The Septic Patient: Pathogenesis and Laboratory Management

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Disclosure

- Jacques Lacroix has presently a consultant agreement with Johnson & Johnson Inc.

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Acronyms

- SIRS: systemic inflammatory response syndrome.
  - Sepsis: SIRS caused by an infection.
- MODS: multiple organ dysfunction syndrome.
- CRP: C-reactive protein.
- PCT: procalcitonin.
- PELOD score: pediatric logistic organ dysfunction score.

Objectives of this lecture

- Background.
- Definitions.
- Pathophysiology of SIRS, sepsis and MODS.
- Biomarkers of sepsis:
  - CRP vs PCT.
- Other markers.
- Conclusion.

Sepsis: epidemiology

- Major public health problem.
- 700,000 cases per year in USA.
- Treatment: > $15 billion per year in USA.
- Incidence of sepsis - increasing 16% a year.
- Mortality is decreasing: 29% to 17.4% last 20 years.
- More people continue to die each year.
- More than 1,000,000,000 US $ have been used to finance randomized clinical trials on sepsis in the last 10 years.

Treatment of sepsis: $$$$$ for randomized clinical trials

Anti-endotoxin

Ab to TNF$_\alpha$

Anti-IL$_1$

IL$_{10}$

Anti-BPI

Ibuprofen

G-CSF

TNF$_\alpha$ receptors

Anti- CD$_{11}$/CD$_{18}$ receptor Ab

Selenium

Anti-PAF

Anti O$_2$ free radicals

Anti-L-selectin

Fibronectin

Vitamin C

Protein C

Pentoxifilline

Vitamin E

Anti-thrombin III

N-acetyl cysteine

SIRS, sepsis & MODS: definitions

- Systemic inflammatory response syndrome (SIRS): abnormal temperature; tachycardia; tachypnea or hyperventilation; high WBC count.
- Sepsis: SIRS caused by infection.
  - Severe sepsis: sepsis plus abnormal Glasgow coma score (GCS), high lactatemia or low urine output (< 1 mL/kg/hour).
  - Septic shock: severe sepsis with hypotension.
- MODS: simultaneous dysfunction of at least 2 organ systems.

Multiple Organ Dysfunction Syndrome (MODS): diagnosis

- Definition of MODS: simultaneous dysfunction of at least 2 organ systems.
- Organs and systems to be considered include:
  - 1. Respiratory.
  - 2. Cardiovascular.
  - 3. Neurological.
  - 4. Hematological.
  - 5. Renal.
  - 6. Hepatic.

The definitions of the diagnostic criteria of organ dysfunction were updated in 2005

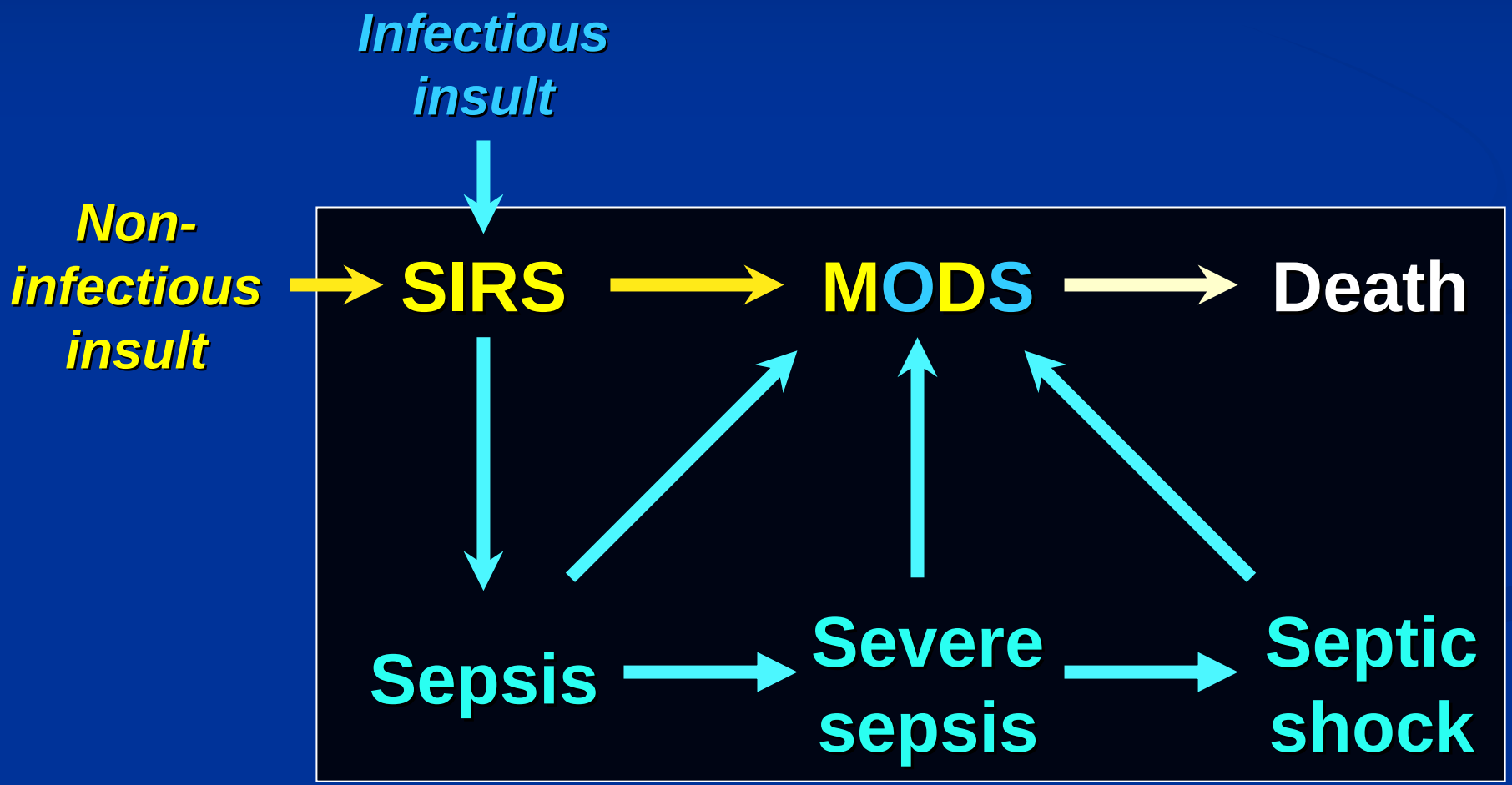
(Goldstein et al. Pediatr Crit Care Med 2005;6:2-8).

