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

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

MODENA MICU INTENSIVE CARE UNIT 2

Potenzialità Terapeutiche delle Immunoglobuline

AGENDA

Guidelines and Evidences

Ig and Pathobiology of Sepsis

Ideas and Data

INFECTIONS & TRANSPLANTATION
Varese, 18-20 Maggio 2017

slides and discussion
girardis.massimo@unimo.it

Disclosures

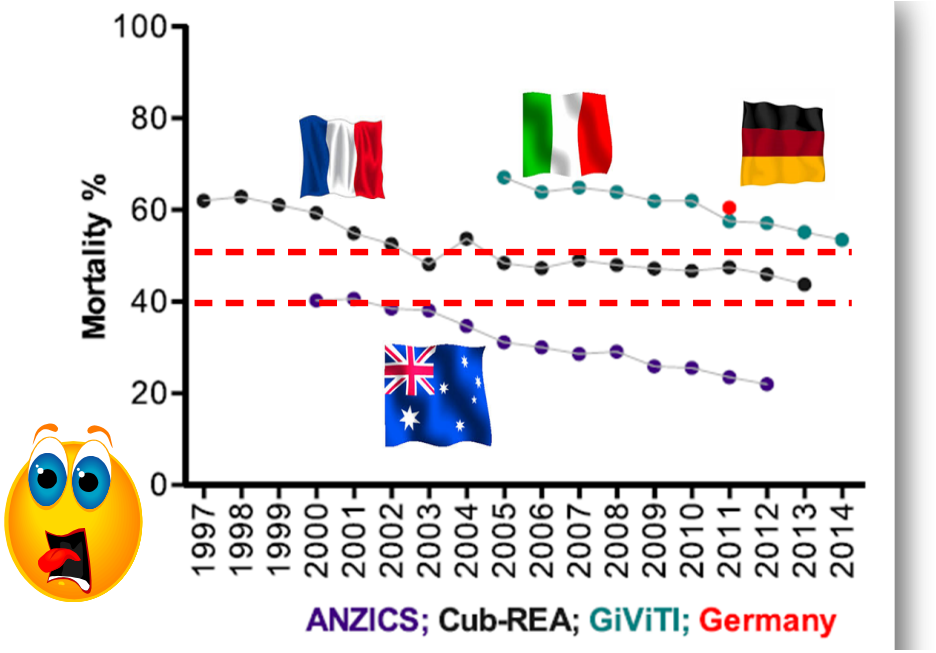
POTENTIAL CONFLICT OF INTEREST
Unrestricted grants, lectures, advisory boards, etc.

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'

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

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.

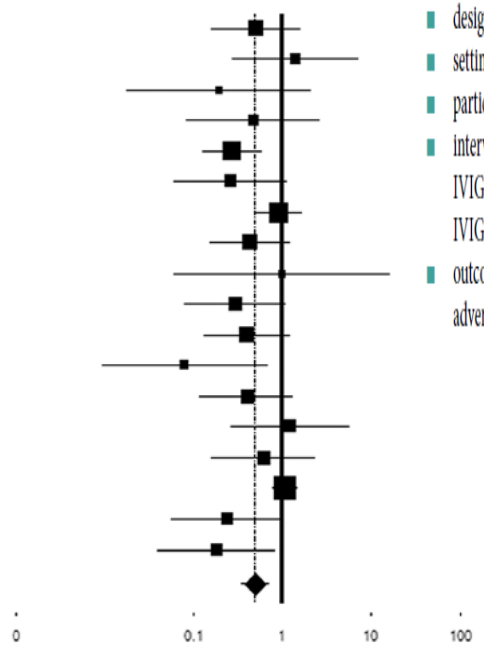
Ig in SEVERE SEPSIS: EVIDENCE IN ADULTS META-ANALYSIS

Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness

Minerva Anestesiologica 2016 May;82(5):559-72

Stefano BUSANI [1], Elisa DAMIANI [2], Ilaria CAVAZZUTI [1], Abele DONATI [2], Massimo GIRARDIS [1*]

	ES	95% CI	W	Sig.	N1	N2
Behre et al. 1995	0.51	0.16 , 1.62	6.17%	0.256	30	22
Burns et al. 1991	1.42	0.27 , 7.44	3.72%	0.676	19	19
Darenberg et al. 2003	0.19	0.02 , 2.15	2.01%	0.182	10	11
De Simone et al. 1988	0.47	0.08 , 2.66	3.44%	0.390	12	12
Dominioni et al. 1996	0.28	0.13 , 0.60	9.20%	0.001	57	56
Grundmann et al. 1988	0.26	0.06 , 1.15	4.43%	0.075	24	22
Hentrich et al. 2006	0.91	0.49 , 1.68	10.89%	0.754	103	103
Karatzas eta al. 2002	0.44	0.15 , 1.25	6.87%	0.124	34	34
Lindquist et al. 1981	1.00	0.06 , 16.29	1.54%	1.000	74	74
Masaoka et al. 2000	0.30	0.08 , 1.09	5.26%	0.067	339	343
Rodriguez et al. 2005	0.41	0.14 , 1.25	6.41%	0.116	29	27
Schedel et al. 1991	0.08	0.01 , 0.70	2.44%	0.022	27	28
Spannbrucker et al. 1987	0.40	0.12 , 1.35	5.76%	0.140	25	25
Toth et al. 2013	1.25	0.27 , 5.83	4.15%	0.776	16	17
Tugrul et al. 2002	0.62	0.16 , 2.42	4.98%	0.496	21	21
Werdan et al. 2007	1.09	0.79 , 1.50	14.01%	0.615	321	303
Wesoly et al. 1990	0.25	0.06 , 1.06	4.49%	0.059	18	17
Yakut et al. 1998	0.19	0.04 , 0.85	4.23%	0.029	21	19
Overall (random-effects model)	0.50	0.34 , 0.71	100.00%	0.000	1180	1153
I2 44.68%, p=0.022						



- 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.

18 RCTs

TABLE II.—*Assessment of study quality.*

Study	Concealment of allocation	Blinding	Randomization procedure	Intention-to-treat analysis	Industry sponsorship	Jadad score
Toth *et al.*[34] 2013	Adequate	Unclear	Adequate	Unclear	Not reported	2
Behre *et al.*[35] 1995	Unclear	Unclear	Unclear	Yes	Not reported	1
Burns *et al.*[36] 1991	Unclear	Adequate	Unclear	No	Yes	5
Darenberg *et al.*[37] 2003	Unclear	Adequate	Unclear	Yes	Yes	5
De Simone *et al.*[38] 1988	Inadequate	Inadequate	Unclear	Yes	Not reported	1
Dominioni *et al.*[39] 1996	Unclear	Adequate	Unclear	No	Not reported	3
Grundmann *et al.*[40] 1988	Unclear	Unclear	Adequate	Yes	Not reported	2
Hentrich *et al.*[41] 2006	Adequate	Inadequate	Adequate	Yes	Yes	3
Karatzas *et al.*[42] 2002	Unclear	Unclear	Unclear	No	Not reported	2
Lindquist *et al.*[43] 1981	Inadequate	Inadequate	Unclear	Unclear	Not reported	3
Masaoka *et al.*[44] 2000	Adequate	Inadequate	Adequate	Yes	Yes	3
Rodriguez *et al.*[45] 2005	Adequate	Adequate	Adequate	Yes	Yes	5
Schedel *et al.*[46] 1991	Adequate	Inadequate	Adequate	No	Yes	3
Spannbrucker *et al.*[47] 1987	Unclear	Unclear	Adequate	Yes	Not reported	1
Tugrul *et al.*[48] 2002	Unclear	Unclear	Adequate	Yes	Not reported	3
Werdan *et al.*[49] 2007	Adequate	Adequate	Adequate	Yes	Yes	5
Wesoly *et al.*[50] 1990	Unclear	Unclear	Adequate	Yes	Not reported	1
Yakut *et al.*[51] 1998	Unclear	Unclear	Unclear	Yes	Not reported	3

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

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	

Which patient may benefit from Ig therapy?

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.

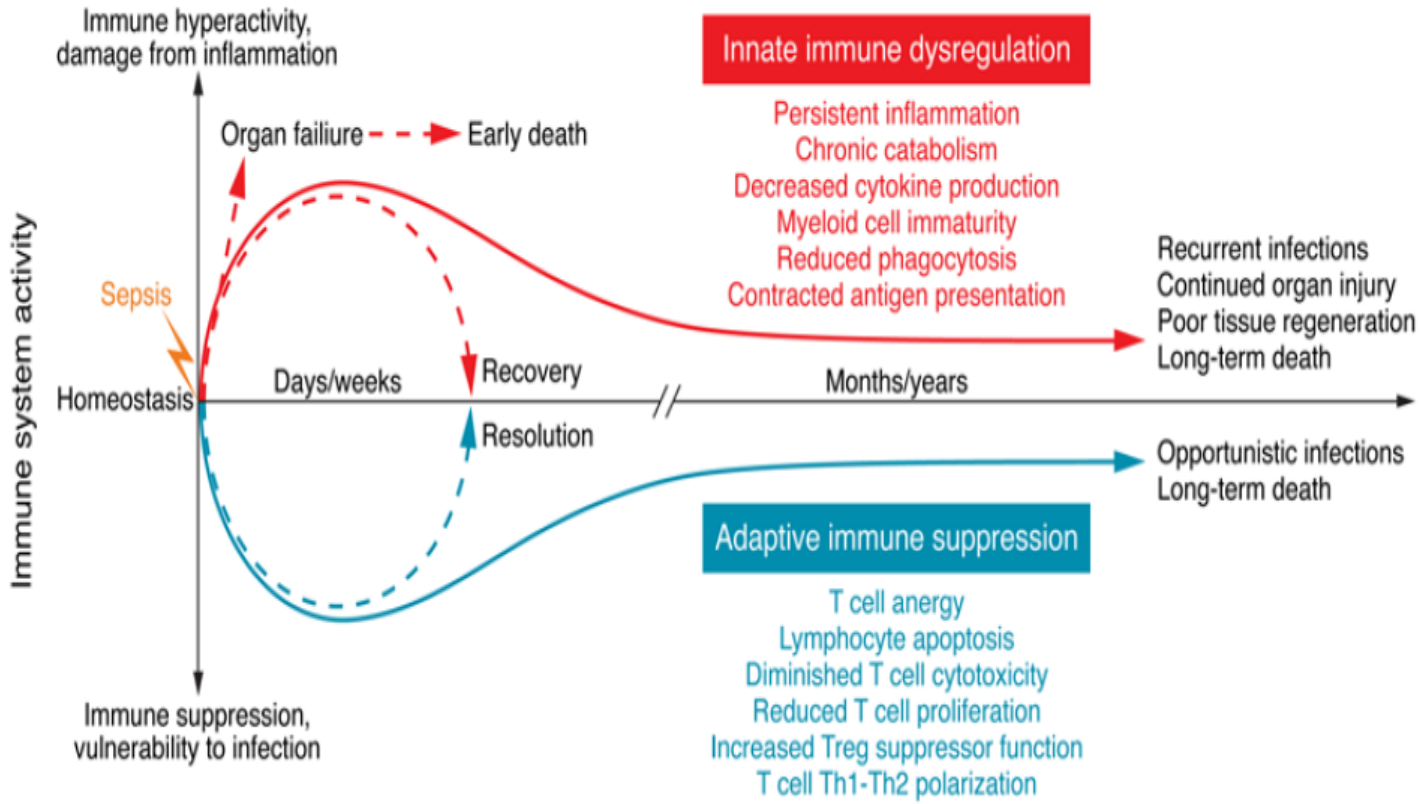


Figure 2. Immune dysregulation in sepsis. New insights into immune dysregulation have been gained using samples from deceased septic patients as well as from severely injured trauma patients. These studies demonstrate an enduring inflammatory state driven by dysfunctional innate and suppressed adaptive 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.

