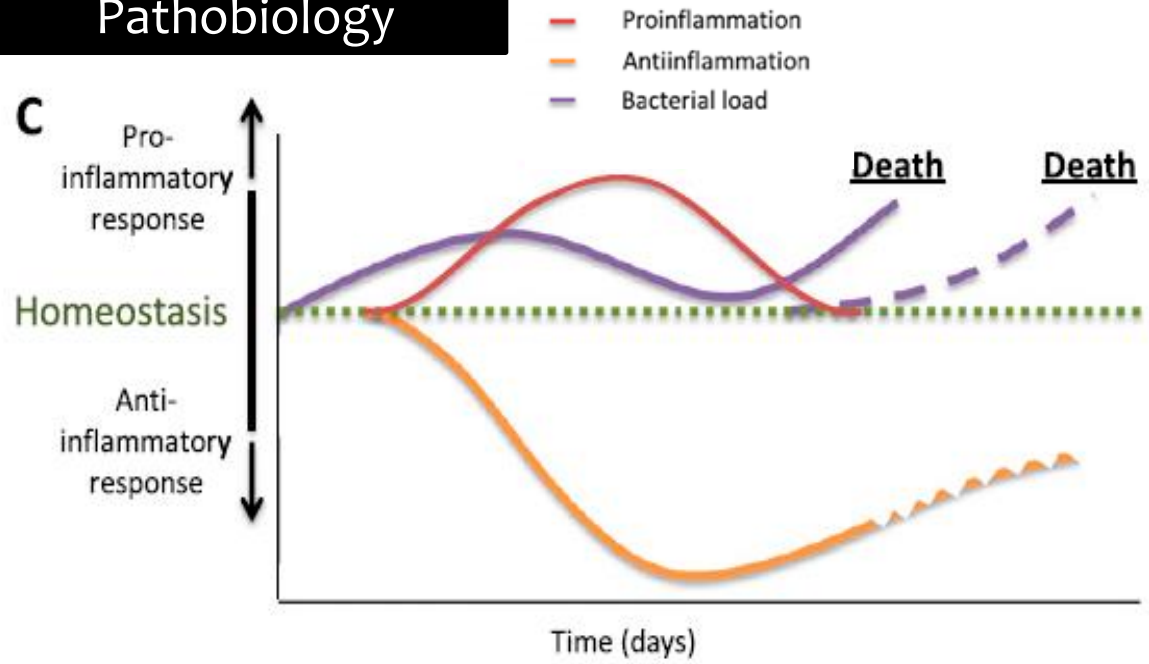


Fig. 2 Logit function from the multivariable logistic regression model in the group of all patients (right) showing the effect of delay in administration of IgM-enriched immunoglobulins on the probability of in-ICU death (solid line) with 95% confidence interval (gray area) adjusted to median value of SAPS II, SOFA D1 and without fungal infection. Comparison with logit functions from the multivariable logistic regression model for MDR-positive patients adjusted for median value of SAPS II (left). ivIgGAM, intravenous IgM- and IgA-enriched immunoglobulins; ICU, intensive care unit; MDR, multidrug resistant; SAPS II, Simplified Acute Physiology Score; SOFA D1, sequential organ failure assessment calculated the first day of administration of ivIgGAM

Which patients may benefit from Ig therapy?

Pathobiology

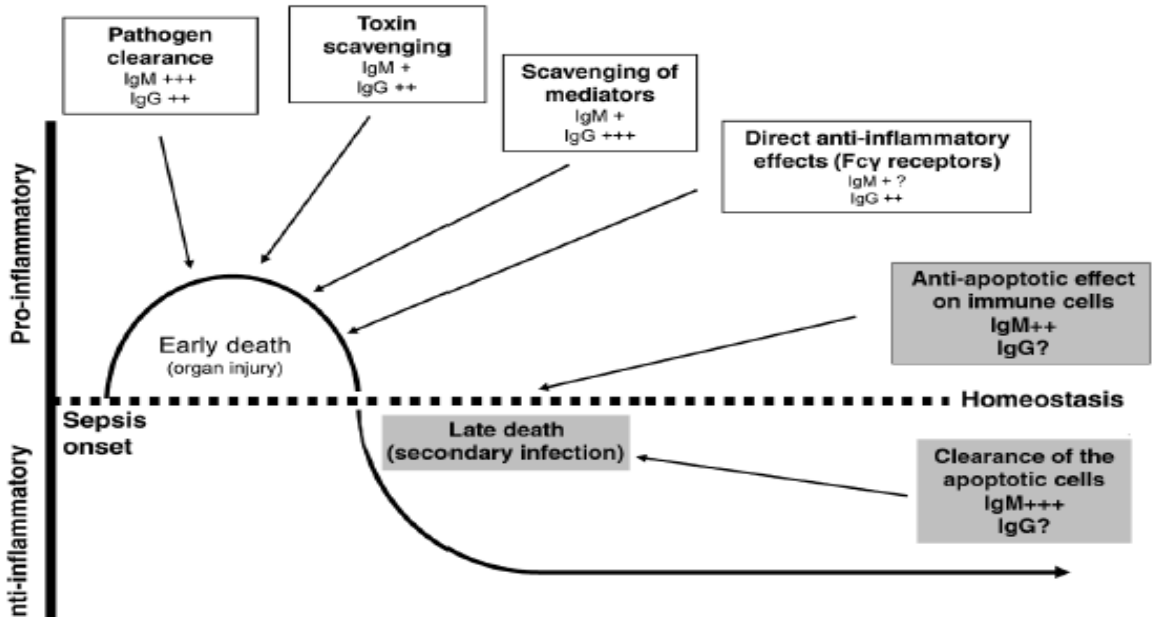


Clinical Scenario

Patient with breakthrough infection after first sepsis *: pronounced and/or sustained anti inflammatory state with persisting bacterial or secondary (opportunistic) infections*

Mode of action

a) Pathogen lysis /phagocytosis
b) Direct Anti-inflammatory
c) Immune-modulation (?)



