# Maneig Multimodal de la Sèpsia

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# Conflict of Interest

Palex

GETINGE

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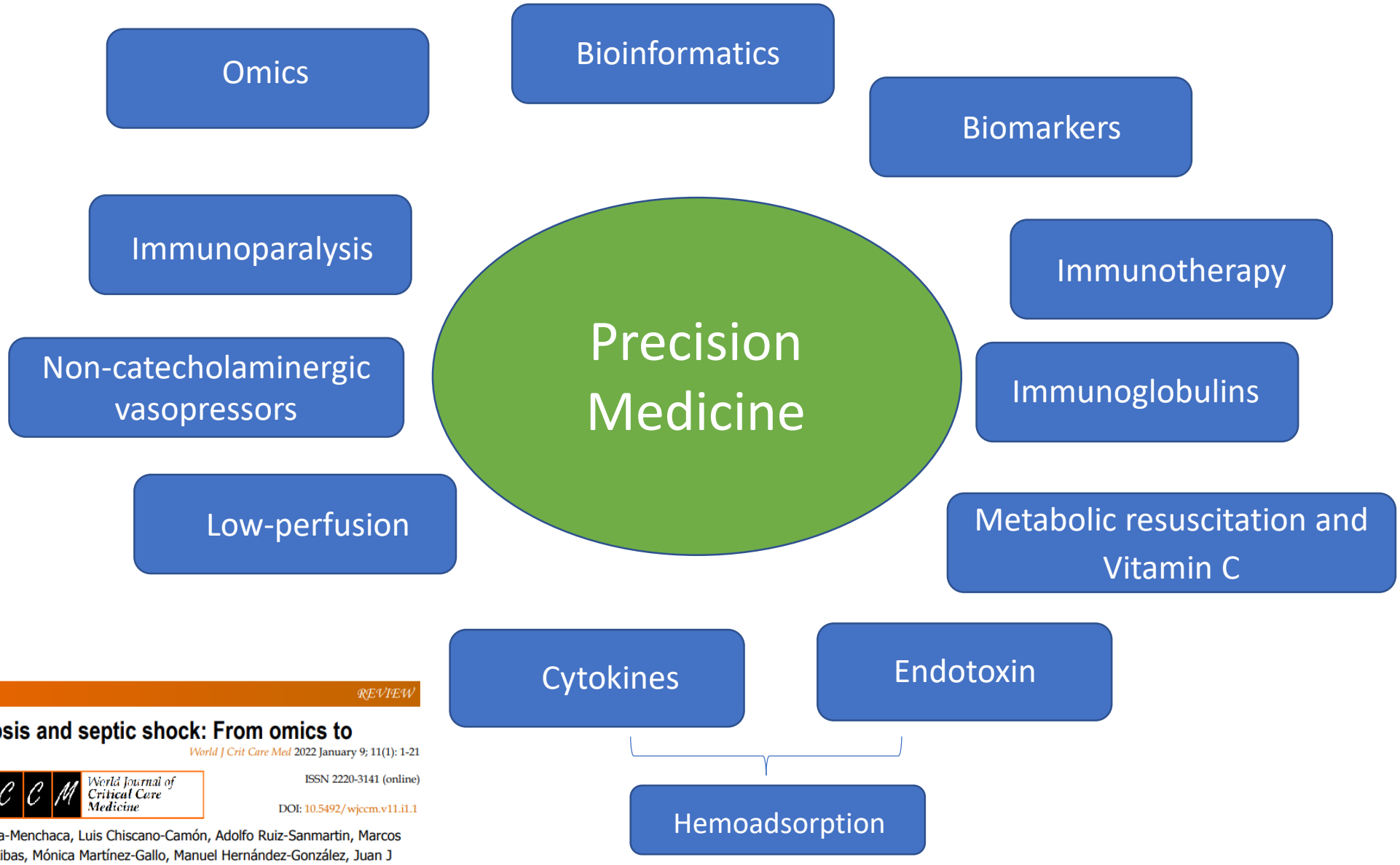
AOP HEALTH




REVIEW

**Precision medicine in sepsis and septic shock: From omics to clinical tools**

*World J Crit Care Med* 2022 January 9; 11(1): 1-21

World Journal of Critical Care Medicine

ISSN 2220-3141 (online)

DOI: 10.5492/wjccm.v11.i1.1

Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Vicent Ribas, Mónica Martínez-Gallo, Manuel Hernández-González, Juan J Gonzalez-Lopez, Nieves Larrosa, Ricard Ferrer

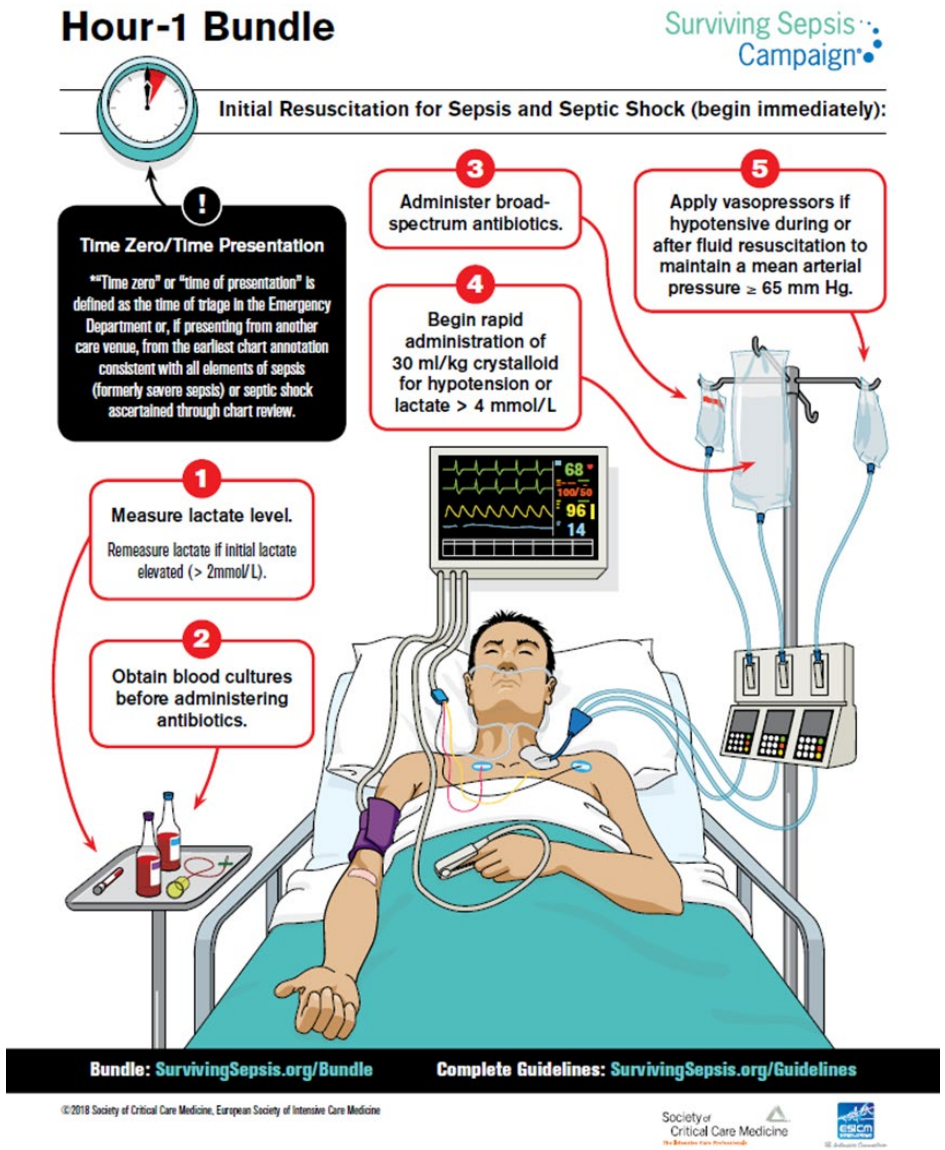
GUIDELINES

# Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

*Intensive Care Med (2021) 47:1181–1247*
https://doi.org/10.1007/s00134-021-06506-y

# Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

**Results:** Overall lower mortality was observed in high (29.0%) versus low (38.6%) resuscitation bundle compliance sites ($p < 0.001$) and between high (33.4%) and low (32.3%) management bundle compliance sites ($p = 0.039$). Hospital mortality rates dropped 0.7% per site for every three months (quarter) of participation ($p < 0.001$). Hospital and intensive care unit length of stay decreased 4% (95% CI: 1% - 7%; $p = 0.012$) for every 10% increase in site compliance with the resuscitation bundle.

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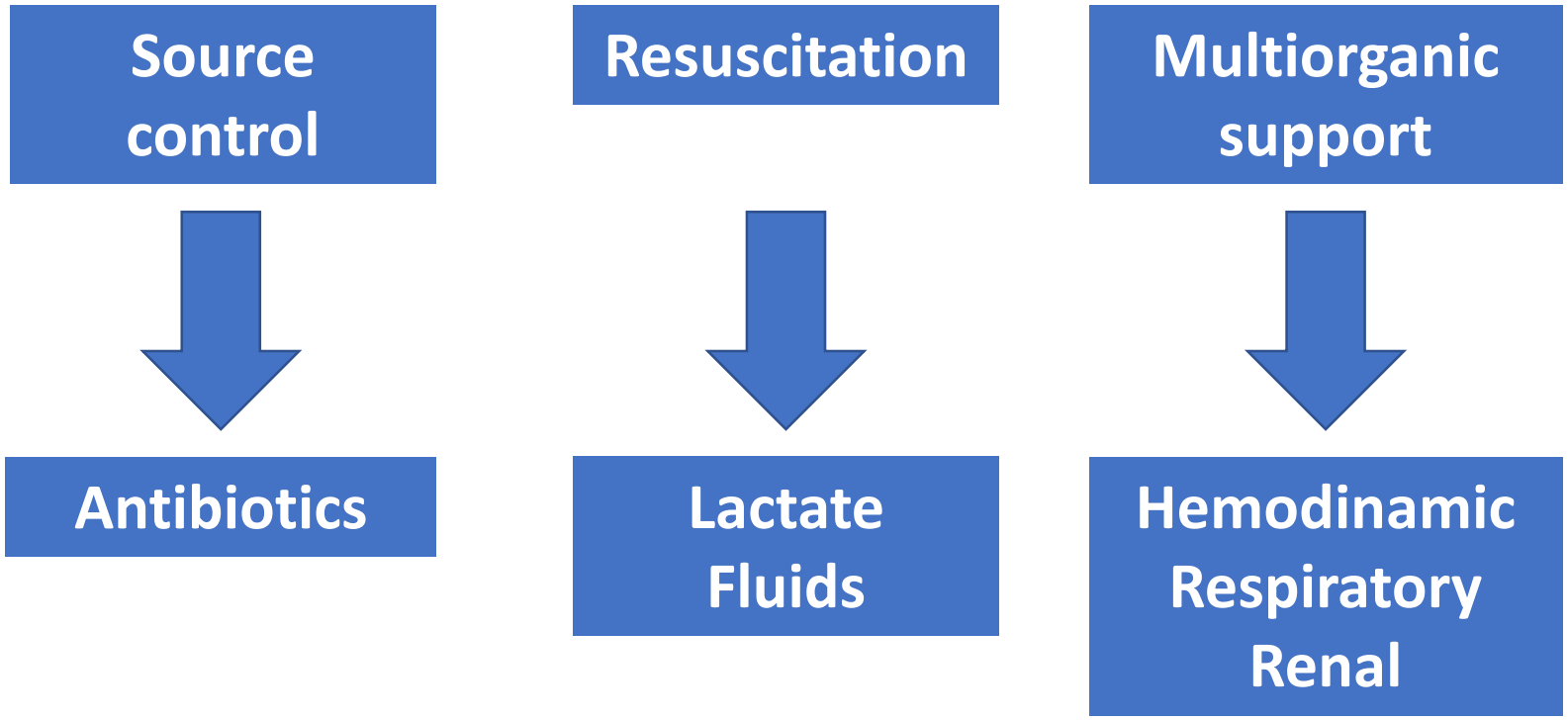
# Treatment SEPSIS – SEPTIC SHOCK




## PERSONALIZED MEDICINE
## Rescue Therapies

**e-Table 2.** Observational Studies for Refractory Shock

| Demographic Characteristics | | | | | Vasopressors[a] | | | | Mortality, No. (%)[b] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Year | Population | Total N | Sepsis (%) | Type | Refractory Shock Threshold | Mean±SD or Median (IQR) | Mortality Threshold | Inpatient | 30-day |
| Benbenishty et al[11] | 2011 | Unselected | 72 | 8.3 | Norepinephrine<br>Epinephrine | 0.5<br>0.5 | 3.3±7.5<br>3.2±10.3 | --- | 39 (54) | --- |
| Brown et al[12c] | 2013 | Unselected | 443 | 54.4 | Norepinephrine equivalents | 1.0 | --- | --- | --- | --- |
| Chou et al[13] | 2011 | CRRT | 279 | 73.5 | Norepinephrine<br>Dopamine | 0.3<br>20 | --- | --- | 237 (85) | --- |
| Dopp-Zemel and Groeneveld[14] | 2013 | Unselected | 113 | 34.5 | Norepinephrine<br>Dopamine | 0.9<br>--- | 1.2 (0.4)<br>2.2 (0) | --- | --- | 74 (66) |
| Dunser et al[15] | 2003 | Unselected | 48 | --- | Norepinephrine<br>Vasopressin | --- | --- | --- | 34 (71) | --- |
| Jenkins et al[16] | 2009 | Unselected | 64 | 78.1 | Norepinephrine<br>Epinephrine | 100 mcg/min<br>100 mcg/min | ---<br>120 mcg/min | --- | 60 (94) | --- |
| Kastrup et al[17] | 2013 | Unselected | 1,543 | 57.4 | Norepinephrine<br>Epinephrine | --- | 0.5±0.8<br>0.6±1.9 | 294.3 mcg/kg<br>70.4 mcg/kg | 275 (18) | --- |
| Katsaragakis et al[18] | 2006 | Surgical | 12 | --- | Norepinephrine | 4 | 4.1-9[d] | --- | 8 (67) | --- |
| Luckner et al[19] | 2005 | Unselected | 316 | 32.6 | Norepinephrine<br>Epinephrine<br>Vasopressin | 0.3<br>0.3<br>--- | 1.1±1.3<br>0.2±0.2<br>--- | 0.5 | 161 (51) | --- |
| Luckner et al[20] | 2007 | Unselected | 78 | 46.2 | Norepinephrine<br>Epinephrine<br>Vasopressin | 0.3<br>0.3<br>--- | 1.1±1.1<br>0.1±0.05<br>--- | --- | --- | 44 (56) |
| Sviri et al[21] | 2014 | Unselected | 166 | --- | Norepinephrine<br>Epinephrine | 40 mcg/min<br>40 mcg/min | --- | --- | 124 (75) | --- |

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a] All doses presented as mcg/kg/min unless specified.
[b] Mortality refers to the entire cohort rather than individual subgroups.
[c] Only 90-day mortality available.
[d] Range.

Jentzer JC et al. Chest. 2018 Aug;154(2):416-426

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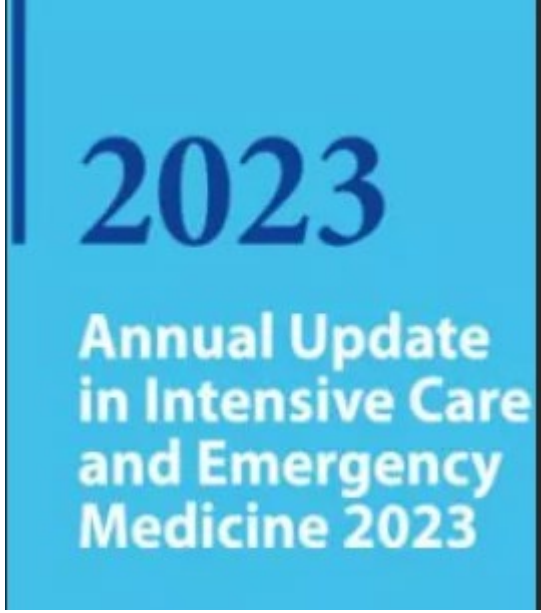
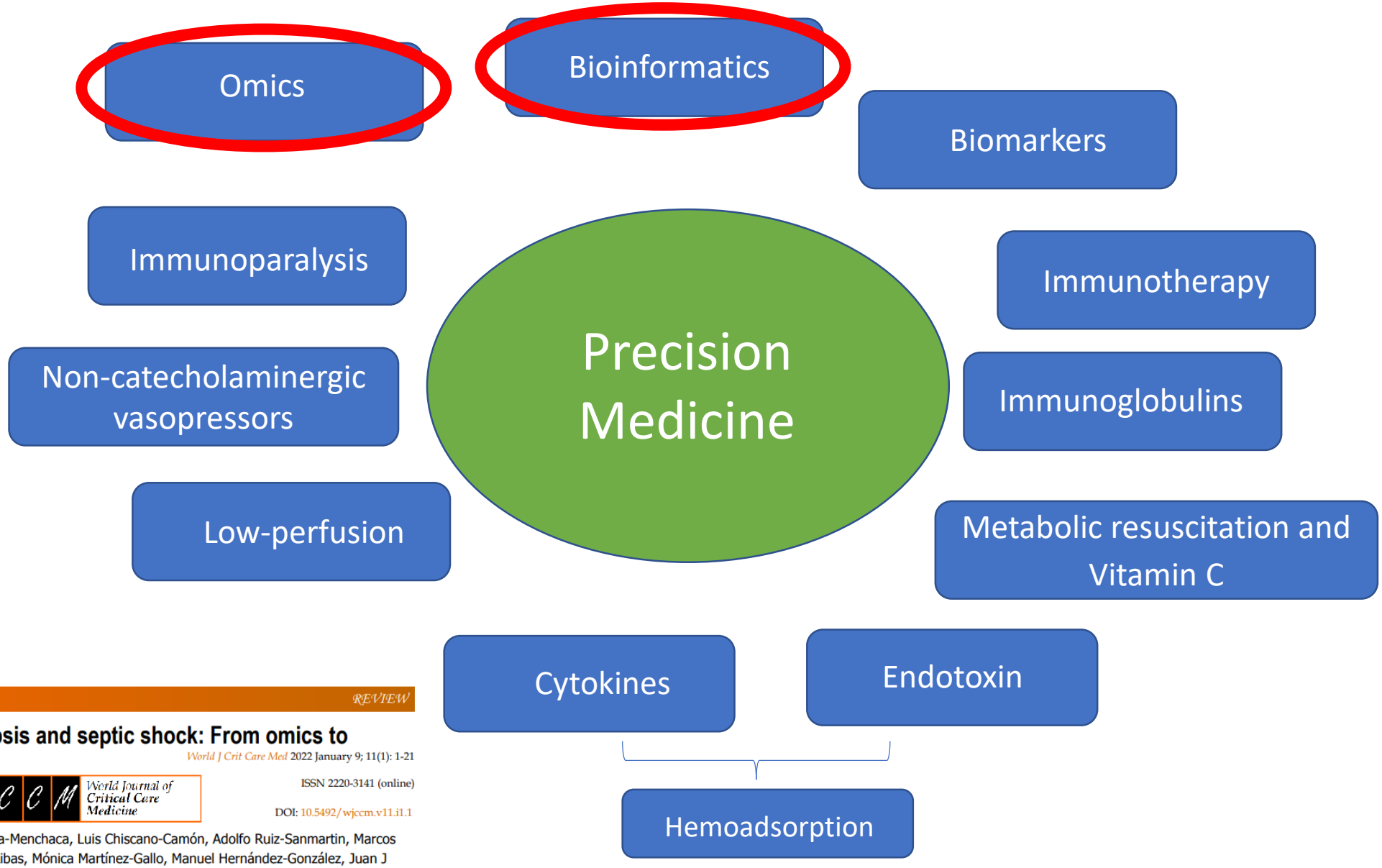
| Precision medicine strategies | | Target (s) | Clinical application |
|---|---|---|---|
| Omics technologies | Genomics and epigenomics | Genetic variants | Prognosis, severity |
| | | Genotypes | Susceptibility to sepsis |
| | Transcriptomics | Gene expression, activity and regulation | Susceptibility to sepsis |
| | | Sepsis response signatures | Severity, prognosis |
| | Metabolomics | Small molecules produced by cells | Prognosis |
| | | Metabolomic profile | Response to treatment |
| | Proteomics | Proteins expressed by the genome under certain conditions | Diagnosis, Prognosis |
| | | Biomarkers | Diagnosis, prognosis |
| Immunoglobulins | | Immunoglobulin levels | Sepsis-associated hypogammaglobulinemia |
| Hemoadsorption | High Endotoxinemia | Endotoxinemia | Rescue therapy |
| | Severe Hypercytokinemia | Cytokine levels | Rescue therapy |
| | Sequential Hemoadsorption | Endotoxin and Cytokine hemoadsorption | Rescue therapy |
| Immunotherapy | | Hyperinflammation vs immunoparalysis<br>Secondary infections and complications<br>Macrophage activation-like syndrome<br>HLA-DR/CD14 expression vs hiperferritinemia | Immunomodulatory therapies |
| Non-catecholaminergic vasopressors | | Vasopressin, Selepressin, Terlipressin<br>Methylene blue, Angiotensin II | Catecholamine sparing agent<br><br>Rescue therapy |
| Low-Perfusion phenotipe | | Patients with septic cardiomyopathy | ECMO |




## Precision Medicine in Septic Shock

L. Chiscano-Camón, J. C. Ruiz-Rodriguez, and R. Ferrer

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| | | |
|---|---|---|
| **Genomics and epigenomics** | Genetic variants | Prognosis, severity |
| | Genotypes | Susceptibility to sepsis |
| **Transcriptomics** | Gene expression, activity and regulation | Susceptibility to sepsis |
| | Sepsis response signatures | Severity, prognosis |
| **Metabolomics** | Small molecules produced by cells | Prognosis |
| | Metabolomic profile | Response to treatment |
| **Proteomics** | Proteins expressed by the genome under certain conditions | Diagnosis, Prognosis |
| | | |

RESEARCH ARTICLE

# Characterization of a proteomic profile associated with organ dysfunction and mortality of sepsis and septic shock

Adolfo Ruiz-Sanmartín[1,2,3], Vicent Ribas[4], David Suñol[4], Luis Chiscano-Camón[1,2,3], Clara Palmada[1,2], Iván Bajaña[1,2], Nieves Larrosa[5,6,7], Juan José González[5,6,7], Núria Canela[8], Ricard Ferrer[1,2,3], Juan Carlos Ruiz-Rodríguez[1,2,3]*

**VALIDATION OF A GENE EXPRESSION-BASED SUBCLASSIFICATION STRATEGY FOR PEDIATRIC SEPTIC SHOCK**

*Crit Care Med.* 2011 November ; 39(11): 2511–2517. doi:10.1097/CCM.0b013e3182257675.

