서울대학교 시스템면역의학연구소

제6회
국제 학술 대회

The 6th International Symposium of Wide River Institute of Immunology

Innate Immunity across the Life

■ **일시** 2019. 10. 11. (금) 12:00~20:00

■ **장소** 서울대학교 시스템면역의학연구소 볼룸

서울대학교 시스템면역의학연구소

인 사 말

안녕하십니까?

서울대학교 시스템면역의학연구소의 개소 5주년을 기념하여 개최하는 제6회 국제학술대회에 참석하여 주신 여러분께 깊은 감사의 말씀을 전합니다. 또한 강의를 수락하여 주신 연자분들께도 특별한 감사의 말씀을 드립니다.

서울대학교 시스템면역의학연구소는 종양 및 다양한 면역 질환의 기전 및 치료법에 대한 연구를 수행하고 있습니다. 또한 의생명과학 분야 여러 핵심 연구 기술들을 지원하는 시스템을 구축하여 현재까지 130여 건의 공동협력 연구를 진행하였으며 이에 따른 우수한 성과가 나오고 있습니다. 이처럼 활발한 협력 연구를 통해 건강한 미래 사회를 구현하기 위해 최선의 노력을 다하겠습니다. 앞으로도 아낌없는 격려와 관심 부탁드립니다.

이번 국제학술대회에서는 패혈증 연구를 선도하는 세계 각국의 연구자를 초청하여 분자 수준에서부터 임상에서의 진단과 치료에의 적용까지의 최신 연구를 소개하는 자리를 마련하였습니다. 본 학회를 통해서 참석자분들의 학문 증진 및 상호 교류를 유도하여 연구의 결실이 보다 풍성하게 무르익을 수 있기를 기원합니다.

제6회 국제학술대회가 성공적으로 마무리 될 수 있도록 여러분의 적극적인 성원을 부탁드리며 다시 한 번 감사의 말씀을 드립니다.

서울대학교 시스템면역의학연구소장 박 준 동

제6회 서울대학교 시스템면역의학연구소 국제학술대회

The 6th International Symposium of Wide River Institute of Immunology
Innate Immunity across the Life

Scientific Program

12:00~13:00 Registration

13:00~13:10 Opening Remark

June Dong Park (Seoul National University, Korea)

Chair: June Dong Park (Seoul National University, Korea)

13:10~13:50 **TGR5: Toll for Regulating Innate Immunity**

Seung-Yong Seong (Seoul National University, Korea)

13:50~14:30 **Mitochondrial DAMPs and Nosocomial Pneumonia**

Kiyoshi Itagaki (BIDMC/Harvard Medical School, USA)

14:30~15:10 **A Novel Gr-1^{+} Myeloid Population that Plays an Essential Role in Mortality during Bacterial Infection**

Yoe-Sik Bae (Sungkyunkwan University, Korea)

15:10~15:40 **Break and WRII Lab Tour**

Chair: Seung-Yong Seong (Seoul National University, Korea)

15:40~16:20 **Tryptophanyl tRNA Synthetase as a Primary Defense System against Infection and its Role in Sepsis**

Mirim Jin (Gachon University, Korea)

16:20~17:00 **Sepsis in Children**

Satoshi Nakagawa (National Center for Child Health and Development, Japan)

17:00~17:40 **Role of Circulating Mitochondrial *N*-formyl Peptides in Patients with Septic Shock**

Woon Yong Kwon (Seoul National University, Korea)

17:40~20:00 Closing and the Banquet

TGR5: Toll for Regulating Innate Immunity

Seung-Yong Seong[1,2,3,4]

[1]Wide River Institute of Immunology, Seoul National University, Korea; [2]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Microbiology and Immunology, Seoul National University College of Medicine; 103 Daehakno, Jongno-gu, Seoul, Korea; [4]Shaperon co., 7 Beobwon-ro 8-gil, Songpa-gu, Seoul, 05855, Seoul, Korea

TGR5, G protein-coupled receptor 19, is also known as G protein-coupled bile acid receptor 1. The single exon encodes a TGR5 protein composed of 330 amino acids with seven transmembrane domains. Although TGR5 is expressed in various tissues such as liver, nervous system, adipocytes, endocrine glands, gall bladder, muscles, and spinal cord, the expression level in these tissues is less than 1/10 of myeloid immune cells. Activation of TGR5 incur various signaling cascades depending on the responder cell type. For example, synthesis and secretion of bile acids, intestinal secretion and motility, energy expenditure, glucose homeostasis, and inflammation is regulated by TGR5 pathway. Although TGR5 has got much attention as a promising new target for metabolic disorders or inflammatory disorders, only deoxycholic acid was licensed for lipoma. Obeticholic acid was also licensed for cholangitis but it interacts with FXR in addition to TGR5. Recently, we showed that taurodexoycholic acid (TDCA) interacts with TGR5, reduces inflammation incurred by activation of neutrophils, increases number of myeloid derived suppressor cells and prolongs survival of mice under sepsis. TDCA changes DNA methylation pattern of chromosome, globally edit proteomes of skin cells, brain cells and myeloid cells in mice model for atopic dermatitis, Alzheimer disease and sepsis, respectively. In addition, inflammasomal activation was suppressed by down-regulating a purinergic receptor in TDCA-treated neutrophils. In addition, cAMP-PKA-NF-κB pathway was controlled by TDCA. Phase I clinical trials for atopic dermatitis using TDCA did not show significant adverse drug reactions. Taken together, TDCA might be a non-classical anti-inflammatory drug (NCAID) for various inflammatory disorders when activation of myeloid inflammatory cells are pathognomonic features.

Curriculum Vitae

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Education and Appointment

1990	**Bachelor**, **MD**, Seoul National University College of Medicine
1992	**MS** in Microbiology and Immunology, Seoul National University College of Medicine
1995	**PhD** in Microbiology and Immunology, Department of Microbiology and Immunology, Seoul National University College of Medicine

Professional Training and Employment

1990-1995	Research Assistant, Department of Microbiology and Immunology, Seoul National University College of Medicine
1995-1998	Doctor for Public Health, Biomedical Research Center, Korea Institute of Science and Technology
1998-2010	Assistant Professor and Associate professor, Department of Microbiology and Immunology, Seoul National University College of Medicine
2001-2004	Research Fellow, NIAID, NIH Bethesda, USA
2004-	Professor, Department of Microbiology and Immunology, Seoul National University College of Medicine
2012-2013	Associate Dean for Planning, Seoul National University College of Medicine
2013-2018	Director, Seoul National University College of Medicine, Wide River Institute of Immunology
2014-2015	Associate Dean for Graduate Study, Seoul National University College of Medicine
2016-	Chair, Department of Microbiology and Immunology of Seoul National University College of Medicine

Selected Publications

1. **Seong SY,** Matzinger P. Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol* 2004;4:469-78.
2. Nam-Hyuk Cho, **Seung-Yong Seong**, Apolipoproteins inhibit the innate immunity activated by necrotic cells or bacterial endotoxin , *Immunol*. 2009 Sep;128(1 Suppl):e479-86. Epub 2008 Dec 17.
3. Jin Hee Kim, Tae Heung Kang, Kyung Hee Noh, Hyun Cheol Bae, Seok-Ho Kim, Young Do Yoo, **Seung-Yong Seong**, Tae Woo Kim, Enhancement of dendritic cell-based vaccine potency by anti-apoptotic siRNAs targeting key pro-apoptotic proteins in cytotoxic $CD8^+$ T cell-mediated cell death. *Immunol Lett*. 2009 Jan 29;122(1):58-67.
4. Lee KM, **Seong SY**. Partial role of TLR4 as a receptor responding to damage-associated molecular pattern. *Immunol Lett*. 2009 Jun 30;125(1):31-9.
5. Na HY, Mazumdar K, Moon HJ, Chang S, **Seong SY**. TLR4-independent and PKR-dependent interleukin 1 receptor antagonist expression upon LPS stimulation. *Cell Immunol*. 2009;259(1):33-40. Epub 2009 Jun 6.
6. Bae MY, Cho NH, **Seong SY**. Protective anti-tumour immune responses by murine dendritic cells pulsed with recombinant Tat-carcinoembryonic antigen derived from Escherichia coli. *Clin Exp Immunol*. 2009

Jul;157(1):128-38.
7. Yang H, Cho NH, **Seong SY**. The Tat-conjugated N-terminal region of mucin antigen 1 (MUC1) induces protective immunity against MUC1-expressing tumours. *Clin Exp Immunol*. 2009 Nov;158(2):174-85
8. Chun KH, **Seong SY**. CD14 but not MD2 transmit signals from DAMP. *Int Immunopharmacol*. 2010 Jan;10(1):98-106.
9. Nam-Hyuk Cho, Taek-Chin Cheong, Ji Hyun Min, Jun Hua Wu, Sang Jin Lee, Daehong Kim, Jae-Seong Yang, Sanguk Kim,Young Keun Kim and **Seung-Yong Seong.** A multifunctional core-shell nanoparticle for dendritic cell based cancer immunotherapy. *Nature Nanotech*. 2011 Sep 11;6(10):675-82.
10. Noh KH, Kim BW, Song KH, Cho H, Lee YH, Kim JH, Chung JY, Kim JH, Hewitt SM, **Seong SY**, Mao CP, Wu TC, Kim TW. Nanog signaling in cancer promotes stem-like phenotype and immune evasion. *J Clin Invest*. 2012 Nov 1;122(11):4077-93.
11. Lee SH, Nam KW, Jeong JY, Yoo SJ, Koh YS, Lee S, Heo ST, **Seong SY**, Lee KH. The Effects of Climate Change and Globalization on Mosquito Vectors: Evidence from Jeju Island, South Korea on the Potential for Asian Tiger Mosquito (Aedes albopictus) Influxes and Survival from Vietnam Rather Than Japan. *PLoS One*. 2013 Jul 24;8(7):e68512.
12. Lee HC, Narayanan S, Park SJ, **Seong SY**, Hahn YS. Transcriptional regulation of IFN-λ genes in hepatitis C virus-infected hepatocytes via IRF-3·IRF-7·NF-κB complex. *J Biol Chem*. 2014 Apr 25;289(17):11861.
13. Cheong TC, Shin EP, Kwon EK, Choi JH, Wang KK, Sharma P, Choi KH, Lim JM, Kim HG, Oh K, Jeon JH, So I, Kim IG, Choi MS, Kim YK, **Seong SY**, Kim YR, Cho NH. Functional Manipulation of Dendritic Cells by Photoswitchable Generation of Intracellular Reactive Oxygen Species. *ACS Chem Biol*. 2015 Mar 20;10(3):757-65.
14. Kim JE, Hong YH, Lee JH, Ahn SW, Kim SM, Park KS, Sung JJ, Lee KW, **Seong SY**. Pattern difference f dissociated hand muscle atrophy in amyotrophic lateral sclerosis and variants. *Muscle Nerve*. 2015 Mar.51(3):333-7
15. Cho JA, Kim TJ, Moon HJ, Kim YJ, Yoon HK, **Seong SY**. Cardiolipin activates antigen-presenting cells via TLR2-PI3K-PKN1-AKT/p38-NF-kB signaling to prime antigen-specific naïve T cells in mice. *Eur J Immunol*. 2018 May;48(5):777-790.
16. Jung YS, Kwon WY, Suh GJ, Moon S, Han MH, Youn JI, Seo SU, Kim KS, **Seong SY**. Low serum Kallistatin level was associated with poor neurological outcome of out-of-hospital cardiac arrest survivors: Proteomics study. *Resuscitation*. 2018 Jul;128:6-10.
17. Chang S, Kim YH, Kim YJ, Kim YW, Moon S, Lee YY, Jung JS, Kim Y, Jung HE, Kim TJ, Cheong TC, Moon HJ, Cho JA, Kim HR, Han D, Na Y, Seok SH, Cho NH, Lee HC, Nam EH, Cho H, Choi M, Minato N, **Seong SY**. Taurodeoxycholate Increases the Number of Myeloid-Derived Suppressor Cells That Ameliorate Sepsis in Mice. *Front Immunol*. 2018 Sep 18;9:1984.
18. Kim HR, Park SM, Seo SU, Jung I, Yoon HI, Gabrilovich DI, Cho BC, **Seong SY**, Ha SJ, Youn JI. The Ratio of Peripheral Regulatory T Cells to Lox-1^{+} Polymorphonuclear Myeloid-derived Suppressor Cells Predicts the Early Response to Anti-PD-1 Therapy in Patients with Non-Small Cell Lung Cancer. *Am J Respir Crit Care Med*. 2019 Jan 15;199(2):243-246.
19. Choi HJ, Yun JW, Kim YH, Kwon E, Hyon MK, Kim JY, Che JH, Kim WH, **Seong SY**, Kang BC. Evaluation of acute and subacute toxicity of sodium taurodeoxycholate in rats. *Drug Chem Toxicol*. 2019 Jun 19:1-9.

Mitochondrial DAMPs and Nosocomial Pneumonia

Kiyoshi Itagaki
BIDMC/Harvard Medical School, USA

Serious injury causes tissue/cellular damages leading to release of mitochondria into circulation. We discovered that these mitochondria act as Damage-Associated Molecular Patterns (DAMPs) to influence immune systems (Nature, 2010). Today, I will discuss our theory of how seriously injured people may develop nosocomial pneumonia and how to prevent or treat this dysfunction without depending on antibiotics that could lead to antibiotics-resistant bacteria by presenting two possible methods focusing on neutrophil-mitochondrial DAMPs interactions.

Curriculum Vitae

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Education and Appointment

1978-1982 **BS** in Marine Biology, The University of Tokyo
1986-1991 **PhD** in Veterinary Pharmacology, The University of Tokyo

Professional Training and Employment

1991-1994 Research Associate in Pharmacology, University of Cincinnati
1994-2000 Intramural Research Training Award Fellow in Signal Transduction, National Institute of Environmental Health Sciences (NIEHS)
2000-2006 Assistant Professor in Surgery, University of Medicine and Dentistry of New Jersey (UMDNJ)
2006-2019 Instructor in Surgery, Harvard Medical School
2019- Associate Professor in Surgery, Harvard Medical School

Selected Publications

1. **Itagaki K**, Koch WJ, Bodi I, Klockner U, Slish DF, Schwartz A. Native-type DHP-sensitive calcium channel currents are produced by cloned rat aortic smooth muscle and cardiac alpha 1 subunits expressed in *Xenopus laevis* oocytes and are regulated by alpha 2- and beta-subunits. *FEBS Lett*. 1992;297(3):221-5.
2. **Itagaki K**, Carver GT, Philpot RM. Expression and characterization of a modified flavin-containing monooxygenase 4 from humans. *J Biol Chem*. 1996;271(33):20102-7.
3. **Itagaki K**, Hauser CJ. Sphingosine 1-phosphate, a diffusible calcium influx factor mediating store-operated calcium entry. *J Biol Chem*. 2003;278(30):27540-7.
4. **Itagaki K**, Kannan KB, Singh BB, Hauser CJ. Cytoskeletal reorganization internalizes multiple transient receptor potential channels and blocks calcium entry into human neutrophils. *J Immunol*. 2004;172(1):601-7.
5. **Itagaki K**, Kannan KB, Hauser CJ. Lysophosphatidic acid triggers calcium entry through a non-store-operated pathway in human neutrophils. *J Leukoc Biol*. 2005;77(2):181-9.
6. Hauser CJ, Kannan KB, Deitch EA, **Itagaki K**. Non-specific effects of 4-chloro-*m*-cresol may cause calcium flux and respiratory burst in human neutrophils. *Biochem Biophys Res Commun*. 2005;336(4):1087-95.
7. **Itagaki K**, Yun JK, Hengst JA, Yatani A, Hauser CJ, Spolarics Z, Deitch EA. Sphingosine 1-Phosphate has Dual Functions in the Regulation of Endothelial Cell Permeability and Ca^{2+} Metabolism. *J Pharmacol Exp Ther*. 2007;323(1):186-91.
8. **Itagaki K**, Zhang Q, Hauser CJ. Sphingosine Kinase Inhibition Alleviates Endothelial Permeability Induced By Thrombin and Activated Neutrophils. *Shock*. 2010;33(4):381-386.
9. **Itagaki K**, Menconi M, Antoniu B, Zhang Q, Gonnella P, Soybel D, Hauser CJ, and Hasselgren PO. Dexamethasone stimulates store-operated calcium entry and protein degradation in cultured L6 myotubes through a phospholipase A2-dependent mechanism. *Am J Physiol Cell Physiol*. 2010;298(5):C1127-39.
10. Zhang Q, Raoof M, Sursal T, Chen Y, Sumi Y, Junger W, Brohi K, **Itagaki K**, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464:104-7.
11. Hauser CJ, Sursal T, Rodriguez EK, Appleton PT, Zhang Q, **Itagaki K**. Mitochondrial DAMPs from femoral reamings activate neutrophils via formyl peptide receptors and P44/42 MAP Kinase. *J Orth*

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12. **Itagaki K**, Barton BE, Murphy TF, Taheri S, Shu P, Huang H, Jordan ML. Eicosanoid-induced store-operated calcium entry in dendritic cells. *J Surg Res*. 2011;169(2):301-10.
13. **Itagaki K**, Adibnia Y, Sun S, Zhao C, Sursal T, Chen Y, Junger W, Hauser CJ. Bacterial DNA induces pulmonary damage via TLR-9 through cross-talk with neutrophils. *Shock*. 2011;36(6):548-52.
14. Sun S, Sursal T, Adibnia Y, Zhao C, Zheng Y, Li H, Otterbein LE, Hauser CJ, **Itagaki K**. Mitochondrial DAMPs Increase Endothelial Permeability through Neutrophil Dependent and Independent Pathways. *PLOS ONE*. 2013;8(3):e59989.
15. **Itagaki K**, Kaczmarek E, Lee YT, Tang IT, Isal B, Adibnia Y, Sandler N, Grimm MJ, Segal BH, Otterbein LE, Hauser CJ. Mitochondrial DNA released by trauma induces neutrophil extracellular traps. *PLoS One*. 2015;10(3):e0120549.
16. **Itagaki K**, Riça I, Zhang J, Gallo D, DePrato M, Otterbein LE, Hauser CJ. Intratracheal instillation of neutrophils rescues bacterial overgrowth initiated by trauma damage-associated molecular patterns. *J Trauma Acute Care Surg*. 2017;82(5):853-860.
17. Kaczmarek E, Hauser CJ, Kwon WY, Riça I, Chen L, Sandler N, Otterbein LE, Campbell Y, Cook CH, Yaffe MB, Marusich M, **Itagaki K**. A Subset of Five Human Mitochondrial Formyl Peptides Mimics Bacterial Peptides and Functionally Deactivates Human Neutrophils. *J Trauma Acute Care Surg*. 2018;85(5):936-943.
18. **Itagaki K**, Kaczmarek E, Kwon WY, Chen L, Vlkova B, Zhang Q, Riça I, Yaffe MB, Gong WH, Wang JM, Gao JL, Jung F, Douglas G, Campbell Y, Marusich MF, Otterbein LE, and Hauser CJ. FPR1 blockade prevents receptor regulation by mitochondrial DAMPs and preserves neutrophil function after trauma. *Critical Care Med*. 2019 (accepted)
19. Philpot RM, Biagini CP, Carver GT, Overby LH, Wyatt MK, **Itagaki K**. Expression and regulation of flavin-containing monoexygenases. Editors; Arinc E and Hodgson E. Molecular Aspects of Oxidative Drug Metabolizing Enzymes, Life Sciences Vol. 303. NATO ASI Series. *New York: Plenum Publishers*; 1999, 71-80.

