Sepsis, an infection gone wrong

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

DEATH
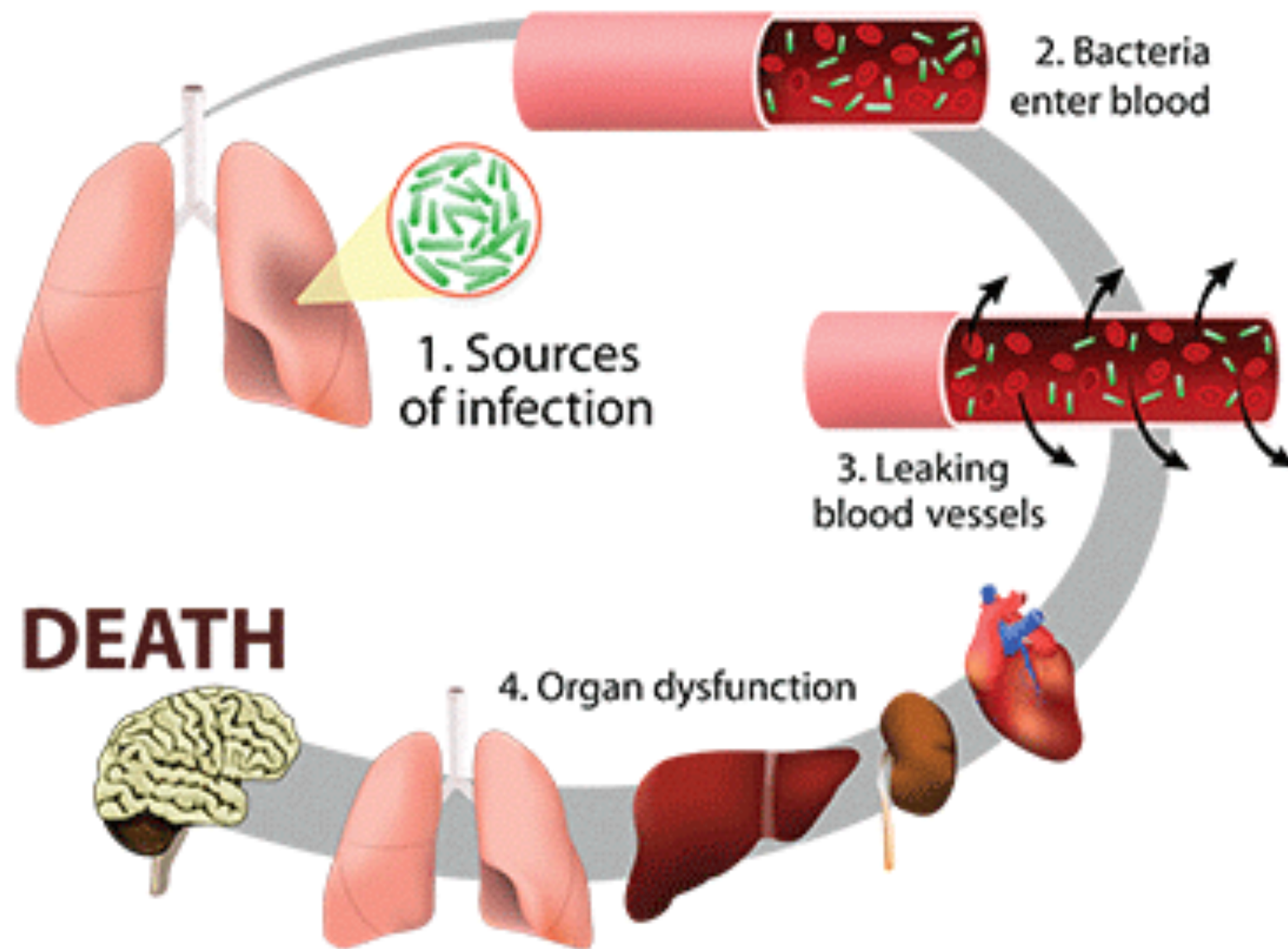
Inflammatory response
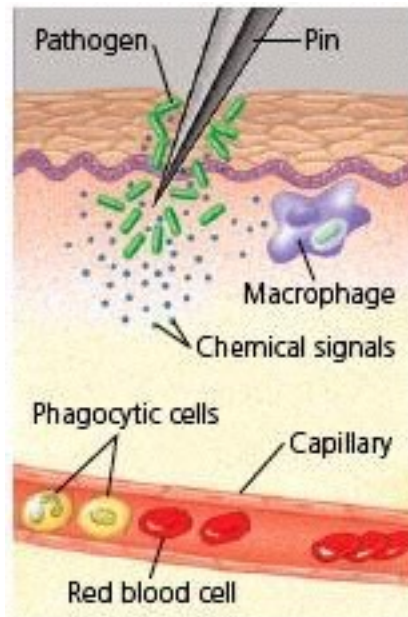
1. Chemical signals released by activated macrophages and mast cells at the injury site cause nearby capillaries to widen and become more permeable.
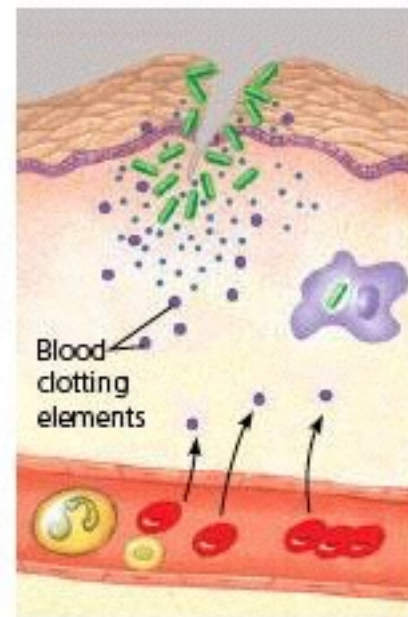
2. Fluid, antimicrobial proteins, and clotting elements move from the blood to the site. Clotting begins.
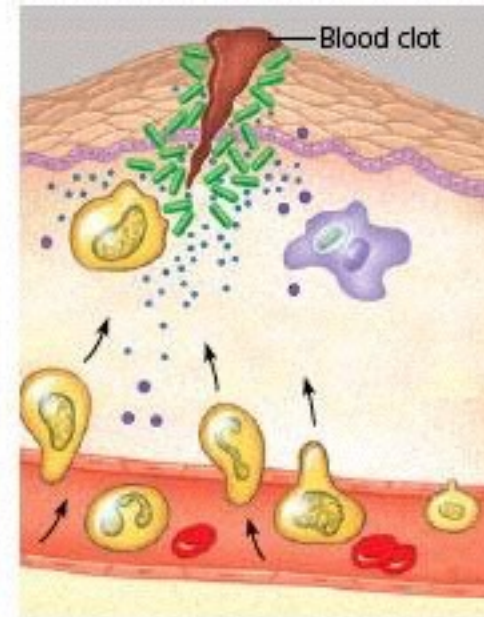
3. Chemokines released by various kinds of cells attract more phagocytic cells from the blood to the injury site.
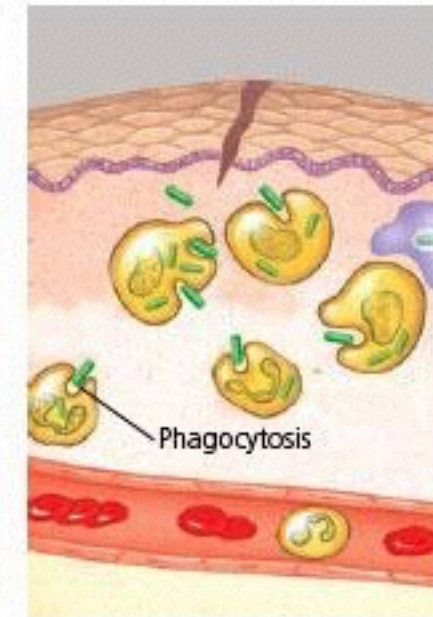
4. Neutrophils and macrophages phagocytose pathogens and cell debris at the site, and the tissue heals.

