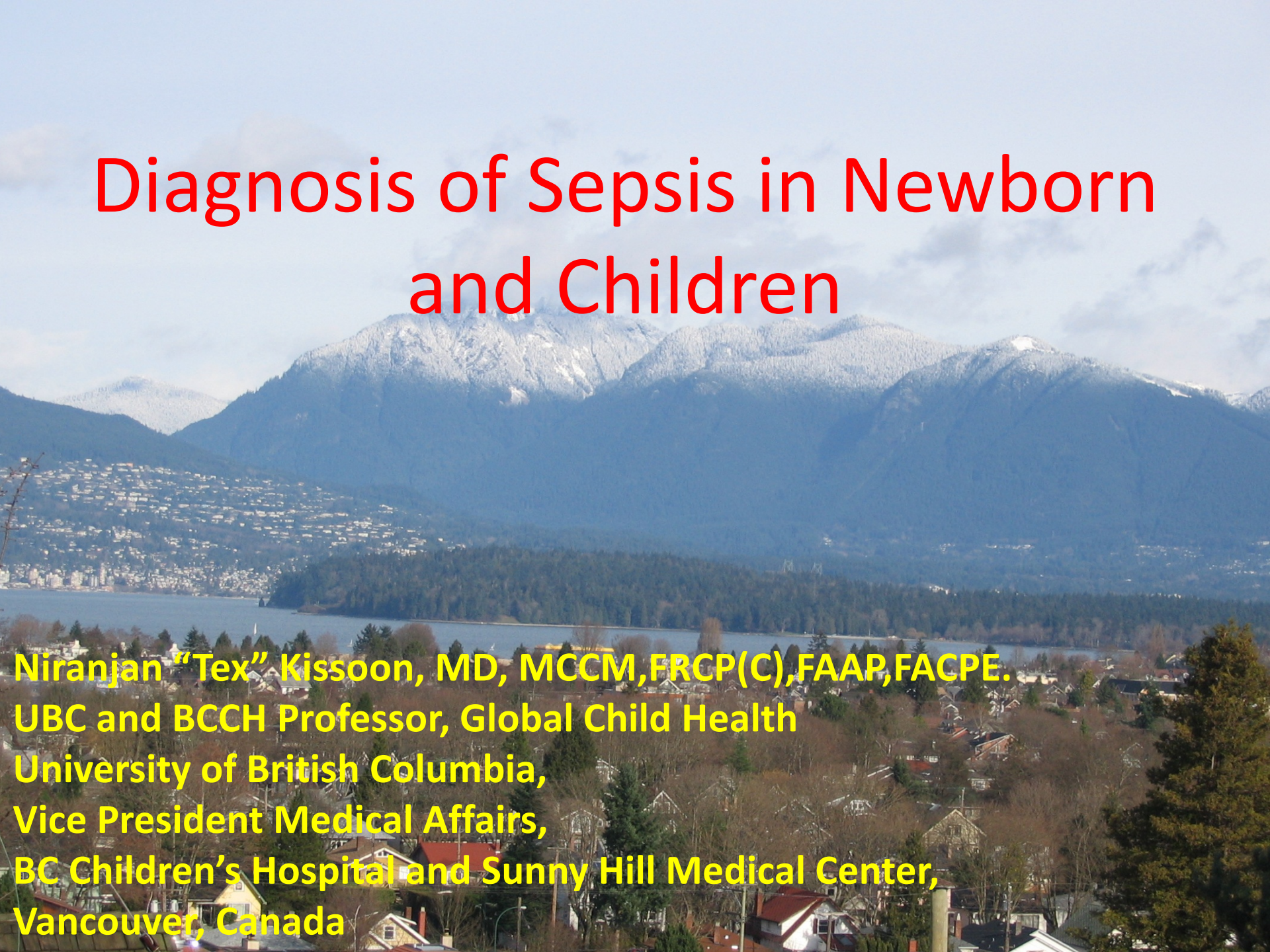
Diagnosis of Sepsis in Newborn and Children



Niranjan "Tex" Kissoon, MD, MCCM,FRCP(C),FAAP,FACPE.
UBC and BCCH Professor, Global Child Health
University of British Columbia,
Vice President Medical Affairs,
BC Children's Hospital and Sunny Hill Medical Center,
Vancouver, Canada

Diagnosis of Sepsis

- What is sepsis?
- Is context dependant
- Varies depending on definitions
- Is changing based on technology and improved knowledge
- Concluding remarks

CANADA

TRENDING Oregon | Election | Leader tracker | Polls | Blue Jays | Citizen Sparks

‘Inadequate patient assessment’: Canadian doctors missing glaring signs of sepsis

SHARON KIRKEY | July 6, 2015 8:35 AM ET
More from Sharon Kirkey | @sharon_kirkey

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André Picard
@picardonhealth

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‘Inadequate patient assessment': Canadian doctors missing glaring signs of #sepsis, by @sharon_kirkey natpo.st/1feGa08 via @nphealth

Special Article

International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*

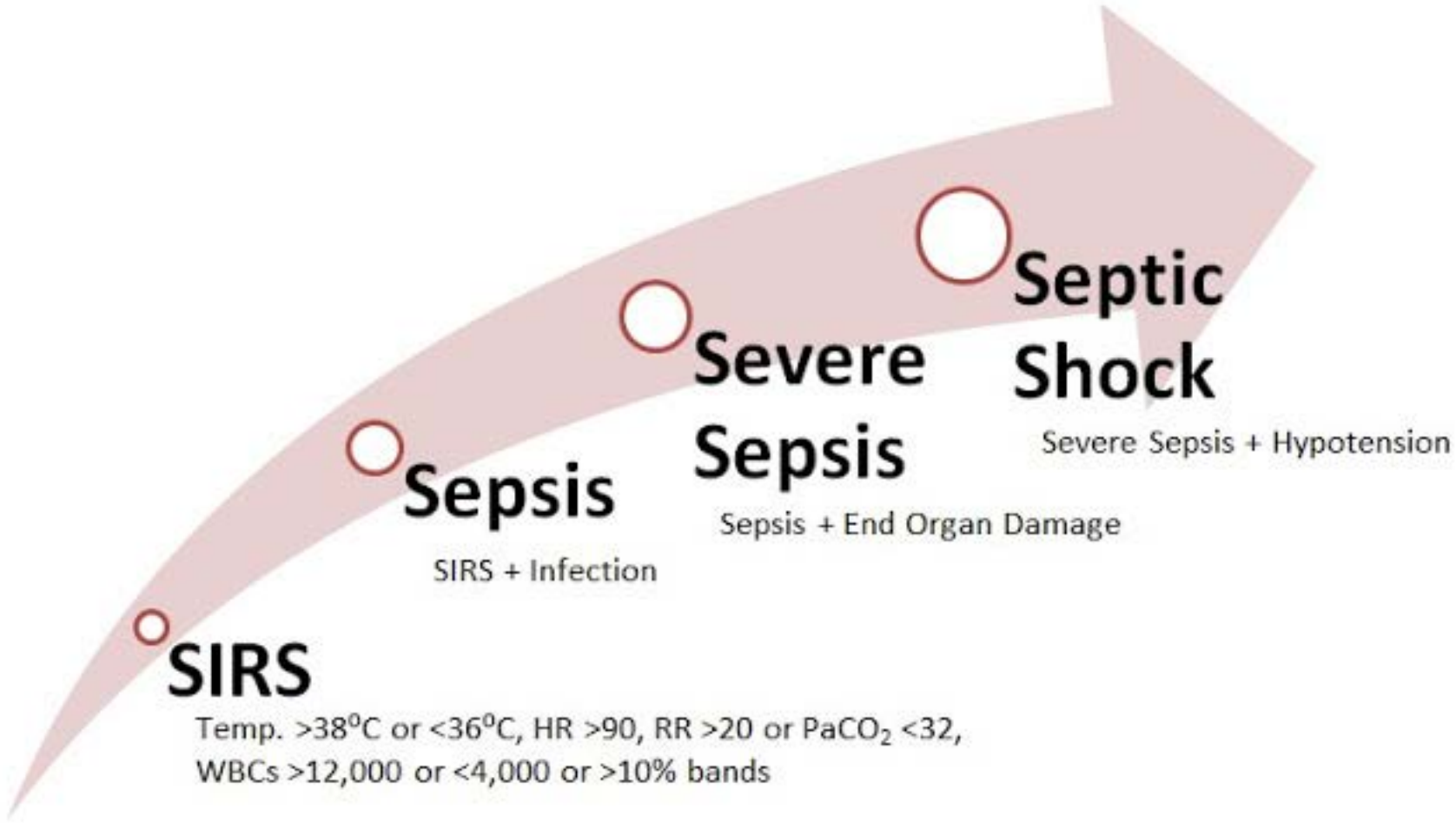
Brahm Goldstein, MD; Brett Giroir, MD; Adrienne Randolph, MD; and the Members of the International Consensus Conference on Pediatric Sepsis