# Proteolysis in septic shock patients: plasma peptidomic patterns are associated with mortality

*British Journal of Anaesthesia*, 121 (5): 1065–1074 (2018)

doi: 10.1016/j.bja.2018.05.072

# Mortality prediction in patients with severe septic shock: a pilot study using a target metabolomics approach

SCIENTIFIC REPORTS | 6:20391 | DOI: 10.1038/srep20391

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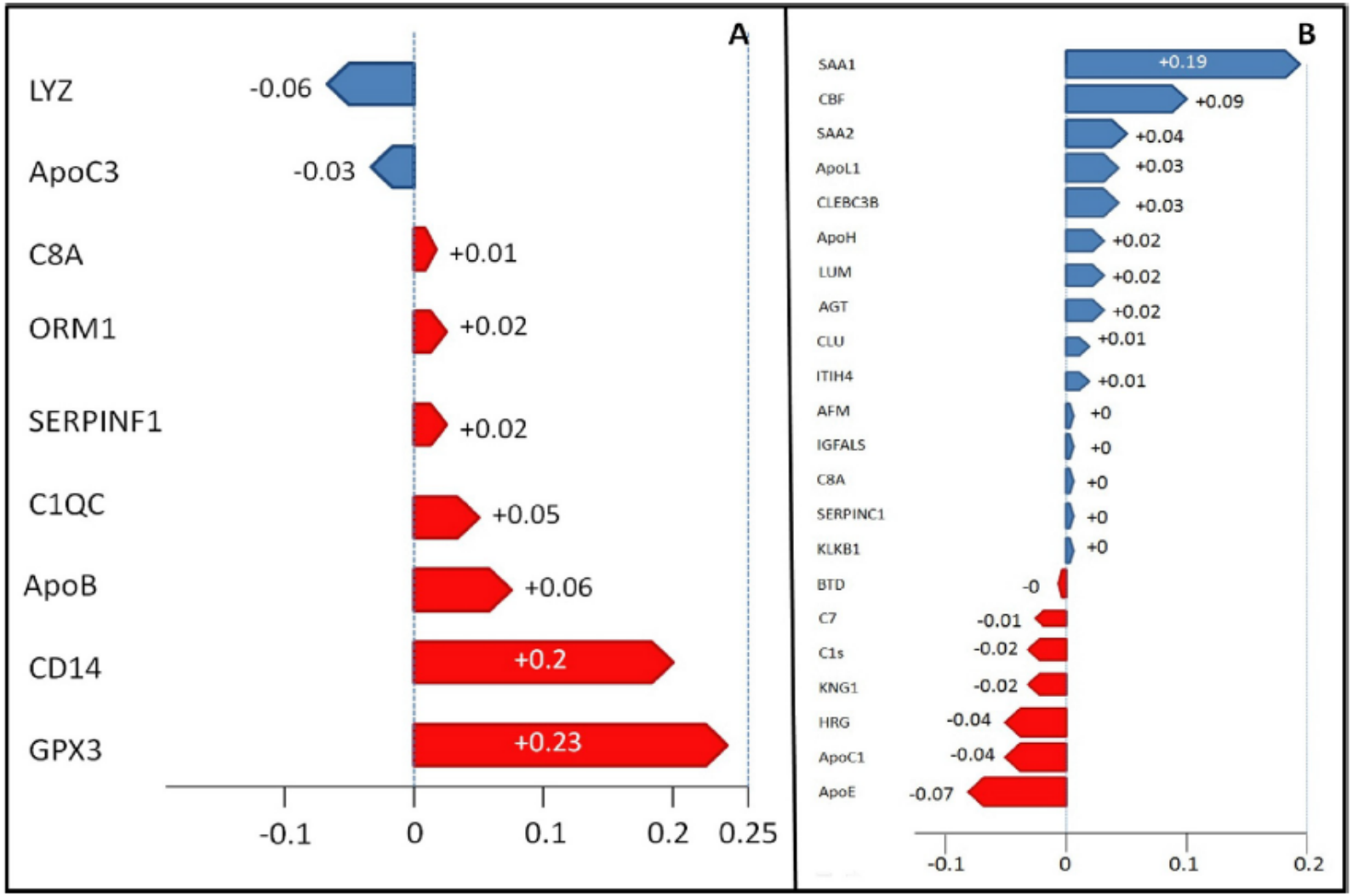


**Prospective, observational and single-center**

**Met the criteria for sepsis**

*Nine proteins (GPX3, APOB, ORM1, SERPINF1, LYZ, C8A, CD14, APOC3 and C1QC) were* ***associated with organ dysfunction (SOFA > 6)*** *with an accuracy of 0.82 ± 0.06, precision of 0.85 ± 0.093, sensitivity 0.81 ± 0.10, specificity 0.84 ± 0.10 and AUC 0.82 ± 0.06.*

Fig 2. Shap values graphics. A) blue = proteins expressed in patients with SOFA ≤ 6, red = proteins expressed in patients with SOFA > 6. B) blue = proteins expressed in patients survivors, red = proteins expressed in patients non-survivors.

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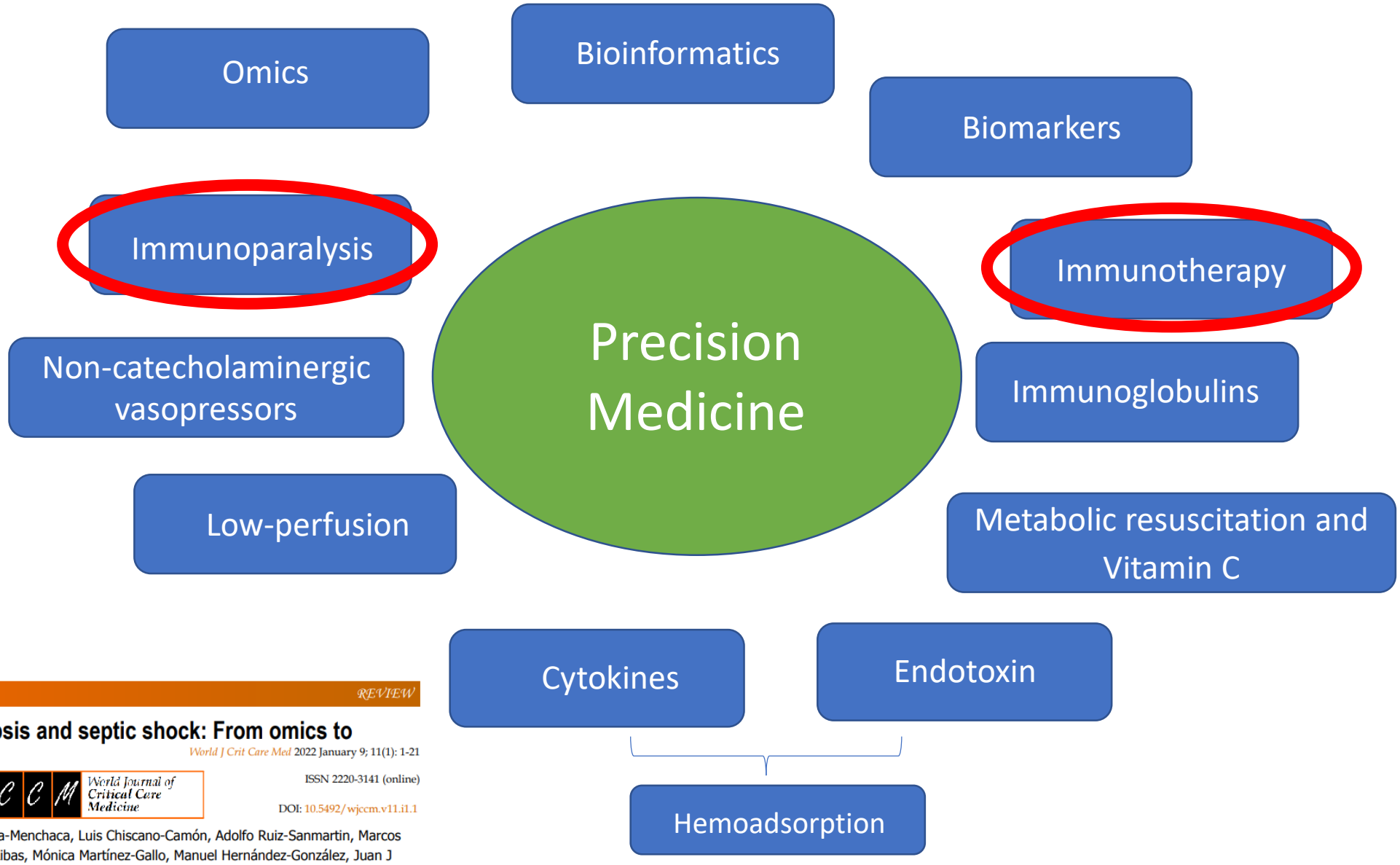


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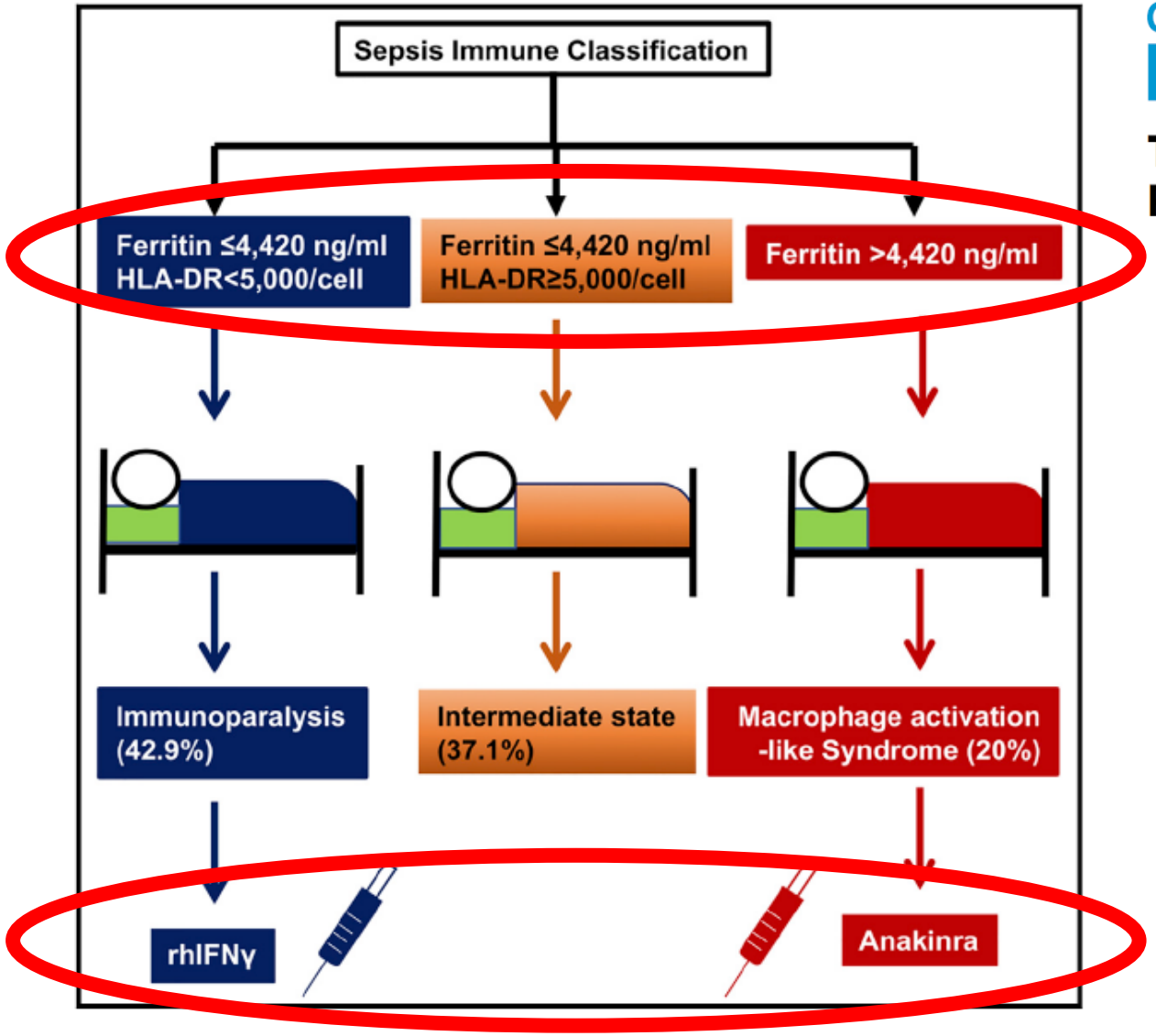



Cell Reports
Medicine

Article

## Toward personalized immunotherapy in sepsis: The PROVIDE randomized clinical trial

*Crit Care Med.* 2016 February ; 44(2): 275–281. doi:10.1097/CCM.0000000000001402.

## Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial

# Precision Immunotherapy for Sepsis

REVIEW
published: 05 September 2018
doi: 10.3389/fimmu.2018.01926

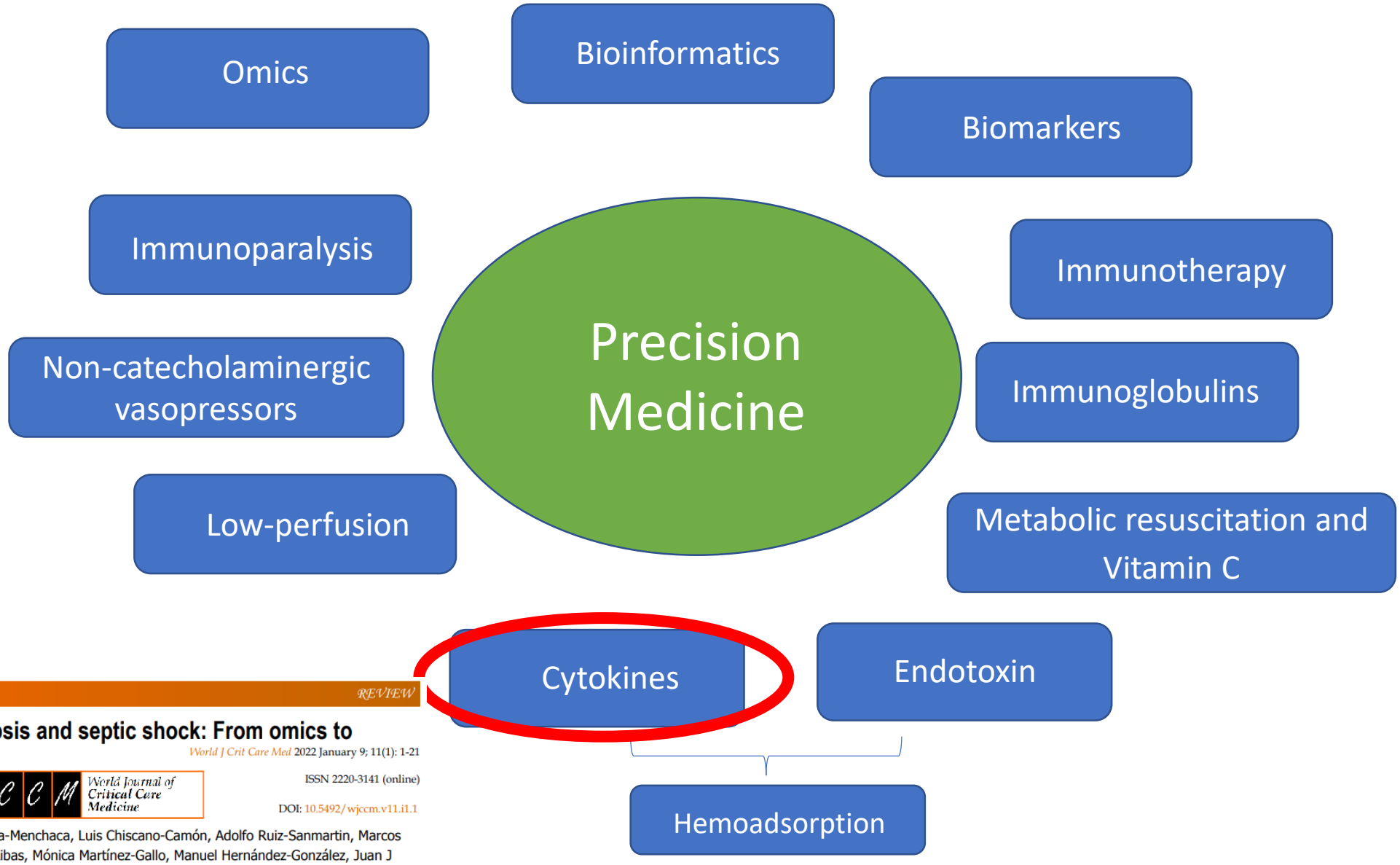
*Annemieke M. Peters van Ton[1], Matthijs Kox[1,2], Wilson F. Abdo[1] and Peter Pickkers[1,2]**

frontiers in Immunology

**TABLE 1** | Examples of immunotherapy in sepsis.

| | Mechanism of action | Summary of evidence |
|---|---|---|
| **IMMUNOSUPPRESSIVE COMPOUNDS** | | |
| anti-TNFα (various) | Blocks pro-inflammatory effects of TNFα | - Individual studies: no beneficial effects (94)<br>- Meta-analysis: reduced 28-day mortality, OR = 0.91 [95% CI 0.83–0.99] (94) |
| IL-1RA (anakinra) | Blocks IL-1 receptor → inhibits downstream pro-inflammatory effects | - Study in unselected population of severe sepsis patients: no effect on mortality (21)<br>- *Post-hoc* analysis in subgroup of hyperinflamed patients with macrophage activation syndrome: lower mortality (93) |
| **IMMUNOSTIMULATORY COMPOUNDS** | | |
| GM-CSF | Enhances antigen presenting capacity and pro-inflammatory cytokine production | - Meta-analysis: no effect on 28-day mortality in sepsis patients (probably underpowered) (107)<br>- Biomarker-guided study (based on mHLA-DR expression): restoration of monocytic immunocompetence, shorter duration of mechanical ventilation, and more swift improvement of disease severity scores as exploratory endpoints (95) |
| IFN-γ | Enhances antigen presenting capacity and pro-inflammatory cytokine production | - Human endotoxemia model (mimicking sepsis-induced immunoparalysis): increased mHLA-DR expression, restored TNFα production and further attenuated IL-10 production (43)<br>- Case series in patients suffering from opportunistic infections not responding to regular treatment: increased mHLA-DR expression and cytokine production by *ex vivo*-stimulated leukocytes (97) |
| Recombinant human IL-7 | Reduces apoptosis and enhances lymphocyte function | - Phase 2 trial in septic shock patients with severe lymphopenia: safe, well-tolerated and reversal of lymphopenia (111) |
| anti-PD-(L)1 | Inhibits PD-1-PD-L1 interaction → reduces apoptosis and promotes T-cell responses | - Preclinical data in sepsis models: promising results (e.g., prevention of sepsis-induced depletion of lymphocytes, increased TNF-α and IL-6 production, decreased IL-10 production, enhanced bacterial clearance, improved survival (102)<br>- Clinical data in the oncology field: effective, especially in advanced melanoma and non-small cell lung cancer.<br>- No clinical trials in sepsis patients yet. |

*TNFα, tumor necrosis factor alpha; IL1RA, Interleukin-1 receptor antagonist; IL-1, interleukin-1; GM-CSF, granulocyte-macrophage colony stimulating factor; IFNγ, interferon gamma IL-7, interleukin-7; anti-PD-L1, programmed death-1 ligand antagonist; OR, odds ratio.*

