1-31-2020

Solving the Sepsis Puzzle: Every Minute Counts

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Solving the Sepsis Puzzle: Every Minute Counts

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SPEMS Pre-Conference Sepsis Class

January 31, 2020

Focused Sepsis Care

- Pre-hospital
- Emergency Department
- General Medicine Floor
- Post-operative Floor

Positive Impact on Mortality

- 31.2% with focused care
- 50.5% without focused care
- 19.3% Increase in Mortality

Focused Sepsis Care

Care should be focused at the first presentation

(Harborview Medical Center, 2019)

Image retrieved from https://www.cdc.gov/sepsis/index.html

Sepsis Syndrome

variety of physical, psychological and emotional problems while recovering

Post Sepsis Syndrome (PSS)

- Lasts ~ 6 to 18 months
- Individuals look well
- Employer, doctor, or family may be unaware of the problems
- Many suffer in silence

(Huang et al., 2019)

Image retrieved from https://phil.cdc.gov/Details.aspx?pid=14179

Physical Symptoms of PSS

Lethargy/excessive tiredness

Poor mobility / muscle weakness

Breathlessness / chest pains

Swollen limbs (excessive fluid in the tissues)

Joint and muscle pains

Insomnia

Hair loss

Dry / flaking skin and nails

Taste changes

Poor appetite

Changes in vision

Changes in sensation in limbs

Repeated infections from the original site or a new infection

Reduced kidney function

Feeling cold

Excessive sweating

(Huang et al., 2019)

Psychological & Emotional Symptoms

Anxiety / fear of sepsis recurring

Depression

Flashbacks

Nightmares

Insomnia (due to stress or anxiety)

PTSD (Post Traumatic Stress Disorder)

Poor concentration

Short term memory loss

Mood swings

(Huang et al., 2019)

Image retrieved from https://phil.cdc.gov/Details.aspx?pid=5704

Recurring Infections

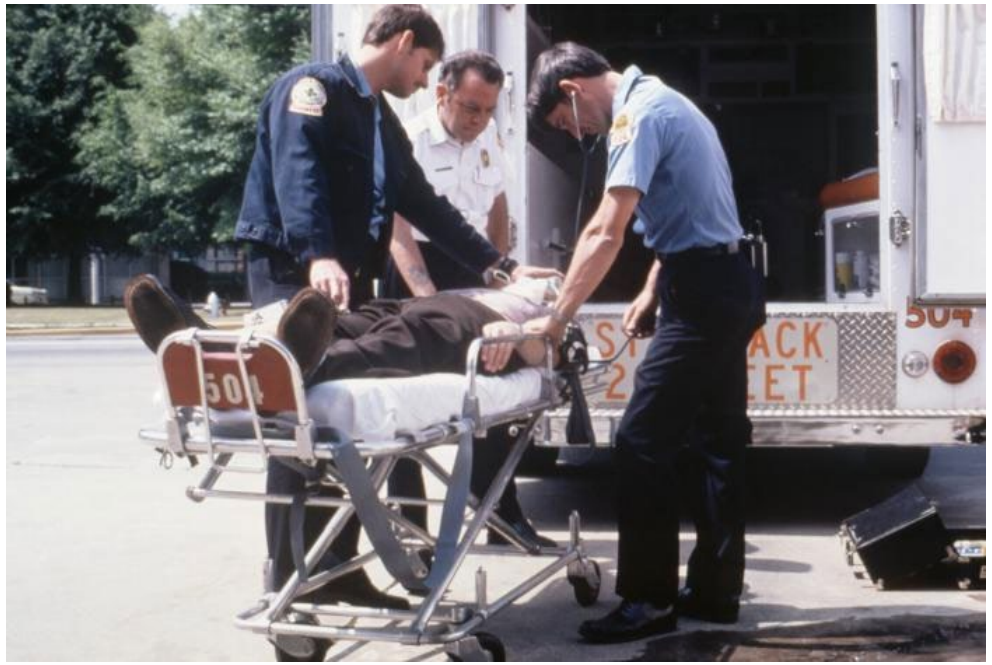
Immune system ineffective for ~ one year leading to one infection after another

People fear they may get sepsis again

It’s important not to neglect any infections

Knowing signs of sepsis impacts healthcare resources

(Huang et al., 2019)



