



Sepsis - when to suspect? How to recognize?

Warsaw, 9th April 2020

Lab tests

- CBC
 - L 2,67 thousand, platelets 122 thousand
 - differential: S 83, M 1, L 16
- CRP 139 mg/l
- Prothrombine 54,8%, APTT 88,7s
- Fibrinogen 1,95g/dl, D-dimers 23 ug/ml (n: < 5)
- Procacythonin 127 ng/ml

2-years old Kuba

- Blood culture:

- *Neisseria meningitidis B*

- Cerebrospinal fluid:

- *aseptic*

- Autopsy:

- *bleedings to the internal organs, including the adrenals glands*

***Meningococcal sepsis
(Meningococemia)***

Septicaemia – rare, difficult to recognize: 80% of paediatric court cases

IAA pap

17.11.2011



foto: Glow Images/East News

Okolo 1,5 mln zł otrzyma od Skarbu Państwa były żołnierz z jednostki w Skwierzynie (Lubuskie), który w wyniku zakażenia zachorował na sepsę i stracił obie nogi.

Clinical course

- Sudden beginning
- Rapid course
- Classic symptoms late, after several hours
- There is little time for proper diagnosis and treatment
- A few hours - night and holiday medical service ?
- Death despite proper treatment and ICU
- 1 hour of treatment delay is a 10% increase in mortality
- Oral antibiotics are ineffective

Sepsis

The Third International Consensus Definition of Sepsis: „life-threatening organ dysfunction caused by dysregulated host response to infection”

- Without timely treatment, sepsis may advance to **septic shock**
- vasodilatory hypotension and elevated lactate level > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation and is associated with increased mortality ($> 40\%$)

Sepsis

- Sepsis is a life-threatening illness caused by pathologic immune response to an infection
 - “overdrive in response to an infection”

Symptoms of sepsis

- A fever above 101°F (38°C) or a temperature below 96.8°F (36°C)
- Heart rate > 90 beats per minute (in adults)
- Breathing rate > 20 breaths per minute (in adults)
- Probable or confirmed infection

You must have two of these symptoms before to diagnose sepsis

- Chills due to fall in body temperature
- Unconsciousness
- Extreme weakness

Symptoms of organ failure

- Problems breathing
- Abnormal heart functions
- Unconsciousness
- Decreased urination
- Patches of discolored skin
- Low platelet count
- Extreme weakness

Sequential Organ Failure Assessment Score

- SOFA score of ≥ 2
- measures function in 6 different domains:
 - **pulmonary (oxygen requirements)**
 - renal (creatinine)
 - **neurologic status (Glasgow Coma Score)**
 - coagulation (platelet counts)
 - liver function (bilirubin)
 - **cardiovascular (systolic blood pressure)**

Zachorowania dzieci w 1 r.ż. (Polska, 2013)

Choroba zakaźna	Liczba zachorowań	Liczba zgonów
Biegunka rotawirusowa	7996	0
Ospa wietrzna	7995	0
Szkarlatyna	158	0
Ropne zap. opon	52	2
ICh meningokokowa	43	5
Odra	6	0
ICh <i>H. influenzae</i>	1	0

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Zachorowania nastolatków: 5-15%

śmiertelność

Choroba zakaźna	Liczba zachorowań (2016)	Liczba zgonów (2015)
Biegunka rotawirusowa	720	0
Ospa wietrzna	13350	0
Szkarlatyna	10139	0
Salmonellozy	990	0
Wirusowe zapalenie opon	146	0
Ropne zap. opon	16	0
ICh meningokokowa	26	2
HIV	0	0

How to recognize sepsis?