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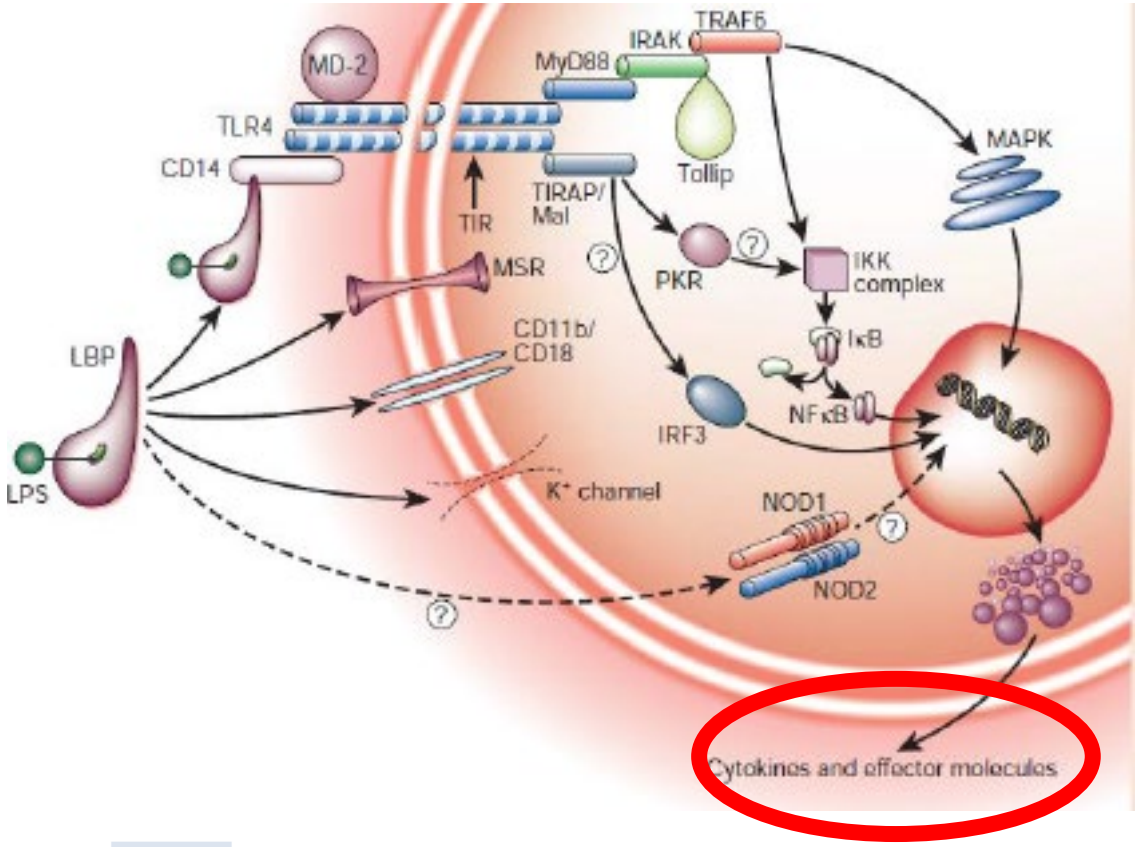
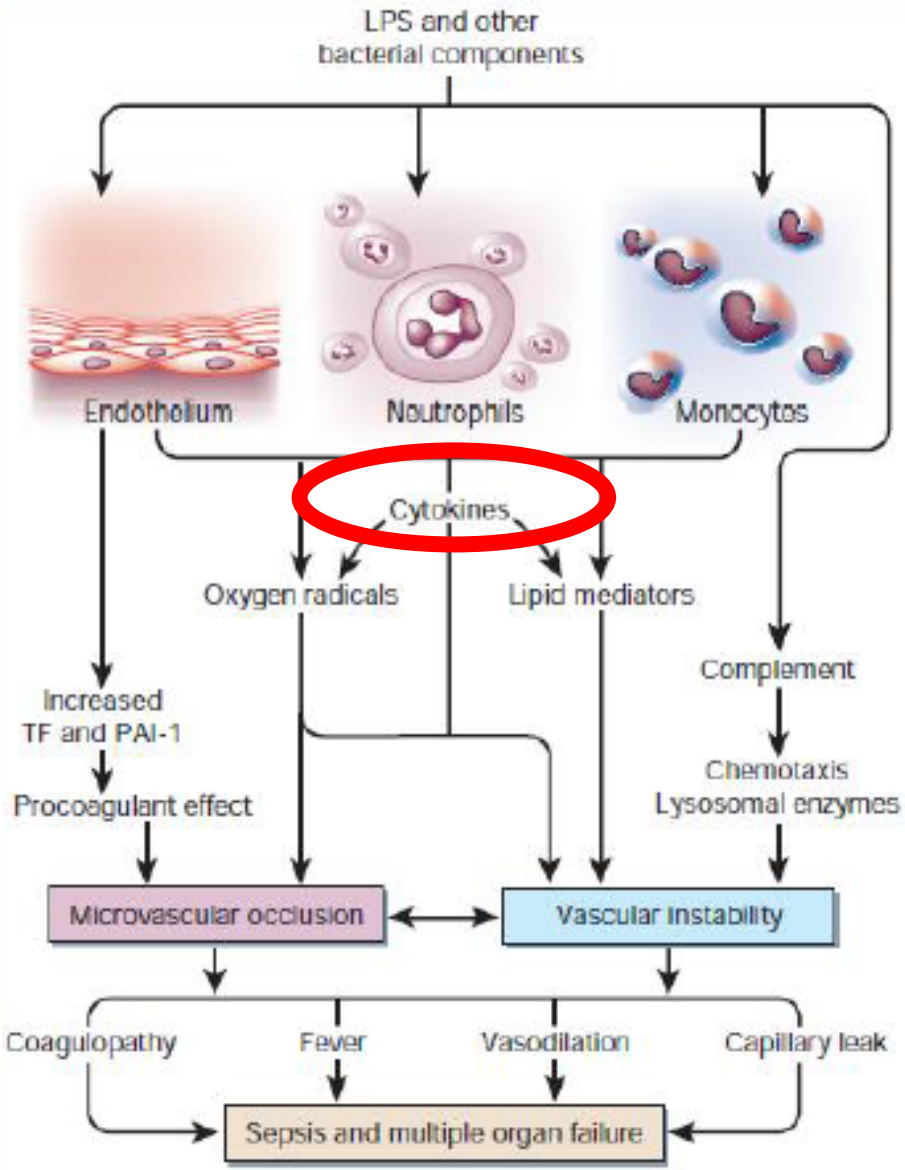


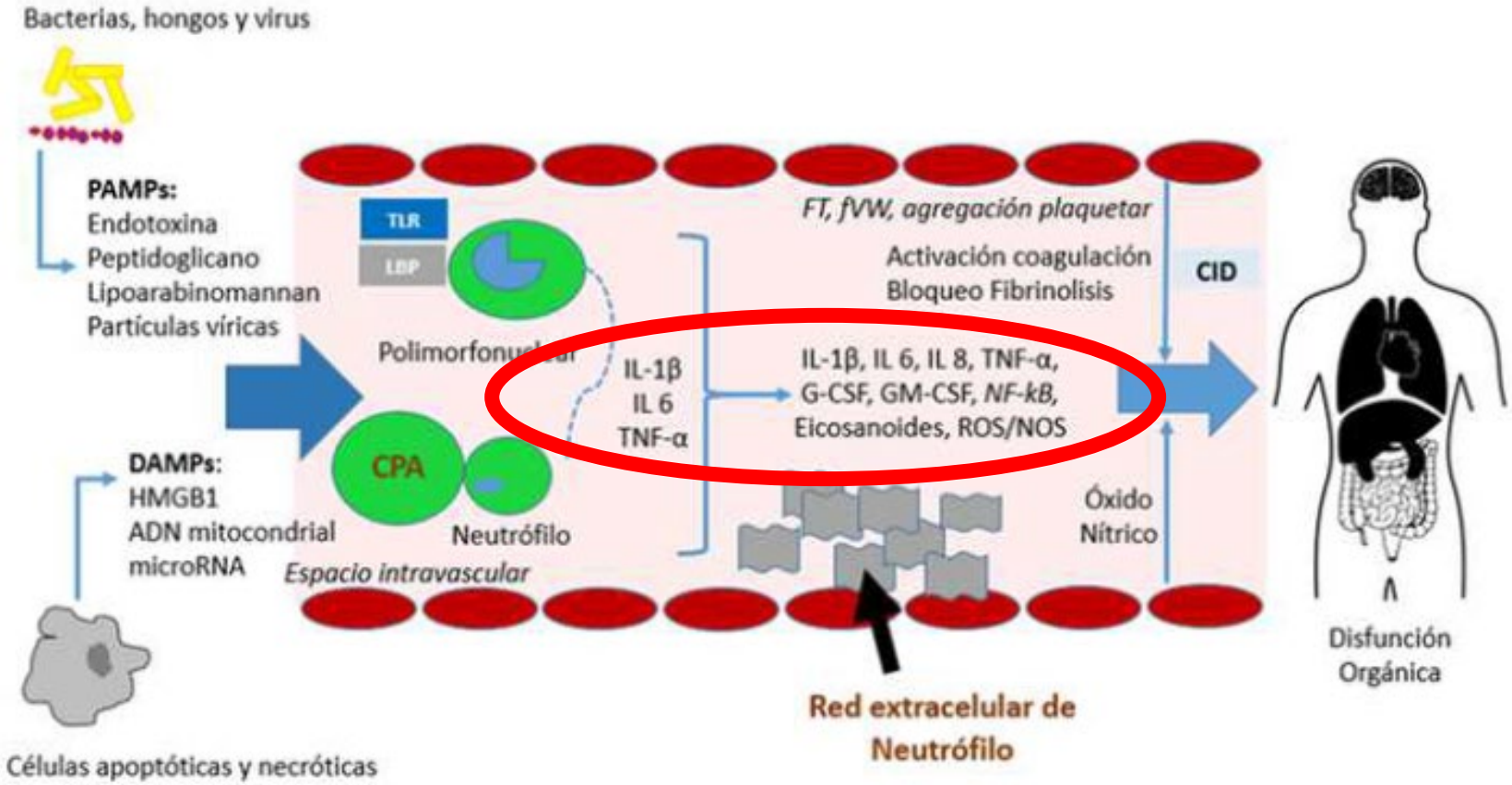




Review > Nature. 2002 Dec 19-26;420(6917):885-91. doi: 10.1038/nature01326.

# The immunopathogenesis of sepsis

Jonathan Cohen [1]

PMID: 12490963 DOI: 10.1038/nature01326




# Sepsis—Pathophysiology and Therapeutic Concepts

*Dominik Jarczak, Stefan Kluge and Axel Nierhaus**

REVIEW
published: 14 May 2021
doi: 10.3389/fmed.2021.628302

frontiers in Medicine

# Blood Purification Studies in the ICU: What Endpoints Should We Use?

Lui G. Forni[a, b, c]

Blood Purification

Critical Care Nephrology

Blood Purif
DOI: 10.1159/000523761

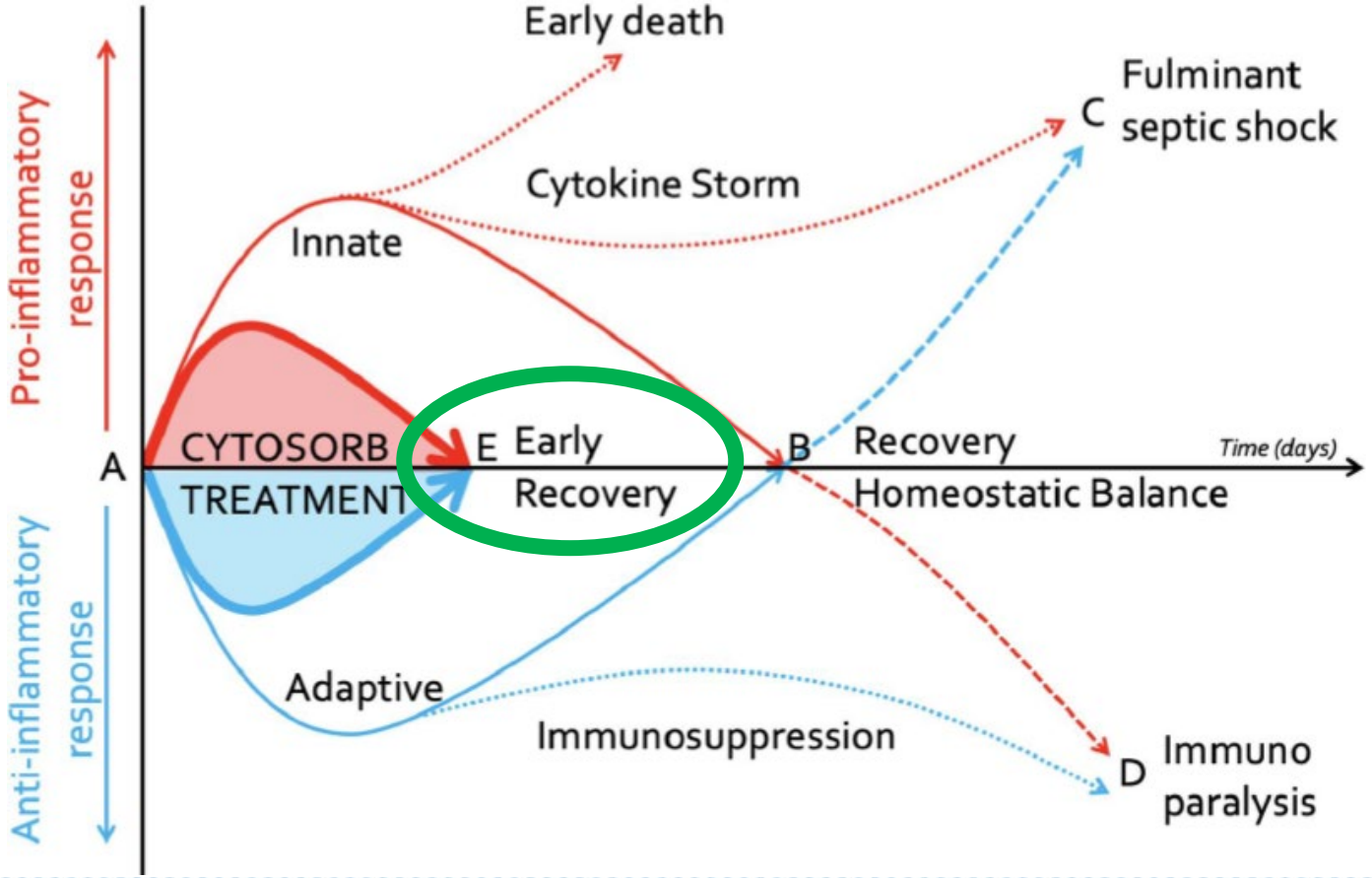
REVIEW Open Access

Honore *et al. Ann. Intensive Care* (2019) 9:56
https://doi.org/10.1186/s13613-019-0530-y

Annals of Intensive Care

# Cytokine removal in human septic shock: Where are we and where are we going?

Patrick M. Honore[1*], Eric Hoste[2], Zsolt Molnár[3], Rita Jacobs[4], Olivier Joannes-Boyau[5], Manu L. N. G. Malbrain[4,6] and Lui G. Forni[7,8]



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Honore *et al. Ann. Intensive Care* (2019) 9:56
https://doi.org/10.1186/s13613-019-0530-y

Annals of Intensive Care

Which patient would **benefit** the most from cytokine removal?

**When to start** cytokine removal therapy in sepsis?

**How long** should cytokine removal therapy last and how long should it be continued?

Which patient **population** should be studied in the future?

What **severity score** of sepsis would be the most appropriate to include in a study looking at cytokine removal therapy in patients with sepsis?

Which **biomarker** should be the most appropriate to include in a study looking at cytokine removal therapy in patients with septic shock?

REVIEW Open Access

Ronco et al. Critical Care (2023) 27:50
https://doi.org/10.1186/s13054-023-04310-2

# Rationale for sequential extracorporeal therapy (SET) in sepsis

Claudio Ronco[1,2*], Lakhmir Chawla[3], Faeq Husain-Syed[4,5] and John A. Kellum[6,7]

**Table 1** Selection of currently available extracorporeal blood purification devices

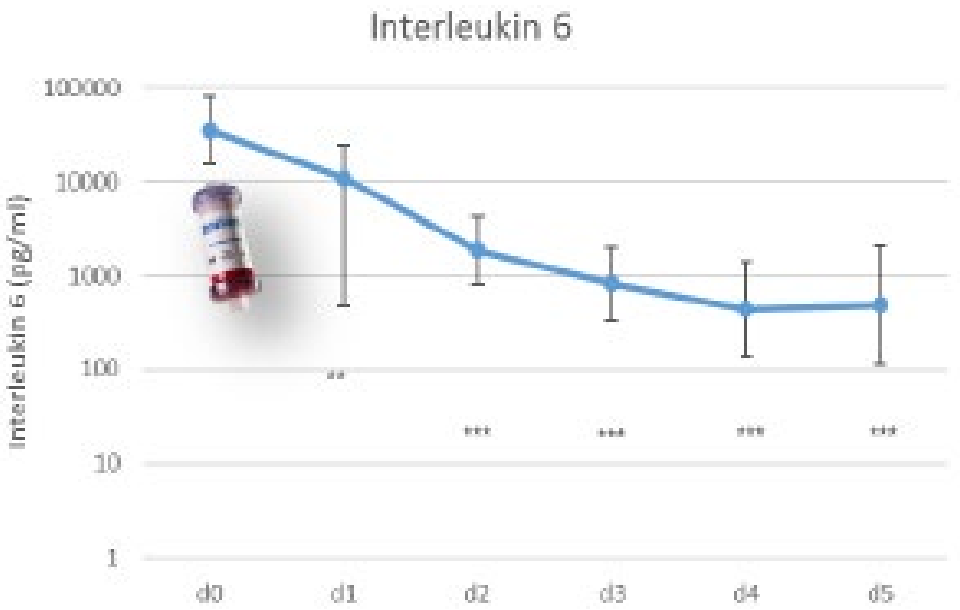
| Device name (manufacturer) | Sorbent type | Intended use | Toxins/mediators removed |
|---|---|---|---|
| Seraph 100 Microbind Affinity Blood Filter (ExThera Medical)[a] | Polyethylene beads with end-point-attached heparin | Septic shock | Bloodstream pathogens, drugs |
| Toraymyxin (Estor; Toray)[a] | Polymyxin B covalently bound to polypropylene-polystyrene fibre | Septic shock | Endotoxin |
| Cytosorb (Cytosorbents)[a] | Crosslinked Divinylbenzene/polyvinylpyrrolidone copolymers | Septic shock, vasoplegic shock (e.g. post-cardiac surgery, extracorporeal membrane oxygenation), liver failure, rhabdomyolysis, intoxication, drug accumulation | Cytokines, myoglobin, free haemoglobin, bilirubin/bile acids, toxins, metals, drugs |
| HA330/380 (Jafron Biomedical)[b] | Polystyrene divinylbenzene copolymer resins | Sepsis, trauma, burns, liver failure, rhabdomyolysis, intoxication, drug accumulation | Cytokines, myoglobin, free haemoglobin, bilirubin/bile acids, toxins, metals, drugs |
| oXiris (Baxter)[c] | AN69 with PEI surface treatment; endotoxin adsorbed by means of ionic interactions at the membrane surface | AKI, sepsis | Uremic toxins, endotoxin, cytokines |
| SepXiris (Baxter)[d] | AN69-ST copolymer membrane | AKI, sepsis | Uremic toxins, cytokines |
| Haemofeel CH (Toray)[e] | PMMA membrane | AKI, sepsis | Uremic toxins, cytokines |

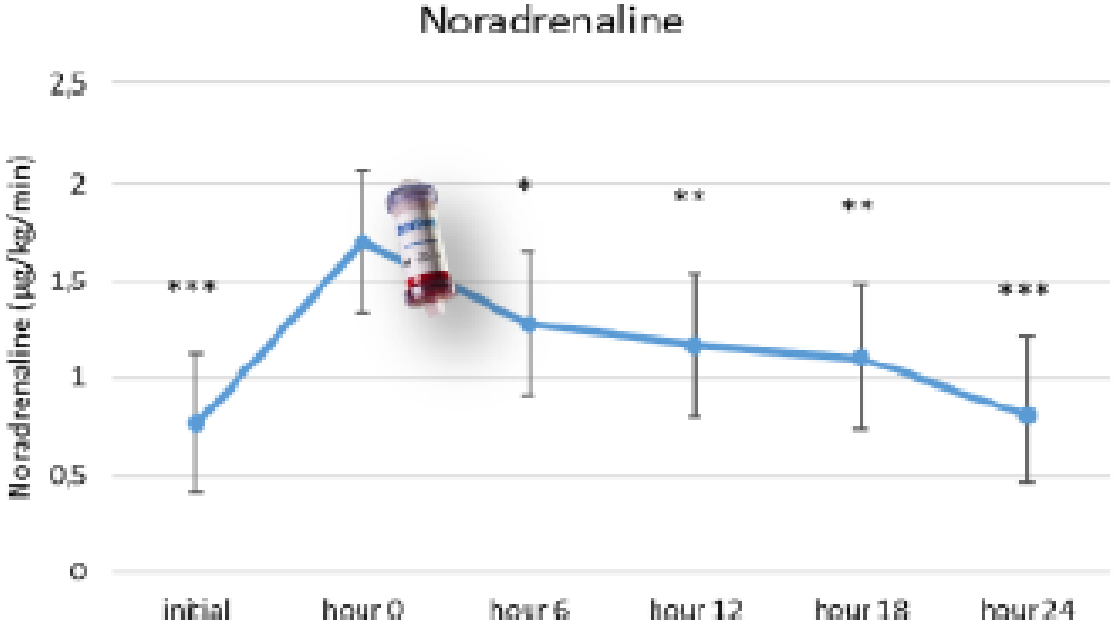
Clinical Trial > J Artif Organs. 2017 Sep;20(3):252-259. doi: 10.1007/s10047-017-0967-4. Epub 2017 Jun 6.

