Diagnostická kritéria sepse u dětí a úvodní léčba

Jiří Žurek

Klinika dětské anesteziologie a resuscitace LF MU,
FN Brno

Mortalita sepse u dětí

- všeobecně nižší než u dospělých (2-10%)
- nemocniční mortalita u těžké sepse
  - 2% (zdraví)
  - 8% (chron. nemocní)

- Odetola FO, Gebremariam A, Freed GL: Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. *Pediatrics* 2007; 119:487–494
- Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8

Definice šoku

Septic shock, most commonly a combination of distributive, hypovolemic, and cardiogenic shock, by definition, requires manifestations of decreased organ perfusion.

Roger's Textbook of Pediatric Intensive Care, 4th Edition, 2008 Lippincott Williams & Wilkins

Klinická manifestace

- Zánětlivá triáda
  - horečka
  - tachykardie
  - teplá, zarudlá kůže
- Hypoperfuse
  - alterace vědomí
  - oligo - anurie
  - > CFT– čas tvorby koagula
  - ↓ wide pulse pressure

Warm Shock

Klinická manifestace

- Hypotenze
  - studená a opocená kůže
  - mramorování
  - tachykardie
  - cyanoza
  - hypoxemie
  - acidoza

Cold shock

….early recognition of pediatric septic shock using clinical examination, not biochemical tests

Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine, Crit Care Med. 2009 Feb;37:666-88

Ideální klinická diagnostika předchází

- hypotenzi
- hypotermii nebo hypertermii
- alteraci stavu vědomí
- periferní vazodilataci (warm shock), nebo vazokonstrikci s capillary refill > 2 sec (cold shock).

Kardiovaskulární systém v sepsi

- ↑ HR → ↑ mortality[1]
  kojenci HR <90/min a >160/min
  děti HR <70/min a >150/min

- hypotenze s capillary refill <3s – mortalita 5%
  hypotenze s capillary refill >3s – mortalita 33%

- ↑ SVR – absence nebo slabá periferní pulsace, chladné končetiny, prodloužený capillary refill

- úprava hemodynamických parametrů na základě terapeutických doporučení ACCM/PALS – redukce mortality o 40% [2]

[1] Pollack et al. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16:1110–1116
[2] Carcillo et al. Early shock reversal is associated with reduced childhood neurologic morbidity and mortality.*Pediatrics* 2009; 124:2 500-508

Dýchací aparát v sepsi

- tachypnoe – kompenzace metabolické acidozy
- dyspnoe, cyanoza kůže a sliznic
- intersticiální, alveolární edém
- sepsis induced lung injury (ALI, ARDS)

Suter PM The Lung in sepsis. The Sepsis Text 2002, Part 6, 609-618

CNS v sepsi

- Hippocrates (460-370 B.C.) – vztah mezi systémovým onemocněním a mozkovou dysfunkcí
- zmatenost, dezorientace, třes, myoklonus, křeče,….septická encefalopatie
- sepse ↑ riziko DMO, PMR, zrakového a sluchového postižení [1]

[1] Schlapbach LJ et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extreme premature infants. Pediatrics 2011;128:348-57

Ledviny v sepsi

- oligurie → anurie; vzestup kreatinin, ↓GF
- modified RIFLE criteria in critically ill children with acute kidney injury[1]