Resolution of the inflammatory response

In sepsis this regulation is disrupted

Why is sepsis important?

Septicemia is the

11th leading

cause of death

in the US

Over 750,000

cases of severe sepsis or

septic shock

annually and rising

Accounts for

20-30% of all

hospital deaths

Patients with sepsis have
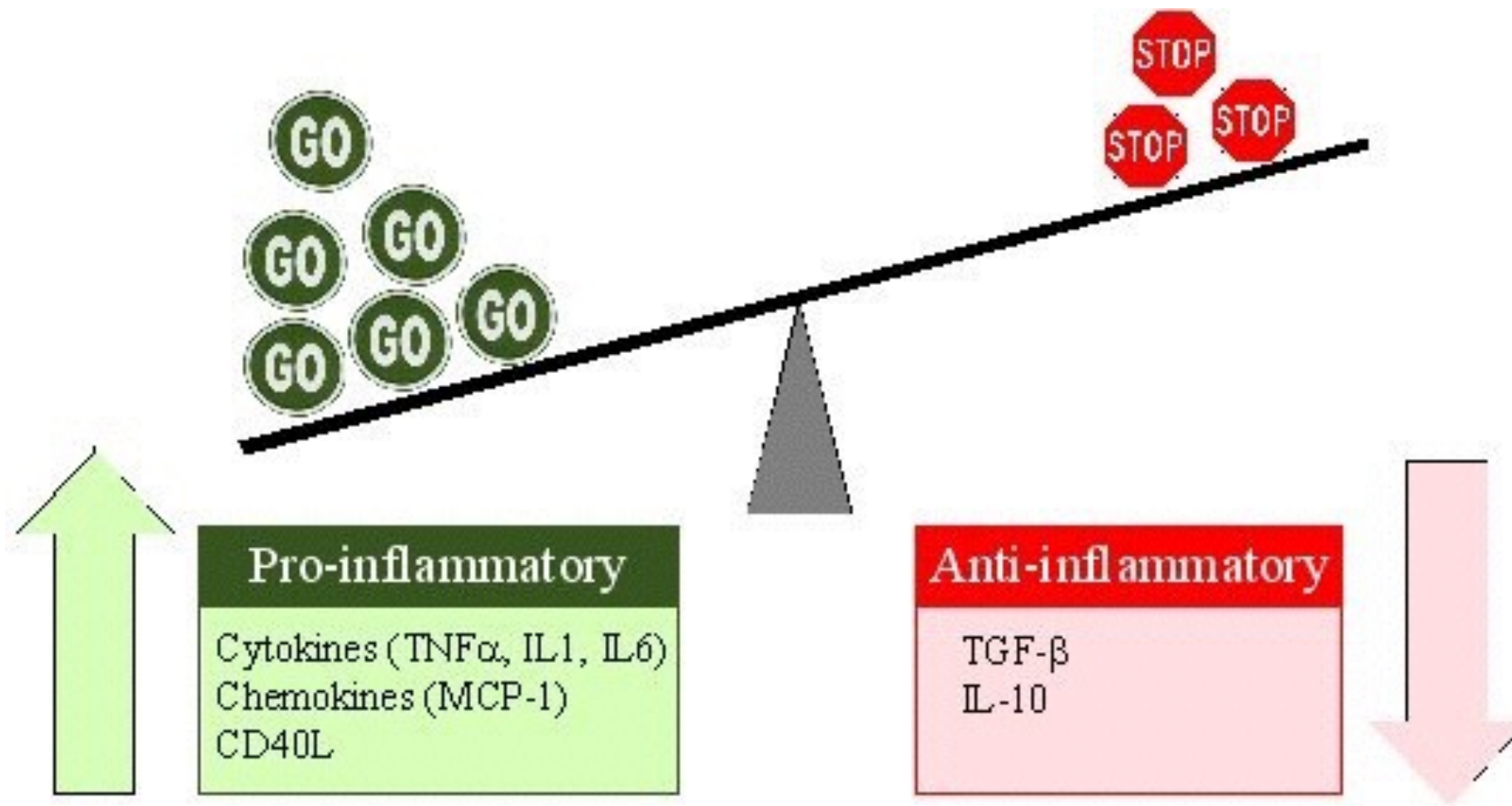
increased

hospital stays

and long-term

morbidities

D. C. Angus, W. T. Linde-Zwirble, J. Lidicker, G. Clermont, J. Carcillo, and M. Pinsky, "Epidemiology of severe sepsis in the united states: Analysis of incidence, outcome, and associated costs of care," *Critical Care Medicine*, vol. 29, no. 7, 2001.

G. Kumar, N. Kumar, T. Taneja, S. Tarima, and E. McGinley, "Nationwide trends of severe sepsis in the 21st century (2000-2007)," *Chest*, vol. 140, no. 5, pp. 1223–1231, 2011.

HCUP Facts and Figures: Statistics on Hospital-based Care in the United States, 2009. Rockville, MD: Agency for Healthcare Research and Quality, 2011.

Why is sepsis important?