THREAT
RISK FACTORS

Risk factors of meningococemia

- **Individual**

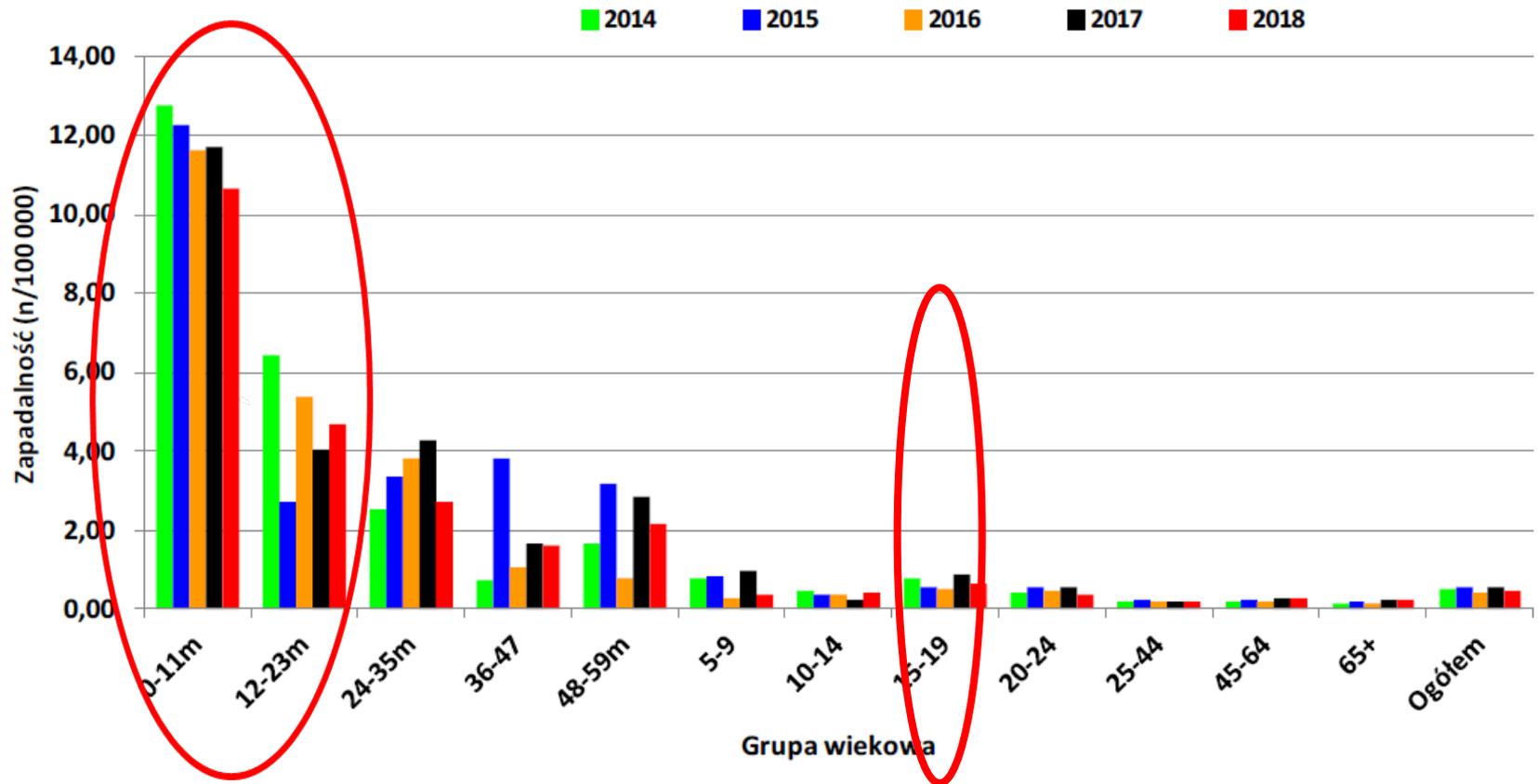
- Age (infants, young children < 2 years, teenagers)
- No specific antibodies in the serum, e.g. infants
- Asplenia and hyposplenism
- Immunodeficiencies, including hypogammaglobulinemia
- Corticosteroid treatment
- Respiratory infections such as flu
- Heart defect, cancer, diabetes

Environmental factors

- Crowding
- Climatic conditions damaging mucous membranes (dry season)
- Active and passive smoking
- Close contact with carriers or patients

Stephens DS, et al. Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. Lancet 2007;369:2196-210. Rosenstein NE, et al. Meningococcal disease. N EJM 2001;344:1378-88. Sparling PF. A plethora of host factors that determine the outcome of meningococcal infection. Am J Med 2002;112:72-4. Stephens DS. Conquering the meningococcus. FEMS Microbiol Rev 2007;31:3-14.