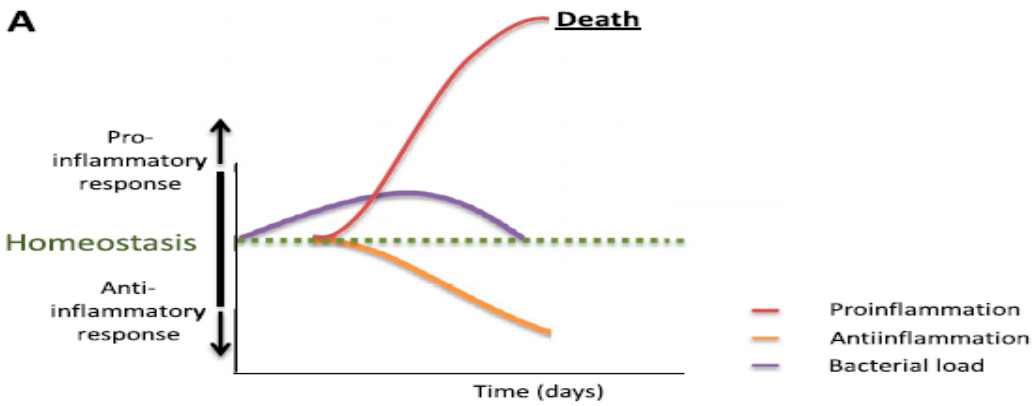
INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

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

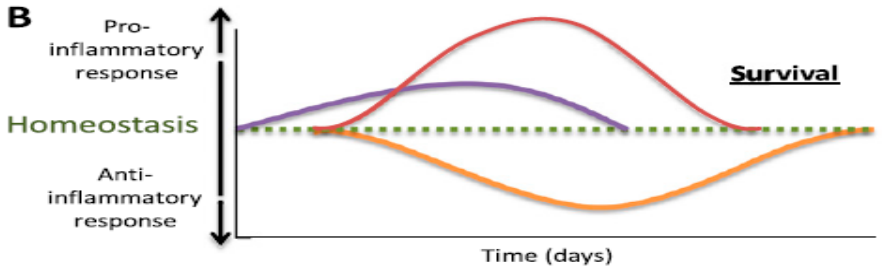
The inflammatory-immune response may vary and depends on

@ Microorganism(s) load and virulence

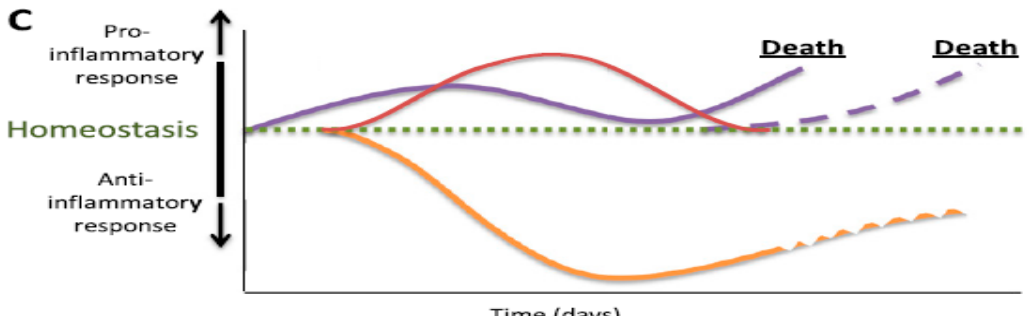
@ Host genetic factors and comorbidities



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

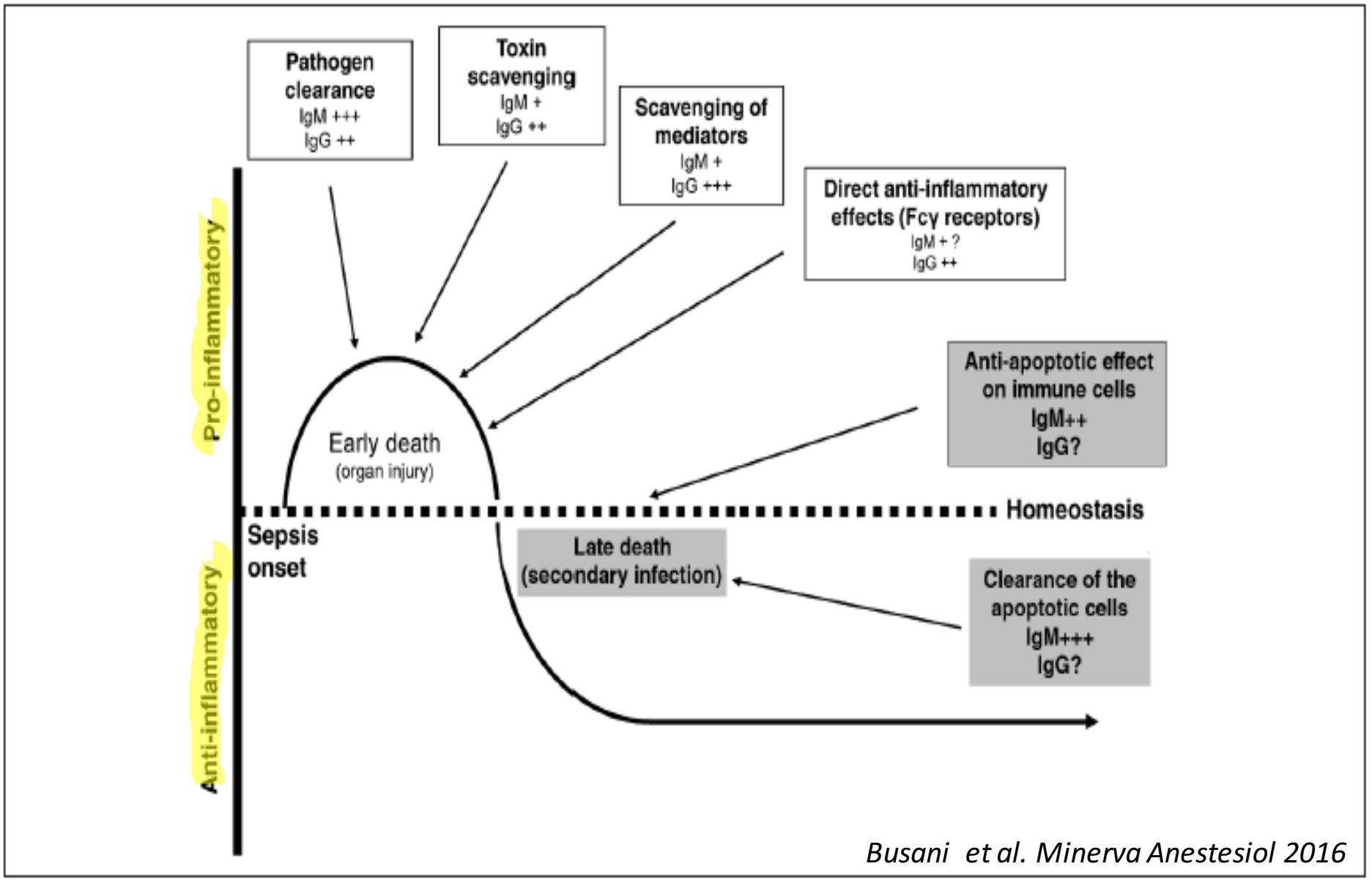


Healthy young adult with CAP responsive to Abx :
adequate proinflammatory re-sponse, combined with an adequate non-sustained antiinflammatory response to pre-vent tissue damage



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

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 PLASMA CONCENTRATION
IMMUNE RESPONSE

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)[†]

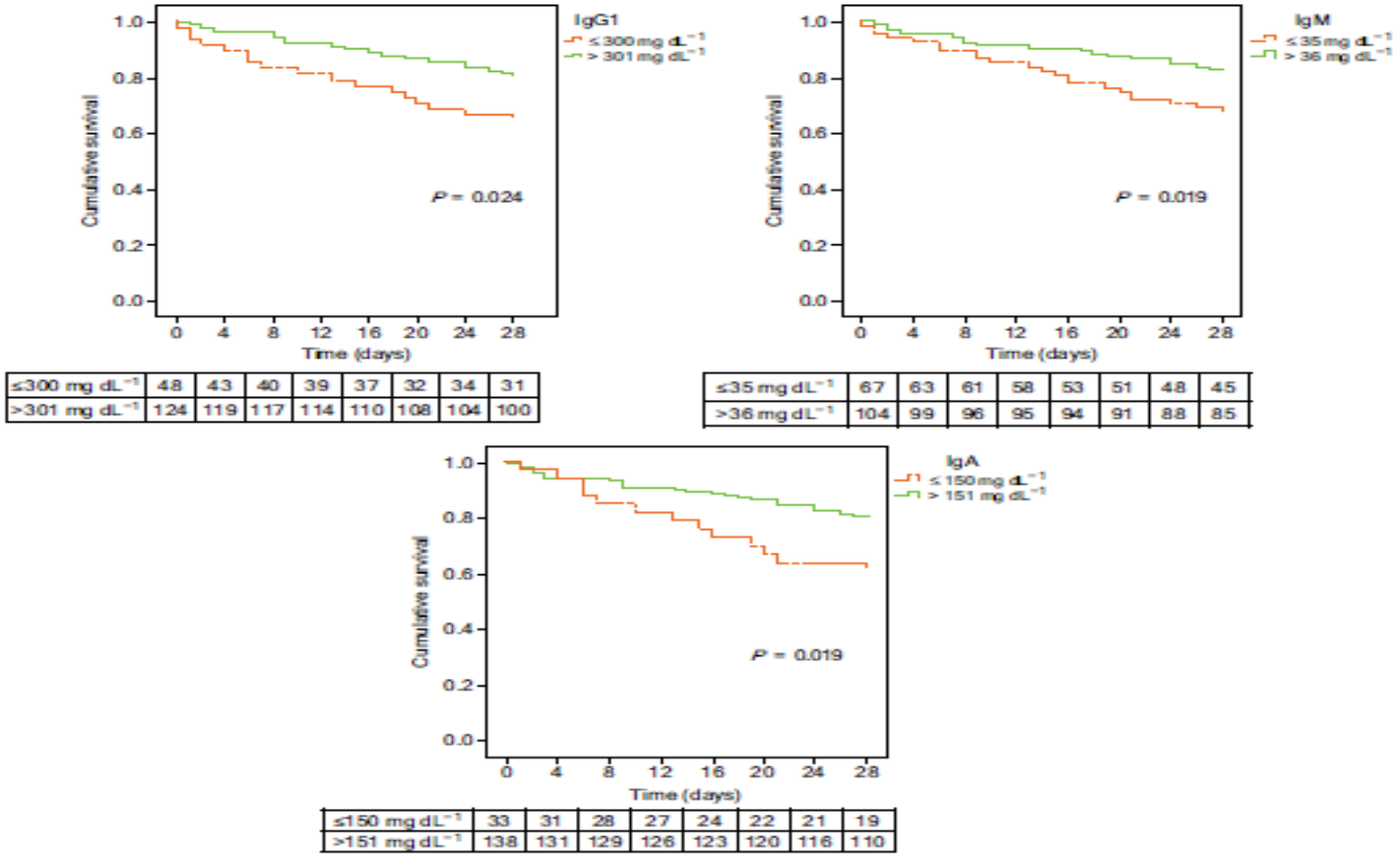


Fig. 1 *Kaplan–Meier curves showing the impact of immunoglobulin levels on survival. Number of surviving (censored) patients over time is shown at the bottom of each graph.*

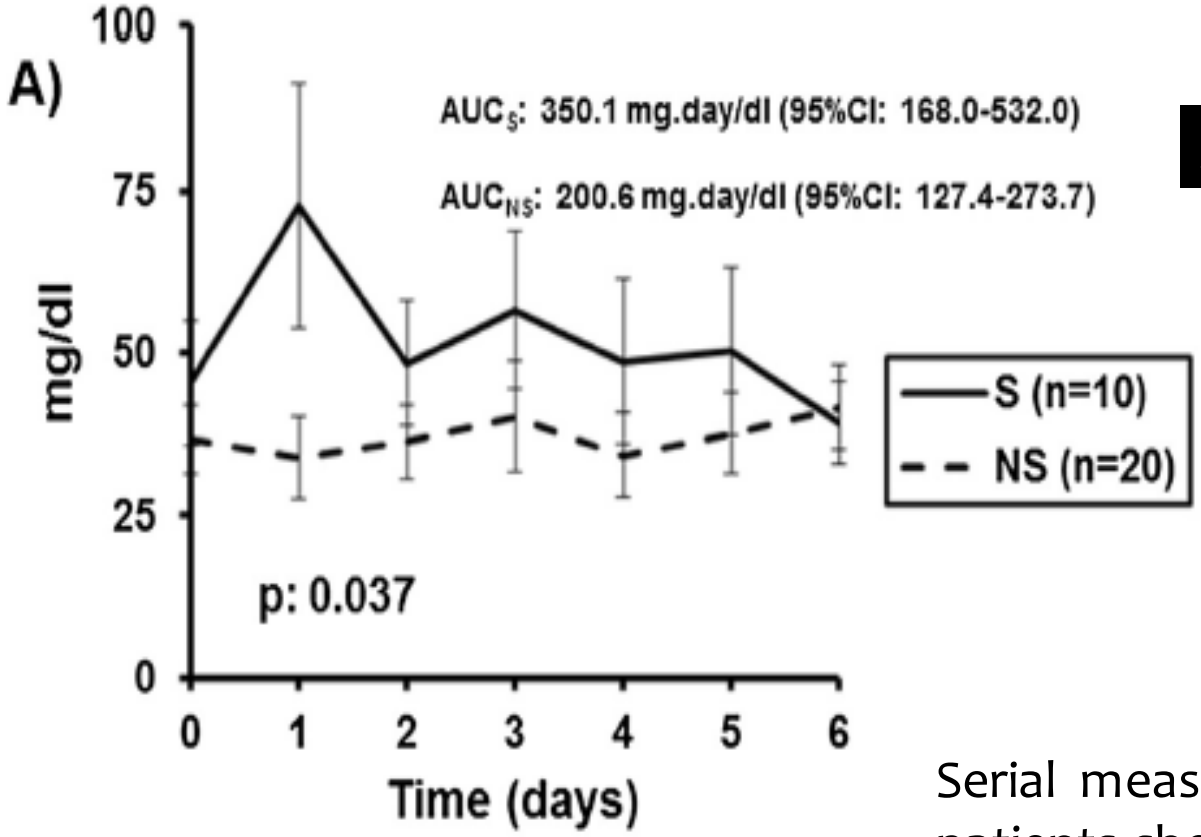
IG PLASMA CONCENTRATION
IMMUNE RESPONSE

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

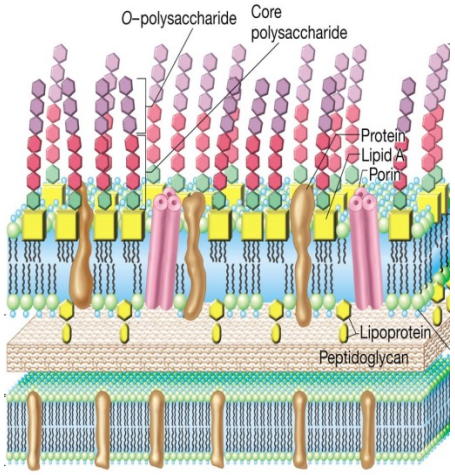
Serial measurements in **septic shock** patients showed that the **distribution of IgM over time was significantly greater** for survivors than for non-survivors