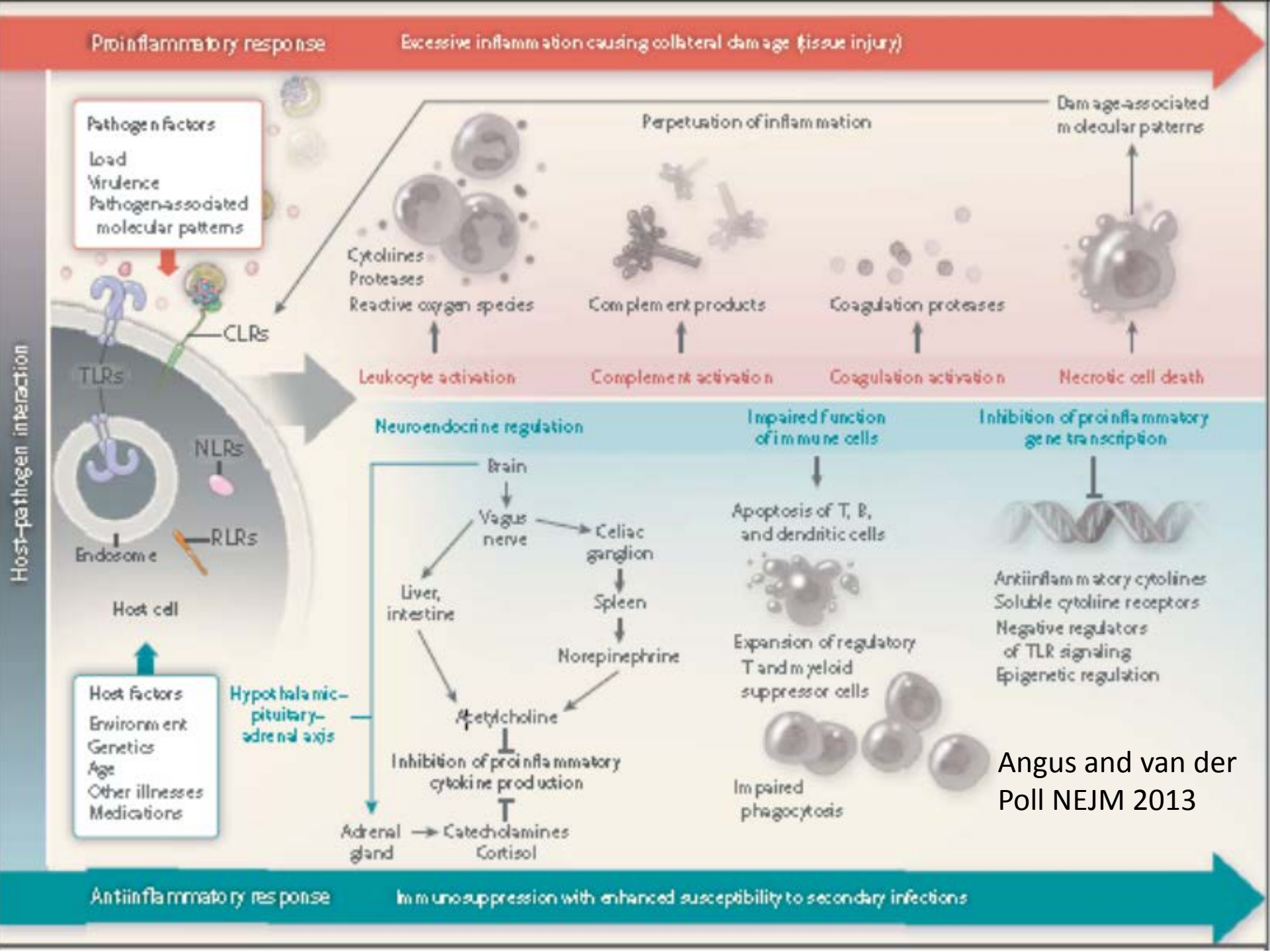
Sepsis

Core temp	<36^{O}C or >38.5^{O}C
Tachycardia	>2SD for age
Respiratory rate	>2SD for age
White cell count	elevated or suppressed for age

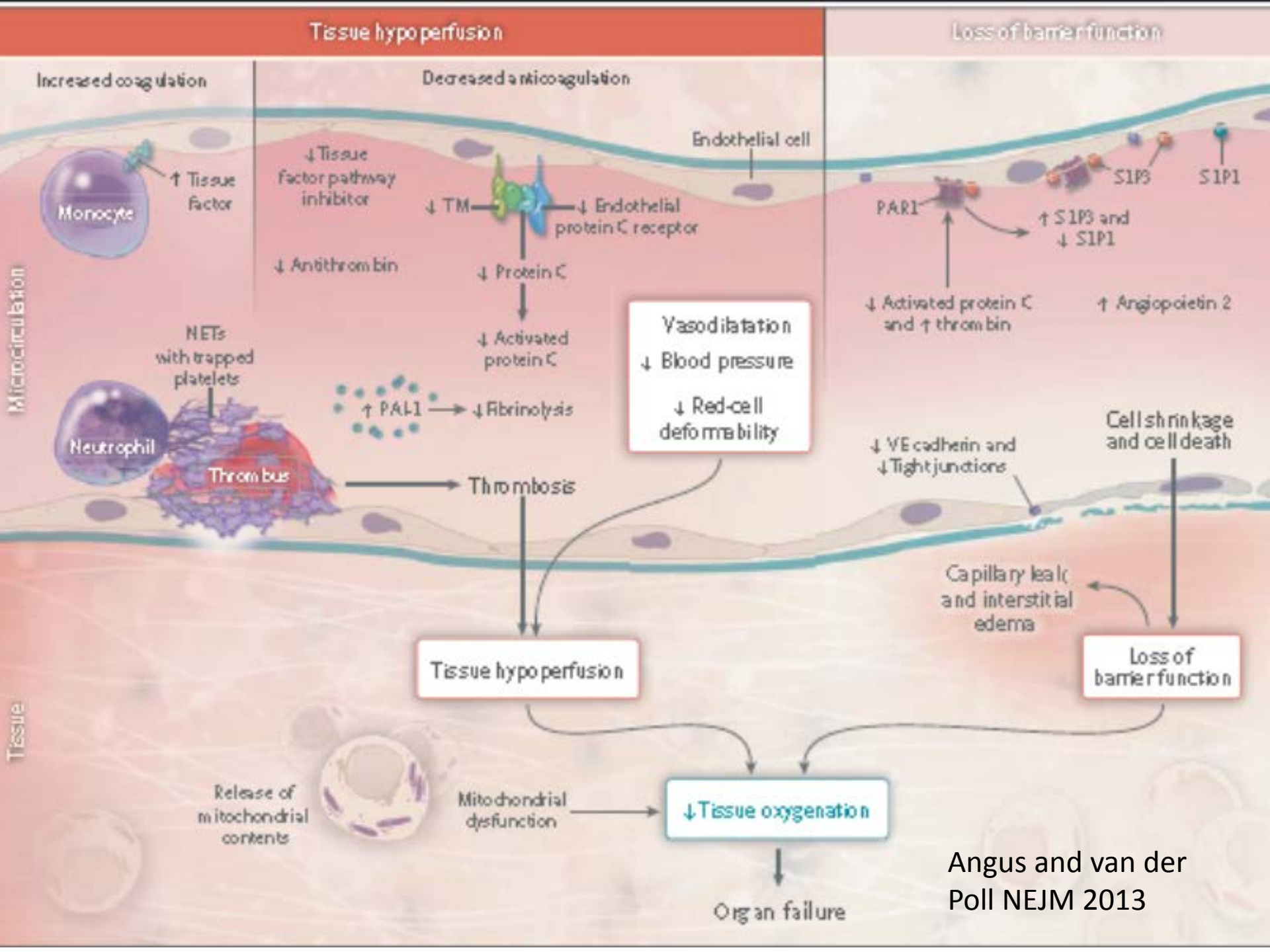
And

A suspected or proven infection caused by any pathogen OR a clinical syndrome Associated with a high probability of infection..

