Septic shock in children. Is it different than adults?

Peter Kanizsai, MD, PhD

associate professor in emergency medicine

SEPSIS KILLS

Sepsis Cases in the Developing World [7]

Sepsis kills

>6,000,000

newborn and small children every year in the Developing world

Sepsis is one of the most common diseases [1]

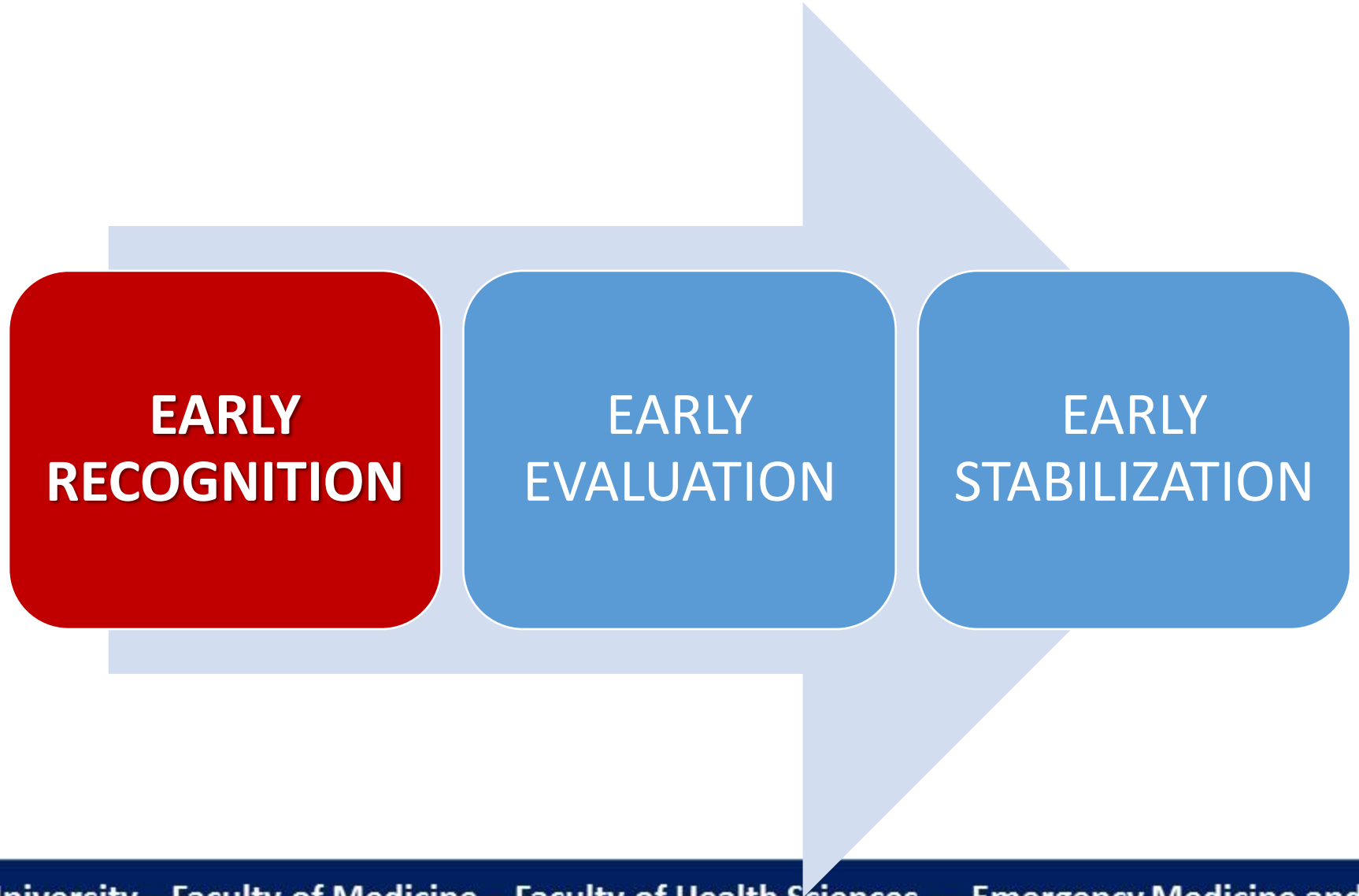
Cases per 100,000 population (US / *Europe)

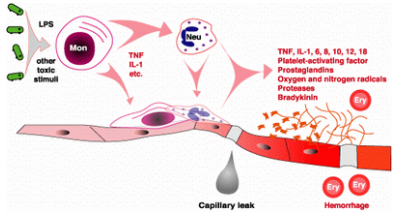
Million US-Dollars spent for state-funded research 2011

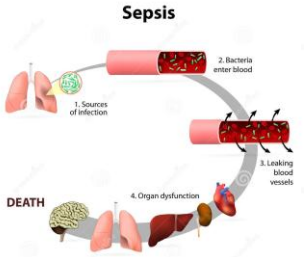
Sepsis research receives the lowest funding [2]

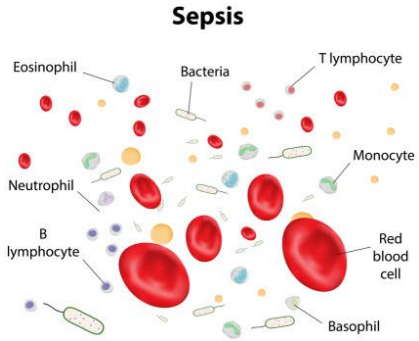
http://www.ipaustralia.com.au/applicant/clinical-excellence-commission/trademarks/1473265/

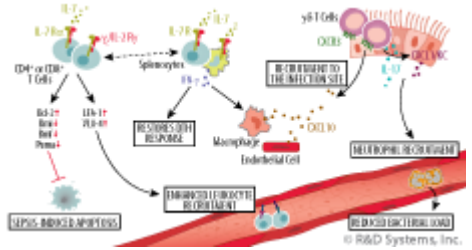
Vincent et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. The Lancet Respiratory Medicine Volume 2, Issue 5, May 2014, Pages 380-386

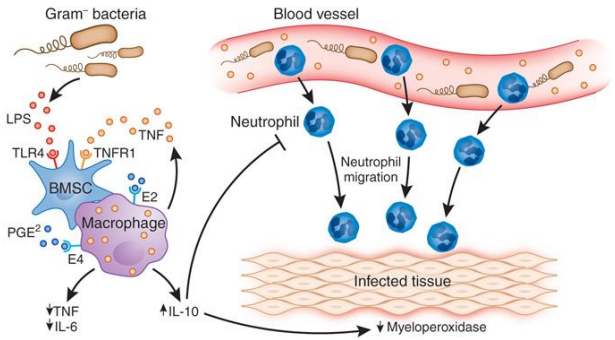

EARLY RECOGNITION
EARLY EVALUATION
EARLY STABILIZATION

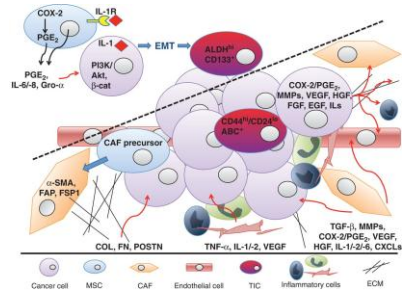

LPS
Mon
other toxic stimuli
TNF IL-1 etc.
Neu
TNF, IL-1, 6, 8, 10, 12, 18
Platelet-activating factor
Prostaglandins
Oxygen and nitrogen radicals
Proteases
Bradykinin
Ery
Capillary leak
Hemorrhage


Sepsis
1. Sources of infection
2. Bacteria enter blood
3. Leaking blood vessels
4. Organ dysfunction
DEATH

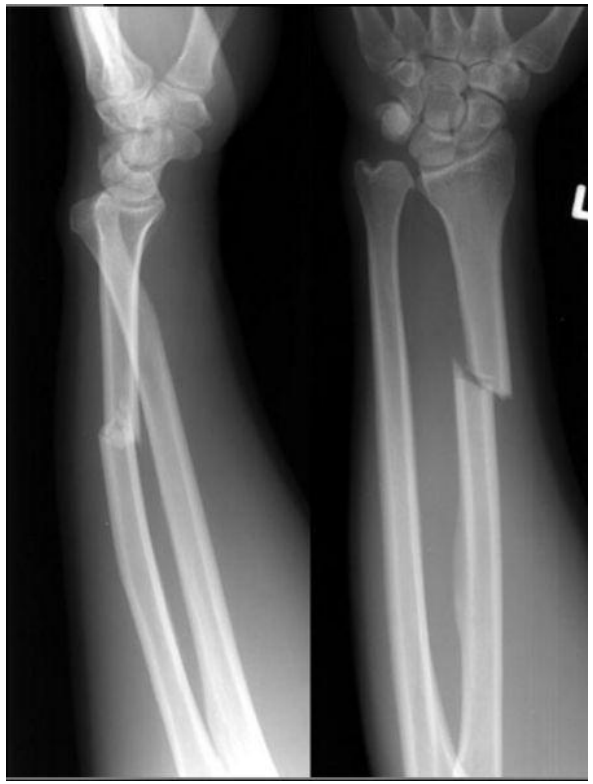

Sepsis
Eosinophil
Bacteria
T lymphocyte
Monocyte
Neutrophil
B lymphocyte
Red blood cell
Basophil