Incidence of invasive meningococcal disease in age groups, 2014-2018, Poland (KOROUN)



How to recognise sepsis?

ALARM SYMPTOMS

POOR GENERAL CONDITION

Main signs & symptoms

- Fever or hypothermia
- Accelerated respiration
- Stomachaches, vomiting, sometimes diarrhea
- Drowsiness
- Impaired consciousness

Signs of meningococcal sepsis



Early warning symptoms

Limb, joint, and muscle pain



Cold hands and feet, shivering



Pale or mottled skin



Fever and vomiting



Fast breathing or breathlessness

- Sudden beginning:
- Foot aches, cold hands and feet, chills, muscle and joint aches, nausea, vomiting, lack of appetite



Particularly serious symptoms

Rash anywhere on the body



Very sleepy, staring expression, and difficult to wake



Confused and delirious

- Patients usually have a haemorrhagic rash that starts with small red spots on the chest and limbs
- Sepsis with septic shock, Waterhouse-Friderichsen syndrome and multi-organ failure may develop.

The order of the appearance of the symptoms is variable, usually not all symptoms occur

Red Flag Symptoms - Early Sepsis

- In all age groups, signs of sepsis and circulatory shut-down were next to develop – 72% of children had limb pain, cold hands and feet, or pale or mottled skin at a median time of 8 hours from onset of illness.
- Parents of younger children also reported drowsiness, rapid or laboured breathing, and sometimes diarrhoea. Thirst was reported in older children.
- A study found limb pain to be highly specific and cold hands / feet moderately specific to meningococcal disease.
- Pallor was frequently found in children with minor infections, and was not a discriminating symptom for meningococcal disease

Heart rate in relationship to the fever

- **Liebermeister's rule: 8 heartbeats / 1°C**

K. von Liebermeister:

Handbuch der Pathologie und Therapie des Fiebers. Leipzig, 1875.

- **8-10 heartbeats per 1°C (children)**

Karjalainen J, Viitasalo M. Fever and cardiac rhythm. *Arch Intern Med.* 1986 Jun;146(6):1169-71.

Davies P, Maconochie I. The relationship between body temperature, heart rate and respiratory rate in children. *Emerg Med J.* 2009 Sep;26(9):641-3.

How to recognize sepsis?

Vital signs:

- Heart rate (≥ 1 year old > 2 SD, < 1 year old < 10 percentile)
- Capillary refill time (> 5 s)
- Limb temperature (difference $> 3^{\circ}\text{C}$)
- Breathing: frequency (> 2 SD), breathing effort
- Consciousness (≤ 11 Glasgow scoring or a drop of 3 points)

Abnormal vital signs

Age Group	Bradycardia	Tachycardia	Respiratory Rate	Systolic Blood Pressure
0 days to 1 week	< 100 beats per minute	> 180 beats per minute	> 50 breaths per minute	< 65 mm Hg
1 week to 1 month	< 100 beats per minute	> 180 beats per minute	> 40 breaths per minute	< 75 mm Hg
1 month to 1 year	< 90 beats per minute	> 180 beats per minute	> 34 breaths per minute	< 100 mm Hg
2-5 years	< 80 beats per minute*	> 140 beats per minute	> 22 breaths per minute	< 94 mm Hg
6-12 years	< 70 beats per minute*	> 130 beats per minute	> 18 breaths per minute	< 105 mm Hg
13 to < 18 years	< 60 beats per minute*	> 110 beats per minute	> 14 breaths per minute	< 117 mm Hg

Lancet 2011 Mar 19;377(9770):1011

Careful clinical examination

- Whole skin evaluation
- Pupil examination
- Arterial pressure (< 5 percentile or < 2 SD)

How to recognize meningococcal sepsis?

**ALARM SYMPTOMS:
HEMORRHAGIC RASH**

Diagnosis of sepsis

- Haemorrhagic lesions usually occur after 12-18 hours from the beginning of the disease
- 1/5 of the patients no rash at all
- If there are no symptoms of meningitis or skin lesions, the probability of a late diagnosis is high

When to suspect sepsis?