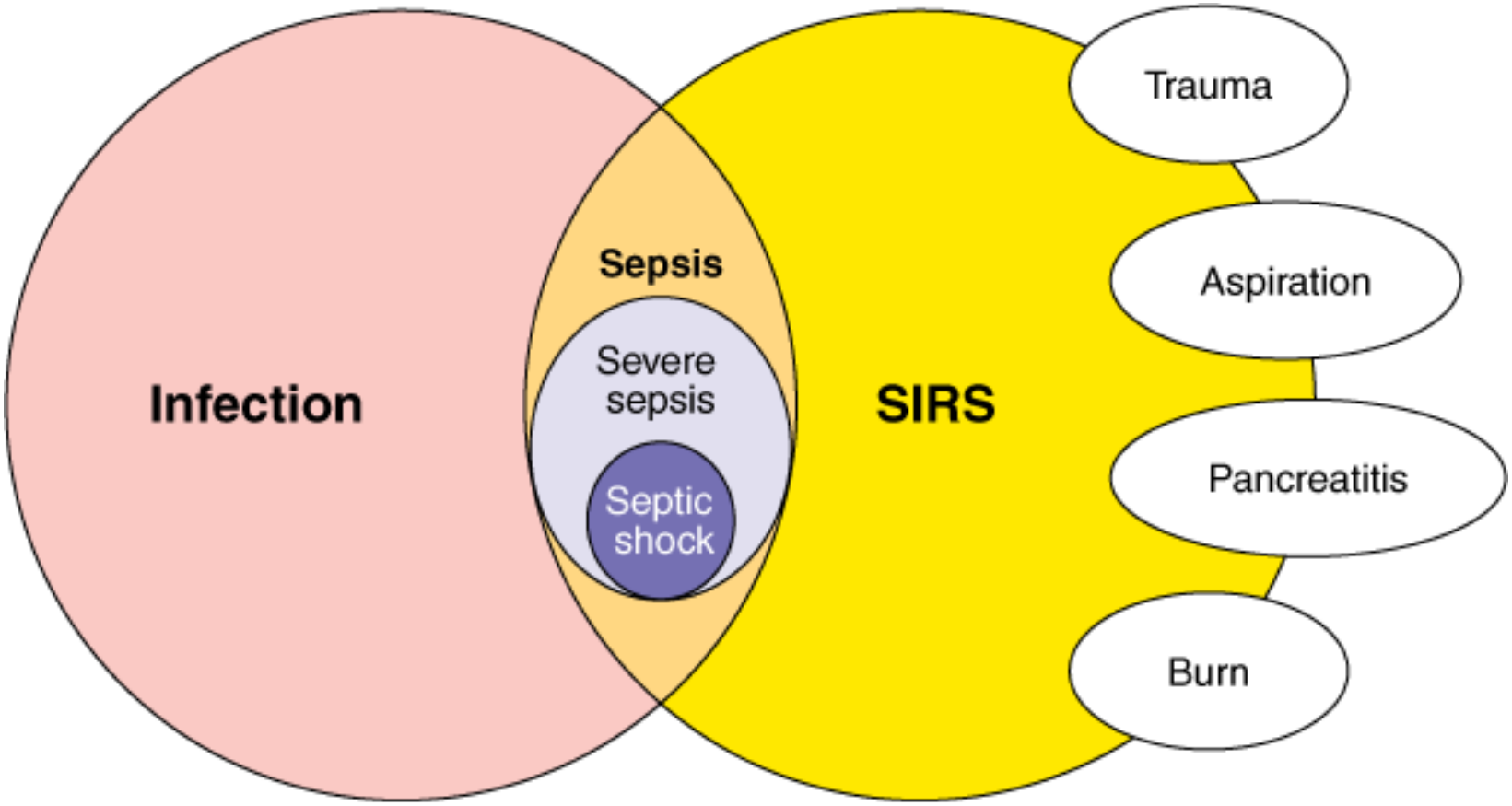

SIRS
Temp. >38°C or <36°C, HR >90, RR >20 or PaCO2 <32,
WBCs >12,000 or <4,000 or >10% bands
Sepsis
SIRS + Infection
Severe Sepsis
Sepsis + End Organ Damage
Septic Shock
Severe Sepsis + Hypotension



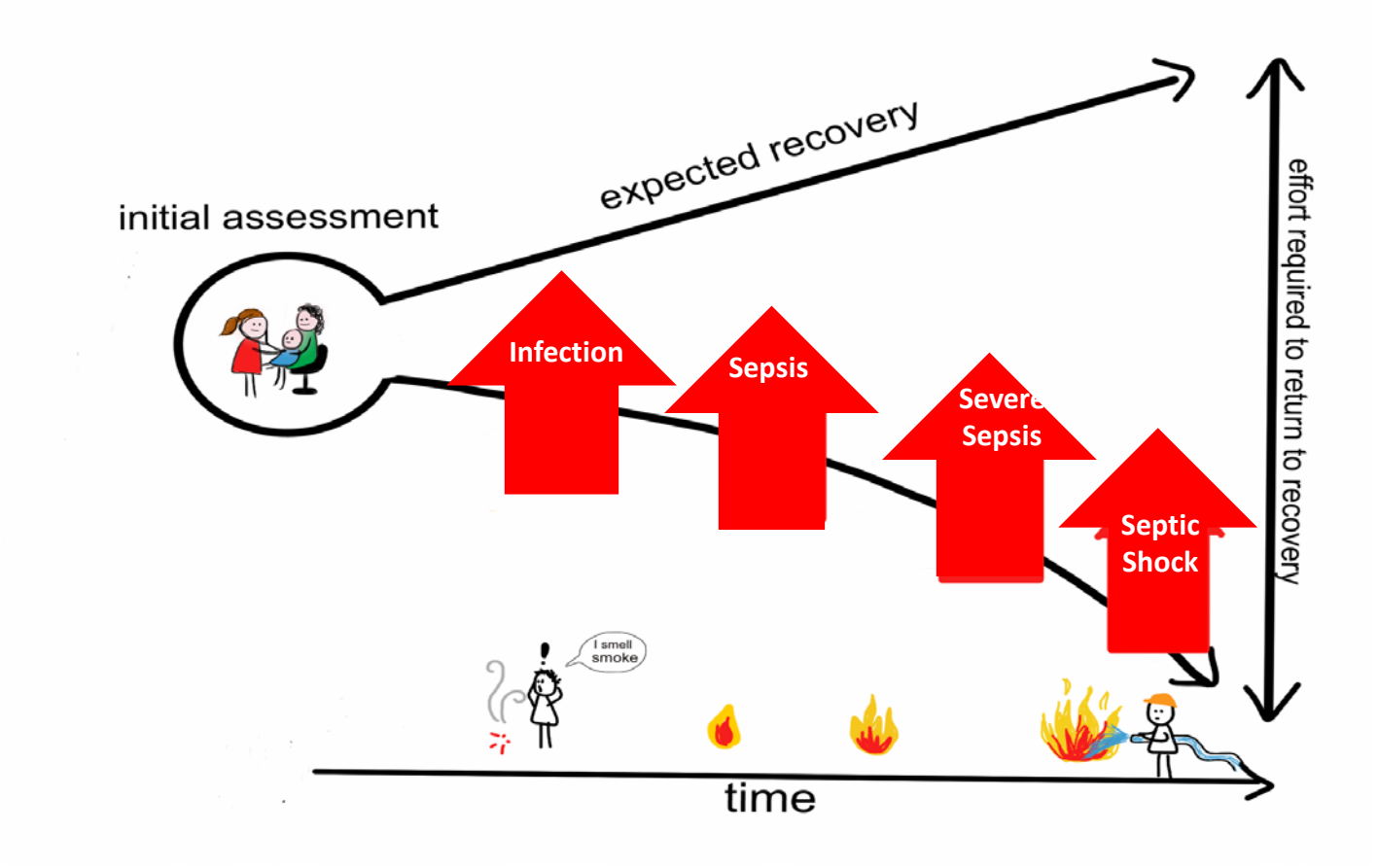
Angus and van der Poll NEJM 2013



Angus and van der Poll NEJM 2013


Infection
Sepsis
Severe sepsis
Septic shock
SIRS
Trauma
Aspiration
Pancreatitis
Burn

Trajectory of Sepsis and Interventions



Diagnosis of Sepsis

- What is sepsis?
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Diagnostic Criteria for Sepsis, Severe Sepsis and Septic Shock

- General Variables
  - Fever, hypothermia, tachycardia, tachypnoea, altered mental status, hypoglycemia, substantial edema
- Inflammatory Variables
  - Leucocytosis, leucopenia, > 10% immature WBC, elevated CRP or calcitonin
- Hemodynamic Variables
  - Arterial hypotension, elevated or decreased mixed venous O2 saturation and cardiac index

Diagnostic Criteria for Sepsis, Severe Sepsis and Septic Shock

- Organ Dysfunction Variables
  - Hypoxemia, oliguria, elevated creatinine, coagulation abnormalities, paralytic ileus, thrombocytopenia, hyperbilirubinemia
- Tissue Perfusion Variables
  - Decreased capillary refill or mottling, hyperlactatemia,
- Severe sepsis (sepsis + organ dysfunction)
- Septic shock (severe sepsis + fluid intractable hypotension or hyperlactatemia

Suspicion of Sepsis in Community

Any Newborn

- feels feverish (hot) or cold
- peri-umbilical pus, swelling or redness
- poor or no sucking (not feeding)
- feeble or no cry
- drowsy, difficult to arose
- convulsion
- repeated vomiting

Any Child

- Not feeding
- Feeling cold
- Convulsion
- Disoriented, difficult to engage
- Repeated vomiting

Interrupting Pathways to Sepsis Project - Bangladesh

Suspicion of Sepsis at Health Facility

SYNDROMIC SEPSIS CASE FINDING TOOL -NEONATE

Instruction: Please look for the danger signs listed below and (✓) Tick in appropriate box

Danger Signs	Look/Ask/Feel	Yes	No
Hypothermia ☐	1. Cold /Clammy Skin		
	2. Blue or Pale Color Skin		
	3. Axillary temperature <96^0 F		
Hyperthermia ☐	4. Axillary temperature > 101.3^0 F		
Altered mental status ☐	5. Unconscious /No movement		
	6. Lethargic/movement only when stimulated		
	7. Difficult to arouse/drowsy		
Convulsion ☐	8. Convulsion- by history (care giver report) or examination		
Respiratory Distress ☐	9. Severe Chest In drawing		
	10. Severe Breathing difficulty/noise breathing		
	11. Respiratory rate >60 (with any other danger sign)		
Umbilical infection ☐	12. Pus/foul smelling discharge from umbilicus		
	13. Red and swollen umbilicus with discharge		
Not Feeding properly ☐	14. Stops feeding properly/sudden loss of appetite		
	15. Poor or no sucking reflex		
	16. Vomits everything out/projectile vomiting		

- 1101 (86%) met the sepsis criteria.
- The SIRS criteria captured 61deaths, sensitivity 95% (95% CI, 90–100%) and specificity and 15% (95% CI, 13–17%).
- Most discriminatory individual component of the SIRS criteria was the WBC count, which alone had a sensitivity of 72% and a specificity of 56% for the identification of in hospital mortality.
- Having any two criteria had sensitivity equal to the full sepsis definition but had lower specificity (0.12).