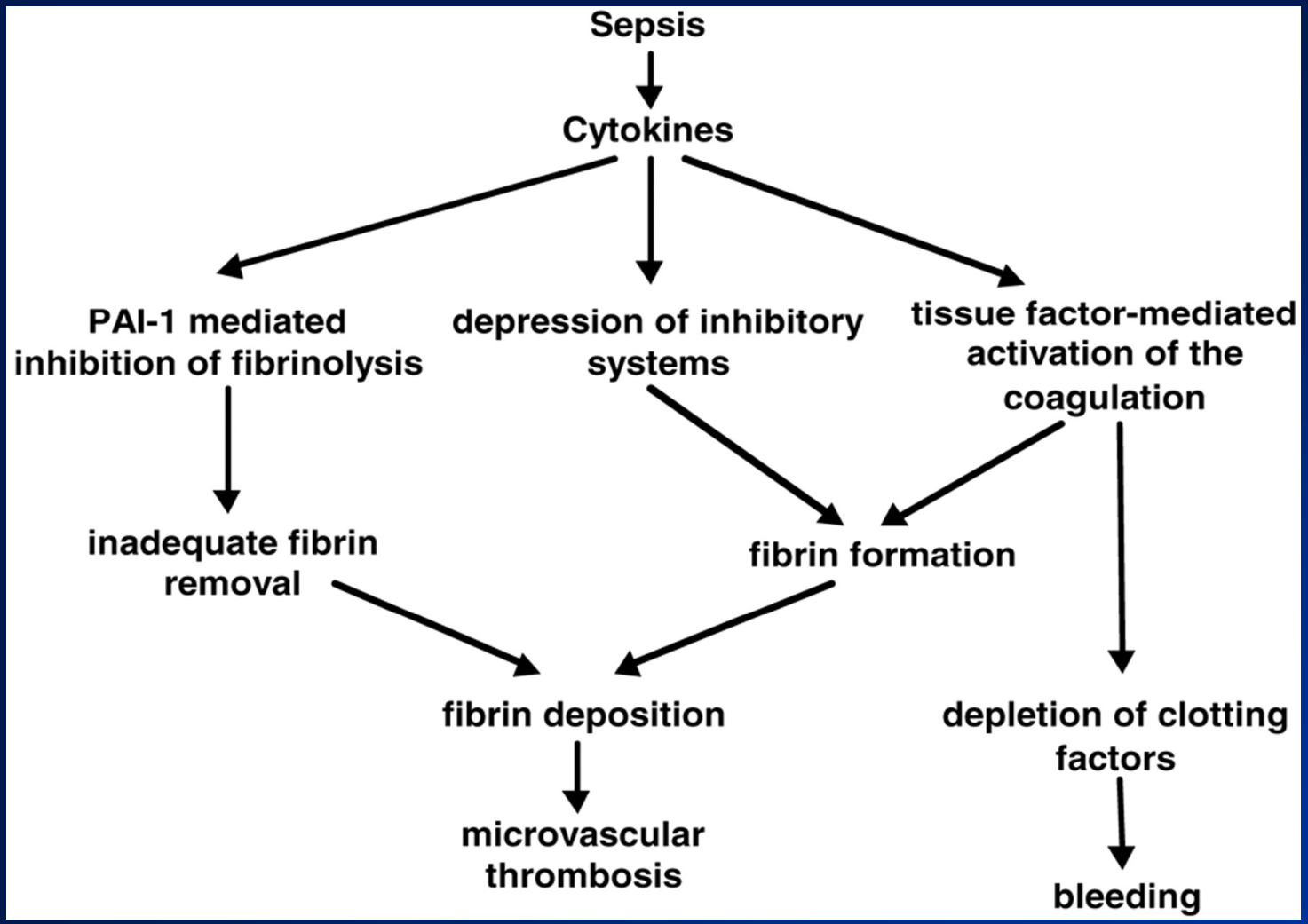
[1] Akcan-Arikan A et al. (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 10:1028–1035

Laboratorní parametry sepse

Specific laboratory tests
Blood, cerebrospinal fluid and urine culture
Direct visualisation of bacteria (Gram stain …..)
Detection of bacterial antigens
Polymerase chain reaction (amplification of bacterial DNA, i.e. 16S rDNA)
Haematological investigations
White blood cell counts, total and differential, platelet count
CRP, procalcitonin, ESR, serum amyloid, other acute phase reactants: haptoglobin, lactoferrin, neopterin, inter-inhibitor proteins (I Ips), lipopolysaccharide-binding protein (LBP), C5a, C5L2, immunoglobulins
Cytokines and receptors
IL-1 , IL-6, IL-8, IL-10
IL-1ra, IL-2rs
IP-10, RANTES, TNF-α, IFN-γ
G-CSF, CSF1, SCF
MIP1-a
sCD14, sICAM-1, CD11b, CD64, CD69, CD25, CD45RO, CD19, CD33, CD66b
Proteomics and genomics

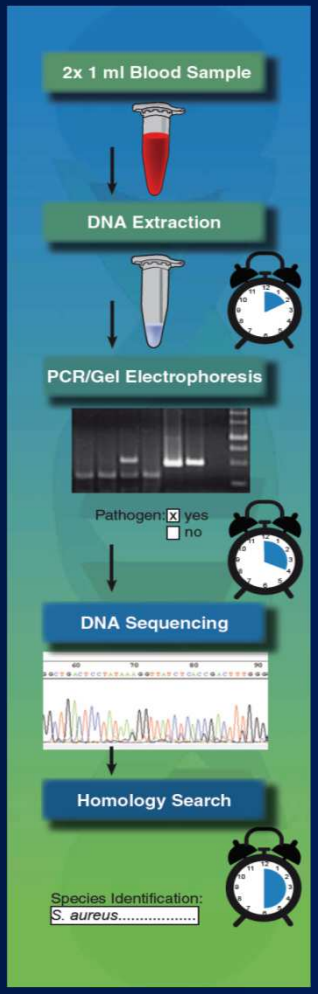
Chirico G et al. Laboratory aid to the diagnosis and therapy of infection in the neonate. Pediatr Rep. 2011 24; 3:e1