A Novel Gr-1$^+$ Myeloid Population that Plays an Essential Role in Mortality during Bacterial Infection

Min Young Park[1], Hyung Sik Kim[1], Ha Young Lee[1], Brian A. Zabel[2], and Yoe-Sik Bae[1,3]

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Severe sepsis, a principal cause of death in intensive care units, occurs when host immune defenses fail to combat invading microbes. Regulation of neutrophil activity by targeting phospholipase D2 (PLD2) modulates pathogenesis of sepsis. PLD2-deficiency caused protective effects against experimental sepsis showing increased survival and decreased vital organ damage. Neutrophil extracellular trap formation and subsequent bacteria killing activity is strongly augmented in PLD2-deficient mice. PLD2 in neutrophils is essential for the pathogenesis of experimental sepsis. Extreme pathophysiological stressors like tumor or rampant bacterial infection induce expansion of otherwise infrequent leukocyte populations. We discovered a novel CD11b$^+$Gr-1$^+$ myeloid cell population induced upon experimental infection with *Staphylococcus aureus* (*S. aureus*). Novel CD11b$^+$Gr-1$^+$ cells have impaired migratory capacity and superoxide anion producing activity. However, novel CD11b$^+$Gr-1$^+$ cells secrete increased levels of several cytokines and chemokines compared to their counterparts. We also found functional role of the novel CD11b$^+$Gr-1$^+$ cells during bacterial infection.

Curriculum Vitae

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Education and Appointment

1990-1996 **BS.** Department of Animal Science and Technology, College of Agriculture and Life Science, Seoul National University, Seoul, Korea
1996-1998 **MS.** Department of Life Science, POSTECH, Pohang, Korea
1998-2000 **PhD.** Division of Molecular and Life Sciences, POSTECH, Pohang, Korea

Professional Training and Employment

2000-2002 Post-doctoral in Division of Molecular and Life Sciences, POSTECH, Pohang, Korea
2002-2010 Full-time instructor, Assistant Professor, Associate Professor in Department of Biochemistry, College of Medicine, Dong-A University, Busan, Korea
2008-2009 Visiting Associate Professor, Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA
2010- Associate Professor, Professor, Department of Biological Sciences, Sungkyunkwan University, Suwon, Korea

Selected Publications (*) as a corresponding author

1. Lee, S. K.[†], Kim, Y. S.[†], Bae, G. H., Lee, H. Y., and **Bae, Y. S.*** (2019) VU0155069 inhibits inflammasome activation independent of phospholipase D1 activity. *Sci. Rep*. In press.
2. Park, Y. J.[†], Park, B.[†], Lee, M., Jeong, Y. S., Lee, H. Y., Sohn, D. H., Song, J. J., Lee, J. H., Hwang, J. S., and **Bae, Y. S.*** (2018) A novel antimicrobial peptide acting via formyl peptide receptor 2 shows therapeutic effects against rheumatoid arthritis. *Sci Rep*. 8:14664.
3. Park, M. Y., Kim, H. S., Lee, M., Park, B., Lee, H. Y., Cho, E. B., Seong, J. Y., and **Bae, Y. S.*** (2017) FAM19A5, a brain-specific chemokine, inhibits RANKL-induced osteoclast formation through formyl peptide receptor 2. *Sci Rep*. 7:15575.
4. Lee, S. K., Kim, S. D., Kook, M., Lee, H. Y., Ghim, J., Choi, Y., Zabel, B. A., Ryu, S. H., and **Bae, Y. S.*** (2015) Phospholipase D2 drives mortality in sepsis by inhibiting neutrophil extracellular trap formation and downregulating CXCR2. *J. Exp. Med*. 212:1381-1390.
5. Kim, S. D., Kim, H. J., Shim, J. W., Lee, H. Y., Lee, S. K., Kwon, S., Jung, Y. S., Baek, S.H., Park, J. S., Zabel B.A., and **Bae, Y. S.*** (2012) Phospholipase C activator m-3M3FBS protects against morbidity and mortality associated with sepsis. *J. Immunol*. 189: 2000-2005.
6. Kim, S. D., Lee, H. Y., Shim, J. W., Kim, H. J., Yoo, Y. H., Park, J. S, Baek, S. H., Zabel, A. B., and **Bae, Y. S.*** (2011) Activation of CXCR2 by extracellular matrix degradation product acetylated-Pro-Gly-Pro has therapeutic effects against sepsis. *American J. Respiratory and Critical Care Medicine* 184:243-251.
7. Lee, H. Y., Lee, S. Y., Kim, S. D., Shim, J. W., Kim, H. J., Kwon, J. Y., Chung, J., Baek, S. H., Chung, J., and **Bae, Y. S.*** (2011) Sphingosylphosphorylcholine stimulates CCL2 production from human umbilical vein endothelial cells. *J. Immunol*. 186: 4347-4353.

A novel Gr-1^{+} myeloid population that plays an essential role in mortality during bacterial infection

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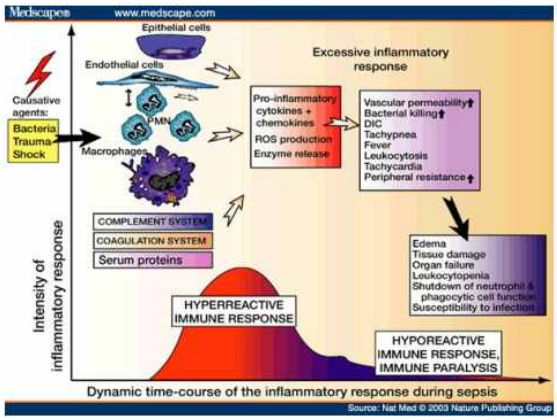
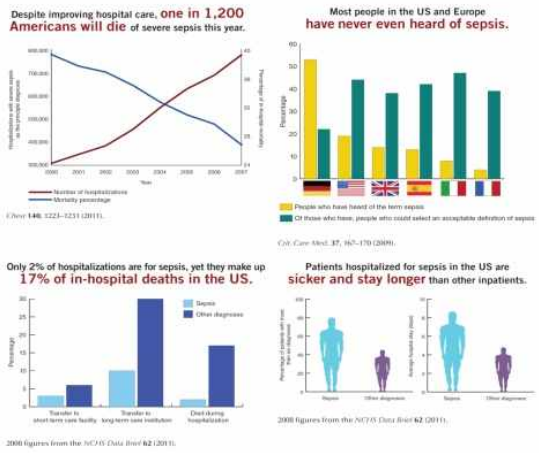
Multiple pathogenic mechanisms in sepsis



Despite improving hospital care, one in 1,200 Americans die annually



Many interventions targeting inflammatory mediator failed to treat sepsis

Medscape® www.medscape.com	
L-NAME (NOS inhibitor) L-NMMA (iNOS inhibitor) Methylene blue (guanylyl cyclase inhibition) PHP (NO scavenger)	NO
AT-III (inhibition of thrombin, Factors IXa, Xa and XIa, XIIa) TFPI (inhibition of Factors X and IX) APC (inactivation of Factors Va and VIIIa)*	Coagulation/inflammation
IFN-γ (reactivation of neutrophil immune functions) G-CSF, GM-CSF (increase of immune-competent blood cells) PGG-glucan (increasing phagocytosis and bacterial killing in PMN)	Neutrophil activation
Bradykinin antagonist	Bradykinin
Pentoxyfylline (phosphodiesterase inhibitor, cAMP increase)	Phosphodiesterase
C1 inhibitor (inhibition of classical and lectin pathway activation)	Complement system
Source: Nat Med © 2003 Nature Publishing Group	

Nat. Med. 2003;9:517

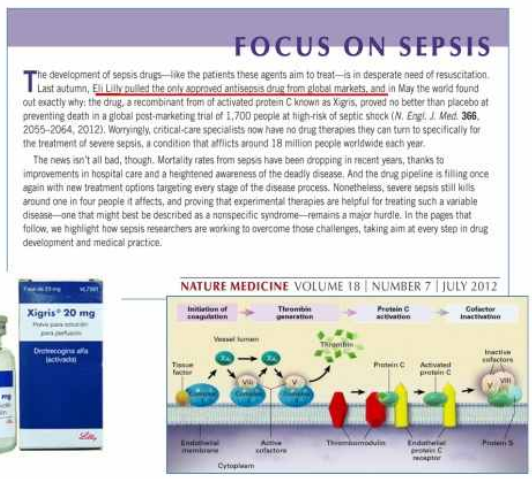
Drotrecogin alfa (activated) (Xigris, marketed by Eli Lilly and Company) is a recombinant form of human activated protein C that has anti-thrombotic, anti-inflammatory, and profibrinolytic properties.
Drotrecogin alpha (activated) belongs to the class of serine proteases.
It is used mainly in intensive care medicine as a treatment for severe sepsis.
However, further evidence is required before it becomes the standard of care.

Many interventions targeting inflammatory mediator failed to treat sepsis

Medscape® www.medscape.com	
Intervention	Target
Glucocorticoids IVIG (improvement of host defenses)	Immune Response
Anti-endotoxin antibodies BPI (neutralizes LPS) LPS elimination (hemofiltration)	LPS
TNF-α antibodies Soluble TNF receptor	TNF-α
IL-1 receptor antagonist	IL-1
Phospholipase A_2 antagonist (reducing PAF) PAF antagonist PAF-acetylhydrolase (PAF inactivation)	PAF
Prostaglandin E1 Thromboxane inhibitors Ketoconazole (thromboxane synthetase inhibitor) Ibuprofen (cyclooxygenase inhibitor)	Arachidonic acid metabolites
Antioxidants: N-acetylcysteine (restoration of cellular antioxidant potential) Selenium (selenium-dependent glutathione peroxidase as O_2^- scavenger)	Oxygen radicals

Nat. Med. 2003; 9: 517

Many interventions targeting inflammatory mediator failed to treat sepsis



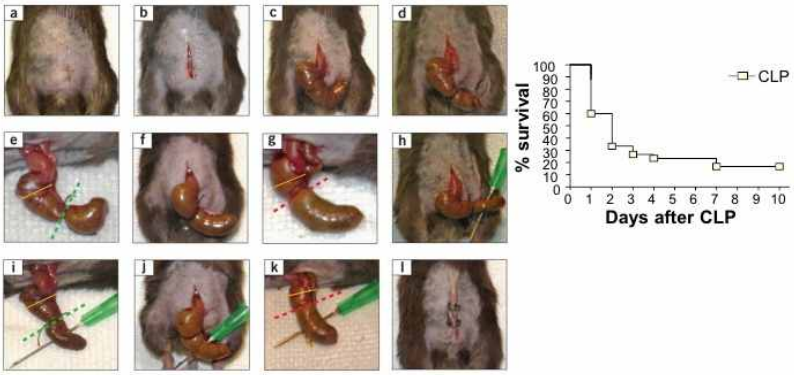
FOCUS ON SEPSIS

The development of sepsis drugs—like the patients these agents aim to treat—is in desperate need of resuscitation. Last autumn, Eli Lilly pulled the only approved antisepsis drug from global markets, and in May the world found out exactly why: the drug, a recombinant from of activated protein C known as Xigris, proved no better than placebo at preventing death in a global post-marketing trial of 1,700 people at high-risk of septic shock (*N. Engl. J. Med.* **366**, 2055–2064, 2012). Worryingly, critical-care specialists now have no drug therapies they can turn to specifically for the treatment of severe sepsis, a condition that afflicts around 18 million people worldwide each year.

The news isn't all bad, though. Mortality rates from sepsis have been dropping in recent years, thanks to improvements in hospital care and a heightened awareness of the deadly disease. And the drug pipeline is filling once again with new treatment options targeting every stage of the disease process. Nonetheless, severe sepsis still kills around one in four people it affects, and proving that experimental therapies are helpful for treating such a variable disease—one that might best be described as a nonspecific syndrome—remains a major hurdle. In the pages that follow, we highlight how sepsis researchers are working to overcome those challenges, taking aim at every step in drug development and medical practice.

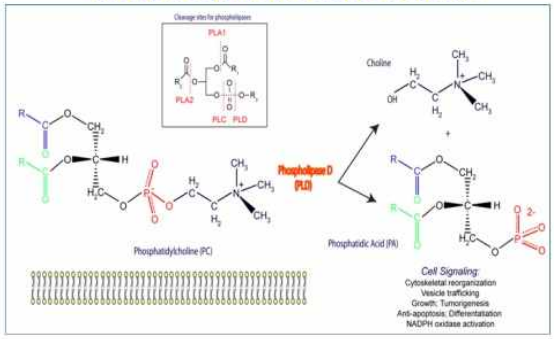
NATURE MEDICINE VOLUME 18 | NUMBER 7 | JULY 2012

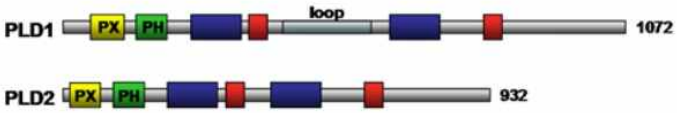
Experimental sepsis animal model: CLP (Cecal Ligation & Puncture)



Nature Protocols 4, 31 – 36 (2008)

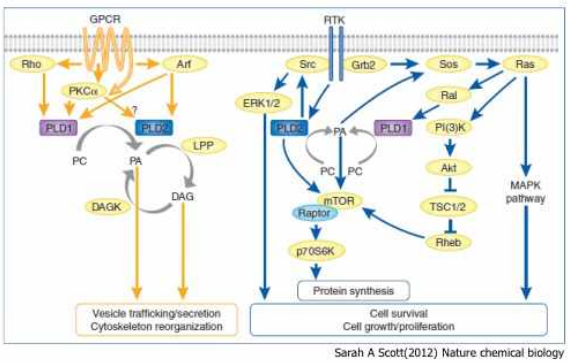
Phospholipase D hydrolyzes phosphatidylcholine into phosphatidic acid & choline





Jenkins GM(2005) Cell Mol Life Sci. 62, 2305.

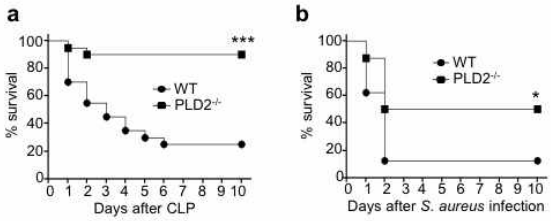
Regulation and cellular roles of PLD



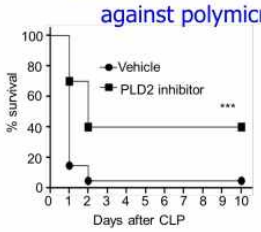
Sarah A Scott(2012) Nature chemical biology

However, the role of PLD on the pathogenesis of sepsis has not been studied yet.

PLD2 deficiency increased survival rate against polymicrobial sepsis or *S. aureus* infection

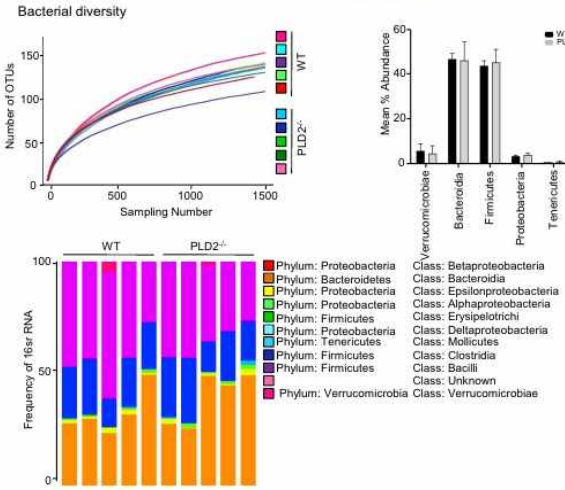


PLD2 inhibitor increased survival rate against polymicrobial sepsis

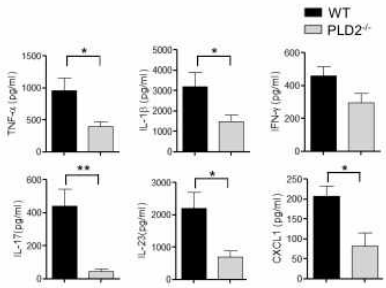


Scott et al (2009) Nature Chemical Biology. 10, 1038.

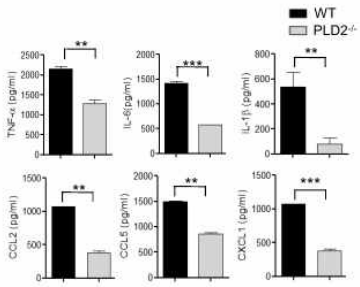
Pyrosequencing analysis of intestinal microbiota from WT and PLD2$^{-/-}$ mice



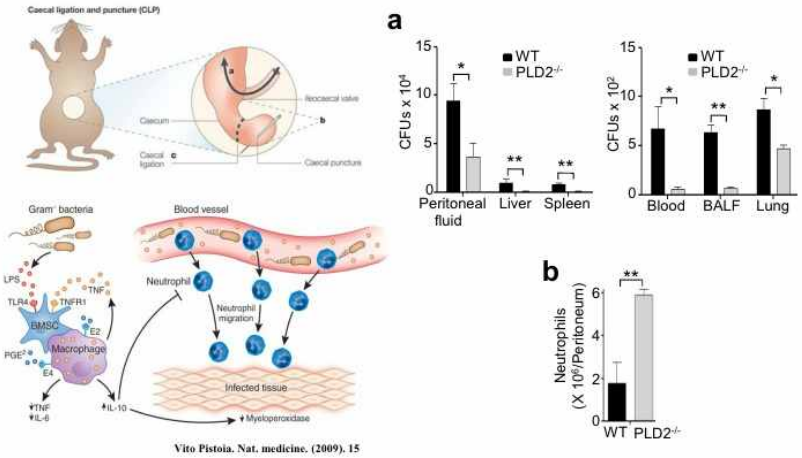
PLD2 is required for the increase of inflammatory cytokines by CLP



PLD2 is required for the increase of inflammatory cytokines by LPS

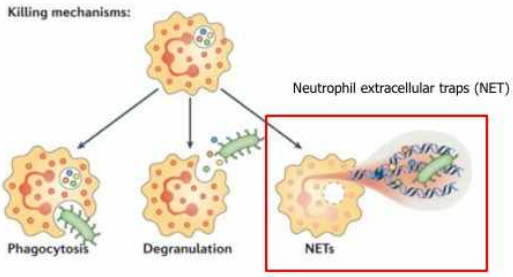


Deficiency of PLD2 shows marked increase of bactericidal activity in CLP sepsis model

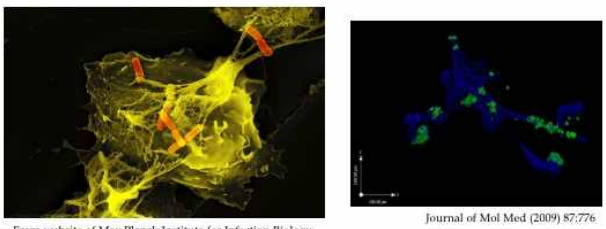


Vito Pistoia. Nat. medicine. (2009). 15

Bacteria killing mechanisms



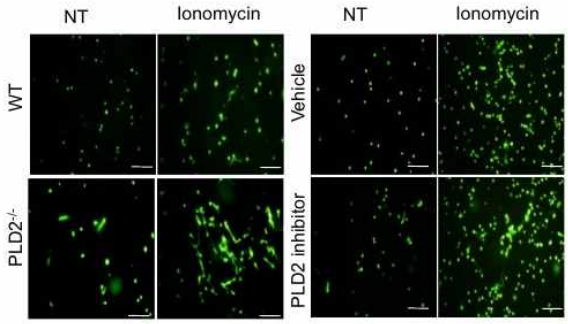
Nature Reviews Immunology (March 2013) 13, 159-175