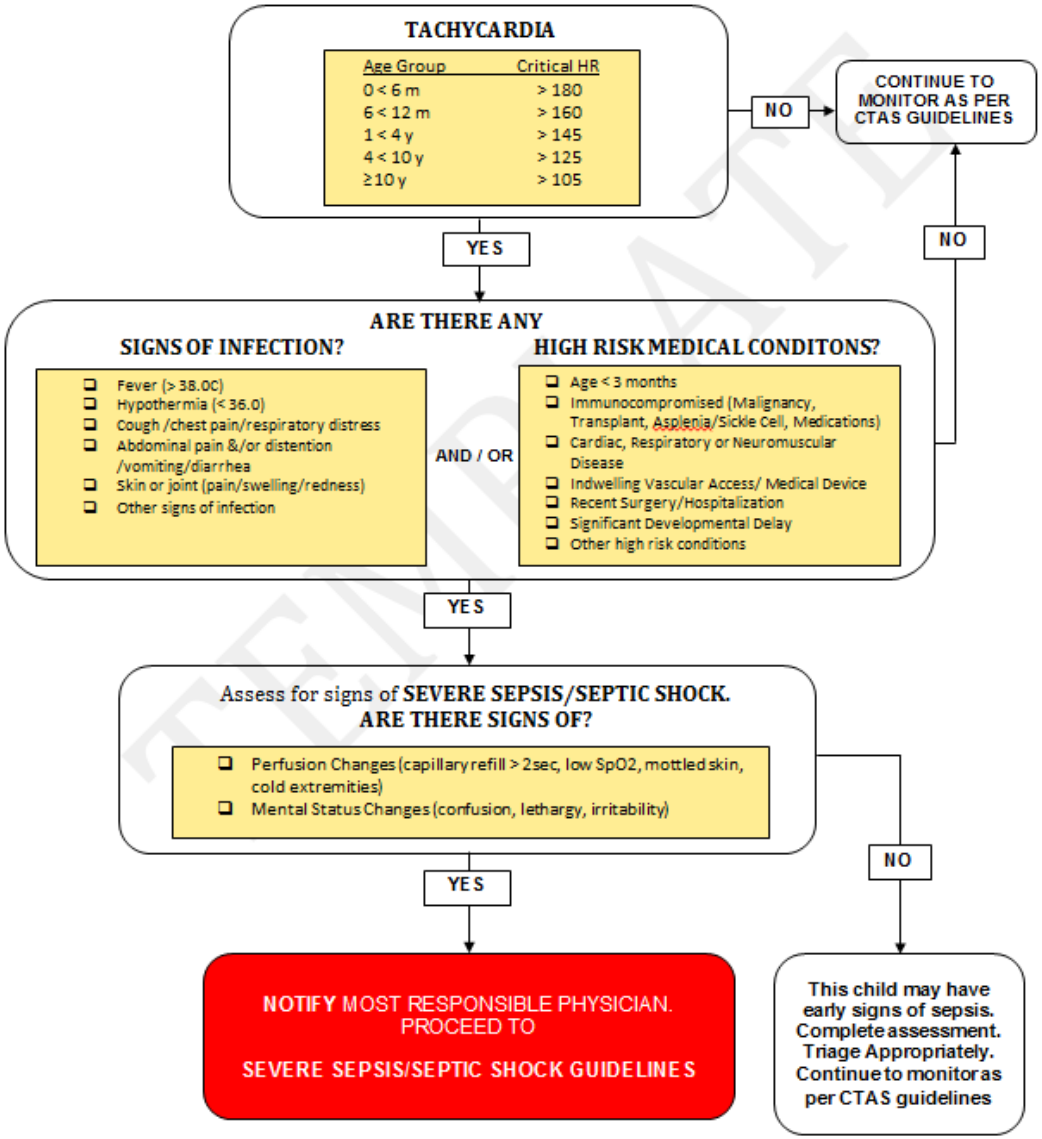
CAPHC SEPSIS SCREENING TOOL

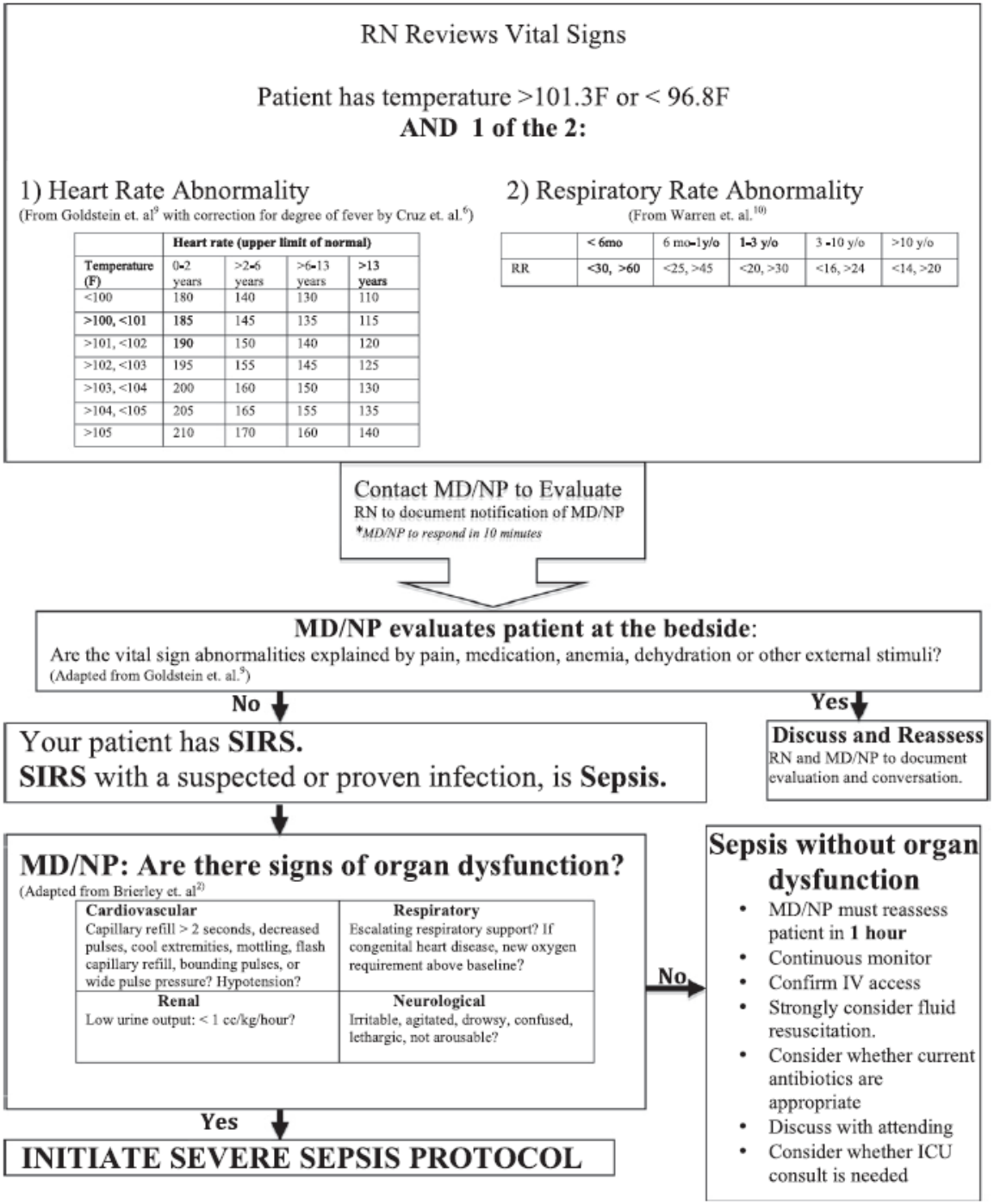
Emergency Department

Patient Identification Label

Patient Age: _____ days/months/years
Vital Signs: Temp: _____ HR: _____ RR: _____ BP: _____ SpO_2: ____
Date/Time: _____

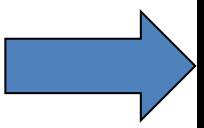
**This is a screening tool to identify patients with severe sepsis. No screening tool can identify all patients with severe sepsis. If you are concerned that a patient might have severe sepsis or another serious condition, notify the responsible physician immediately regardless of whether they meet the criteria in this tool.





Bradshaw C, et al. Implementation of an Inpatient Pediatric Sepsis Identification Pathway. *Pediatrics.* 2016;137(3):e20144082

Sepsis



Paediatric Sepsis 6

Severe sepsis is a **CLINICAL EMERGENCY**. Signs and symptoms of sepsis in children can be subtle and deterioration to shock rapid. Early initiation of simple treatment improves outcomes.

THE UK SEPSIS TRUST

YOU CAN MAKE A DIFFERENCE

Patient Name: Date of Birth: Unit number:

Recognition:

If a child with suspected or proven infection AND has at least 2 of the following:

- Core temperature < 36°C or > 38.5°C
- Inappropriate tachycardia (Refer to local criteria / APLS Guidance)
- Altered mental state (including: sleepiness / irritability / lethargy / floppiness)
- Reduced peripheral perfusion / prolonged capillary refill!

Think: could this child have SEPSIS or SEPTIC SHOCK?
If in doubt, consult a senior clinician.!