- Lab tests:
 - Blood morphology, gasometry, CRP, procalcitonin

CBC

- Leukocytosis or leukopenia
- > 10% young forms (bands)
- Thrombocytopenia (< 150 000. / < 80 000.)
- **Insufficient virus/bacteria differentiation**

Seebach JD, Morant R, Ruegg R, Seifert B, Fehr J. The diagnostic value of the neutrophil left shift in predicting inflammatory and infectious disease. *Am J Clin Pathol* 1997; 107:582–591.

Wile MJ, Homer LD, Gaehler S, Phillips S, Millan J. Manual differential cell counts help predict bacterial infection. A multivariate analysis. *Am J Clin Pathol* 2001;115:644-649.

Can you differentiate bacterial from viral pediatric infections based on the CBC? *J Fam Pract.* 2007 May;56(5):390-392

Abnormal leukocytosis

Age Group	Leukocyte Count
0 days to 1 week	$> 34 \times 10^3/\text{mm}^3$
1 week to 1 month	$> 19.5 \times 10^3/\text{mm}^3$ or $< 5 \times 10^3/\text{mm}^3$
1 month to 1 year	$> 17.5 \times 10^3/\text{mm}^3$ or $< 5 \times 10^3/\text{mm}^3$
2-5 years	$> 15.5 \times 10^3/\text{mm}^3$ or $< 6 \times 10^3/\text{mm}^3$
6-12 years	$> 13.5 \times 10^3/\text{mm}^3$ or $< 4.5 \times 10^3/\text{mm}^3$
13-18 years	$> 11 \times 10^3/\text{mm}^3$ or $< 4.5 \times 10^3/\text{mm}^3$

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 Jan;6\(1\):2-8,](#)

CBC

Parameter	Cutt off	Sensitivity	Specificity	LR (95% CI)
Leukocytosis	15,000/mm ³	64%-82%	67%-75%	1.9-2.7 (1.1-3.8)
Absolute neutrophil count	10,000/mm ³	64%-76%	76%-81%	3.0-3.3 (1.6-6.2)

Can you differentiate bacterial from viral pediatric infections based on the CBC? *J Fam Pract.* 2007 May;56(5):390-392

Blood gases

- Metabolic acidosis
- BE > -5 mEq/l
- Lactate (> 2 SD)
- Hypoxia
- Oxygenation index: $\text{PaO}_2/\text{FiO}_2 < 300$
- $\text{PaCO}_2 > 65$ mmHg

Can you differentiate bacterial from viral pediatric infections based on the CBC? *J Fam Pract.* 2007 May;56(5):390-392

Blood gases

Oxygenation index: $\text{PaO}_2/\text{FiO}_2 < 300$

E.g. PaO_2 97 mmHg

FiO_2 (air) = 0.21

Oxygenation index $97 : 0.21 = 462$

Can you differentiate bacterial from viral pediatric infections based on the CBC? *J Fam Pract.* 2007 May;56(5):390-392