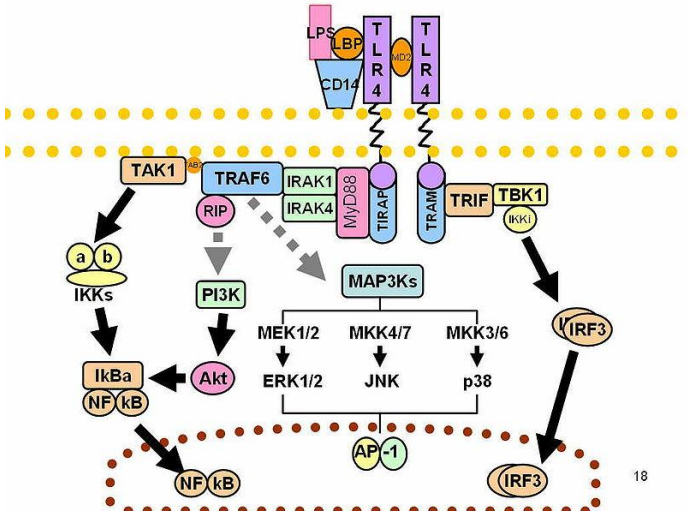

Macrophage
Endothelial Cell
© R&D Systems, Inc.


Gram⁻ bacteria
Blood vessel
LPS
TNF
TLR4
TNFR1
BMSC
E2
Macrophage
PGE2
E4
Neutrophil
Neutrophil migration
Infected tissue
TNF
IL-6
IL-10
Myeloperoxidase


COX-2
PGE2
IL-1R
IL-1
EMT
PI3K/ Akt, β-cat
IL-6/-8, Gro-α
CAF precursor
α-SMA, FAP, FSP1
COL, FN, POSTN
TNF-α, IL-1/-2, VEGF
Cancer cell
MSC
CAF
Endothelial cell
TIC
Inflammatory cells
ECM

But how?..





http://radiopaedia.org/play/2031/case/12221/studies/12534

http://pl.wikipedia.org/wiki/Sepsa

2013. Surviving Sepsis Campaign

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Creatinine increase > 0.5 mg/dL or 44.2 µmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 µL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 µmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

TABLE 2. Severe Sep

Severe sepsis definition = s -induced tissue hypoperfusion o an dysfunction (any of the following thought to be due to nfection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite luid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence s infection source
Acute lung injury with Pao_2/Fio_2 < 200 in the pres pneumonia fection source
Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (internationa lized ratio > 1.5)

Adapted from Levy MM, Fink rshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definiti ference. *Crit Care Med* 2003; 31: 1250–1256.

SEPSIS-3

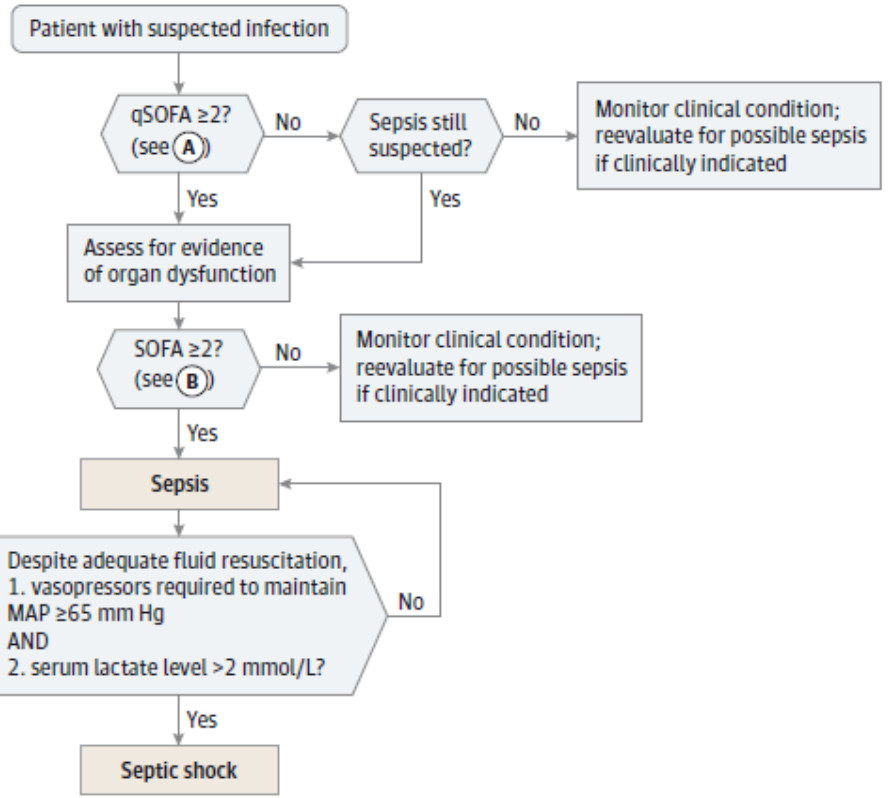
Clinical Review & Education

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

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



A qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables

- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

Clinical Review & Education

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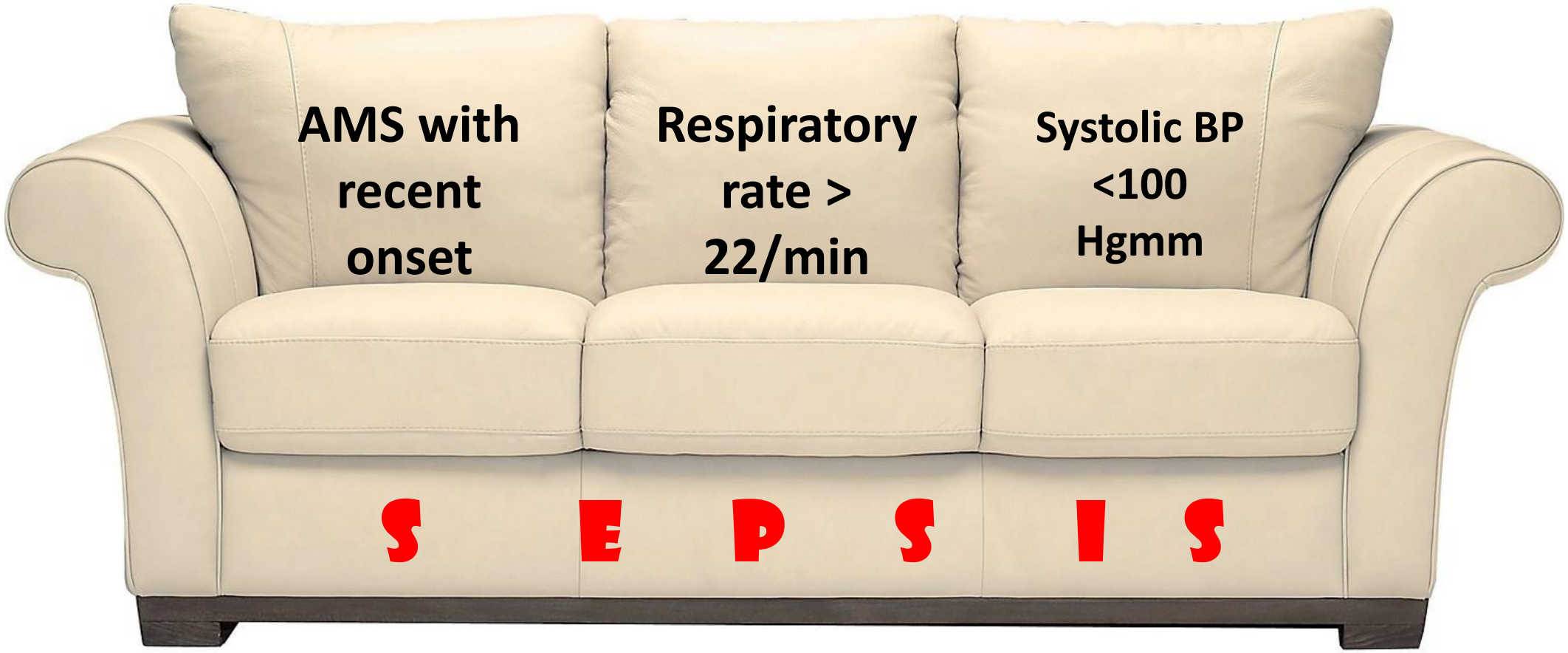
qSOFA


AMS with recent onset
Respiratory rate > 22/min
Systolic BP <100 Hgmm
S E P S I S

The task force focused on adult patients yet recognizes the need to develop similar updated definitions for pediatric populations and the use of clinical criteria that take into account their age-dependent variation in normal physiologic ranges and in patho-physiologic responses.