Time	Initials

Complete all elements within 1 hour

Respond with Paediatric Sepsis 6:

	Time	Initials
1. Give high flow oxygen:		
2. Obtain intravenous/ intraosseous access & take blood tests:		
a. Blood cultures		
b. Blood glucose - treat low blood glucose		
c. Blood gas (+ FBC, lactate & CRP as able for baseline)		
3. Give IV or IO antibiotics:		
- Broad spectrum cover as per local policy		
4. Consider fluid resuscitation:		
- Aim to restore normal circulating volume and physiological parameters		
- Titrate 20 ml/kg Isotonic Fluid over 5 - 10 min and repeat if necessary		
- Caution with fluid overload > Examine for crepitations & hepatomegaly		
5. Involve senior clinicians / specialists early:		
6. Consider inotropic support early:		
- If normal physiological parameters are not restored after ≥ 40 ml/kg fluids		
- NB adrenaline or dopamine may be given via peripheral IV or IO access!		

Record any reasons for variation from Paediatric Sepsis 6 overleaf

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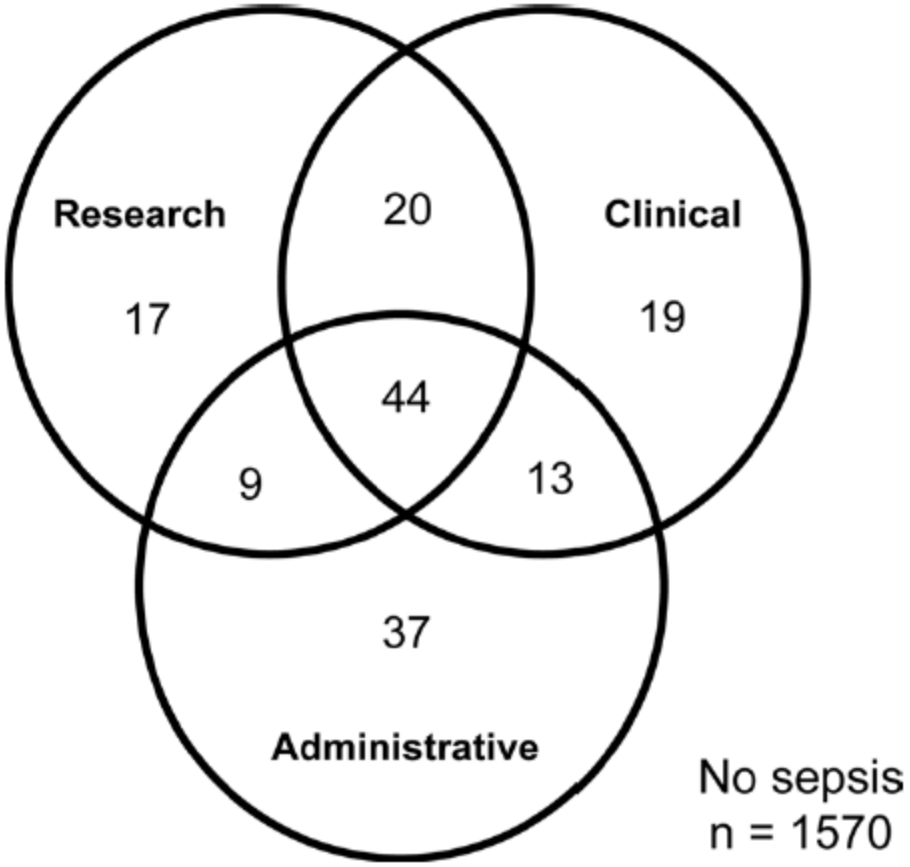
Defining Pediatric Severe Sepsis



PICU – 42 beds, 1729 patients

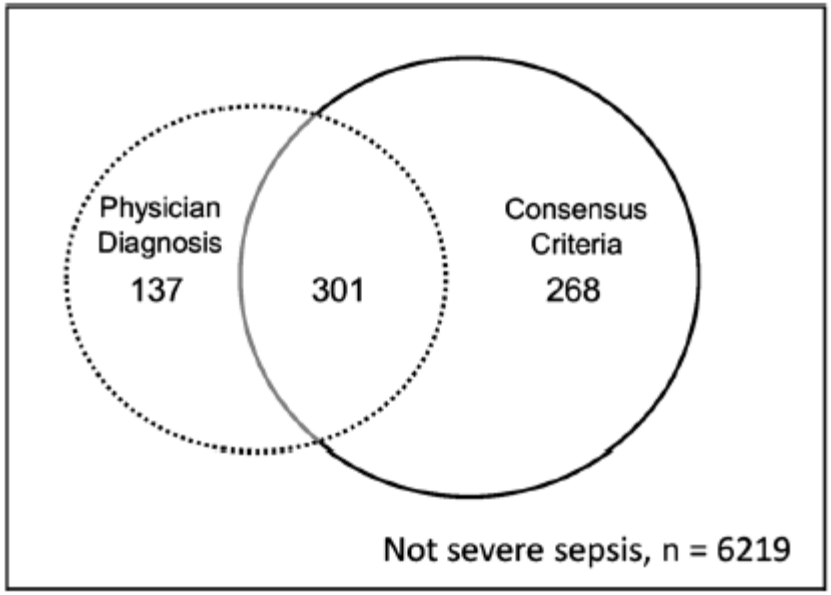
Consensus guidelines (research criteria)
N= 90 (5.2%)

Diagnosis by healthcare professionals (clinical criteria) n= 92 (5.6%)

ICD 9 (administrative criteria)
N=103 (6.0%)

Weiss SL et al PCCM 2012

Discordant Identification of Severe Sepsis



Agreement was lowest in North America (31 %) moderate in Australia and New Zealand (45 %) and Europe (51 %); and highest in Asia (72 %), Africa (72 %), and South America (85 %).

- Only 301/706 patients (42.6 %) were identified by both criteria (κ 0.57 ± 0.02).
- The 137/438 of patients (31 %) who did not meet consensus criteria were younger, had a lower severity of illness, and a lower PICU mortality than those who met consensus criteria or both definitions.

Weiss et al. Critical Care (2015) 19:325

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Sepsis Detection Methods
Algorithmic Alert vs. Physician Judgement

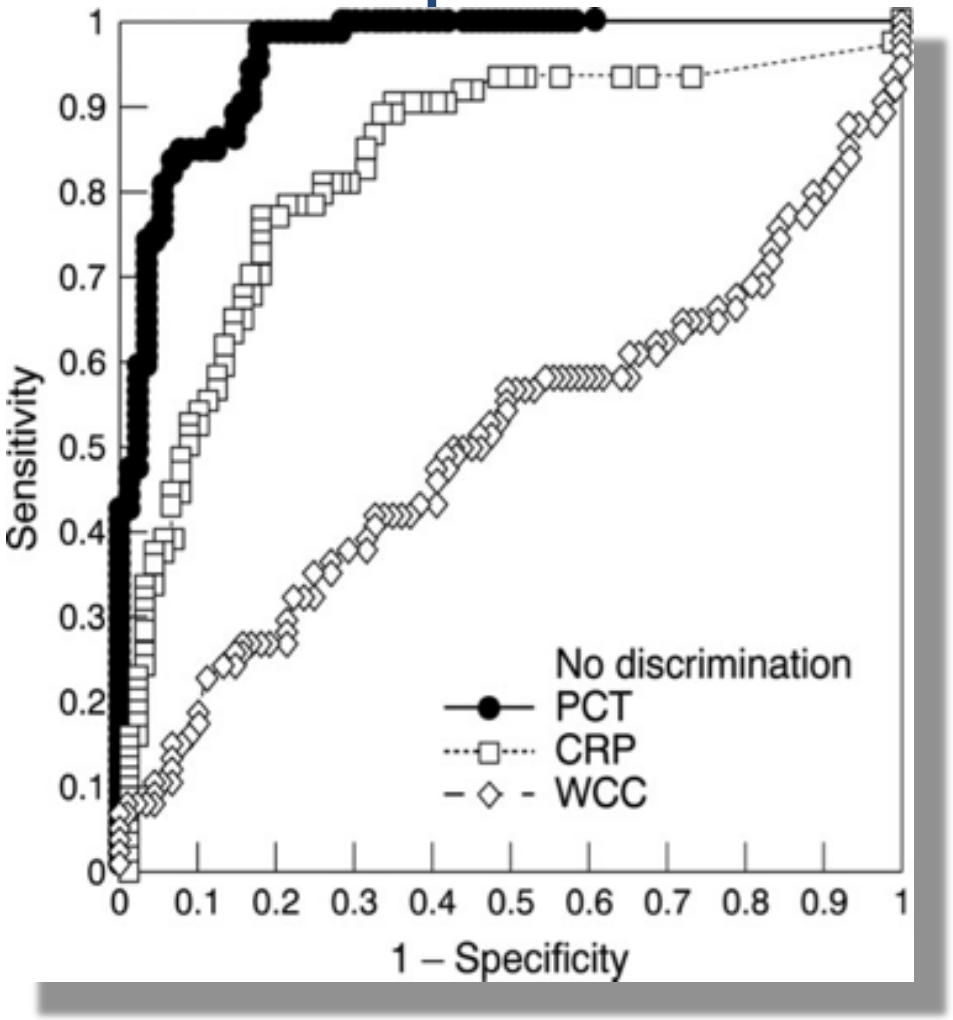
Test characteristics of sepsis screening tests.