$24.3 billion
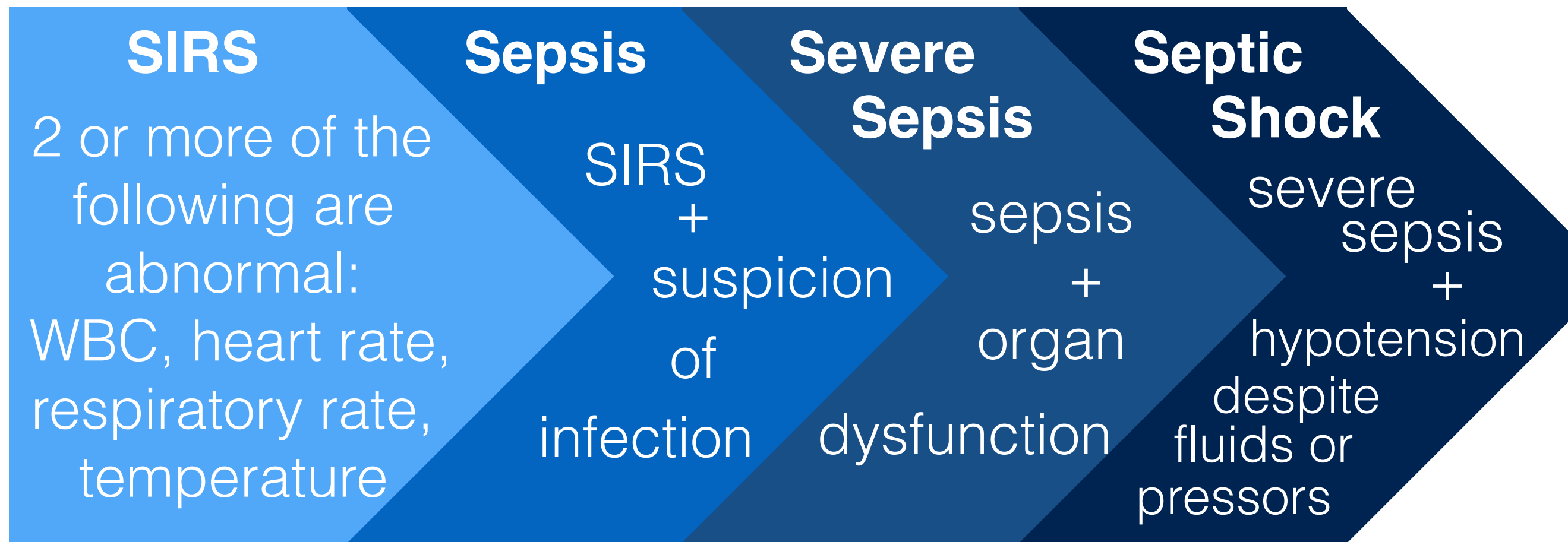dollars spent nationally

Top 5 most expensive conditions

Increased spending hasn't improved outcomes

Sepsis-2 Consensus Definition

SIRS
2 or more of the following are abnormal: WBC, heart rate, respiratory rate, temperature

Sepsis
SIRS + suspicion of infection

Severe Sepsis
sepsis + organ dysfunction

Septic Shock
severe sepsis + hypotension despite fluids or pressors

Defining sepsis clinically: Sepsis-2 vs Sepsis-3

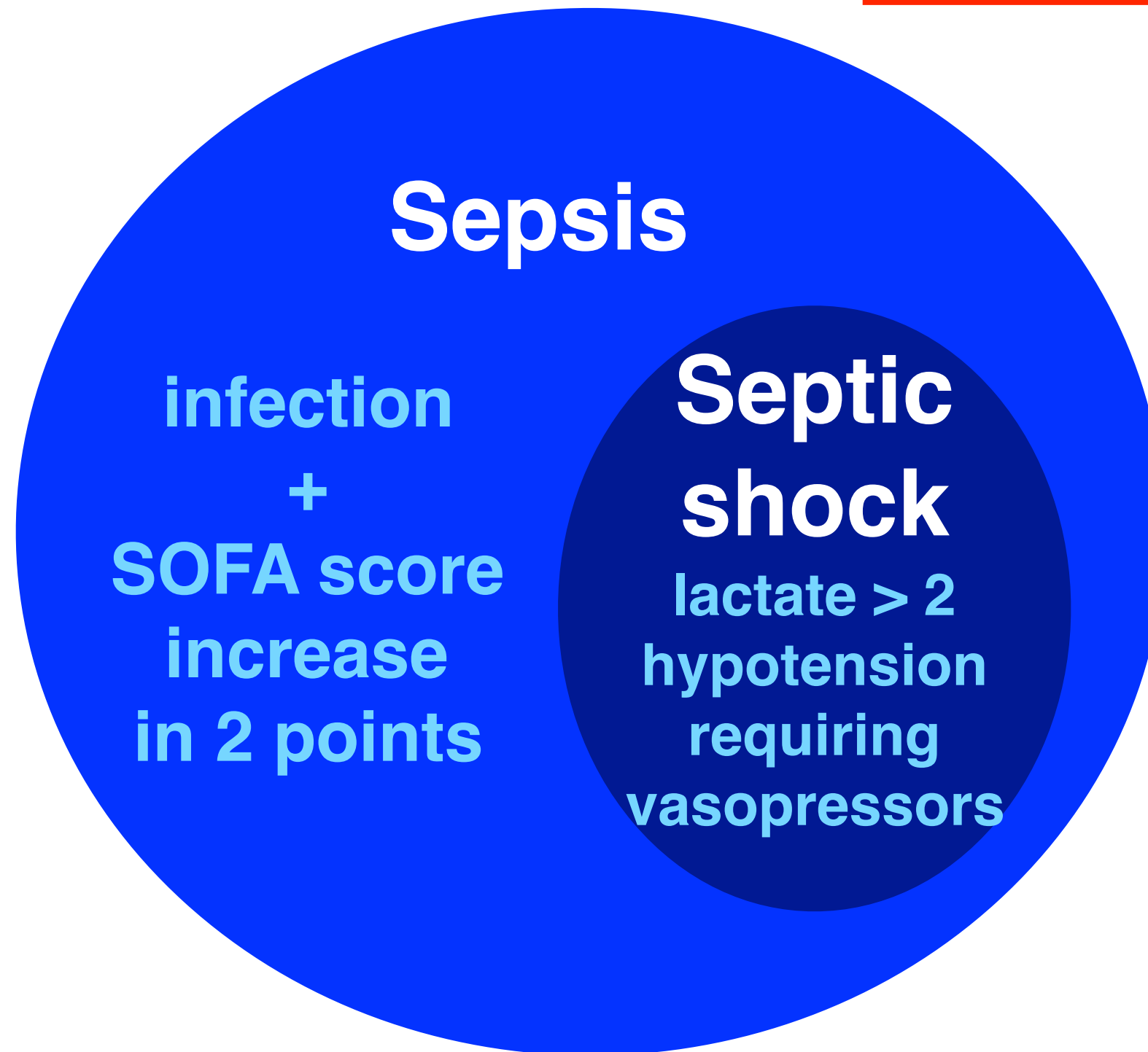# Systemic Inflammatory Response Syndrome (SIRS)