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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Surviving Sepsis

J. Sedation/Analgesia/Drug Toxicities

1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis (grade 1D).

2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events (grade 1C).

K. Glycemic Control

1. Control hyperglycemia using a similar target as in adults ≤ 180 mg/dL. Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant (grade 2C).

L. Diuretics and Renal Replacement Therapy

1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 10% total body weight fluid overload (grade 2C).

M. Deep Vein Thrombosis Prophylaxis

No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

N. Stress Ulcer Prophylaxis

No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis.

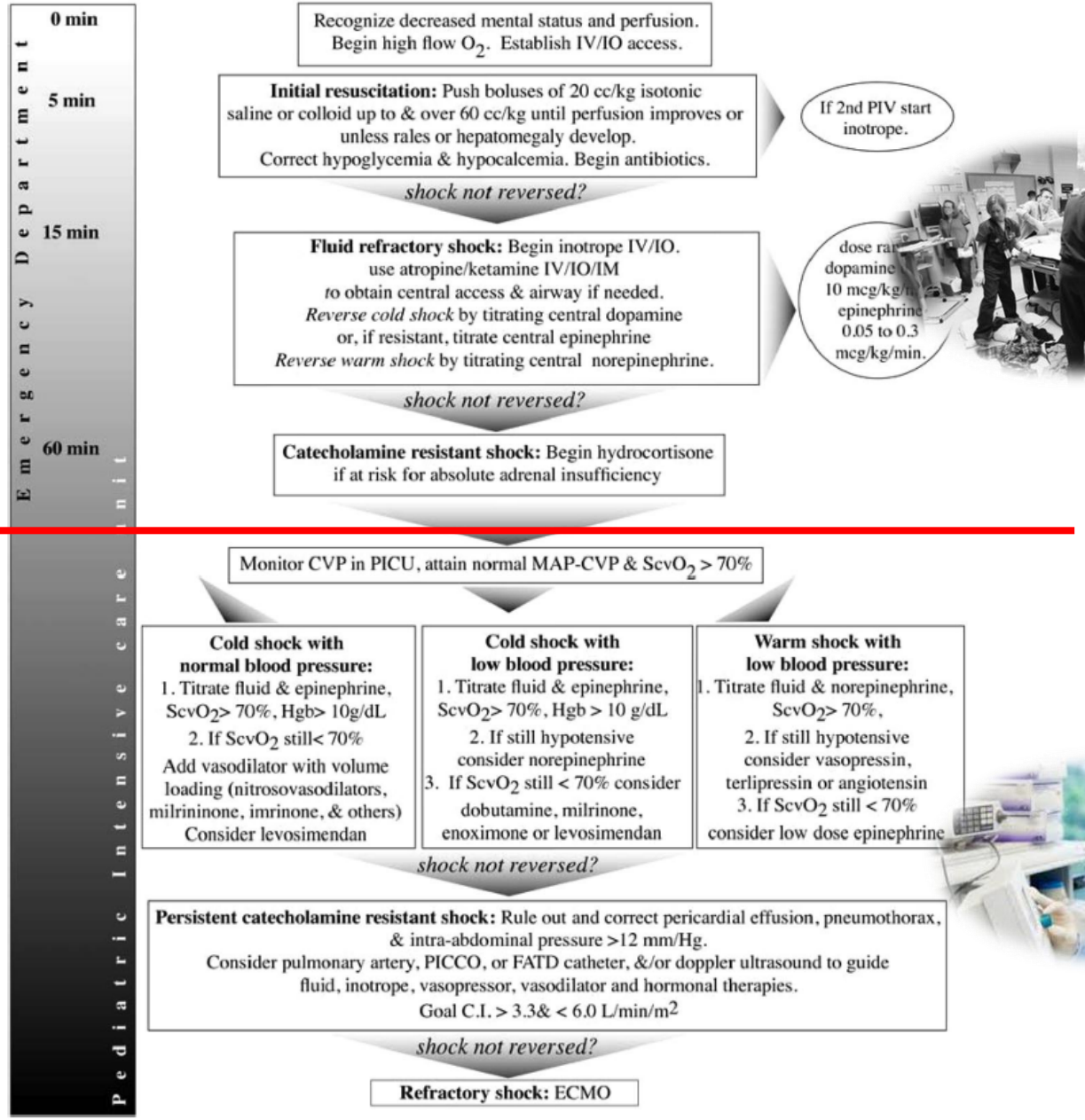
O. Nutrition

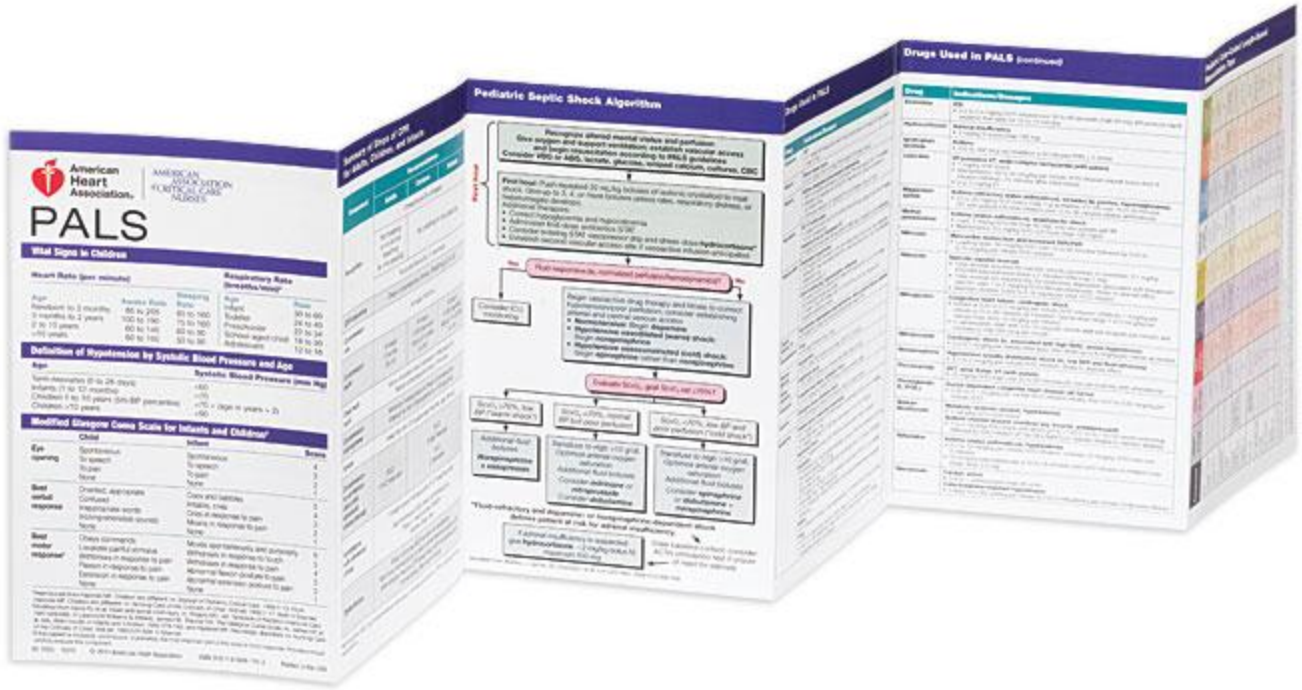
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

MANAGEMENT OF PAEDIATRIC SEPSIS
ANAESTHESIA TUTORIAL OF THE WEEK 278

28TH JANUARY 2013

Dr Erica Dibb-Fuller, Dr Timothy Liversedge.
Great Ormond Street Hospital, UK.
Correspondence to ericadibbfuller@gmail.com




American Heart Association.
AMERICAN ASSOCIATION OF CRITICAL-CARE NURSES
PALS
Vital Signs in Children
Definition of Hypotension by Systolic Blood Pressure and Age
Modified Glasgow Coma Scale for Infants and Children*
Pediatric Septic Shock Algorithm
Drugs Used in PALS (continued)