Test	Algorithmic Alert	Physician Judgment	Combined Method	Sequential Method
	Test Characteristic (95% CI)			
Sensitivity	92.1 (91.67–92.43)	72.73 (72.1–73.35)	96.6 (96.3–96.9)	68.2 (67.5–68.8)
Specificity	83.4 (82.91–83.95)	99.51 (99.41–99.61)	83.3 (82.8–83.8)	99.6 (99.6–99.7)
Positive predictive value	2.5 (2.24–2.67)	40.25 (39.56–40.94)	2.6 (2.3–2.8)	47.6 (46.9–48.3)
Negative predictive value	99.96 (99.93–99.99)	99.88 (99.83–99.93)	99.98 (99.96–100)	99.86 (99.80–99.91)
Positive likelihood ratio	5.6 (5.18–5.95)	148.79 (117.2–1900)	5.8 (5.5–6.1)	200.8 (151.8–266.7)
Negative likelihood ratio	0.09 (0.05–0.19)	0.27 (0.19–0.39)	0.04 (0.01–0.12)	0.32 (0.24–0.43)
Receiver operative characteristic curve area	0.88 (0.85–0.91)	0.86 (0.81–0.91)	0.90 (0.88–0.92)	0.84 (0.79–0.89)

Severe sepsis/septic shock prevalence: 88 (0.45%)

Balamuth F et al *Acad Emerg Med*. 2015 November ; 22(11): 1298–1306

What is the probability this patient is septic?



Lactate Clearance, Normalization and Organ Dysfunction in Sepsis

Table VI. Absolute and relative change in lactate level from the first to the final lactate level, by clearance and normalization status

	Lactate clearance (n = 70)	Lactate nonclearance (n = 7)	Lactate normalization (n = 62)	Lactate non-normalization (n = 15)
Absolute change in lactate level	−0.73 mmol/L [−0.3, −1.55]	0.55 mmol/L [0.47, 1.69]	−0.58 mmol/L [−0.27, −1.44]	−0.33 mmol/L [−.19, −.58]
% change in lactate level	−32.1% [−19.5, −55.2%]	35.3% [16.0, 61.9%]	−33.4% [−19.4, −58.1%]	−11.9% [35.2%, −30.6%]

Results presented as median [IQR].

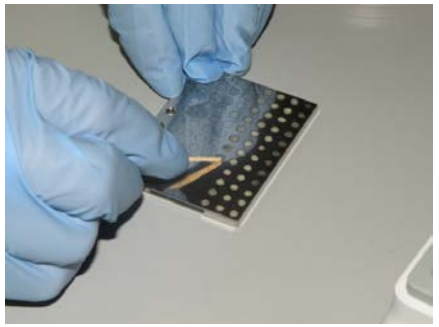
- Lactate normalization was associated with decreased risk of persistent organ dysfunction (RR 0.46, 0.29-0.73.
- Lactate clearance was not (RR 0.70, 0.35-1.41.

Scott HF et al J Pediatr 2016;170:149-55

Still Laborious and Slow?

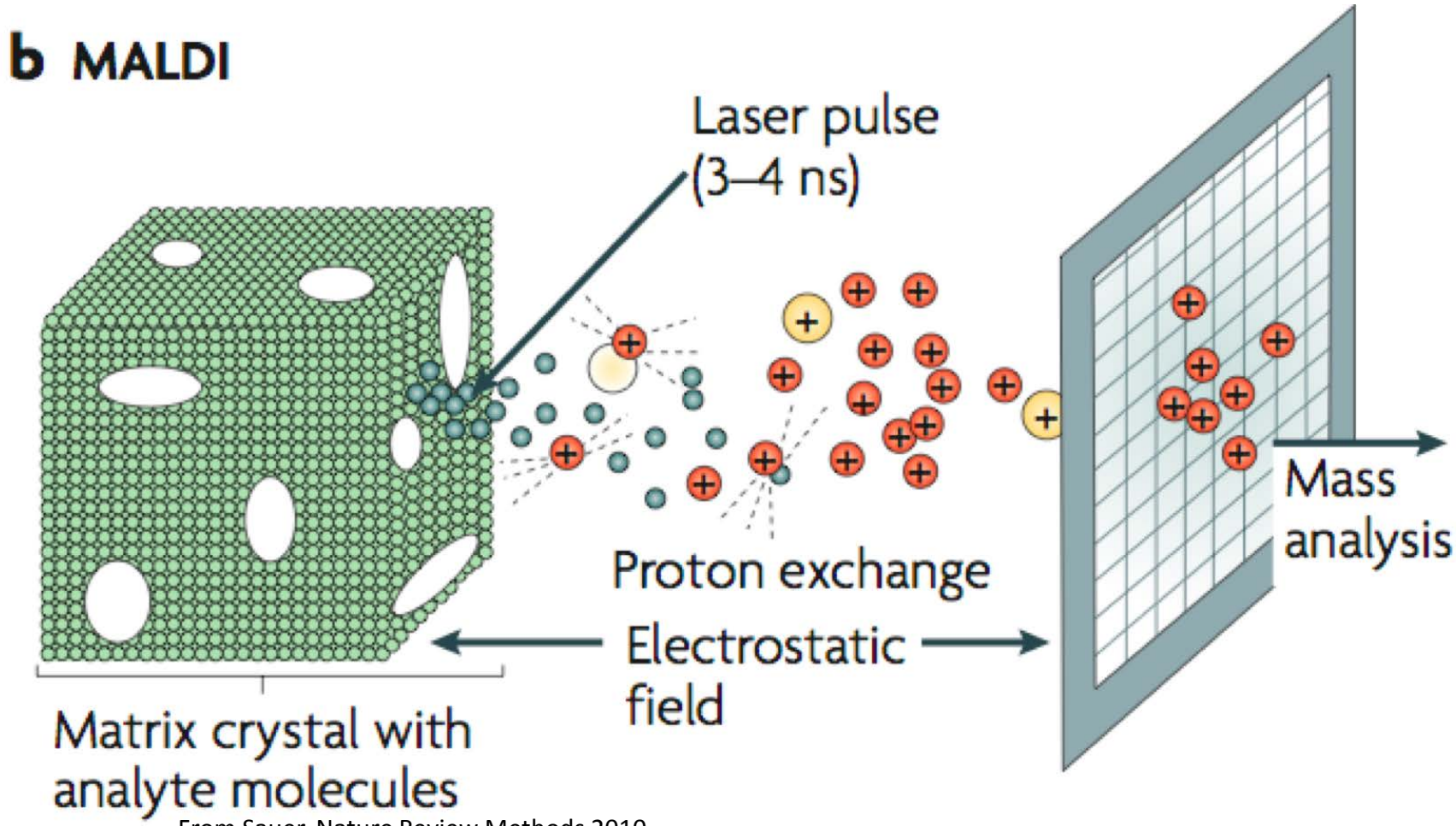
- Colonies or or a positive blood culture bottle!

- Plate Innoculated



- Instrument Loaded

Matrix Assisted Laser Desorption/Ionization (MALDI)



From Sauer, Nature Review Methods 2010

PCR Followed by Mass Spec

- Whole samples and paired blood cultures (247 from 175 patients)
- Blood Culture
  - Agreement between PCR-MS and conventional method (blood culture) = 94%
  - Sensitivity 97%, specificity 99% for PCR-MS
- PCR-MS identified 13 more pathogens not found by conventional means

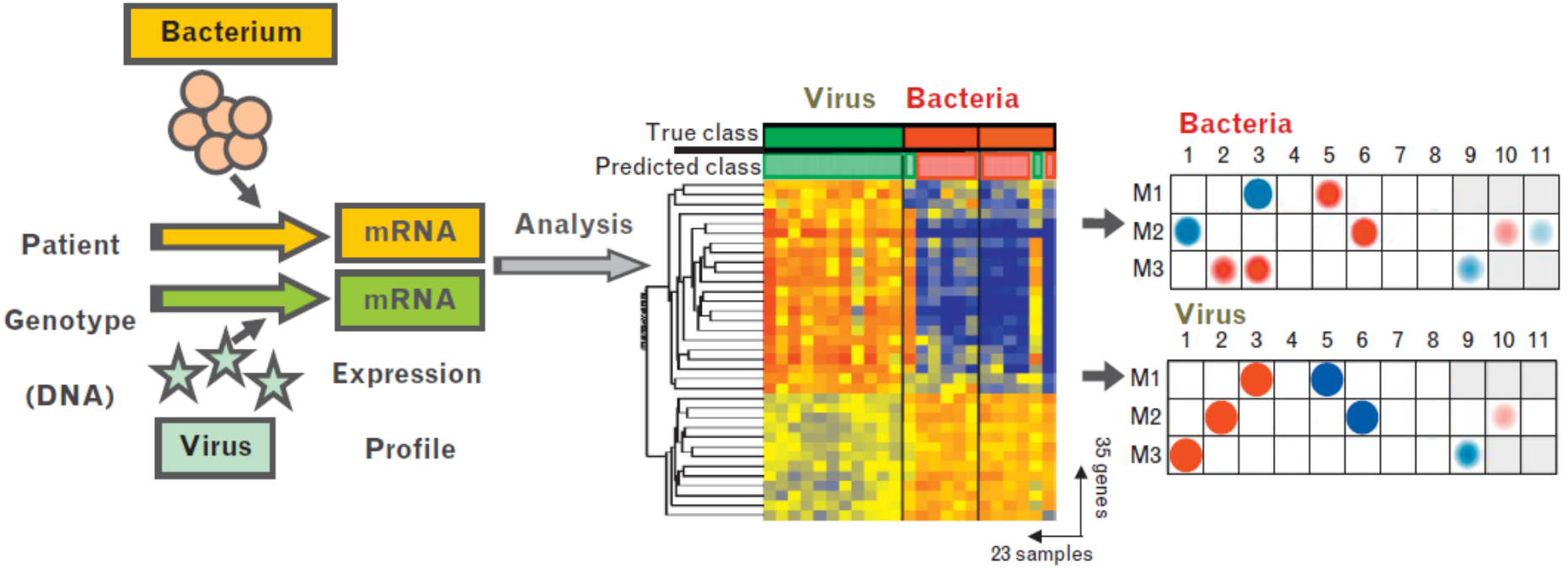
Elena Jordana-Lluch et al PLOS One 2013

Rapid Molecular Diagnostics

- Biomarkers - characteristics that can be measured and evaluated as an indicator of pathological processes or responses to a therapeutic intervention
- Ideal for all biomarkers
  - sensitivity, specificity, predictive value
- Ideal for acute conditions
  - readily obtainable from body fluids or tissue samples
  - test results available in a relatively short period