From website of Max Planck Institute for Infection Biology

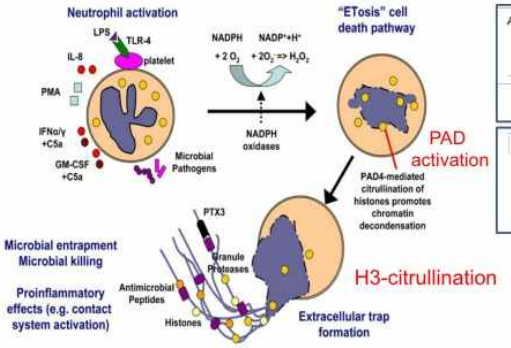
Journal of Mol Med (2009) 87:776

Deficiency of PLD2 shows marked increase of ionomycin-induced NET formation

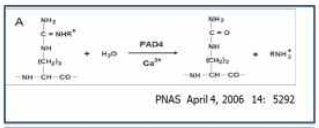


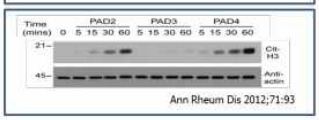
Mechanism of "NETosis"

Peptidylarginine deminase 4 (PAD4) leads to histone citrullination in neutrophils

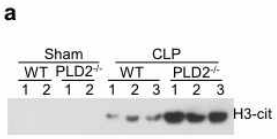


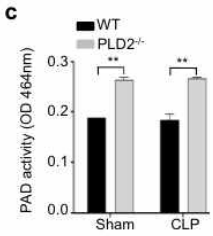
Journal of Mol Med (2009) 87:775

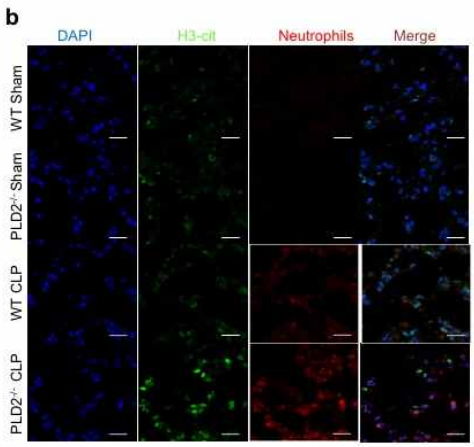




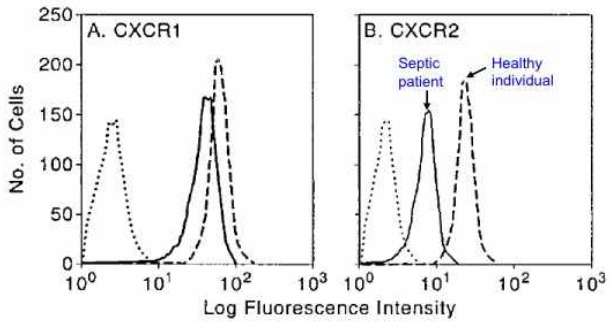
PLD2 deficiency enhanced histone 3 citrullination and PAD activity, resulting in NET formation





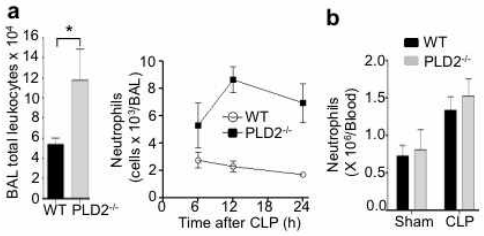


Clinical data show that the expression of CXCR2 is down-regulated by 50% in neutrophils of patients with sepsis

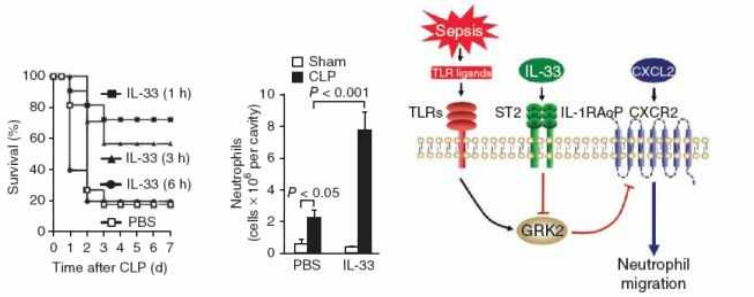


Cummings et al (1999) J. Immunol. 162, 2341.

PLD2 deficiency elicits increased neutrophil recruitment to the inflamed site

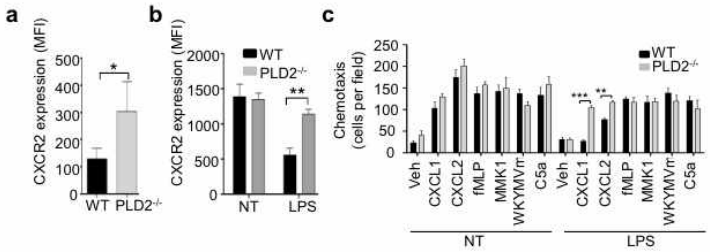


IL-33 attenuates sepsis and increases neutrophils influx to the site of infection and bacteria clearance

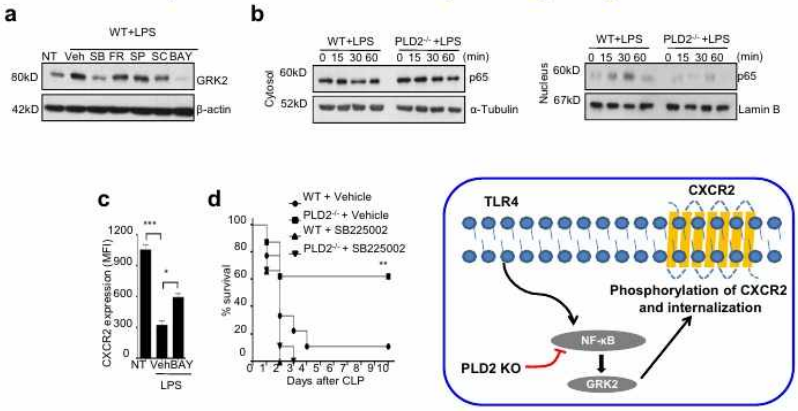


Jose C Alves-Filho(2010) Nat Medicine. 16.708

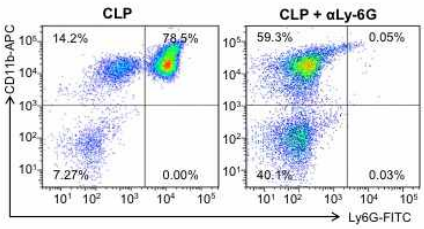
Deficiency of PLD2 shows marked increase of neutrophil recruitment into BAL by downregulating GRK2



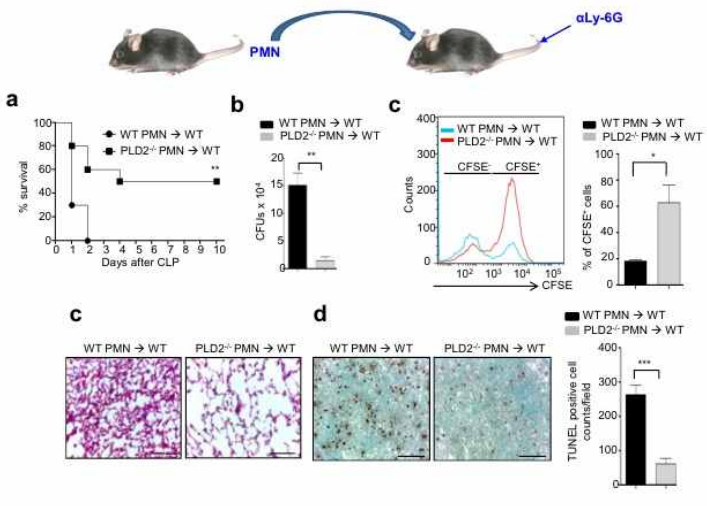
Deficiency of PLD2 shows marked increase of neutrophil recruitment into BAL by downregulating GRK2



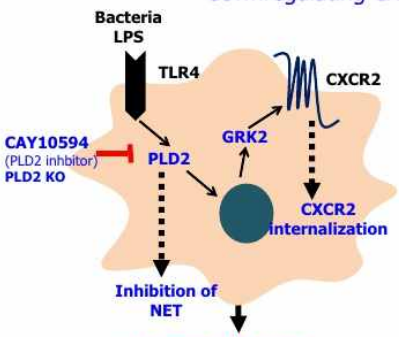
Neutrophil depletion with anti-Ly6G antibody and adoptively transfer of neutrophils



Adoptive transfer of neutrophils isolated from PLD2 deficiency mice protects against CLP



Phospholipase D2 drives mortality in mouse polymicrobial sepsis by inhibiting neutrophil extracellular trap formation and downregulating CXCR2

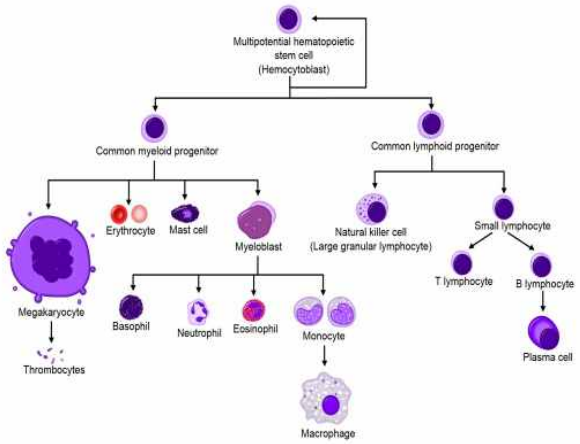


- **Bactericidal activity**
- **Decrease of proinflammatory cytokines**
- **Inhibition of leukocyte apoptosis**
- **Increase of NET formation**
- **GRK2 expression/CXCR2 downregulation**

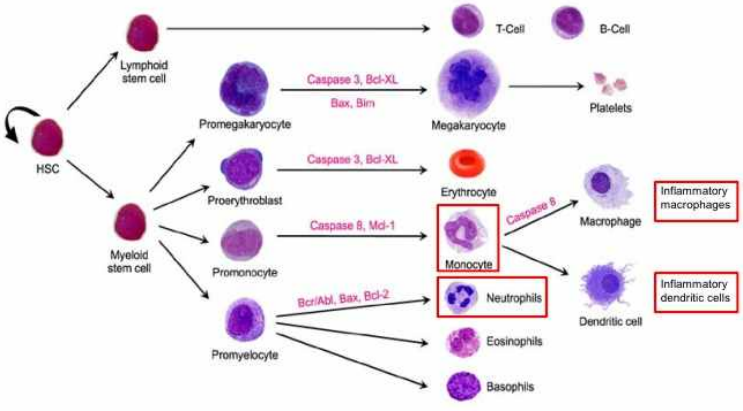
→ **Novel Therapeutic Drugs for Sepsis**

Lee et al (2015) J Exp Med 212, 1381.

Hematopoiesis

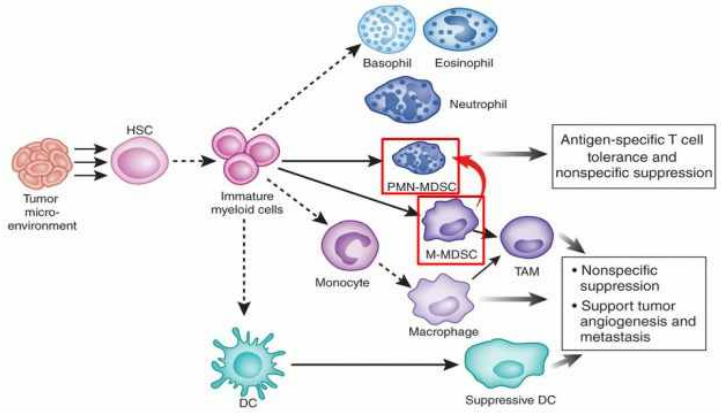


CD11b⁺ Gr-1⁺ myeloid cells in myeloid cells lineage
(Homeostasis, Inflammation condition)



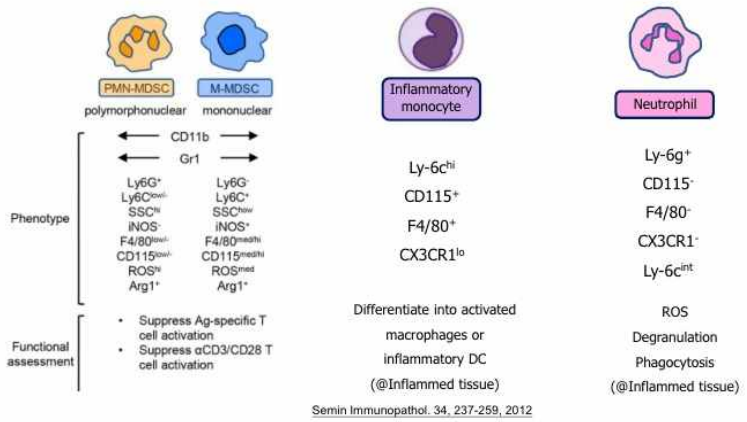
Blood Res. 50, 73-79, 2015

CD11b⁺ Gr-1⁺ myeloid cells in myeloid cells lineage
(Cancer condition)



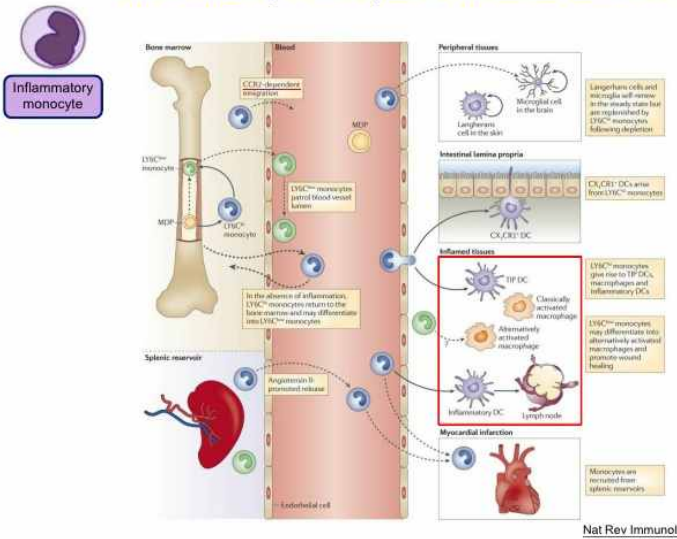
Nat Immunol. 14, 197-199, 2013

CD11b⁺Gr-1⁺ cells



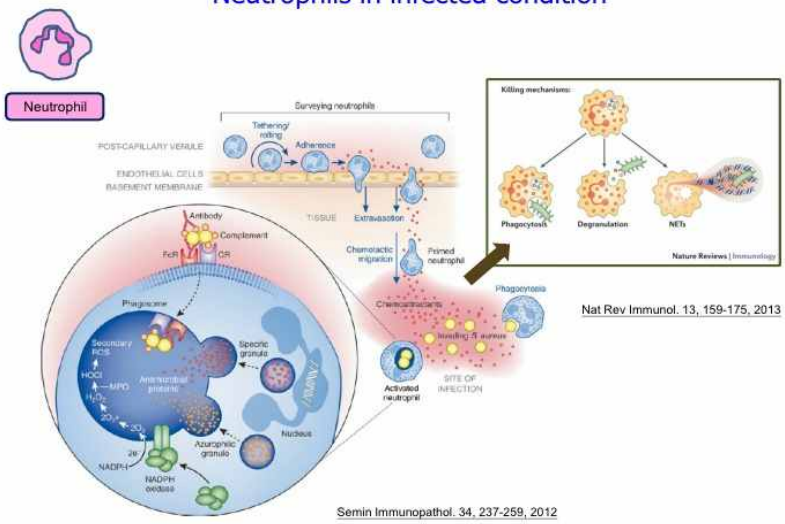
Semin Immunopathol. 34, 237-259, 2012

Inflammatory monocytes in infected condition



Nat Rev Immunol. 11, 762-774, 2011

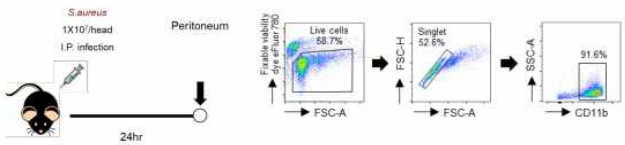
Neutrophils in infected condition



Nat Rev Immunol. 13, 159-175, 2013

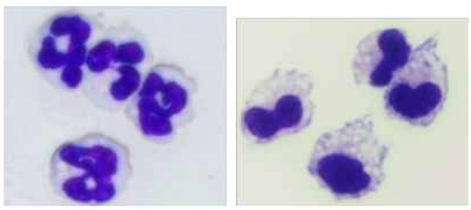
Semin Immunopathol. 34, 237-259, 2012

A novel CD11b⁺Gr-1⁺ myeloid cell population is generated upon experimental *S. aureus* infection

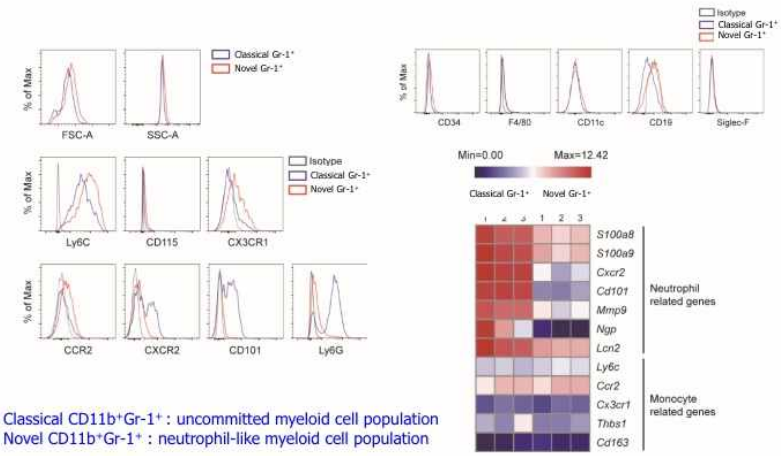


Classical CD11b⁺Gr-1⁺ myeloid cells

Novel CD11b⁺Gr-1⁺ myeloid cells

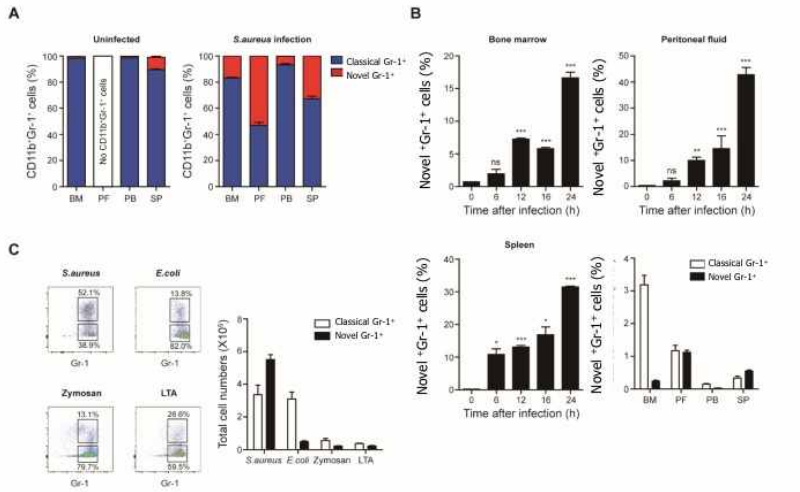


A novel CD11b⁺Gr-1⁺ myeloid cell population is generated upon experimental *S. aureus* infection