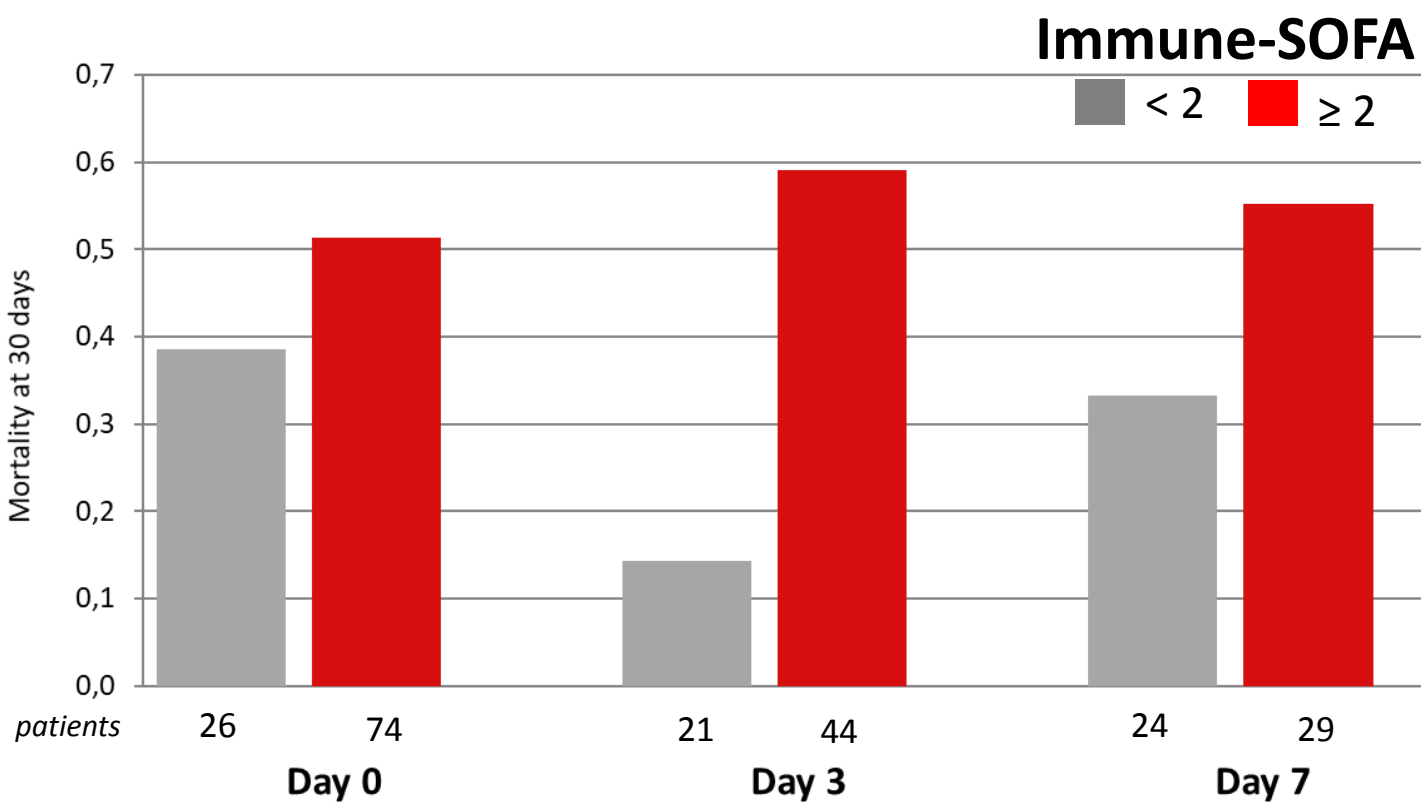
IMMUNO-MONITORING

ICU–Modena University
2016-2017
100 septic shock

Immune System	0	1	2	3	4
Monocyte HLA-DR (mAb) or Lymphocytes (n/mcl) or HSV/CMV reactivation	8000 or > 1200 or NO	6-8000 or 900—1200 or NO	5000-8000 or 600-900 or YES/NO	2500- 5000 or 400-600 or YES	<2500 or < 400 or YES

ImmunoMonitoring
HLA-DR*; CMV;
Lympho
DAY-0 (shock onset)
DAY-4
DAY-7
DAY-14

*** Not available**
WEND



IMMUNE DYSFUNCTION & MDR infections

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

Lancet Infect Dis 2013; 13: 260–68

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

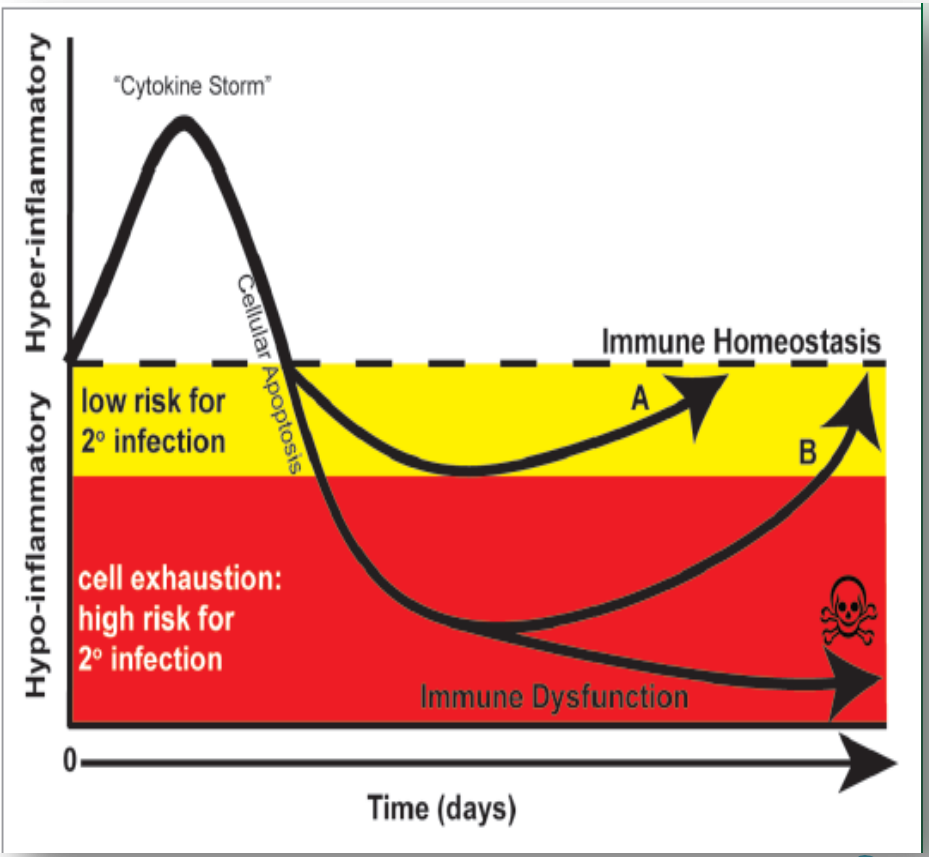


Table: Potential biomarker and clinical-laboratory findings

Decreased monocyte HLA-DR expression
Persistent severe lymphopenia
Increased PD-1 or PD-L1 expression
Decreased TNFα production in stimulated blood
Increased T-regulatory cells
Infections with relatively avirulent or opportunistic pathogens (*Enterococci* spp, *Acinetobacter* spp, *Candida* spp, etc)
Reactivation of cytomegalovirus or HSV
Elderly patients with malnutrition and multiple comorbidities

Ig Therapy & MDR infections

ORIGINAL ARTICLE

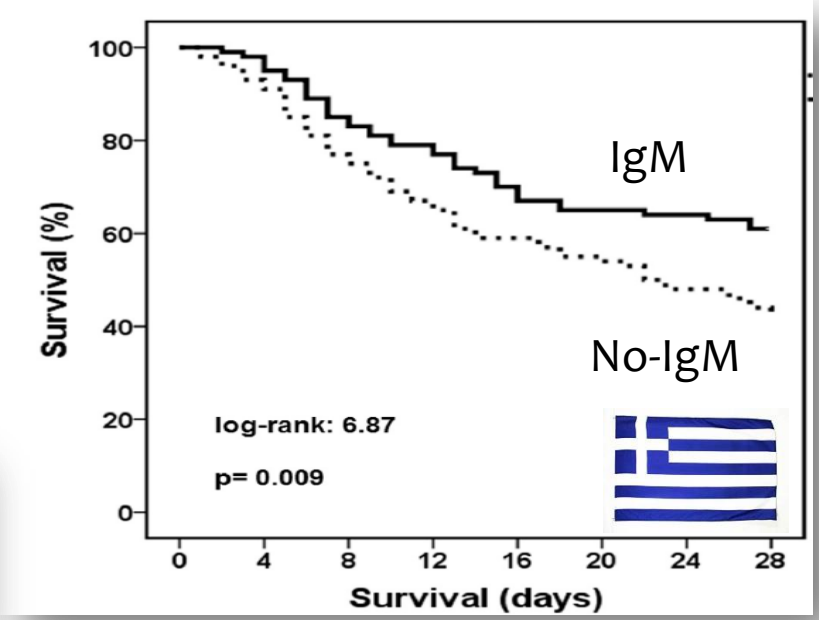
Improving outcomes of severe infections by multidrug-resistant pathogens with polyclonal IgM-enriched immunoglobulins