0-5 minutes

Signs of poor perfusion

- Decreased (altered) mental status
- Cold extremities
- Delayed CRT
- Weak pulses, differential central and peripheral pulses
- Low urine output (if measured)
- Hypotension or low BP – age dependent

Assess ABCs

- Provide 100% oxygen at high flow rate (15L)
- Early intubation in neonates and infants
- Respiratory support, including mechanical ventilation

Establish IV access and start monitoring

- 2 large-bore peripheral IVs or IOs
- Blood sampling: blood gas, lactate, glucose, ionized calcium, FBC, cultures

http://emedicine.medscape.com/article/2072410-overview

5-15 minutes

Fluid and electrolyte resuscitation

Push 20 mL/kgcrystalloid IV/IO over 5-20min
Repeat 20 mL/kg bolus push of fluid (up to 60 mL/kg) until clinical symptoms improve or patient develops respiratory distress/rales/ hepatomegaly
May continue to require additional fluid above 60 mL/kg (fluid refractory)
Fluid needs may approach 200 mL/kg in warm septic shock (warm extremities, flash capillary refill)

Correct hypoglycemia:

Glucose levels in hypoglycemia
Glucose dosage: 0.5-1 g/kg IV/IO

Correct hypocalcemia for low ionized calcium:

Calcium gluconate 100 mg/kg IV/IO (max 2g) PRN
Calcium chloride 20 mg/kg IV/IO PRN

http://emedicine.medscape.com/article/2072410-overview

5-60 minutes

Infection control (5-60min)

Immediate considerations:
•Administer antibiotics immediately after cultures obtained (blood, urine, +/- CSF/ sputum)
•Do not delay antibiotics to wait for cultures; initial antibiotics should be given within 1h

***General treatment recommendations*:**
•Empiric therapy should be used for unknown etiology of sepsis;
•Tailoring of therapy to address suspected pathogens or to achieve adequate drug penetration may be necessary;
•Broader initial coverage may be needed for initial stabilization
•Dosing varies by age and weight (see specific recommendations and dosages immediately below)

Duration of therapy:
•Determined by ultimate source of infection; 7-10d is typically sufficient
•Above regimens may be empiric therapy for 48-72h, until cultures and sensitivities are known, so as to accurately tailor treatment
•If culture-negative sepsis, antibiotic choice and duration determined by severity of presentation and most likely pathogen
•Infectious disease consultation may be necessary

http://emedicine.medscape.com/article/2072410-overview

15-60 minutes

Fluid-refractory shock (persisting after 60 mL/kg fluid)

CVP, vasopressors

Shock persists following vasopressor initiation

Fluid, CVP, $ScvO_2$

Fluid refractory and vasopressor-dependent shock

Hydrocortisone 2 mg/kg

Continued shock

PiCCO, ECMO

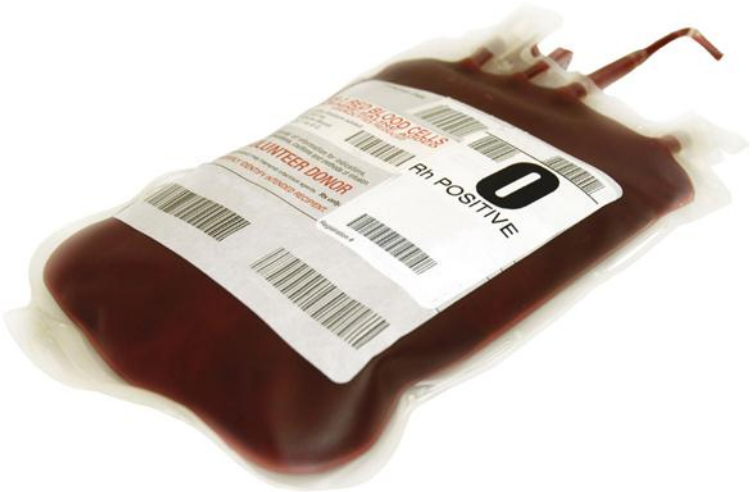
http://emedicine.medscape.com/article/2072410-overview

Supplemental treatment

Blood transfusion considered for Hb < 100 g/L (ideal threshold for transfusion unknown)

Optimize oxygenation through ventilation

IV immunoglobulin can be considered (?)