IG & Micro-organisms
IMMUNE RESPONSE

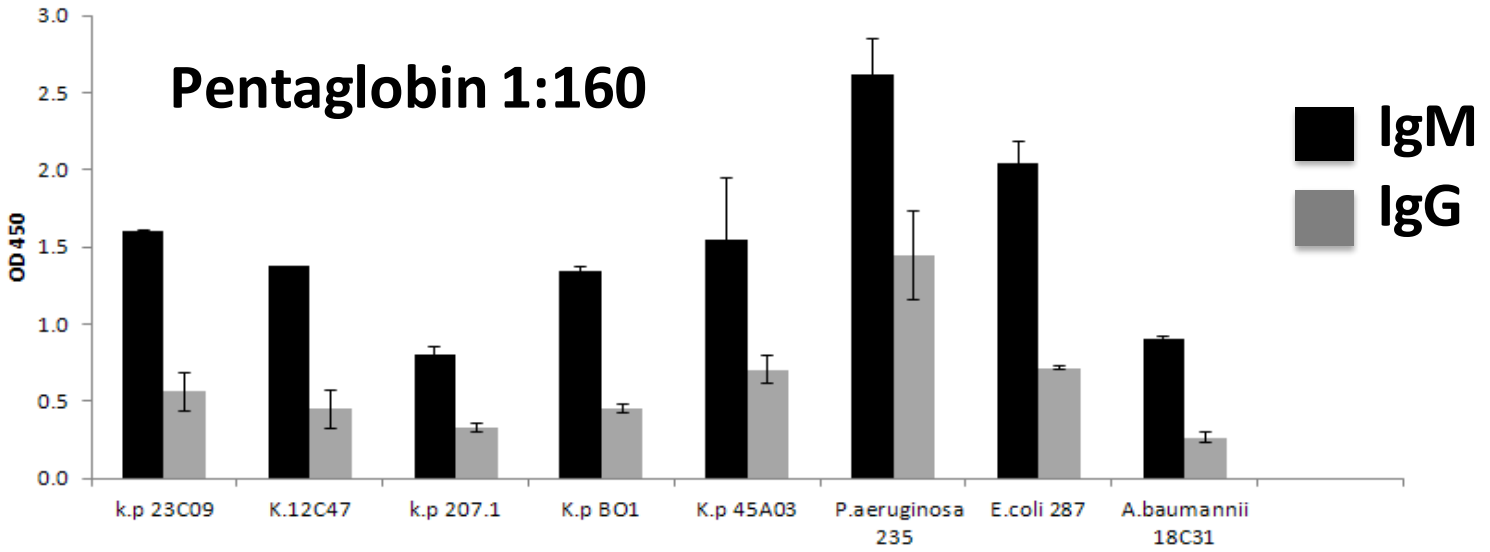
@ Are IgM-enriched human Ig preparations reactive against surface antigens of MDR/XDR Gram-negatives representative of recent epidemiology?

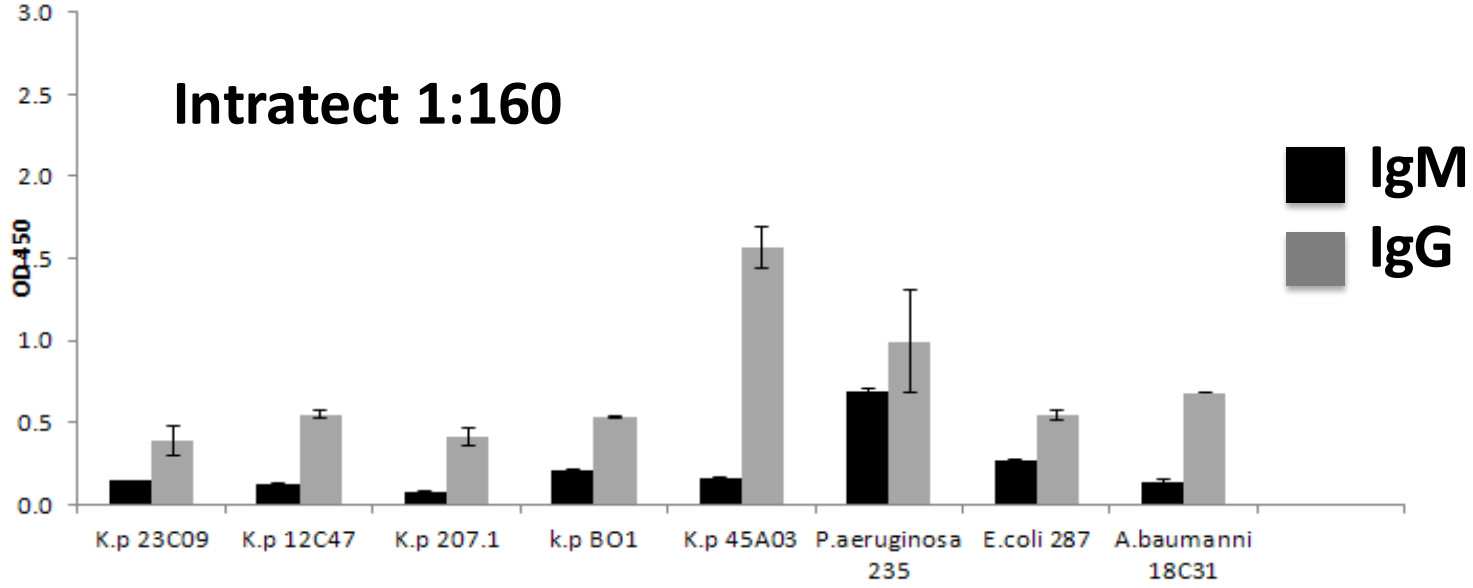
@ Are there differences in reactivity between IgM-enriched and conventional Ig preparations?

ELISA assays against lipopolysaccharide (LPS) fractions and outer membrane protein (OMP) fractions

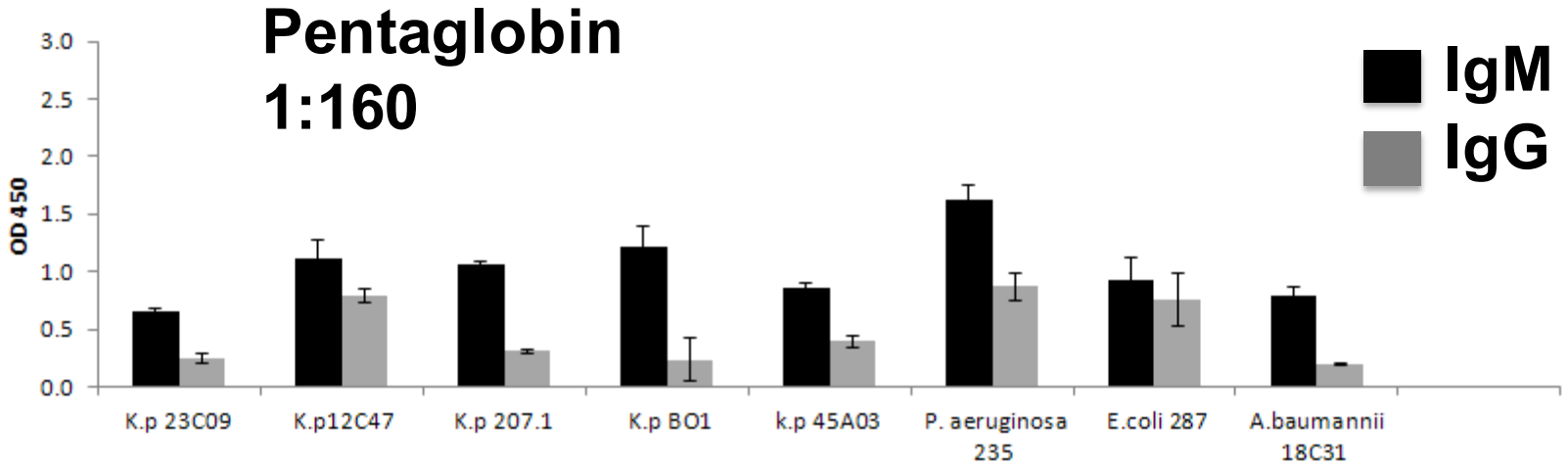


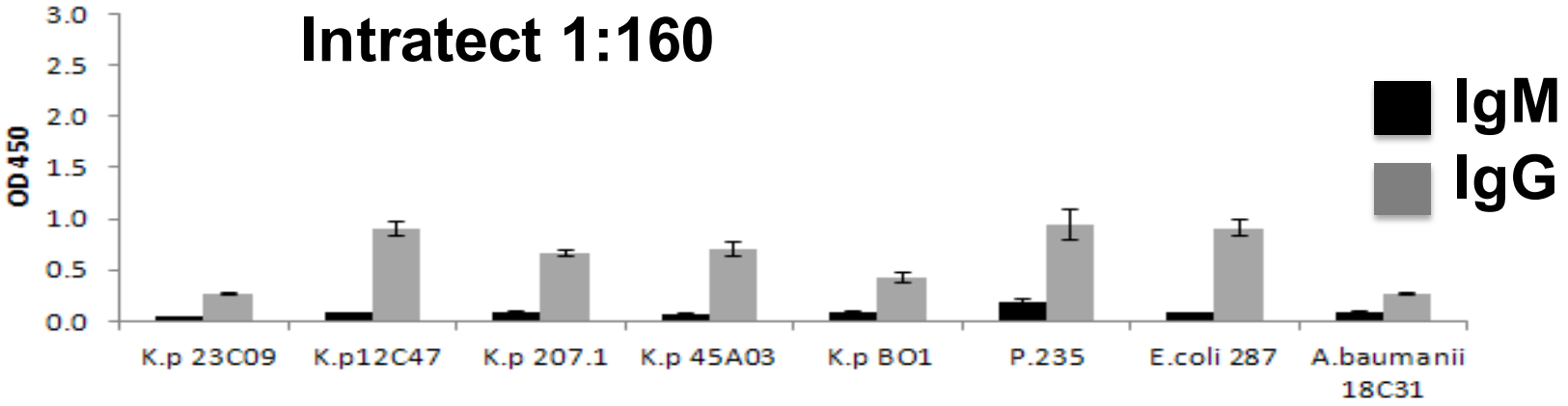
ELISA assays against LPS fractions - all strains





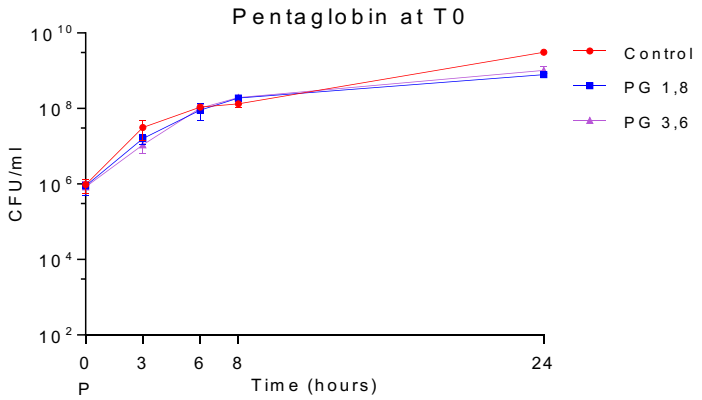
ELISA assays against OMP fractions - all strains

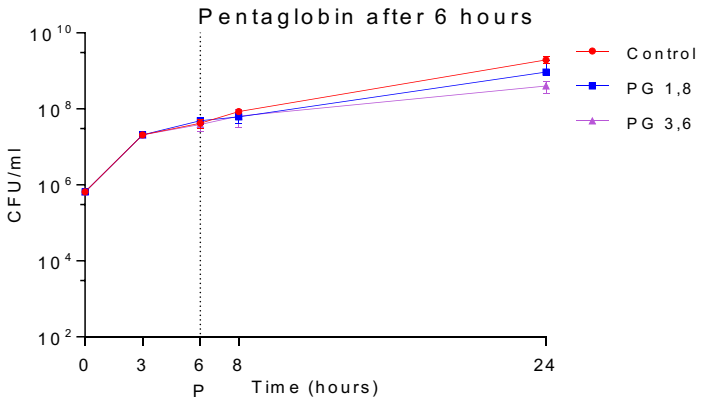


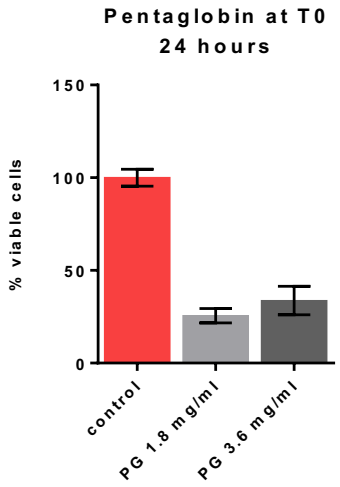


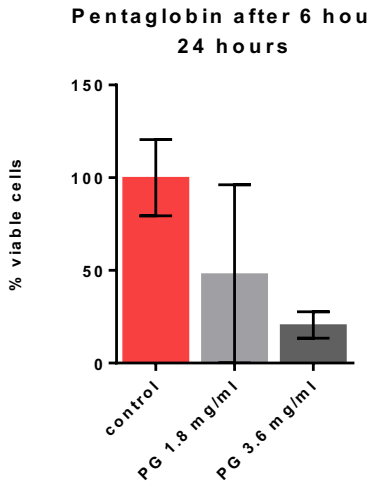
Potential antimicrobial activity of Pentaglobin in Time-Kill experiments