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Epidemiology

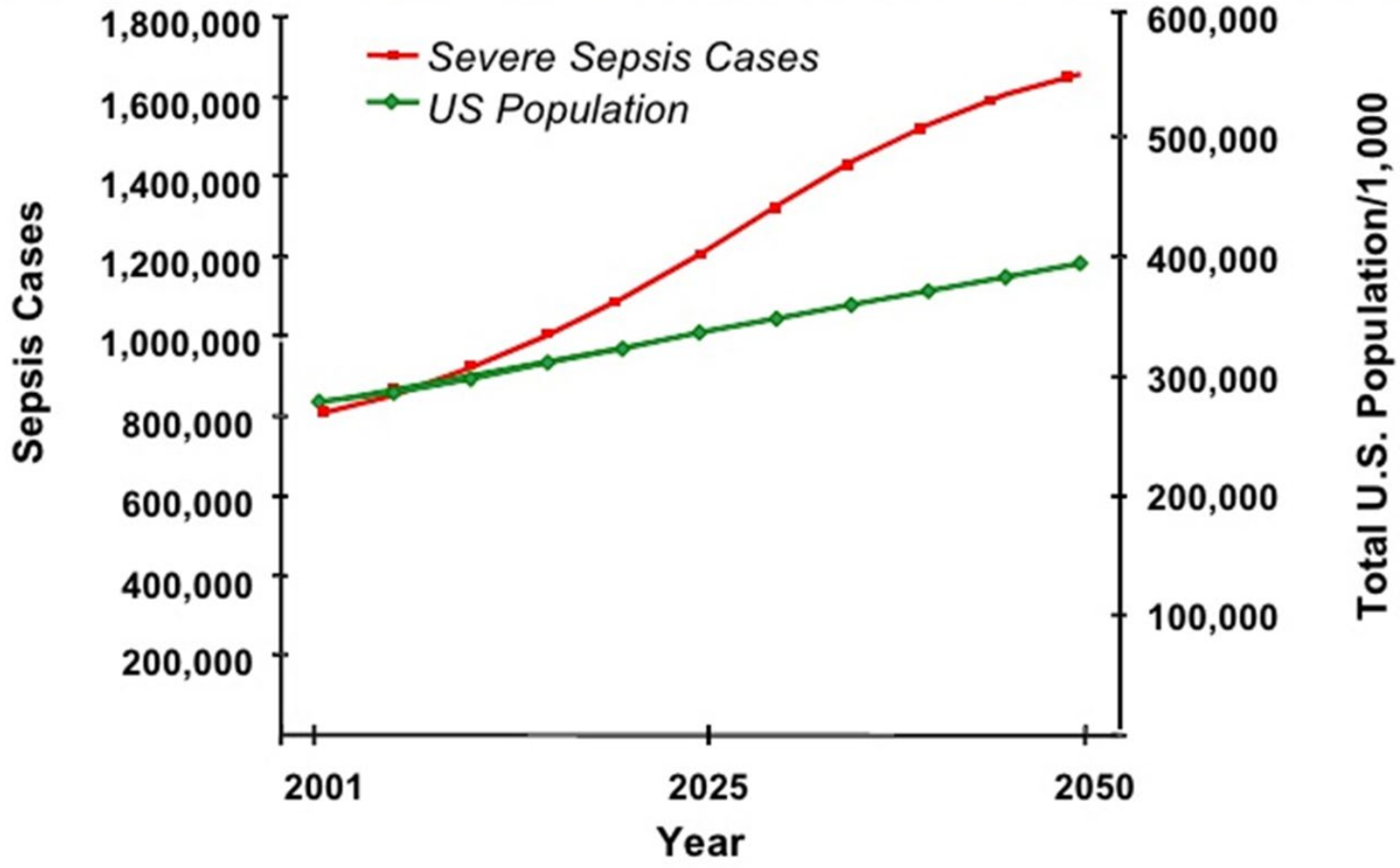
One national database analysis of discharge records from hospitals in the US estimated an annual rate of more than 1,665,000 cases of sepsis between 1979 and 2000.