Patient meets any two of the following criteria:

- Heart rate > 90 beats per minutes
- Temperature > 100.4°F or < 96.8°F
- Respiratory rate > 20 breaths per minute
- WBC > 12k cells/mm^3 or < 4k cells/mm^3

An estimated 70-90% of all patients meet the SIRS criteria at some point during their hospital stay

Sequential Organ Failure Assessment (SOFA) Scores

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score				
	0	1	2	3	4
Respiration					
Pao$_2$/Fio$_2$, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10^3/µL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio$_2$, fraction of inspired oxygen; MAP, mean arterial pressure; Pao$_2$, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as µg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Sepsis-3 Consensus Definition

qSOFA

respiratory rate >= 22 bpm

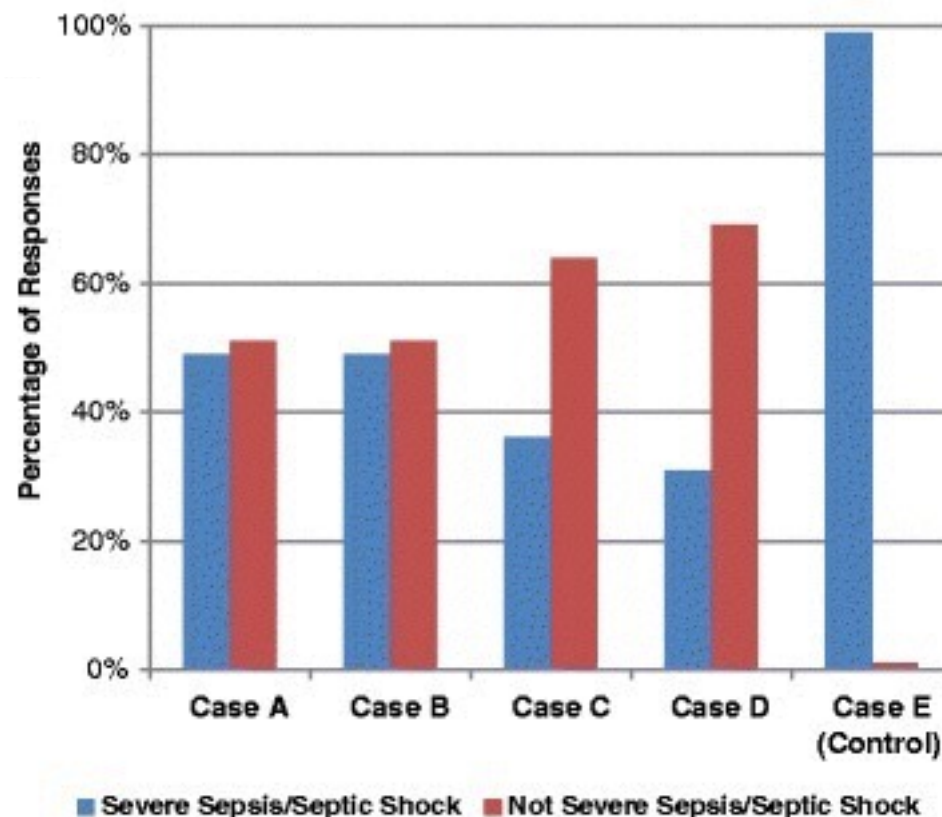**altered mental status**

systolic BP <= 100 mmHg

**Any two and
suspicion of
infection**

AUROC for predicting mortality among non-ICU
patients of 0.81 (95% CI 0.80-0.82)

Extensive debate continues about the benefits of using the new definitions
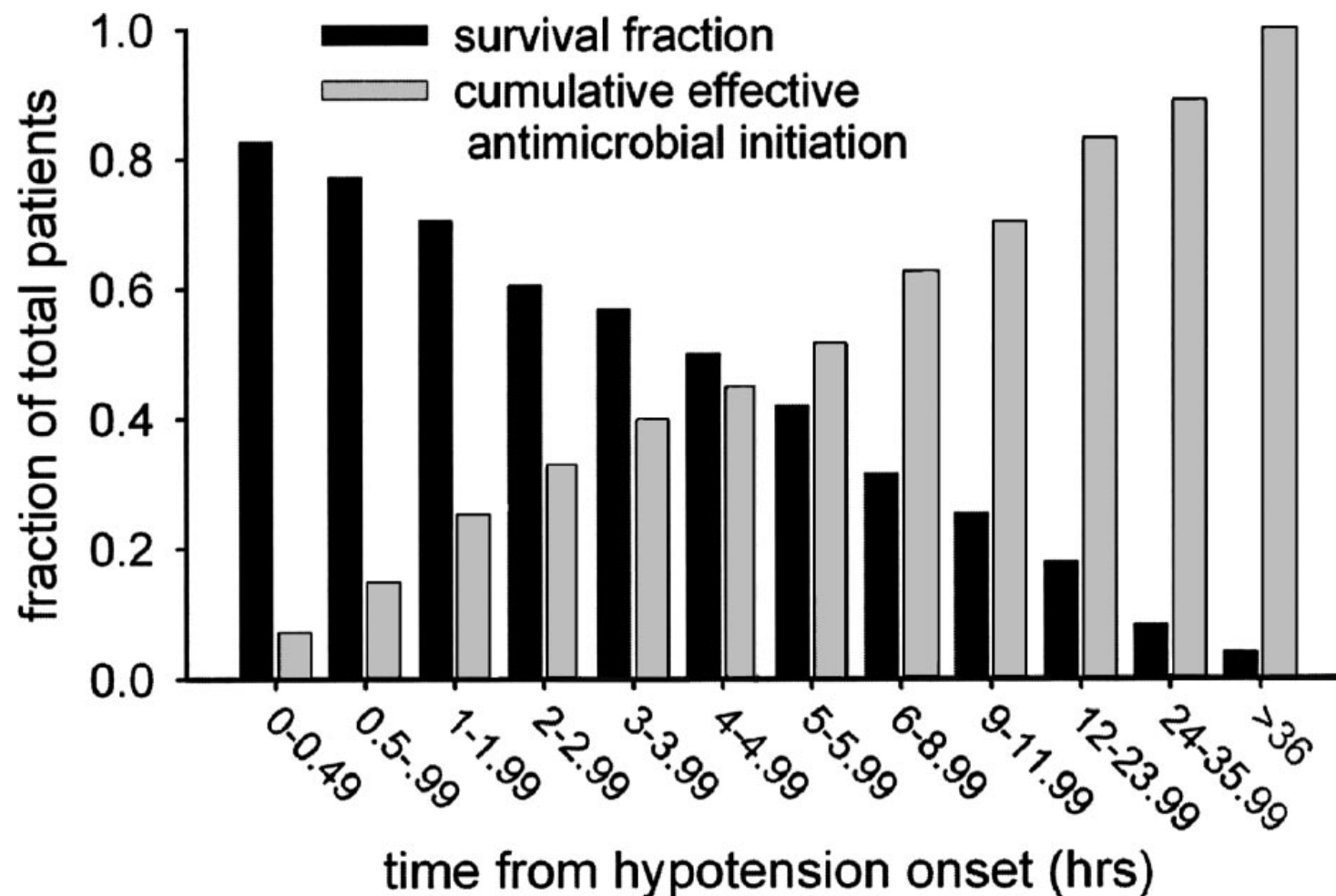
Diagnosis is challenging