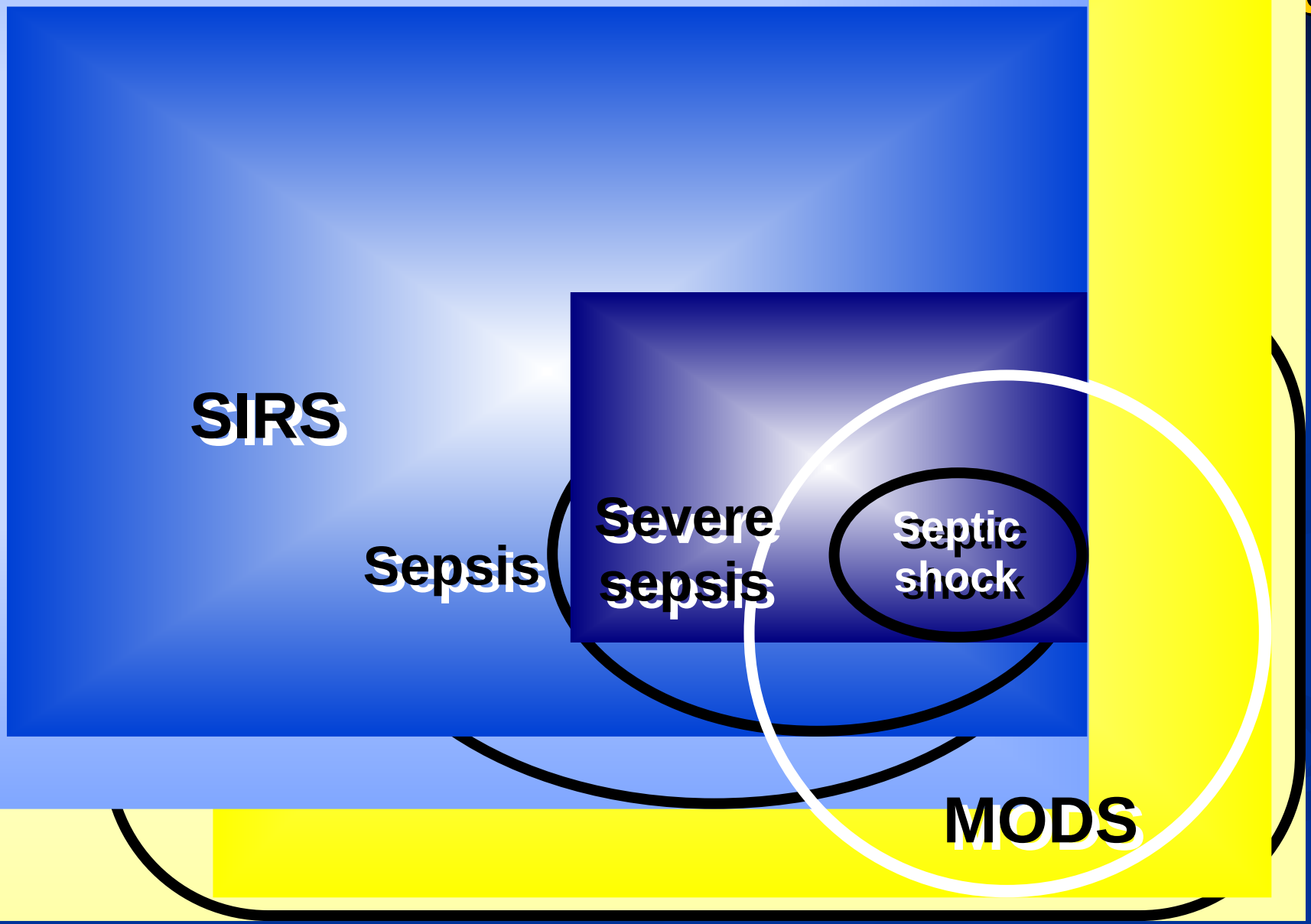
Pediatric MODS: diagnostic criteria

1) Respiratory dysfunction (only 1 criteria is required):

- 1.1) $PaO_2/FiO_2 < 300$ in absence of cyanotic heart disease or preexisting lung disease.
- 1.2) Proven need of > 50% FiO_2 to maintain $SaO_2 \geq 92\%$.
- 1.3) $PaCO_2 > 65$ torr (8.7 kPa) or 20 mmHg over baseline $PaCO_2$.
- 1.4) Need for nonelective invasive or noninvasive mechanical ventilation.
  - In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

Relationship between SIRS, sepsis, severe sepsis, septic shock & MODS




SIRS
Sepsis
Severe sepsis
Septic shock
MODS

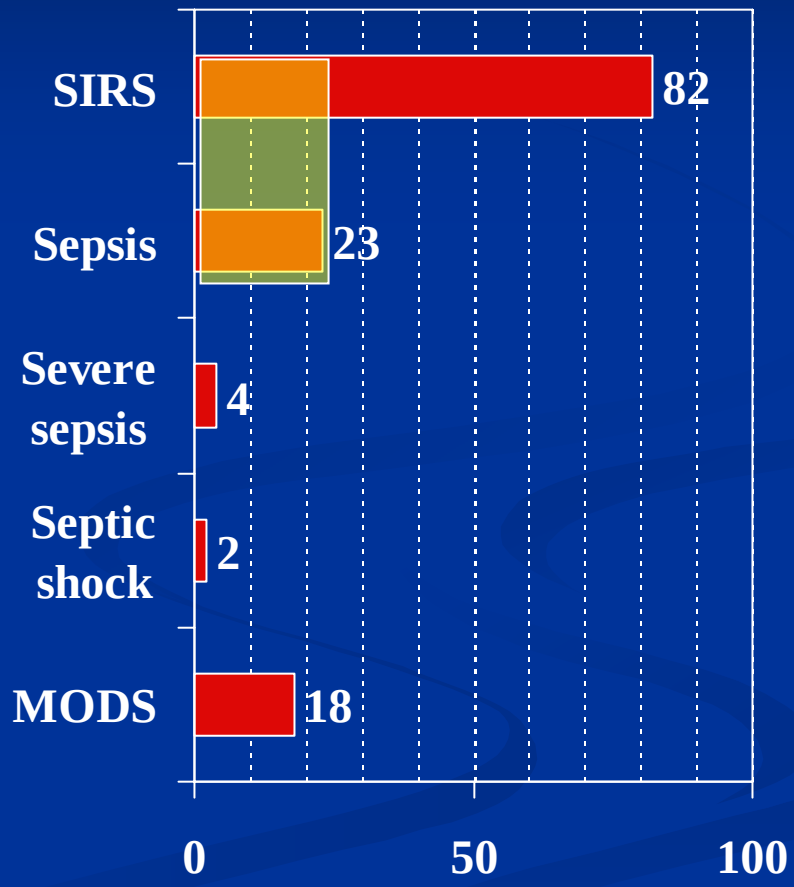
SIRS, sepsis and MODS: epidemiology

- Incidence rates of SIRS, sepsis, severe sepsis and septic shock in PICU.

  Proulx F, et al. Chest 1996;109:240-54.

- The incidence rate of MODS in PICU ranges from 11% to 25 %.

  Proulx et al. Crit Care Med 1994;22: 1025-31.



Proportion (%) of critically ill children in PICU.

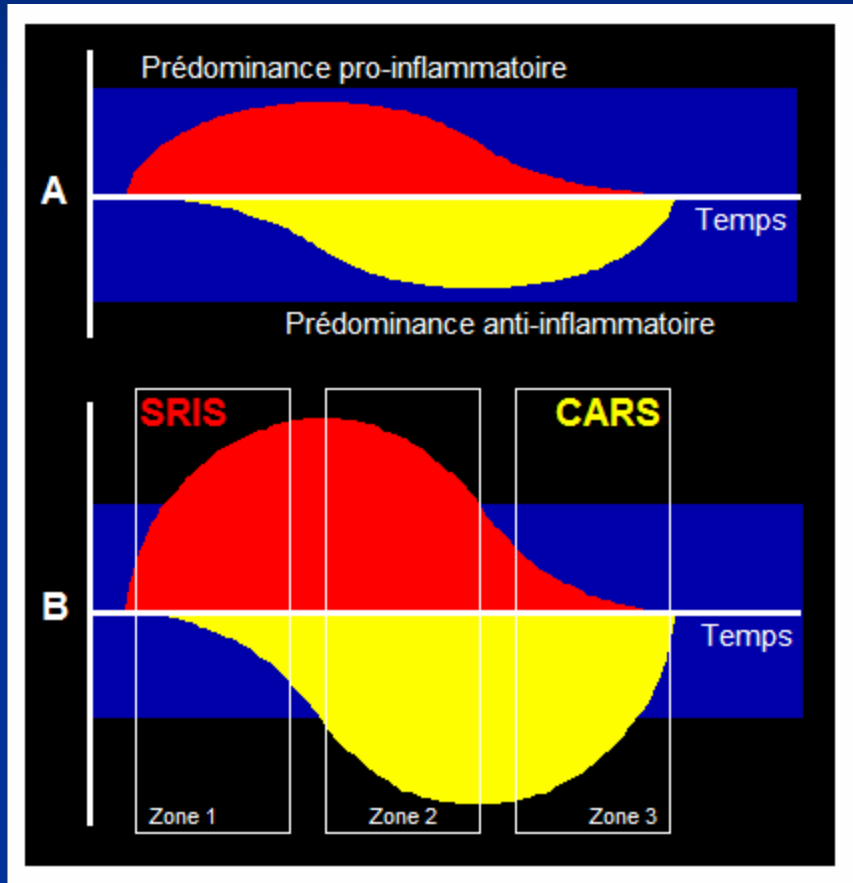
Pathophysiology of SIRS, sepsis and MODS

- In SIRS and sepsis, the release of inflammatory mediators is not limited to local sites, but it becomes systemic.
  - Sepsis, SIRS and MODS "… can be thought of as the endocrine expression of cytokine effects because it requires a systemic response from signals that normally function on an autocrine or paracrine level."