***A. baumannii* 18C31**





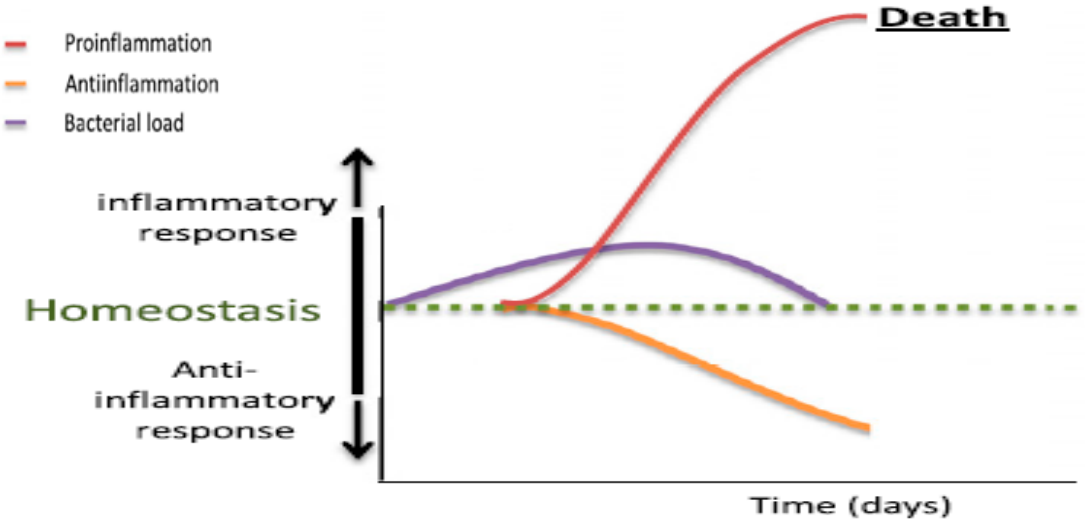




A delay in growth was observed only with *A. baumannii* 18C31 strain after 24 hours of exposure to Pentaglobin

Which patients may benefit from Ig therapy?

Pathobiology

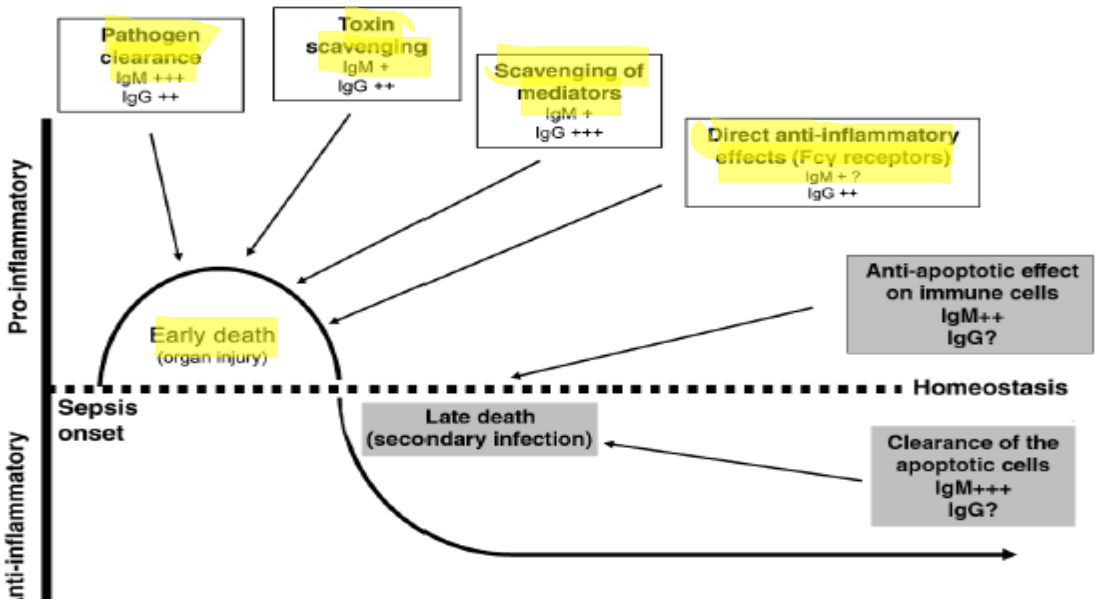


Clinical Scenario

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



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

	All included patients	
End point	IVIG group (n = 10)	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.

Severe Pneumonia: CIGMA RCT -Phase II Study

Unpublished
Courtesy by BIOTEST

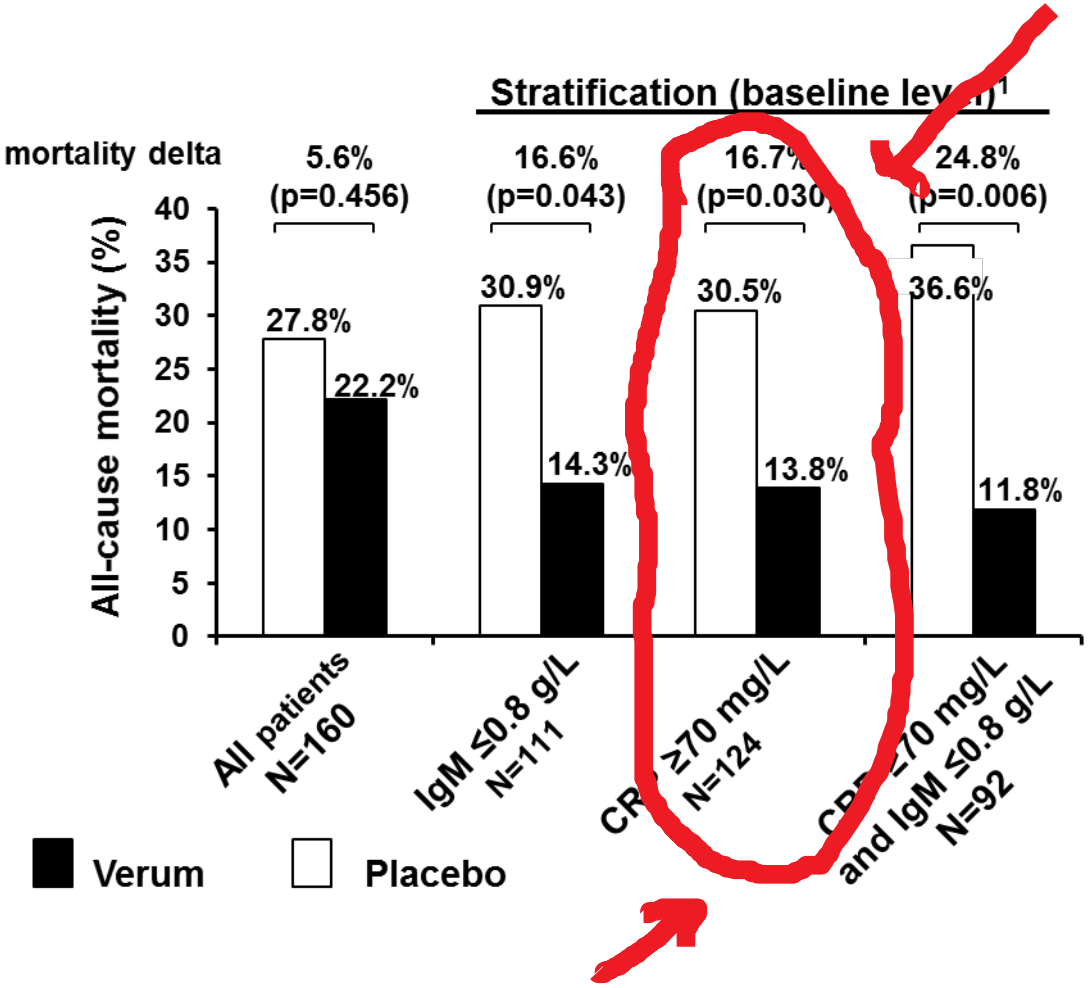
Objectives:

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)

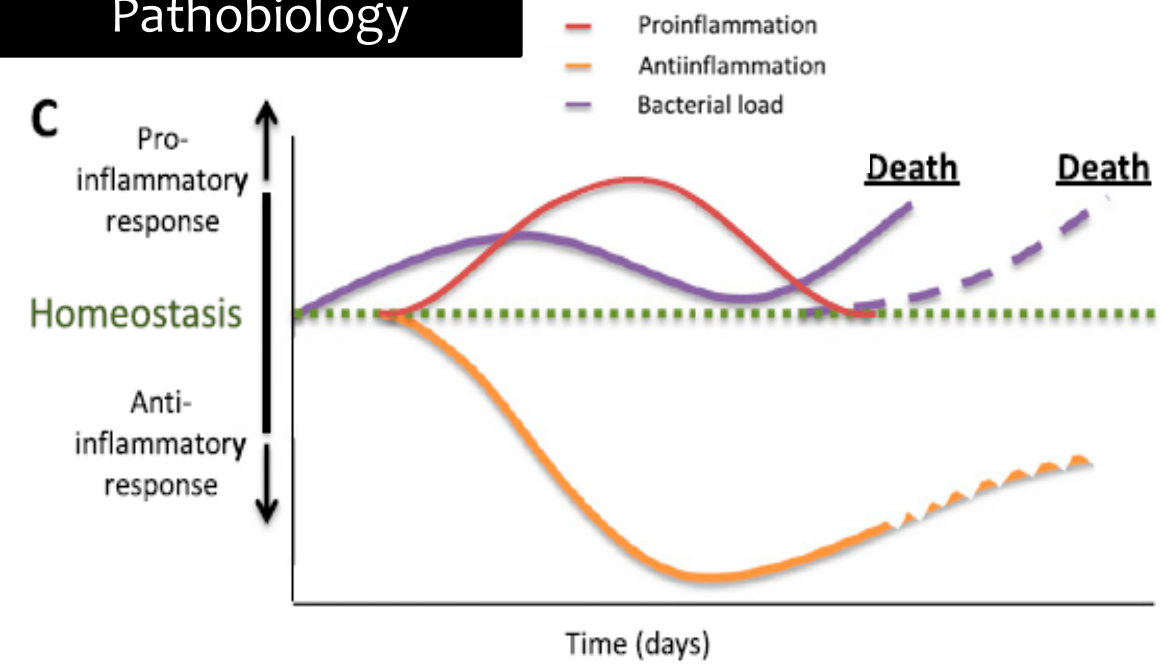
Primary endpoint:
VFDs (mean 11.0 vs. 9.6 days, respectively, p=0.173)

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



Which patients may benefit from Ig therapy?

Pathobiology

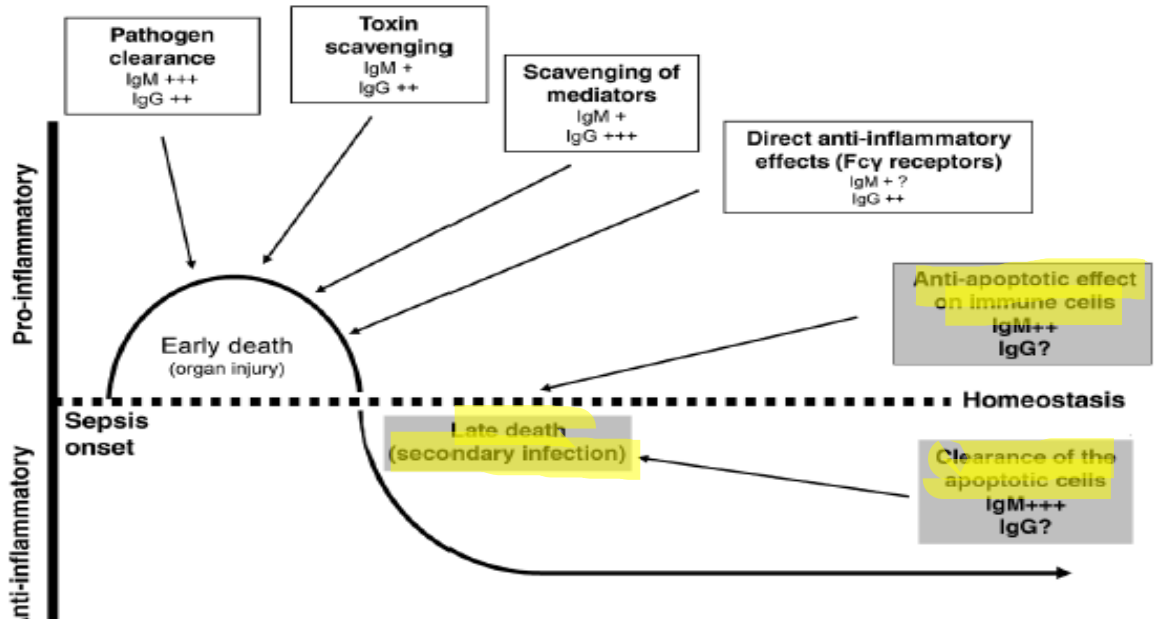


Clinical Scenario

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 (?)