94 intensivists were asked to classify cases of suspected or confirmed infection and organ dysfunction based on the sepsis guidelines. **Despite advanced knowledge of the guidelines, interrater agreement was poor.**

Rhee C, Kadri SS, Danner RL; Suffredini AF, Massaro AF, Kitch BT, Lee G, Klompas M. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. Crit Care. 2016 Apr 6;

Early detection decreases mortality and morbidity

7% increase in mortality for every hour that treatment is delayed after the onset of hypotension (systolic BP < 90 bpm)

[Kumar et al. 2006]

Emphasis on early identification of sepsis

Treating sepsis: the latest evidence

✔ **Antibiotics**
Early administration

✔ **Fluids**
Several liters initially
- ✔ Colloids
- ✔ Crystalloid
- ✘ Starches
- ✘ High chloride

✔ **Vasopressors**
1–6 hours after onset
- ✔ Norepinephrine
- ✔ Epinephrine
- ✔ Vasopressin
- ✘ Dopamine
- ✘ Phenylephrine

✔ **Enteral feeding**

✔ **Insulin therapy**

✘ **Deep sedation**

❓ **Molecular targeted therapies**

✔ **Lung protective ventilation**

✘ **Goal oriented therapy**

✘ **EGDT**
Early goal directed therapy

✔ **Urinary catheter**

134
116/69

Sepsis bundles

Pt meets criteria for severe Sepsis &/or Septic Shock (Time of Presentation or TOP)

Document **POSITIVE** severe sepsis or septic shock screen in CareConnect

NURSES

Initiate Severe Sepsis &/or Septic Shock Bundle (per adult sepsis Nursing protocol *& core measure* requirements)

NURSES

3 HOURS

NURSES

&/or

MD/NP

RN to contact MD/NP to request orders for IV Abx & fluid bolus

COMPLETE WITHIN 1 HOUR (max)
Following initial time of presentation (TOP)

Initial Lactate Level (per nursing protocol, no co-sign required)

Blood Cultures X 2 sets (per nursing protocol, no co-sign required) *NOTE: 4 bottles total; minimum of 8-10mL per bottle*

Administer IV broad spectrum antibiotic *or other approved combination of antibiotics* (RN to contact MD to request orders for Abx)

IF SBP <90 or >40 below baseline or MAP <65 -OR- *Initial* Lactate level ≥36mg/dL
- - - - - -
Total bolus minimum of 30mL/kg must complete in < 3hrs from TOP; Administer only 0.9% NS or LR fluids

If initial lactate >18mg/dL

+3 HOURS

If hypotension persists within 1hour of completing 30mL/kg fluid bolus, continue interventions. If pt. no longer hypotensive after 30ml/kg, STOP)

If INITIAL Lactate is ≥36mg/dL, must perform repeat volume & tissue perfusion assessment

COMPLETE WITHIN 6 HOURS (max)
Following initial time of presentation (TOP)

REPEAT serum Lactate level per nursing protocol If most recent lactate level >18mg/dL

Initiate VASOPRESSORS (contact MD for orders) Vasopressors to be initiated for hypotension unresponsive to fluid bolus of 30mL/kg

AND

Repeat volume & tissue perfusion assessment including (ALL *must* be documented by physician/NP):
- Complete Vital signs, AND
- Cardiopulmonary exam, AND
- Capillary refill evaluation, AND
- Peripheral pulse evaluation, AND
- Skin exam
- OR -

Any *two* of the following:
- Central venous pressure (CVP) measurement
- Central venous oxygen (sCVO2) measurement
- Bedside cardiovascular ultrasound

Approaches to sepsis identification
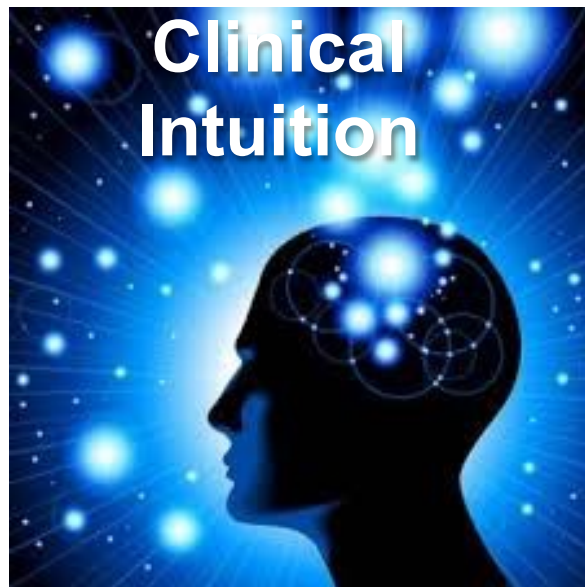
Screening checklists

Evaluation for Severe Sepsis Screening Tool

Instructions: Use this optional tool to screen patients for severe sepsis in the emergency department, on the medical/surgical floors, or in the ICU.

1. Is the patient's history suggestive of a new infection?

☐ Pneumonia, empyema   ☐ Bone/joint infection   ☐ Implantable device infection
☐ Urinary tract infection   ☐ Wound infection
☐ Acute abdominal infection   ☐ Blood stream catheter infection   ☐ Other infection
☐ Meningitis   _____
☐ Skin/soft tissue infection   ☐ Endocarditis

___ Yes ___ No

2. Are any two of following signs & symptoms of infection both present and new to the patient? Note: laboratory values may have been obtained for inpatients but may not be available for outpatients.