    Pinsky MR. Balancing the inflammatory response in sepsis. In: Vincent JL, ed. Yearbook of intensive care and emergency medicine. Berlin: Springer 1998:3-13.
- MODS can happen if the amount of systemic mediators is high enough. Typically, inflammation autoregulatory processes are dysregulated. MODS is characterized by…
  - High blood levels of inflammatory mediators:
    - pro-inflammatory (ex. TNF_{α}, IL_1)
    - and anti-inflammatory (ex. IL_{10})
  - Increased programmed cell deaths (apoptosis).
  - Both necrosis and apoptosis.

Pathophysiology of SIRS (±CARS), sepsis and MODS

- Pannel A. Normally controlled inflammatory reaction.
  - The pro- and anti-inflammatory response will remain normal (blue area) if the insult is weak and/or local.
- Pannel B. Abnormal inflammatory reaction that is typical of a case of MODS.



SIRS: systemic inflammatory response syndrome.

CARS: compensatory anti-inflammatory response syndrome.

To differentiate SIRS from sepsis: what is the problem?

- It is possible to look "septic" without being infected.
  - Sepsis, in old Greek, means putrefaction, not infection.
- Evidence that SIRS and MODS can be caused by non-infectious process:
  - Injection of TNF_{α} to animals causes the appearance of a septic state with signs and symptoms of sepsis.
  - No infection is found even by autopsy in more than half of cases of SIRS, even when the patients presented all the clinical hallmarks of a septic state.
- Examples of non-infectious causes of SIRS and MODS:
  - Cellular respiratory insufficiency (hypoxia, mitochondrial dysfunction).
  - Non-infectious shock (cardiac, hypovolemic, hemorrhagic, etc).
  - Severe trauma and many other non infectious "insults".

Why would if be useful to differentiate SIRS from sepsis?

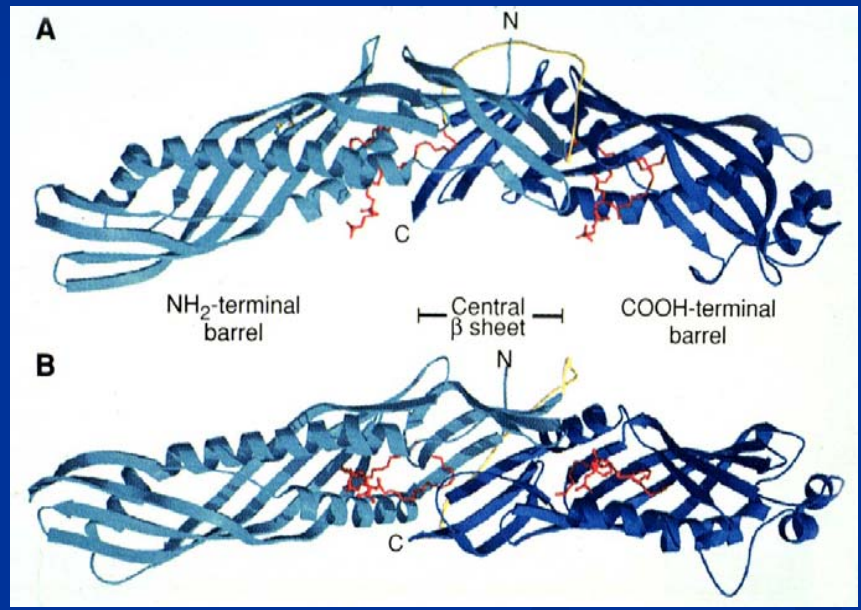
- Antibiotics are required when a sepsis is caused by a bacterial infection.
- Antibiotics are probably not required in SIRS and non bacterial sepsis.
- Antibiotic pressure increases the risk to select resistant bacteria.
  - Ex.: methicillin-resistant *Staphylococcus aureus* (MRSA).
- Therefore, it would be useful to limit antibiotics to cases of bacterial sepsis.
  - To do so, we need reliable markers of bacterial infection that can differentiate SIRS and sepsis when a decision must be made on antibiotics (cultures are too slow).

Serum biomarkers of sepsis

- An increased level of many inflammatory mediators is observed during a case of sepsis/SIRS.
  - Serum biomarkers not specific to infections:
    - Acute phase reaction molecules.
      - Adhesins (selectins).
      - Complement cascade molecules.
      - Molecules of the coagulation system.
      - Other mediators: CRP, PCT, etc.
    - Cytokines (TNF, IL_1, IL_6, IL_8, IL_{10}, PAF, CSF, etc).
  - Some serum biomarkers are specific to bacterial infections:
    - BPI, endotoxin, PCR, etc.

Serum biomarkers related to the infection itself

- Bactericidal/ permeability-increasing (BPI) protein
- Nature: mediator released to kill bacteria.
- No study on its diagnostic nor on its prognostic value.
- Not available at the bedside.



Serum biomarkers related to the infection itself

- Blood level of endotoxemia.
  - Pitfall: most toxins are quite specific to some species or some group of bacterial species.
  - If the practitioner looks for the wrong bacterial species, the result will be negative even if there is an infection.
- PCR (polymerase chain reaction) to bacterial molecules.
  - PCR are also specific to bacterial species, but one can test simultenaously an array of species.
  - The good set of PCR remains to be determined.
- The validity of CRP and PCT to detect sepsis seems better.

Serum biomarkers of sepsis: CRP

- C-reactive protein (CRP) is an acute phase reactant.
- Synthesized by liver in response to IL_6, TNF_α & $IL_{1\beta}$.
- Secretion:
  - starts within 4-6 hours
  - doubles every 8 hours
  - peaks after 36 hours.
- Low cost of the test: 5 U$.
- Results available within a few minutes.
- Frequently used presently on hospital wards and emergency units.

Serum biomarkers of sepsis: procalcitonin (PCT)

- No definitive role before its conversion to calcitonin.
- Normally, serum PCT concentration is undetectable.
- Increases:
  - Sepsis / endotoxin and cytokine administration
    - IL_2, IL_6 and TNF_α.
- Secretion:

  - begins within 4 hours
  - peaks at 8 h (CRP peaks after 36 hours)
  - remains elevated at 24 hours.
- Moderate cost of the test: 10 U$.
- Results available within a few minutes.

Serum biomarkers of sepsis

- We conducted a meta-analysis of published studies to compare the accuracy of serum PCT and CRP as diagnostic markers of bacterial infection.

  Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum Procalcitonin and C-reactive protein levels as markers of bacterial infection: A systematic review and meta-analysis. Clin Infect Dis 2004;39:206-17.

- Studies published in Medline from January 1, 1970 through May 30, 2002.
- Simultaneous evaluation of PCT and CRP.
- Endpoint: diagnosis of bacterial infections.

Meta-analysis on CRP and PCT: data selection

- Prospective studies.
- Hospitalized patients.
- No restriction was placed on age.
- Relevant articles were selected by three independent reviewers.
  - Discrepancies or disagreements, if any, were resolved by consensus.