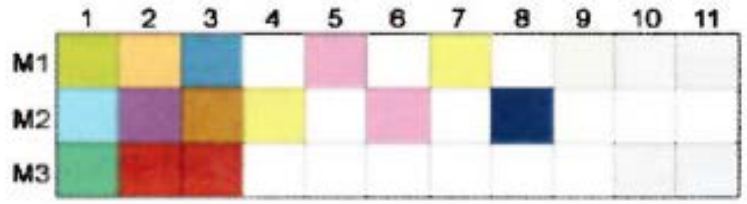
Atkinson AJ Jr, et al.: Clin Pharmacol Ther 2001.

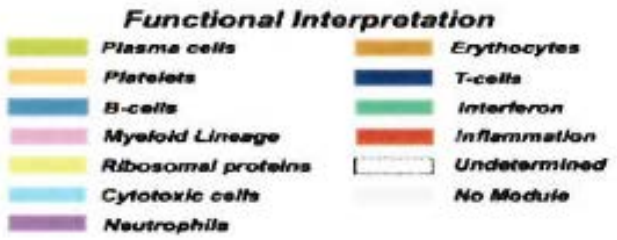
Gene Expression Profiles

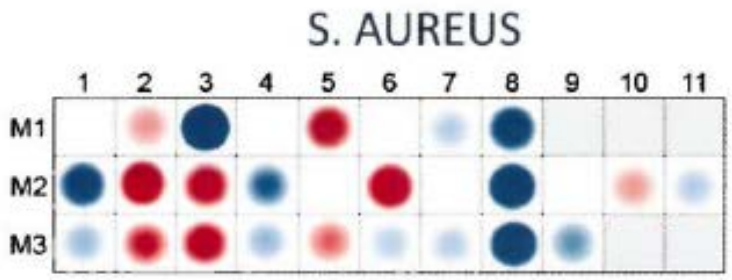


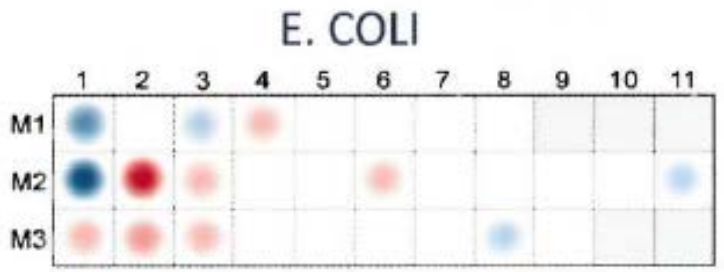
Ramilo O, Mejias A. Cell Host Microbe 2009; 6:199–200.

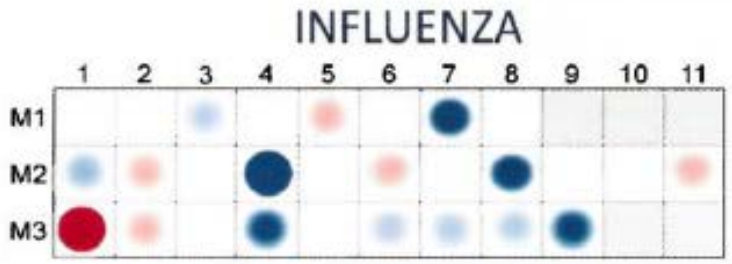
Transcriptional Profiling: Ready for prime time

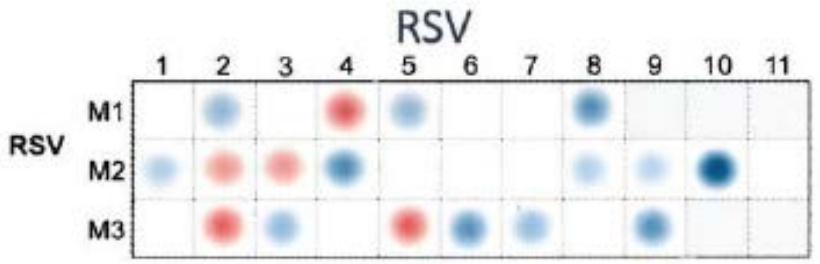












Mejias A and Ramilo O Transcriptional profiling in infectious diseases J Infection 2014;68:S94

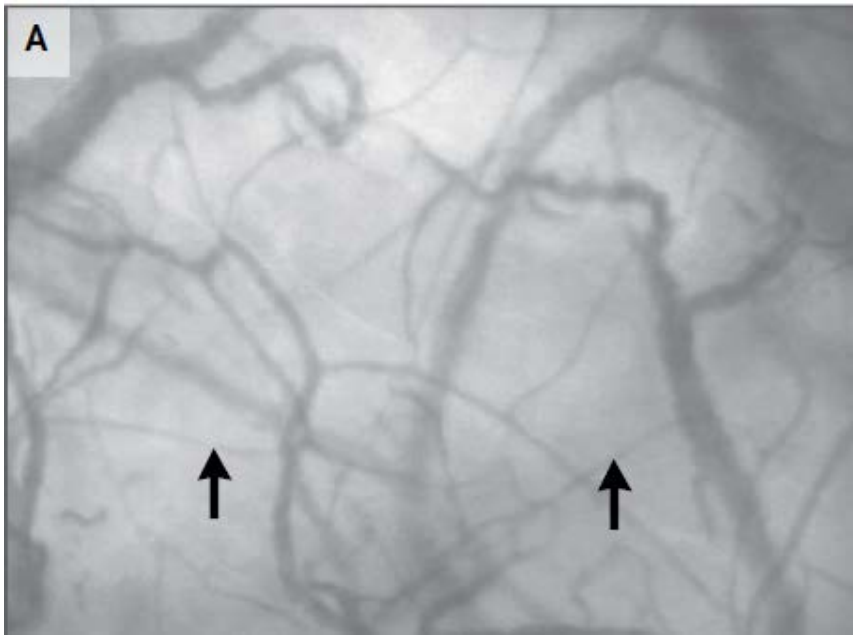
New Diagnostic Biomarkers in Pediatric Sepsis

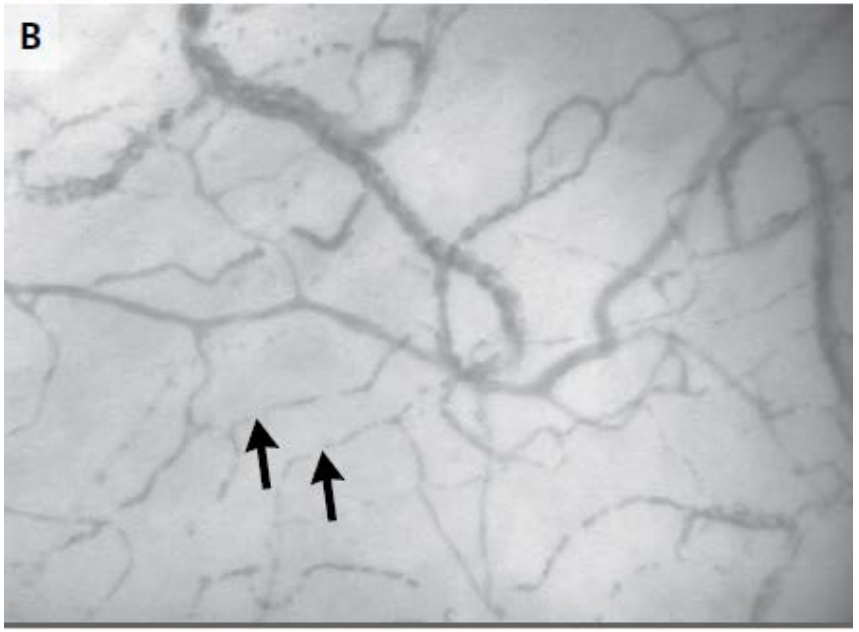
Table 1. Association of study measurements with severity of illness, organ dysfunction, and clinical outcome in septic patients[a].