http://emedicine.medscape.com/article/2072410-overview

Therapeutic endpoints

Heart rate normalized for age

Capillary refill < 2sec

Normal pulse quality

No difference in central and peripheral pulses

Warm extremities

Blood pressure normal for age

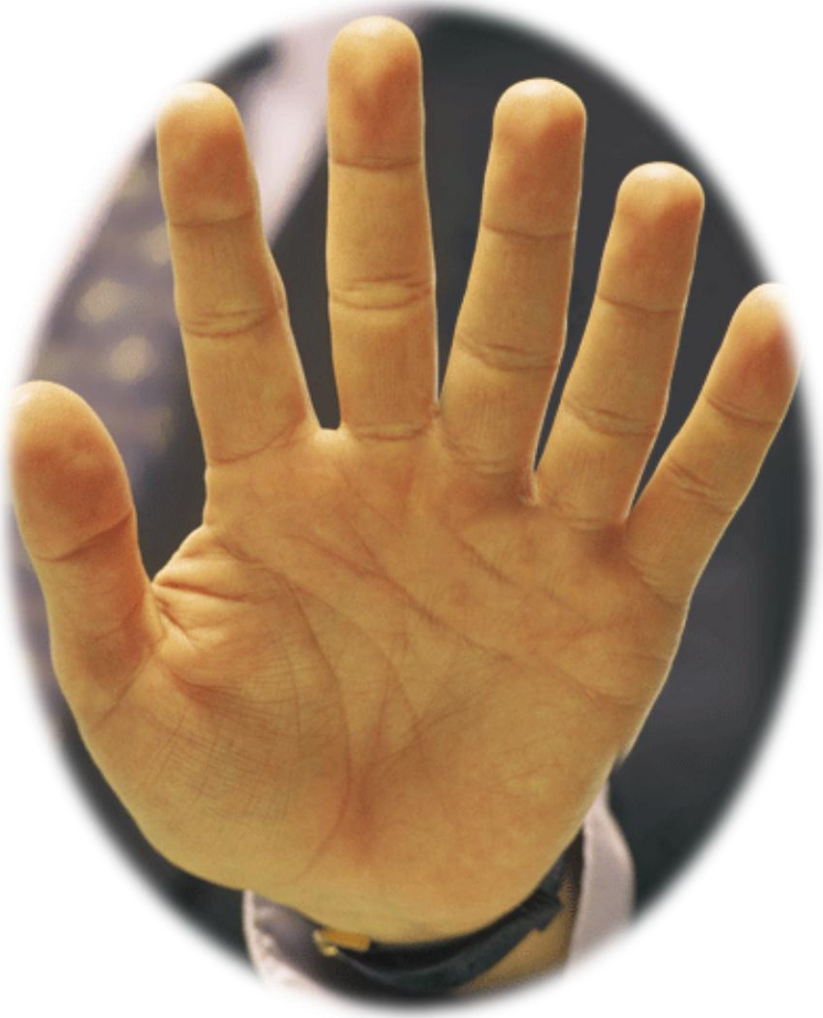
Urine output >1 mL/kg/h

Normal mental status

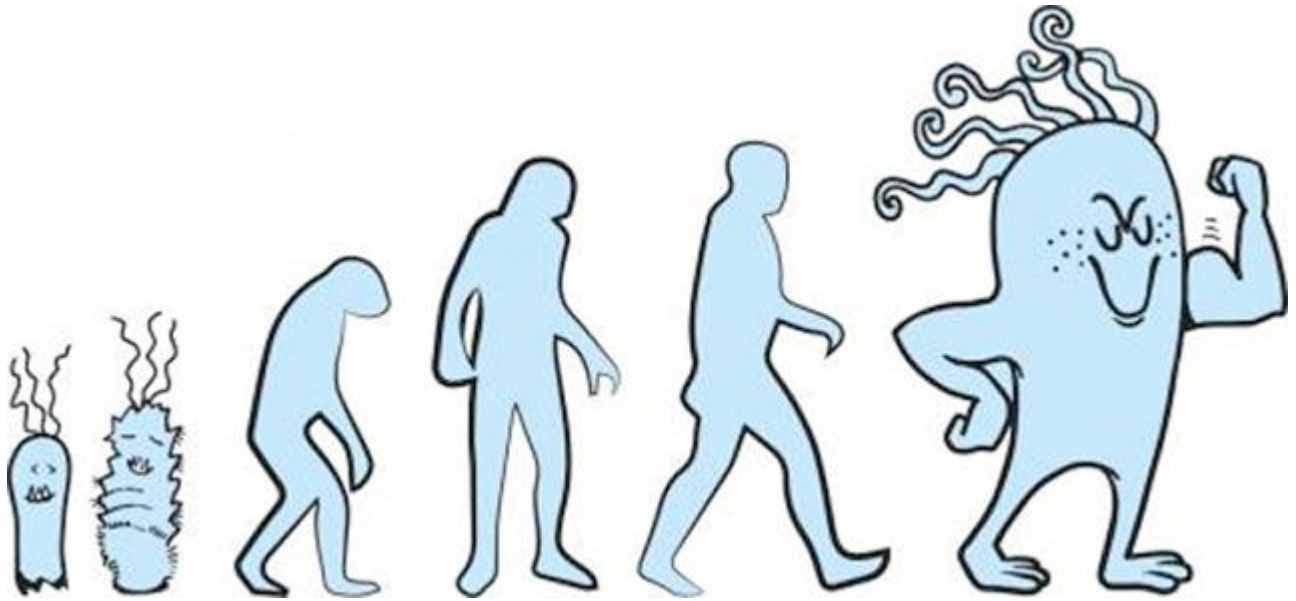
CVP >8 mmHg

http://emedicine.medscape.com/article/2072410-overview

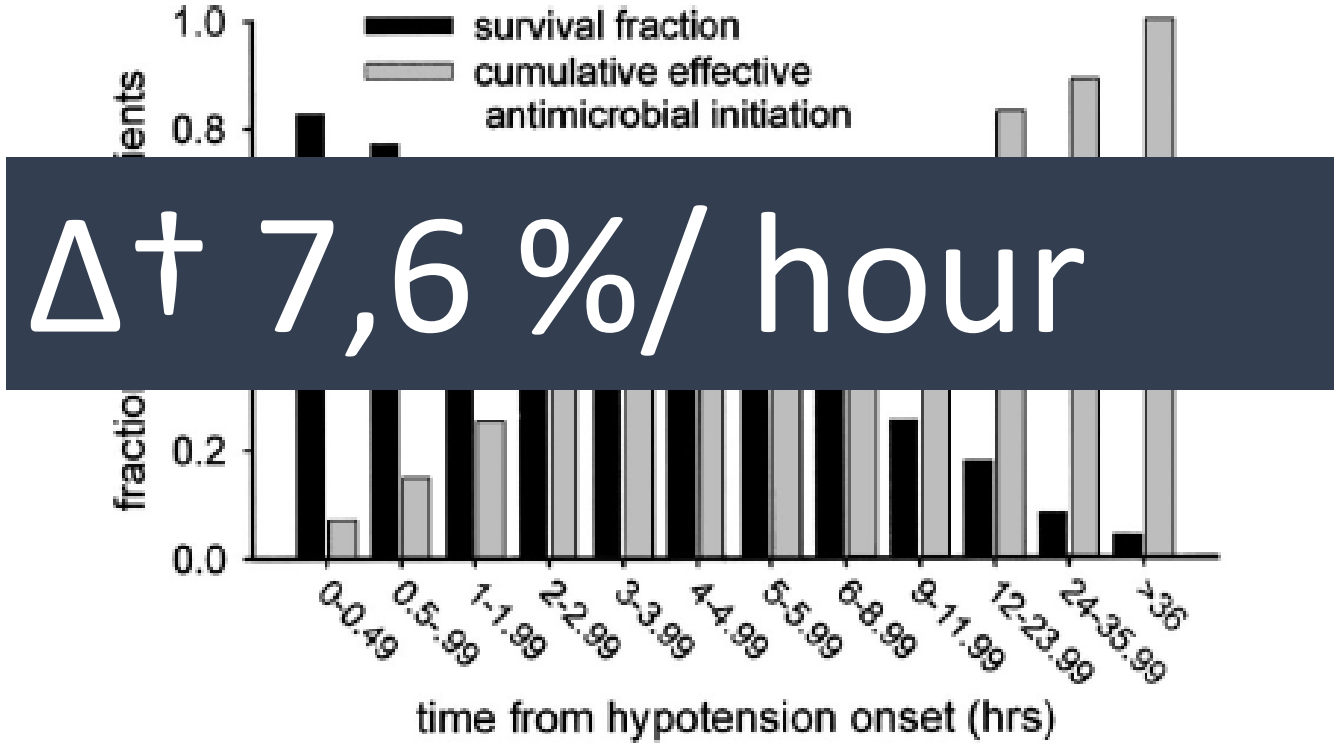
SEPIS SIX



1. Deliver high-flow oxygen.
2. Take blood cultures.
3. Administer empiric intravenous antibiotics.
4. Measure serum lactate and send full blood count.
5. Start intravenous fluid resuscitation.
6. Commence accurate urine output measurement.



Problems with delay

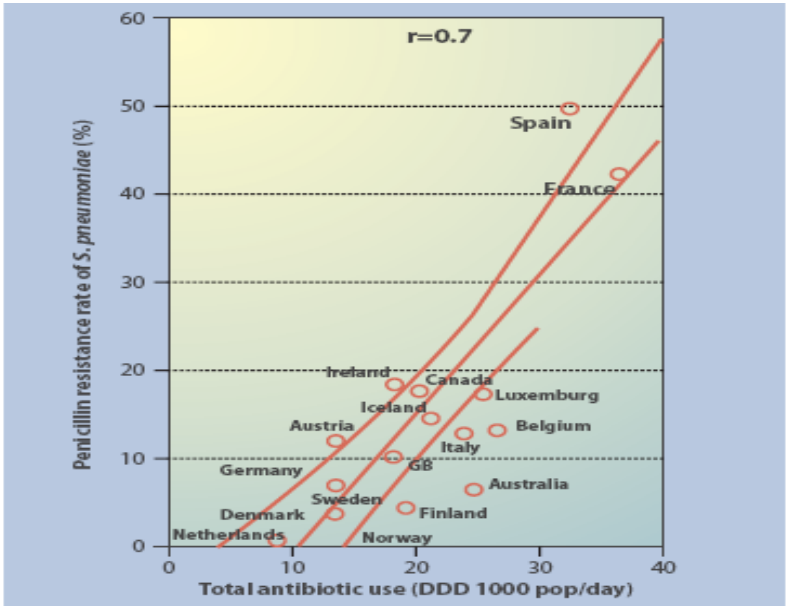


Δ† 7,6 %/ hour

Kumar A, et al. *Crit Care Med* 2006; 34: 1589-96

Antibiotics: remedies with controversy and confusion

Problems with resistance



Albrich W, et al. *Emerg Infect Dis* 2004; 10: 514-517

Increased rate of fungal infections after 7 days.
Increased polyresistance after 10 days.

Marchetti O et al. *Clin* Infect *Dis* 2004;38:311-320

Carlet *et al. Critical Care* 2012, 16:145
http://ccforum.com/content/16/4/145

CRITICAL CARE

EDITORIAL

The Barcelona Declaration from the World Alliance against Antibiotic Resistance: engagement of intensivists

Jean M Carlet*[1], Antonio Artigas[2], Michael S Niederman[3] and Antoni Torres[4], on behalf of World Alliance against Antibiotic Resistance

- Microorganisms resistant to almost every antibiotic are already present in the ICUs of many countries, requiring the use of old and toxic antibiotics such as colistin
- **No new antibacterial agent active against Gram-negative bacteria is expected in the next 5 years**
- The European Centre for Diseases Control estimate is that 25,000 patients in Europe might die from infections due to resistant organisms every year

„We engage ourselves to use antibiotics wisely, only when necessary, and to systematically re-evaluate therapy at day 2 or 3 of therapy. This last point is absolutely key for the success of the programme."