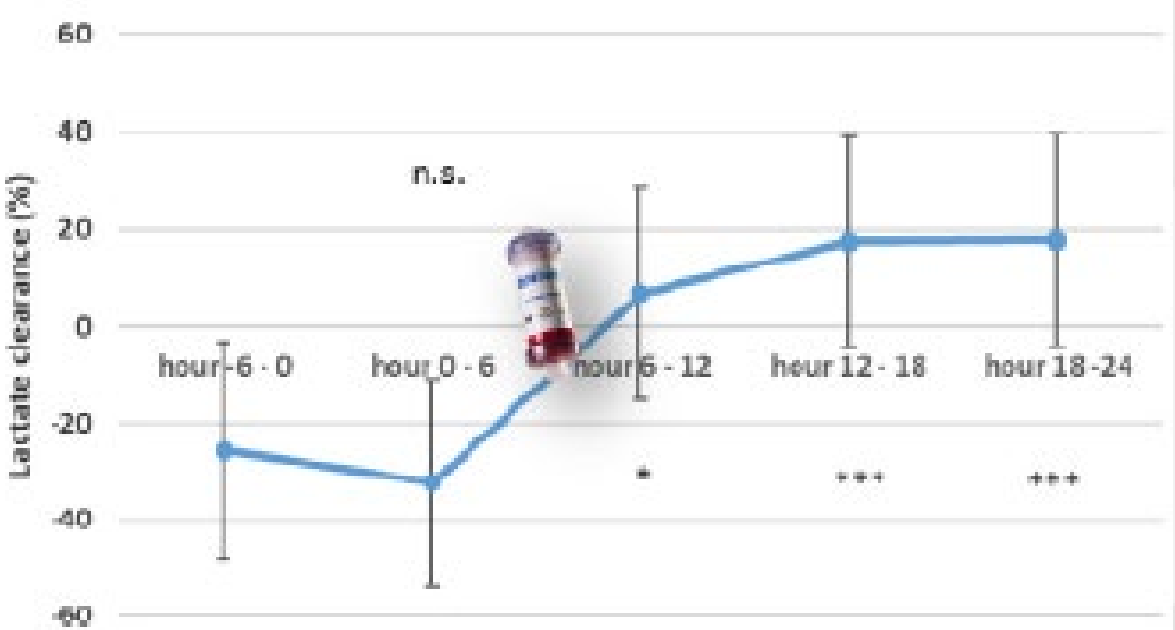
# Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study

Sigrun Friesecke [1], Stephanie-Susanne Stecher [2], Stefan Gross [3], Stephan B Felix [2 3], Axel Nierhaus [4]

PMID: 28589286 DOI: 10.1007/s10047-017-0967-4

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› World J Crit Care Med. 2021 Jan 9;10(1):22-34. doi: 10.5492/wjccm.v10.i1.22.

# Multicentered prospective investigator initiated study to evaluate the clinical outcomes with extracorporeal cytokine adsorption device (CytoSorb®) in patients with sepsis and septic shock

Rajib Paul [1], Prachee Sathe [2], Senthil Kumar [3], Shiva Prasad [4], Ma Aleem [5], Prashant Sakhalvalkar [2]

PMID: 33505870 PMCID: PMC7805252 DOI: 10.5492/wjccm.v10.i1.22

**45 patients with septic shock, a significant vasopressor dose reduction was observed in patients treated with cytokine hemoadsorption. Norepinephrine was reduced by 51.4%, epinephrine by 69.4%, and vasopressin by 13.9%. Also, a reduction in IL-6 levels by 52.3% and lactate levels by 39.4% was observed in the survivors. A survival rate of 75% was documented in patients who received treatment within 24 hours of intensive care unit (ICU) admission. Sixty-eight percent of patients who received treatment within 24-48 h after ICU admission survived.**

Crit Care. 2019 Sep 18;23(1):317. doi: 10.1186/s13054-019-2588-1.

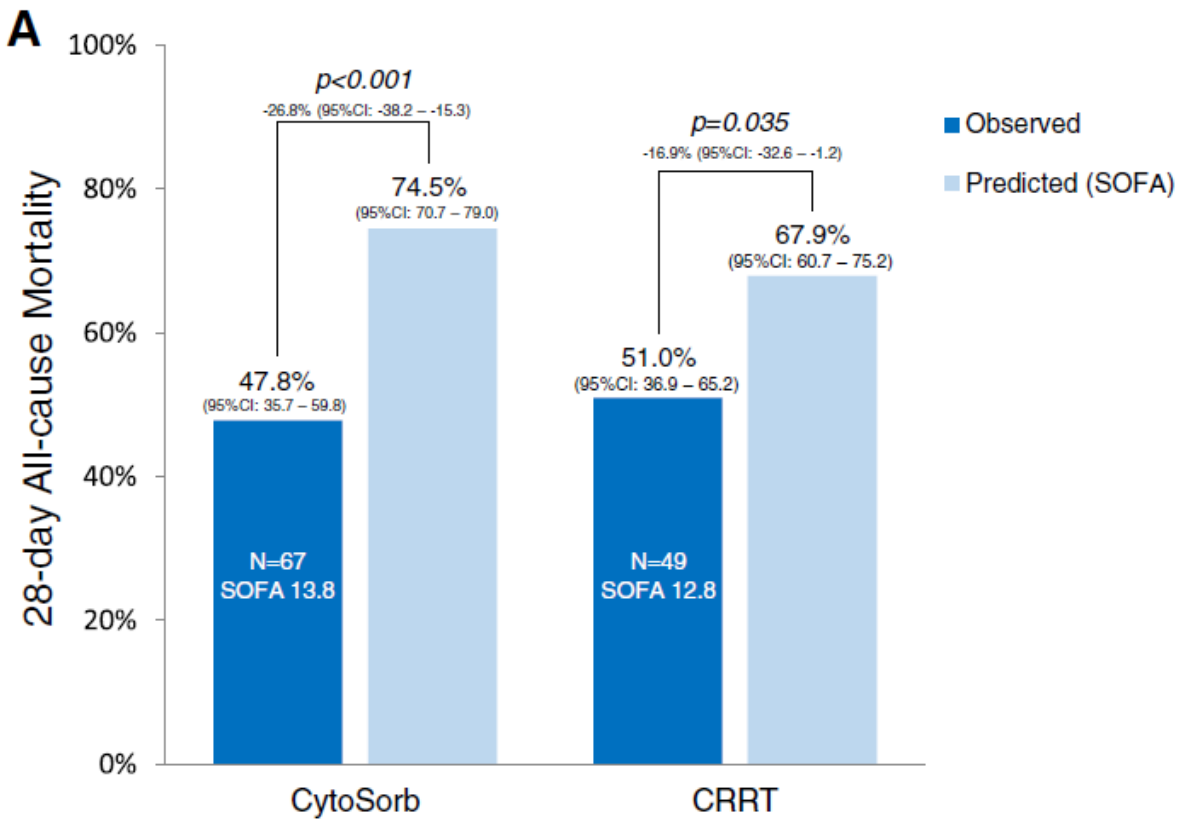
# Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study

Willem Pieter Brouwer [1 2], Servet Duran [3], Martijn Kuijper [4], Can Ince [5]

PMID: 31533846 PMCID: PMC6749645 DOI: 10.1186/s13054-019-2588-1

CytoSorb was associated with a decreased observed versus expected 28-day all-cause mortality.

At the start of therapy, CytoSorb-treated patients had higher lactate levels ($p < 0.001$), lower mean arterial pressure ($p = 0.007$) and higher levels of noradrenaline ($p < 0.001$) compared to the CRRT group.

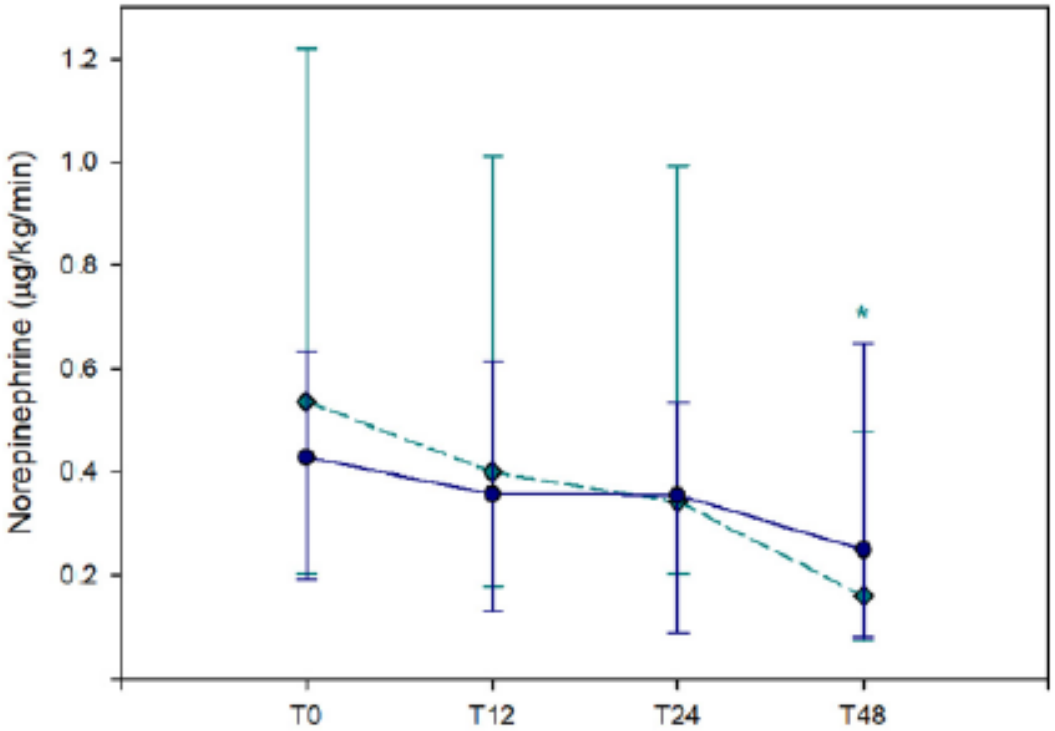


Randomized Controlled Trial > J Crit Care. 2019 Feb;49:172-178. doi: 10.1016/j.jcrc.2018.11.003. Epub 2018 Nov 10.

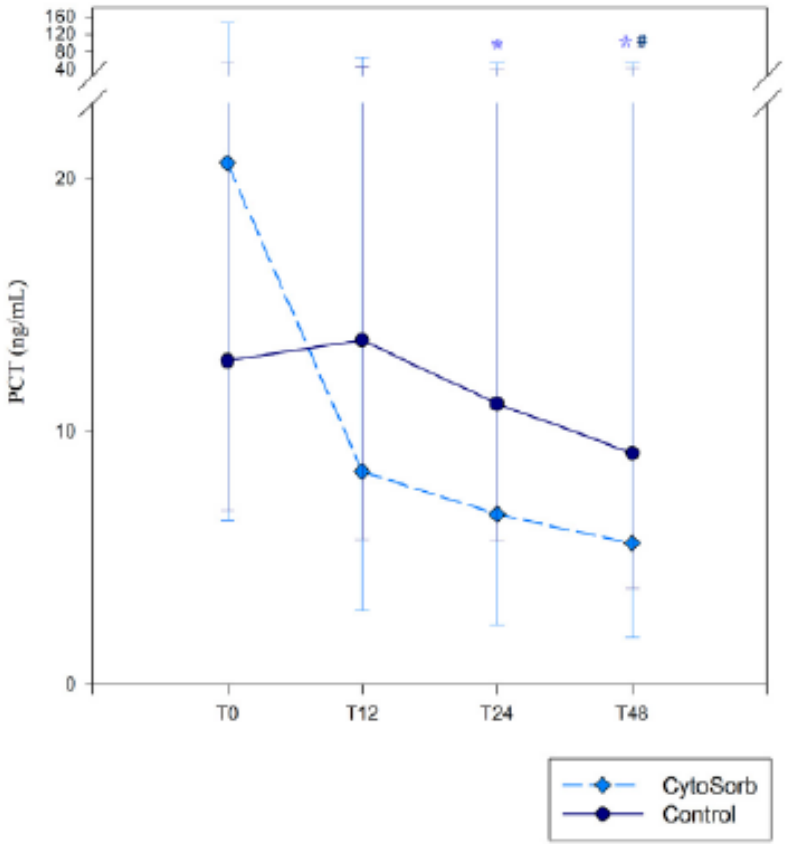
# Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study

Fatime Hawchar [1], Ildikó László [2], Nándor Öveges [3], Domonkos Trásy [4], Zoltán Ondrik [5], Zsolt Molnar [6]

PMID: 30448517 DOI: 10.1016/j.jcrc.2018.11.003




**Significant effects on norepinephrine requirements, PCT and Big-endothelin-1 concentrations compared to controls**

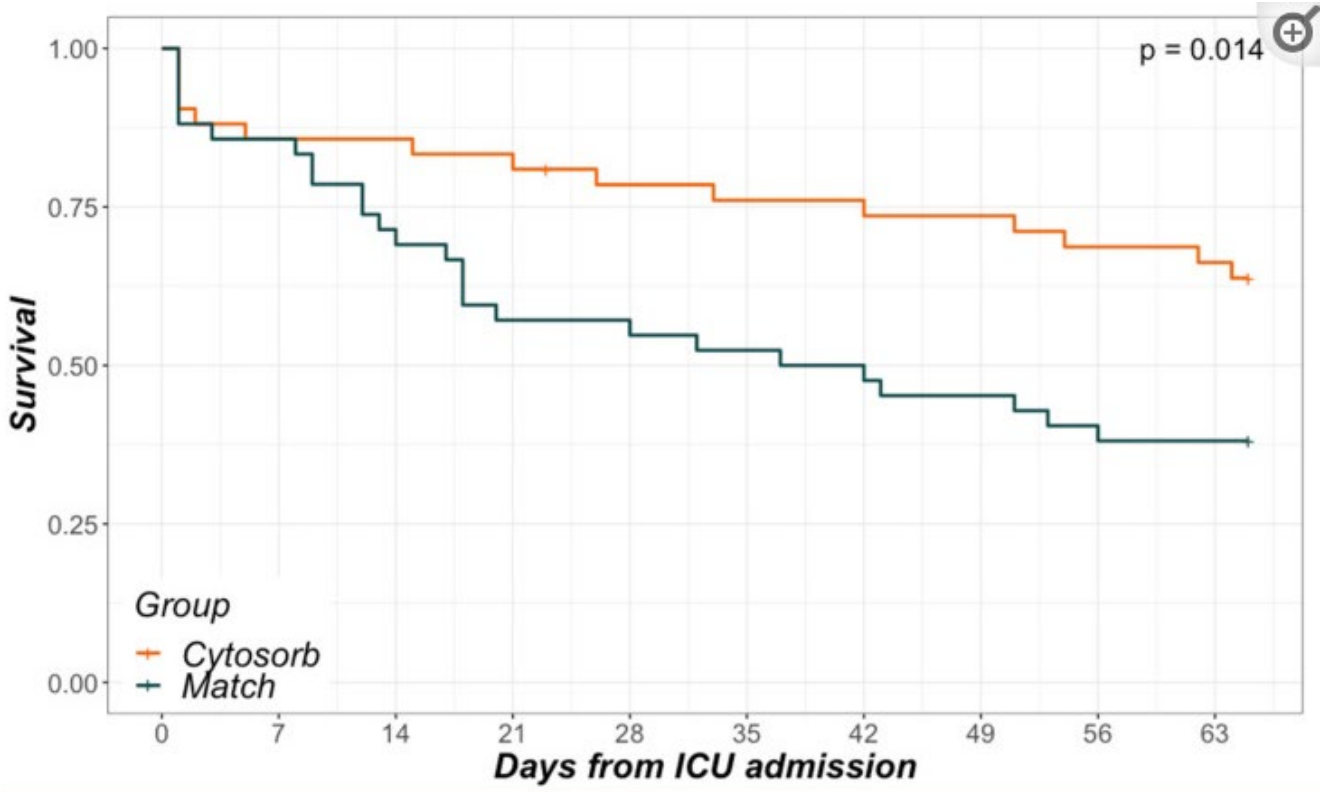


Biomedicines. 2020 Dec; 8(12): 539.
Published online 2020 Nov 26. doi: 10.3390/biomedicines8120539
PMCID: PMC7760738
PMID: 33255912

# Hemoadsorption with CytoSorb in Septic Shock Reduces Catecholamine Requirements and In-Hospital Mortality: A Single-Center Retrospective 'Genetic' Matched Analysis

Christopher Rugg, Riko Klose, Rouven Hornung, Nicole Innerhofer, Mirjam Bachler, Stefan Schmid, Dietmar Fries, and Mathias Ströhle*

**In a case-control study of septic shock patients who received cytokine hemoadsorption with CytoSorb®, the median catecholamine requirements approximately halved within 24 hours after the initiation of therapy. In-hospital mortality was significantly lower in the CytoSorb® group (35.7% vs 61.9%; p = 0.015).**

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Clinical Trial > Blood Purif. 2020;49(1-2):107-113. doi: 10.1159/000502540. Epub 2019 Aug 21.

# Changes in Cytokines, Haemodynamics and Microcirculation in Patients with Sepsis/Septic Shock Undergoing Continuous Renal Replacement Therapy and Blood Purification with CytoSorb

Samuele Zuccari [1], Elisa Damiani [1], Roberta Domizi [1], Claudia Scorcella [1], Mario D'Arezzo [2], Andrea Carsetti [1], Simona Pantanetti [1], Sara Vannicola [1], Erika Casarotta [1], Andrea Ranghino [2], Abele Donati [3], Erica Adrario [1]

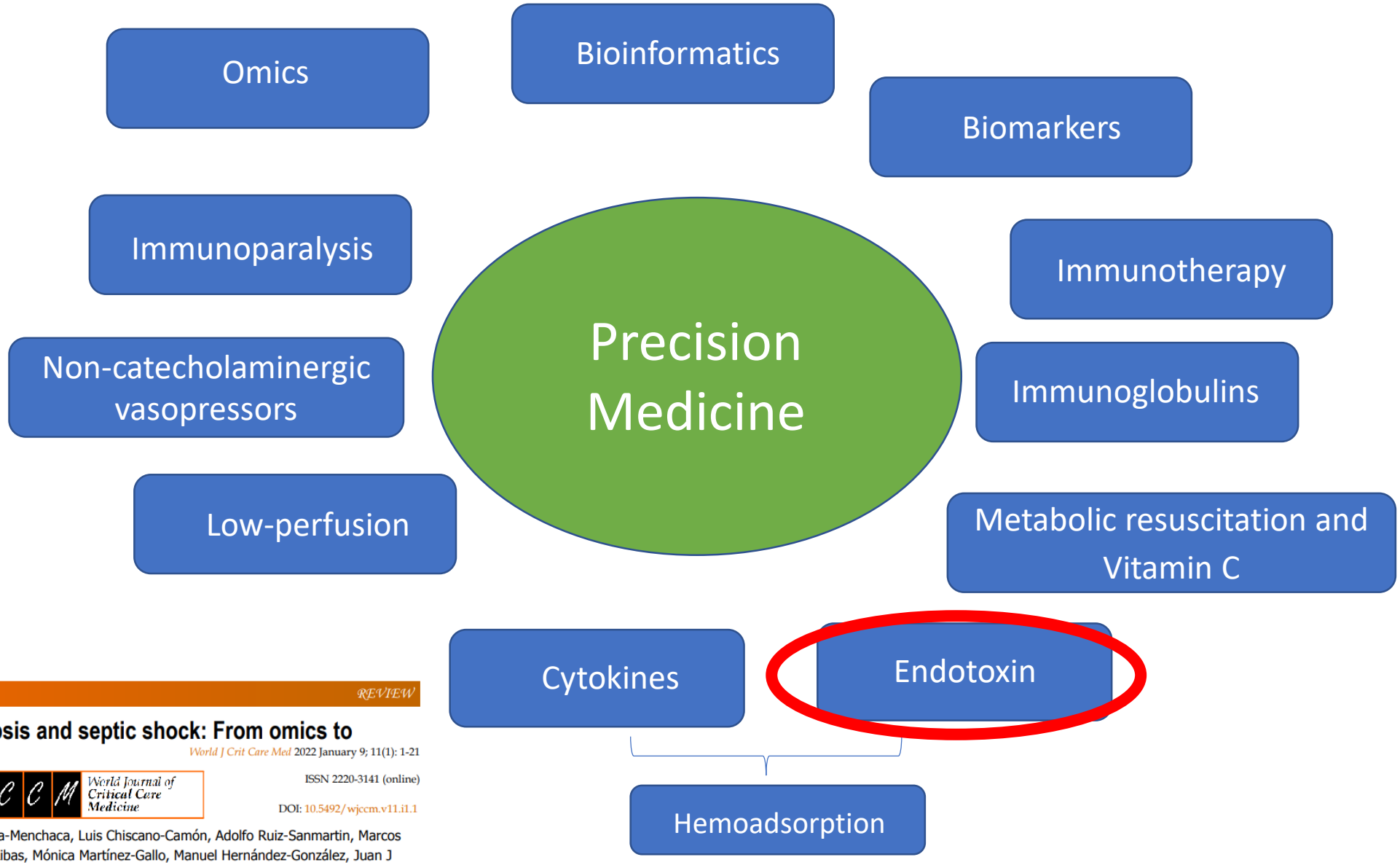
PMID: 31434083 DOI: 10.1159/000502540

**Nine patients; plasma levels of IL-8 decreased at 24 h ($p < 0.05$ versus 6 h); no significant variation was found for other cytokines. Haemodynamic parameters and vasopresor requirement remaind substantially stable during 24-h treatment;. nonetheless an increase in sublingual microcirculatory density was observed and microvascular flow quality tended to improve over time.**