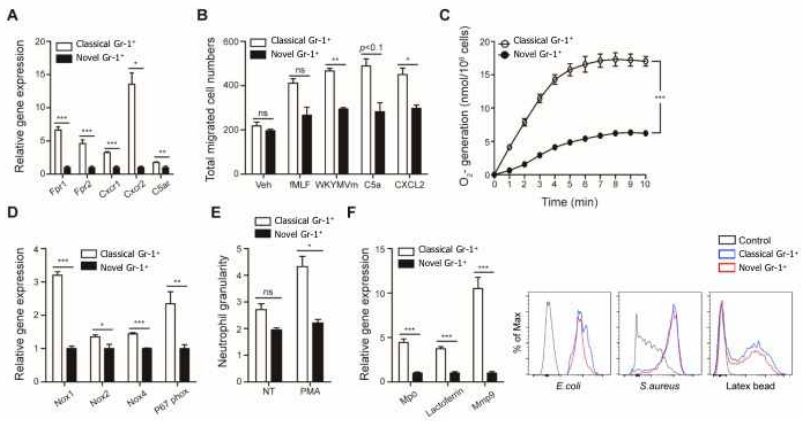


Classical CD11b⁺Gr-1⁺ : uncommitted myeloid cell population
Novel CD11b⁺Gr-1⁺ : neutrophil-like myeloid cell population

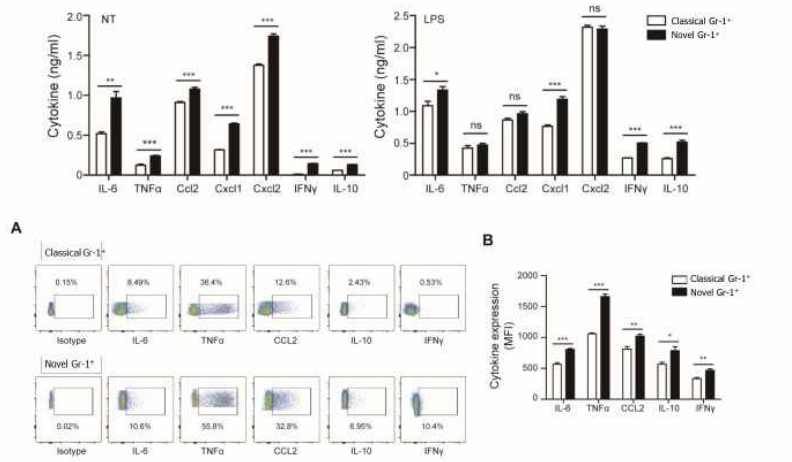
A novel CD11b$^+$Gr-1$^+$ myeloid cell population is generated upon experimental *S. aureus* infection



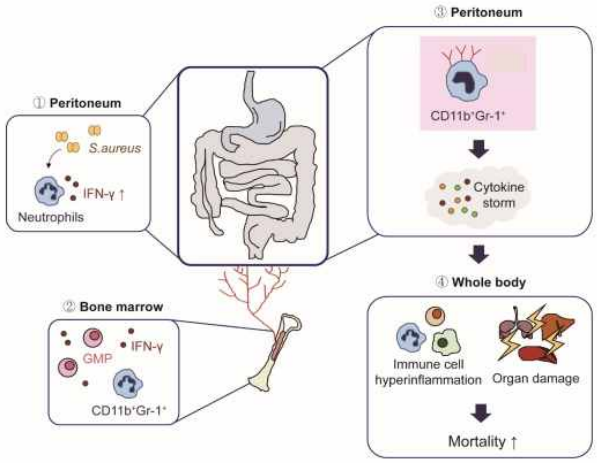
CD11b$^+$Gr-1$^+$ myeloid cells have impaired migratory activity and superoxide anion production



CD11b$^+$Gr-1$^+$ myeloid cells produce abundant amounts of inflammatory cytokines



A novel CD11b^{+}Gr-1^{+} myeloid cell population generated from bacterial infection plays essential role in mortality



Acknowledgements

SUNG KYUN KWAN UNIVERSITY
Lab. of Infectious & Inflammatory Disease
감염 및 염증질환 연구실

Yoe-Sik Bae, PhD

Ha Young Lee, PhD
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Ji Chul Kim
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Ye Sun Kim
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Kwang Min Cho
Sang Won Ko
Soo Jin Yoo
Ji Won Bang

POSTECH
Sung Ho Ryu, PhD
Jaewang Ghim, PhD

PAIRE
Brian A. Zabel, PhD

Tryptophanyl tRNA Synthetase as a Primary Defense System against Infection and its Role in Sepsis

Mirim Jin

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Department of Health Science and Technology, GAIST and Lee Gil Ya Cancer and Diabetes Institutes, Gachon University Incheon, Republic of Korea

The *N*-terminal truncated form of a protein synthesis enzyme, tryptophanyl tRNA synthetase (mini-WARS1), is secreted as an angiostatic ligand. However, the secretion and function of the full-length WRS (FL-WARS) remain unknown. Here we report that the FL-WARS1, but not mini-WARS1 is rapidly secreted upon pathogen infection to prime innate immunity. FL-WARS1 was secreted from monocytes and directly bound to macrophage via a toll-like receptor 4 (TLR4)-myeloid differentiation factor 2 (MD2) complex to induce phagocytosis and chemokine production. Administration of FL- WARS1 into *Salmonella typhimurium*-infected mice reduced the levels of bacteria and improved mouse survival whereas its titration with the specific antibody aggravated the infection. The N-terminal 154-amino acid eukaryotic specific peptide of WARS1 was enough to recapitulate FL-WARS1 activity and its interaction mode with TLR4-MD2 is now suggested. Based on these results, secretion of FL-WARS1 appears to work as a primary defense system against infection, acting before full activation of innate immunity. Consistent with our finding, blood levels of FL-WARS1 were increased in sepsis patients but not in those with chronic sterile inflammation. In a retrospective analysis of sepsis cohorts, it was found that plasma WARS1 levels are not only reflecting sepsis severity and but also predicting outcomes. The possibility of WARS1 as a theranostic target for sepsis will be discussed.

Curriculum Vitae

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1984-1988 **BS**. College of Pharmacy, Sookmyung Women's University, Korea
1988-1990 **MS**. College of Pharmacy, Seoul National University, Korea
1993-1996 **PhD**. College of Pharmacy, Seoul National University, Korea

Professional Training and Employment

1996-1997 Post-doctoral Fellow, Department of Microbiology and Immunology, University, of Western Ontario, Canada
1998-2000 Research Professor, Graduate School of Biotechnology, Korea University
2001-2005 Director (R&D), PanGenomics, Co. Ltd, Korea
2005-2007 Instructor, College of Korean Medicine, Daejeon University, Korea
2007-2011 Assistant Professor, College of Korean Medicine, Daejeon University, Korea
2011-2016 Associate Professor, College of Korean Medicine, Daejeon University, Korea
2016-2018 Associate Professor, College of Medicine, Gachon University, Korea
2018- Professor, College of Medicine, Gachon University, Korea

Selected Publications (* Corresponding author)

1. Jin M*. Unique roles of tryptophanyl-tRNA synthetase in immune control and its therapeutic implications. *Exp Mol Med*. 2019
2. Jin M*, Son M. DA-9701(Motilitone): A Multi-Targeting Botanical Drug for the Treatment of functional Dyspepsia. *Int J Mol Sci*. 2018
3. Chun E, Yoon S, Parveen A, Jin M*. Alleviation of Irritable Bowel Syndrome-Like Symptoms and Control of Gut and Brain Responses with Oral Administration of *Dolichos lablab* L. in a Mouse Model. *Nutrients*. 2018
4. Shin J, Jin M*. Potential Immunotherapeutics for Immunosuppression in Sepsis. *Biomol Ther* (Seoul). 2017
5. Choi JE, Park DM, Chun E, Choi JJ, Seo JH, Kim S, Son J, Do M, Kim SY, Park YC, Jung IC, Jin M*. Control of stress-induced depressive disorders by So-ochim-tang-gamibang, a Korean herbal medicine. *J Ethnopharmacol*. 2014
6. Ahn YH, Park S, Choi JJ, Park BK, Rhee KH, Kang E, Ahn S, Lee CH, Lee JS, Inn KS, Lee JY, Jeon Y, Huh JW, Jin M*, Kim S*. Secreted tryptophanyl-tRNA synthetase as a primary defence system against infection. *Nat Microbiol*. 2016
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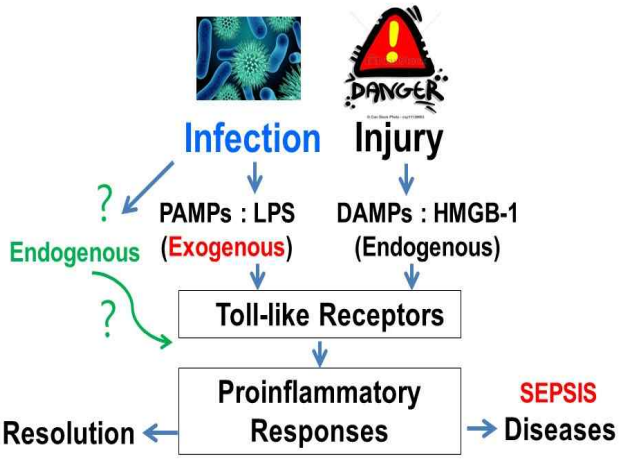
Secreted Tryptophanyl (W) tRNA Synthetase (WARS1) as a Primary Defense System against Infection & its Role in Sepsis

Mirim Jin, Ph D
College of Medicine, Gachon University

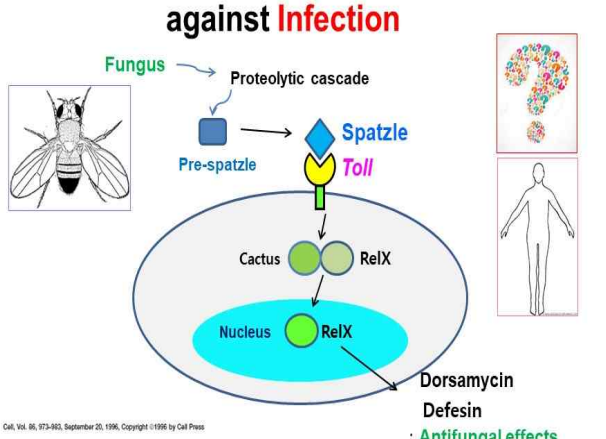
2019. 10. 11

Harmful Challenges



PAMPs:Pathogen Associated Molecular Pattern
DAMPs: Damage Associated Molecular Pattern

Spatzle: Drosophila Endogenous *Toll* Ligand against Infection



The Dorsoventral Regulatory Gene Cassette *spätzle/Toll/cactus* Controls the Potent Antifungal Response in Drosophila Adults

Bruno Lemaitre et al., Cell. 1996

2011 Nobel Prize in Medicine

Bruce A. Beutler
Prize share: 1/4

Jules A. Hoffmann
Prize share: 1/4

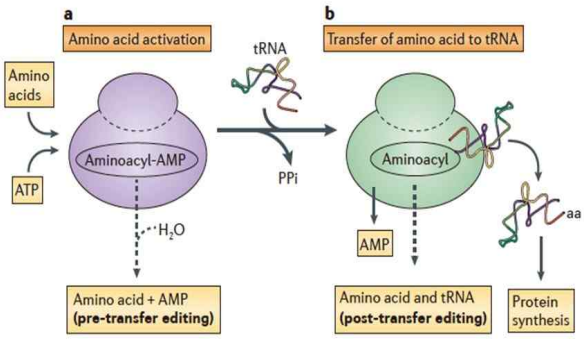
Ralph M. Steinman
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly

Human Endogenous TLR Ligand against Infection?

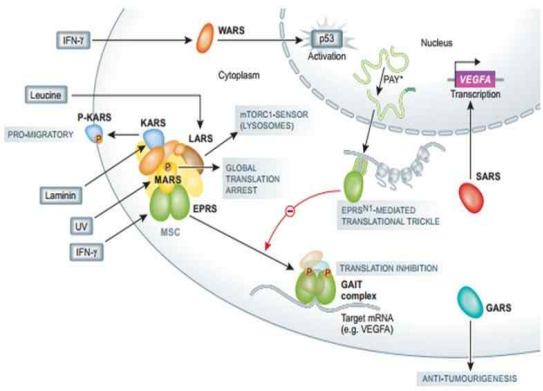
the activation of innate immunity" and the other half to Ralph M. Steinman *"for his discovery of the dendritic cell and its role in adaptive immunity".*

Aminoacyl-tRNA Synthetase: The 1st Catalyst for Protein Synthesis



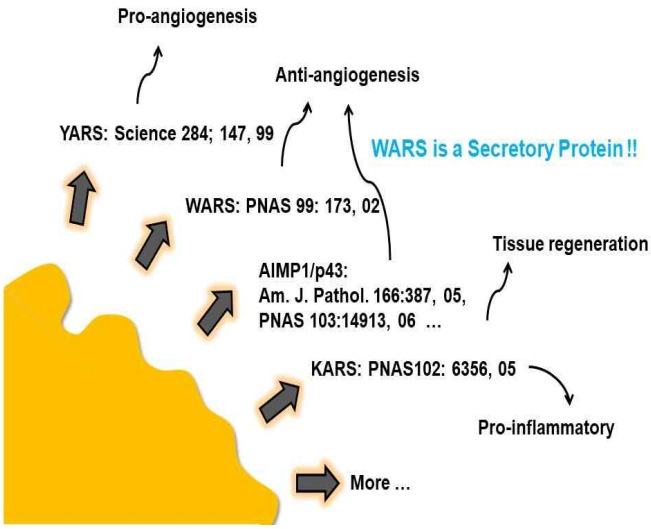
Kim et al., Nat Rev Cancer 2011

Non-catalytic Signaling Functions of ARSs

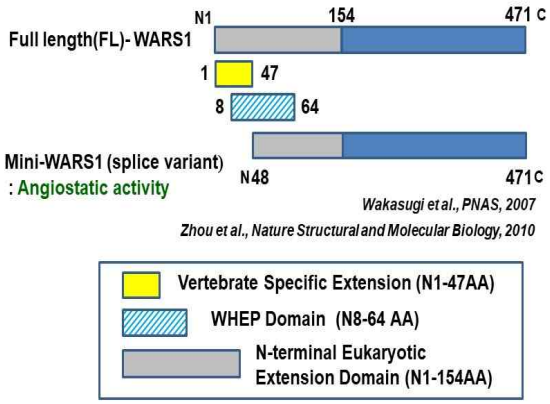


Yao et al., EMBO Mol Med 2013

Secretion of ARSs



Schematic Presentation of Human Tryptophanyl-tRNA Synthetase (WARS1)



Secretion of FL-WARS1 ? When ? Why ?

CLUES

Vibrio cholera

Ellis, C. N., et al., (2015). Comparative proteomic analysis reveals activation of mucosal innate immune signaling pathways during cholera. Infect Immun *83*, 1089-1103.

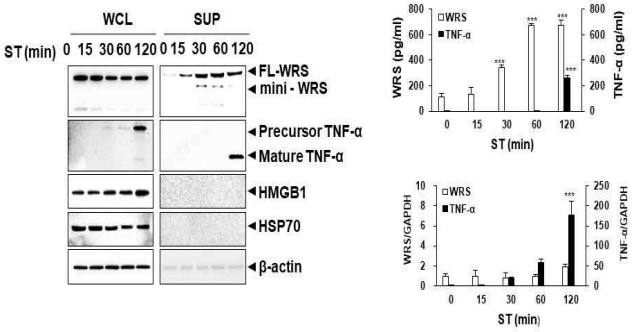
Human cytomegalovirus

Zhu, H., et al., (1998). Cellular gene expression altered by human cytomegalovirus: global monitoring with oligonucleotide arrays. Proc Natl Acad Sci U S A *95*, 14470-14475.

Human hepatitis B virus

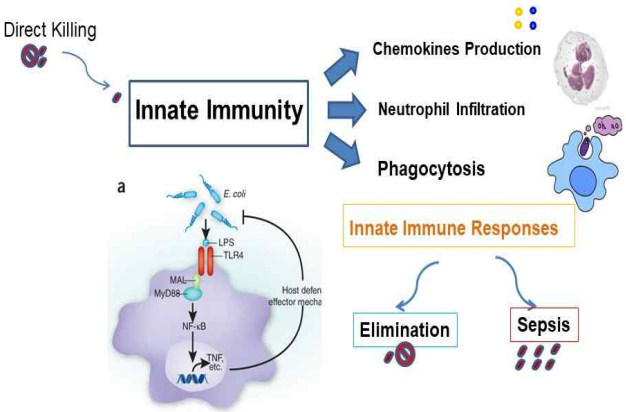
Wieland, S., et al., (2004). Genomic analysis of the host response to hepatitis B virus infection. Proc Natl Acad Sci U S A *101*, 6669-6674.