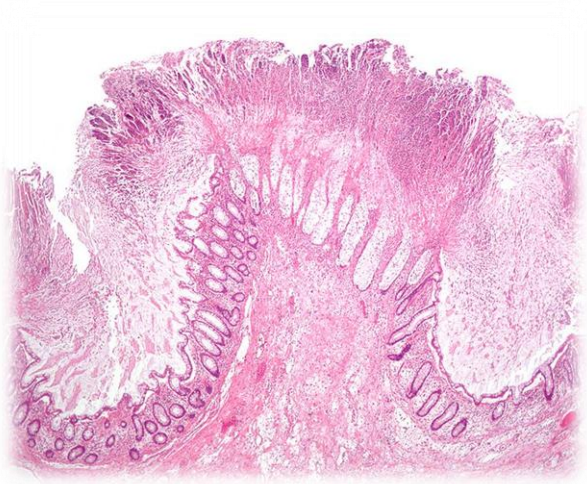
Antibiotics: remedies with controversy and confusion

Problems with AB associated colitis

Especially with amoxicillin, cephalosporins and clindamycin

Incidence: 97 hospitals across 34 European countries, the incidence of *C. diff* in hospitalized patients was 41 per 100,000 patient-days[1]

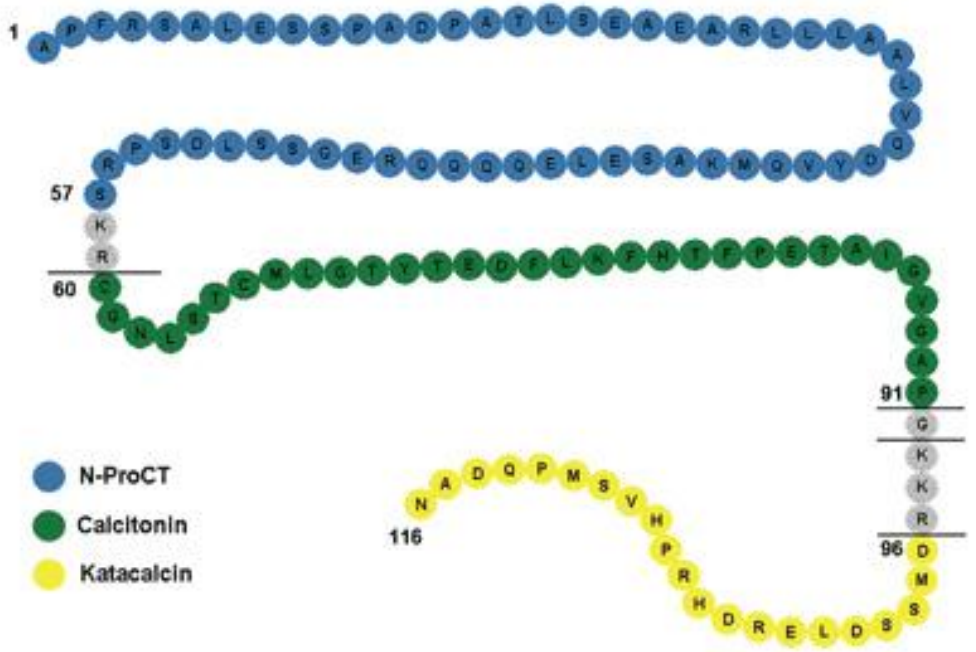
Treatment: metronidazol+vancomycin



[1] Bauer MP et al: *Lancet*. 2011; 377(9759):63-73

Problems with cost

Why do we need PCT?



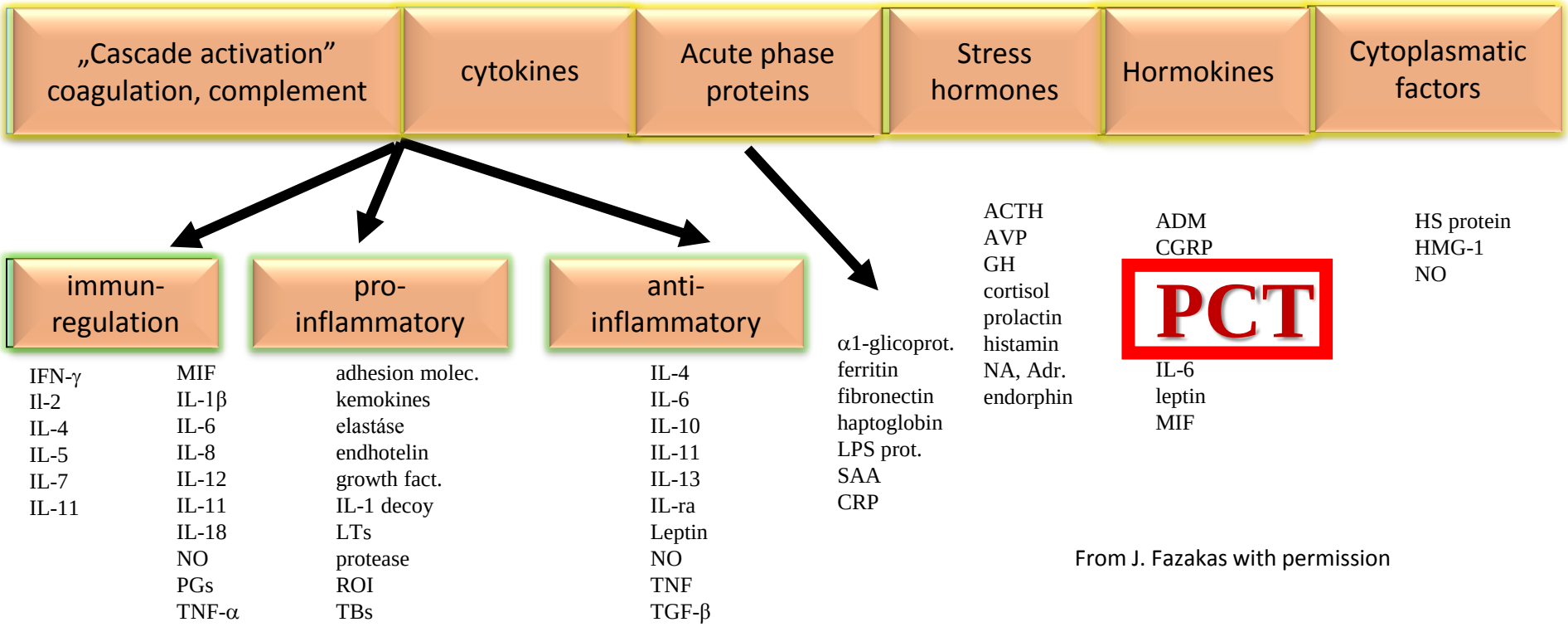
https://www.aacc.org/publications/cln/2009/july/Pages/series0709.aspx

Innate inflammatory response:
cell stress, insult, damage, bacteria

PCT

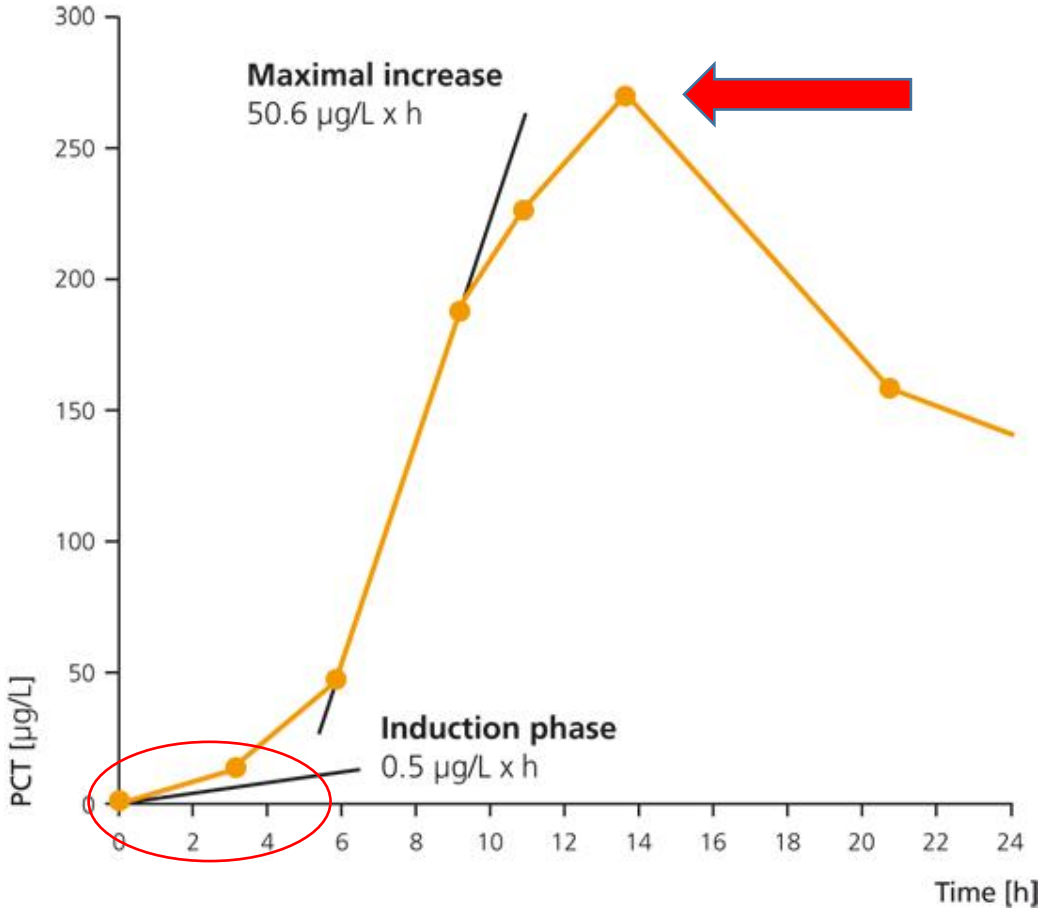
leucocyte, lymphocyte, „endothel", „parenchymal" cells
TLR4, CD14, MD2, mannos-MBL, NOD, NALP, „P" substance