Clin Microbiol Infect 2016; **22**: 499–506

E. J. Giamarellos-Bourboulis[1], N. Tziolos[1], C. Routsi[2], C. Katsenos[3], I. Tsangaris[4], I. Pneumatikos[5], G. Vlachogiannis[6],

- Retrospective case-control study: **200 patients** (100 with and 100 without IgGAM) with microbiologically confirmed **severe infections by MDR Gram-negative bacteria** acquired after ICU admission.

The present study provides promising data supporting the use of polyclonal IgM-enriched immunoglobulin preparations as adjunctive of antimicrobial treatment for the management of severe infections caused by MDR Gram-negative bacteria.

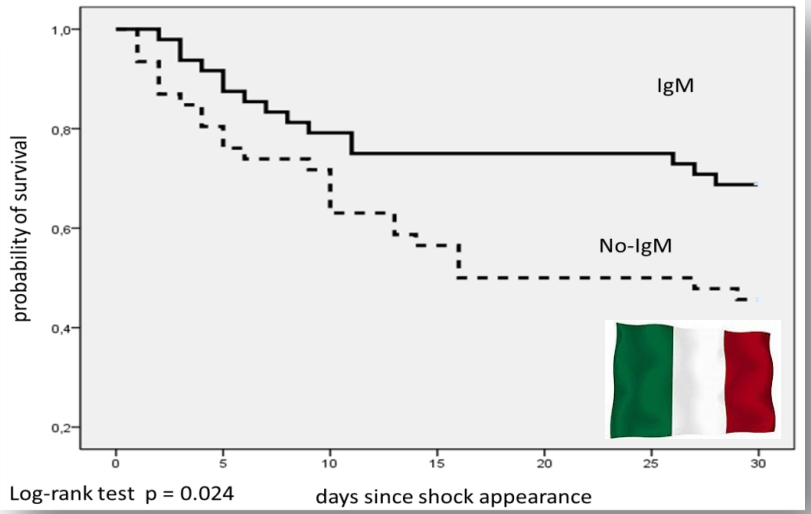


Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria: Risk Factors and Impact of Sepsis Treatments

Journal of Intensive Care Medicine

Stefano Busani, MD[1], Giulia Serafini, MD[1], Elena Mantovani, MD[1],

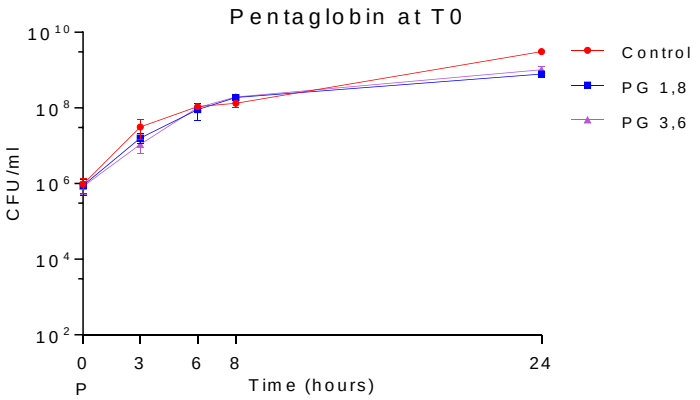
- Retrospective analysis of **94 ICU patients** with **septic shock by MDR bacteria**
- All **therapeutic interventions were similar** between ICU survivors and no-survivors, **except for IgM preparation** provided more frequently in survivors group (P < .05)
- IgM analysis by propensity score-based matching (1:1): 74 patients 37 IgM vs 37 no IgM

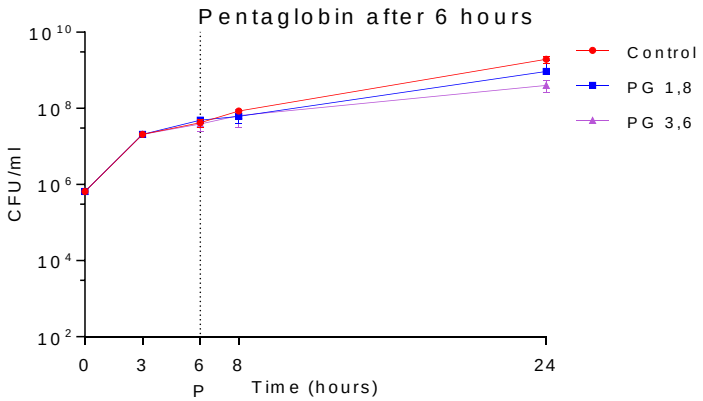


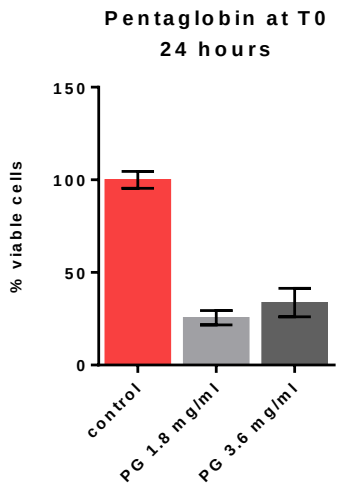
retrospective study showed that in patients with septic shock caused by MDR bacteria, history of cancer and infection sustained by *A baumannii* increase the risk of mortality and that standard sepsis treatments do not seem to provide any protective effect. Adjunctive therapy with IgM preparation seems to be beneficial, but further appropriate studies are needed to confirm the results observed.

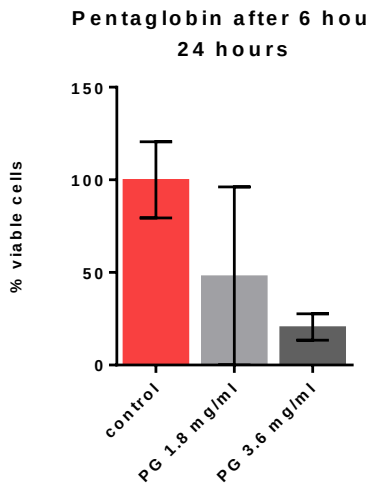
Potential antimicrobial activity of Pentaglobin in Time-Kill experiments

***A. baumannii* 18C31**









A delay in growth was observed only with *A. baumannii* 18C31 strain after 24 hours of exposure to Pentaglobin

IMMUNE DYSFUNCTION

@ **12 heart recipients with hypo IgG** (<500 mg/dL) **received IVIG** (2 doses of 200 mg/kg then up to 5 additional doses of 300 mg/kg to maintain IgG >750 mg/dL. IgG)

@ Matched with **13 recipients with post- transplant hypo IgG not receiving IVIG** and with **11 recipients wIthoutHGG during the same study period.**

@ The primary outcome measure was development **of severe infection during the study period**.