FL-WARS is promptly Secreted by Infections without *de novo* Synthesis

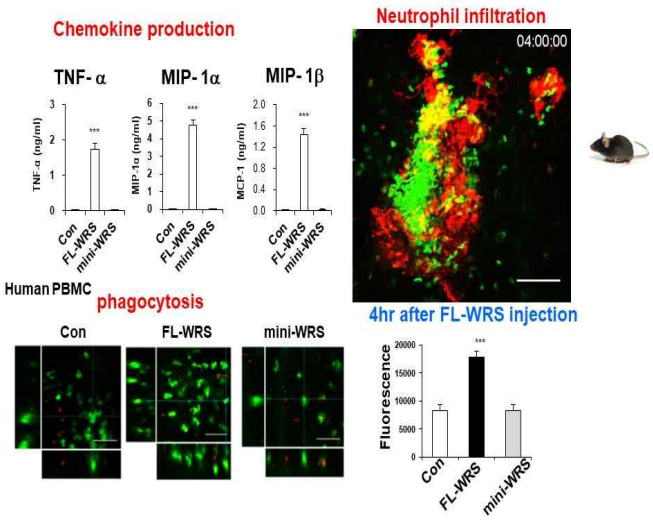


Ahn et al., Nature Microbiology, 2016

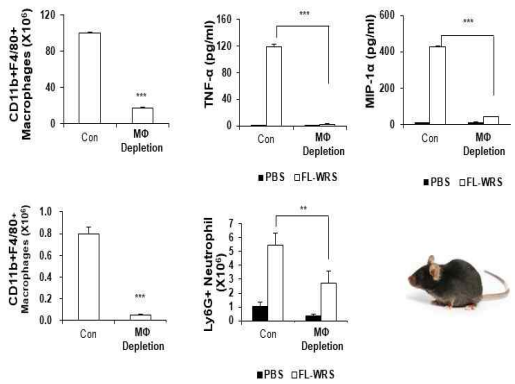
What Does Secreted FL-WARS1 Do ? Infection and Innate Immune Responses



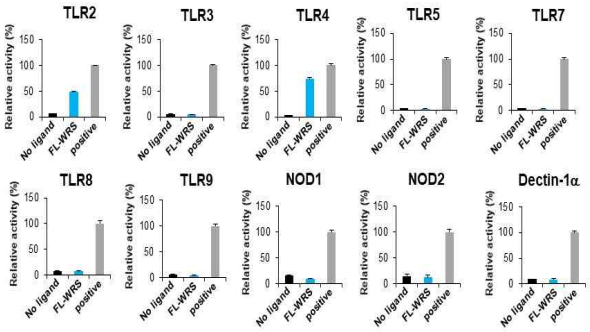
FL-WARS1 Induces Innate Immune Responses



Secreted FL-WARS1 Targets Macrophages



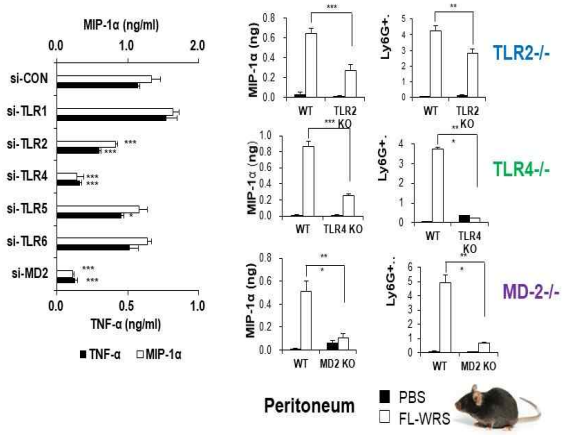
FL-WARS1 Activates TLR2 and TLR4-MD2 Signaling



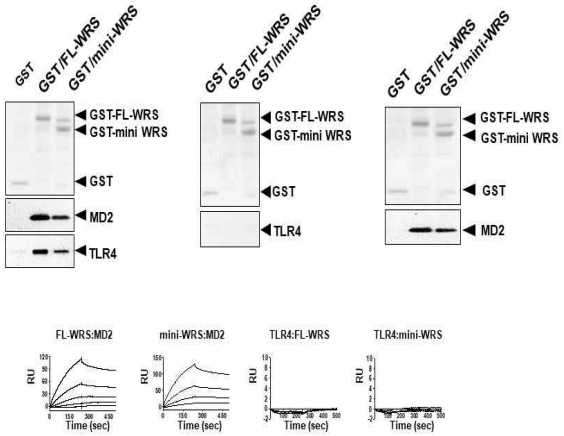
Positive Controls

TLR2: HKLM (heat-killed *Listeria monocytogenes*) at 10^8 cells/mL; TLR3: Poly(I:C) at 1 μg/mL ; TLR4: *E.coli* K12 LPS at 100 ng/mL
TLR5: *S.typhimurium* flagellin at 100 ng/mL ; TLR7: CL097 at 1 μg/mL; TLR8: CL075 at 10 μg/mL + Poly(dT) 10 μM
TLR9: CpG ODN 1826 at 100 ng/mL ; NOD1: C12-iEDAP at 100 ng/mL; NOD2: L18-MDP at 100 ng/mL ; Dectin-1α: Zymosan Depleted (hot alkali treated *S. cerevisiae*) at 10 μg/mL

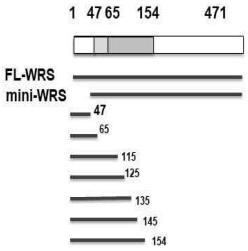
Abolishment of FL-WARS1-induced Innate Immune Responses in TLR2, TLR4 and MD2 K/O



FL-WARS1 directly Binds to MD-2 and TLR4

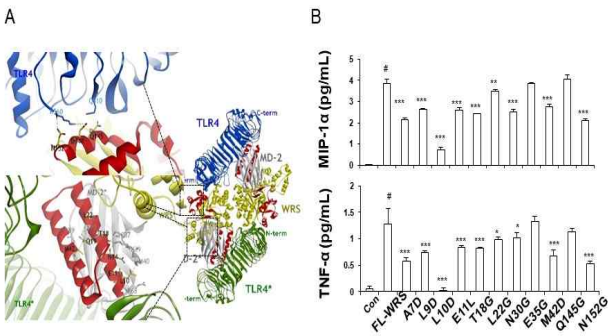


Two Binding Domains of FL-WARS1 to TLR4 and MD2



WRS	TLR4 Binding	MD2 Binding	Cytokine induction
FL (N471)	-	+	+
mini (Δ47)	-	+	-
N47	+	+	-
N65	+	+	-
N115	-	-	-
N125	-	-	-
N135	-	-	-
N145	+	-	+
N154	+	-	+

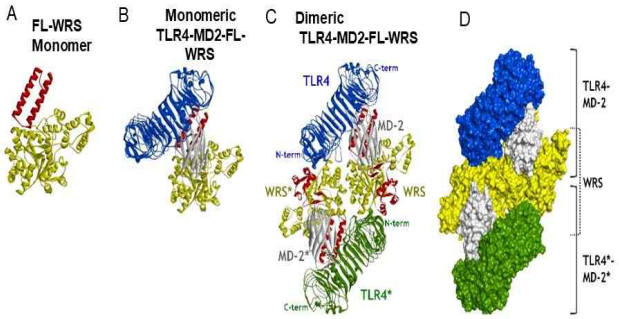
2019-10-04



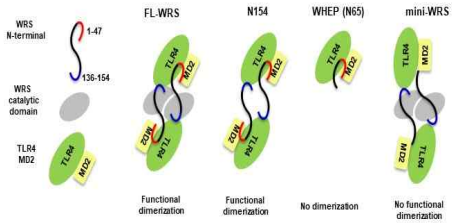
WRS Mutants	A7D	L9D	L10D	E11L	T18G	L22G
Putative Binding Sites	TLR4 MET41	TLR4 VAL30	MD2 MET40	MD2 ARG68	MD2 LYS39	MD2 CYS37
WRS Mutants	N30G	E35G	M42D	Q145G	N152G	
Putative Binding Sites	MD2 THR84	MD2 ASN86	MD2 MET145	TLR4 GLN510	TLR4 LYS560	

Proposed Working Mechanism of FL-WARS1 for TLR4-MD2 Activation

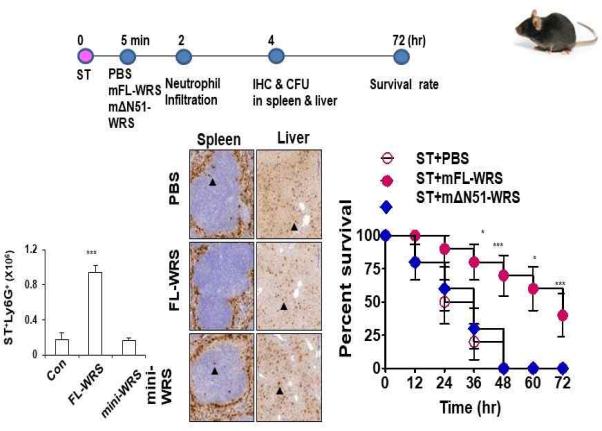
Protein-Protein Docking Study



Cartoon Illustration of TLR4-MD2-FL-WARS1 Interaction Modeling

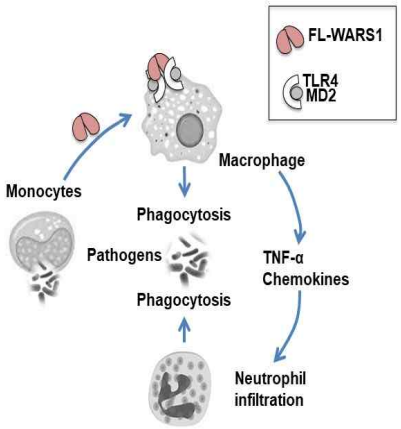


Injection of FL-WARS1 Increases Survival Rate in ST-Infected Mice



Ahn et al., Nature Microbiology, 2016

Summary



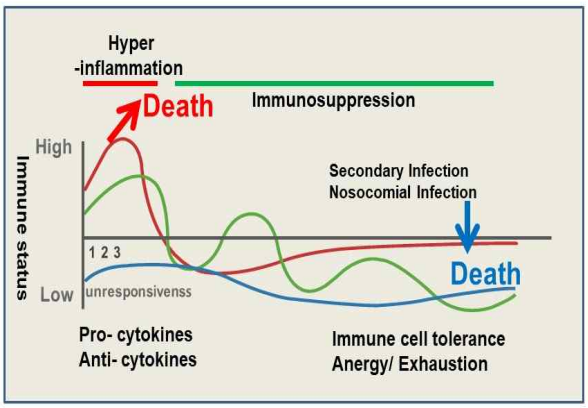
Sepsis

Sepsis "A life-threatening organ dysfunction due to a dysregulated host response to infection",
Sequential (sepsis-related) Organ Failure Assessment (**SOFA**) score > 2 or more–point change as a means of identifying sepsis

Septic shock is defined as "A subset of sepsis where **underlying circulatory and cellular/metabolic abnormalities** are profound enough to substantially **increase mortality**."

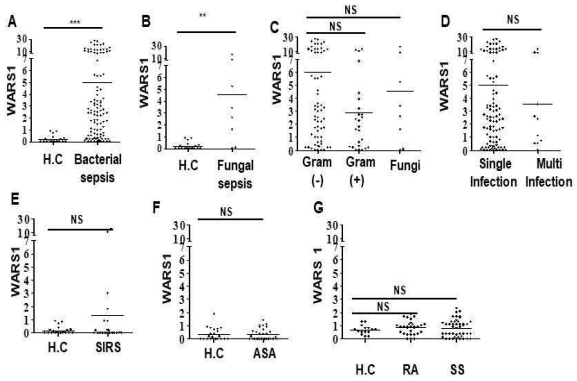
" By the 3th International Consensus Definition for Sepsis and Septic Shock-3 (2016)

Current Understanding of Sepsis Pathophysiology



WARS might be a Theragnostic (Therapy + Diagnosis) Target for Sepsis

High Levels of WARS1 in the Blood of Sepsis Patients but not Sterile Chronic Inflammatory Diseases



HC, healthy control(n=20) Sepsis (n=100) SIRS (n=25),sytemic inflammatory response syndrome ASA(n=30); Asthma, RA Rheumatoid arthritis, SS, Sjogren's syndrome **p<0.01 ***p<0.001

Acknowledgements

Gachon University
Park Sunyoung
Park Bo-kyung, PhD

Biocon, SNU
Kim Sunghoon, PhD
Ahn Young Ha, PhD

Daejeon University
Jeong June Choi, PhD

Asan Medical Center
University of Ulsan College of Medicine
Huh Jin Won MD, PhD

KAIST, Kim Philhan, PhD
KRICT, Lee, Joo-Youn PhD

Seoul St Mary's Hospital , Catholic University

Ewha University
Shim Hyunbo, PhD

Yonsei University College of Medicine

Thank you very much

Sepsis in Children

Satoshi Nakagawa
Critical Care Medicine,
National Center for Child Health and Development, Japan

Sepsis is common in children.

The World Health Organization reports that almost 6 million deaths are observed in children under 5 years old every year. The major causes are infections, including pneumonia, diarrhea, malaria and meningitis. If these conditions are associated to organ dysfunction, we consider that they are sepsis.

However, we do not have precise epidemiology of sepsis in children yet. A study from the United States indicates that sepsis occurs at 0.9/1,000 pediatric population. An international point-of-prevalence study indicates that Pediatric Intensive Care Unit admission due to sepsis accounts 8.2% of all admissions. Sepsis mortality is around 20% in children, however, if the patient has underlying co-morbidity, it increases.

There are several tools developed to predict severity and possible mortality with sepsis in children. A study focused on c-reactive protein and ferritin levels and the others focused on the organ dysfunctions. In the organ dysfunction scoring, hypotension and lactate level in the early phase seem the key.

Immune function associated with sepsis has not been well explored. A study indicates that both innate and adaptive immunity may be altered by sepsis in children. Another study indicates that mortality is very common in the patients with sepsis who presented with macrophage activation syndrome picture. Immuno- paralysis may occur with sepsis and survivors tend to recover from this condition but non-survivors do not. The other study presented several phenotypes of sepsis presentation in children. In this study, one phenotype group may have higher mortality associated with corticosteroid use, but the other did not see this relation.

Curriculum Vitae

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Education and Appointment

1984	MD, Tohoku University, Japan
1984-1985	Rotating Internship (Internal Medicine, Surgery, OB&GYN, Pediatrics, Anesthesia and Emergency Medicine), Okinawa Chubu Hospital, Okinawa, Japan
1985-1987	Resident, Department of Pediatrics, Okinawa Chubu Hospital, Okinawa, Japan
1987-1988	Staff, Department of Pediatrics, Okinawa Miyako Hospital, Okinawa, Japan

Professional Training and Employment

1988-1991	National Children's Hospital Pediatric Anesthesia and Intensive Care Training Program, Japan
1993-1994	Uiversity of Toronto Pediatric Critical Care Medicine Fellowship Program, Canada
1995-1996	Instructor, Department of Pediatrics, Tufts University School of Medicine, Boston, MA, USA
1996-2002	Assistant Director, Pathophysiology Research, Children's Medical Research Center, National Center for Child Health and Development, Japan
2002-	Associate Director, Division Chief of Critical Care Medicine, Department of Anesthesia and Critical Care, National Center for Child Health and Development, Japan

Selected Publications

1. **Nakagawa S**, Sakai H, Miyasaka K. Case 21, 4-year-8-month-old girl with a fistula between airway and great vessels. In: Rogers MC, Helfaer MA, Eds. Case Studies in Pediatric Intensive Care. *Baltimore: Williams & Wilkins*, 1993:123-127.
2. **Nakagawa, S**. Acute respiratory distress syndrome in pediatrics in Japan. In: Miyasaka K, Fuhrman BP Ed. Partial Liquid Ventilation. *Tokyo: Blackwell Science Japan*, 1997:115-118.
3. **Nakagawa S**, Bohn D. Respiratory support of critically ill children. *Clinical Intensive Care* 12:1-9, 2001.
4. Sawaguchi A, Sawaguchi T, Appointed Research Group. Japanese national SIDS project, 1998-2000 research for the improvement of infant mortality. *Forensic Sci Int* 130S:S1-S7, 2002.
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7. Shime N, Kawasaki T, Saito O, Akamine Y, Toda Y, Takeuchi M, Sugimura H, Sakurai Y, Iijima M, Ueta I, Shimizu N, **Nakagawa S**. Incidence and risk factors for mortality in pediatric severe sepsis, results from national pediatric intensive care registry in Japan. *Intensive Care Med* 2012; 38:1191-97.
8. Tokuhira N, Shime N, Inoue M, Kawasaki T, Sakurai Y, Kurosaka N, Ueta I, **Nakagawa S**. Mechanically ventilated children with 2009 pandemic influenza A/H1N1, results from the national pediatric intensive care registry in Japan. *Pediatr Crit Care Med* 2012; 13:E294-98.
9. Okumura A, **Nakagawa S**, Kawashima H, *et al*. Severe form of encephalopathy associated with 2009 pandemic influenza A (H1N1) in Japan. *J Clin Virol* 2013; 56: 25-30.
10. **Nakagawa S**, Shime N. Respiratory rate criteria for pediatric systemic inflammatory response syndrome. *Pediatr Crit Care Med* 2014; 15:182.

11. Tsuboi N, Nozaki H, Ishida Y, Kanazawa I, Inamoto M, Hayashi K, Nishimura N, **Nakagawa S**, *et al*. Early rehabilitation after pediatric liver transplantation. *J Pediatr Intensive Care* 2017 Sep; 6(3): 199–205.
12. Marshall JC, Bosco L, Adhikari NK, Connolly B, Diaz JV, Dorman T, Fowler RA, Meyfroidt G, **Nakagawa S**, *et al*. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care* 2017; 37:270-276.
13. Shime N, Kawasaki T, **Nakagawa S**. Proposal of a new Sequential Organ Failure Assessment score for possible validation. *Pediatr Crit Care Med* 2017; 18:98-99.
14. Nishimura N, Kasahara M, Ishikura K, **Nakagawa S**. Current status of pediatric transplantation in Japan. *J Intensive Care* 2017; 5:48.
15. **Nakagawa S**, Ueda R, Nomura O. Lower risk group of brief resolved unexplained events is minority of infants with apparent life-threatening events. *Arch Dis Child Educ Pract Ed* 2018; 103:95-98
16. Nishida O, Ogura H, Egi M, Fujishima S, Hayashi Y, Iba T, Imaizumi H, Inoue S, Kakihana Y, Kotani J, Kushimoto S, Masuda Y, Matsuda N, Matsushima A, Nakada T, **Nakagawa S**, *et al*. The Japanese practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). *J Intens Care* 2018; 6:7.
17. Tsuboi N, Abe M, Matsumoto S, Nishimura N, **Nakagawa S**. The effect of clinical experience on the learning curve of pediatric intensive care unit residents for the central venous catheter placement procedure. *J Pediatr Intensive Care* 2018;7:39-42.
18. Matsumoto S, **Nakagawa S**. Extracorporeal membrane oxygenation for diffuse alveolar hemorrhage by idiopathic pulmonary hemosiderosis, a case report and a review of the literature. *J Pediatr Intensive Care* 2019 Sep;8(3):181-186.
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Sepsis in Children

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National Center for Child Health and Development
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Global Maternal, Newborn, and Child Health — So Near and Yet So Far

Zulfiqar A. Bhutta, M.B., B.S., Ph.D., and Robert E. Black, M.D.

From the Centre for Global Child Health, Hospital for Sick Children (SickKids), Toronto (Z.A.B.); the Center of Excellence in Women and Child Health, Aga Khan University, Karachi, Pakistan (Z.A.B.); and the Institute for International Programs, Bloomberg School of Public Health, Johns Hopkins University, Baltimore (R.E.B.). Address reprint requests to Dr. Bhutta at the Centre for Global Child Health, Hospital for Sick Children (SickKids), Toronto, ON M5G 0A4, Canada, or at zulfiqar.bhutta@sickkids.ca.

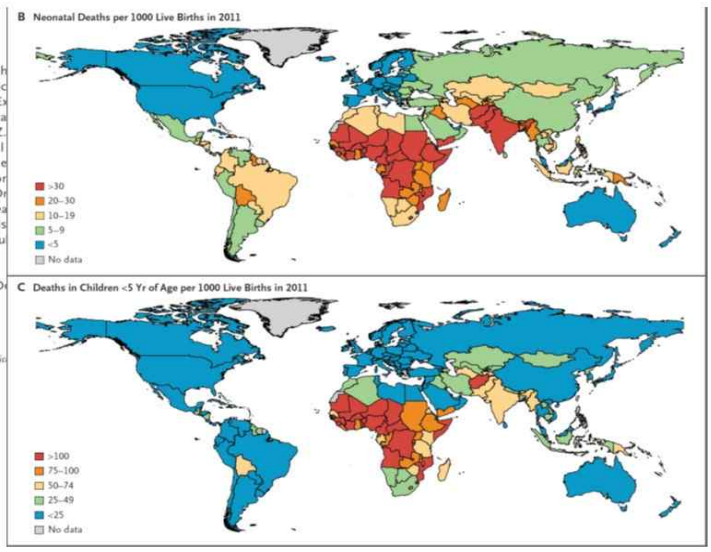
This article was updated on December 5, 2013, at NEJM.org.