☐ Hyperthermia > 38.3 °C (101.0 °F)   ☐ Tachypnea > 20 bpm   ☐ Hyperglycemia (plasma glucose >140 mg/dL) or 7.7 mmol/L in the absence of diabetes
☐ Hypothermia < 36 °C (96.8°F)   ☐ Leukocytosis (WBC count >12,000 μL−1)
☐ Altered mental status   ☐ Leukopenia (WBC count < 4000 μL−1)
☐ Tachycardia > 90 bpm

___ Yes ___ No

If the answer is yes, to both questions 1 and 2, *suspicion of infection* is present:

✓ Obtain: **lactic acid, blood cultures**, CBC with differential, basic chemistry labs, bilirubin.
✓ At the physician's discretion obtain: UA, chest x-ray, amylase, lipase, ABG, CRP, CT scan.

3. Are any of the following organ dysfunction criteria present at a site remote from the site of the infection that are NOT considered to be chronic conditions? Note: in the case of bilateral pulmonary infiltrates the remote site stipulation is waived.

☐ SBP < 90 mmHg or MAP <65 mmHg
☐ SBP decrease > 40 mm Hg from baseline
☐ Creatinine > 2.0 mg/dl (176.8 mmol/L) or urine output < 0.5 ml/kg/hour for 2 hours
☐ Bilirubin > 2 mg/dl (34.2 mmol/L)
☐ Platelet count < 100,000 μL
☐ Lactate > 2 mmol/L (18.0 mg/dl)
☐ Coagulopathy (INR >1.5 or aPTT >60 secs)
☐ Acute lung injury with PaO2/FiO2 <250 in the absence of pneumonia as infection source
☐ Acute lung injury with PaO2/FiO2 <200 in the presence of pneumonia as infection source

___ Yes ___ No

If *suspicion of infection* is present AND *organ dysfunction* is present, the patient meets the criteria for SEVERE SEPSIS and should be entered into the severe sepsis protocol.

Date: ____/____/____ (circle: dd/mm/yy or mm/dd/yy)   Time: ____:____ (24 hr. clock)

Version 7.2.13

Sepsis Best Practice Alerts (BPAs) embedding into the EHR

Alert if patient
- meets at least two of the SIRS criteria,
    - Heart rate > 90 beats per minutes
    - Temperature > 100.4°F or < 96.8°F
    - Respiratory rate > 20 breaths per minute
    - WBC > 12k cells/mm^3 or < 4k cells/mm^3

AND,

- hypotensive (systolic BP < 90 mmHg) or
- hypoperfusive (lactate >= 4.0)

R. Dellinger, M. Levy, A. Rhodes, and et al., "Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock," Critical Care Medicine, vol. 41, no. 2, pp. 580–637, 2013.

Nonspecific alarms pose a huge burden

187 audible alerts per bed per day in a typical ICU

An estimated 72-99% of these are false alerts

Burden of alerts results in delayed reactions or even ignoring potentially critical alerts

Clinical alerts are consistently ranked as a top patient safety concern by the ECRI Institute

Drew BJ, Harris P, Ze`gre-Hemsey JK, Mammone T, Schindler D, et al. (2014) Insights into the Problem of Alarm Fatigue with Physiologic Monitor Devices: A Comprehensive Observational Study of Consecutive Intensive Care Unit Patients. PLoS ONE 9(10)

Sendelbach S, Funk M. (2013) Alarm Fatigue: A Patient Safety Concern. American Association of Critical-Care Nurses Advanced Critical Care 25(4). 378-386.

General purpose severity scores

Acute physiology and chronic health evaluation II (APACHE II)

Simplified Acute Physiology Score II (SAPS II)

Sequential organ failure assessment (SOFA) scores

Modified early warning score (MEWS)

Sepsis severity score

predict mortality, not septic shock

High fidelity physiologic monitoring

Moorman et al. created HeRO Monitor to predict neonatal sepsis from continuous waveform data

Interest in finding new biomarkers, but so far limited success

Procalcitonin

C-reactive protein

Lactate

Individually they lack specificity

Other statistical approaches

Gultepe et al. 2014 learned Bayesian network to predict lactate and mortality in patients with sepsis
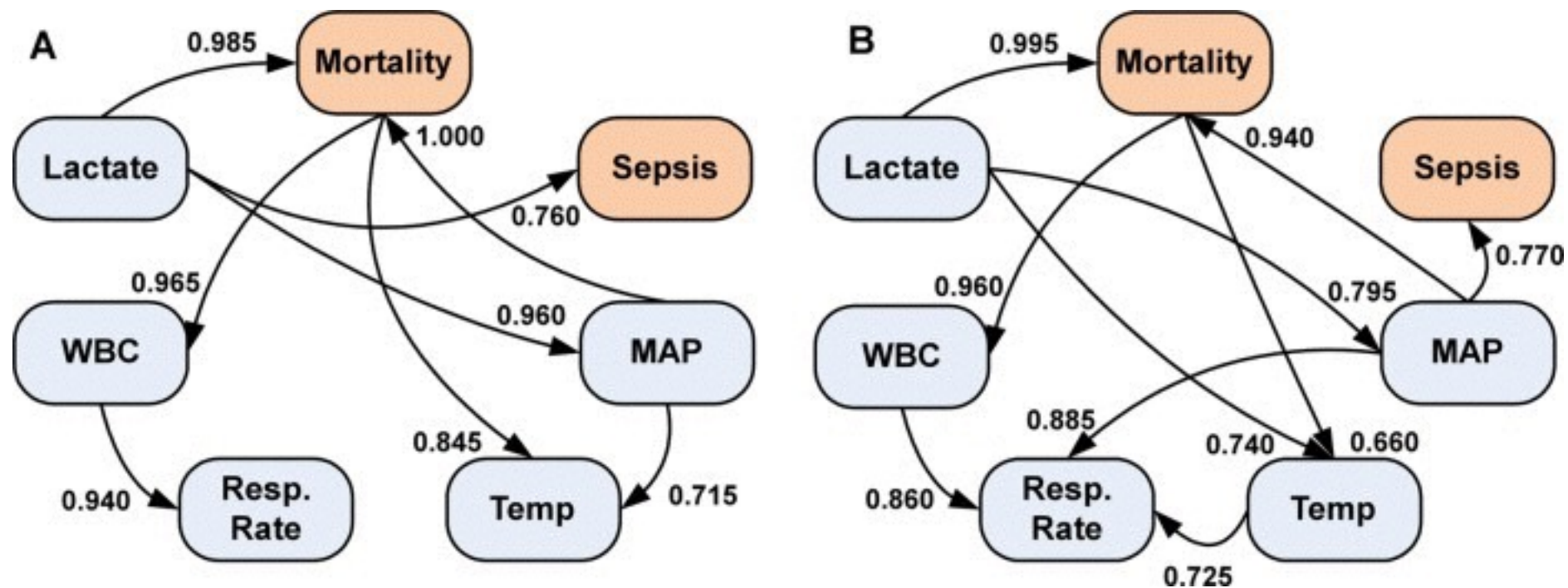
Fig. Bayesian networks from the five clinical measurements and two outcomes. (A) The Bayesian network structure determined from the mean of the five clinical measurements. (B) The Bayesian network structure from the median of five clinical measurements.