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

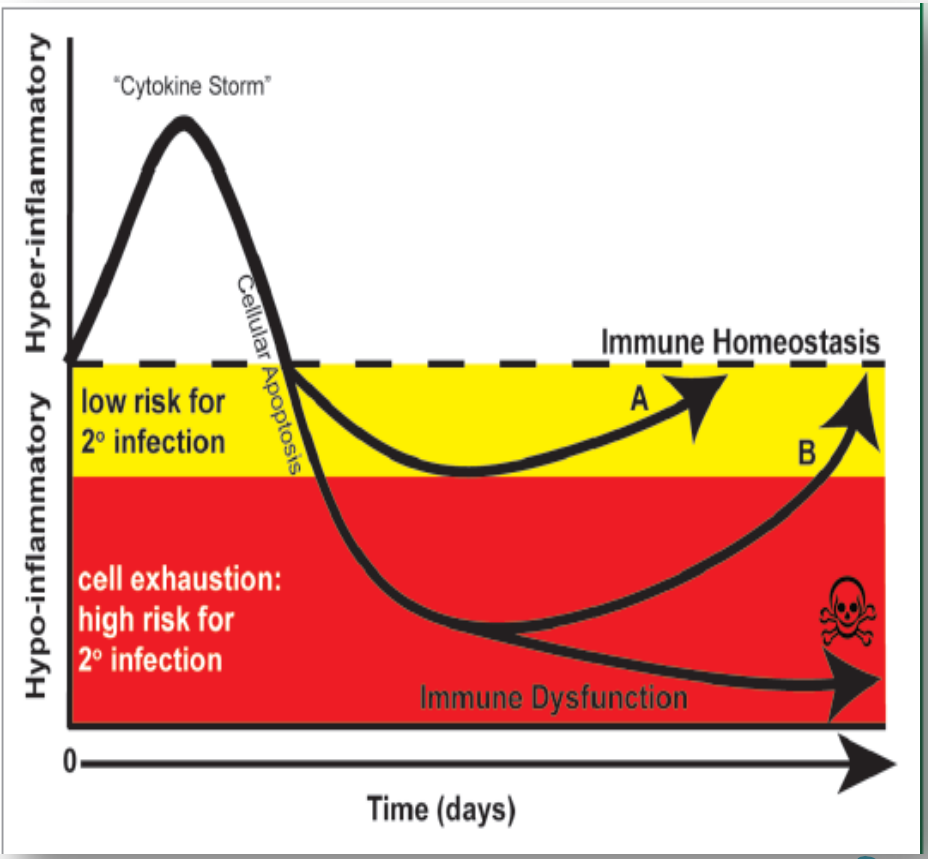


Table: Potential biomarker and clinical-laboratory findings

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

MDR infections and IgM

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

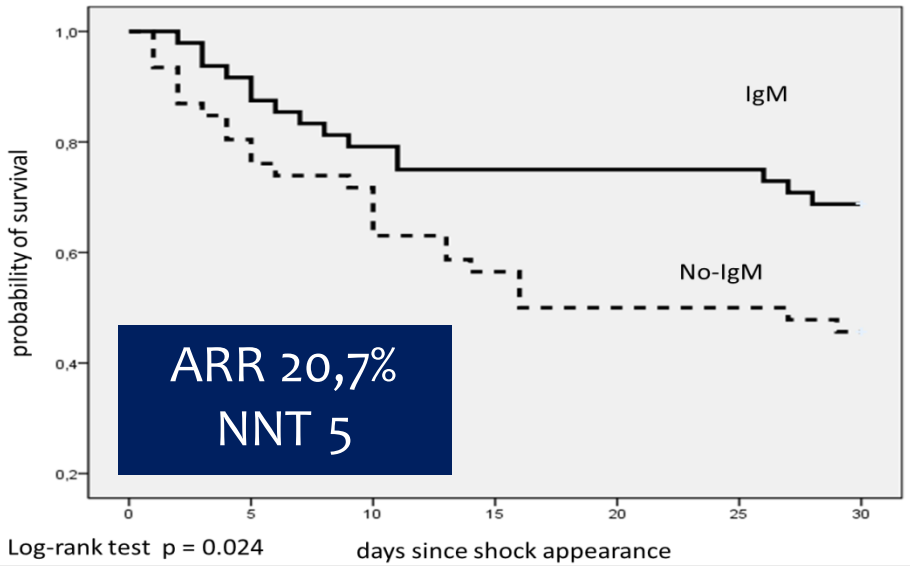
Journal of Intensive Care Medicine

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

- Retrospective analysis of 94 ICU patients with septic shock by MDR bacteria (2008-2013)
- History of cancer and infection sustained by A baumannii increase the risk of mortality
- Standard sepsis treatments do not seem to provide any protective effect
- Adjunctive therapy with IgM preparation was associated with a decrease in mortality rate.

Table 3. Multivariate Analysis of Risk Factors for 30 Days Mortality.[a]

	OR	95% CI	P
Preexisting condition cancer	2.97	1.14-7.71	.026
Infection by Acinetobacter baumannii	3.2	1.01-10.21	.050
IgM preparation	0.28	0.14-0.59	.001



Propensity Score Matching age, year of admission, type of admission, primary site of infection, pre-existing diseases, SOFA and SAPS II score, 6-hour and 24 hour bundles compliance.

	No IgM (N=37)	IgM (N=37)	P value
30 days mortality	19 (51,4)	11 (29,7)	0,013

Multivariate logistic regression
OR 0,31; CI 95% 0,12–0,78

Ig Therapy & MDR infections

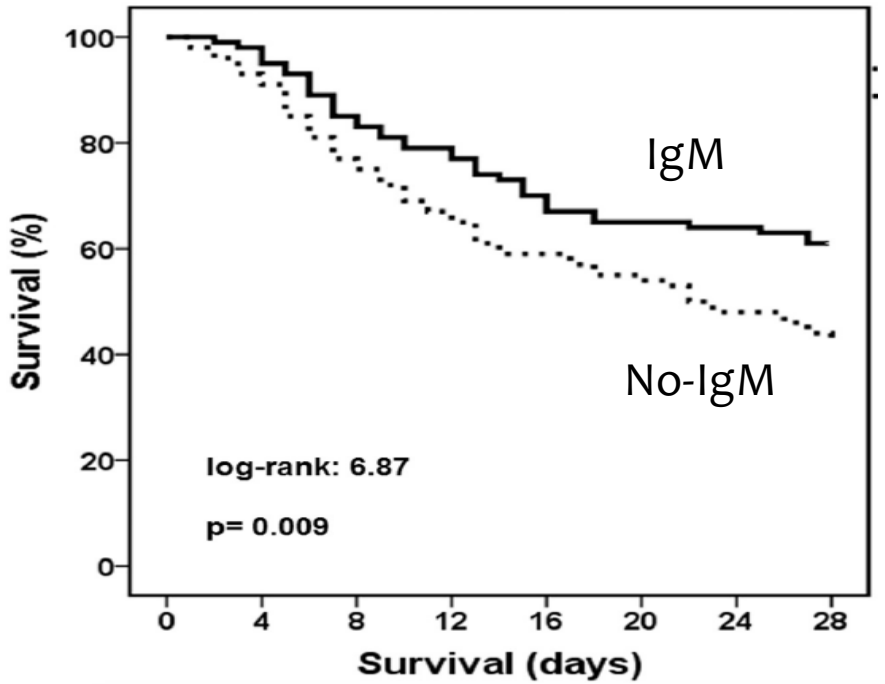
ORIGINAL ARTICLE

- 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.

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],



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.

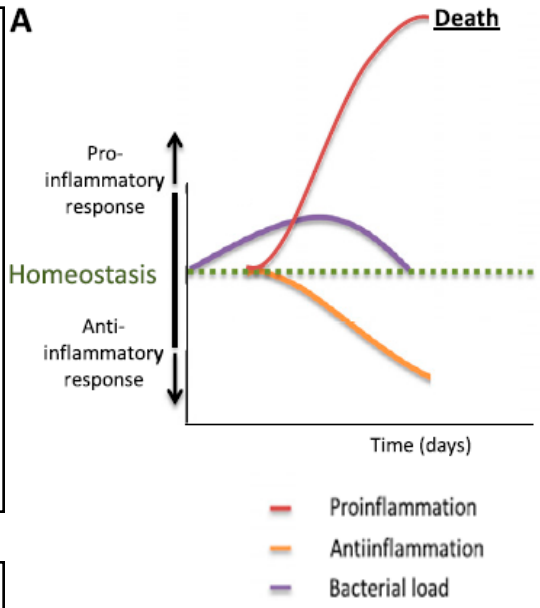
Which patients may benefit from Ig therapy?

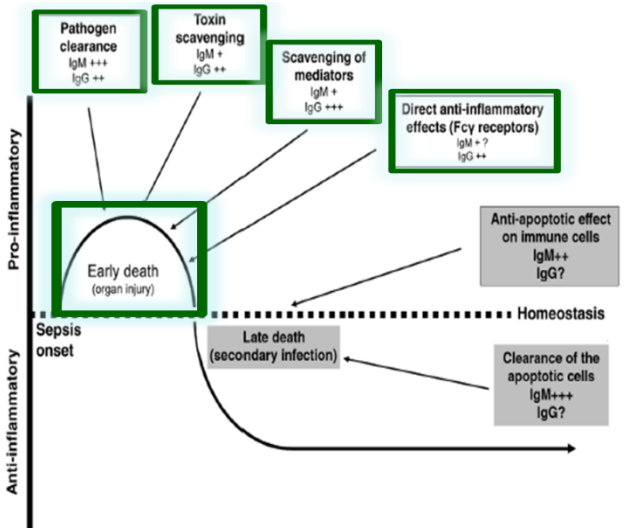
Clinical Scenario

Pathobiology

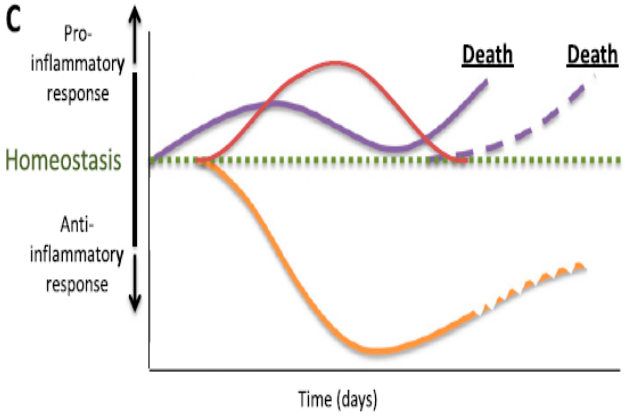
Mode of action

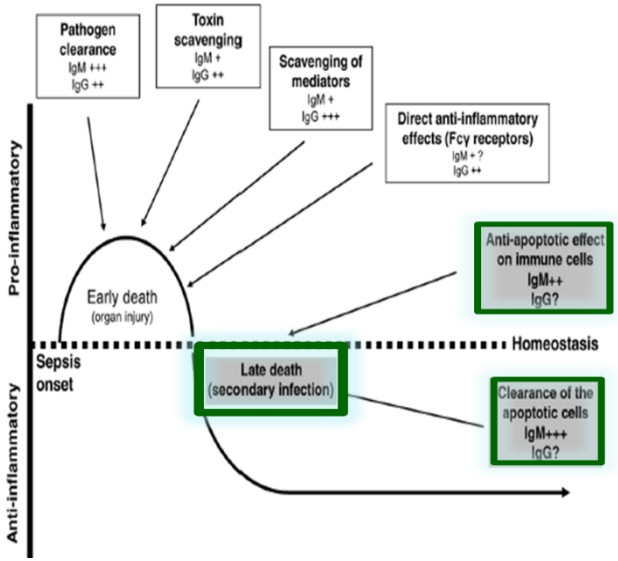
Healthy young adult with severe pneumonia by Strept Pneumonia:
Overwhelming pro-inflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure



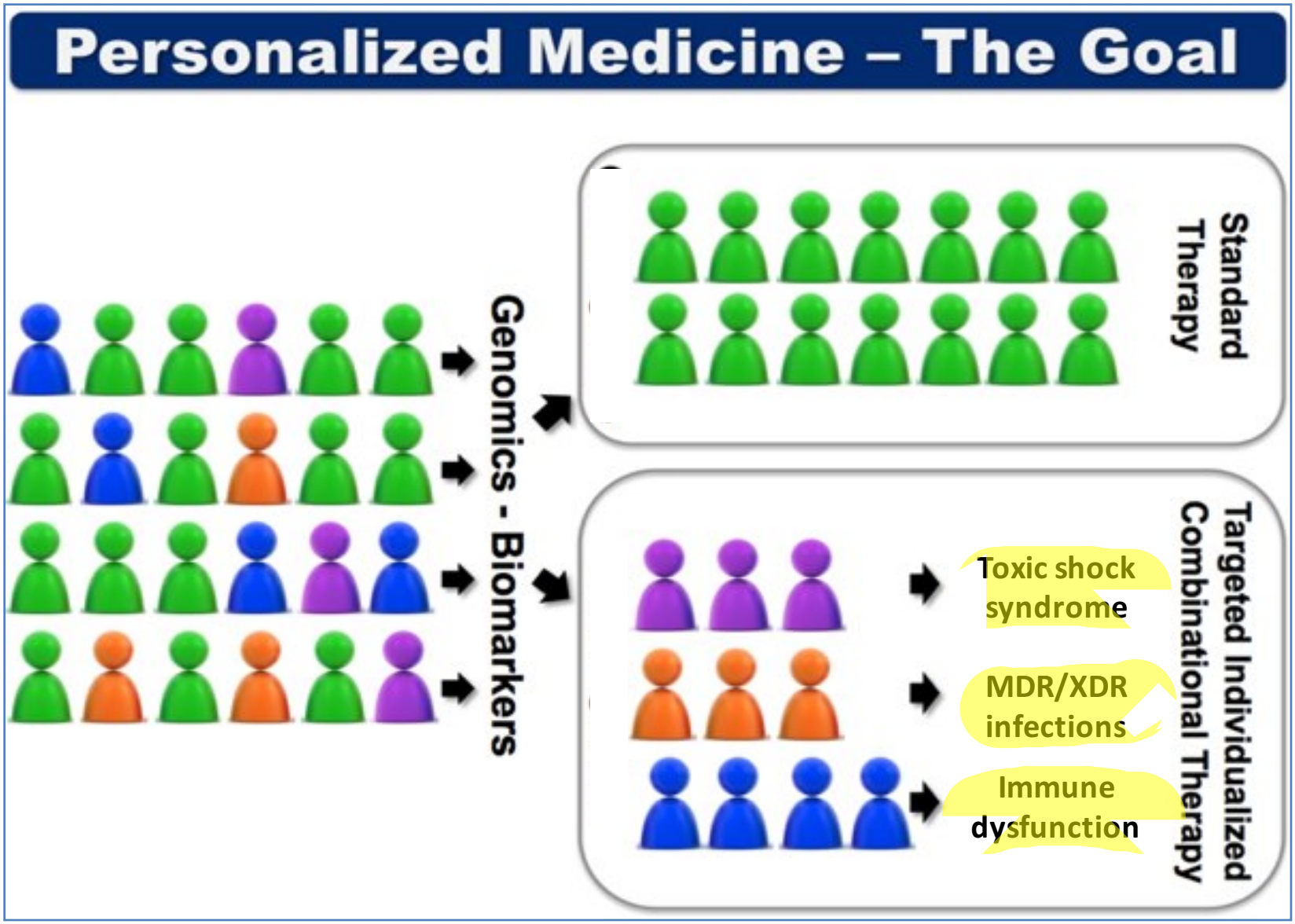


Patient with breakthrough infection after first sepsis :
Proinflammatory response combined with a pronounced or sustained anti inflammatory state with persisting bacterial or secondary (opportunistic) infections



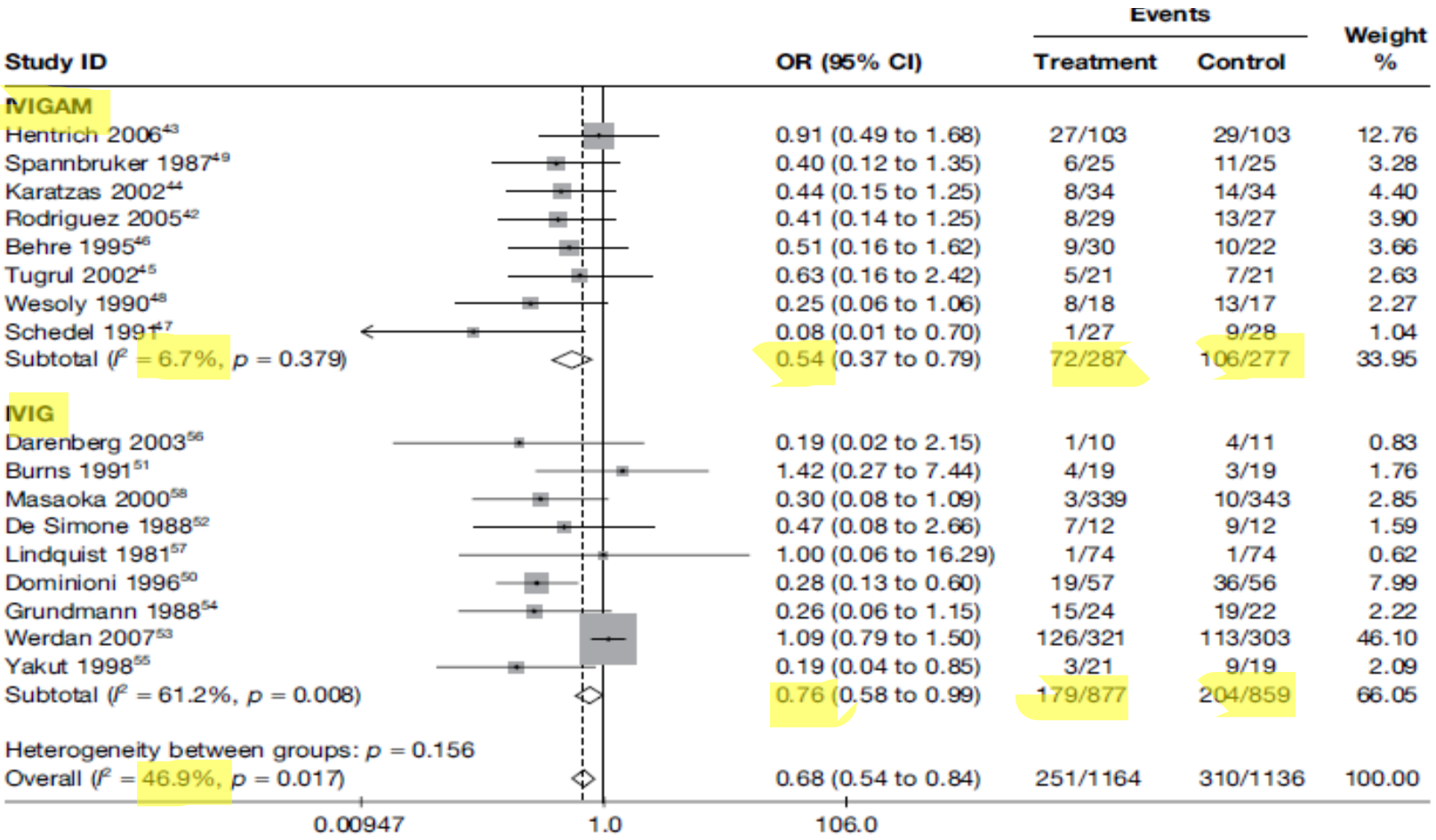


TAKE HOME PICTURE



Ig in SEVERE SEPSIS: EVIDENCE IN ADULTS META-ANALYSIS

IgG vs IgGAM



Studies using IgGAM showed a more consistent mortality reduction in the treatment arm as compared to those where standard polyclonal IgG were used.

Kreymann et al. Crit Care Med 2007
Soares et al. Health Technology Assessment 2010
Alejandra et al. Cochrane Database Syst Rev. 2013
Busani et al. Minerva Anestesiol 2016

Ig Therapy & MDR infections

ORIGINAL ARTICLE

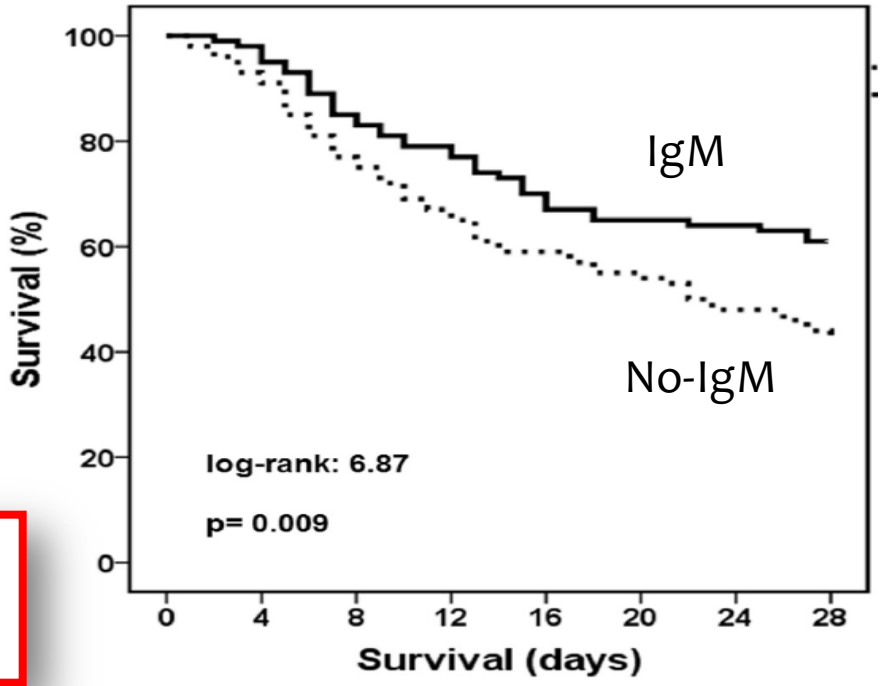
Improving outcomes of severe infections by multidrug-resistant pathogens with polyclonal IgM-enriched immunoglobulins

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.

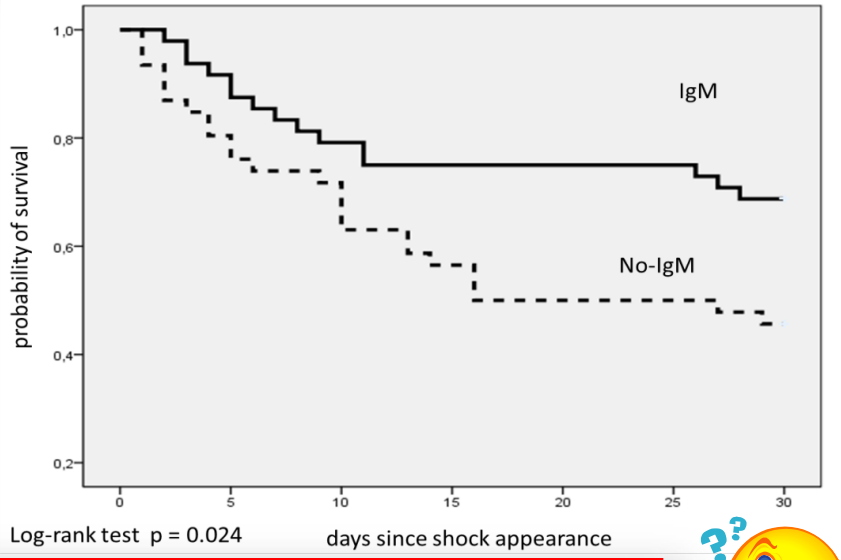


Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria: Risk Factors and Impact of Sepsis Treatments

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.

Septic Shock
IgM protocol

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

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

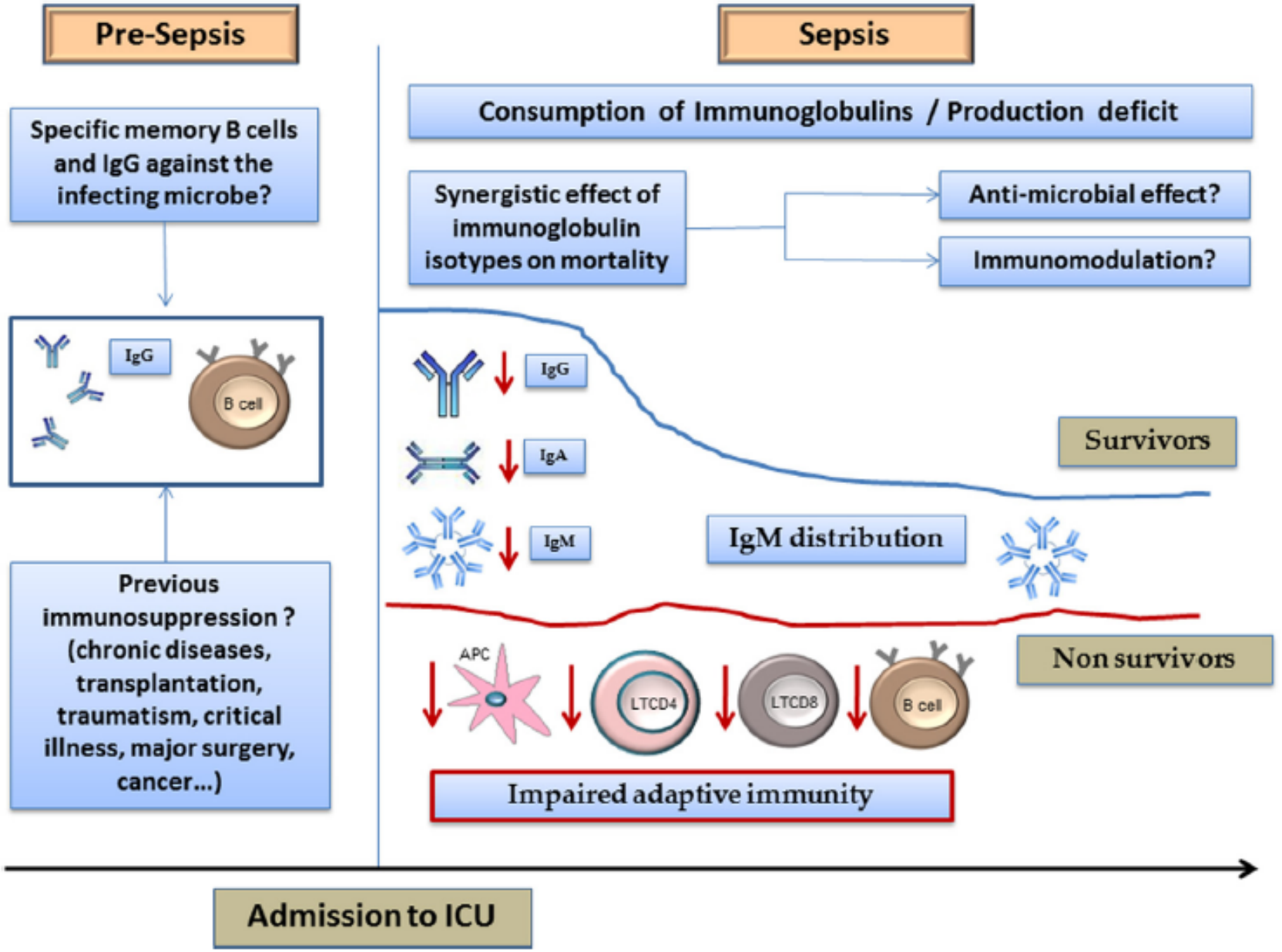
NO

IgM therapy
Time: 12-24 hours
- 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



Giamarellos-Bourboulis EJ et al. Int J Antimicrob Agents (2015) ;46; 1:S25-8.