Coagulation imbalance during sepsis



Zeerleder S et al. Chest 2005;128:2864-2875

Polymerase Chain Reaction - PCR

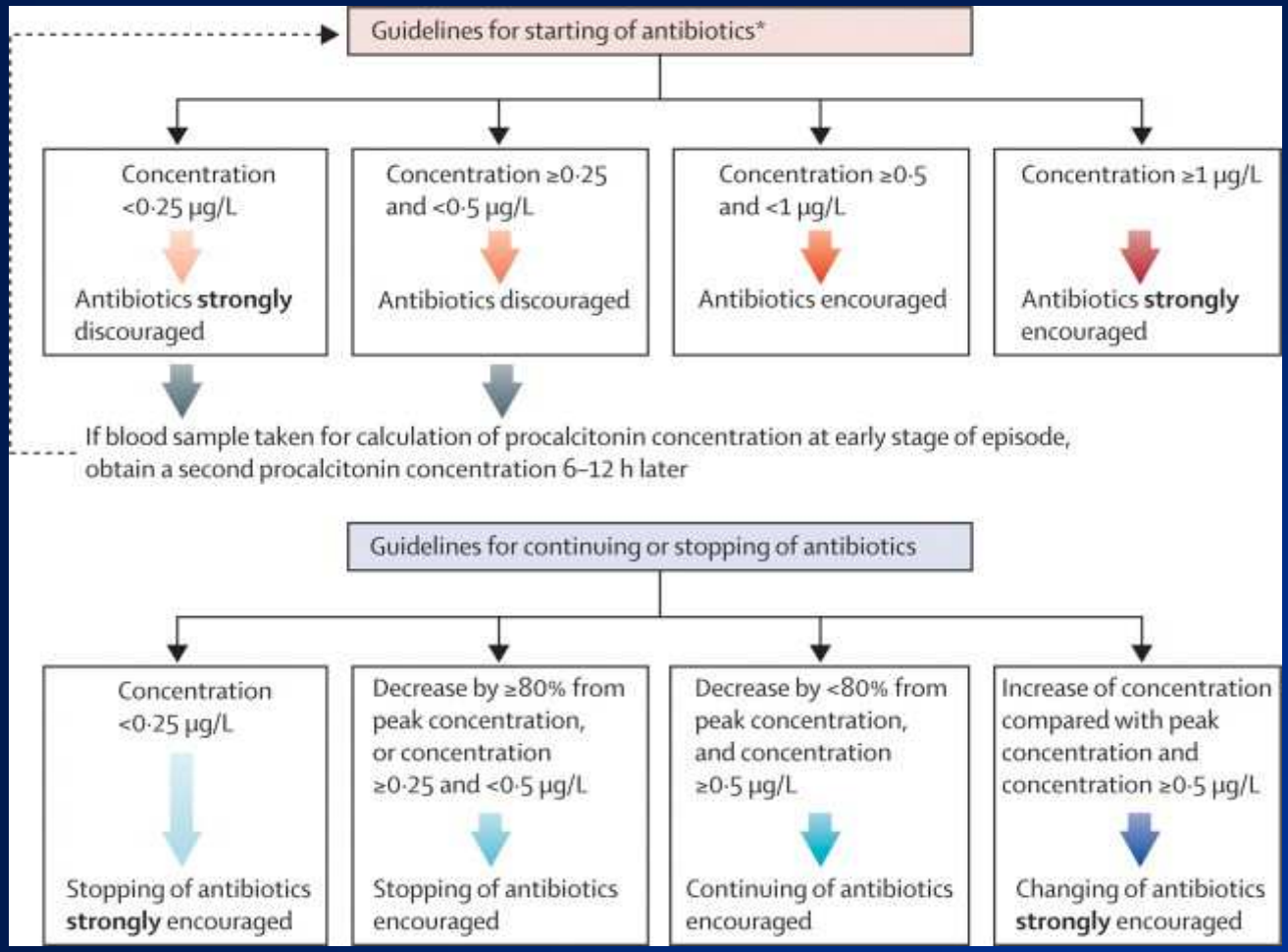


Lucignano B et al. Multiplex PCR Allows Rapid and Accurate Diagnosis of Bloodstream Infections in Newborns and Children with Suspected Sepsis. J Clin Microbiol. 2011;49 :2252-8

Millar M et al. Accuracy of bacterial DNA testing for central venous catheter-associated bloodstream infection in children with cancer. Health Technol Assess 2011 Feb;15:1-114.

Resti M et al. Community-acquired bacteremic pneumococcal pneumonia in children: diagnosis and serotyping by real-time polymerase chain reaction using blood samples. Clin Infect Dis. 2010 51:1042-9.