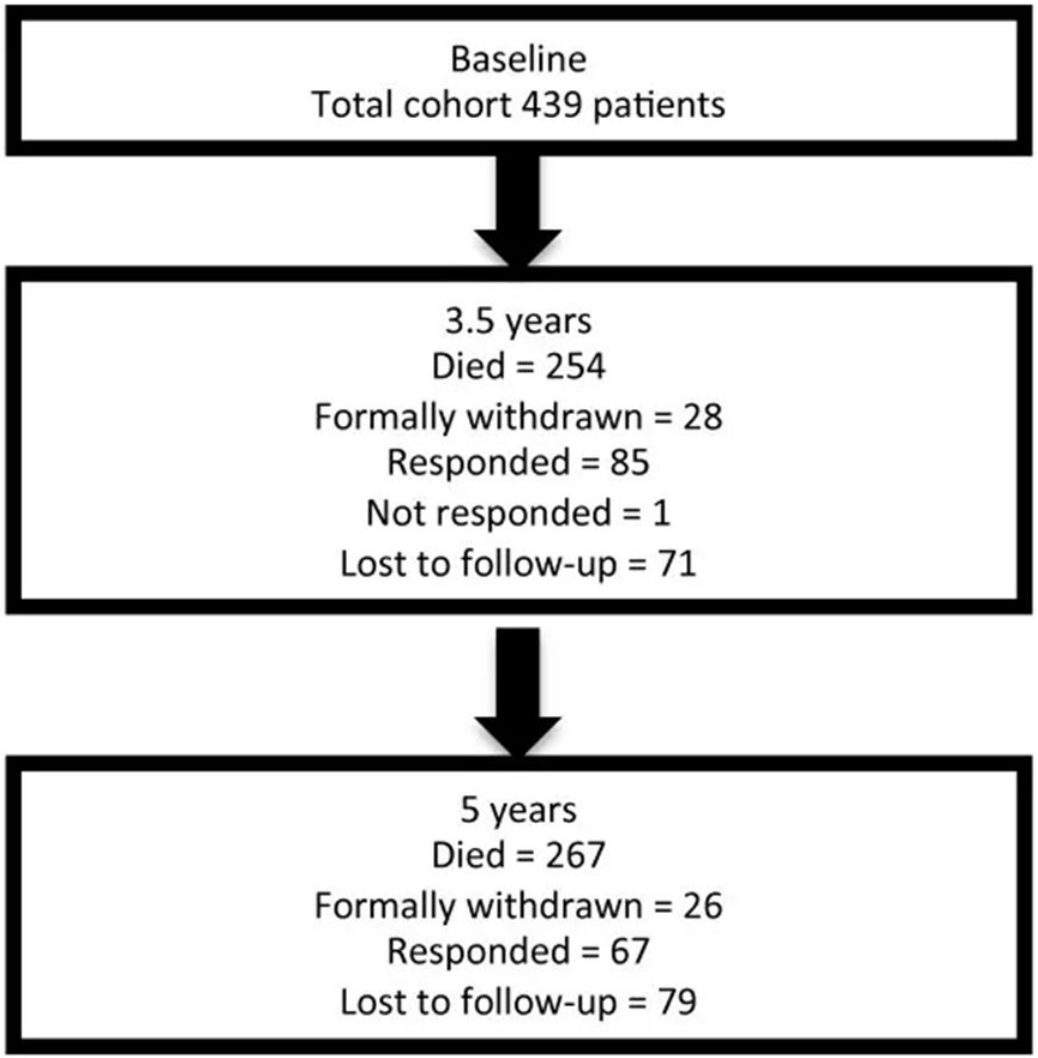
(Elixhauser, Friedman, & Stranges, 2009)

Another retrospective population-based analysis reported increased rates of sepsis and septic shock from 13 to 78 cases per 100,000 between 1998 and 2009.

(Walkey et al., 2013)

Projected Incidence of Severe Sepsis in the US: 2001 - 2050





(Cuthbertson et al., 2013)

Mortality & Quality of Life Study

Patients completed questionnaires by telephone survey at 3.5 and 5 years after ICU admission

Mortality and QOL outcome results were similar to other critically ill cohorts

Cohort study in 26 adult ICUs measured mortality using clinical databases and quality of life at 3.5 and 5 years after severe sepsis.