Humoral adaptive response



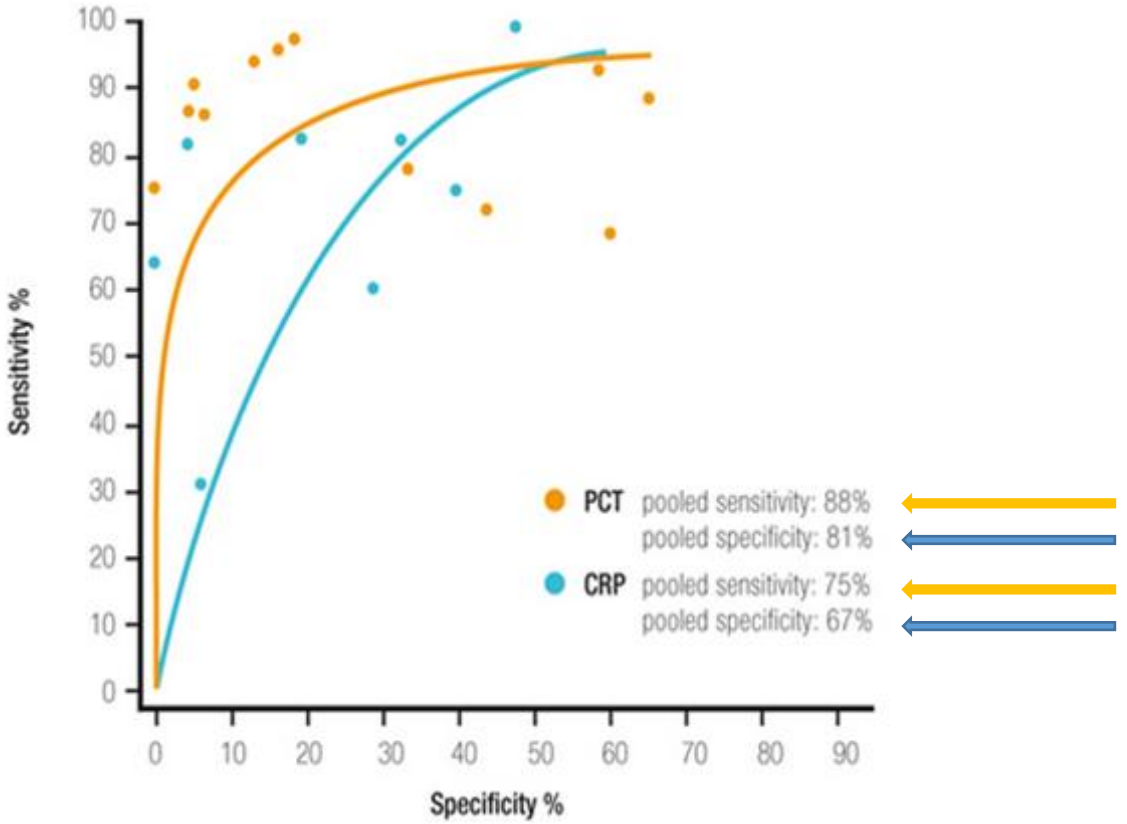
From J. Fazakas with permission

Kinetics of procalcitonin



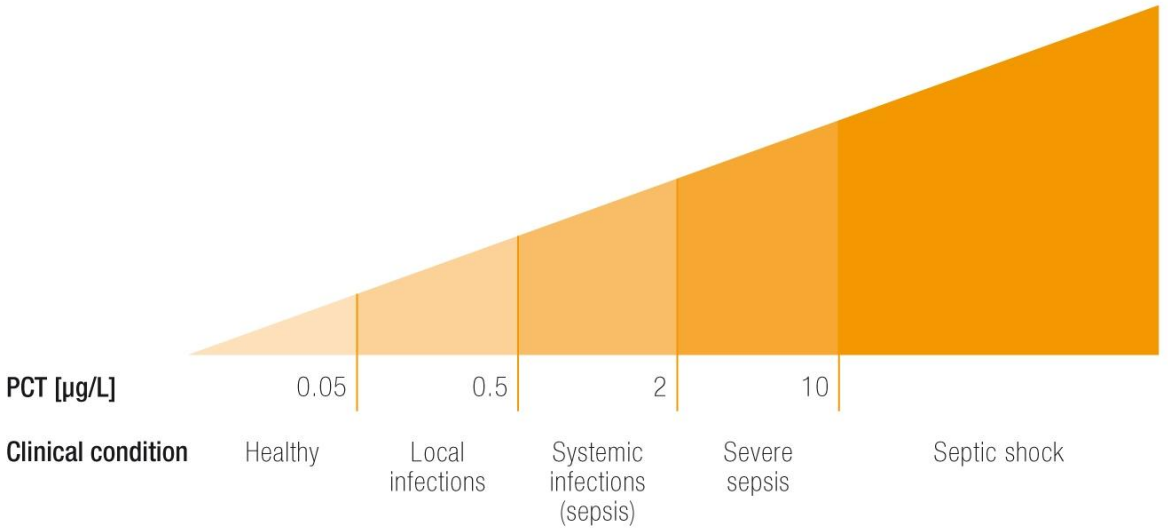
Brunkhorst F.M. et al., *Intens Care Med* 1998,24: 888-892

Why better than CRP? Kinetics.



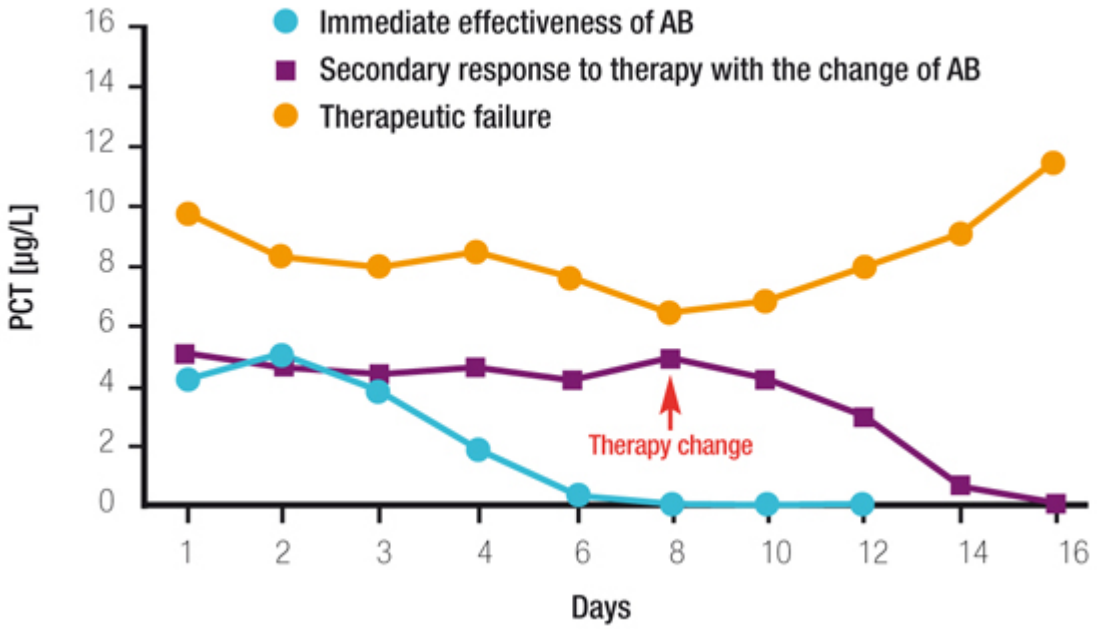
http://www.procalcitonin.com/default.aspx?tree=_2_2

Why better than CRP?
Risk stratification.



http://www.procalcitonin.com/default.aspx?tree=_2_2

Why better than CRP? Therapy guidance.



http://www.procalcitonin.com/default.aspx?tree=_2_2

Clinica Chimica Acta 451 (2015) 215–218

Contents lists available at ScienceDirect

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

Review

Procalcitonin and community-acquired pneumonia (CAP) in children

Bivona Giulia [a], Agnello Luisa [a], Scazzone Concetta [a], Lo Sasso Bruna [a], Bellia Chiara [a], Ciaccio Marcello [a,b,*]