Immunoglobulins in severe sepsis

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)*)

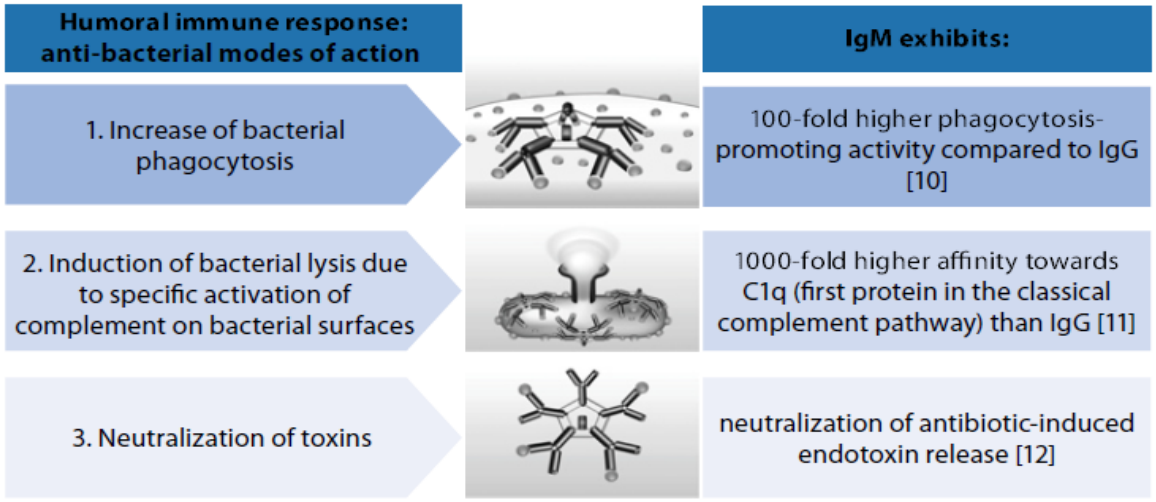
- The use of ivIgGAM may be ***considered*** for treatment of adult patients with severe sepsis or septic shock.

→ **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.*

IgM: HOW IT WORKS ?

- 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.



Ehrenstein et al. Nature Review 2010

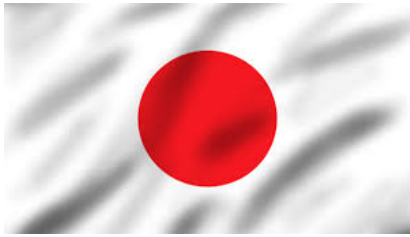
Fig. 1 The role of IgM in the humoral immune response

QUESTION 2: Intravenous polyclonal immunoglobulins may be useful as adjunctive therapy in critically ill patients with intra-abdominal sepsis ?

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?

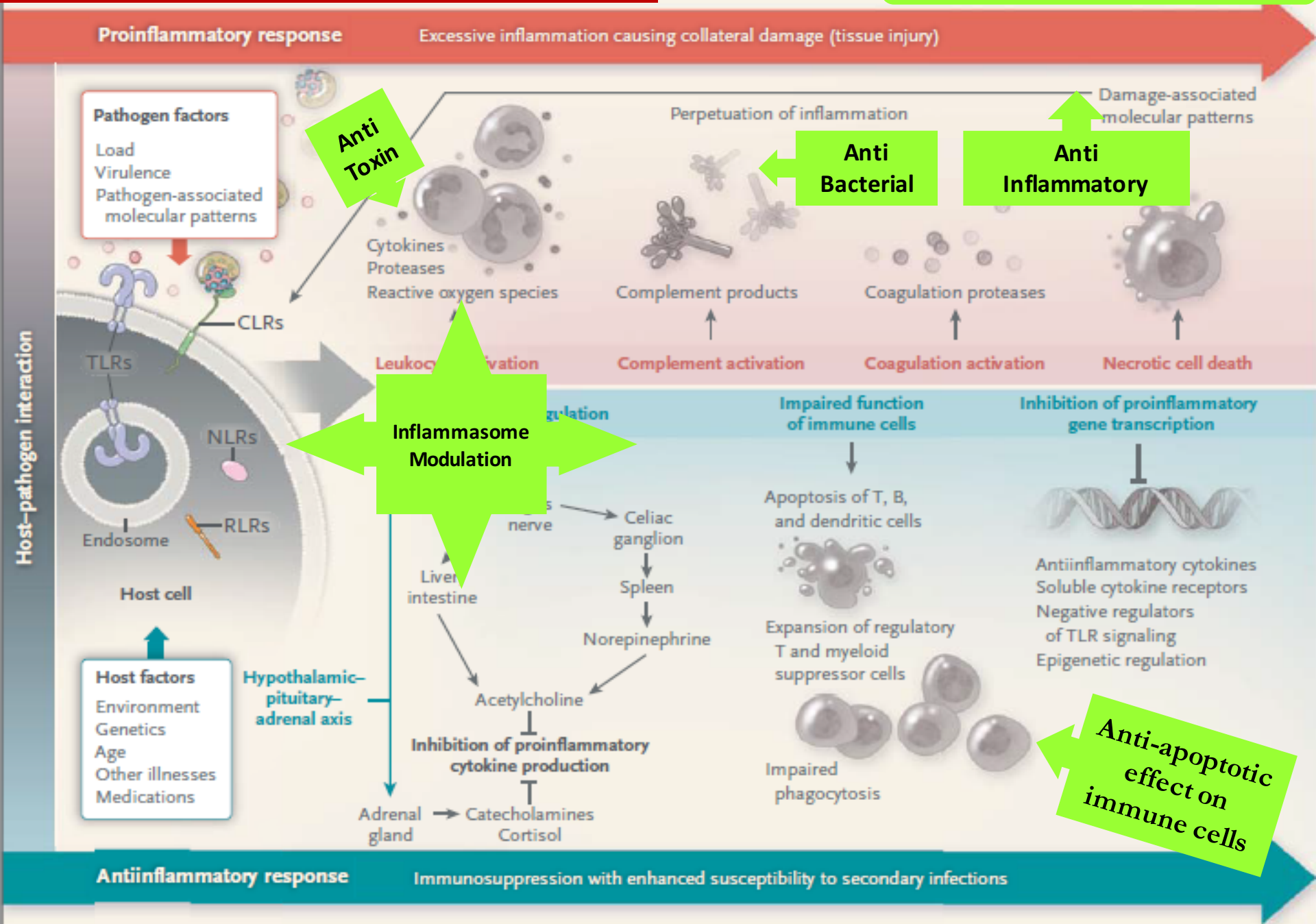
A3: A total immunoglobulin dose of ≥0.2 g/kg should be administered for ≥3 days (2C).

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

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

Ig Therapy: HOW MAY IT WORK ?

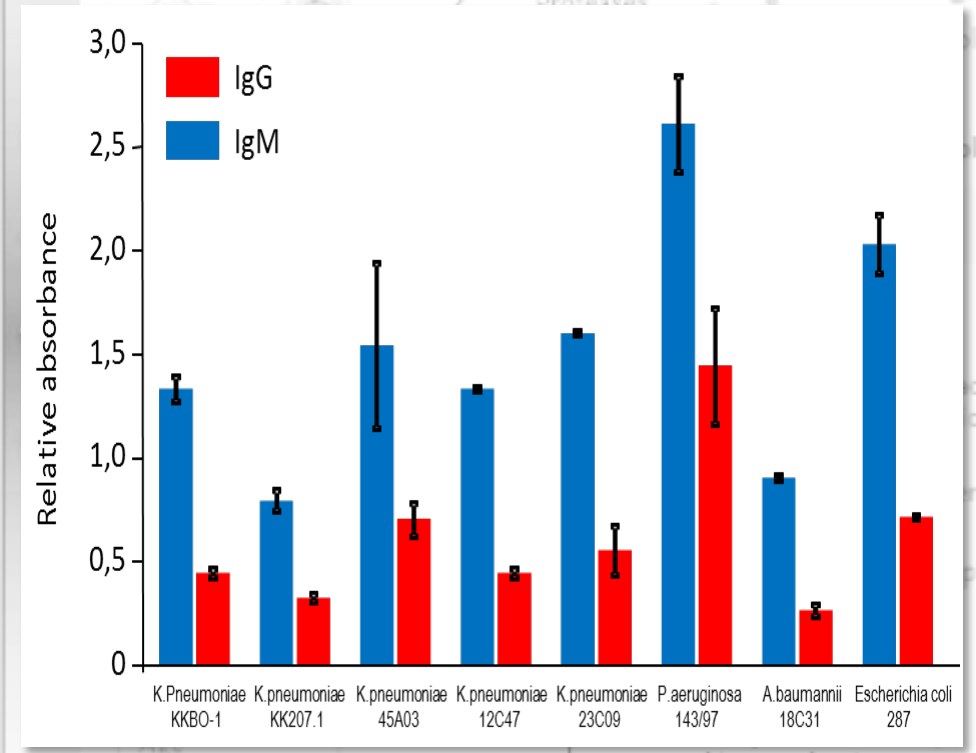
Pleiotropic effects



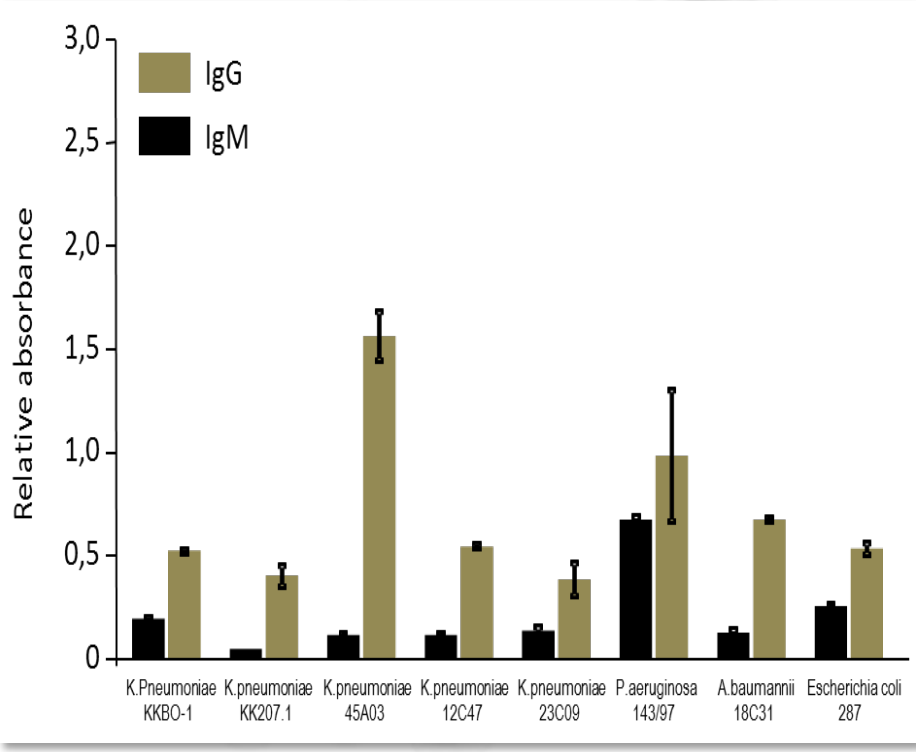
Why IgM preparation ?

Antibody titers vs ‘Italian 2013-2014 MDR’ bacteria

IgM - Pentaglobin©



IgG - Intratect ©



Courtesy by by Prof. Gian Maria Rossolini, Dpt. of Medical Biotechnologies - University of Siena and University of Florence I (Italy)

CONFIDENTIAL

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 b

Pathophysio Reasoning

The role a of IgG and IgM atory and imr been well des

Clinical Experience

In numero nous Ig provides pos questions remain open

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

say

yes

35th ISICEM

(OR MAYBE)

Parachutes reduce the risk effect s not been proved with rand

BMJ 2003;327:1459–61

Ig in SEVERE SEPSIS: WHAT EVIDENCE IN ADULTS?

Z. Molnar, ISCIEM Book, 2013

Requirements	Comments and concepts	Reference
Severity	Persistence of septic shock or severe sepsis with > 2 organ dysfunctions after initial resuscitation/treatment	Heintrich et al. Expert opinion
Timing	As early as possible. Best effects are expected if treatment is initiated within the first 8 h of sepsis	Berlot et al.
	Late start of treatment (48 h) is not recommended	Expert opinion
Target groups/subgroups with the highest benefit probability	Abdominal infections in surgical patients (peritonitis) presumably Gram-negative bacterial infections	Rodriguez et al.
	Meningococcal sepsis Toxic shock syndrome Overwhelming post splenectomy infection Necrotizing fasciitis	Expert opinion
Dosage (80 kg)	50 ml/h for the first 6 h (15 g), followed by 15 ml/h for 72 h (54 g), daily re-evaluation	Expert opinion
Exclusion criteria	Standing Do Not Resuscitation order or limitation of therapy, incurable metastatic malignant disease, neutropenia due to haematological malignancies and according to Summary Products Characteristics	Expert opinion

Ig in SEVERE SEPSIS: WHAT EVIDENCE IN ADULTS?