Meta-analysis on CRP and PCT: data selection

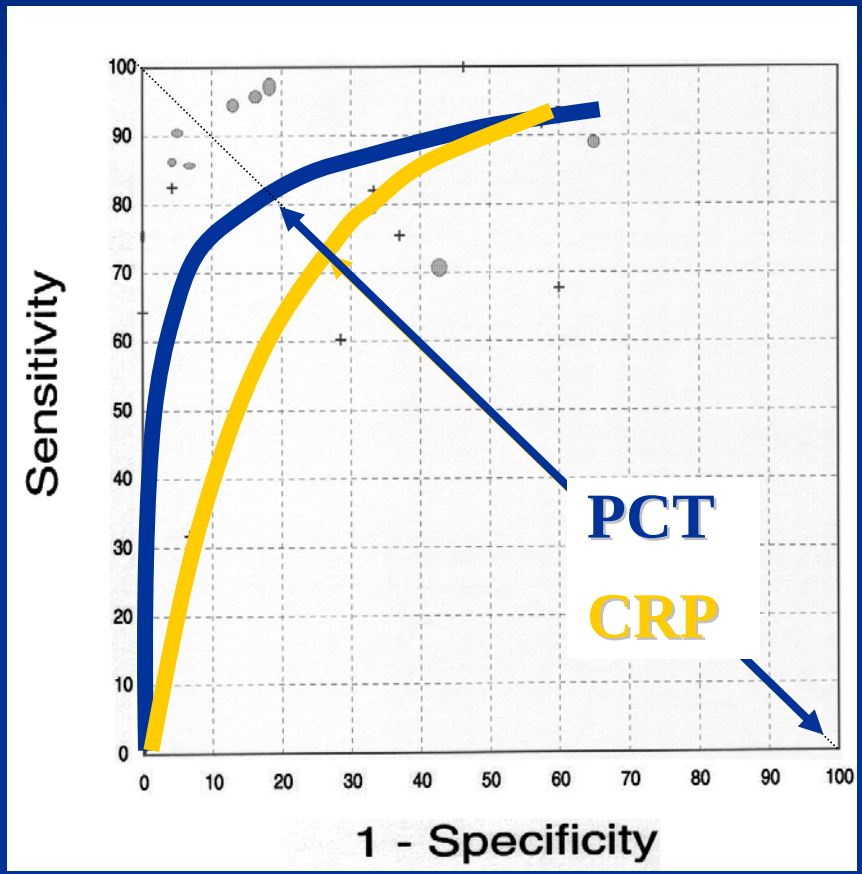
- Step 1 - key words 351
- Step 2 - abstracts 109
- Step 3 - papers 22
- Step 4 - analysis (1497 patients) 12
  - No infection (905 patients) 10
  - Infection (592 patients) 3

Meta-analysis on CRP and PCT: data extraction

Test	Gold Standard: BACTERIAL	Gold Standard: CONTROL (no infection / viral)
PCT or CRP +	TP:	FP:
PCT or CRP –	FN:	TN:

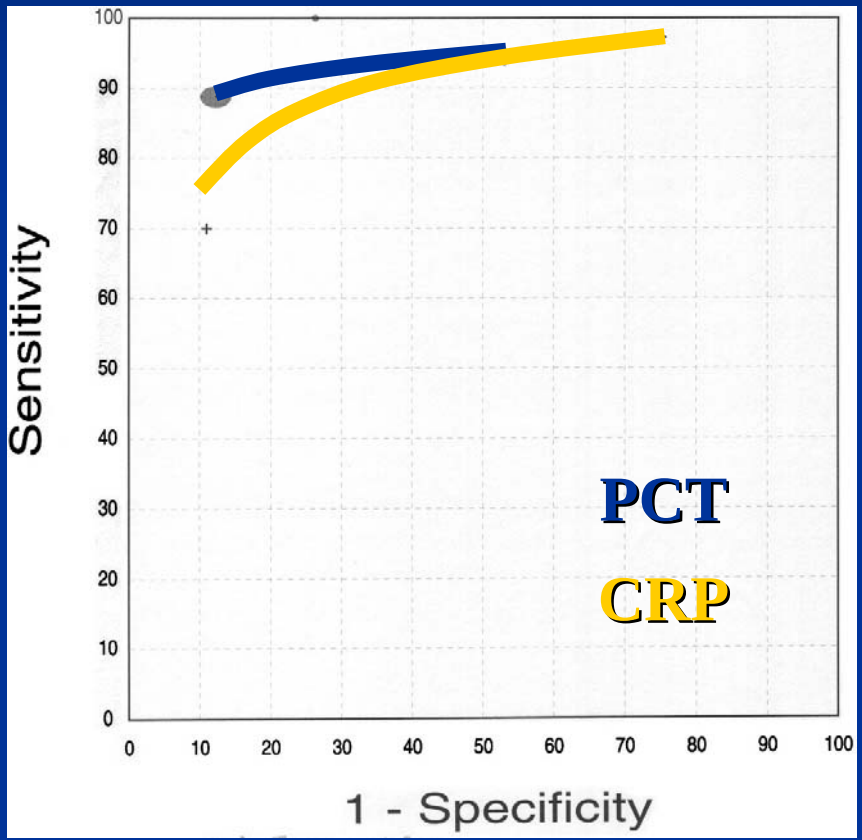
N = ____ N = ____

Meta-analysis on CRP and PCT: Bacterial vs non-infective causes



- Sensitivity
  - PCT 0.88 [95% CI: 0.80 – 0.93]
  - CRP 0.75 [0.62 – 0.84]
  - Δ 0.13 [0.08 - 0.17], $p < 0.05$
- Specificity
  - PCT 0.81 [0.67 – 0.90]
  - CRP 0.67 [0.56 – 0.77]
  - Δ 0.14 [0.08 - 0.20], $p < 0.05$
- Q value (distance between right lower corner and ROC curve):
  - PCT 0.82
  - CRP 0.73

Meta-analysis on CRP and PCT: Bacterial vs viral causes



- Sensitivity
  - PCT 0.92 [0.86 – 0.95]
  - CRP 0.86 [0.65 – 0.95]
  - Δ 0.06 [0.005 – 0.11], $p < 0.05$
- Specificity
  - PCT 0.73 [0.42 – 0.91]
  - CRP 0.70 [0.19 – 0.96]
  - Δ 0.03 [0.04 – 0.1], $p > 0.05$
- Q value
  - PCT 0.89
  - CRP 0.83

Meta-analysis on CRP and PCT: Conclusion

- The overall accuracy of PCT is higher than that of CRP for differentiating between
  - bacterial infections and non-infective causes of inflammation
  - bacterial and viral infections
- PCT is a good marker for bacterial infection and should be favored over CRP for use in clinical practice.
- However, the usefulness and cost-benefit of these tests remained to be determined.

Meta-analysis on CRP and PCT: External validity

- Limitations of the studies included in the meta-analysis and of the meta-analysis itself:
  - CRP and PCT were frequently collected hours and even days after the patients were first seen by MD, not when a decision to prescribe antibiotics was made.
  - Both tests may be less accurate when measured right at the beginning of a sepsis when antibiotics are prescribed.
- We need to know how reliable are the results of PCT and CRP when the question about the infectious nature of an inflammatory process is raised, ie when the physician considers that a patient may have a sepsis, not afterwards.
  - Prospective study on the accuracy of CRP and PCT to diagnose sepsis immediately when the MD considers the diagnosis.

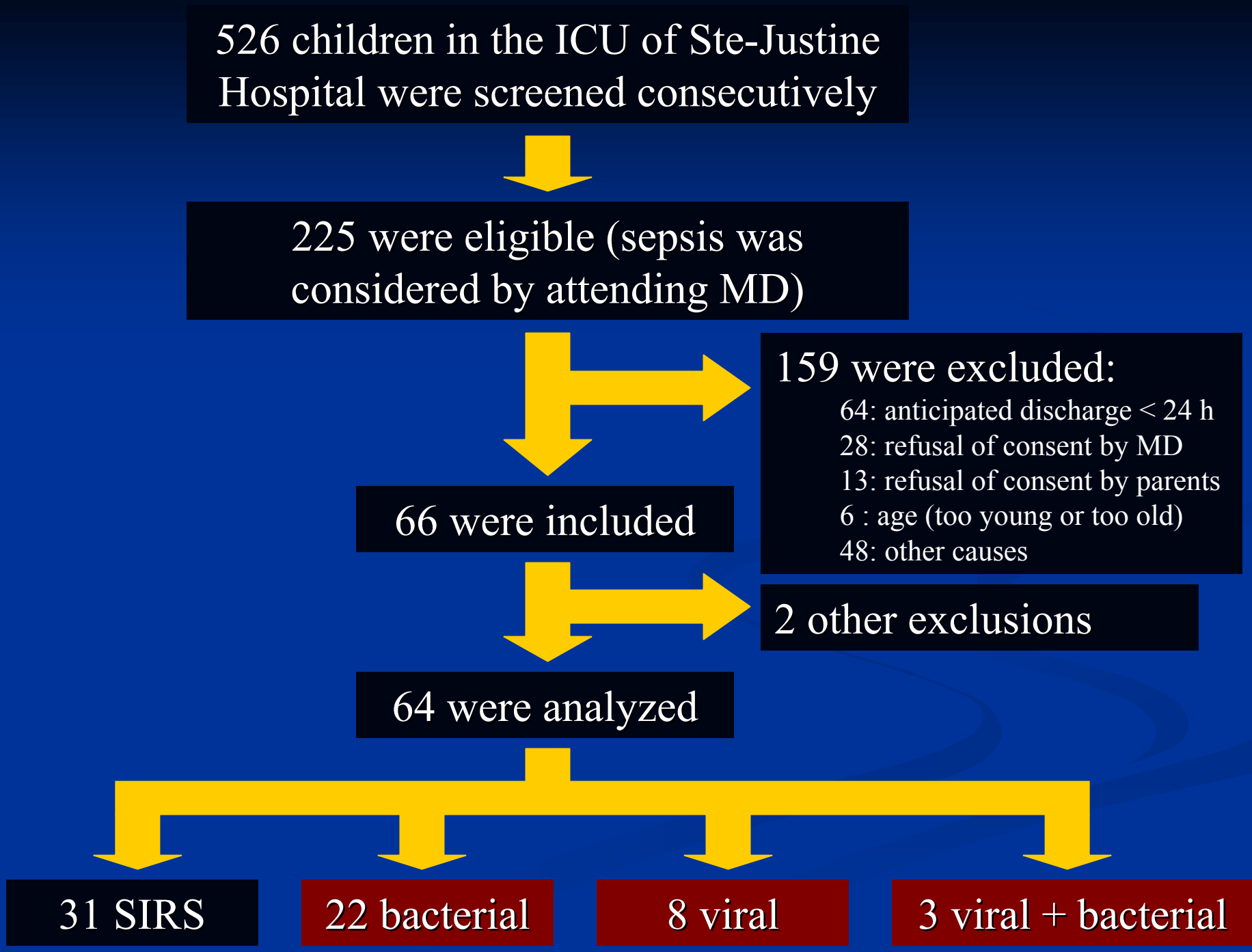
Early diagnosis of sepsis with CRP or PCT in PICU