MORTALITY

439 patients recruited

58% mortality at 3.5 years

61% mortality at 5 years

85 at 3.5 years follow-up

67 responded at 5 years follow-up

QUALITY OF LIFE

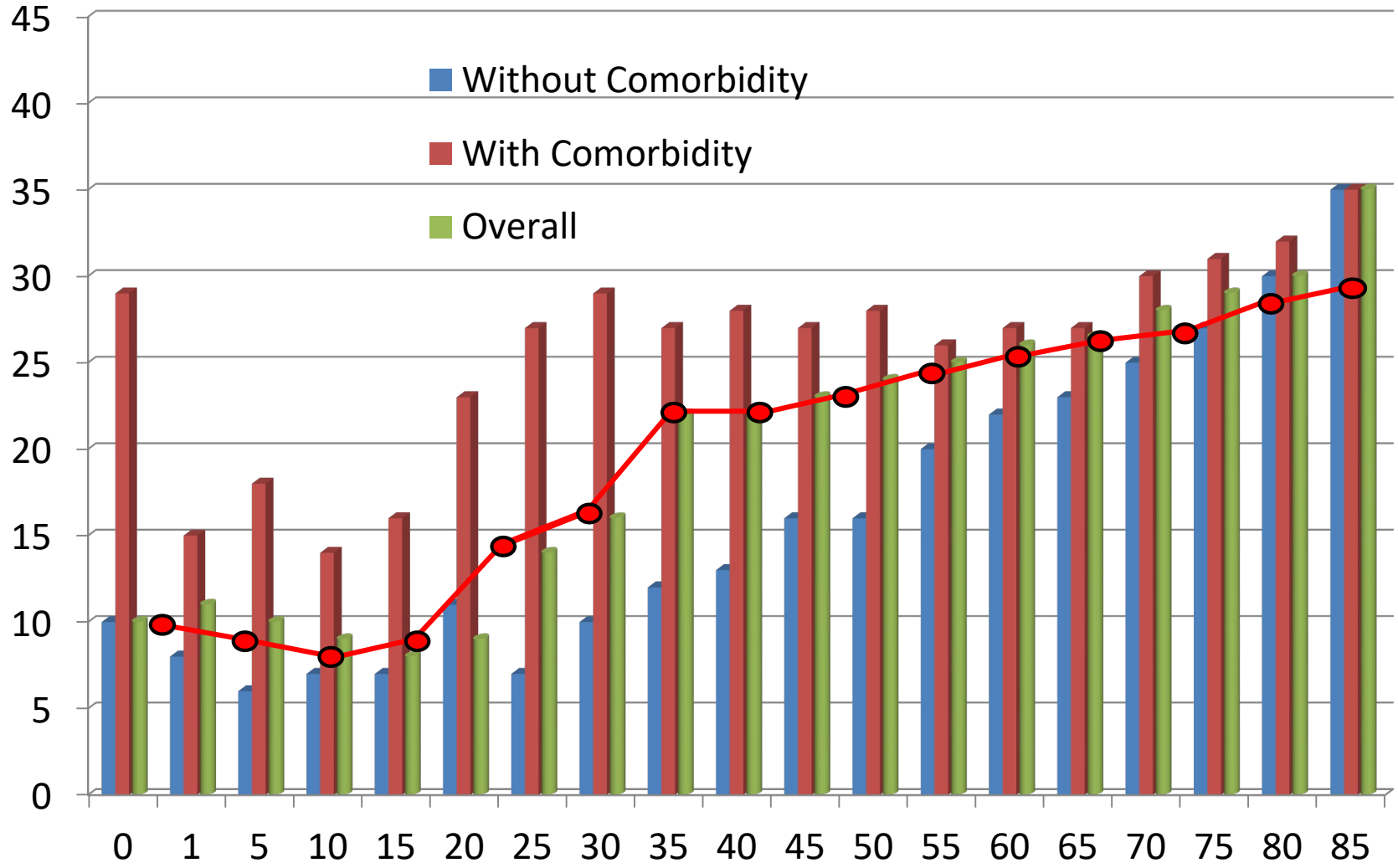
Physical component score low compared to population

Mental component score slightly lower than population

80% of patients were satisfied with their current quality of life (QOL)

(Cuthbertson et al., 2013)