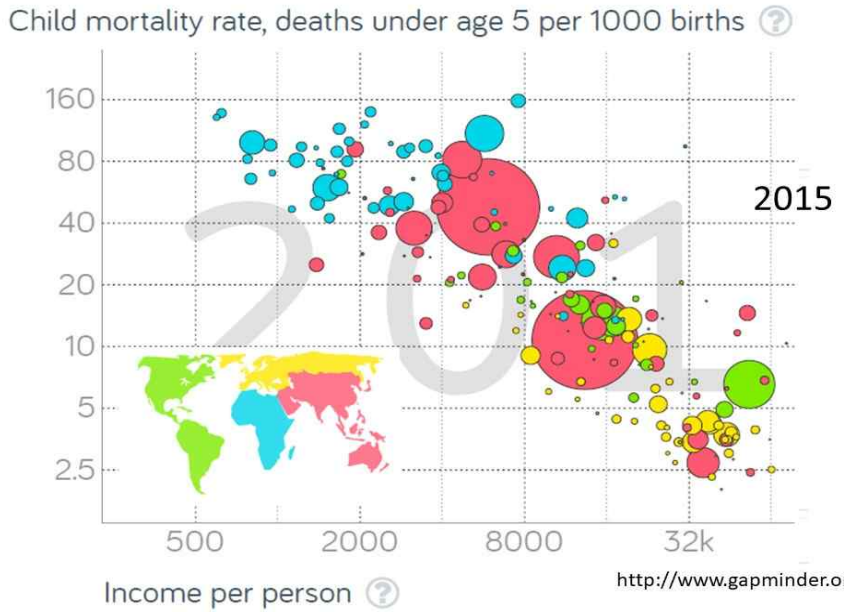
N Engl J Med 2013;369:2226-35.
DOI: 10.1056/NEJMra1111853

A LITTLE MORE THAN 13 YEARS AGO, WORLD LEADERS ASSEMBLED IN NEW York to sign the Millennium Declaration to address some of the greatest moral dilemmas of our times — unequal global health, poverty, and inequities in development — and to establish a set of interrelated goals and targets to be met by 2015. Key goals included the Millennium Development Goal (MDG) 4 targeting a reduction in mortality among children younger than 5 years of age by two thirds and MDG 5 targeting a reduction in maternal mortality by three quarters, both from 1990 base figures. With less than 3 years to go, despite overall global progress, these two MDGs are seriously off target for many countries.[1]

Recent assessment of global statistics suggests that despite major gains, among the 75 so-called Countdown countries that have 98% of all maternal deaths and deaths among children younger than 5 years of age, only 17 are on track to reach the MDG 4 target for child mortality and only 9 are on track to reach the MDG 5 target for maternal mortality.[2] However, estimates from the Institute for Health Metrics and Evaluation suggest that 31 countries will achieve MDG 4, 13 countries

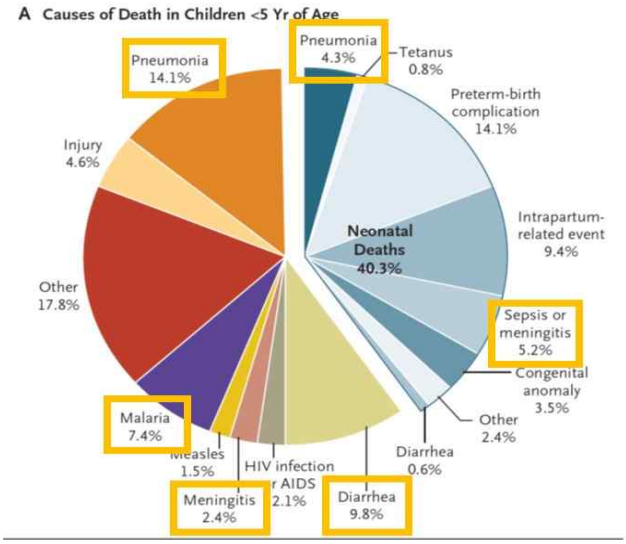
Global Maternal, Newborn, and Child Health — So Near and Yet So Far





http://www.gapminder.org/

Global Maternal, Newborn, and Child Health — So Near and Yet So Far



From the Centre for Global Child Health, Hospital for Sick Children (SickKids), Toronto (Z.A.B.); the Center of Excellence in Women and Child Health, Aga Khan University, Karachi, Pakistan (Z.A.B.); and the Institute for International Programs, Bloomberg School of Public Health, Johns Hopkins University, Baltimore (R.E.B.). Address reprint requests to Dr. Bhutta at the Centre for Global Child Health, Hospital for Sick Children (SickKids), Toronto, ON M5G 0A4, Canada, or at zulfiqar.bhutta@sickkids.ca.

This article was updated on December 5, 2013, at NEJM.org.

N Engl J Med 2013;369:2226-35.
DOI: 10.1056/NEJMra1111853

Trends in the Epidemiology of Pediatric Severe Sepsis*

Mary E. Hartman, MD, MPH[1]; Walter T. Linde-Zwirble, BA[2]; Derek C. Angus, MD, MPH[3,4]; R. Scott Watson, MD, MPH[3,4]

Objectives: In the past decade, guidelines have been developed for the early detection and management of severe sepsis in children and neonates. However, severe sepsis continues to be a significant U.S. healthcare problem, accounting for over 720,000 annual hospitalizations. Large-scale epidemiologic studies of severe sepsis continue to be limited, particularly in children. We present data from 1995, 2000, and 2005 in seven U.S. states, examining how case mix, outcome, and resource use for pediatric severe sepsis have changed over time.

Design: We constructed a database including all acute-care hospitalizations for children in the seven states. For each case, we extracted data on demographic characteristics; the principal diagnosis, up to six secondary diagnoses, and six procedures as classified by the *International Classification of Diseases*, 9th Revision, Clinical Modification codes; and in-hospital fatality. We identified patients with severe sepsis using *International Classification of Diseases*, 9th Revision, Clinical Modification codes for both infection and acute organ failure.

Setting: Retrospective observational cohort dataset from seven U.S. states from 1995, 2000, and 2005.

Subjects: Children in the U.S. 0–19 years old.

Interventions: None.

Measurements and Main Results: In 2005, 17,542 children were hospitalized with severe sepsis in the seven states; there was an 81% increase in pediatric severe sepsis cases since 1995 and a 45% increase since 2000. This corresponded to an increase in prevalence from 0.56 to 0.89 cases per 1,000 pediatric population. Between 1995 and 2005, the prevalence of severe sepsis in newborns more than doubled, from 4.5 to 9.7 cases per 1,000 births. The most common infecting organisms in all 3 years were *Staphylococcus* species. From 1995 to 2005, the case-fatality rate decreased from 10.3% to 8.9%. Case fatality associated with *Staphylococcus aureus* increased, whereas fatality associated with *Streptococcus pneumoniae* decreased by 75%. Nationally, there were 75,255 pediatric hospitalizations in 2005 involving severe sepsis, with an associated cost of $4.8 billion.

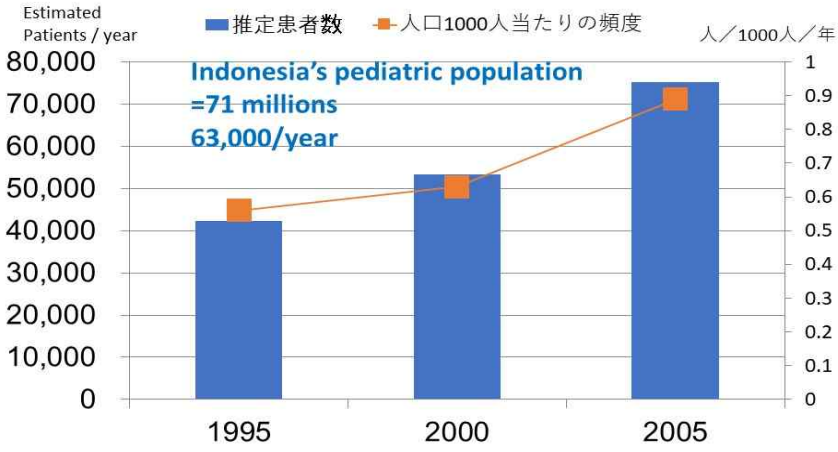
Conclusions: Between 1995 and 2005, the prevalence of severe sepsis in U.S. children steadily rose, due to a significant increase in the prevalence of severe sepsis in newborns. (*Pediatr Crit Care Med* 2013; 14:686–693)

Key Words: epidemiology; outcome; pediatric critical care; pediatrics; sepsis; severe sepsis

International collaborative efforts to improve the diagnosis and treatment of sepsis have been in place for nearly a decade (1, 2), but severe sepsis continues to be recognized as a significant healthcare problem (3–7). According to recent estimates by the U.S. Centers for Disease Control, the rate of hospitalization for sepsis more than doubled between 2000 and 2008

Trends in Pediatric Severe Sepsis (USA)

Hartman ME, et al. PCCM 2013; 14:686-693.



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932 **1561**

Variable	1995 (n = 9,047)	2000 (n = 12,089)	2005 (n = 17,542)
Case fatality, %	10.3	8.8	8.9

Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study

Scott L. Weiss[1*], Julie C. Fitzgerald[1*], John Pappachan[2,3], Derek Wheeler[4,5], Juan C. Jaramillo-Bustamante[6], Asma Salloo[7], Sunit C. Singhi[8], Simon Erickson[9], Jason A. Roy[10], Jenny L. Bush[1], Vinay M. Nadkarni[1], and Neal J. Thomas[1,11]; for the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

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Am J Respir Crit Care Med Vol 191, Iss 10, pp 1147–1157, May 15, 2015

Abstract **8.2 % of PICU patients**

Rationale: Limited data exist about the international burden of severe sepsis in critically ill children.

Objectives: To characterize the global prevalence, therapies, and outcomes of severe sepsis in pediatric intensive care units to better inform interventional trials.

Methods: A point prevalence study was conducted on 5 days throughout 2013–2014 at 128 sites in 26 countries. Patients younger than 18 years of age with severe sepsis as defined by consensus criteria were included. Outcomes were severe sepsis point prevalence, therapies used, new or progressive multiorgan dysfunction, ventilator- and vasoactive-free days at Day 28, functional status, and mortality.

Measurements and Main Results: Of 6,925 patients screened, 569 had severe sepsis (prevalence, 8.2%; 95% confidence interval, 7.6–8.9%). The patients' median age was 3.0 (interquartile range [IQR], 0.7–11.0) years. The most frequent sites of infection were respiratory (40%) and bloodstream (19%). Common therapies included mechanical ventilation (74% of patients), vasoactive infusions (55%), and corticosteroids (45%). Hospital mortality was 25% and did not differ by age or between developed and resource-limited countries. Median ventilator-free days were 16 (IQR, 0–25), and vasoactive-free days were 23 (IQR, 12–28). Sixty-seven percent of patients had multiorgan dysfunction at sepsis recognition, with 30% subsequently developing new or progressive multiorgan dysfunction. Among survivors, 17% developed at least moderate disability. Sample sizes needed to detect a 5–10% absolute risk reduction in outcomes within interventional trials are estimated between 165 and 1,437 patients per group.

Conclusions: Pediatric severe sepsis remains a burdensome public health problem, with prevalence, morbidity, and mortality rates similar to those reported in critically ill adult populations. International clinical trials targeting children with severe sepsis are warranted.

Keywords: multiple organ failure; sepsis; pediatrics

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Admission POPC, n (%)	
Good performance	290 (51.2)
Mild disability	85 (15.0)
Moderate disability	90 (15.9)
Severe disability or coma	102 (18.0)
Lactate, maximum, mmol/L*	1.8 (1.1–3.5)
Scv_{O_2}, minimum, %†	66 (55–75)
Pa_{O_2}/FI_{O_2}, minimum, mm Hg‡	158 (96–251)
PIM-3 score§	4.1 (1.7–8.7)
PELOD score‖	11 (2–12)
Type of PICU admission, n (%)	
Medical	460 (81.1)
Surgical, scheduled	53 (9.4)
Surgical, unscheduled	34 (6.0)
Trauma	20 (3.5)
Source of admission, n (%)	
Emergency department¶	167 (29.5)
Hospital floor	158 (27.9)
Operating room	50 (8.8)
Other hospital**	166 (29.3)
Other	26 (4.6)
Organ dysfunction present at screening,†† n (%)	
Respiratory	469 (82.7)
Cardiovascular	398 (70.2)
Hematologic	175 (30.9)
Hepatic	143 (25.2)
Neurologic	119 (21.0)
Renal	93 (16.4)

May 15, 2015

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Am J Respir Crit Care Med Vol 191, Iss 10, pp 1147–1157, May 15, 2015

Table 2. Site of Infection and Microbiologic Etiology of Severe Sepsis

Characteristic	n (%)
Primary site of infection	
Respiratory	228 (40.2)
Primary bloodstream	108 (19.1)
Abdominal	47 (8.3)
Central nervous system	25 (4.4)
Genitourinary	21 (3.7)
Skin	20 (3.5)
Other	29 (5.1)
Unknown	89 (15.7)

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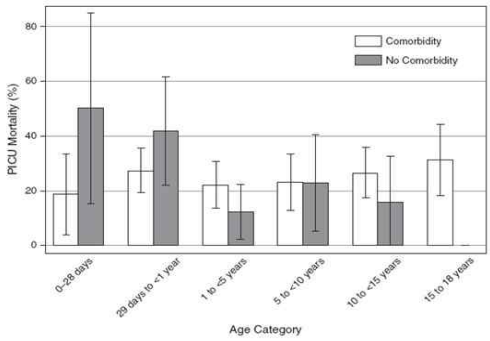
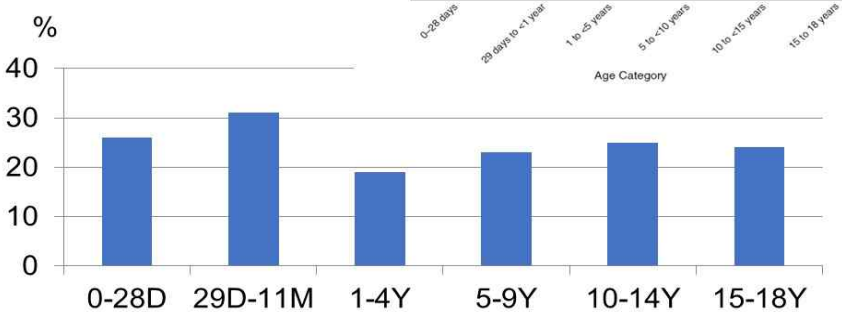
Microbiology*	
Total patients with positive isolate†	371 (65.4)
Gram-negative bacteria	158 (27.9)
Pseudomonas species	45 (7.9)
Klebsiella species	36 (6.4)
Escherichia coli	32 (5.6)
Enterobacter species	17 (3.0)
Acinetobacter species	14 (2.5)
Other	55 (9.7)
Gram-positive bacteria	150 (26.5)
Staphylococcus aureus	65 (11.5)
Methicillin-resistant *Staphylococcus aureus*	20 (3.5)
Enterococcus species	25 (4.4)
Staphylococcus epidermis	21 (3.7)
Streptococcus pneumonia	10 (1.8)
Other	45 (7.9)
Anaerobic bacteria	1 (0.2)
Other bacteria	3 (0.5)
Fungi	76 (13.4)
Candida species	67 (11.8)
Aspergillus species	3 (0.5)
Other	8 (1.4)
Parasites	3 (0.5)
Viruses	119 (21.0)
Rhinovirus	32 (5.6)
Respiratory syncytial virus	22 (3.9)
Adenovirus	20 (3.5)
Cytomegalovirus	13 (2.3)
Influenza	12 (2.1)
Human metapneumovirus	12 (2.1)
Epstein-Barr virus	8 (1.4)
Other virus	27 (4.8)

Mortality in sepsis (SPROUT Study)

Weiss SL, et al. Am J Respir Crit Care Med 2015;191:1147-57.





Intensive Care Med (2012) 38:1191–1197
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Keywords Severe sepsis · Septic shock · Paediatric · Mortality · Risk factors

1.4 % of PICU patients
vs.
8.4% by SPROUT Study

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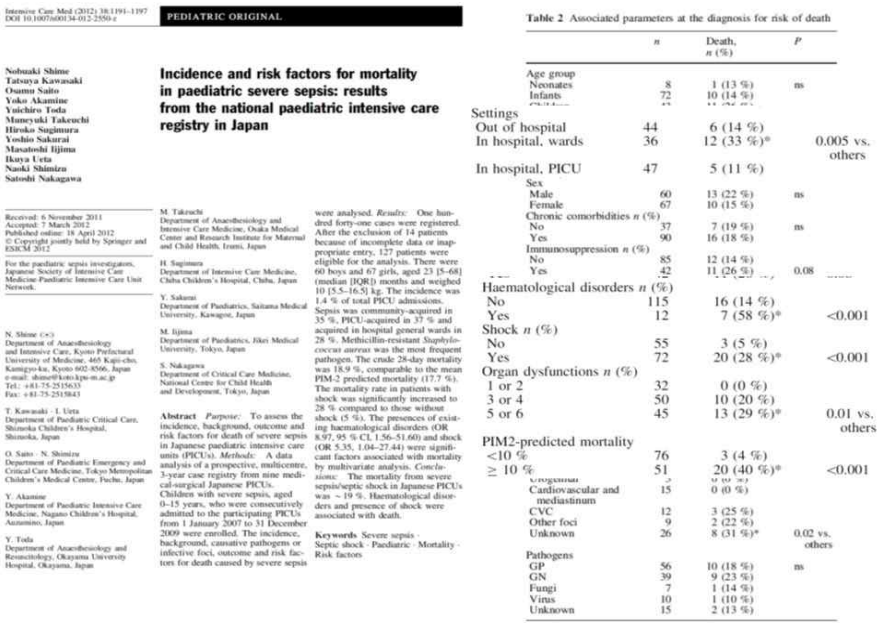
Incidence and risk factors for mortality in paediatric severe sepsis: results from the national paediatric intensive care registry in Japan

	Out of hospital	In hospital, wards	In hospital, PICU	Total
Numbers (%)	44 (35 %)	36 (28 %)	47 (37 %)	127 (100 %)
Age (months)*	24 (7.75–70.5)	28 (11.75–108)	10 (1.5-3.9)	20 (5–68)
Weight (kg)	10 (6.8–18)	10 (7.05–20.5)	7.07 (4.05–11.25)	9.0 (5.5–16.5)
Male, *n* (%)	23 (52 %)	22 (61 %)	15 (32 %)	60 (47 %)
Mortality (%)				
PIM2-predicted	19.7 %	21.9 %	12.6 %	17.7 %
28-day*	13.6 %	33.3 %	10.6 %	18.9 %
SMR	0.69	1.52	0.84	1.07
In hospital*	18.1 %	41.6 %	21.3 %	26.8 %
MV				
Performed, *n* (%)	41 (93 %)	35 (97 %)	40 (85 %)	116 (91 %)
Duration, days*	8 (5–13)	10 (6–18)	16.5 (7–31)	11 (6–20.25)
Length of PICU stay, days*	9 (6.75–14.5)	13.5 (7.75–24.35)	21 (10–39)	14 (7–35)



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Keywords Severe sepsis · Septic shock · Paediatric · Mortality · Risk factors

Table 2 Associated parameters at the diagnosis for risk of death

	n	Death, *n* (%)	*P*	
Age group				
Neonates	8	1 (13 %)	ns	
Infants	72	10 (14 %)		
Settings				
Out of hospital	44	6 (14 %)		
In hospital, wards	36	12 (33 %)*		0.005 vs. others
In hospital, PICU	47	5 (11 %)		
Sex				
Male	60	13 (22 %)	ns	
Female	67	10 (15 %)		
Chronic comorbidities *n* (%)				
No	37	7 (19 %)	ns	
Yes	90	16 (18 %)		
Immunosuppression *n* (%)				
No	85	12 (14 %)		
Yes	42	11 (26 %)	0.08	
Haematological disorders *n* (%)				
No	115	16 (14 %)		
Yes	12	7 (58 %)*		<0.001
Shock *n* (%)				
No	55	3 (5 %)		
Yes	72	20 (28 %)*		<0.001
Organ dysfunctions *n* (%)				
1 or 2	32	0 (0 %)		
3 or 4	50	10 (20 %)		
5 or 6	45	13 (29 %)*		0.01 vs. others
PIM2-predicted mortality				
<10 %	76	3 (4 %)		
≥ 10 %	51	20 (40 %)*		<0.001
Cardiovascular and mediastinum	15	0 (0 %)		
CVC	12	3 (25 %)		
Other foci	9	2 (22 %)		
Unknown	26	8 (31 %)*		0.02 vs. others
Pathogens				
GP	56	10 (18 %)	ns	
GN	39	9 (23 %)		
Fungi	7	1 (14 %)		
Virus	10	1 (10 %)		
Unknown	15	2 (13 %)		

High Levels of Morbidity and Mortality Among Pediatric Hematopoietic Cell Transplant Recipients With Severe Sepsis: Insights From the Sepsis PRevalence, OUtcomes, and Therapies International Point Prevalence Study*

PCCM 2017; 18:1114-25.