- **Objectives**:
  - Primary objective: to compare the validity of PCT and CRP for early diagnosis of sepsis caused by bacterial infections in critically ill children with SIRS.
  - Secondary objectives: to estimate the validity of PCT and CRP as markers of severity of disease at inclusion and as predictors of poor outcome in PICU.
- **Design**: Prospective descriptive study of a cohort of consecutive cases of SIRS in a multidisciplinary pediatric intensive care unit (PICU).

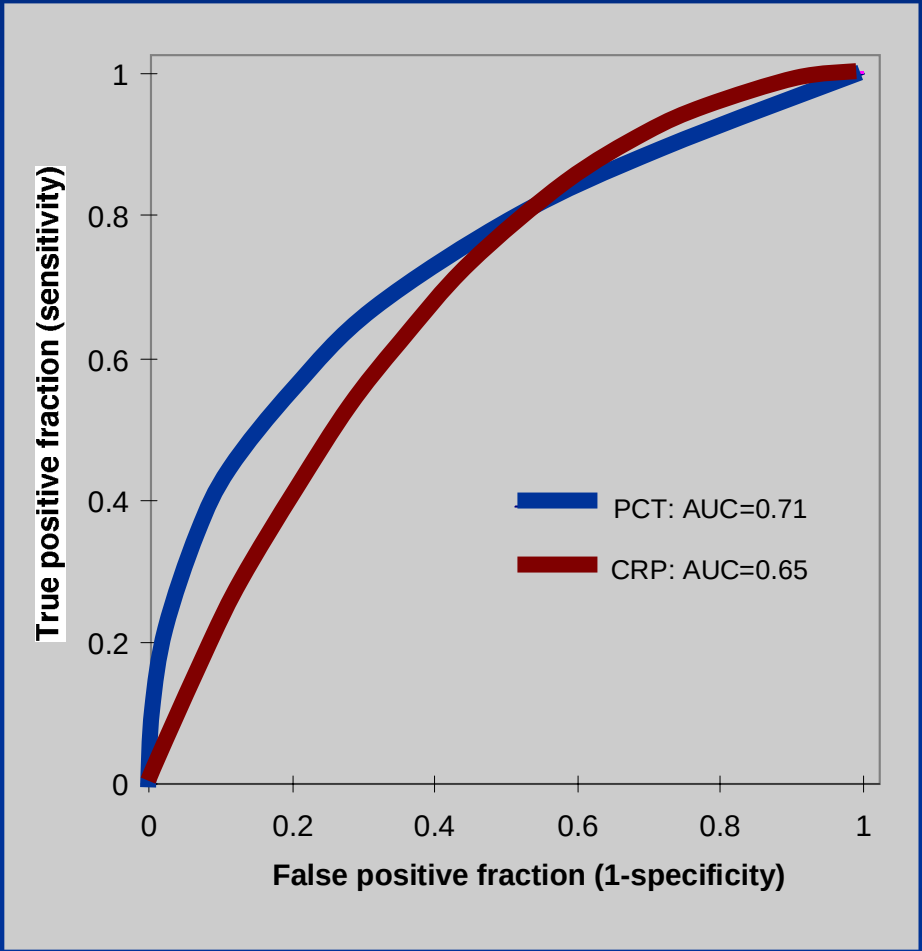
St-Louis P, Simon L, Gauvin F, Proulx F, Amre D, Lacroix J. The comparative utility of procalcitonin and C-reactive protein as markers of sepsis in a pediatric ICU population with SIRS. 2005 AACC Annual Meeting, Orlando, Florida.

Early diagnosis of sepsis with CRP or PCT in PICU: methods

- During a 6 month period (June to December 2002), all patients admitted to the PICU at Sainte-Justine Hospital were screened daily to identify possible cases of sepsis.
- At inclusion, a blood sample was obtained (PCT and CRP levels), as well as an array of cultures.
- Baseline data, as well as daily data on severity of illness, organ dysfunction and outcome were collected.
- Diagnosis of bacterial infection was made a posteriori by an adjudicating process (consensus of experts).
- Receiver operating characteristic (ROC) curves were plotted for PCT and CRP levels and the diagnostic accuracy of each test was assessed by calculating its area under the ROC curve (AUC).


526 children in the ICU of Ste-Justine Hospital were screened consecutively
225 were eligible (sepsis was considered by attending MD)
159 were excluded:
64: anticipated discharge < 24 h
28: refusal of consent by MD
13: refusal of consent by parents
6 : age (too young or too old)
48: other causes
66 were included
2 other exclusions
64 were analyzed
31 SIRS
22 bacterial
8 viral
3 viral + bacterial

Early diagnosis of sepsis with CRP or PCT in PICU: results



- Comparison between Area under Receiver Operating Characteristic curves (AUC) of serum PCT and CRP to differentiate critically ill children with sepsis (bacterial SIRS) vs without sepsis (non-bacterial SIRS).
- The AUC for PCT is greater than the AUC for CRP, but this is not statistically significant (0.71 vs 0.65, p = 0.43).