Need a high sensitivity high specificity tool that can easily be implemented using routinely collected data

Electronic Health Records (EHRs)

Medical history

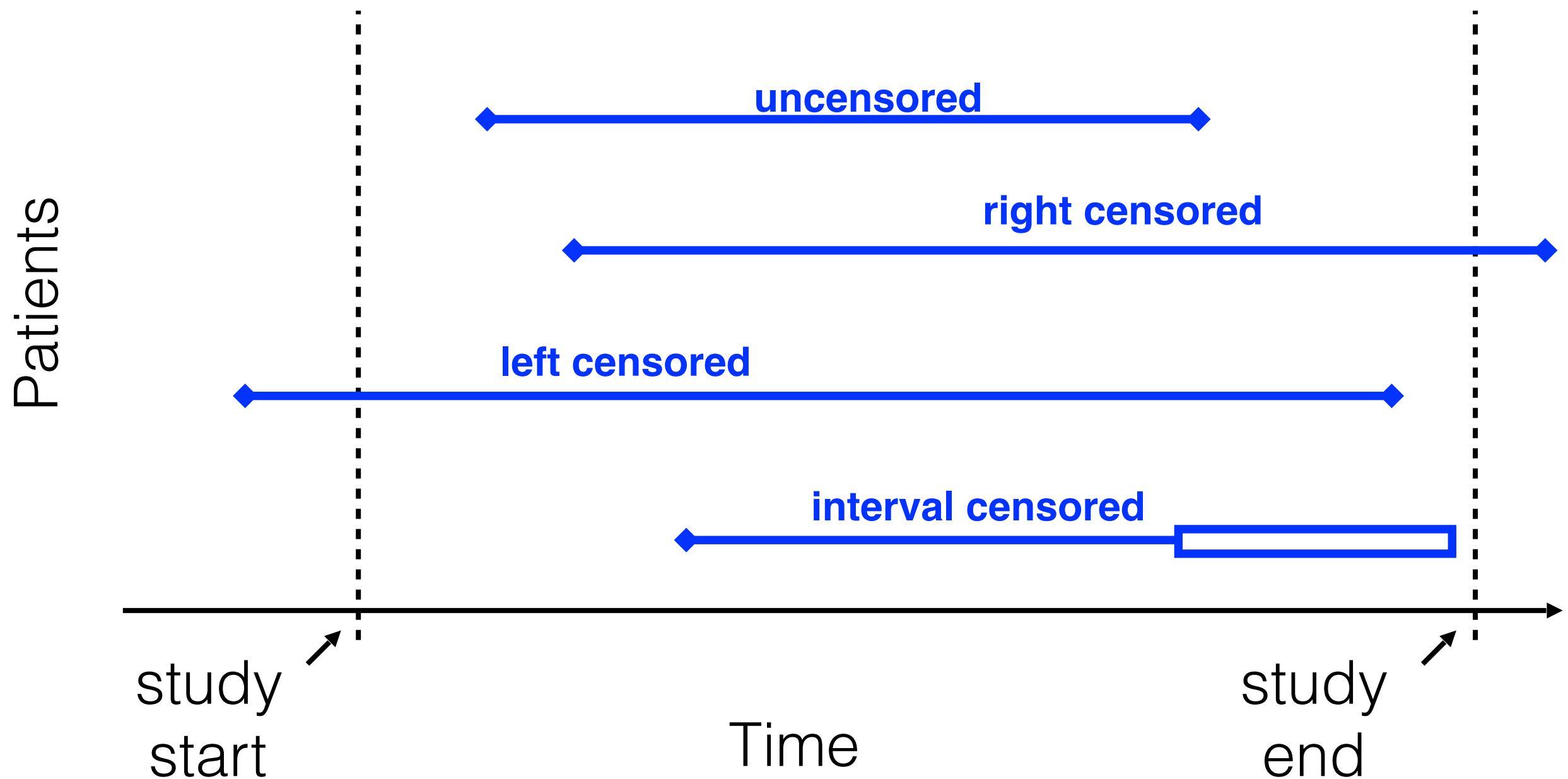Vital signs

Laboratory tests

Procedures

Medications

Clinical notes

Use signals to learn a time to event model
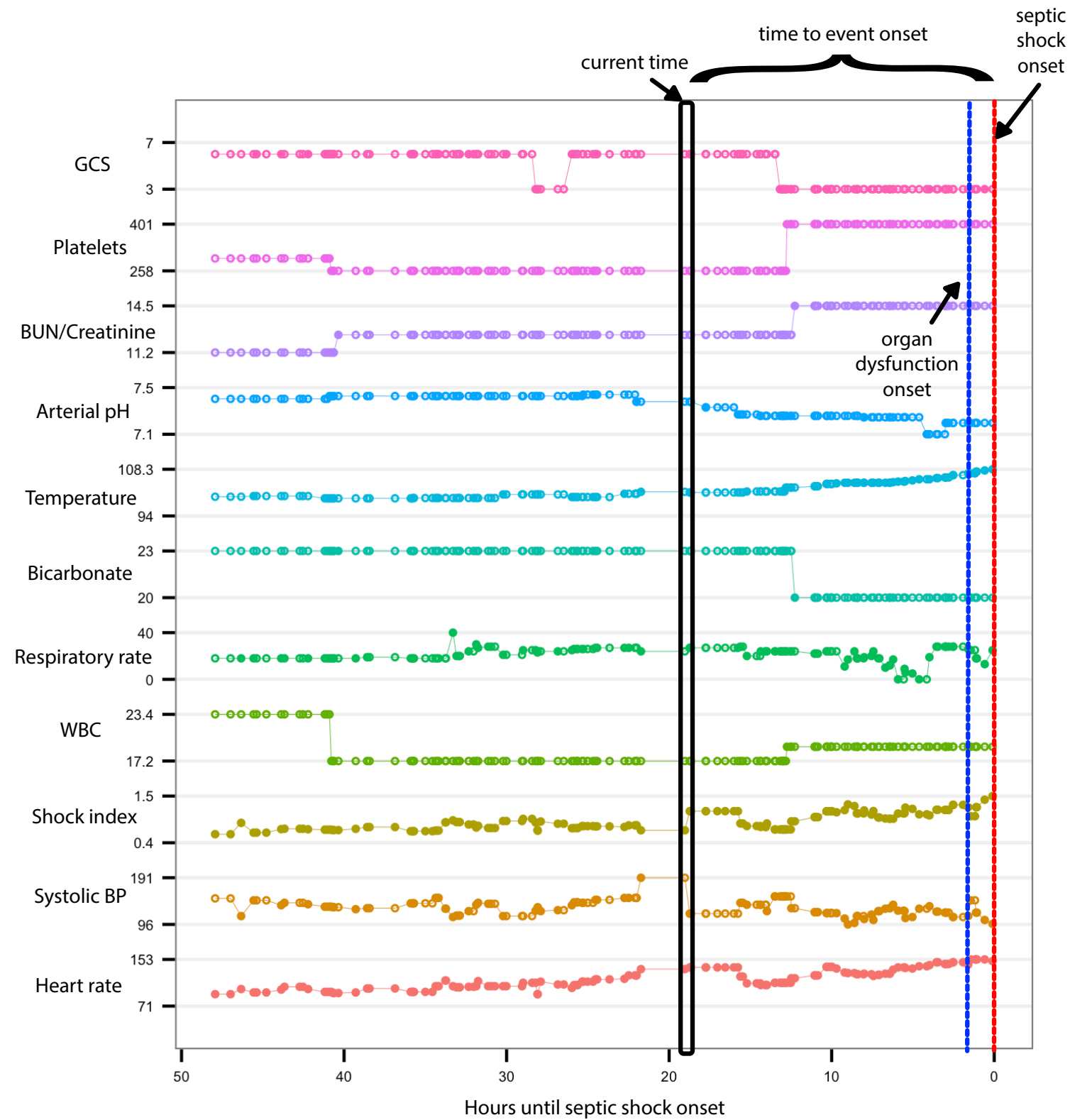
Censoring