Early intravenous immunoglobulin replacement in hypogammaglobulinemic heart transplant recipients: results of a clinical trial

Transpl Infect Dis 2016; 18: 832–843

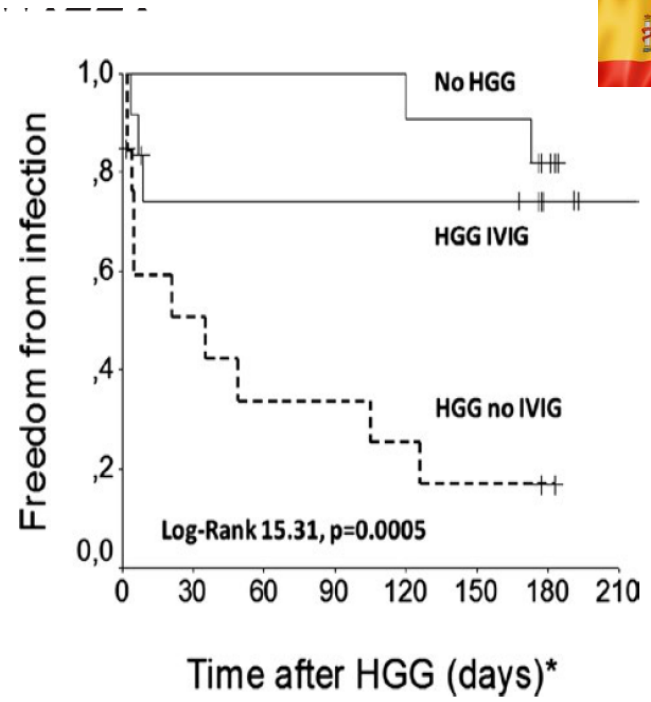


FIGURE 4 Kaplan-Meier curves showing the freedom from severe infection during follow-up. Group "HGG IVIG"=12 patients treated with IVIG during the clinical trial. Group "HGG no IVIG"=13 patients with HGG who were not treated with IVIG. Group "No HGG"=11 patients who were not found to have HGG during follow-up. HGG=IgG <500 mg/dL during the post-transplantation screening. In non-HGG patients, time after the study point during the screening phase in which the lowest IgG levels were observed after transplantation. HGG, hypogammaglobulinemia; IVIG, intravenous immunoglobulin; IgG, immunoglobulin G

Which patients may benefit from Ig therapy?

OPEN QUESTIONS:
(also for designing appropriate trials)

@ Identification by specific immune-biomarkers (e.g. FLC or Ig or Lympho) ?

@ Time for administration : what's early ? Always early ?

@ Dosages

i) Different dosages in different phenotypes ?

ii) Therapy Duration: which approach ?

@ Role of Ig as pre-emptive therapy or in infections W/O sepsis

New ongoing Trials:
PERFORM/SORRISO, PEPPER, FAT, PENTALLO, Trimodulin phase III

Which patient may benefit from ?

IgM Use TO-PIRO score

Use of IgM-Enriched Intravenous Immunoglobulin in Severe Bacterial Infections: TO-PIRO SCORE from an Expert Consensus

Francesco Giuseppe De Rosa[1], Silvia Corcione[1], Carlo Tascini[2], Daniela Pasero[3], Andrea Rocchetti[4], Massimo Massaia[5], Paolo Solidoro[6]*, Massimo Girardis[7]*

Items	Criteria	Score
Predisposition	• Uncontrolled cancer	1
	• Colonization by MDR bacteria and/or candida	1
	• Neutropenia or immunosuppressive drugs (monoclonal/steroids/micophenolate/cyclosporin) or allogenic stem cell transplant or splenectomy	2
Insult	• Necrotizing fasciitis, invasive meningococcal/ pneumococcal diseases, *Streptococcus pyogenes*; CA-MRSA	5
	• MDR infections or nosocomial infections	2
	• Secondary/tertiary peritonitis	2
Response	• Leucocytes < 600/ul	2
	• IgM < 60 mg/dl	2
	• PCT > 10 ng/l and CRP >20 mg/dl	1
	• PCT > 100 ng/l ***or*** endotoxin > 0.6 ***or*** IL-6>1000 pg/ml ***or*** adrenomedullin > 4 nm/l ***or*** presepsin 1400 ng/l	2
	• Disseminated intravascular coagulation	1
Organ	• Septic shock	3
	• Sepsis with ≥ 1 organ failure	2
	• Infection without sepsis	1

TO-PIRO SCORE	Recommendation	Timing
TO-PIRO ≤ 5	The use of IgM-Ig may be beneficial according to clinical scenario	-
TO-PIRO > 5-10	The use of IgM-Ig is suggested: evidence suggest a potential benefit in these patients	Administered within 24h from clinical presentation
TO-PIRO >10	Use of IgM-Ig is strongly recommended: evidence showed a low mortality rate associated to the use of IgM-Ig	As soon as possible and within 6 h

IgM Use
TO-PIRO score

Validation of the score

@ Modena ICU
@ 60 Patients with septic shock (2014-2017) treated by IgM
@ TO-PIRO Score (without CID score)
  @ Overall Median (IQR) 9 (7-11)

@ Italian ICUs
@ 94 patients sepsis/septic shock treated by IgM
@ TO-PIRO Score
  @ Overall mean (SD) 8,7 (2,5)

Score	N patients	ICU Mortality
≤5	3	33%
5-10	40	43%
> 10	17	59%

Score	N patients	ICU Mortality
≤5	11	9 %
5-10	51	21 %
> 10	32	59%

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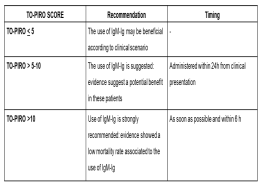
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico



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TO-PIRO >10	Use of IgM-Ig is strongly recommended: evidence showed a low mortality rate associated to the use of IgM-Ig	As soon as possible and within 1 h

Project SORRISO

Italian Registry on IgM use

(Cortesy of G. Berlot & M. Bixio)

Septic Shock
IgM protocol

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UNIVERSITAS STUDIORUM MUTINENSIS ET REGIENSIS
1175

MODENA ICU INTENSIVE CARE UNIT 2

Community Acquired
Septic Shock

Overwhelming shock
Noradrenaline > 0.4 mcg/kg/min
High endothelial dysfunction (CID score)
e.g. Necrotizing fasciitis, pnuemo/meningococcal

YES

IgM therapy (ASAP-HD)
Time: ASAP (within 3 hours)
Dose: 500 mg/kg/day (first day), then 250 mg/kg/day for 3-5 days or up to clinical improvement

NO

Immunosuppressed
Immunosup. Therapy (including long term CS use)
Neutropenic
Previous Abx therapy (30 days)
Significant comorbidities with multiple H admissions

YES

IgM therapy (12H-SD)
Time: 6-12 hours (Noradr > 0,1 mcg/kg/min)
Dose: 250 mg/kg/day for 3-5 days