Clotting

- INR > 2

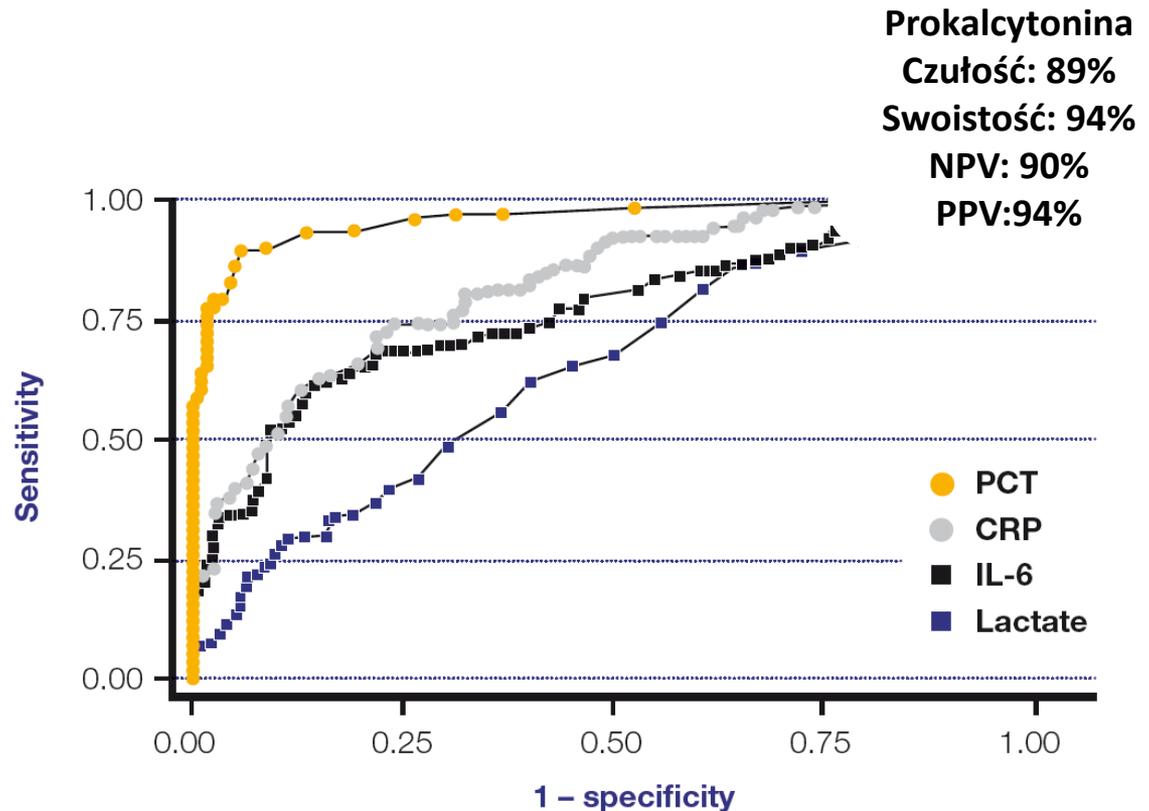
CRP – interpretation

- CRP >20 mg/l typical for bacterial otitis media
- CRP >35 mg/l typical for bacterial pharyngitis
- CRP >20-40 mg/l typical for pyelonephritis
- CRP >50 mg/l typical for bacterial pneumonia, <10 mg/l for viral pneumonia
- CRP >100 mg/l typical for severe bacterial infection

It measures the intensity of inflammation rather than determining etiology

Biomarkers of sepsis

Prokalcytonina
Najlepszy marker odróżniający
sepsę od SIRS o innym
podłożu
Dokładne różnicowanie z
zapaleniem nieinfekcyjnym



Simon L. et al. Clin Infect Dis. 2004;
39:206-217.

Lab tests in sepsis

- ESR: not recommended
- CRP: not recommended
- IL-6: not recommended
- PCT: recommended
- PCT <0.5 ng/ml strongly indicates a viral infection

How to control the problem of sepsis and septic shock?

- **Early diagnosis**
 - training of general practitioners
 - education of the population
 - Early intravenous antibiotic therapy
- **Standards implementation**
 - education of medical staff
 - Rapid hospitalization
 - Rehydration
 - adequate antibiotic therapy
 - Intensive care
- **Prevention**
 - Meningococcal vaccination B, C

I.V. access

- A sick child with septicemia should have an intravenous access or, in case of technical difficulties, an intraosseous access within the first 5 minutes.
- It is best for a sick child with septicemia to have two intravenous accesses