Procalcitonin



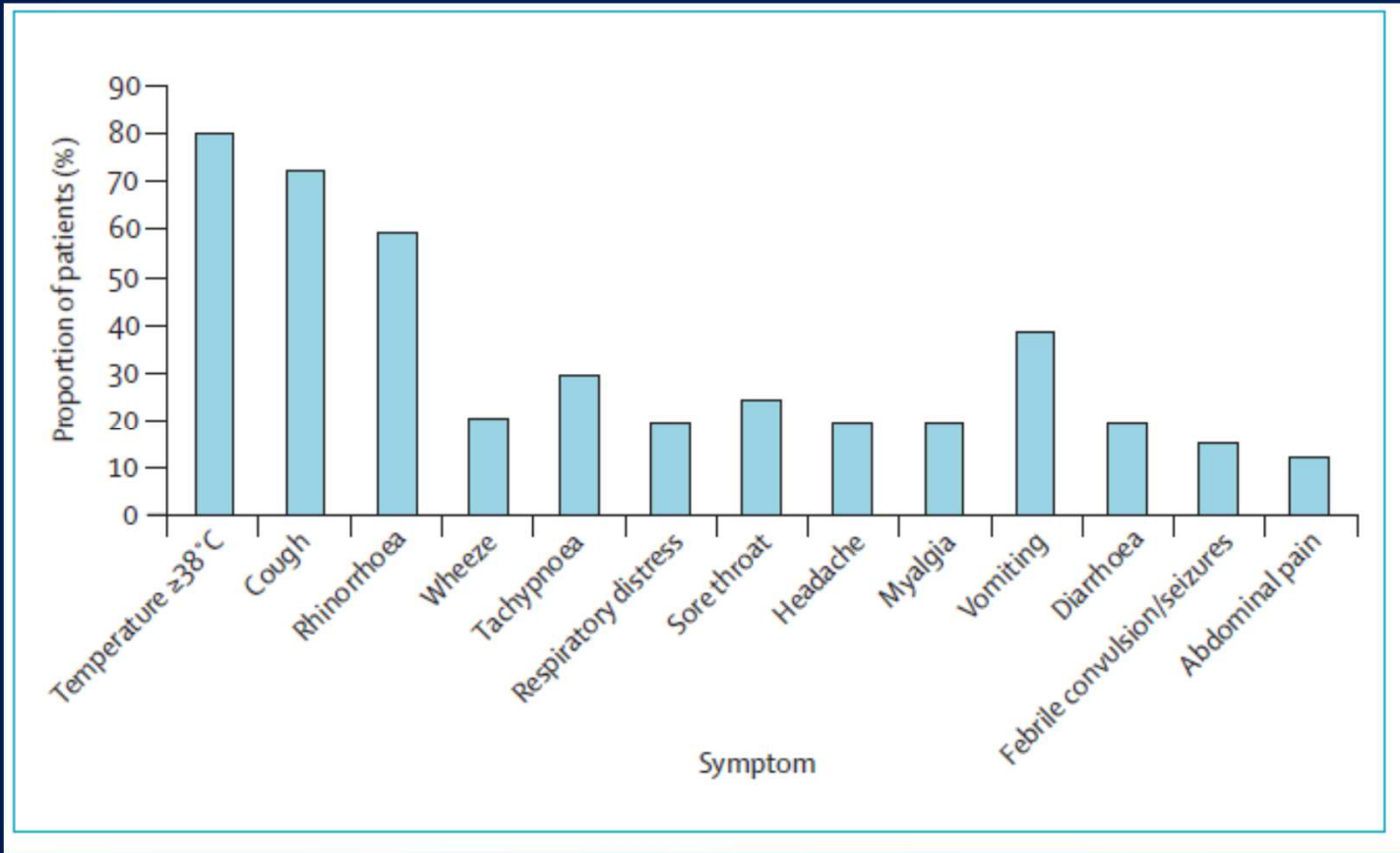
Bouadma L et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010 6:463-74

Respiratory Syncytial Virus (RSV)

- horečka, kašel, tachypnoe, cyanoza, dušnost, chrůpky, „sepsislike presentation“
- stěr z nosohltanu, odsátí sekretu, laváž

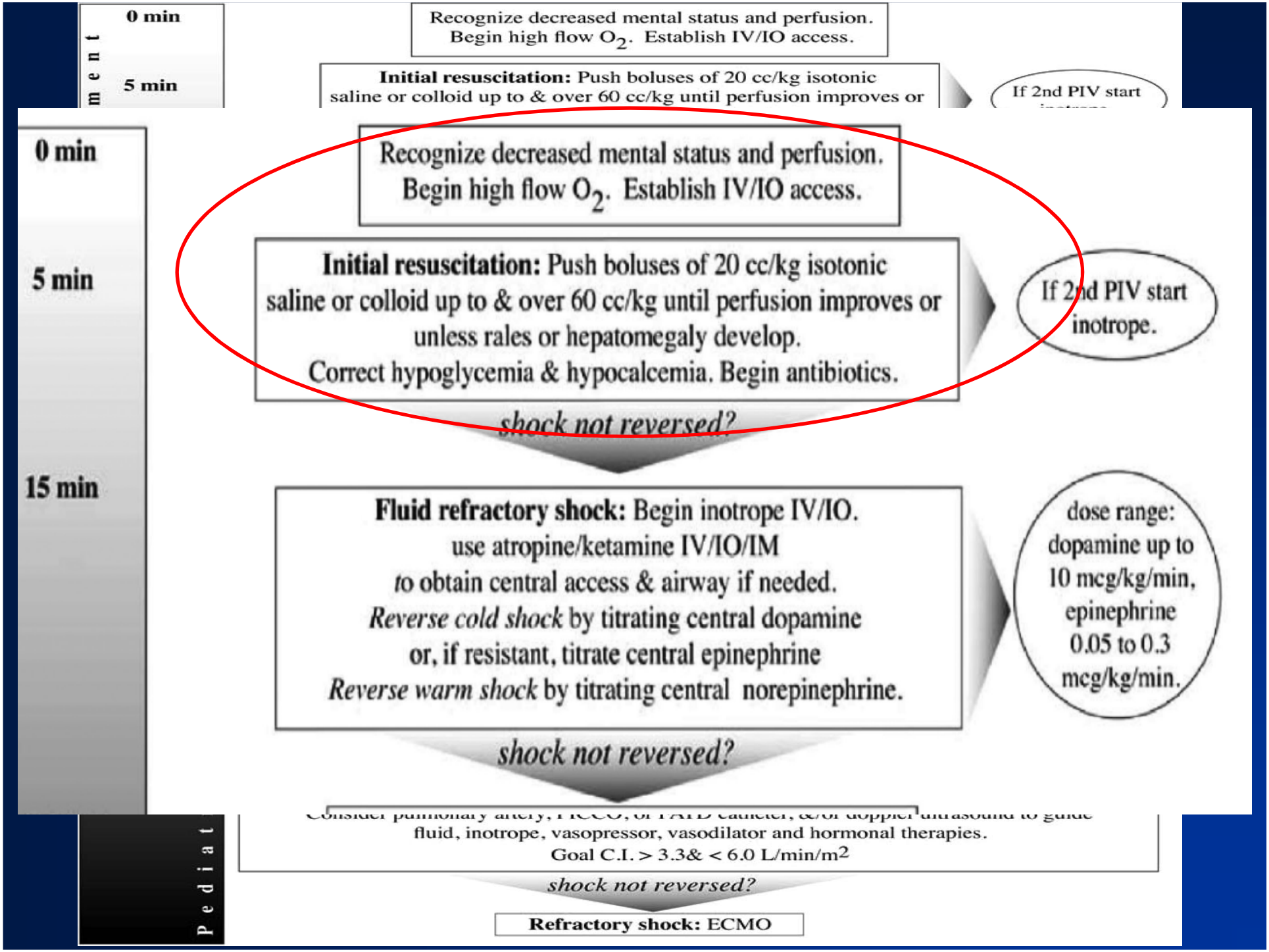
  dg. enzymatická imunoanalýza, detekující protilátky proti RSV