NO

IgM therapy (24-SD-Conditional)
Time: 12-24 hours IF
- Noradr > 0,1 mcg/kg/min and not descaling
  AND/OR
- Significant or worsening CID score

Dose: 250 mg/kg/day for 3-5 days

YES

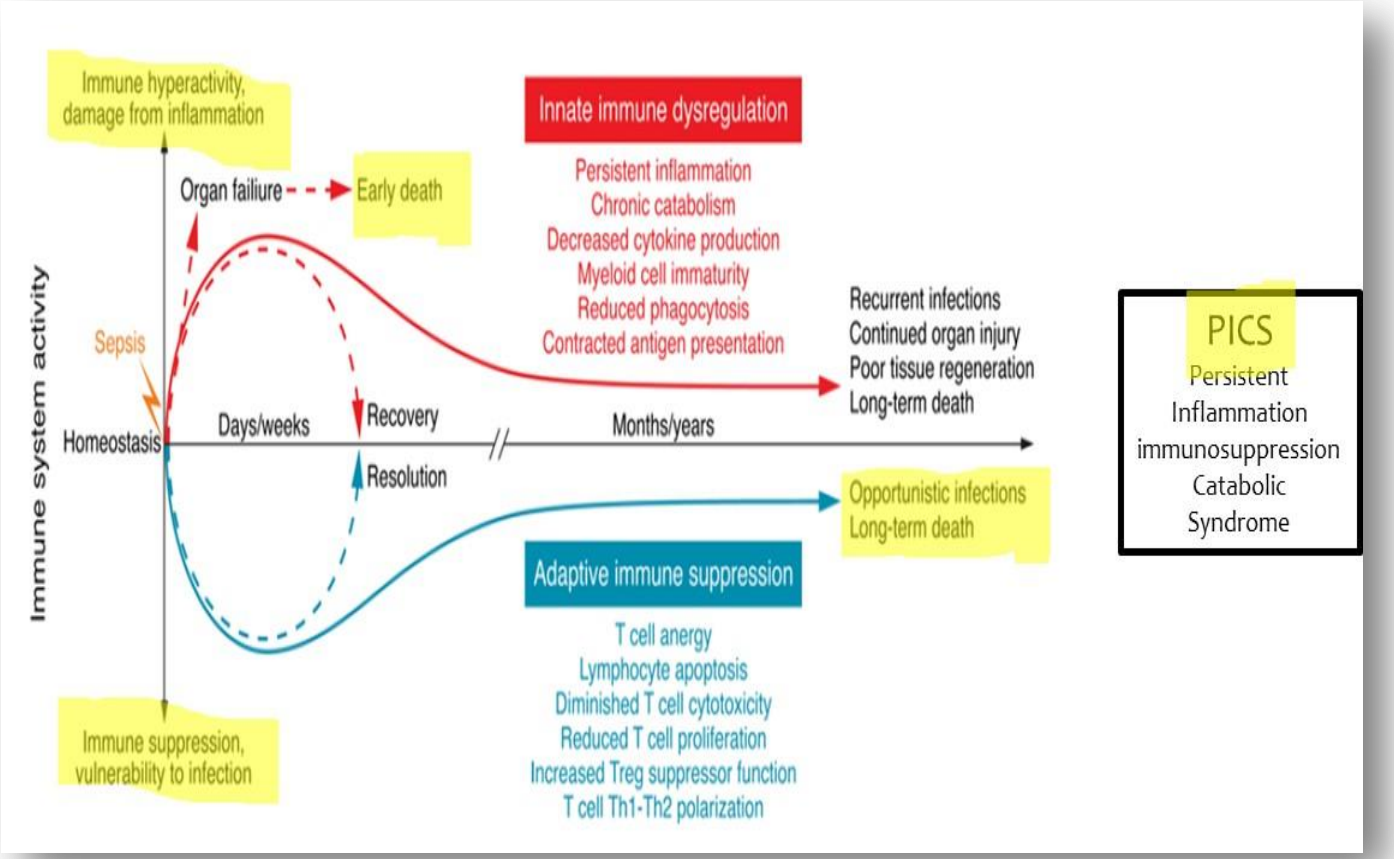
Hospital Acquired
Septic Shock

Adjunctive Therapies in Sepsis: Yes or No ?

No, of course….

But

it depends on ……..



TAKE HOME MESSAGES (and PICTURE)

Clinical Decision making

American Thoracic Society Documents

Am J Respir Crit Care Med Vol 185, Iss. 10, pp 1117–1124, May 15, 2012

An Official Multi-Society Statement: The Role of Clinical Research Results in the Practice of Critical Care Medicine

- The results of clinical research, pathophysiologic reasoning, and clinical experience represent different kinds of medical knowledge crucial for effective clinical decision making.

Clinical Research

Polyclonal IgG reduced mortality among adults with sepsis but this benefit was not seen in trials with low risk of bias. For IgM enriched Ig, the trials on adults were small and the totality of the evidence is still insufficient to support a robust conclusion of benefit…..

Pathophysio Reasoning

The role and the pleiotropic mechanisms of action of IgG and IgM in supporting and modulating the inflammatory and immune response of the host to infections has been well described in animal models

Clinical Experience

In numerous clinical experiences the use of intravenous Ig provides positive results. However, many clinical questions remain open

- In which patient ? (grade of sepsis, type of infection, immune-biomarkers)
- At what time ? (late use possible)
- Which dosage ? (titrate dose by biomarkers)

Parachutes reduce the risk … not been proved with rand … effect … os

BMJ 2003;327:1459–61

Clin Infect Dis. 2017 Nov 22. [Epub ahead of print]

IDSA POSITION STATEMENT:
Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines

Summary: The Infectious Diseases Society of America elected not to endorse the Surviving Sepsis Campaign Guidelines due to lack of agreement with the Society of Critical Care Medicine regarding specific recommendations related to diagnosis and therapy for patients with apparent or documented sepsis/septic shock.

A. DISTINGUISHING SEPSIS FROM NON-INFECTIOUS SYNDROMES: The Surviving Sepsis Campaign Guidelines do not differentiate between patients with suspected sepsis and suspected septic shock (one-size-fits-all recommendations). Reasonable to use antibiotic in suspected septic shock. Caution to use antibiotics in suspected sepsis, gain time, because many are not sepsis….overuse of antibiotics
B. TIME TO INITIATION OF EMPIRIC ANTIBIOTIC THERAPY: antimicrobials as soon as possible to patients with severe infections. But aggressive fixed time period may lead to an increased use of broad-spectrum antibiotics to uninfected patients with syndromes that look like infections.
C. BLOOD CULTURES AND IV ACCESS CATHETERS : Not clear specification on blood cultures in patients with catheters, the removal strategy and the management of implanted catheters
D. COMBINATION AND MULTIDRUG THERAPY: Confusing terms for combination, empiric, targeted, multidrug strategy. Many indications are not based on evidences (particularly in combination therapy)
E. PROCALCITONIN: The guidelines indicate that procalcitonin "can be used". Our interpretation is that RCTS demonstrate that procalcitonin guidance for duration of antibiotic therapy is feasible and safe in critically ill patients with infections
F. PK/PD-PROPHYLAXIS-ANTIBIOTIC THERAPY DURATION

INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

The Journal of Clinical Investigation REVIEW

Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

jci.org Volume 126 Number 1 January 2016

Matthew J. Delano[1] and Peter A. Ward[2]

[1]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, Michigan, USA. [2]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

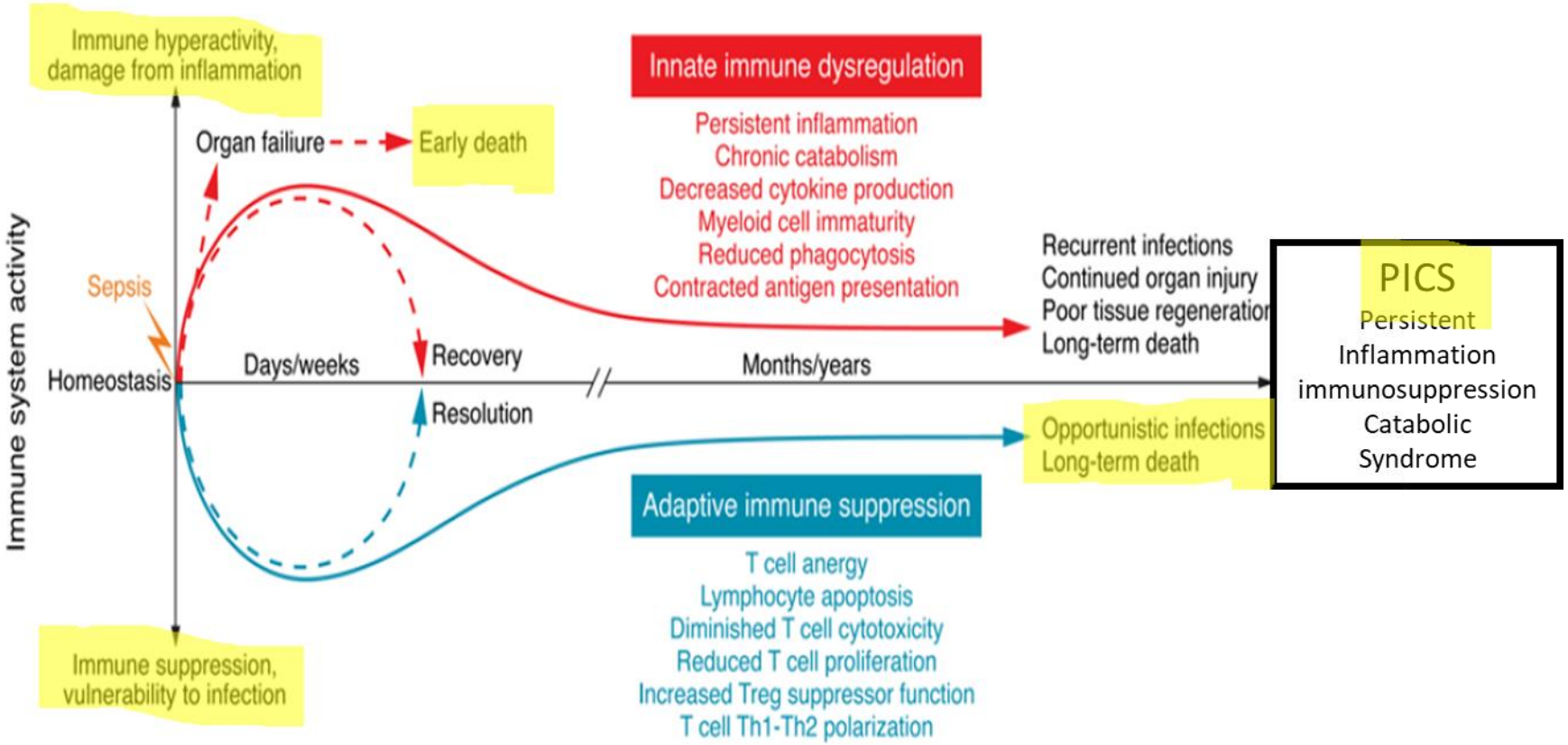


Figure 2. Immune dysregulation in sepsis. New insights into immune dysregulation have been gained using samples from deceased septic patients as well as from severely injured trauma patients. These studies demonstrate an enduring inflammatory state driven by dysfunctional innate and suppressed adaptive immunity that culminates in persistent organ injury and death of the patient. Although the initial inflammatory process, if unabated, contributes to organ failure and early mortality, this process is largely ameliorated by improvements in patient management protocols. However, considering that the vast majority of sepsis survivors are elderly with highly comorbid conditions, the short-term gains in survival have merely been pushed back by several months to a year. Although theories about the processes underlying this observation are numerous, the widespread consensus is that persistent derangements in innate and adaptive immune system cellular function are the main culprits driving long-term mortality.

EBM and INTENSIVE CARE

American Thoracic Society Documents

Am J Respir Crit Care Med Vol 185, Iss. 10, pp 1117–1124, May 15, 2012

An Official Multi-Society Statement: The Role of Clinical Research Results in the Practice of Critical Care Medicine

THIS OFFICIAL STATEMENT OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP), THE AMERICAN THORACIC SOCIETY (ATS), AND THE SOCIETY OF CRITICAL CARE MEDICINE (SCCM) WAS APPROVED BY THE ACCP BOARD OF REGENTS, JUNE 2011, BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2011, AND BY THE SCCM COUNCIL, SEPTEMBER 2011

- The results of clinical research, pathophysiologic reasoning, and clinical experience represent different kinds of medical knowledge crucial for effective clinical decision making.
- Each kind of medical knowledge has various strengths and weaknesses when utilized in the care of individual patients.
- No single source of medical knowledge is sufficient to guide clinical decisions.
- No kind of medical knowledge always takes precedence over the others.

TAKE HOME PICTURE

Sepsis is a high precision TEAM WORKING

EBM and INTENSIVE CARE

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- Clinical practice guidelines and protocols are not prescriptive, and clinicians must understand and be able to articulate appropriate reasons to adhere to or diverge from them in particular cases.

TABLE 1. CLINICAL EXAMPLES IN WHICH CLINICIAN VALUES, CLINICAL EXPERIENCE, OR REASONING BASED ON PATHOPHYSIOLOGY MAY REASONABLY RESULT IN DIVERGENCE FROM PRACTICE SUGGESTED BY EMPIRICAL EVIDENCE