Early diagnosis of sepsis with CRP or PCT in PICU: results

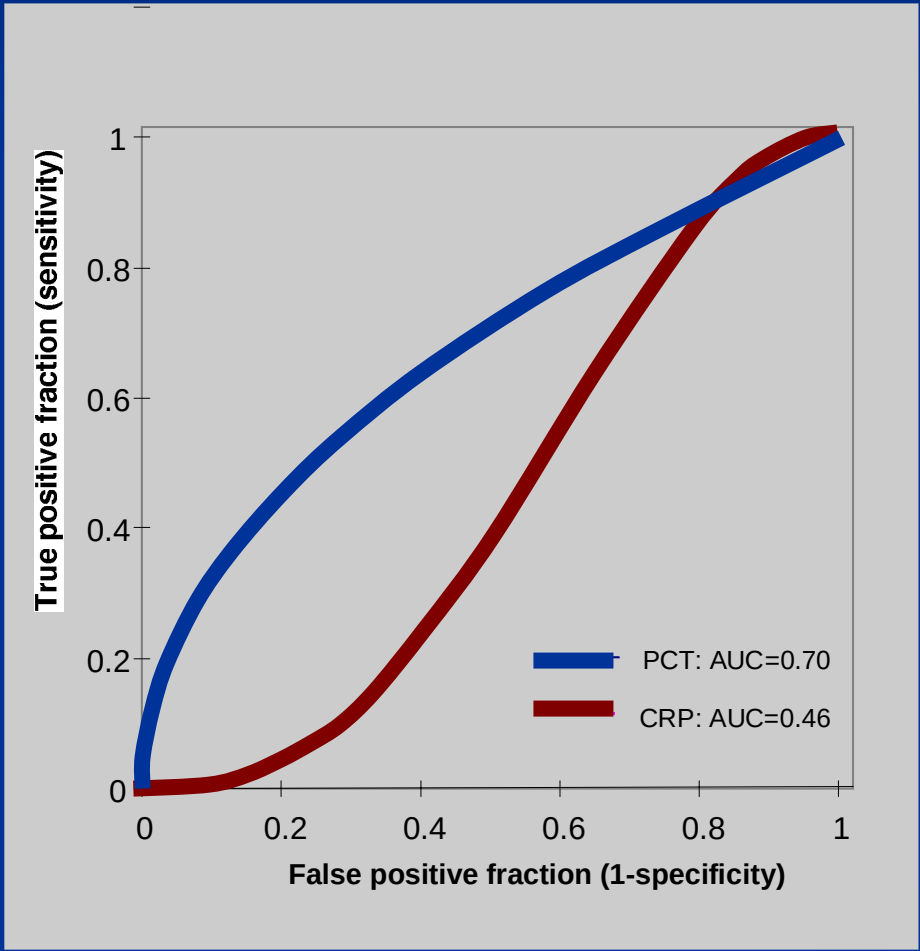
Test	Threshold	Sensitivity	Specificity	PLR	NLR
PCT (ng/mL)	0.5	81.8%	35.9%	1.28	0.51
	2.5	68.2%	74.4%	2.66	0.43
	5.0	50.0%	82.1%	2.79	0.61
CRP (mg/L)	40	95.4%	42.1%	1.65	0.10
	60	59.1%	55.3%	1.32	0.74
	100	40.9%	79.0%	1.94	0.75

- PCT was always better than CRP: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR).
- Bayes approach: a positive PCT levels increases the likelihood of bacterial infection from 32% (bedside clinical judgment alone) to 68% (clinics+PCT).

Early estimation of prognosis of cases of sepsis by PCT and CRP

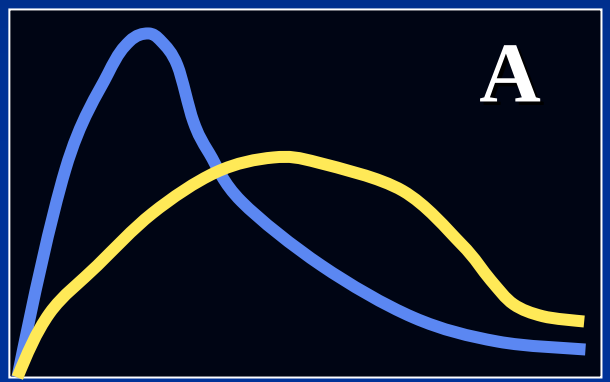
- Definition of bad outcome: any of the following criteria was found in a patient during the PICU stay:
  - 1) length of mechanical ventilation after inclusion ≥ 7 days;
  - 2) length of stay in the PICU post inclusion ≥ 10 days;
  - 3) maximal number of organ dysfunction post inclusion ≥ 3;
  - 4) worst PELOD after inclusion >15;
  - 5) death.
- Capacity to predict bad outcome:
  - Higher PCT levels were associated with "poorer outcome" (24.1 ng/mL ± 39.2 vs 7.2 ng/mL ± 20.6; p = .02)
  - This was not the case with CRP levels.

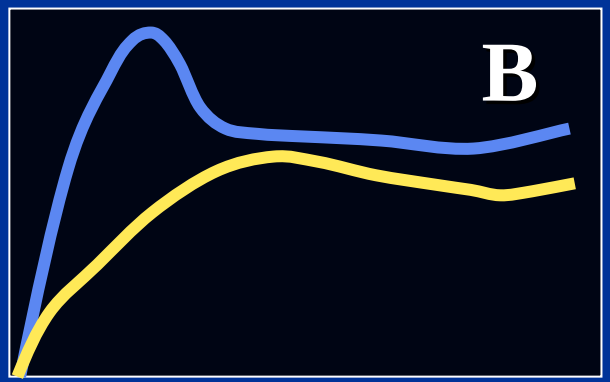
Early evaluation of severity of sepsis+prediction of bad outcome



- Capacity to describe severity of illness (presence of MODS) at inclusion (AUC):
  - PCT: AUC = 0.70
  - CRP: AUC = 0.48
  - PCT > CRP ($p = 0.045$).

Early estimation of prognosis of cases of sepsis: other biomarkers





- IL_6 and IL_{10} can also predict outcome of severe sepsis/MODS.
- Panel A: normal SIRS and sepsis.
  - High blood levels of pro-inflammatory cytokines, like IL_6, followed by high level of anti-inflammatory cytokines, like IL_{10}, which causes a decrease of IL_6.
- Panel B: severe sepsis / MODS.
  - The blood levels of both pro- (i.e. IL_6) and anti-inflammatory (i.e. IL_{10}) cytokines remain high.

Crit Care Med 2002; 30:S58-63.

- Are PCT or CRP better predictors of outcome than IL_6 and/or IL_{10}?
  - We do not know.

Early estimation of prognosis of cases of sepsis: clinical markers

- Sympathetic drive is inappropriate at onset of septic shock.

  Am J Respir Crit Care Med 1999:160:458-65.

- Experimental human endotoxemia decreases heart rate variability.

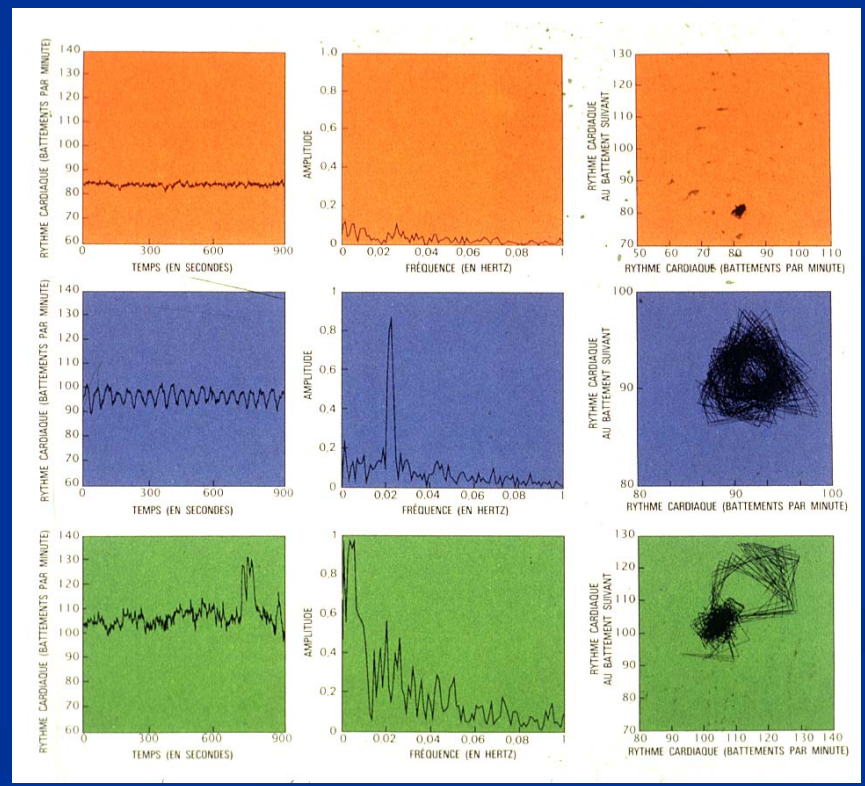
  Crit Care Med 1996;24:1117-24.

- Degree of uncoupling of heart rhythm is related to outcome.
  - In sepsis and septic shock.

    Crit Care Med 2000;28:2051-7.
  - Post abdominal aortic surgery.

    Crit Care Med 2001;29:1738-43.
- Can this be clinically useful?
- Is it better than PCT or CRP?