H1N1 u dětí



Lister P et al. Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. Lancet 2009 22;605-7

- rychlé a správné vyhodnocení klinického stavu
- správný odběr materiálu na diagnostiku
- odpovídající terapie a monitorace


0 min
5 min
15 min
Recognize decreased mental status and perfusion.
Begin high flow O_2. Establish IV/IO access.
Initial resuscitation: Push boluses of 20 cc/kg isotonic saline or colloid up to & over 60 cc/kg until perfusion improves or unless rales or hepatomegaly develop.
Correct hypoglycemia & hypocalcemia. Begin antibiotics.
If 2nd PIV start inotrope.
shock not reversed?
Fluid refractory shock: Begin inotrope IV/IO.
use atropine/ketamine IV/IO/IM
to obtain central access & airway if needed.
Reverse cold shock by titrating central dopamine
or, if resistant, titrate central epinephrine
Reverse warm shock by titrating central norepinephrine.
dose range: dopamine up to 10 mcg/kg/min, epinephrine 0.05 to 0.3 mcg/kg/min.
shock not reversed?
fluid, inotrope, vasopressor, vasodilator and hormonal therapies.
Goal C.I. > 3.3& < 6.0 L/min/m2
shock not reversed?
Refractory shock: ECMO

Úvodní resuscitace

- O2 – obličejová maska, nosní brýle, CPAP
- periferní intravenózní, event. intraoseální přístup
- zajištění DC – intubace, UPV →↑ nitrohrudní tlak → hemodynamická nestabilita

- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Iniciální terapeutický cíl

- capillary refill ≤ 2 s
- normální tlak krve v závislosti na věku
- normální AS bez diferencí mezi periferií a centrem
- teplé končetiny, diuréza > 1 ml/kg/hr, normální stav vědomí
- ScvO2 sateurace ≥ 70% a cardiac index mezi 3.3 -6.0 l/min/m2

- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Intensive Care Med (2008) 34:1065–1075
DOI 10.1007/s00134-008-1085-9

PEDIATRIC ORIGINAL

Cláudio F. de Oliveira
Débora S. F. de Oliveira
Adriana F. C. Gottschald
Juliana D. G. Moura
Graziela A. Costa
Andréa C. Ventura
José Carlos Fernandes
Flávio A. C. Vaz
Joseph A. Carcillo
Emanuel P. Rivers
Eduardo J. Troster

ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation

ScvO2 goal-directed therapy >70%
- nižší mortalita (28-day mortality 11.8% vs. 39.2%, $p = 0.002$)
- méně nově vzniklých orgánových dysfunkcí ($p = 0.03$)

ScvO2 goal-directed therapy >70% vyžaduje během prvních 6h
- více krystaloidů 28 (20–40) vs. 5 (0–20) ml/kg; $p < 0.0001$
- více krevních transfuzí 45.1% vs. 15.7%; $p = 0.002$)
- větší inotropní podporu 29.4% vs. 7.8%; $p = 0.01$)

Úvodní ATB terapie

- podání ATB do 1hod od doby dg. těžké sepse
- odběr hemokultury před podáním ATB; bez zpoždění podání ATB
- výběr ATB dle doporučení místního ATB střediska
- i.m., per os podání při nemožnosti zajistit i.v. vstup
- kontrola zdroje infekce

- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Tekutinová resuscitace – první hodina

- **<u>začátek rychlý bolus 20ml/kg :</u>**

  - izotonický krystaloid nebo 5% albumin
  - přetlakovou infuzí nebo „z ruky“
  - titrace - adekvátní TK a akce srdeční
  - kvalitní periferní pulsace, capillary refill
  - úroveň vědomí, diuréza
  - zvýšení dechové práce, šelest, cvalový rytmus (gallop) nebo hepatomegalie– oběhové přetížení!!!.....ionotropní podpora
  - anemie – podání krevní transfuze
  - korekce hypoglykémie a hypokalcémie

- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Tekutinová resuscitace – první hodina

- **<u>iniciální resuscitace většinou vyžaduje 40 - 60ml/kg</u>**

  - non-responders – hemodynamický monitoring
  - malé změny v CVP – lze podat další tekutiny
  - velký objem tekutin není spojen s ↑ ARDS, nebo s edémem mozku

- **<u>capillary leak</u>**
  - → ↑ zvýšená potřeba tekutin; několik dnů

Feltes TF et al. Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall stress analysis. *Crit Care Med* 1994; 22:1647–1659
Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: barriers to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support Guidelines in a pediatric intensive care unit in a developing world

Oliveira CF et al.