**Table 2**. Sublingual microcirculation and NIRS-derived variables

| | Baseline | 6 h | 24 h | *p* value* |
|---|---|---|---|---|
| Total small vessel density, mm/mm$^2$ | 14.9 (13.9 to 16.9) | 17 (16 to 18.7) | 17.9 (15.3 to 20)# | 0.015 |
| Perfused small vessel density, mm/mm$^2$ | 13.9 (13.3 to 16.4) | 15.7 (15 to 17.3)# | 17 (14.8 to 18.6)## | 0.003 |
| MFI, AU | 2.50 (2.37 to 2.62) | 2.67 (2.62 to 2.75) | 2.83 (2.58 to 3.00) | 0.046 |
| Percentage of perfused small vessels | 89 (86 to 92) | 92 (91 to 93) | 93 (92 to 94) | 0.048 |
| $StO_2$, % | 83 (74 to 91) | 87 (82 to 90) | 85 (83 to 88) | 0.528 |
| $StO_2$ downslope, %/min | −6 (−10.8 to −5.3) | −7.7 (−10.4 to −3.3) | −9 (−13.9 to −7.5) | 0.442 |
| $StO_2$ upslope, %/min | 153 (106 to 186) | 164 (118 to 253) | 144 (58 to 194) | 0.654 |
| Area of hyperemia, % * min | 13.8 (5.3 to 15.2) | 10.7 (5.1 to 17.8) | 10.6 (6.7 to 18.4) | 0.764 |
| Tissue haemoglobin index, AU | 10.6 (6.5 to 16.7) | 12.9 (9.8 to 18.4) | 11.1 (9.1 to 13.7) | 0.236 |


| | IL-6 plasmatic concentration |
|---|---|
| **Kobe 2007** | 23300 (26500) pg/ml. |
| **Schadler 2017** | Treatment group: [162–874] pg/ml<br><br>Control group: 590 [125–2147] pg/ml. |
| **Friesecke 2017** | 25523 (1052 - 491260) pg/ml. |
| **Schittek 2020** | Treatment group: 5000 (939 – 5000) pg / ml.<br><br>Control group: not measured |
| **Mehta 2020** | 1962.04 (229.09) pg/ml. |
| **Garcia 2021** | HA group: 23897 (23179) pg/ml<br><br>Non-HA group: 26543 (21373) |
| **Scharf 2021** | Cytosorb® treatment: 60529 (10108 – 84000000)<br><br>No-Cytosorb®: 25660 (10051 – 600000) |
| **Paul 2021** | 889.15 (1307.43) pg/ml |
| **Hawchar 2022** | 4240 (0->$10^7$) pg/ml |




REVIEW

**Precision medicine in sepsis and septic shock: From omics to clinical tools**

*World J Crit Care Med* 2022 January 9; 11(1): 1-21

World Journal of Critical Care Medicine

ISSN 2220-3141 (online)

DOI: 10.5492/wjccm.v11.i1.1

Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Vicent Ribas, Mónica Martínez-Gallo, Manuel Hernández-González, Juan J Gonzalez-Lopez, Nieves Larrosa, Ricard Ferrer

Review > Blood Purif. 2014;37 Suppl 1:5-8. doi: 10.1159/000356831. Epub 2014 Jan 20.

# Endotoxin removal: history of a mission

Claudio Ronco [1]

*…hemodynamic instability, multiple organ failure, and death…*

# Diagnostic and Prognostic Implications of Endotoxemia in Critical Illness: Results of the MEDIC Study

John C. Marshall,[1] Debra Foster,[4] Jean-Louis Vincent,[6] Deborah J. Cook,[5] Jonathan Cohen,[11] R. Phillip Dellinger,[9,a] Steven Opal,[7] Edward Abraham,[8] Stephen J. Brett,[10] Terry Smith,[2] Sangeeta Mehta,[3] Anastasia Derzko,[4] and Alex Romaschin[1,4]

*…correlation between plasma endotoxin concentrations and severity of septic shock, organ dysfunction, and mortality…*

# Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

## The EUPHAS Randomized Controlled Trial

**Design, Setting, and Patients** A prospective, multicenter, randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) conducted at 10 Italian tertiary care intensive care units between December 2004 and December 2007. Sixty-four patients were enrolled with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection.

**Intervention** Patients were randomized to either conventional therapy (n=30) or conventional therapy plus 2 sessions of polymyxin B hemoperfusion (n=34).

*A significant decrease in 28-day mortality was noted in the intervention group (32%) compared to the standard treatment group (53%)*

**Table 3.** Physiological End Points by Treatment Group at Baseline and 72 Hours[a]

| | Polymyxin B Hemoperfusion | | | Conventional Therapy | | |
|---|---|---|---|---|---|---|
| | Mean (95% CI) | | | Mean (95% CI) | | |
| Physiological End Points | Baseline (n = 34) | 72 Hours (n = 34) | *P* Value | Baseline (n = 30) | 72 Hours (n = 27) | *P* Value |
| Mean arterial pressure, mm Hg | 76 (72-80) | 84 (80-88) | .001 | 74 (70-78) | 77 (72-82) | .37 |
| Inotropic score | 29.9 (20.4-39.4) | 6.8 (2.9-10.7) | <.001 | 28.6 (16.6-40.7) | 22.4 (9.3-35.5) | .14 |
| Vasopressor dependency index, $mm\ Hg^{-1}$ | 4.3 (2.7-5.9) | 0.9 (0.3-1.5) | <.001 | 4.1 (2.3-6.0) | 3.3 (1.3-5.3) | .26 |
| $PaO_2/FIO_2$ | 235 (206-265) | 264 (236-292) | .049 | 217 (188-247) | 228 (199-258) | .79 |
| Renal replacement therapy, No. (%) | 13 (38) | 15 (44) | .50 | 6 (20) | 8 (30) | .50 |

Abbreviations: CI, confidence interval; $FIO_2$, fraction of inspired oxygen.
[a] See "Methods" section for formulas for inotropic score and vasopressor dependency index. In the conventional therapy group, 3 patients died before 72 hours (n=2

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# Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial

Intensive Care Med (2015) 41:975–984
DOI 10.1007/s00134-015-3751-z

243 patients with septic shock within 12 h after emergency surgical treatment for secondary peritonitis due to organ perforation.

Patients receiving hemoperfusion with PMX (119 patients) received conventional therapy plus two sessions of PMX hemoperfusion.

There were no significant differences in the SOFA score or the 28-day mortality rate between the PMX and control groups (27.7% vs. 19.5%).

The severity of disease and mortality rates were low in the study population.

Among the 220 sessions performed, early interruption was observed in 25 cases (11 %), mostly during the first session and mainly due to circuit coagulation.

The two PMX hemoperfusion sessions were achieved in only 81 of 119 patients (69.8 %).

Of note, plasma EAA levels were not measured.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

## The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

**ORIGINAL**

*Intensive Care Med (2018) 44:2205–2212*
https://doi.org/10.1007/s00134-018-5463-7

# Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

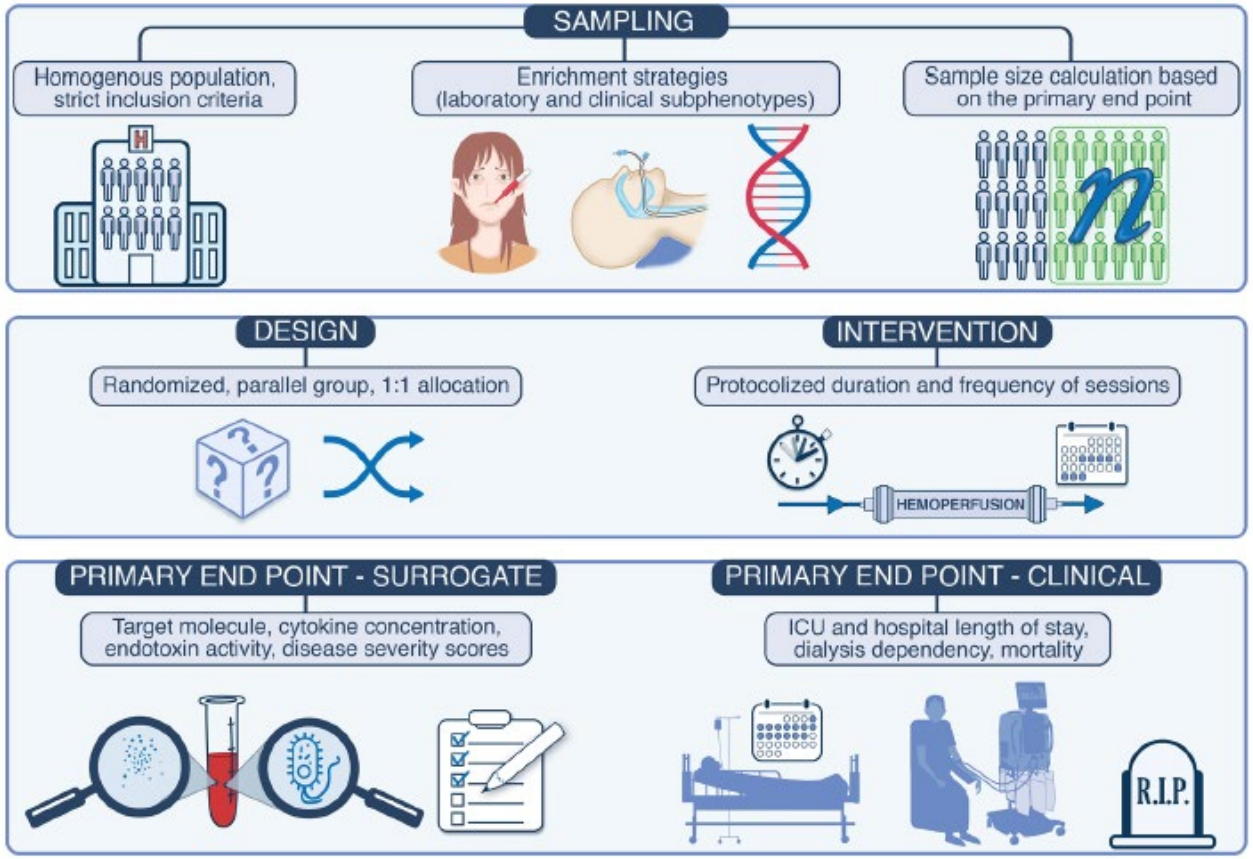
*post hoc* study of 194 of the patients with EAA values between 0.6-0.89 and observed an improvement in survival in patients who received therapy with PMX

NARRATIVE REVIEW

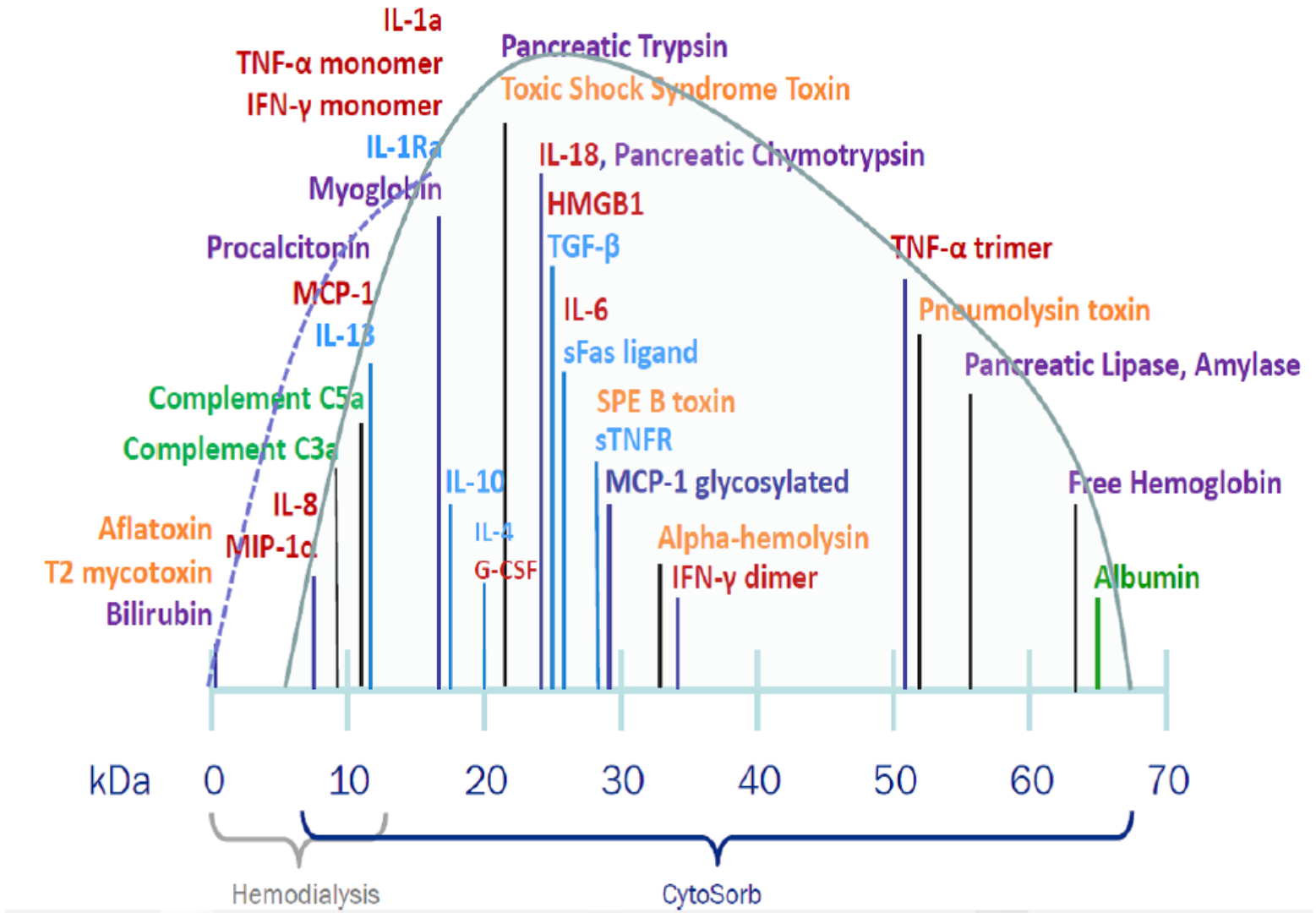
*Intensive Care Med (2022) 48:1397–1408*
https://doi.org/10.1007/s00134-022-06810-1

# Hemoperfusion in the intensive care unit

Zaccaria Ricci[1,2*], Stefano Romagnoli[2,3], Thiago Reis[4,5,6], Rinaldo Bellomo[7,8] and Claudio Ronco[9]




"… initial randomized controlled trials should assess **different primary endpoints rather than mortality** to also assess other important effects of extracorporeal blood purification such as ventilation-free days, vasopressor therapy-free days, invasive organ support-free days or intensive care unit-free days …"




**"… Due to the critical importance of optimal antimicrobial treatment in sepsis, it seems crucial to understand and compensate for such extracorporeal loss during …"**

# Mechanistic Considerations and Pharmacokinetic Implications on Concomitant Drug Administration During CytoSorb Therapy

*Critical Care Explorations*
May 2022 • Volume 4 • Number 5
DOI: 10.1097/CCE.0000000000000688

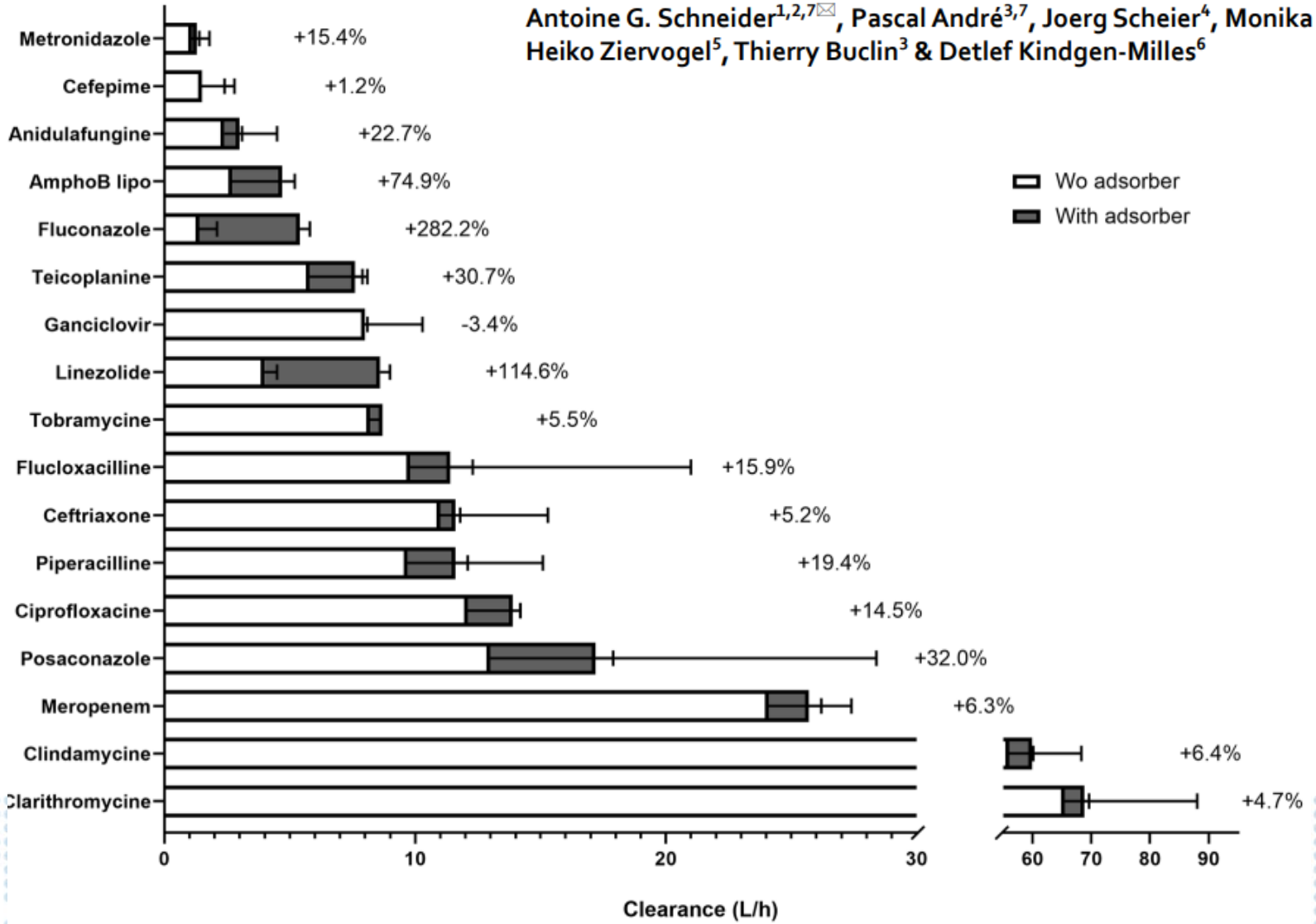
## Classification of Drugs According to Clinical Significance of CytoSorb Adsorption

| Insignificant In Vivo Removal | Low In Vitro Removal | Moderate or High In Vitro Removal | Significant In Vivo Removal |
|---|---|---|---|
| Negligible clearance increase (<25%) or low percentage removal (<30%) | <30% percentage removal but no in vivo data available | >30% percentage removal but no in vivo data available | >25% clearance increase or >30% percentage removal |
| **General view on clinically expected drug removal per category, based on available data** | | | |
| Unlikely to be removed to a clinically significant extent with CytoSorb therapy | Clinically significant removal by CytoSorb therapy cannot be excluded, and dose adjustments may be warranted. TDM is recommended to guide dosing wherever available | CytoSorb therapy possibly results in clinically significant removal, and dose adjustments may be warranted. TDM is recommended to guide dosing wherever available | Clinically significant removal has been demonstrated or is to be expected with CytoSorb therapy, and dose adjustments likely are warranted. TDM is recommended to guide dosing wherever availablex |

# Pharmacokinetics of anti-infective agents during CytoSorb hemoadsorption

Scientific Reports | (2021) 11:10493 | https://doi.org/10.1038/s41598-021-89965-z

Antoine G. Schneider[1,2,7]✉, Pascal André[3,7], Joerg Scheier[4], Monika Schmidt[5], Heiko Ziervogel[5], Thierry Buclin[3] & Detlef Kindgen-Milles[6]

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# Mechanistic Considerations and Pharmacokinetic Implications on Concomitant Drug Administration During CytoSorb Therapy