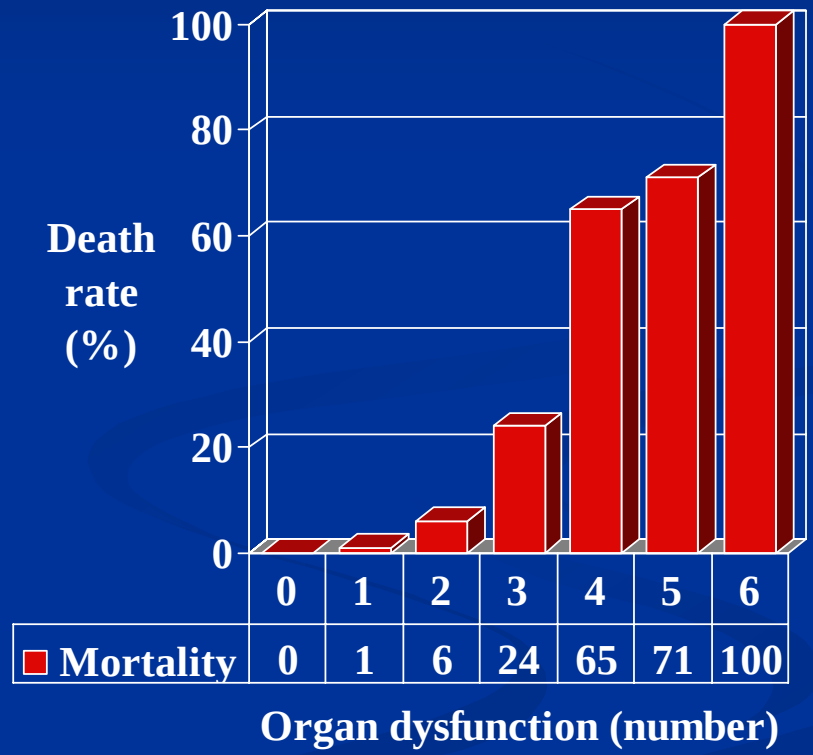
HEART RATE VARIABILITY



Early estimation of prognosis of cases of sepsis: clinical markers

Number of organ dysfunction

- Mortality increases with the number of organ dysfunctions.
- However, the predictive "weight" of each organ is different.
  - For example, more deaths are associated with cardiovascular than with hepatic dysfunction.
- It is not optimal to add indicators with different weight.
  - More weight (more points) should be attributed to more "significant" organ dysfunction.
  - Even more weight should be given to more dysfunctional organ.



Leteurtre et al. Arch Pédiatr 2004;11:732

Early estimation of prognosis of cases of sepsis: clinical markers

PELOD score

- The development study included 594 patients and 51 deaths from 3 PICU (2 French, 1 Canadian).

  Leteurtre et al. Med Decision Making 1999;19:349-410

- The validation study included 1806 patients and 115 deaths from 7 PICU (2 French, 3 Canadian, 2 Swiss).

  Leteurtre. Lancet 2003;362:192-7

- Six systems and 12 variables contributed significantly to outcome and were integrated into PELOD score.

ARTICLES

Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study

Stéphane Leteurtre, Alain Martinot, Alain Duhamel, François Proulx, Bruno Grandbastien, Jacques Cotting, Ronald Gottesman, Ari Joffe, Jurg Pfenninger, Phillippe Hubert, Jacques Lacroix, Francis Leclerc

Summary

Background Multiple organ dysfunction syndrome is more frequent than death in paediatric intensive care units. Estimation of the severity of this syndrome could be a useful additional outcome measure in clinical trials in such units. We aimed to validate the paediatric logistic organ dysfunction (PELOD) score and estimate its validity when recorded daily (dPELOD).

Methods We did a prospective, observational, multicentre cohort study in seven multidisciplinary, tertiary-care paediatric intensive care units of university-affiliated hospitals (two French, three Canadian, and two Swiss). We included 1806 consecutive patients (median age 24 months; IQR 5–90). PELOD score includes six organ dysfunctions and 12 variables and was recorded daily. For each variable, the most abnormal value each day and during the whole stay were used in calculating the dPELOD and PELOD scores, respectively. Outcome was vital status at discharge. We used Hosmer-Lemeshow goodness-of-fit tests to evaluate calibration and areas under receiver operating characteristic curve (AUC) to estimate discrimination.

Findings 370 (21%) patients had no organ dysfunction, 471 (26%) had one, 457 (25%) had two, and 508 (28%) had three or more. Case fatality rate was 6·4% (115 deaths). PELOD score was significantly higher in non-survivors (mean 31·0 [SE 1·2]) than survivors (9·4 [0·2]; p<0·0001). Calibration (p=0·54) and discrimination (AUC=0·91, SE=0·01) of PELOD and dPELOD (p=0·39; AUC=0·79) scores were good.

Interpretation PELOD and dPELOD scores are valid outcome measures of the severity of multiple organ dysfunction syndrome in paediatric intensive care units; their use should significantly reduce the sample size required to complete clinical trials in critically ill children.

Lancet 2003; **362:** 192-97
See Commentary page 180

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Introduction

Death is thought by many intensive care consultants to be the most reliable endpoint for clinical trials in intensive care units. However, with death as the primary outcome measure, the low death rate in paediatric intensive care units (about 6%[1-3] *vs* >20% in adult intensive care units[4]) increases the sample size required to complete a clinical trial, which reduces the feasibility of doing clinical trials in such units. A surrogate outcome can be substituted (or at least added) to a gold standard such as death rate, if its relation to the gold standard is very good, and if the prevalence of what it measures is substantially greater than that of the gold standard. Multiple organ dysfunction syndrome is more frequent than death in paediatric intensive care units—the rate ranges from 11% to 27%.[5-9] Thus, a score that could be used to estimate the severity of multiple organ dysfunction syndrome could be an additional outcome measure to death in critically ill patients.[10] The difference in rate should significantly reduce the sample size required to complete a clinical trial if multiple organ dysfunction syndrome is chosen as the primary outcome measure rather than death. Three multiple organ dysfunction syndrome scores have been validated in adults for this purpose,[4,10] but none in children. In a prospective, multicentre study, we developed a paediatric multiple-organ dysfunction syndrome score, the paediatric logistic organ dysfunction (PELOD) score.[11] This score was developed against mortality as in all such studies in adults. In this study, we aimed to validate the PELOD score, which is based on the most abnormal values of variables measured during the entire paediatric intensive care unit stay; and to estimate the validity of the PELOD score when recorded daily (dPELOD).

Methods

Participants

We prospectively included all consecutive patients admitted to seven multidisciplinary, tertiary-care paediatric intensive care units of university-affiliated hospitals (two French, three Canadian, and two Swiss). Exclusion criteria were age 18 years or older, premature, pregnant, length of stay in unit less than 4 h, admission in a state of continuous cardiopulmonary resuscitation without achieving stable vital signs for at least 2 h, transfer to another paediatric intensive care unit, and admissions for scheduled procedures normally cared for in other hospital locations.

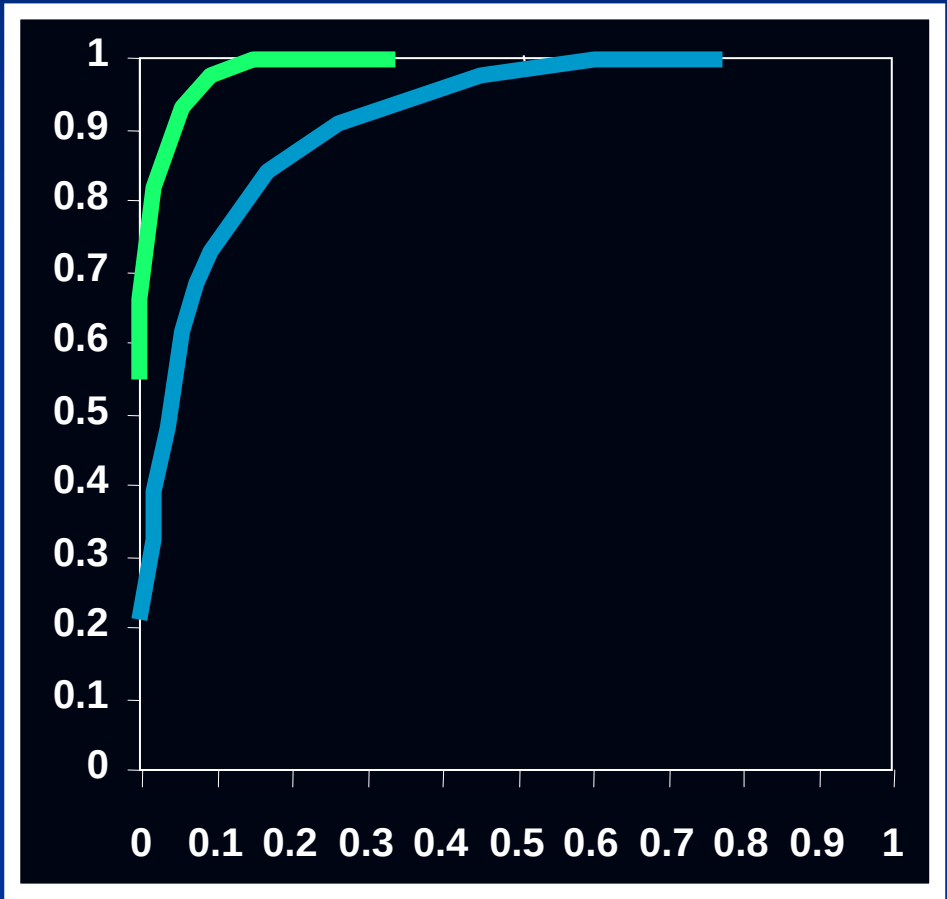
All ethics committees of the participating hospitals approved the study. All patients' parents gave oral informed consent.