		MMP-9/TIMP-1		MrProANP		A-FaBP	
Outcomes		**rs**	**P**	**rs**	**P**	**rs**	**P**
Severity of illness and Organ Dysfunction	PIM-2	-0.57	<0.001	0.60	<0.001	0.25	0.092
	PELOD	-0.74	<0.001	0.62	<0.001	0.36	0.013
Clinical Outcome	ICU LOS	-0.68	<0.001	0.69	<0.001	0.37	0.011
	Hospital LOS	-0.66	<0.001	0.62	<0.001	0.34	0.020
	Inotrope-free days	0.23	0.299	-0.07	0.748	-0.24	0.337
	Ventilator-free days	-0.242	0.277	-0.16	0.497	-0.43	0.072
	GOS[b]	0.45	0.036	-0.19	0.404	0.014	0.956

Alqahtani MF et al PLoS ONE 2016; 11(4): e0153645.

Sidestream Dark-Field Images of Sublingual Microcirculation





Vincent JL and De Backer D NEJM 369;18;2013

Persistent low microcirculatory vessel density in nonsurvivors of sepsis

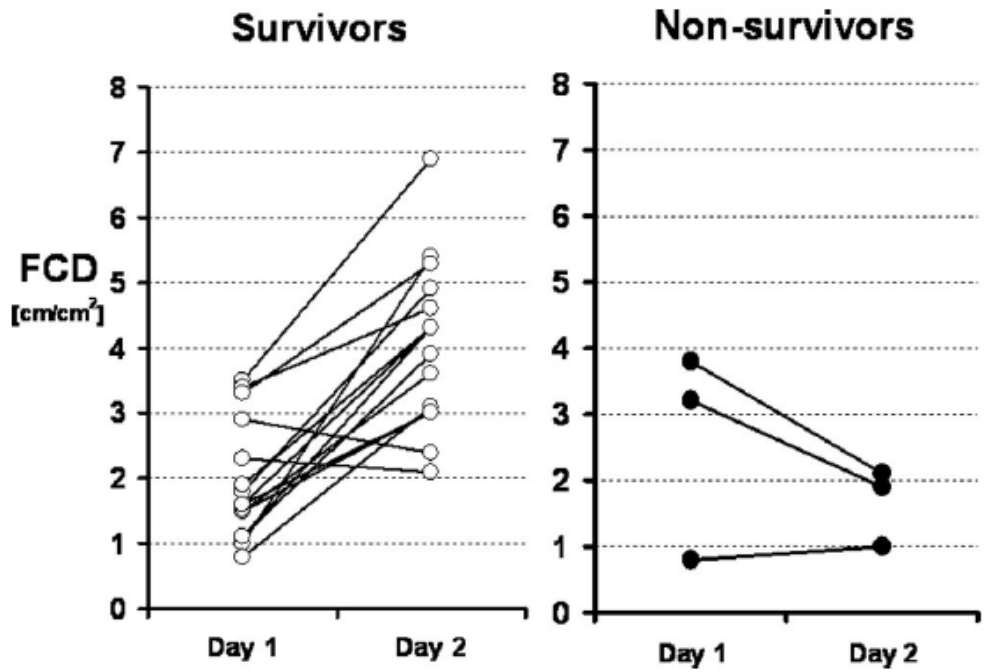


Figure 2. The functional capillary density (*FCD*) improved in survivors. Day 1: 1.7 cm/cm^2 (0.8–3.4); day 2: 4.3 cm/cm^2 (2.1–6.9) (p = .001). The FCD in nonsurvivors did not change. Day 1: 3.2 cm/cm^2 (0.8–3.8); day 2: 1.9 cm/cm^2 (1.0–2.1). The median FCD on day 2 was lower in nonsurvivors: 1.9 cm/cm^2 (1.0–2.1) vs. 4.3 cm/cm^2 (2.1–6.9) (p = .009).

Top A et al Crit Care Med 2011;39:8

Mortality Prediction in PICU

- Septic shock (2005 consensus) was sensitive but not specific (AUC = 0.69; 95% CI 0.65–0.72).
- Oxygenation markers, ventilator support, hypotension, cardiac arrest, serum lactate, pupil responsiveness, and immunosuppression were the best-performing predictors (0.843; 0.811–0.875).
- The sepsis score performed comparably when applied to all children admitted with invasive infection (0.810; 0.781–0.840).

Schlapbach L J et al Intensive Care Med 2017;

Mortality Prediction in PICU

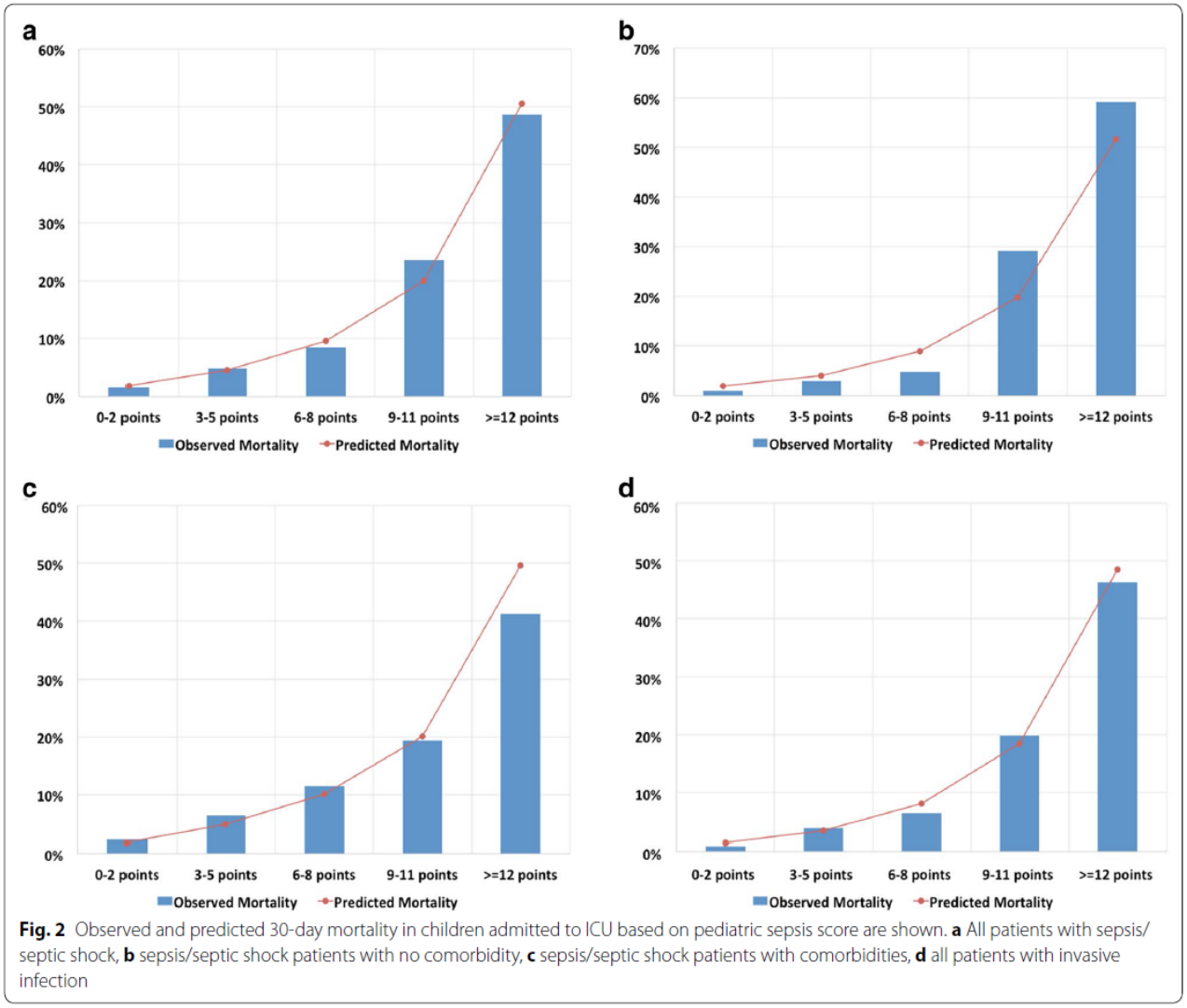


Fig. 2 Observed and predicted 30-day mortality in children admitted to ICU based on pediatric sepsis score are shown. **a** All patients with sepsis/septic shock, **b** sepsis/septic shock patients with no comorbidity, **c** sepsis/septic shock patients with comorbidities, **d** all patients with invasive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

Every one-point increase was associated with a 28.5% (23.8–33.2%) increase in the odds of death.

Children with a score ≥6 had 19.8% mortality and accounted for 74.3% of deaths.

Schlapbach L J et al Intensive Care Med 2017;

Clinicians' gut feeling about serious infections in children: observational study

Ann Van den Bruel *clinical lecturer*[1], Matthew Thompson *director*[1], Frank Buntinx *professor*[2], David Mant *emeritus professor*[1]

[1]Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Oxford OX2 6GG, UK; [2]Department of General Practice, Catholic University of Leuven, Leuven, Belgium

- Intuition that something was wrong despite the clinical assessment of non-severe illness substantially increased the risk of serious illness (LR 25.5, 95% CI 7.9 to 82.0)
- Strongly associated with gut feeling : children's overall response (drowsiness, no laughing), abnormal breathing, weight loss, and convulsions.
- Strongest contextual factor was the parents' concern that the illness was different from their previous experience (OR 36.3, 95% CI 12.3 to 107).

BMJ 2012

Conclusions

- Sepsis is a life threatening organ dysfunction caused by a dysregulated host response to infection
- Present definitions and methods of diagnosis are imperfect
- Approaches are context dependent and should be pragmatic
- Move afoot to change the current state.