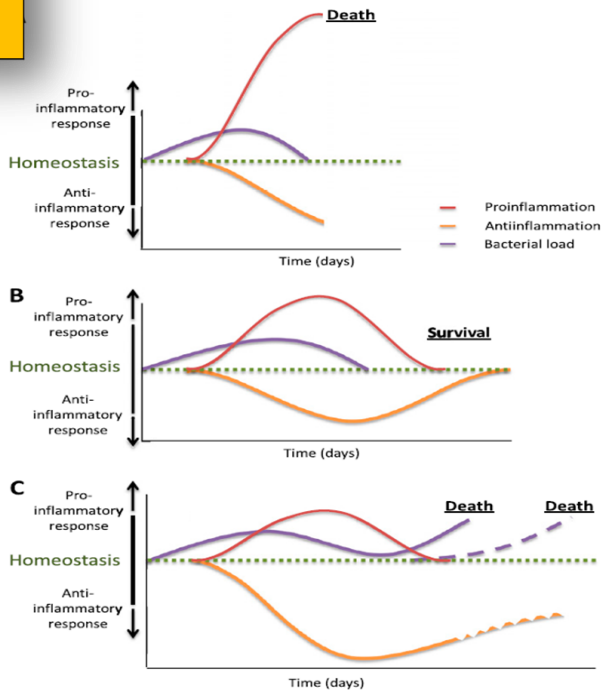
Treatment	Unique Patient Scenario	Explicit Rationale for Diverging from Empirical Evidence
Low tidal volume ventilation for severe ARDS	Nonsustained but hemodynamically significant episodes of ventricular tachycardia at low tidal volume that improves with higher tidal volume	Clinician experience prompts decision to use higher tidal volume than clinical research supports
Low tidal volume ventilation for severe ARDS	Elevated plateau pressures in the context of abdominal compartment syndrome	Pathophysiologic reasoning about transpulmonary pressures supports a decision to allow higher plateau pressures
Inhaled nitric oxide for severe ARDS	Single organ failure and severe life-threatening hypoxia	Pathophysiologic reasoning leads clinician to implement therapy without proven benefit for improving hospital survival

Adjunctive Therapies in Sepsis: Yes or No ?

No, of course….But

PREDISPOSITION:	Pre-existing illness, genetic polymorphisms	Difficult Patient
INSULT:	Site of infection, type of infection, virulence and sensitivity of infecting pathogens;	Difficult Micro-organisms Or Site
RESPONSE	SIRS, other signs of sepsis, activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR)	Difficult Immune Inflammatory Response
OR AN DYSFU CTION	Time and number of failing organs	

ARE ALL THE PATIENTS WITH SEPTIC SHOCK SIMILAR ?

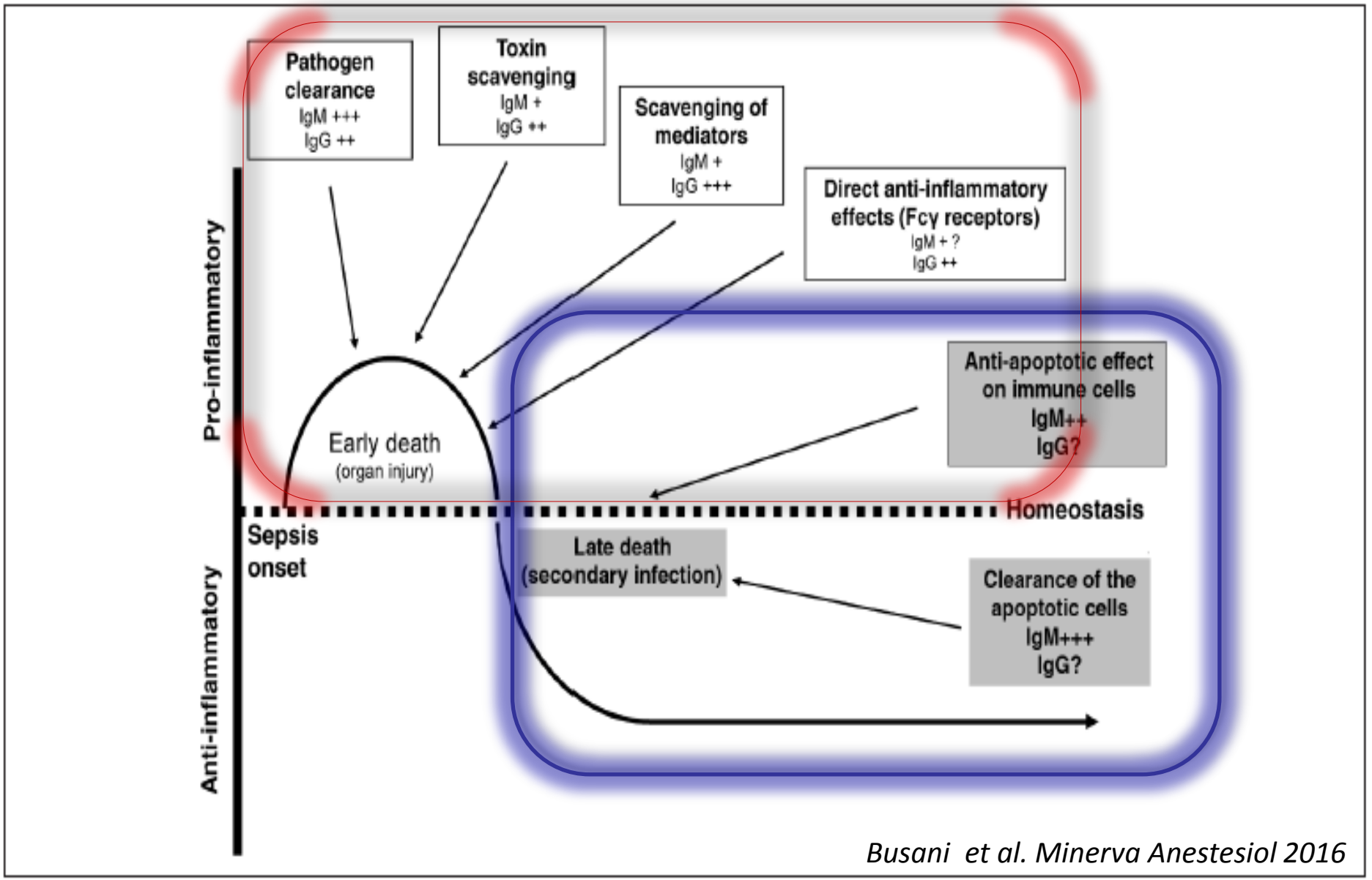


Healthy young adult with bacteremia by N. Meningitides/S. Pyogen/ S. Pneumonia:
Overwhelming proinflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure

Healthy young adult with CAP responsive to Abx :
adequate proinflammatory re-sponse, combined with an adequate non-sustained antiinflammatory response to pre-vent tissue damage

Patient with breakthrough infection after first sepsis :
Proinflammatory response combined with a pronounced or sustained anti inflammatory state with persisting bacterial or secondary (opportunistic) infections

Ig: HOW IT WORKS ?



Busani et al. Minerva Anestesiol 2016

Figure 1.—Possible mechanism of action of Ig in the proinflammatory and immunosuppressive phases of sepsis.