IgM enriched in septic shock

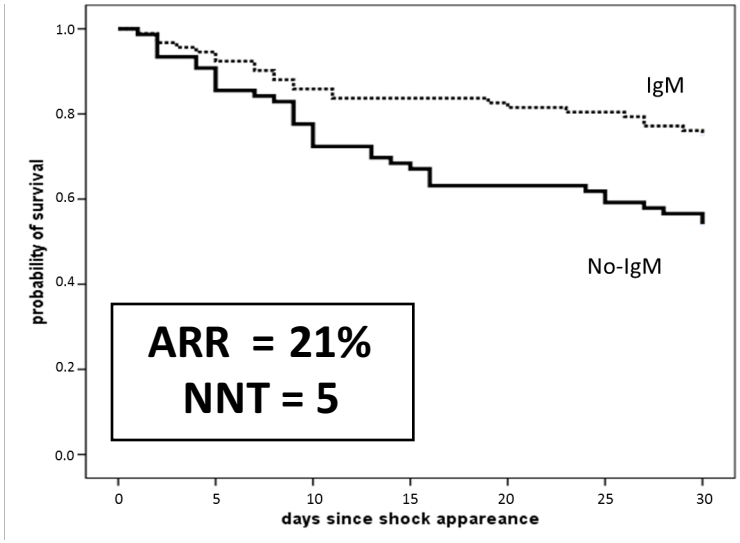
Intensive Care Med (2014) 40:1888–1896
DOI 10.1007/s00134-014-3474-6

ORIGINAL

Ilaria Cavazzuti
Giulia Serafini
Stefano Busani
Laura Rinaldi
Emanuela Biagioni
Marta Buoncristiano
Massimo Girardis

Early therapy with IgM-enriched polyclonal immunoglobulin in patients with septic shock

	No IgM (N=76)	IgM (N=92)	P value
30 days mortality;	35 (46,1)	23 (25,0)	0,004



ods: In 2008 we introduced IgM as a possible adjunctive therapy to be provided within 24 h after shock onset in the management protocol for patients with septic shock. In this retrospective study we included the adult patients suitable for IgM therapy admitted to our ICU from January 2008 to December 2011. An

Conclusions

Ig and the dose used. Our experience suggests that early adjunctive treatment with IgM at a dose of 250 mg/kg per day for 3 days results in an approximately 20 % reduction in the absolute risk of 30-day mortality in patients with septic shock treated according to guidelines. However, additional studies are needed to confirm these results and better evaluate the use of IgM therapy early on in patients with septic shock.

NEGATIVE TRIALS SINCE…

PROBLEM EXTENT

CEMETERY SECTION 2010-2014

Steroid

Glycemia

rh APC

EGDT

Albumine

CVVH high volume

CPFA

HES

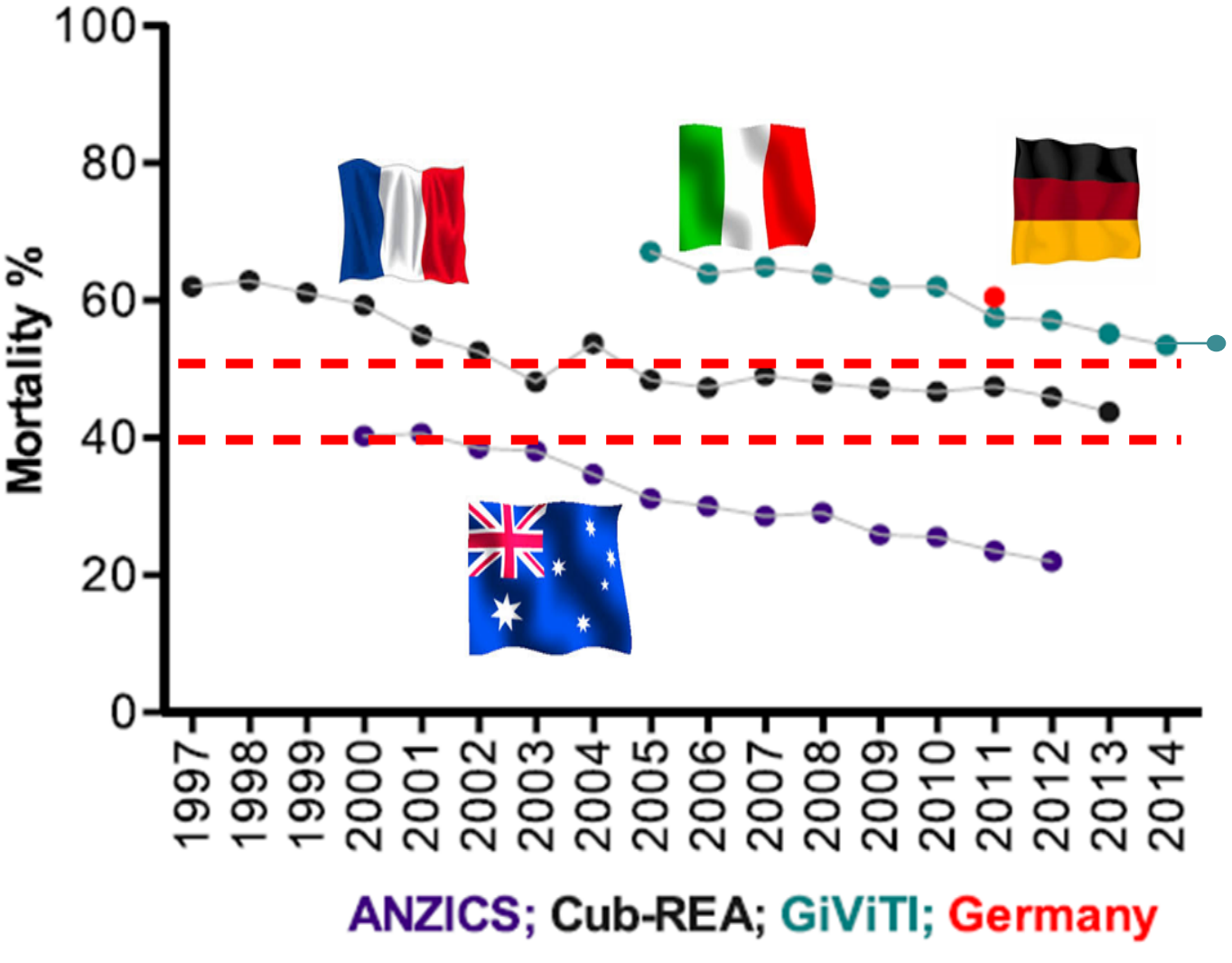
Selenium

Eritoran (anti-LPS)

SEPTIC SHOCK: 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
DOI 10.1186/s13054-015-1164-6



EBM and SEPSIS

GUIDELINES

Intensive Care Med (2008) 34:17–60
DOI 10.1007/s00134-007-0934-2

SPECIAL ARTICLE

R. Phillip Dellinger
Mitchell M. Levy
Jean M. Carlet
Julian Bion
Margaret M. Parker
Roman Jaeschke

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

50 Strong Recommendations (1 A-C)

19 Weak Recommendations (2 B-D)

Special Articles

February 2013

(*Crit Care Med* 2013; 41:580–637)

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

34 Strong Recommendations (1 A-C),

35 Weak Recommendations (2 B-D),

7 Ungraded Recommendations

The majority of STRONG recommendations
'DO NOT USE'

CONFERENCE REPORTS AND EXPERT PANEL

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

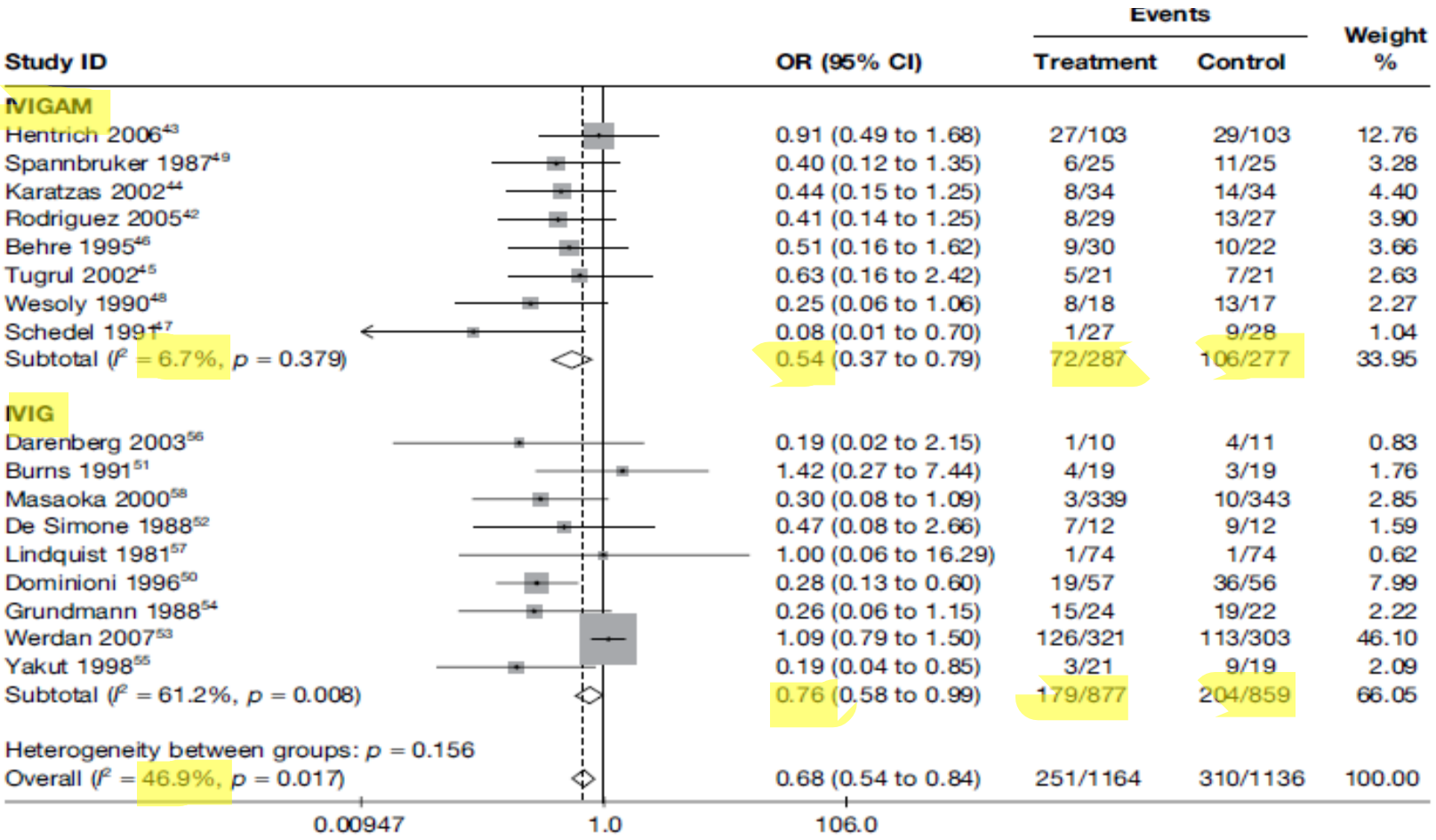
31 Strong Recommendations (1 A-C)

42 Weak Recommendations (2 A-D)

18 Best Practice Statement (ungraded)

Ig in SEVERE SEPSIS: EVIDENCE IN ADULTS META-ANALYSIS

IgG vs IgGAM

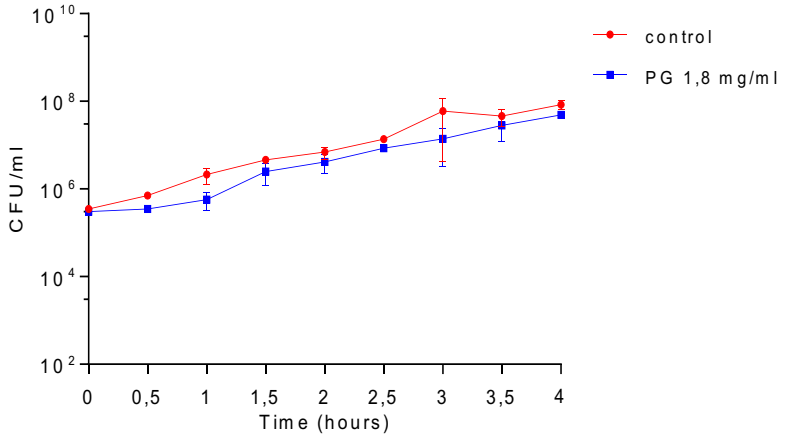


Studies using IgGAM showed a more consistent mortality reduction in the treatment arm as compared to those where standard polyclonal IgG were used.

Kreymann et al. Crit Care Med 2007
Soares et al. Health Technology Assessment 2010
Alejandra et al. Cochrane Database Syst Rev. 2013
Busani et al. Minerva Anestesiol 2016

Potential antimicrobial activity of Pentaglobin in Time-Kill experiments

A. baumannii 18C31



Significant delay in growth after 30 minutes of exposure to Pentaglobin