Pediatr Emerg Care 2008 Dec;24 :810-5

- 90 pacientů; 83% septický šok, 17% těžká sepse
- 80 pacientů preexistující „severe chronic diseases“
- 20 ml/kg 60 min – mortalita 73%; > 40 ml/kg 33% ($p < 0.05$)

léčba do 30 min. po dg vs. léčba > 60 min. po dg.

↓ mortality o 40% ($p < 0.05$)

Jaké tekutiny?

- **Krystaloidy**

  - 0,9% NaCl, Ringer laktát

  [12]……..balancované roztoky?

- **Koloidy**

  - dextran, želatina, 5% albumin

  [12]……..HES?

- **FFP**

  - korekce PT, APTT

  - hypotenze – vazoaktivní kininy, ↑ koncentrace citrátu

Tekutinová resuscitace – po první hodině

- **perzistentní hypovolemie** [1]
  - capillary leak; několik dní

- **další dodávka tekutin – dosažení optimálních hodnot** [1]
  - perfuzní tlak
  - CVP
  - end-diastolický tlak – ECHO
  - optimalizace tlaku v zaklínění v plicnici (PAWP)
  - CO

[1] Brierley et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Car. Med. 2009 Feb;37(2):666-88

Hemoglobin

- Obsah kyslíku v arteriální krvi: CaO_2 = **Hb** x SaO_2 x 1,39 + 0,03 x PaO_2
- Dodávka (transport) kyslíku: $DO_2 = CO \times CaO_2$

- Koncentrace hemoglobinu

  minimum 100g/l [1][2]

  Hemoglobin > 100g/l – krystaloidy

  Hemoglobin < 100 g/l - transfuze erytrocytů

[1]de Oliveira CF et al: ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008; 34: 1065–1075

[2]Rivers E et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 346:1368–1377

Tekutinová resuscitace – po první hodině

- **při prodlouženém INR**

  - podání čerstvě zmražené plazmy

- **po EGDT → přetížení tekutinami přibližně o 10% → ledviny nejsou schopny tuto tekutinu eliminovat!**

  - použití diuretik event. peritoneální dialýzy nebo kontinuálních eliminačních metod

- **↑ hladina laktátu a vzestup AG**

  - zajistit dostatečnou dodávku kyslíku (ScvO2 > 70%)… Hb > 100 g/l

  - hodnota CI > 3,3 l/min/m2…dostatečnou dodávkou tekutin

    … použitím vasoaktivních látek

- **hodnota glykémie v rozmezí 4,4 – 8,3 mmol/l**

  - izotonický roztok 10% glukózy

  - hyperglykemie …inzulin

Roztoky glukózy < 10% nejsou schopny zajistit dostatečnou dodávku glukózy

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
		no. (%)									
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17
4 Weeks											
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07–1.78)	0.01	1.40 (1.08–1.80)	0.01	1.01 (0.80–1.28)	0.91	1.39 (1.11–1.74)	0.004
Neurologic sequelae — no./total no. (%)‡	22/990 (2.2)	19/996 (1.9)	20/997 (2.0)	0.95 (0.51–1.77)	0.87	1.10 (0.61–2.01)	0.74	1.16 (0.63–2.14)	0.62	1.03 (0.61–1.75)	0.92
Neurologic sequelae or death — no./total no. (%)‡	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04–1.65)	0.02	1.36 (1.08–1.71)	0.008	1.04 (0.84–1.28)	0.71	1.33 (1.09–1.64)	0.005

Acute Management of Dengue Shock Syndrome: A Randomized Double-Blind Comparison of 4 Intravenous Fluid Regimens in the First Hour

Ngo Thi Nhan,[1] Cao Xuan Thanh Phuong,[1,a] Rachel Kneen,[2,3] Bridget Wills,[2,3] Nguyen Van My,[1] Nguyen Thi Que Phuong,[1] Chu Van Thien,[1] Nguyen Thi Thuy Nga,[1] Julie A. Simpson,[2,3] Tom Solomon,[2,3] Nicholas J. White,[2,3] and Jeremy Farrar[2,3]

[1]Dong Nai Paediatric Hospital, Bien Hoa, Dong Nai Province, [2]Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City, Vietnam; and [3]Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Table 1. WHO guidelines for the diagnosis of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

DHF grade	Duration of fever, d	Hemorrhage	Thrombocytopenia: platelets/mm^3	Increased vascular permeability
I	>2, ≤7	Positive tourniquet test only	≤100,000	Plasma leakage[a]
II	>2, ≤7	Spontaneous bleeding[b]	≤100,000	Plasma leakage[a]
III (DSS)	>2, ≤7	Positive tourniquet test and/or spontaneous bleeding[b]	≤100,000	Plasma leakage[a] and circulatory failure with pulse pressure ≤20 mm Hg or hypotension for age
IV (DSS)	>2, ≤7	Positive tourniquet test and/or spontaneous bleeding[b]	≤100,000	Plasma leakage[a] and profound shock with undetectable pulse and blood pressure

Nhan NT et al, *CID* 2001; 32: 204 – 213

Table 3. Effect of treatment group on selected clinical and laboratory parameters.