Ig and Streptococcal Toxic Shock

Intravenous Immunoglobulin G Therapy in Streptococcal Toxic Shock Syndrome: A European Randomized, Double-Blind, Placebo-Controlled Trial CID 2003:37

- High-dose **intravenous polyclonal immunoglobulin G** as adjunctive therapy in **streptococcal toxic shock syndrome** (70% necrotizing fasciitis)
- The trial was prematurely terminated because of slow patient recruitment

End point	All included patients: IVIG group (*n* = 10)	All included patients: Placebo group (*n* = 11)
Primary: mortality day 28, no. (%) of patients	1 (10)	4 (36)
Secondary		
Time to resolution of shock,[a] h		
Mean	88	122
Median (range)	96 (2–159)	108 (47–294)
Time to no further progression of NF/cellulitis, h		
Mean	68[b]	36[c]
Median (range)	20 (2–168)[b]	24 (19–72)[c]
Mortality day 180, no. (%) of patients	2 (20)	4 (36)

Clinical Efficacy of Polyspecific Intravenous Immunoglobulin Therapy in Patients With Streptococcal Toxic Shock Syndrome: A Comparative Observational Study CID 2014:59

Anna Linnér,[1] Jessica Darenberg,[2] Jan Sjölin,[3] Birgitta Henriques-Normark,[2,4,5] and Anna Norrby-Teglund[1]

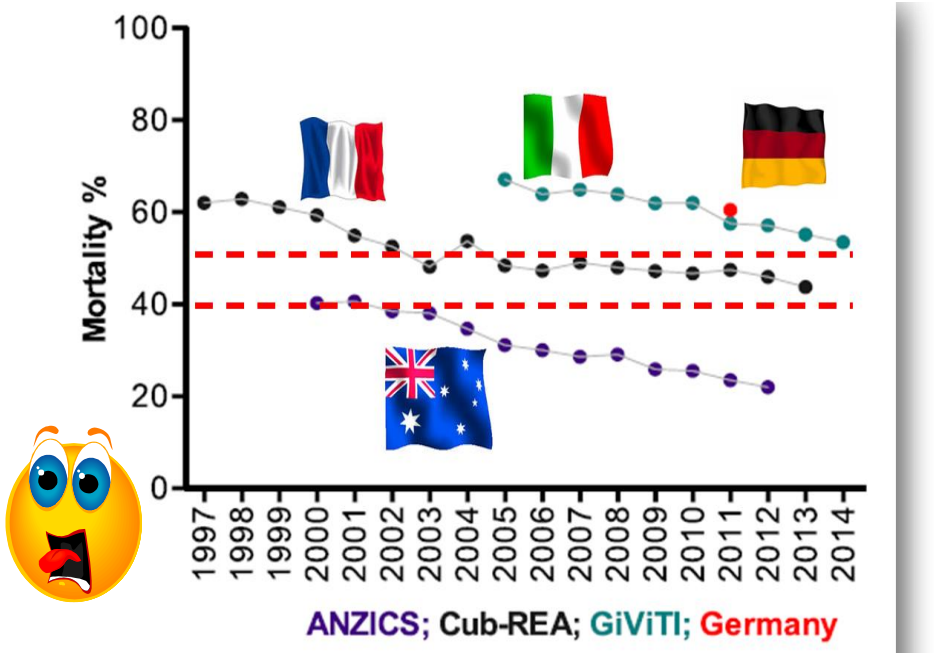
- **streptococcal toxic shock syndrome** prospectively identified in a nationwide Swedish surveillance study (2002-2004): **67 patients.**
- 23 patients received IgG.

	Age <80 y			Age >80 y		
	IVIG (n = 21)	Non-IVIG (n = 35)	*P* Value	IVIG (n = 2)	Non-IVIG (n = 9)	*P* Value
Survival	18 (85.7)	20 (57.1)	.039	2 (100)	2/9 (22.2)	NS

presented in this study. Taken together with the high morbidity and mortality of these infections as well as a detailed mechanistic action of IVIG, our results strongly suggest that clinicians ought to consider the use of IVIG in the treatment of STSS.

SEPSIS
SHORT CIRCUIT

MORTALITY IS STILL HIGH and NOT REALLY DECREASING (at least in Europe and in real life)



Shankar-Hari *et al. Critical Care* (2015) 19:445

NEGATIVE TRIALS SINCE 5-10 Y
leading to low (or very low) level of evidence for the majority of sepsis treaments

SPECIAL EDITORIAL

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

1 Hour- Bundle

Table 1 Bundle elements with strength of recommendations and under-pinning quality of evidence [12, 13]

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

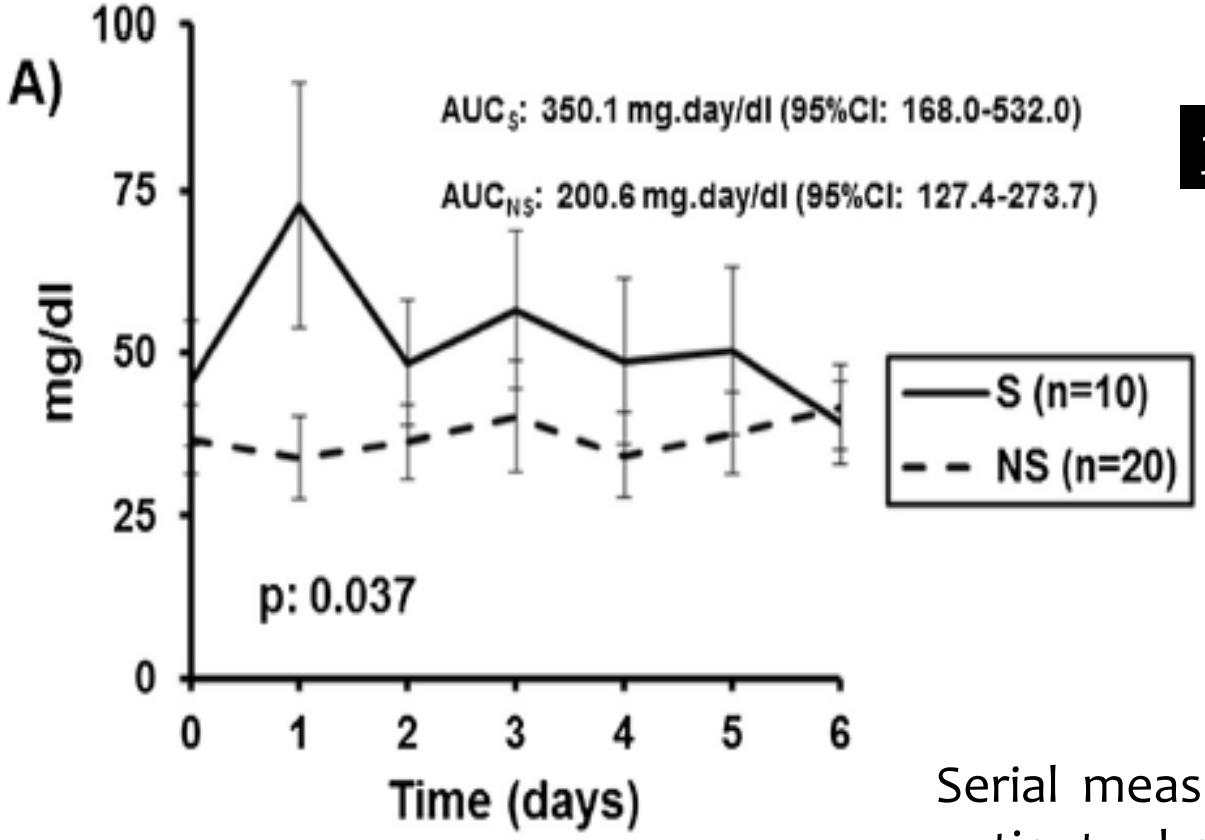
IMMUNE DYSFUNCTION

Giamarellos-Bourboulis *et al. Critical Care* 2013, **17**:R247
http://ccforum.com/content/17/5/R247

CRITICAL CARE

RESEARCH Open Access

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



30 septic shock patients

Serial measurements in **septic shock** patients showed that the **distribution of IgM over time was significantly greater** for survivors than for non-survivors