[a] Sezione Biochimica Clinica e Medicina Molecolare, Dipartimento di Biopatologia e Biotecnologie Mediche, Università degli studi di Palermo, Italy
[b] UOC Medicina di Laboratorio-Corelab, AOUP Policlinico P. Giaccone, Palermo, Italy

Thorough literature search
PCT and CAP etiology
PCT and disease severity
PCT and AB administrarion
PCT vs other markers

Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir

August 2015, Volume: 7, Issue: 4, Pages: 1190-1195, DOI: 10.14661/2015.1190-1195

Predictive values for procalcitonin in the diagnosis of neonatal sepsis

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Table 3. The sensitivity, the specificity, PPV, and NPV of PCT and CRP

	Cut-off value	Sensitivity	Specificity	PPV	NPV
CRP	12 mg/l	72.9%	100%	93.2%	69.7
Procalcitonin	1.1 pg/ml	80%	85.7%	84.4%	81.1%

CRP= C-reactive protein, PPV= Positive predictive value, NPV= Negative Predictive value

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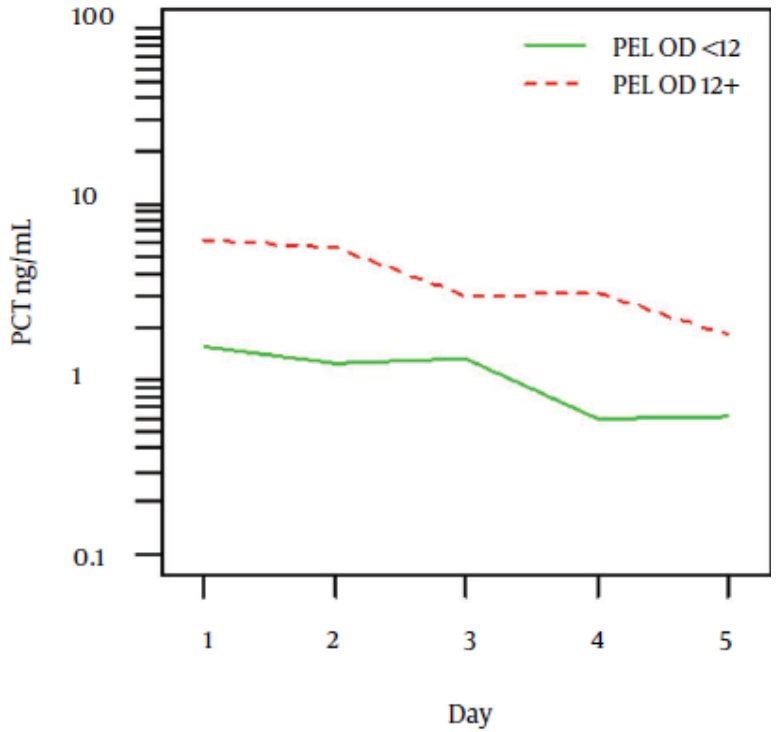
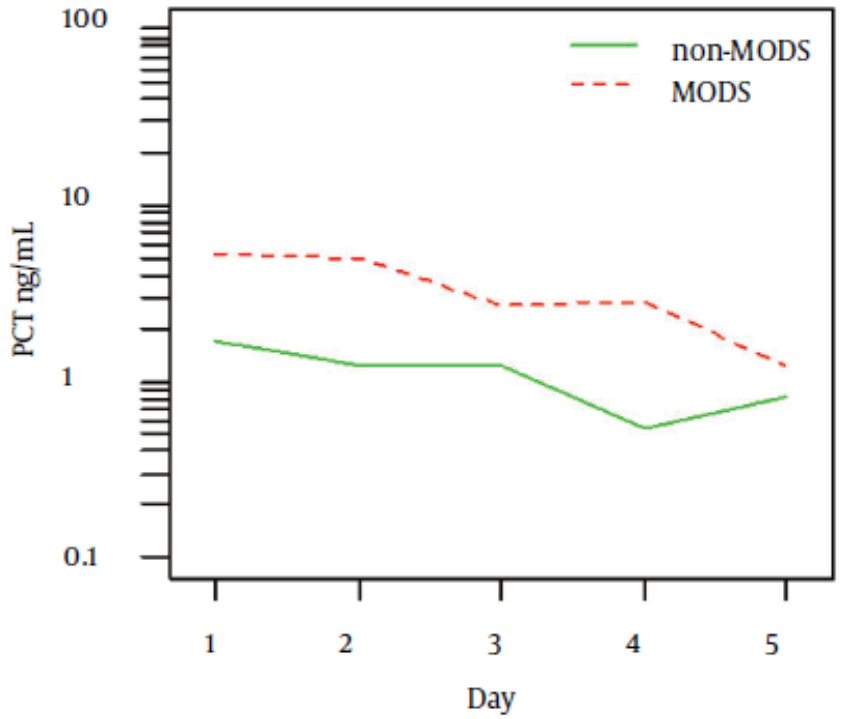
Procalcitonin Biomarker Kinetics to Predict Multiorgan Dysfunction Syndrome in Children With Sepsis and Systemic Inflammatory Response Syndrome

Jiri Zurek [1,*]; Martin Vavrina [1]

Organ system and variable	Points assigned			
	0	1	10	20
Neurologic*				
Glasgow coma score	12–15	7–11	4–6	3
	and		*or*	
Pupillary reaction	Both reactive		Both fixed	
Cardiovascular				
Heart rate, beats/min				
< 12 years	≤ 195		> 195	
≥ 12 years	≤ 150		> 150	
	and		*or*	
Systolic blood pressure, mm Hg				
< 1 mo	> 65		35–65	< 35
≥ 1 mo–< 1 yr	> 75		35–75	< 35
≥ 1 yr–< 12 yr	> 85		45–85	< 45
≥ 12 yr	> 95		55–95	< 55
Renal				
Creatinine, µmol/L (mg/dL)				
< 7 d	< 140 (< 1.59)		≥ 140 (≥ 1.59)	
≥ 7 d–< 1 yr	< 55 (< 0.62)		≥ 55 (≥ 0.62)	
≥ 1 yr–< 12 yr	< 100 (< 1.13)		≥ 100 (≥ 1.13)	
≥ 12 yr	< 140 (< 1.59)		≥ 140 (≥ 1.59)	
Respiratory				
PaO_2:FiO_2 ratio, mm Hg	> 70		≤ 70	
	and		*or*	
$PaCO_2$, mm Hg (kPa)	≤ 90 (≤ 11.7)		> 90 (> 11.7)	
	and			
Mechanical ventilation†	No ventilation	Ventilation		
Hematologic				
Leukocyte count, × 10^9/L	≥ 4.5	1.5–4.4	< 1.5	
	and	*or*		
Platelet count, × 10^9/L	≥ 35	< 35		
Hepatic				
Glutamic oxaloacetic transaminase, IU/L	< 950	≥ 950		
	and	*or*		
Prothrombin time, % of standard (international normalized ratio)	> 60 (< 1.40)	≤ 60 (≥ 1.40)		

Note: FiO_2 = fraction of inspired oxygen, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood, PaO_2 = partial pressure of oxygen in arterial blood.
*For the Glasgow coma score, use the lowest value. If the patient is sedated, record the estimated coma score before sedation. Assess the patient only with known or suspected acute central nervous system disease. For pupillary reactions, nonreactive pupils must be > 3 mm; do not assess after iatrogenic pupillary dilatation.
†The use of mask ventilation is not considered to be mechanical ventilation.





Eur J Emerg Med. 2014 Apr;21(2):112-7. doi: 10.1097/MEJ.0b013e328361fee2.

Procalcitonin as a biomarker for early sepsis in the emergency department.

Hicks CW, Engineer RS, Benoit JL, Dasarathy S, Christenson RH, Peacock WF.

- proadrenomedullin (MRproADM)
- midregional proatrial natriuretic peptide (MRproANP)
- procalcitonin (PCT)* ✓
- Copeptin
- proendothelin-1 (proET-1)

*median 0.32 ng/ml (IQR 0.19-1.17) vs. 0.18 ng/ml (IQR 0.07-0.54); P=0.04

Multimarker approach

Pierrakos and Vincent *Critical Care* 2010, **14**:R15
http://ccforum.com/content/14/1/R15

CRITICAL CARE

RESEARCH Open Access

Sepsis biomarkers: a review

Charalampos Pierrakos, Jean-Louis Vincent*

Key messages:

- More than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis.
- None has sufficient specificity or sensitivity to be routinely employed in clinical practice (on its own).
- Combinations of several biomarkers may be more effective than single biomarkers, but this requires further evaluation.

Septic shock in children. Is it different than adults?

EGDT?

Albumin vs. crystalloid?

Role of inotropes/vasoactive agents?

Higher metabolic challenge?

Thank you for your attention!