Outcome variable	Solution administered: All patients (n = 222)	Dextran 70 (n = 55)	Gelatin (n = 56)	Lactate Ringer's (n = 55)	"Normal" saline (n = 56)	P
Primary						
PPRT, h median (range)	0.75 (0.25–7)	0.50 (0.25–3)	0.50 (0.25–2)	0.75 (0.25–7)	0.75 (0.25–3)	.030[a]
PPRT >1 h, no. (%) of patients	21 (9.5)	3 (5.5)	3 (5.4)	11 (20)	4 (7.1)	.022[a]
Mean h ± SD	11.7 ± 5.5	15 ± 6.8	11.4 ± 4	10 ± 4.1	10.3 ± 5.6	.068
Range	1.5–23	2.5–23	3–17	3–16	1.5–23	
Secondary						
Decrease in hematocrit at 1 h, %						
Mean ± SD	8.4 ± 3.8	11.5 ± 3.3	9.7 ± 3.0	5.7 ± 2.8	6.5 ± 2.9	<.001[a]
Range	−2 to 19	2 to 19	0 to 16	−2 to 13	0 to 17	
Decrease in pulse at 1 h, beats/min						
Total volume of iv fluid infused, mL/kg						
Mean ± SD	134.1 ± 20.6	134.3 ± 22.1	135 ± 23.5	134.2 ± 19.9	132.9 ± 16.6	.954
Range	89–212	89–189	93–212	103–182	106–172	
Requirement for dextran after first hour, no. (%) of patients	69 (31.1)	17 (30.9)	15 (26.8)	20 (36.4)	17 (30.4)	.749
Volume of dextran after first hour, mL/kg (n = 69)[b]						
Mean ± SD	28.3 ± 12.7	22.1 ± 6.1	30.7 ± 11.6	33.5 ± 14.3	26.3 ± 14.3	.035[a]
Range	10–69	10–37.5	15–57	15–64	15–69	
Required frusemide, no. (%) of patients	35 (15.7)	8 (14.5)	10 (17.9)	8 (14.5)	12 (21.4)	.328

NOTE. PPRT, pulse pressure recovery time.

[a] Significant P value.

[b] In 6 patients the pulse at presentation with shock was too rapid and weak to count accurately; thus n = 216 for the whole study group (A, 55; B, 56; C, 50; D, 55).