Rescue vehicle on 2 wheels: antibiotic + fluids



T., Kawasaki. Update on pediatric sepsis: a review.
J Intensive Care. 2017

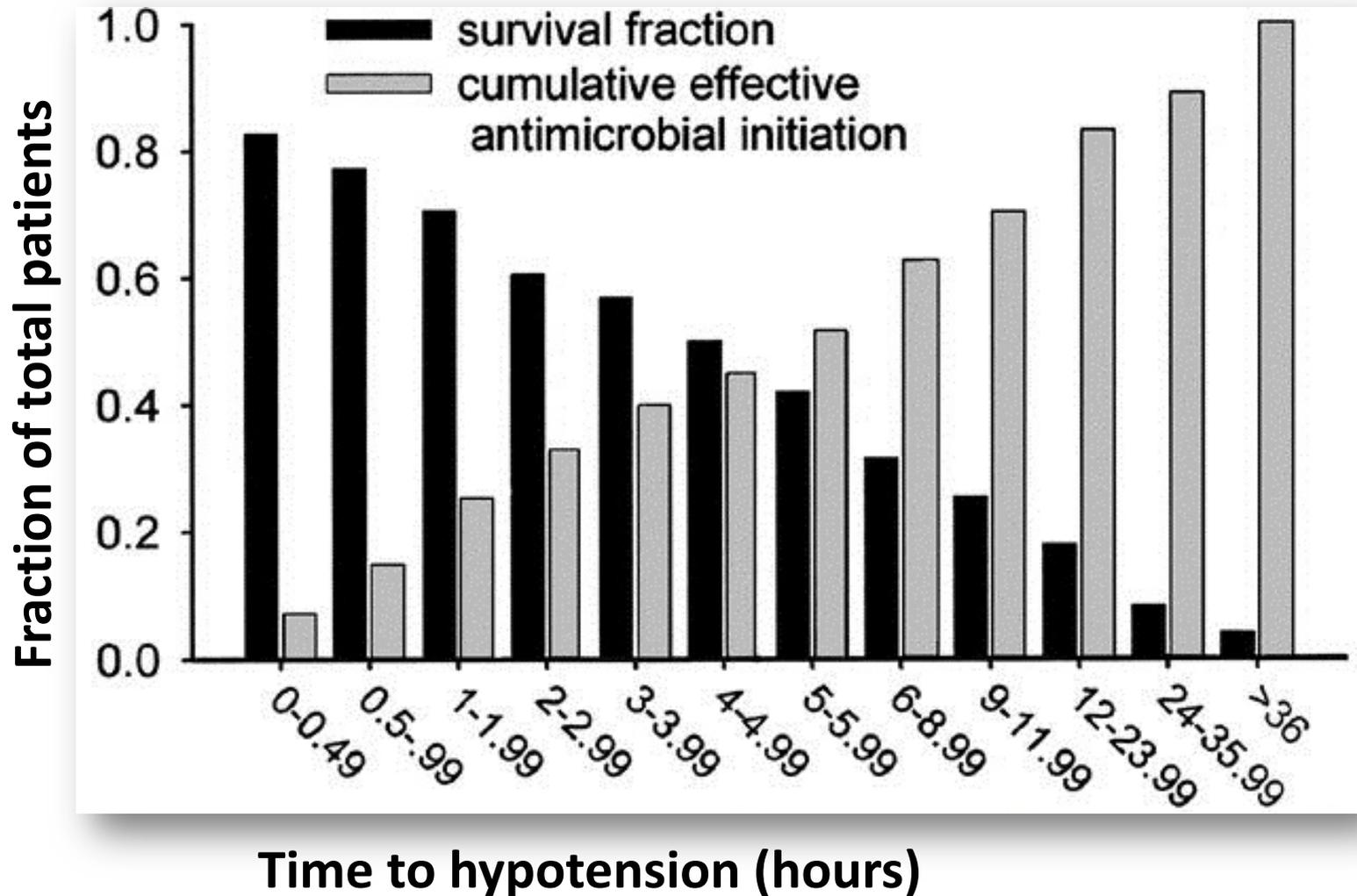
Treatment

- Antibiotic administration and rapid hydration of the patient - two wheels of the "rescue vehicle" in dealing with a child who is suspected of sepsis

Antibiotics

- The antibiotic should be administered within the first hour of detection of high or moderate risk factors for sepsis in a sick child

Effect of time of antibiotic administration on the survival



Fluid resuscitation

- Rapid administration of large volumes (boluses) of isotonic fluid (i.e. with Na⁺ 130-154 mmol/l) in 20 ml/kg for less than 10 minutes.
- Boluses can be repeated 3 times to a total volume of 60 ml/kg
- The patient should be constantly observed, paying attention to possible volumetric overload of the heart, which manifests itself in decreased saturation, crackling over the lungs or hepatomegaly.
- Children over 16 years of age and adults are given 500 ml boluses for 15 minutes.
- After each bolus, it is necessary to assess whether the improvement or development of fluid therapy complications has taken place

National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management. *NG51. London: NICE. 2016,*

References

- Meningitis.org
<https://www.meningitis.org/healthcare-professionals/resources>
- NICE Sepsis: recognition, diagnosis and early management [NG51]