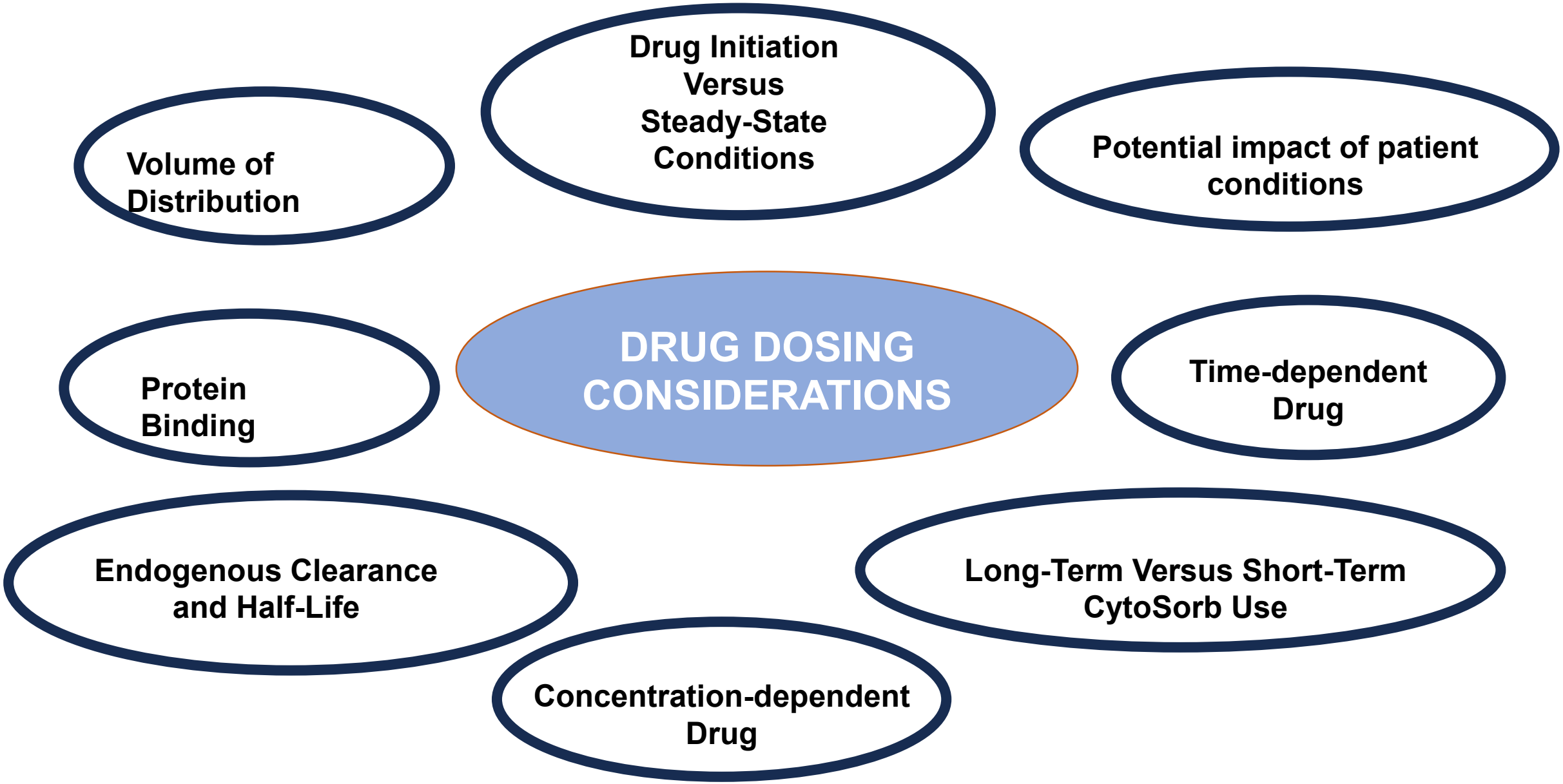
*Critical Care Explorations*

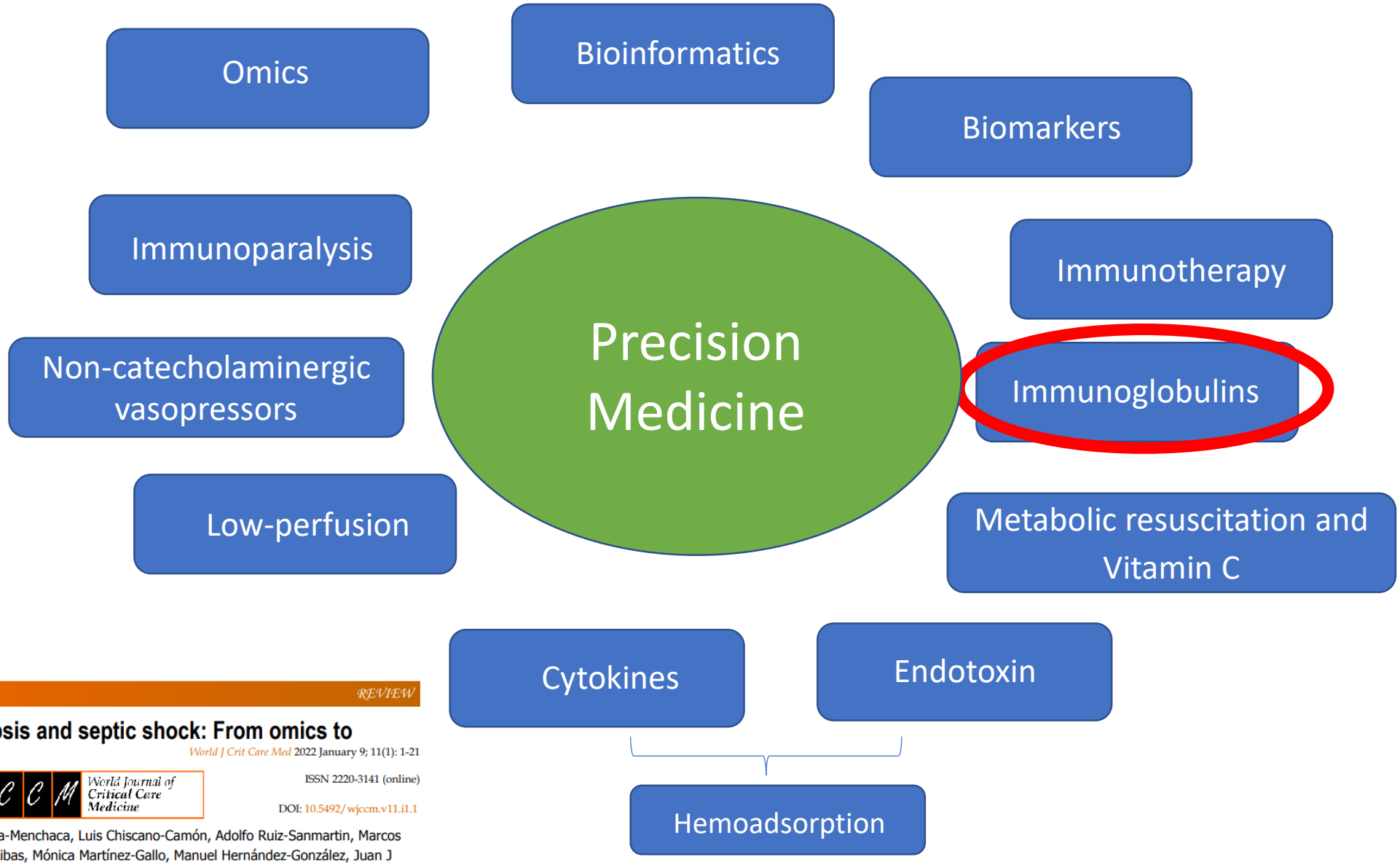
May 2022 • Volume 4 • Number 5

**DOI: 10.1097/CCE.0000000000000688**

"… Clinical decision-making regarding adjustments in drug dosing should always be made in the broader clinical context, supported by therapeutic drug monitoring when available …"

| Insignificant In Vivo Removal | | Low In Vitro Removal | Moderate or High In Vitro Removal | | Significant In Vivo Removal | | | |
|---|---|---|---|---|---|---|---|---|
| Clindamycin (7, 15, 16) | A, H | | Cyclosporine (8, 9) | L | Linezolid (7, 17) | A, H | | 115 |
| Flucloxacillin (7, 13) | I, A | | Dabigatran (18) | L | Posaconazole (7) | A | | 32 |
| Ganciclovir (7) | A | | Diazepam (9) | L | Teicoplanin (7, 8, 19) | I, A, H | | 31 |
| Meropenem (7, 13, 15, 17, 28) | I, A, H | | Digoxin (8, 9) | VL | Tobramycin[a] (7, 8) | I, A | | |
| Metronidazole (7) | A | | Edoxaban (20) | L | Vancomycin (8, 10, 13, 19, 21) | I, H | >60 | |
| Piperacillin (7, 13, 15) | I, A, H | | Gentamycin (8, 13) | S | Apixaban (22) | H | | |
| | | | Iodixanol (23) | S | | | | |
| | | | Ibuprofen (9) | S | | | | |
| | | | Phenobarbital (8) | S | | | | |
| | | | Phenytoin (8) | S | | | | |
| | | | Quetiapine (9) | VL | | | | |
| Anidulafungin (7) | A | Amikacin (8) | Amiodarone (9) | VL | Amphotericin B (11) | A | | 75 |
| Cefepime (7) | A | Paracetamol (9) | Amitriptyline (9) | VL | Bivalirudin (15) | H | > 60 | |
| Ceftriaxone (7) | A | (Acetaminophen) | Amlodipine (11) | VL | Digitoxin (12) | H | > 60 | |
| Ciprofloxacin (7, 13) | I, A | Theophylline (8) | | | Flecainide (14) | H | > 60 | |
| Clarithromycin (7) | A | | Carbamazepine (8) | L | Fluconazole (7, 13) | I, A | | 282 |


Drug Initiation Versus Steady-State Conditions
Volume of Distribution
Potential impact of patient conditions
DRUG DOSING CONSIDERATIONS
Protein Binding
Time-dependent Drug
Endogenous Clearance and Half-Life
Long-Term Versus Short-Term CytoSorb Use
Concentration-dependent Drug




REVIEW

**Precision medicine in sepsis and septic shock: From omics to clinical tools**

*World J Crit Care Med* 2022 January 9; 11(1): 1-21

World Journal of Critical Care Medicine

ISSN 2220-3141 (online)

DOI: 10.5492/wjccm.v11.i1.1

Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Vicent Ribas, Mónica Martínez-Gallo, Manuel Hernández-González, Juan J Gonzalez-Lopez, Nieves Larrosa, Ricard Ferrer

Review > Cochrane Database Syst Rev. 2013 Sep 16;2013(9):CD001090.
doi: 10.1002/14651858.CD001090.pub2.

# Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock

**Polyclonal IVIG versus placebo or no intervention for sepsis, severe sepsis and septic shock**

**Patient or population:** adult patients with sepsis, severe sepsis and septic shock
**Intervention:** polyclonal IVIG
**Comparison:** placebo or no intervention

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Placebo or no intervention | Polyclonal IVIG | | | |
| All-cause mortality, adults, standard polyclonal IVIG | Study population | | RR 0.81 (0.7 to 0.93) | 1430 (10 studies) | ⊕⊕⊕⊖ moderate[1] |
| | 365 per 1000 | 296 per 1000 (256 to 340) | | | |
| | Moderate | | | | |
| | 423 per 1000 | 343 per 1000 (296 to 393) | | | |
| All-cause mortality, adults, IgM-enriched polyclonal IVIG | Study population | | RR 0.66 (0.51 to 0.85) | 528 (7 studies) | ⊕⊕⊕⊖ moderate[2] |
| | 375 per 1000 | 247 per 1000 (191 to 318) | | | |
| | Moderate | | | | |
| | 412 per 1000 | 272 per 1000 (210 to 350) | | | |

**Significant reductions in mortality in adults with sepsis compared to placebo or no intervention (relative risk (RR) 0.81; 95% confidence interval (CI) 0.70 to 0.93 and RR 0.66; 95% CI 0.51 to 0.85, respectively).**

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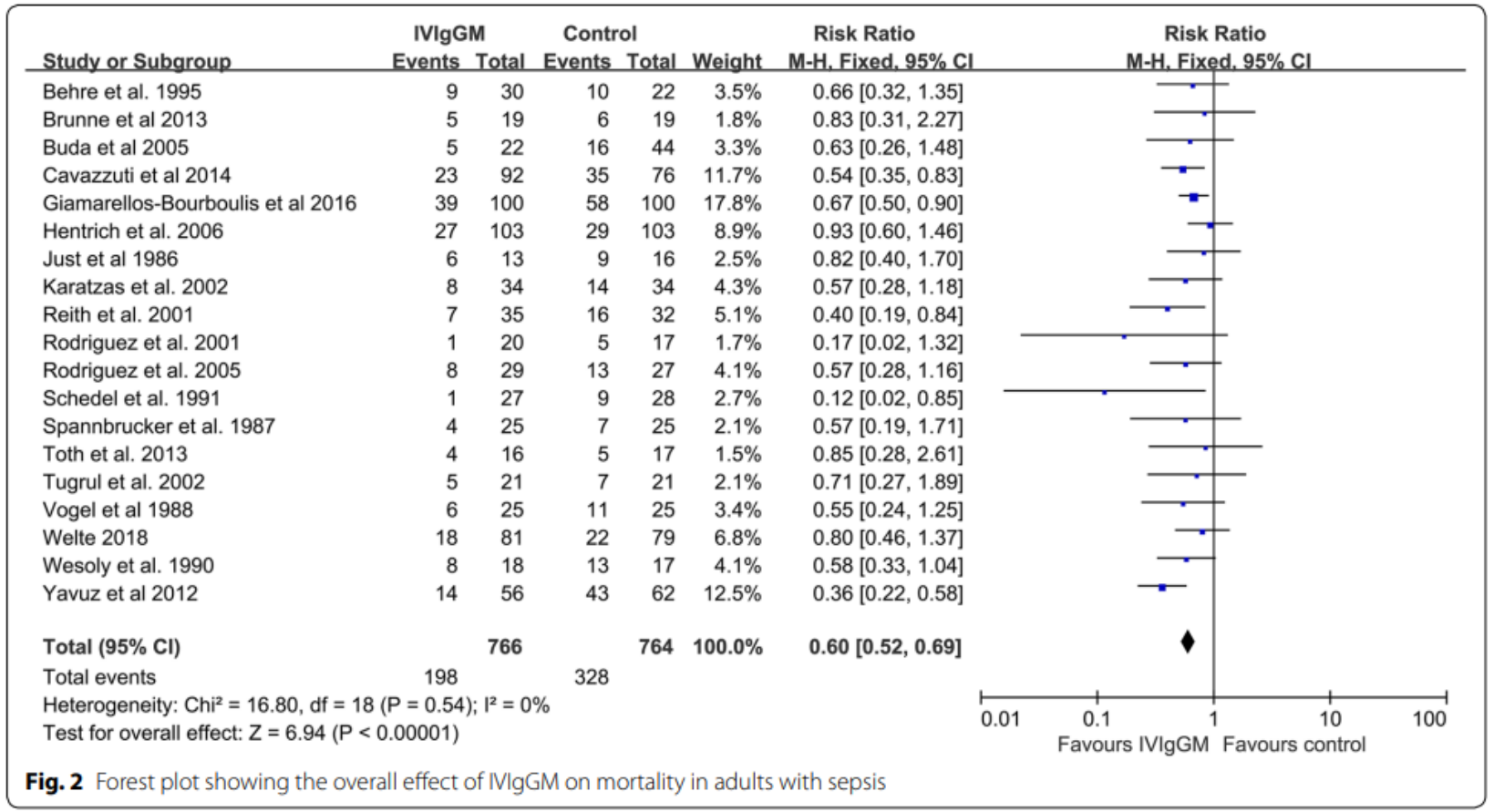
RESEARCH Open Access

# The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis

Cui et al. Ann. Intensive Care (2019) 9:27
https://doi.org/10.1186/s13613-019-0501-3

**Pooled analyses showed that the use of IVIgGM reduced the mortality risk of septic patients (relative risk 0.60; 95% confidence interval [CI] 0.52–0.69, *I*2 = 0%).**



| Study or Subgroup | IVIgGM Events | IVIgGM Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Behre et al. 1995 | 9 | 30 | 10 | 22 | 3.5% | 0.66 [0.32, 1.35] |
| Brunne et al 2013 | 5 | 19 | 6 | 19 | 1.8% | 0.83 [0.31, 2.27] |
| Buda et al 2005 | 5 | 22 | 16 | 44 | 3.3% | 0.63 [0.26, 1.48] |
| Cavazzuti et al 2014 | 23 | 92 | 35 | 76 | 11.7% | 0.54 [0.35, 0.83] |
| Giamarellos-Bourboulis et al 2016 | 39 | 100 | 58 | 100 | 17.8% | 0.67 [0.50, 0.90] |
| Hentrich et al. 2006 | 27 | 103 | 29 | 103 | 8.9% | 0.93 [0.60, 1.46] |
| Just et al 1986 | 6 | 13 | 9 | 16 | 2.5% | 0.82 [0.40, 1.70] |
| Karatzas et al. 2002 | 8 | 34 | 14 | 34 | 4.3% | 0.57 [0.28, 1.18] |
| Reith et al. 2001 | 7 | 35 | 16 | 32 | 5.1% | 0.40 [0.19, 0.84] |
| Rodriguez et al. 2001 | 1 | 20 | 5 | 17 | 1.7% | 0.17 [0.02, 1.32] |
| Rodriguez et al. 2005 | 8 | 29 | 13 | 27 | 4.1% | 0.57 [0.28, 1.16] |
| Schedel et al. 1991 | 1 | 27 | 9 | 28 | 2.7% | 0.12 [0.02, 0.85] |
| Spannbrucker et al. 1987 | 4 | 25 | 7 | 25 | 2.1% | 0.57 [0.19, 1.71] |
| Toth et al. 2013 | 4 | 16 | 5 | 17 | 1.5% | 0.85 [0.28, 2.61] |
| Tugrul et al. 2002 | 5 | 21 | 7 | 21 | 2.1% | 0.71 [0.27, 1.89] |
| Vogel et al 1988 | 6 | 25 | 11 | 25 | 3.4% | 0.55 [0.24, 1.25] |
| Welte 2018 | 18 | 81 | 22 | 79 | 6.8% | 0.80 [0.46, 1.37] |
| Wesoly et al. 1990 | 8 | 18 | 13 | 17 | 4.1% | 0.58 [0.33, 1.04] |
| Yavuz et al 2012 | 14 | 56 | 43 | 62 | 12.5% | 0.36 [0.22, 0.58] |
| **Total (95% CI)** | | **766** | | **764** | **100.0%** | **0.60 [0.52, 0.69]** |
| Total events | 198 | | 328 | | | |

Heterogeneity: Chi² = 16.80, df = 18 (P = 0.54); I² = 0%
Test for overall effect: Z = 6.94 (P < 0.00001)



**Fig. 2** Forest plot showing the overall effect of IVIgGM on mortality in adults with sepsis

RESEARCH Open Access

Cui et al. Ann. Intensive Care (2019) 9:27
https://doi.org/10.1186/s13613-019-0501-3

# The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis

**Table 3 Summary of findings table**

Patient or population: patients with Sepsis or septic shock

Settings: Intensive care medicine

Intervention: IVIgGM

Comparison: Control

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants(studies) | Quality of the evidence(GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | *Control* | *IVIgGM* | | | |
| New Outcome Follow-up: 12-70 days | *Study population* | | *RR 0.60* (0.52 to 0.69) | 1530 (19 studies) | ⊕⊕⊖⊖ *low*[1] |
| | *429 per 1000* | *258 per 1000* (223 to 296) | | | |
| | *Moderate* | | | | |
| | *412 per 1000* | *247 per 1000* (214 to 284) | | | |
| Length of mechanical ventilation | The mean length of mechanical ventilation in the intervention groups was *3.16 lower (5.71 lower to 0.61 lower)* | | | 264 (4 studies) | ⊕⊕⊖⊖ *low*[1] |
| Length of stay on ICU | The mean length of stay on ICU in the intervention groups was *0.38 higher* (3.55 lower to 2.80 higher) | | | 530 (8 studies) | ⊕⊖⊖⊖ *very low*[1] |

GUIDELINES

# Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

LOW

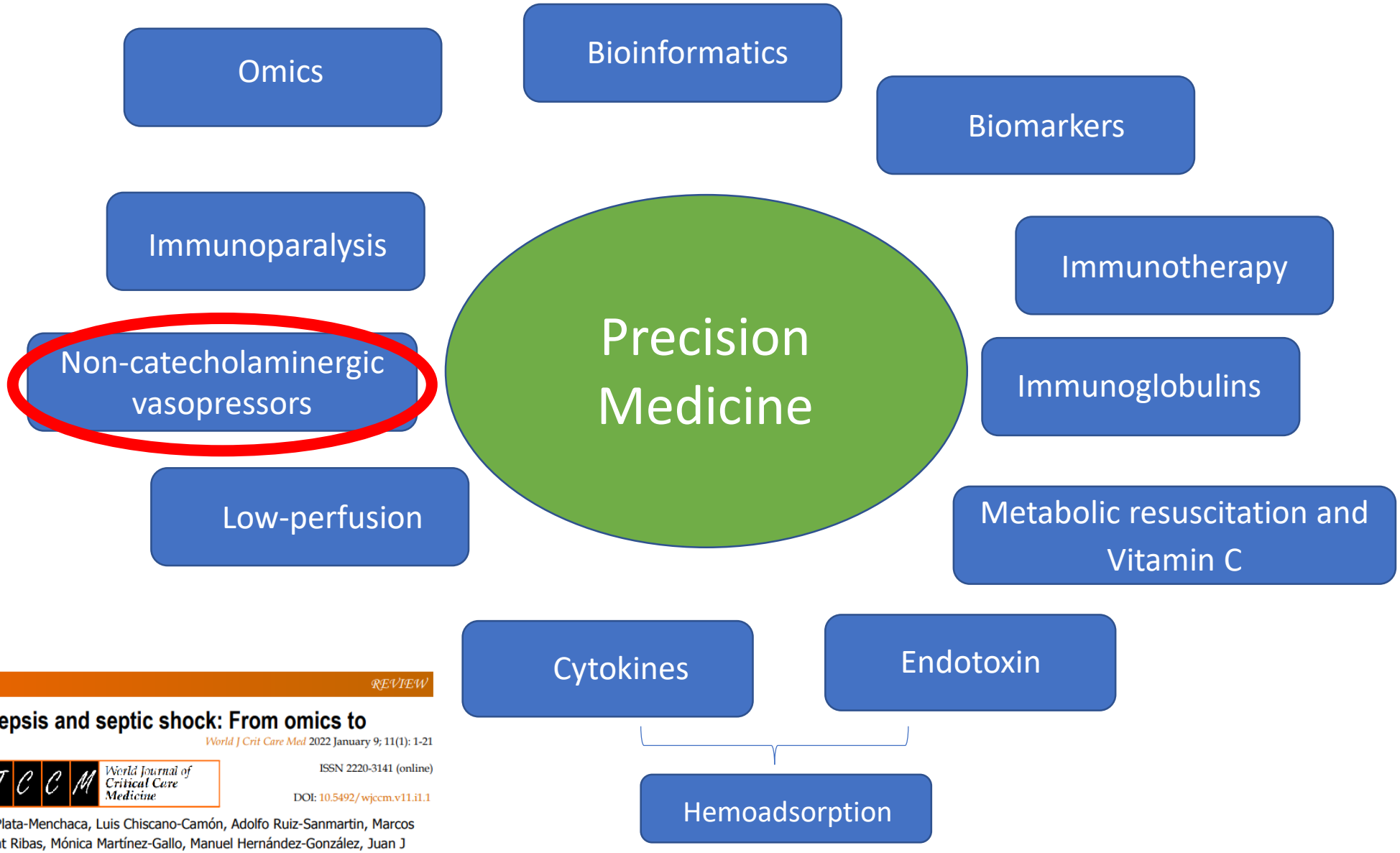
62 For adults with sepsis or septic shock we **suggest against** using intravenous immunoglobulins

Clinical Trial › Intensive Care Med. 2018 Apr;44(4):438-448. doi: 10.1007/s00134-018-5143-7. Epub 2018 Apr 9.