Procedures

The development of the PELOD score has been described.[11] Each unit had to enrol consecutive admissions for at least 3 months. Clinical data were

PELOD: system	Variables	Maximum points
Respiratory	PaO_2/FiO_2	10
	PCO_2	
	Mechanical ventilation	
Cardiovascular	Heart rate	20
	Systolic blood pressure	
Neurological	Glasgow coma score	20
	Pupillary reaction	
Hepatic	ALT (SGOT)	1
	Coagulation (INR)	
Renal	Creatinine	10
Hematological	White blood cells	10
	Platelets	

PELOD development and validation: results



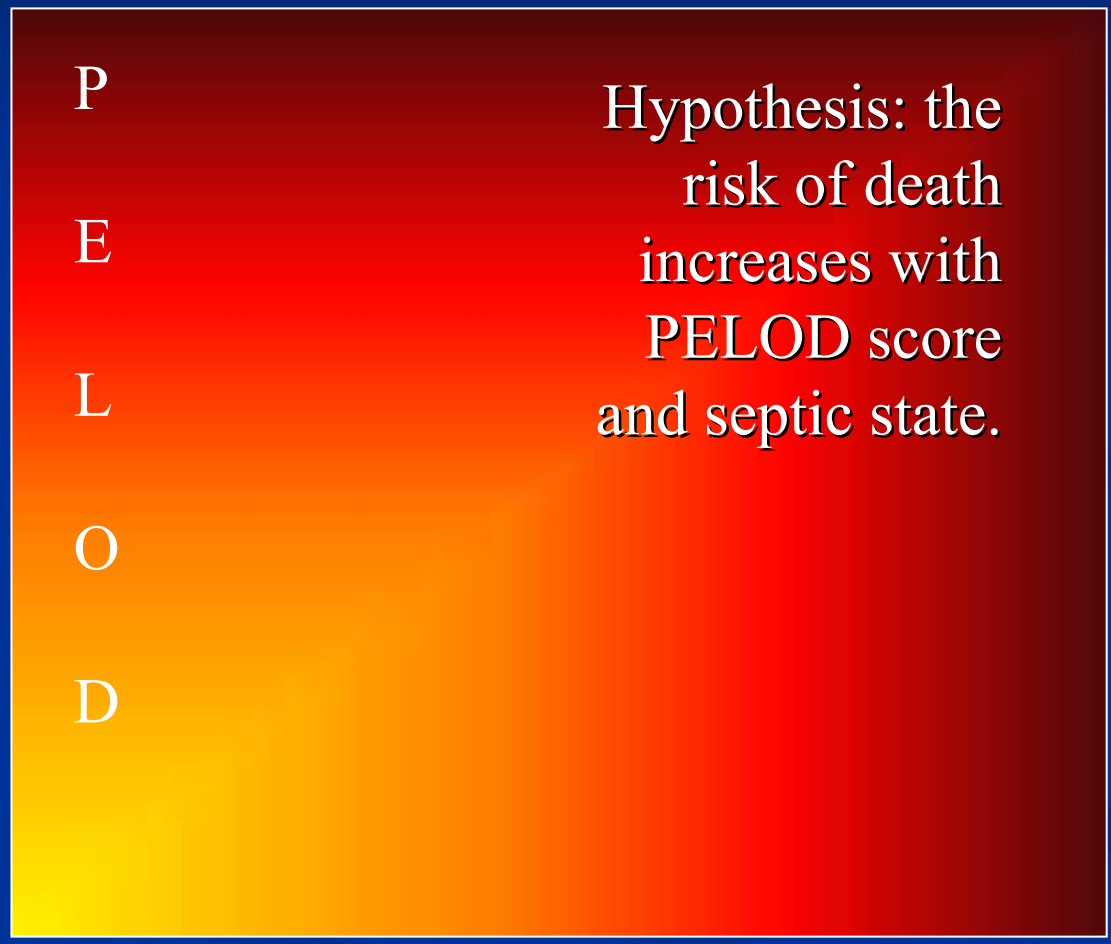
- Discrimination (area under ROC curves ± SE).
  - **Development: 0.98 ±0.01**
  - **Validation: 0.91 ±0.01**
- Calibration: (higher p value is better).
  - **Development: p = 0.44 (3 df)**
  - **Validation: p = 0.54 (5 df)**

Leteurtre et al. Lancet 2003;362:192-7

Markers, sepsis state and outcome

- Is there some accrual in the information collected if one takes into account a clinical marker, like the PELOD score, and the worst sepsis state in critically ill patients?
- In other words, does knowing both the PELOD score and the worst septic state improve our capacity to predict death in ICU?

Leclerc F, et al. Am J Respir Crit Care Med 2005;171:348-53.



Septic state	Hazard ratio (95%CI)
Hazard ratios of SIRS and sepsis were similar.	
SIRS, sepsis*	7.43 (1.01-54.8)
Severe sepsis*	27.40 (3.26-230-4)
Septic shock*	61.40 (7.8-486.1)

* Hazard ratio of death not adjusted for PELOD.

Septic state	Hazard ratio (95%CI)
PELOD	1.096^{point} (1.077-1.116)
SIRS, sepsis*	9.04 (1.23-66.6)
Severe sepsis*	18.8 (2.24-157.7)
Septic shock*	32.6 (4.2-253.9)

* Hazard ratio of death adjusted for PELOD.

PELOD and sepsis state

- Hazard ratio (HR) of death = (HR^{PELOD}) x (HR septic state)
- Ex: PELOD score = 24.
  - $HR^{PELOD} = 1.096^{24}$
  - HR severe sepsis = 18.8
- Combined hazard ratio of death:
  - $= 1.096^{24}$ x 18.8 = 169.6.
- Hazard ratio of death for unadjusted severe sepsis was 27.40 rather than 169.6.

Leteurtre et al. Arch Pédiatr 2004;11:732.

Septic state	Hazard ratio (95%CI)
PELOD	1.096^{point} (1.08-1.12)
SIRS, sepsis*	9.04 (1.23-66.6)
Severe sepsis*	18.8 (2.24-157.7)
Septic shock*	32.6 (4.2-253.9)

Biomarkers of sepsis: conclusion

- PCT seems better than CRP to differentiate bacterial infection from SIRS.
  - However, the accuracy of PCT and CRP to diagnose bacterial infection in PICU patients with a systemic inflammatory process is only moderate, possibly due to the early stage of the disease when the question is raised at the bedside.
- PCT is also better than CRP to estimate severity of disease at inclusion and to predict poor outcome in critically-ill children.
  - Is it better than the PELOD score or heart variability?

TAKE HOME MESSAGES

- Serum biomarkers can be used…
  - To differentiate SIRS and sepsis (to diagnose bacterial infection).
  - To estimate severity of cases of sepsis.
  - To predict outcome of cases of sepsis.
- What is the better biomarker to address these tasks is unknown.
  - However, PCT is better than CRP for all these tasks.
- The accrual of information that these biomarkers bring to clinical data remains to be determined.
  - This accrual must be estimated using a Bayesian approach (revised likelihood ratio).

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