Robert B. Lindell, MD[1]; Shira J. Gertz, MD[2]; Courtney M. Rowan, MD[3]; Jennifer McArthur, DO[4]; Florian Beske, MD[5]; Adrian Plunkett, MBBS[6]; Scott L. Weiss, MD, MSCE[1]; Neal J. Thomas, MD, MSc[7]; Vinay M. Nadkarni, MD, MSc[1]; Julie C. Fitzgerald, MD, PhD[1]; for the Sepsis PRevalence, OUtcomes

TABLE 4. Comparison of Outcomes of Patients With Hematopoietic Cell Transplant and Patients Without Hematopoietic Cell Transplant

Outcomes	HCT (*n* = 37)	No HCT (*n* = 530)	*p*
PICU mortality, *n* (%)	24 (65)	115 (22)	**< 0.001**
Hospital mortality, *n* (%)	25 (68)	120 (23)	**< 0.001**
PICU LOS (d), median (IQR)	19 (10–36)	15 (7–35)	0.222
PICU-free days[a] out of 28, median (IQR)	0 (0–5)	7 (0–19)	**0.009**
PICU-free days[a] out of 60, median (IQR)	0 (0–37)	39 (0–51)	**0.001**
Hospital LOS (d), median (IQR)	42 (19–74)	26 (13–53)	**0.034**
Ventilator-free days[b], median (IQR)	15 (0–25)	19 (1–25)	0.255
Vasoactive-free days[b], median (IQR)	23 (17–27)	25 (18–28)	0.212
New mild disability in survivors[c], *n* (%)	1 (8)	115 (28)	0.193
New moderate disability in survivors[c], *n* (%)	1 (8)	72 (18)	0.700

Risk of death in pediatric sepsis

A Systemic Inflammation Mortality Risk Assessment Contingency Table for Severe Sepsis

Joseph A. Carcillo, MD[1]; Katherine Sward, PhD[2]; E. Scott Halstead, MD, PhD[1]; Russell Telford, MAS[2]; Adria Jimenez-Bacardi, MD[1]; Bita Shakoory, MD[3]; Dennis Simon, MD[1]; Mark Hall, MD[4]; on behalf of the *Eunice Kennedy Shriver* National Inst Pediatric Critical Care Research Networ

Objectives: We tested the hypothesis that a C-reactive and ferritin-based systemic inflammation contingency t track mortality risk in pediatric severe sepsis.
Design: Prospective cohort study.
Setting: Tertiary PICU.
Patients: Children with 100 separate admission epis severe sepsis were enrolled.
Interventions: Blood samples were attained on day 2 of se bi-weekly for biomarker batch analysis. A 2×2 contingen using C-reactive protein and ferritin thresholds was develc
Measurements and Main Results: A C-reactive pr 4.08 mg/dL and a ferritin of 1,980 ng/mL were found to b cutoffs for outcome prediction at first sampling ($n = 10$ the Youden index. PICU mortality was increased in the "h

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Supplemental digital content is available for this article. Direct tions appear in the printed text and are provided in the HTML versions of this article on the journal's website (http://journals. pccmjournal).
Supported, in part, by R01GM108818 (to Dr. Carcillo) from th

Box A	Box B
'Intermediate Risk' CRP < 4.08 mg/dL, and Ferritin ≥ 1,980 ng/mL **Mortality 0/0 (0%)**	'High Risk' CRP ≥ 4.08 mg/dL, and Ferritin ≥ 1,980 ng/mL **Mortality 6/13 (46.15%)**
Box C	**Box D**
'Low Risk' CRP ≤ 4.08 mg/dL, and Ferritin ≤ 1,980 ng/mL **Mortality 0/44 (0%)**	'Intermediate Risk' CRP ≥ 4.08 mg/dL, and Ferritin < 1,980 ng/mL **Mortality 2/43 (4.65%)**

PEDIATRIC ORIGINAL

Prediction of pediatric sepsis mortality within 1 h of intensive care admission

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Table 3 Statistically derived pediatric sepsis score

	Definition	Points by severity level			
		0	3	5	10
Respiratory	PaO_2/FiO_2 ratio	≥300	100 to <300	<100	
	Ventilation during the first hour	No	Yes		
Circulatory	Systolic BP <5th percentile				
	<12 months		<65		
	>1 to <2 years		<67 (M), <68 (F)		
	>2 to <3 years		<70 (M), <71 (F)		
	>3 to <4 years		<73 (M), <71 (F)		
	>4 to <5 years		<75 (M), <74 (F)		
	>5 to <6 years		<78 (M), <76 (F)		
	>6 to <7 years		<78 (M), <78 (F)		
	>7 to <8 years		<79 (M), <78 (F)		
	>8 to <9 years		<82 (M), <81 (F)		
	>9 to <10 years		<82 (M), <83 (F)		
	>10 to <11 years		<85 (M), <85 (F)		
	>11 to <12 years		<87 (M), <85 (F)		
	>12 to <13 years		<89 (M), <87 (F)		
	>13 to <14 years		<90 (M), <90 (F)		
	>14 to <15 years		<94 (M), <92 (F)		
	>15 to <16 years		<95 (M), <93 (F)		
	Cardiac arrest pre admission	No		Yes	
Metabolic	Lactate (mmol/l)	<3.0	3.0 to <6.0	6.0 to <10.0	≥10.0
Neurologic	Pupils	Both reactive			Both dilated, unresponsive

PEDIATRIC ORIGINAL

Prediction of pediatric sepsis mortality within 1 h o

Luregn J. Schlapbach[1,2,3*], G
John Beca[10], Anthony Slate
behalf of the Australian & N
Evaluation (CORE) and Aust

Abstract
Purpose: The definitions of needed to inform similar app
Methods: Multicenter coh tralia and New Zealand in th severity, using 30-day morta derived using variables avail
Results: Of 42,523 pediatric diagnosed as having sepsis within 48 h of admission. Th cific in predicting mortality (lactate >2 mmol/l discrimina tory support, hypotension, c best-performing predictors (one-point increase was asso had 19.8% mortality and acc children admitted with invas
Conclusions: We observed definitions of sepsis severity derangements at ICU admis

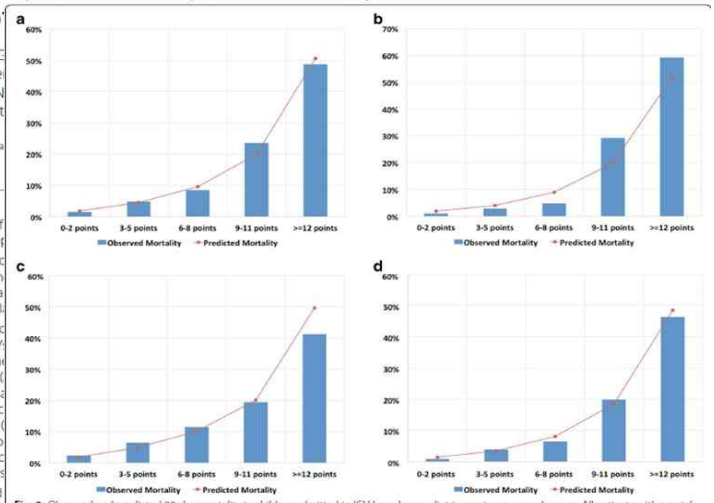


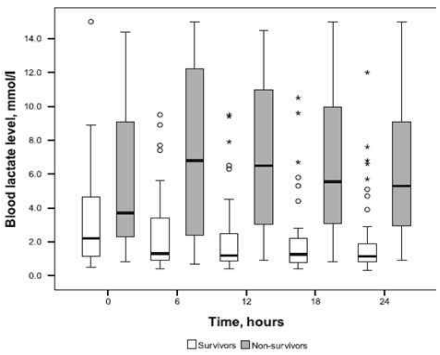
Fig. 2 Observed and predicted 30-day mortality in children admitted to ICU based on pediatric sepsis score are shown. **a** All patients with sepsis/septic shock, **b** sepsis/septic shock patients with no comorbidity, **c** sepsis/septic shock patients with comorbidities, **d** all patients with invasive infection

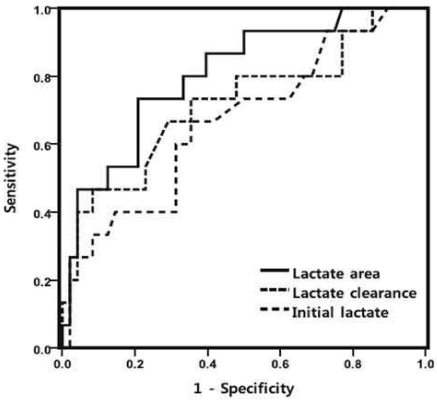
Intensive Care Med (2013) 39:1818–1823
DOI 10.1007/s00134-013-2959-z

ORIGINAL

Young A Kim
Eun-Ju Ha
Won Kyoung Jhang
Seong Jong Park

Early blood lactate area as a prognostic marker in pediatric septic shock





Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.

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Group Information. The Sepsis Definitions Task Force members are the authors listed above.
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Adult medicine has new sepsis definition

Box 3. New Terms and Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

SOFA Score

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

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

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

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

Proposal of a New Pediatric Sec Organ Failure Assessment Scor Validation

Pediatr Crit Care Med 2017;18-98-

Age Group	Systolic Arterial Blood Pressure (mm Hg)	Serum Creatinine (mg/dL)
0 d to 1 wk	60	0.8
1 wk to 1 mo	65	0.3
1 mo to 1 yr	70	0.4
2–5 yr	75	0.6
6–12 yr	80	0.7
13–18 yr	90	1.0

TABLE 1. Proposed Pediatric Sequential Org

Organ	Variable	0	1	2	3	4
Respiratory	Pao_2/Fio_2	> 400	≤ 400 O_2 therapy	≤ 300 Noninvasive ventilatory support	≤ 200 Ventilatory support	≤ 100 Ventilatory support
Hematologic	Platelet count (× 10^3/ mm^3)	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver	Bilirubin (mg/dL)	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Cardiovascular	Cardiovascular support		Systolic arterial blood pressure < age-based cutoff, mm Hg	Dopamine ≤ 5 μg/kg/min or dobutamine at any dose	Dopamine > 5 μg/kg/min or adrenaline/ noradrenaline ≤ 0.1 μg/kg/min	Dopamine > 15 μg/kg/min or adrenaline/ noradrenaline > 0.1 μg/kg/min
CNS	Glasgow Coma Scale	15	13–14	10–12	6–9	< 6
Renal	Creatinine (mg/dL)	< 1 × age-based cutoff	1–1.6 × age-based cutoff	1.7–2.8 × age-based cutoff	2.9–4.1 × age-based cutoff	≥ 4.2 × age-based cutoff

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Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children

Travis J. Matics, DO; L. Nelson Sanchez-Pinto, MD, MBI

IMPORTANCE The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) uses the Sequential Organ Failure Assessment (SOFA) score to grade organ dysfunction in adult patients with suspected infection. However, the SOFA score is not adjusted for age and therefore not suitable for children.

OBJECTIVES To adapt and validate a pediatric version of the SOFA score (pSOFA) in critically ill children and to evaluate the Sepsis-3 definitions in patients with confirmed or suspected infection.

DESIGN, SETTING, AND PARTICIPANTS This retrospective observational cohort study included all critically ill children 21 years or younger admitted to a 20-bed, multidisciplinary, tertiary pediatric intensive care unit between January 1, 2009 and August 1, 2016. Data on these children were obtained from an electronic health record database. The pSOFA score was developed by adapting the original SOFA score with age-adjusted cutoffs for the cardiovascular and renal systems and by expanding the respiratory criteria to include noninvasive surrogates of lung injury. Daily pSOFA scores were calculated from admission until day 28 of hospitalization, discharge, or death (whichever came first). Three additional pediatric organ dysfunction scores were calculated for comparison.

EXPOSURES Organ dysfunction measured by the pSOFA score, and sepsis and septic shock according to the Sepsis-3 definitions.

MAIN OUTCOMES AND MEASURES The primary outcome was in-hospital mortality. The daily pSOFA scores and additional pediatric organ dysfunction scores were compared. Performance was evaluated using the area under the curve. The pSOFA score was then used to assess the Sepsis-3 definitions in the subgroup of children with confirmed or suspected infection.

RESULTS In all, 6303 patients with 8711 encounters met inclusion criteria. Each encounter was treated independently. Of the 8482 survivors of hospital encounters, 4644 (54.7%) were male and the median (interquartile range [IQR]) age was 69 (7-156) months. Among the 229 nonsurvivors, 127 (55.4%) were male with a median (IQR) age of 43 (8-144) months. In-hospital mortality was 2.6%. The maximum pSOFA score had excellent discrimination for in-hospital mortality, with an area under the curve of 0.94 (95% CI, 0.92-0.95). The pSOFA score had a similar or better performance than other pediatric organ dysfunction scores. According to the Sepsis-3 definitions, 1231 patients (14.1%) were classified as having sepsis and had a mortality rate of 12.1%, and 347 (4.0%) had septic shock and a mortality rate of 32.3%. Patients with sepsis were more likely to die than patients with confirmed or suspected infection but no sepsis (odds ratio, 18; 95% CI, 11-28). Of the 229 patients who died during their hospitalization, 149 (65.0%) had sepsis or septic shock during their course.

CONCLUSIONS AND RELEVANCE The pSOFA score was adapted and validated with age-adjusted variables in critically ill children. Using the pSOFA score, the Sepsis-3 definitions were assessed in children with confirmed or suspected infection. This study is the first assessment, to date, of the Sepsis-3 definitions in critically ill children. Use of these definitions in children is feasible and shows promising results.

JAMA Pediatr. doi:10.1001/jamapediatrics.2017.2352
Published online August 7, 2017

Table 1. Pediatric Sequential Organ Failure Assessment Score

	Score[a]				
Variables	0	1	2	3	4
Respiratory					
Pao_2/Fio_2[b] or Spo_2/Fio_2[c]	≥400 / ≥292	300-399 / 264-291	200-299 / 221-264	100-199 With respiratory support / 148-220 With respiratory support	<100 With respiratory support / <148 With respiratory support
Coagulation					
Platelet count, $\times 10^3/\mu L$	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or μg/kg/min[d]					
<1 mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride >5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride >15 or epinephrine >0.1 or norepinephrine bitartrate >0.1
1-11 mo	≥55	<55			
12-23 mo	≥60	<60			
24-59 mo	≥62	<62			
60-143 mo	≥65	<65			
144-216 mo	≥67	<67			
>216 mo[e]	≥70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

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JAMA Pediatr. doi:10.1001/jamapediatrics.2017.2352
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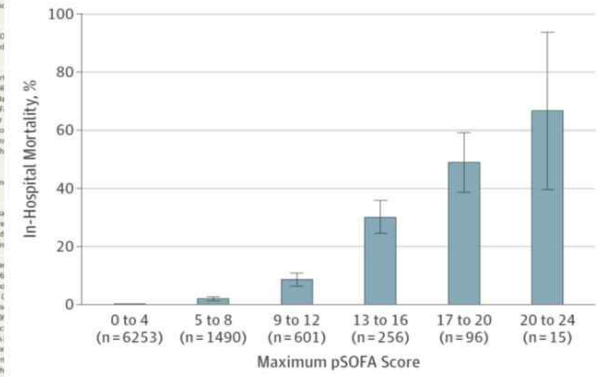
Figure. In-Hospital Mortality Rate Based on the Maximum Pediatric Sequential Organ Failure Assessment (pSOFA) Score



Maximum pSOFA score was the highest daily pSOFA score achieved by day 28 after pediatric intensive care unit admission, discharge, or death (whichever came first). Error bars represent 95% CIs.

Immune function in pediatric sepsis

Early Immune Function and Duration of Organ Dysfunction in Critically Ill Children with Sepsis

Jennifer A. Muszynski[1,2], Ryan Nofziger[3], Melissa Moore-Clingenpeel[1,4], Kristin Greathouse[2], Larissa Anglim[2], Lisa Steele[2], Josey Hensley[2], Lisa Hanson-Huber[2], Jyotsna Nateri[2], Octavio Ramilo[2,5], and Mark W. Hall[1,2]

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Am J Respir Crit Care Med Vol 198, Iss 3, pp 361–369, Aug 1, 2018

Abstract

Rationale: Late immune suppression is associated with nosocomial infection and mortality in adults and children with sepsis. Relationships between early immune suppression and outcomes in children with sepsis remain unclear.

Objectives: Prospective observational study to test the hypothesis that early innate and adaptive immune suppression are associated with longer duration of organ dysfunction in children with severe sepsis or septic shock.

Methods: Children younger than 18 years of age meeting consensus criteria for severe sepsis or septic shock were sampled within 48 hours of sepsis onset. Healthy control subjects were sampled once. Innate immune function was quantified by whole blood *ex vivo* LPS-induced TNF-α (tumor necrosis factor-α) production capacity. Adaptive immune function was quantified by *ex vivo* phytohemagglutinin-induced IFN-γ production capacity.

Measurements and Main Results: One hundred two children with sepsis and 35 healthy children were enrolled. Compared with healthy children, children with sepsis demonstrated lower LPS-induced TNF-α production ($P < 0.0001$) and lower phytohemagglutinin-induced IFN-γ production ($P < 0.0001$). Among children with sepsis, early innate and adaptive immune suppression were associated with greater number of days with multiple organ dysfunction syndrome and greater number of days with any organ dysfunction. On multivariable analyses, early innate immune suppression remained independently associated with increased multiple organ dysfunction syndrome days (adjusted relative risk, 1.2; 95% confidence interval, 1.03–1.5) and organ dysfunction days (adjusted relative risk, 1.2; 95% confidence interval, 1.1–1.3).

Conclusions: Critically ill children with severe sepsis or septic shock demonstrate early innate and adaptive immune suppression. Early innate and adaptive immune suppression are associated with longer durations of organ dysfunction and may be useful markers to help guide future investigations of immunomodulatory therapies in children with sepsis.