# 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)

**Purpose:** The CIGMA study investigated a novel human polyclonal antibody preparation (trimodulin) containing ~ 23% immunoglobulin (Ig) M, ~ 21% IgA, and ~ 56% IgG as add-on therapy for patients with severe community-acquired pneumonia (sCAP).

**Results:** Overall, there was no statistically significant difference in VFDs between trimodulin (mean 11.0, median 11 [n = 81]) and placebo (mean 9.6; median 8 [n = 79]; p = 0.173). Twenty-eight-day all-cause mortality was 22.2% vs. 27.8%, respectively (p = 0.465). Time to discharge from intensive care unit and mean duration of hospitalization were comparable between groups. Adverse-event incidences were comparable. Post hoc subset analyses, which included the majority of patients (58-78%), showed significant reductions in all-cause mortality (trimodulin vs. placebo) in patients with high CRP, low IgM, and high CRP/low IgM at baseline.




REVIEW

**Precision medicine in sepsis and septic shock: From omics to clinical tools**

*World J Crit Care Med* 2022 January 9; 11(1): 1-21

World Journal of Critical Care Medicine

ISSN 2220-3141 (online)

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Juan Carlos Ruiz-Rodriguez, Erika P Plata-Menchaca, Luis Chiscano-Camón, Adolfo Ruiz-Sanmartin, Marcos Pérez-Carrasco, Clara Palmada, Vicent Ribas, Mónica Martínez-Gallo, Manuel Hernández-González, Juan J Gonzalez-Lopez, Nieves Larrosa, Ricard Ferrer

# Vasopressors in septic shock: which, when, and how much?

Rui Shi[1,2], Olfa Hamzaoui[3], Nello De Vita[1,2], Xavier Monnet[1,2], Jean-Louis Teboul[1,2]

## When to use vasopressors? The earlier, the better

**Table 1** The major vasopressors and their related effects

| Agents | Receptors | Major effects | Major side-effects |
|---|---|---|---|
| Norepinephrine | $\alpha_1$, $\beta_1$ | ↑ venous and arterial tone<br>↑ preload, ↑ contractility | Cardiac arrhythmia<br>Peripheral ischemia<br>Inadvertent immunomodulation |
| Epinephrine | $\alpha_1$, $\beta_1$, $\beta_2$ | ↑ contractility, ↑ preload<br>↑ venous and arterial tone<br>↑ heart rate | Tachycardia, tachyarrhythmia<br>Peripheral ischemia<br>Splanchnic ischemia<br>Increased myocardial oxygen consumption<br>lactic acidosis, hyperglycemia |
| Dopamine | $\alpha_1$, $\beta_1$<br>$D_1$, $D_2$ | ↑ contractility, ↑ heart rate<br>↑ venous and arterial tone<br>↑ renal and mesenteric vasodilation | Tachycardia, tachyarrhythmia |
| Angiotensin II | $ATR_1$, $ATR_2$ | ↑ venous and arterial tone<br>↑ ACTH, ADH, aldosterone (reabsorption) | Tachycardia<br>Peripheral ischemia<br>Thromboembolic events |
| Vasopressin | $V1_a$<br>V2<br>$V1_b$ | ↑ venous and arterial tone, platelet aggregation<br>↑ water retention, release of coagulation factors<br>↑ corticotropic axis stimulation, insulin secretion | Peripheral ischemia<br>Mesenteric ischemia<br>Cardiac arrhythmia |
| Terlipressin | $V1_{a,b} > V2$ | ↑ venous and arterial tone, platelet aggregation<br>↑ water retention, release of coagulation factors | Peripheral ischemia<br>Mesenteric ischemia<br>Cardiac arrhythmia |
| Selepressin | $V1_a$ | ↑ venous and arterial tone, platelet aggregation<br>↓ vascular leakage | Peripheral ischemia<br>Cardiac arrhythmia |

# Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

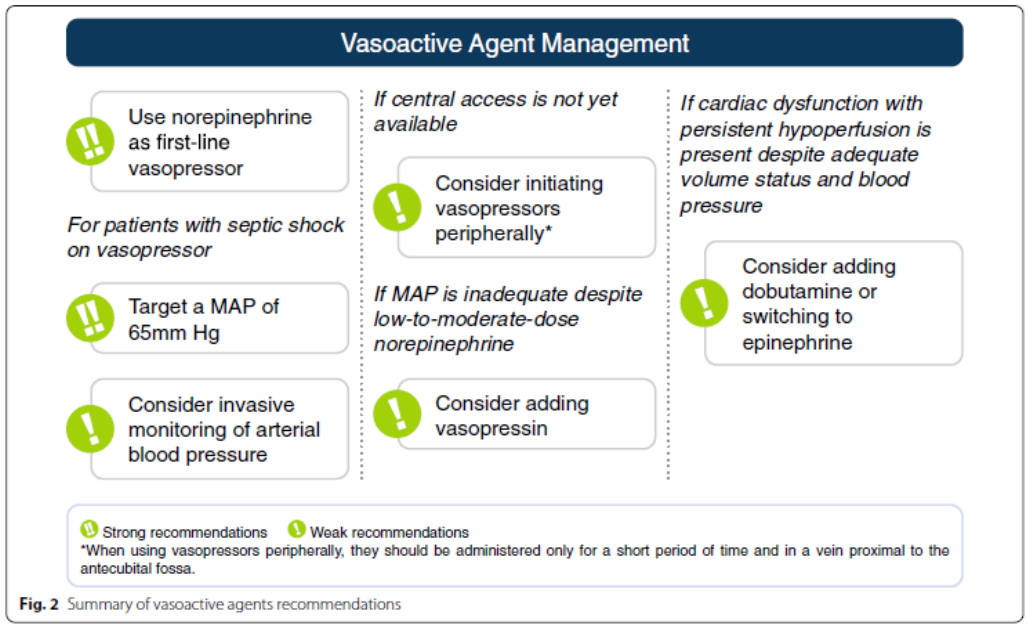



**Fig. 2** Summary of vasoactive agents recommendations

MODERATE

38 For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine.

## Recommendations

37. For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors. *Strong recommendation*
Dopamine. *High quality evidence*
Vasopressin. Moderate-quality evidence
Epinephrine. Low-quality evidence
Selepressin. *Low-quality evidence*
Angiotensin II. *Very low-quality evidence*

**Remark**
In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine

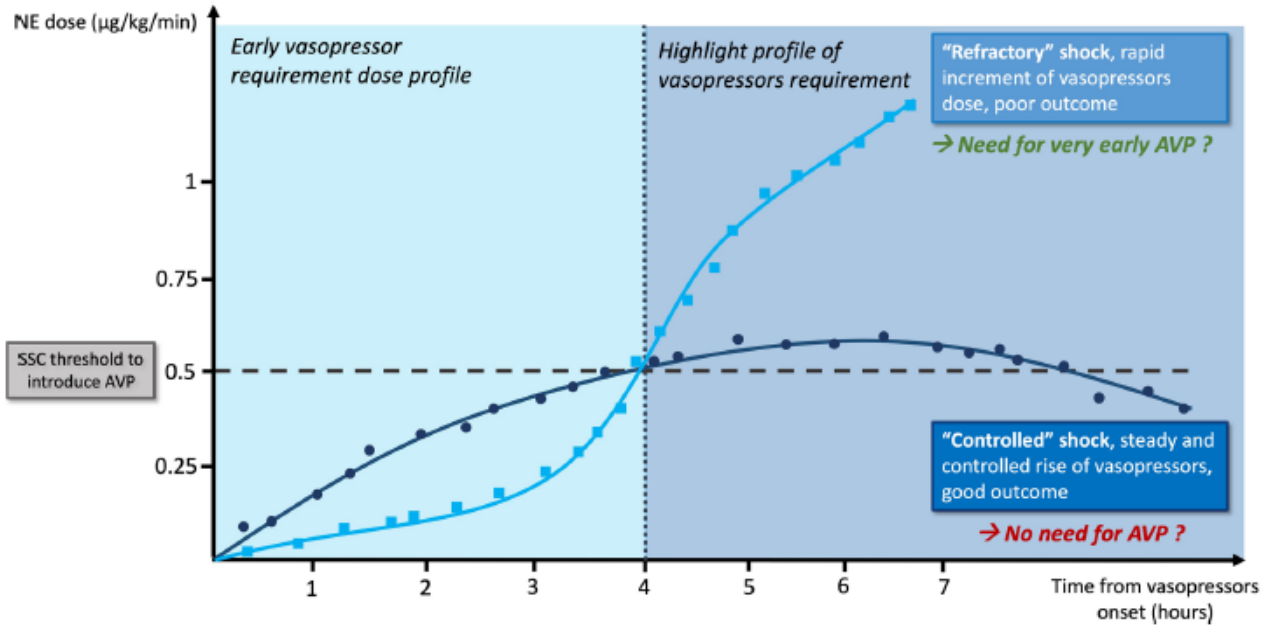
38. For adults with septic shock on norepinephrine with inadequate MAP levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine
*Weak recommendation, moderate-quality evidence*

**Remark**
In our practice, vasopressin is usually started when the dose of norepinephrine is in the range of 0.25–0.5 μg/kg/min

39. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine
*Weak recommendation, low-quality evidence*

40. For adults with septic shock, we **suggest against** using terlipressin
*Weak recommendation, low quality of evidence*

The latest SSC recommendations suggest adding vasopressin instead of scaling norepinephrine above 0.25-0.5 g/kg/min when it is not possible to reach a MAP ≥ 65 mmHg (weak recommendation, moderate quality of evidence)




COMMENT Open Access

# When to start vasopressin in septic shock: the strategy we propose

Guerci et al. Critical Care (2022) 26:125
https://doi.org/10.1186/s13054-022-04001-4

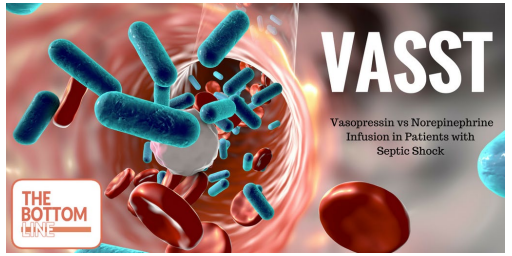
Philippe Guerci[1,2*], Thibaut Belveyre[1,2], Nicolas Mongardon[3,4,5] and Emmanuel Novy[1,6]

# Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

Rusell et al, N Engl J Med 2008;358:877-87

**Vasopressin low doses 0,01-0,03 u/min**




## Study of the effects of low-dose vasopressin as a catecholamine saver and not as an assessment of vasopressin in patients with refractory shock unresponsive to catecholamines.

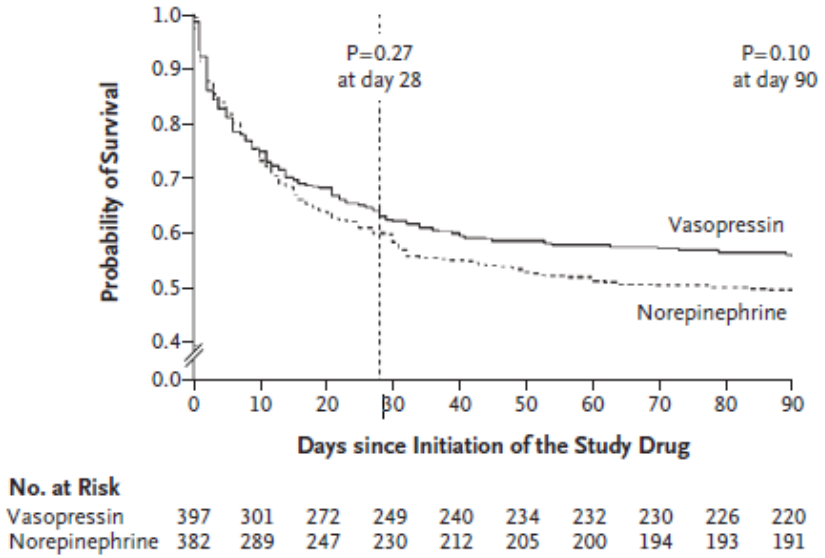



**Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.***

| Stratum | Norepinephrine Group | Vasopressin Group | P Value† | Absolute Risk Reduction (95% CI) | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | *no./total no. (%)* | | | % | |
| More severe septic shock | | | | | |
| 28-day mortality | 85/200 (42.5) | 88/200 (44.0) | 0.76 | −1.5 (−11.2 to 8.2) | 1.04 (0.83 to 1.3) |
| 90-day mortality | 105/199 (52.8) | 103/199 (51.8) | 0.84 | 1.0 (−8.8 to 10.8) | 0.98 (0.81 to 1.18) |
| Less severe septic shock | | | | | |
| 28-day mortality | 65/182 (35.7) | 52/196 (26.5) | 0.05 | 9.2 (−0.1 to 18.5) | 0.74 (0.55 to 1.01) |
| 90-day mortality | 83/180 (46.1) | 69/193 (35.8) | 0.04 | 10.4 (0.4 to 20.3) | 0.78 (0.61 to 0.99) |

* Patients with more severe septic shock were defined as those who required at least 15 μg of norepinephrine per minute or the equivalent at the time of randomization. Those with less severe septic shock were defined as those who required 5 to 14 μg of norepinephrine per minute or the equivalent at the time of randomization.
† Two-sided P values are based on Pearson's chi-square test.

## Conclusions

**No overall difference in 28 or 90 d mortality**

**Low dose vasopressin infusíon allowed a rapid decrease in NE dose**

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Societat Catalana de Medicina Intensiva i Crítica

# Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

## The VANISH Randomized Clinical Trial


| | Vasopressin | | | Norepinephrine | | | Vasopressin vs Norepinephrine, Absolute Difference (95% CI)[b] |
|---|---|---|---|---|---|---|---|
| | Hydrocortisone[a] | Placebo | Total[a] | Hydrocortisone | Placebo | Total | |
| 28-d Survivors who never developed kidney failure, No./total (%)[c] | 46/81 (56.8) | 48/84 (57.1) | 94/165 (57.0) | 46/77 (59.7) | 47/80 (58.8) | 93/157 (59.2) | −2.3 (−13.0 to 8.5)[d] |
| Kidney failure–free days in other patients, median (IQR), d[e] | 5 (0-23) | 12 (1-25) | 9 (1-24) | 13 (0-25) | 14 (1-24) | 13 (1-25) | −4 (−11 to 5)[d] |
| 28-d Mortality, No./total (%) | 33/100 (33.0) | 30/104 (28.8) | 63/204 (30.9) | 29/101 (28.7) | 27/103 (26.2) | 56/204 (27.5) | 3.4 (−5.4 to 12.3) |
| ICU mortality, No./total (%) | 32/100 (32.0) | 26/104 (25.0) | 58/204 (28.4) | 24/101 (23.8) | 27/103 (26.2) | 51/204 (25.0) | 3.4 (−5.2 to 12.0) |
| Hospital mortality, No./total (%) | 35/100 (35.0) | 33/104 (31.7) | 68/204 (33.3) | 31/101 (30.7) | 29/103 (28.2) | 60/204 (29.4) | 3.9 (−5.1 to 12.9) |
| Kidney failure, No./total (%) | 41/101 (40.6) | 46/104 (44.2) | 87/205 (42.4) | 46/101 (45.5) | 51/103 (49.5) | 97/204 (47.5) | −5.1 (−15.2 to 5.0) |
| Survivors | 21/67 (31.3) | 26/74 (35.1) | 47/141 (33.3) | 26/72 (36.1) | 29/76 (38.2) | 55/148 (37.2) | −3.8 (−15.5 to 7.9) |
| Nonsurvivors | 20/33 (60.6) | 20/30 (66.7) | 40/63 (63.5) | 20/29 (69) | 22/27 (81.5) | 42/56 (75) | −11.5 (−29.6 to 6.6) |
| Duration of kidney failure, median (IQR), d | 4 (1 to 7) | 2 (1 to 6) | 3 (1 to 7) | 3 (2 to 6) | 4 (2 to 8) | 4 (2 to 8) | −1 (2 to 0) |
| Survivors | 4 (2 to 7) | 3 (2 to 8) | 4 (2 to 8) | 4 (2 to 8) | 4 (3 to 8) | 4 (2 to 8) | 0 (−3 to 2) |
| Nonsurvivors | 2 (1 to 7) | 2 (1 to 3) | 2 (1 to 7) | 3 (2 to 5) | 2 (1 to 8) | 3 (2 to 7) | −1 (−3 to 0) |
| Use of RRT, No./total (%) | 29/101 (28.7) | 23/104 (22.1) | 52/205 (25.4) | 32/101 (31.7) | 40/103 (38.8) | 72/204 (35.3) | −9.9 (−19.3 to −0.6) |

Gordon AC et al. *JAMA*. 2016; 316(5): 509-518

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 3, 2017 VOL. 377 NO. 5

# Angiotensin II for the Treatment of Vasodilatory Shock

**Table 2. Primary and Secondary End Points.***

| End Point | Angiotensin II (N=163) | Placebo (N=158) | Odds or Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| Primary efficacy end point: MAP response at hour 3 — no. (%)† | 114 (69.9) | 37 (23.4) | Odds ratio, 7.95 (4.76–13.3) | <0.001 |
| Secondary efficacy end points | | | | |
| Mean change in cardiovascular SOFA score at hour 48† | −1.75±1.77 | −1.28±1.65 | | 0.01 |
| Mean change in total SOFA score at hour 48¶ | 1.05±5.50 | 1.04±5.34 | | 0.49 |
| Additional end points | | | | |
| Mean change in norepinephrine-equivalent dose from baseline to hour 3¶ | −0.03±0.10 | 0.03±0.23 | | <0.001 |
| All-cause mortality at day 7 — no. (%) | 47 (29) | 55 (35) | Hazard ratio, 0.78 (0.53–1.16) | 0.22 |
| All-cause mortality at day 28 — no. (%) | 75 (46) | 85 (54) | Hazard ratio, 0.78 (0.57–1.07) | 0.12 |

RESEARCH Open Access

Wieruszewski *et al. Critical Care* (2023) 27:175
https://doi.org/10.1186/s13054-023-04446-1

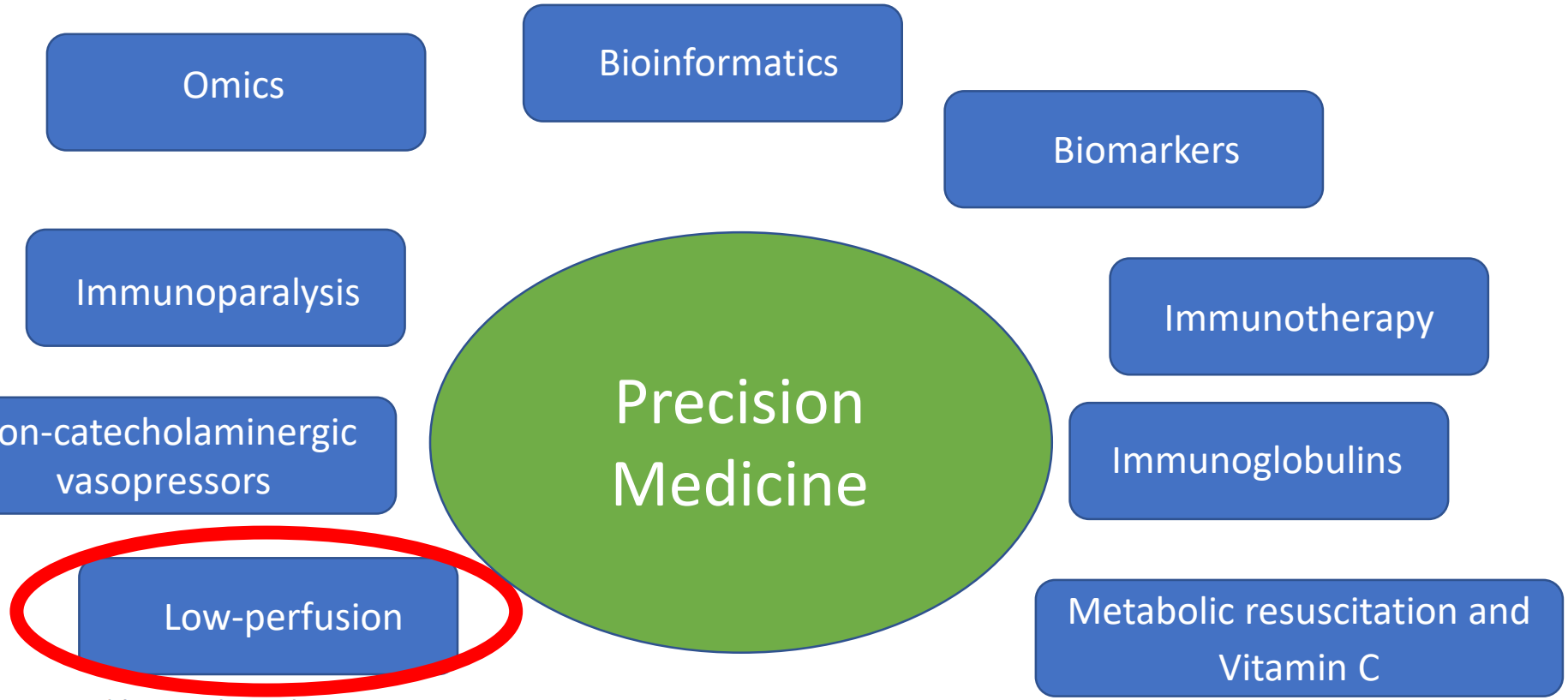
# Initiating angiotensin II at lower vasopressor doses in vasodilatory shock: an exploratory post-hoc analysis of the ATHOS-3 clinical trial

**Table 2** Hemodynamic, Vasopressor, and Exploratory Endpoint Data

| | Low-NED (≤0.25 µg/kg/min) | | HR (95% CI) | *p*-value | High-NED (>0.25 µg/kg/min) | | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|---|
| | Placebo (n = 48) | AT II (n = 56) | | | Placebo (n = 110) | AT II (n = 107) | | |
| MAP response at hour 3, n (%) | 12 (25.0) | 44 (78.6) | | < 0.001 | 25 (22.7) | 70 (65.4) | | < 0.001 |
| MAP change from baseline to hour 3, mmHg | 2 (− 1–8) | 11 (7–16) | | < 0.001 | 4 (− 1–10) | 11 (5–16) | | < 0.001 |

**Table 3** Primary and secondary outcomes

| *Primary outcome, 28-day survival in the Low-NED (≤0.25 µg/kg/min) subgroup* | | | |
|---|---|---|---|
| Placebo (n = 48) | AT II (n = 56) | HR (95% CI) | *p*-value |
| 48% (33%–61%) | 64% (50%–75%) | 0.51 (0.27, 0.95) | 0.03 |




Review > World J Crit Care Med. 2022 Jan 9;11(1):1-21. doi: 10.5492/wjccm.v11.i1.1.