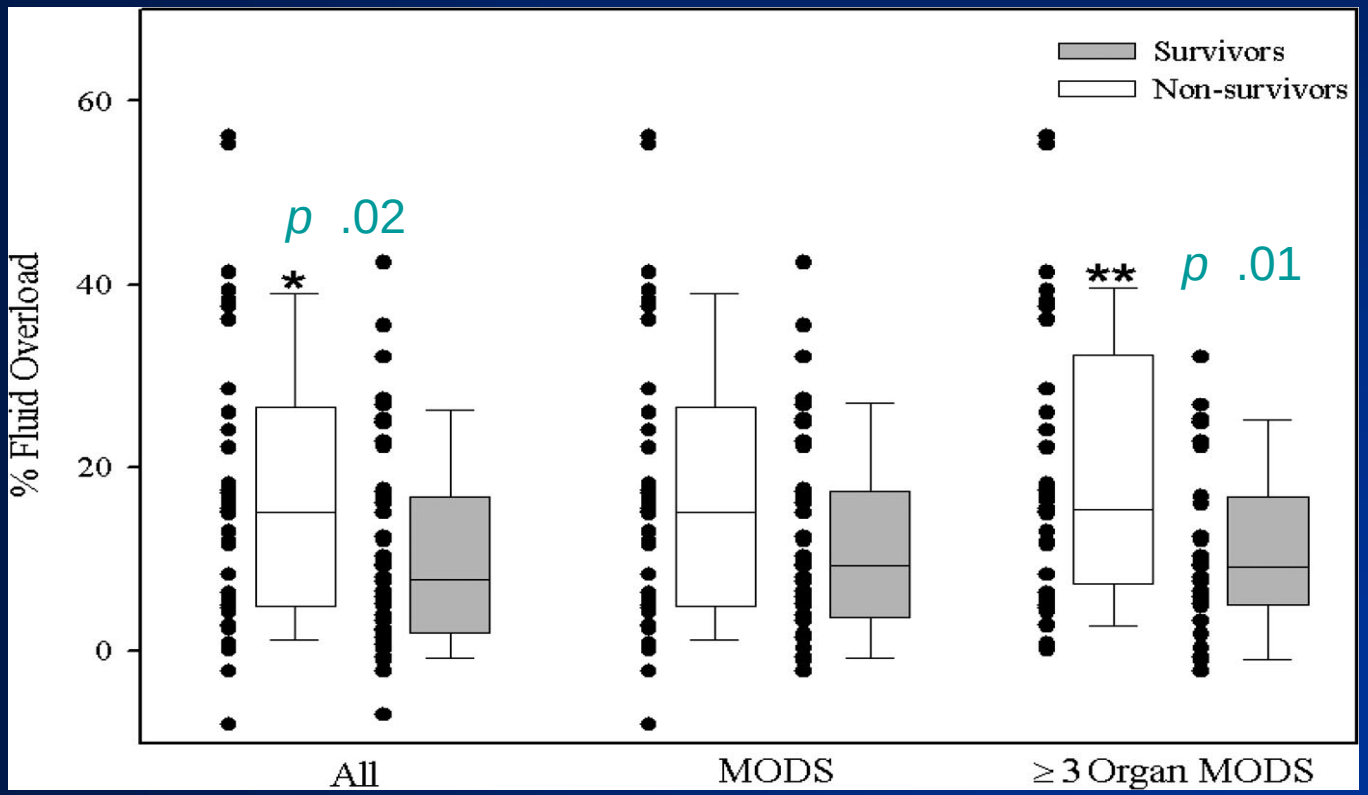
Mortalita 0 %

Nhan NT et al, *CID* 2001; 32: 204 – 213

Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis*

Jason A. Foland, MD; James D. Fortenberry, MD, FAAP, FCCM; Barry L. Warshaw, MD, FAAP; Robert Pettignano, MD, FAAP, FCCM; Robert K. Merritt, MA; Micheal L. Heard, RN; Kris Rogers, RN; Chris Reid, RRT; April J. Tanner, RN; Kirk A. Easley, MS

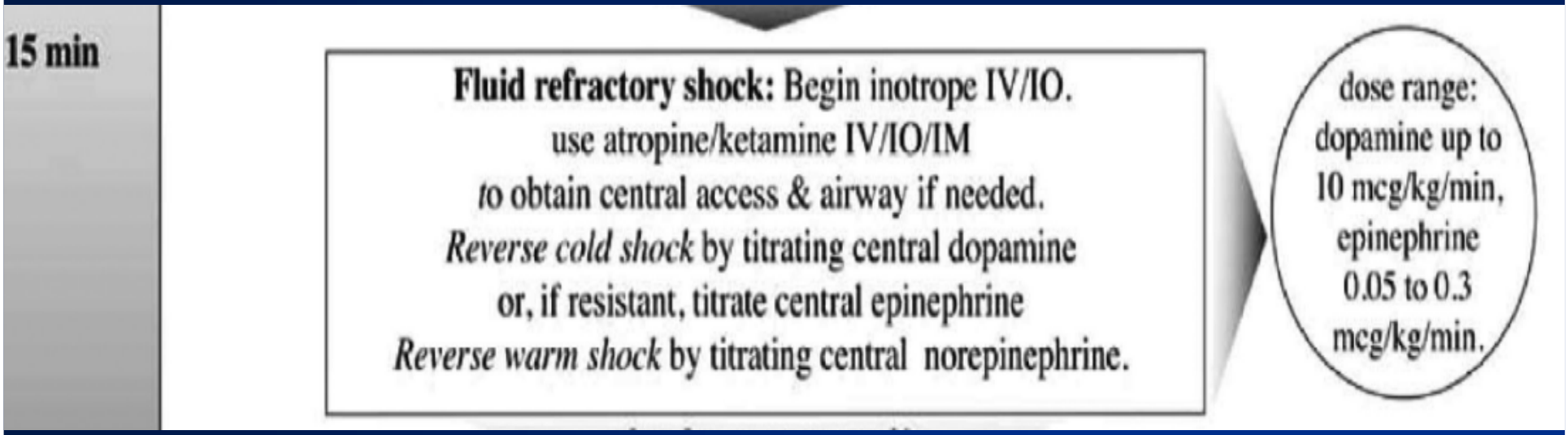
Crit Care Med 2004 Vol. 32, No. 8



Úvodní tekutinová resuscitace

- **začátek rychlý bolus 20ml/kg….. 40 - 60ml/kg…..200ml/kg**
- **izotonický krystaloid, 5% albumin**
- **Hb > 100g/l**
- **FFP**

Inotropes/Vasopressors/Vasodilators – první hodina



- Thompson MJ, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; 367:397–403
- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637

Kortikosteroidy

- **u dětí bez odpovědi na tekutinovou resuscitaci a na katecholaminy rezistentním šokem, s předpokládanou či potvrzenou adrenální insuficiencí**

  - 25% dětí se septickým šokem ma absolutní AI
  - iniciální léčba 50 mg/m2/24 hod → 50mg/kg/den
  - hladina sérového kortizolu

- Dellinger RP et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock:2012. Crit Car. Med. 2013;41:580-637
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Surviving Sepsis Guidelines Updated

Preview from the 41th Society of Critical Care Medicine Meeting

Jun 16, 2012

http://pulmccm.org/2012/critical-care-review/surviving-sepsis-guidelines-updated-at-sccm-meeting/