Keywords: pediatrics; multiple organ failure; sepsis; immune system

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Measurements and Main Results: C
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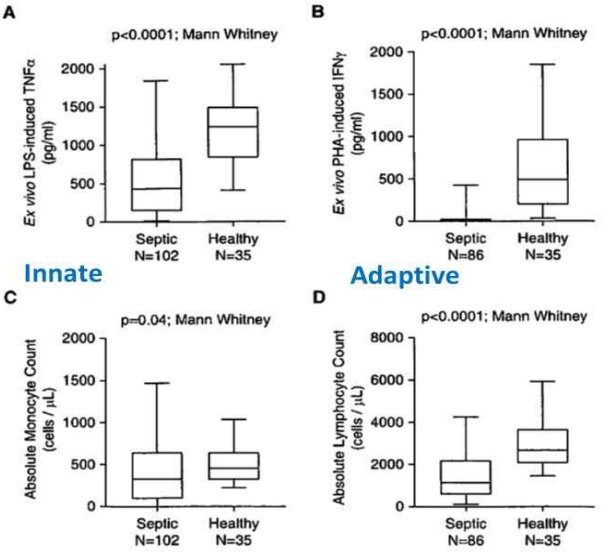

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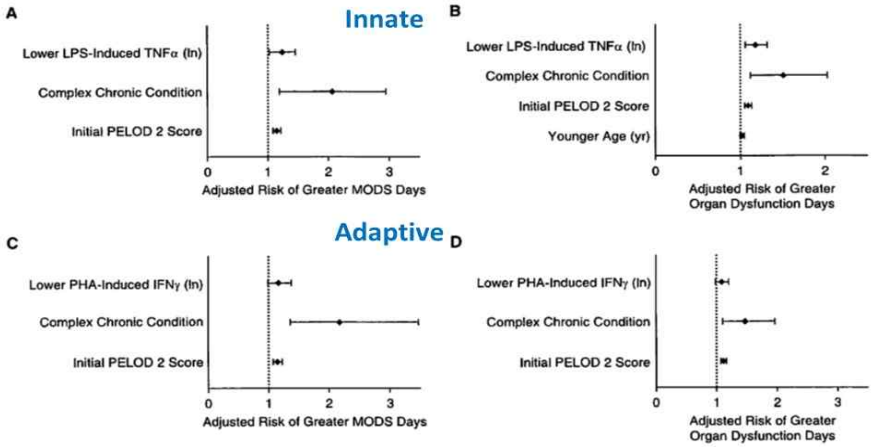

Three Hypothetical Inflammation Pathobiology Phenotypes and Pediatric Sepsis-Induced Multiple Organ Failure Outcome*

(*Pediatr Crit Care Med* 2017; 18:513–523)

Joseph A. Carcillo, MD[1]; E. Scott Halstead, MD[1]; Mark W. Hall, MD[2]; Trung C. Nguyen, MD[3]; Ron Reeder, PhD[4]; Rajesh Aneja, MD[1]; Bita Shakoory, MD[5]; Dennis Simon, MD[1]; on behalf of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network Investigators

Design: Prospective cohort study comparing children with severe sepsis and any of three phenotypes: 1) immunoparalysis-associated multiple organ failure (whole blood ex vivo tumor necrosis factor response to endotoxin < 200 pg/mL), 2) thrombocytopenia-associated multiple organ failure (new onset thrombocytopenia with acute kidney injury and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 activity < 57%), and/or 3) sequential multiple organ failure with hepatobiliary dysfunction (respiratory distress followed by liver dysfunction with soluble Fas ligand > 200 pg/mL), to those without any of these phenotypes.

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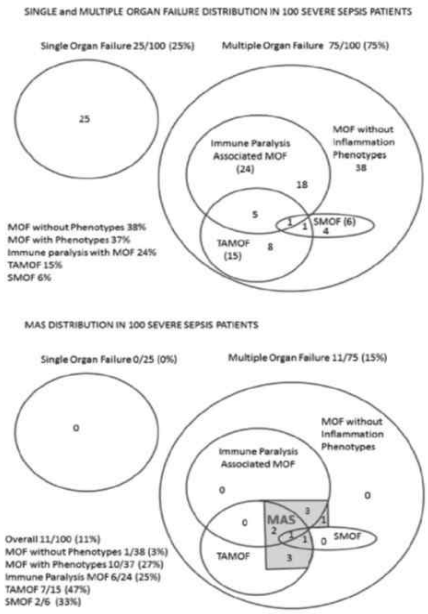

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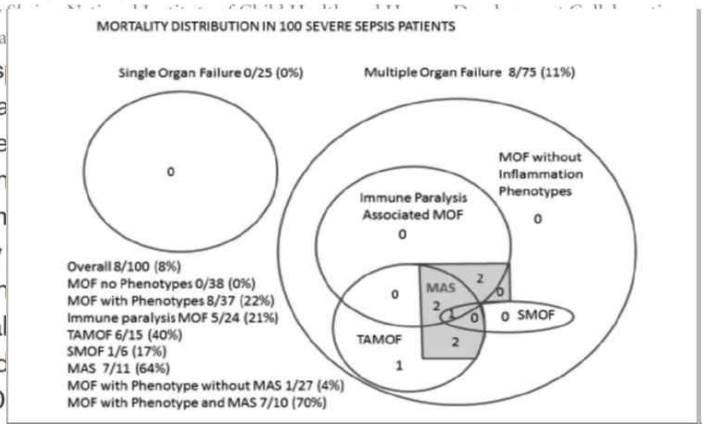

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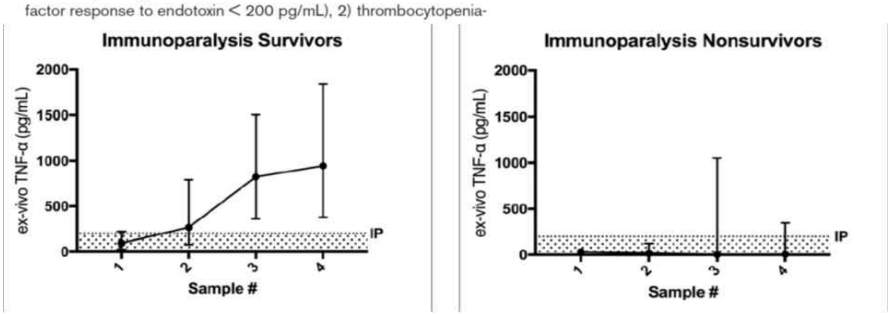

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6], Michael T. Bigham[7], Scott L. Weiss[8], Julie Fitzgerald[8], Paul A. Checchia[9], Keith Meyer[10], Thomas P. Shanley[11], Michael Quasney[11], Mark Hall[12], Rainer Gedeit[13], Robert J. Freishtat[14], Jeffrey Nowak[15], Raj S. Shekhar[16], Shira Gertz[17], Emily Dawson[18], Kelli Howard[1], Kelli Harmon[1], Eileen Beckman[1], Erin Frank[1], and Christopher J. Lindsell[19]

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Am J Respir Crit Care Med Vol 191, Iss 3, pp 309–315, Feb 1, 2015

Abstract

Rationale: Using microarray data, we previously identified gene expression–based subclasses of septic shock with important phenotypic differences. The subclass-defining genes correspond to adaptive immunity and glucocorticoid receptor signaling. Identifying the subclasses in real time has theranostic implications, given the potential for immune-enhancing therapies and controversies surrounding adjunctive corticosteroids for septic shock.

Objectives: To develop and validate a real-time subclassification method for septic shock.

Methods: Gene expression data for the 100 subclass-defining genes were generated using a multiplex messenger RNA quantification platform (NanoString nCounter) and visualized using gene expression mosaics. Study subjects ($n = 168$) were allocated to the subclasses using computer-assisted image analysis and microarray-based reference mosaics. A gene expression score was calculated to reduce the gene expression patterns to a single metric. The method was tested prospectively in a separate cohort ($n = 132$).

Measurements and Main Results: The NanoString-based data reproduced two septic shock subclasses. As previously, one subclass had decreased expression of the subclass-defining genes. The gene expression score identified this subclass with an area under the curve of 0.98 (95% confidence interval [CI_{95}] = 0.96–0.99). Prospective testing of the subclassification method corroborated these findings. Allocation to this subclass was independently associated with mortality (odds ratio = 2.7; CI_{95} = 1.2–6.0; $P = 0.016$), and adjunctive corticosteroids prescribed at physician discretion were independently associated with mortality in this subclass (odds ratio = 4.1; CI_{95} = 1.4–12.0; $P = 0.011$).

Conclusions: We developed and tested a gene expression–based classification method for pediatric septic shock that meets the time constraints of the critical care environment, and can potentially inform therapeutic decisions.

Keywords: sepsis; gene expression; subclassification; adaptive immunity; glucocorticoids

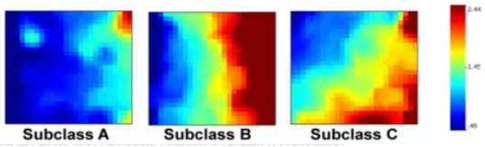

Table 1. Clinical and Demographic Data for the Derivation Cohort

	Subclass A	Subclass B
n	57	111
Median age (IQR), yr	1.4 (0.2–2.9)	3.0 (1.5–7.3)
Males, n (%)	36 (63)	64 (58)
28-d mortality, n (%)	12 (21)	11 (10)†
Complicated course, n (%)	24 (42)	26 (23)*
Median PRISM score (IQR)	16 (12–23)	13 (9–20)*
Median WBC count $\times 10^3/mm^3$ (IQR)	10.0 (3.8–16.9)	14.6 (7.7–19.9)*
Median neutrophil count $\times 10^3/mm^3$ (IQR)	6.1 (2.4–11.4)	10.9 (4.5–16.8)*
Median lymphocyte count $\times 10^3/mm^3$ (IQR)	1.8 (0.9–3.5)	1.5 (0.7–2.5)*
Median monocyte count $\times 10^3/mm^3$ (IQR)	0.6 (0.1–1.4)	0.6 (0.2–1.3)
No. with gram-negative bacteria (%)	11 (19)	26 (23)
No. with gram-positive bacteria (%)	16 (28)	28 (25)
No. with other pathogen isolated (%)	6 (11)	5 (5)
No. with no pathogen identified (%)	24 (42)	52 (47)
No. with comorbidity (%)	11 (19)	46 (41)†
No. with malignancy (%)	1 (2)	8 (7)
No. with immune suppression (%)	3 (5)	11 (10)
No. with bone marrow transplantation (%)	1 (2)	5 (5)

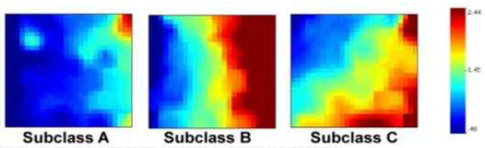

Table 2. Clinical and Demographic Data for the Test Cohort

	Subclass A	Subclass B
n	63	69
Median age (IQR), yr	1.4 (0.3–3.9)	4.1 (1.3–6.6)*
Males, n (%)	34 (54)	39 (57)
28-d mortality, n (%)	11 (17)	4 (5)†
Complicated course, n (%)	27 (43)	11 (16)†
Median PRISM score (IQR)	11 (6–18)	11 (8–19)
Median WBC count $\times 10^3/mm^3$ (IQR)	8.6 (2.9–14.7)	13.4 (6.2–20.8)*
Median neutrophil count $\times 10^3/mm^3$ (IQR)	4.6 (0.8–8.6)	11.9 (4.8–16.6)*
Median lymphocyte count $\times 10^3/mm^3$ (IQR)	2.3 (1.3–4.3)	1.2 (0.5–2.1)*
Median monocyte count $\times 10^3/mm^3$ (IQR)	0.5 (0.1–0.9)	0.5 (0.3–1.2)
No. with gram negative bacteria (%)	17 (27)	12 (17)
No. with gram positive bacteria (%)	10 (16)	13 (19)
No. with other pathogen isolated (%)	5 (8)	13 (19)
No. with no pathogen identified (%)	31 (49)	31 (45)
No. with comorbidity (%)	16 (25)	26 (38)
No. with malignancy (%)	6 (10)	5 (7)
No. with immune suppression (%)	6 (10)	9 (13)
No. with bone marrow transplantation (%)	0 (0)	3 (4)

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	Outcome Variable	Independent Variable	Odd Ratio	95% C.I.	P value
Subclass A n = 120	Mortality n = 23	PRISM Score	1.109	1.044 – 1.179	<0.001
		Corticosteroids	4.070	1.386 – 11.947	0.011
		Age	1.107	0.932 – 1.315	0.248
		Comorbidity	0.938	0.263 – 3.345	0.921
	Complicated Course n = 51	PRISM Score	1.080	1.031 – 1.131	0.001
		Corticosteroids	1.897	0.865 – 4.160	0.110
		Age	0.980	0.855 – 1.122	0.765
		Comorbidity	0.749	0.290 – 1.934	0.550
Subclass B N = 180	Mortality N = 15	PRISM Score	1.122	1.058 – 1.190	<0.001
		Corticosteroids	1.125	0.348 – 3.638	0.844
		Age	1.032	0.870 – 1.224	0.720
		Comorbidity	0.570	0.166 – 1.953	0.371
	Complicated Course N = 37	PRISM Score	1.106	1.058 – 1.157	<0.001
		Corticosteroids	1.109	0.496 – 2.478	0.802
		Age	1.009	0.895 – 1.137	0.889
		Comorbidity	0.461	0.195 – 1.088	0.077

Pediatric sepsis

- Epidemiology: still unclear
- Risk factors
  - Underlying disease (Hem-Onc)
  - Shock
  - High lactate levels
  - Number of organ dysfunctions
  - Ferritin?
  - Other biomarkers?
- Immune functions
  - Need to be explored

Role of Circulating Mitochondrial *N*-Formyl Peptides in Patients with Septic Shock

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Secondary nosocomial infections were associated with an increase in mortality of septic shock patients who survived from the early hyper-inflammatory phase. To prevent secondary infection, neutrophil (PMN) should migrate to secondary infective sites (chemotaxis, CTX). Among mitochondrial damage-associated molecular patterns (DAMPs) released from injured tissues, mitochondrial *N*-formyl peptides (mtFPs) bind to formyl peptide receptor 1 (FPR1) on PMN membrane, induce homologous and heterologous desensitization of G protein-coupled receptors, suppress PMN CTX to bacterial FPs in secondary infective sites, and increase susceptibility towards secondary nosocomial infection. Therefore, we hypothesized that septic shock would induce mtFPs release from damaged tissues during the early hyper-inflammatory phase and that released mtFPs would contribute to a development of secondary infections and an increase in delayed mortality of septic shock patients who survived from the early hyper-inflammatory phase.

This was a retrospective observational study using prospectively collected clinical data and plasma samples. We enrolled healthy volunteers and septic shock patients who were admitted from the emergency department (ED) to the emergency intensive care unit (EICU) from February 2016 to January 2019. Exclusion criteria were age < 18 years old, death or survival discharge from the ICU within 72 hours post-ICU admission, transfer to other facilities within 72 hours, presence of an advanced directive to withhold or withdraw life-sustaining treatment, no informed consent, insufficient blood samples, or follow-up loss. Septic shock was diagnosed and managed according to the SEPSIS-3 guideline. After admission to the ICU, we collected demographic and laboratory data. Blood samples were obtained from patients at 0, 24, and 72 hours after the admission to the EICU through an arterial catheter. Among 13 human mtFPs, the most potent agonist for calcium mobilization and PMN chemotaxis was nicotinamide adenine dinucleotide dehydrogenase subunit 6 (ND6) followed by ND3, ND4,

ND5, and cytochrome c oxidase subunit 1 (Cox1). Therefore, in the present study, we measured the plasma ND6 level using a Human NADH-ubiquinone oxidoreductase chain 6 (MT-ND6) ELISA Kit. The primary outcome was a development of secondary infections including ventilator-associated pneumonia (VAP), central line-associated blood stream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI) during hospital stay. The secondary outcome was the 90-day mortality. Cumulative survival and secondary infections were analyzed using the Kaplan-Meier survival analysis with Log-rank post-hoc test. Demographic and laboratory data were analyzed using the Student's t-test and Chi-square test. Serial data were analyzed using the stepwise logistic regression analysis (with an entry level of 0.05 and a stay level of 0.05). Then, to find out which parameters were independently associated with primary or secondary outcomes, the multivariable logistic regression analysis was applied.

Among 189 patients admitted to the EICU with septic shock, 92 patients were excluded, and 97 patients were enrolled. Sixty-two patients (63.9%) were 90-day survivors, and thirty-five (36.1%) were 90-day non-survivors. In fifteen patients (15.5%), secondary infections were developed. Mechanical ventilator was applied to 39 patients (40.2%). Central venous and urinary catheters were inserted to 97 patients (100.0%). VAP, CLABSI, and CAUTI were developed in 5, 9, and 2 patients, respectively. In one patient, VAP and CLABSI were simultaneously developed. Most of the secondary infections were developed from 4 to 25 days post-EICU admission. The plasma ND6 level in secondary infection-positive patients was continuously higher than that in secondary infection-negative patients at 0, 24, and 72 hours post-EICU admission ($p < 0.001$). The plasma ND6 level in 90-day non-survivors was also continuously higher than that in 90-day survivors at 0, 24, and 72 hours post-EICU admission ($p = 0.015$). In multivariable analysis, the higher plasma ND6 level at admission was independently associated with a development of secondary infections (odds ratio = 1.003, 95% confidence interval 1.001 – 1.005, $p = 0.002$), but was not independently associated with an increase in 90-day mortality (odds ratio = 1.000, 95% confidence interval 1.000 – 1.001, $p = 0.080$). However, the cumulative mortality of secondary infection-positive patients was significantly higher than that of secondary infection-negative patients ($p < 0.001$). In particular, the mortality of secondary infection-positive patients rapidly increased from 14 days post-EICU admission.

In septic shock patients, mtFPs were released from damaged tissues into circulating blood. Circulating mtFPs contributed to a development of secondary

nosocomial infections resulting in an increase in the 90-day mortality of septic shock patients who survived from the early hyper-inflammatory phase. These results indicate that the elimination of circulating mtFPs may be considered as a noble therapeutic strategy to prevent a development of secondary infections and the subsequent delayed mortality in patients with septic shock.

Curriculum Vitae

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Education and Appointment

1990-1997 MD, Medical science, Seoul National University College of Medicine
2003-2005 MS, Medical science, Kangwon National University College of Medicine
2006-2008 PhD, Emergency Medicine, Graduate School of Seoul National University College of Medicine

Professional Training and Employment

1997-1998 Full rotation internship, Seoul National University Hospital
1998-2002 Resident, Emergency Medicine, Seoul National University Hospital
2002-2003 Clinical fellowship, Emergency Medicine, Samsung Medical Center
2006-2007 Clinical fellowship, Emergency Medicine, Seoul National University Hospital
2007-2014 Assistant Professor, Emergency Medicine, Seoul National University Hospital
2017-2018 Postdoctoral Research Fellow, Department of Surgery, Beth Israel Deaconess Medical Center/Harvard Medical School
2014- Associate Professor, Emergency Medicine, Seoul National University College of Medicine/ Seoul National University Hospital

Selected Publications

1. Jung YS, **Kwon WY**, Suh GJ, Moon S, Han MH, Youn JI, Seo SU, Kim KS, Seong SY. Low serum Kallistatin level was associated with poor neurological outcome of out-of-hospital cardiac arrest survivors: Proteomics study. *Resuscitation* 2018;128:610.
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