# Precision medicine in sepsis and septic shock: From omics to clinical tools

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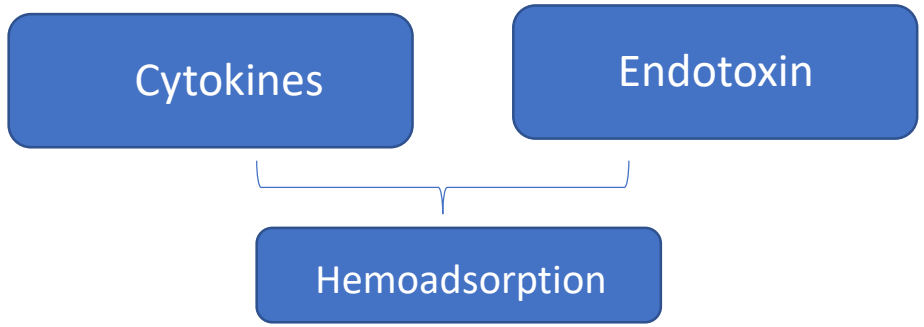
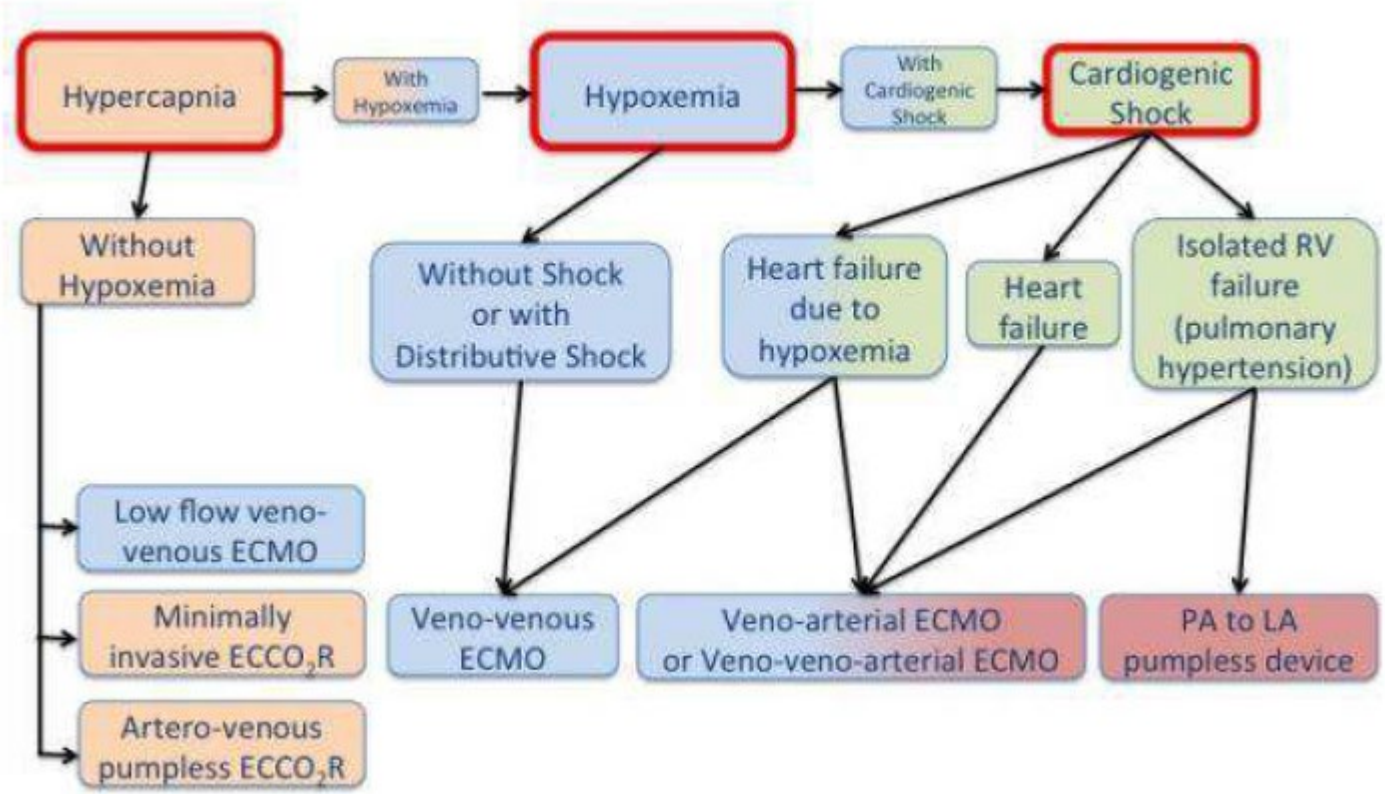



PMID: 35433311 PMCID: PMC8788206 DOI: 10.5492/wjccm.v11.i1.1

Review > Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23.

# Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts

Eddy Fan [1 2], Luciano Gattinoni [3], Alain Combes [4], Matthieu Schmidt [4], Giles Peek [5], Dan Brodie [6], Thomas Muller [7], Andrea Morelli [8], V Marco Ranieri [8], Antonio Pesenti [3], Laurent Brochard [9 10], Carol Hodgson [11], Cecile Van Kiersbilck [12], Antoine Roch [13], Michael Quintel [14], Laurent Papazian [13]



Multicenter Study > Lancet. 2020 Aug 22;396(10250):545-552.
doi: 10.1016/S0140-6736(20)30733-9.

# Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Nicolas Bréchot [1], David Hajage [2], Antoine Kimmoun [3], Julien Demiselle [4], Cara Agerstrand [5], Santiago Montero [6], Matthieu Schmidt [7], Charles-Edouard Luyt [7], Guillaume Lebreton [8], Guillaume Hékimian [9], Erwan Flecher [10], Elie Zogheib [11], Bruno Levy [3], Arthur S Slutsky [12], Daniel Brodie [5], Pierre Asfar [4], Alain Combes [7]; International ECMO Network

**Multicentric** retrospective study where **patients treated with VA-ECMO had more severe myocardial dysfunction, more severe haemodynamic impairment and more severe organ failure than did controls**, with p<0·0001 for each comparison, **however survival at 90 days for patients treated with VA-ECMO was significantly higher** than for controls (60% vs 25%, risk ratio [RR] for mortality 0·54, 95% CI [0·40–0·70]; p<0·0001).

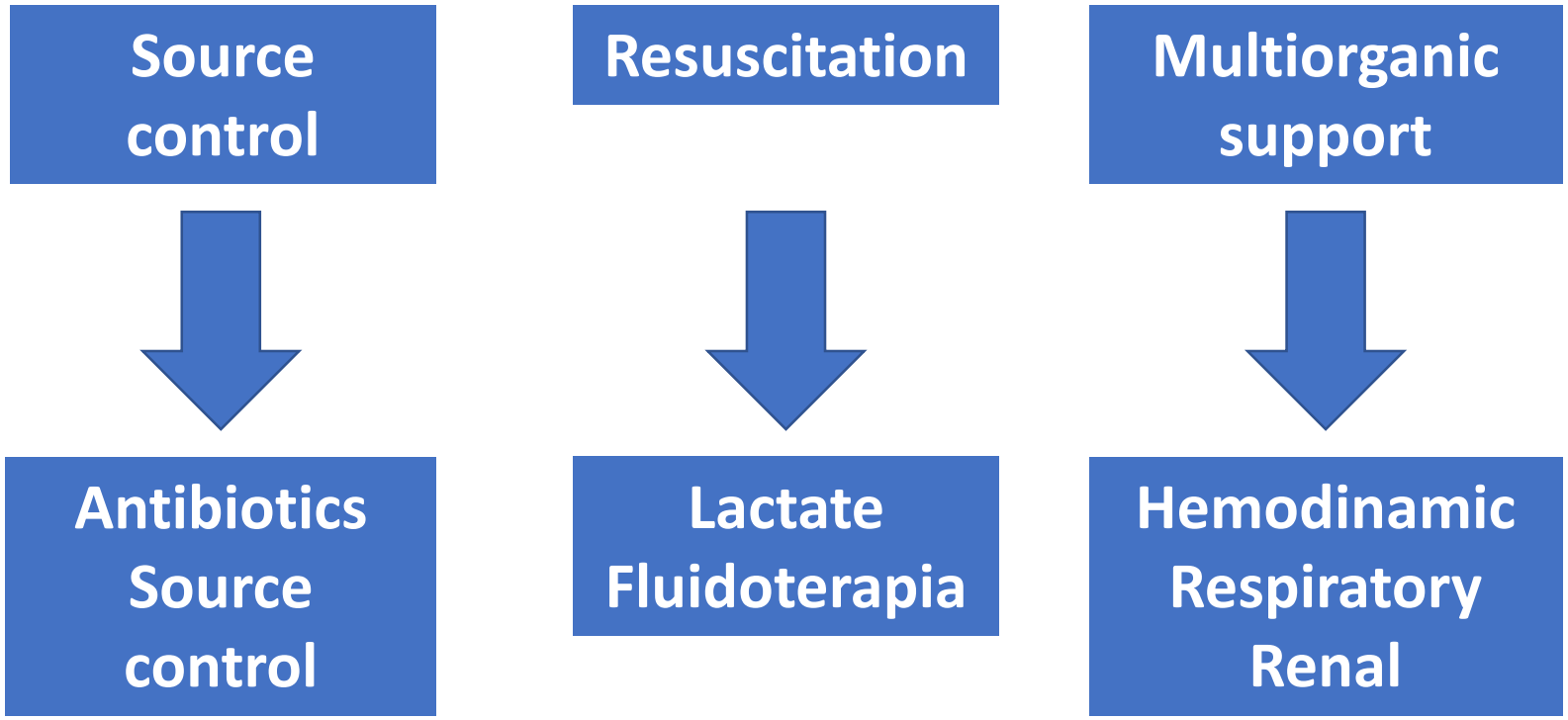
Meta-Analysis > Crit Care. 2021 Jul 14;25(1):246. doi: 10.1186/s13054-021-03668-5.

# Venoarterial extracorporeal membrane oxygenation as mechanical circulatory support in adult septic shock: a systematic review and meta-analysis with individual participant data meta-regression analysis

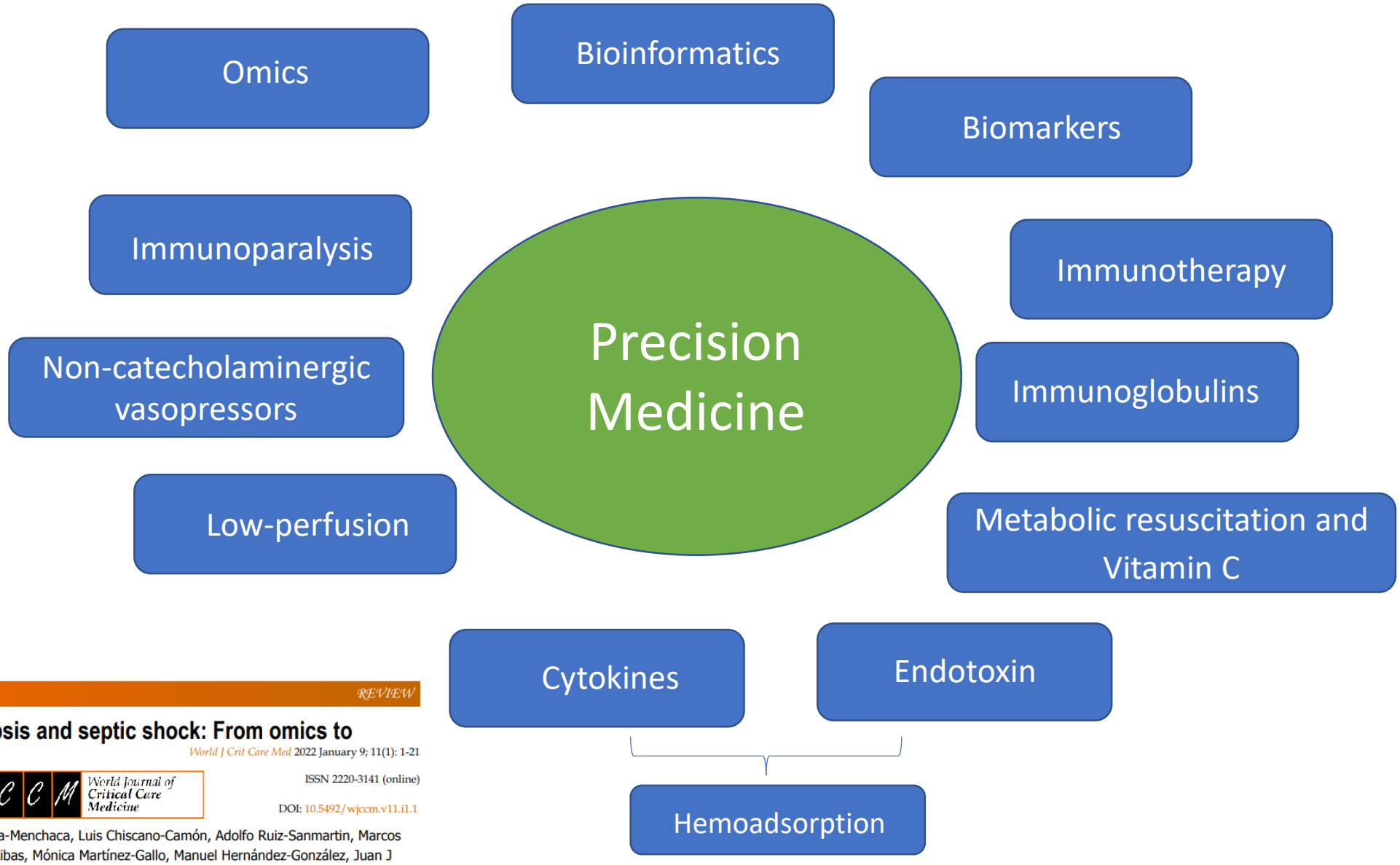
Ryan Ruiyang Ling [# 1], Kollengode Ramanathan [# 2 3], Wynne Hsing Poon [1], Chuen Seng Tan [4], Nicolas Brechot [5 6], Daniel Brodie [7], Alain Combes [5 8], Graeme MacLaren [1 9]

Systemic review including 14 observational studies with 468 patients that concluded that when treated with VA ECMO, the majority of patients with septic shock and severe sepsis-induced myocardial depression survive. However, VA ECMO has poor outcomes in adults with septic shock without severe left ventricular depression. **Pooled survival was 36.4%. Survival among patients with left ventricular ejection fraction (LVEF) < 20%** (62.0%, 95%-CI: 51.6%-72.0%) **was significantly higher than those with LVEF > 35%** (32.1%, 95%-CI: 8.69%-60.7%, p = 0.05).

# Treatment SEPSIS – SEPTIC SHOCK




## PERSONALIZED MEDICINE
## Rescue Therapies

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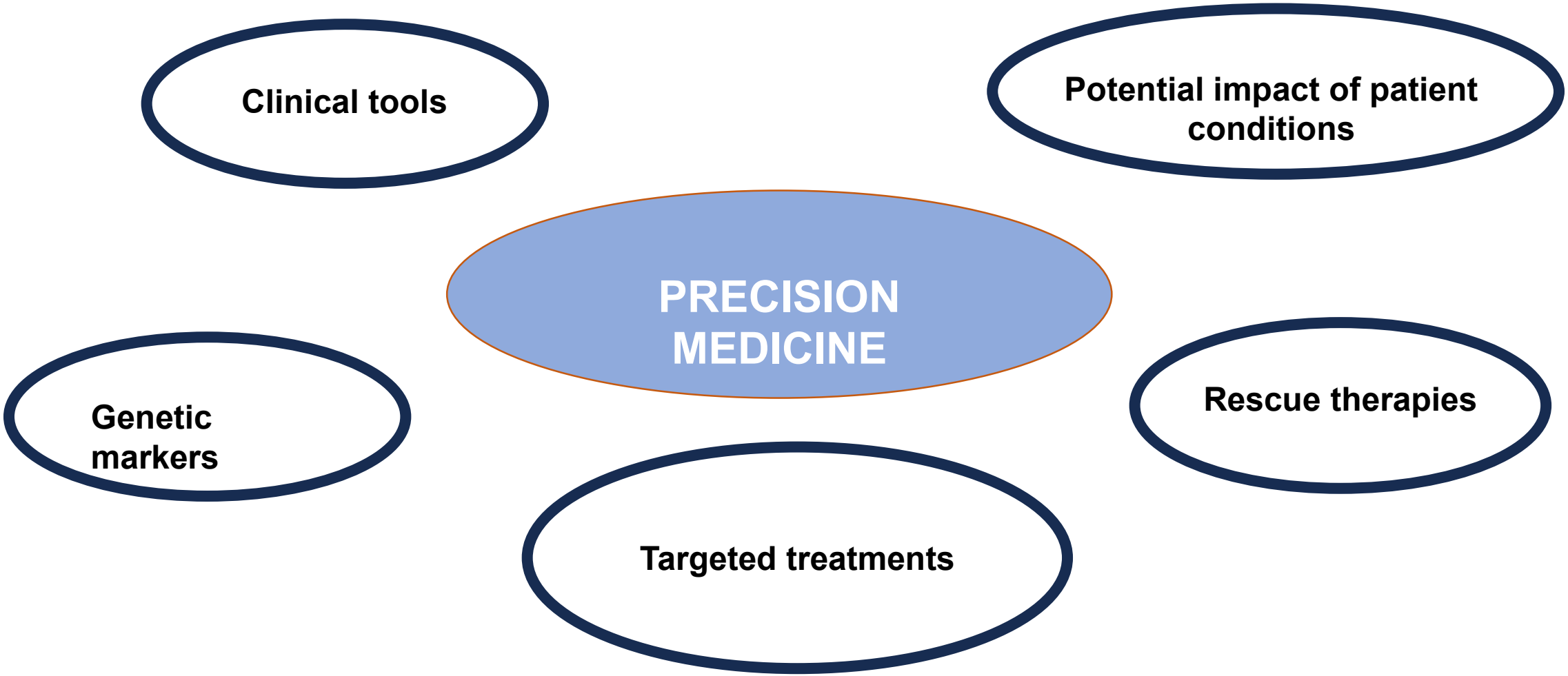
# Conclusions



# ¡Gracias!

**Luis Chiscano Camón**

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Shock, Organ Dysfunction and Resuscitation Research Group. Vall d'Hebron Research Institute (VHIR)

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