In the traditional case with only right censoring,

C time of censoring

$Y = \min\{T, C\}$ outcome

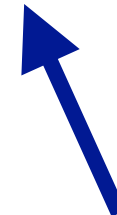# Multiple imputation Cox proportional hazards model

baseline hazard

$$\lambda(t_m|x_i) = \lambda_0(t_m)e^{\beta x_i}$$

impute the time multiple times in the case of interval censoring

feature-dependent term

Earliness of predictions

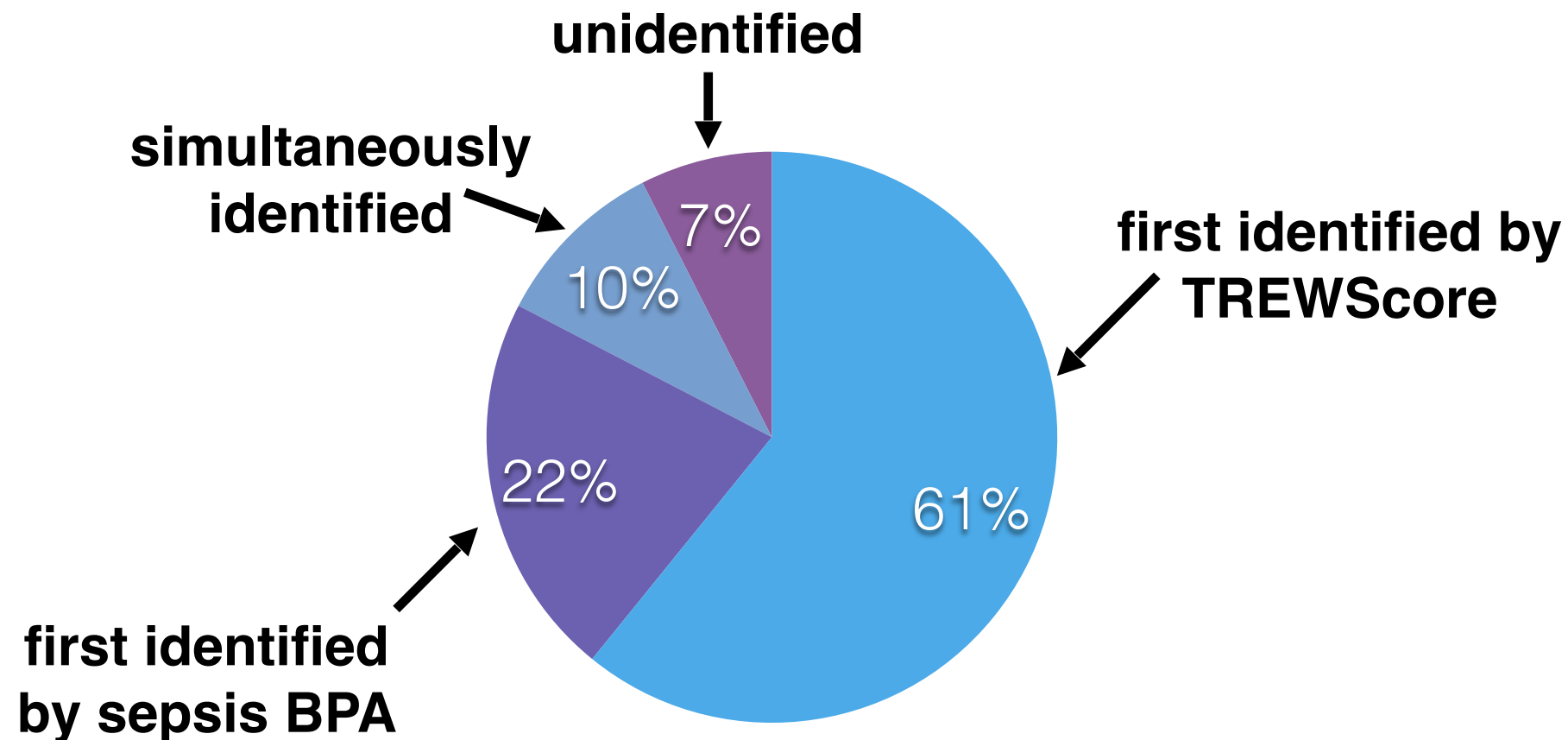Results computed at a **TPR of 0.85** and corresponding **FPR of 0.33**

TREWScore identified patients a **median 28.2 (IQR 10.6-94.2)** hours prior to shock onset

68.8 % of these were identified a **median 7.43 (IQR 2.53-25.4)** hours prior to any sepsis-related organ dysfunction

Earliness compared to a sepsis BPA

Identification prior to septic shock onset

unidentified
simultaneously identified
first identified by TREWScore
first identified by sepsis BPA

7%
10%
22%
61%

TREWScore identified **99 more patients** prior to sepsis-related organ dysfunction (**58.6% increase** in total number of patients identified prior to organ dysfunction)