Mortality of Severe Sepsis by Age in US



Neonatal Sepsis

Early-onset

85% < 24 hours

5% 24-48 hours

Some 48-72 hours

Image retrieved from https://phil.cdc.gov/Details.aspx?pid=22494

Maternal GBS colonization

Premature rupture of membranes

Preterm rupture of membranes

Prolonged rupture of membranes

Prematurity

Maternal urinary tract infection

Chorioamnionitis

Neonatal Sepsis

Late-onset

4-90 days of life

Acquired from caregiving environment

Image retrieved from https://phil.cdc.gov/Details.aspx?pid=22494

Prematurity

Central venous catheterization >10 days

Nasal cannula or continuous positive airway pressure (CPAP) use

H2-receptor blocker or proton pump inhibitor use

GI tract pathology

Neonatal Sepsis Presentation

Most are nonspecific signs and symptoms

- Apnea and dusky episodes for no clear reason
- Lethargy, poor color, hypoactivity, poor capillary refill
- Feeding intolerance
- Abdominal distention
- Tachypnea
- Temperature instability

There is NO Gold Standard for diagnosis of neonatal infection

Image retrieved from https://phil.cdc.gov/Details.aspx?pid=23090

Pediatric Sepsis

Anticipate Pediatric Sepsis Clinical Practice Guidelines (CPGs) with a great deal of changes published some time this year.

Last written recognition of pediatric sepsis in CPGs was in 2005 Surviving Sepsis Campaign (SSC) guidelines

Lactate is important to children mortality & diagnosis

Quality of life should be a goal!

(Harborview Medical Center, 2019)

Pediatric Sepsis

National Institutes of Health supported LAPSE study findings published in 2019 looking at life after pediatric sepsis including all-cause mortality & functional status (12 academic PICUs in the US; N=389)

- Boys found to be at higher risk of septic shock
- Within 6-12 months, 35% of the cohort were not back to baseline functional status
- 13% died by 12 months
- Poor outcome in quality of life scores in 25%
- Considered a landmark study & seminal work
- Findings include validation pediatric shock is life-threatening & life-altering with kids dying from MODS

(Harborview Medical Center, 2019)

Other Higher Risk Groups

Maternal

Oncologic

Chronic renal failure

HIV infection

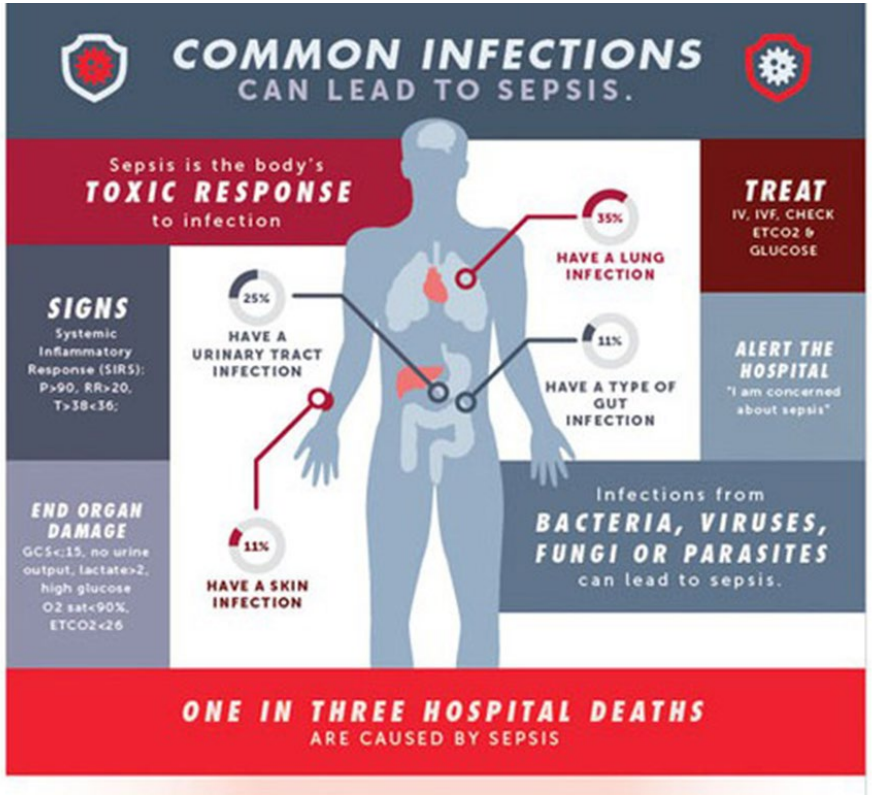
Chronic liver failure

Congestive heart failure

Splenectomy

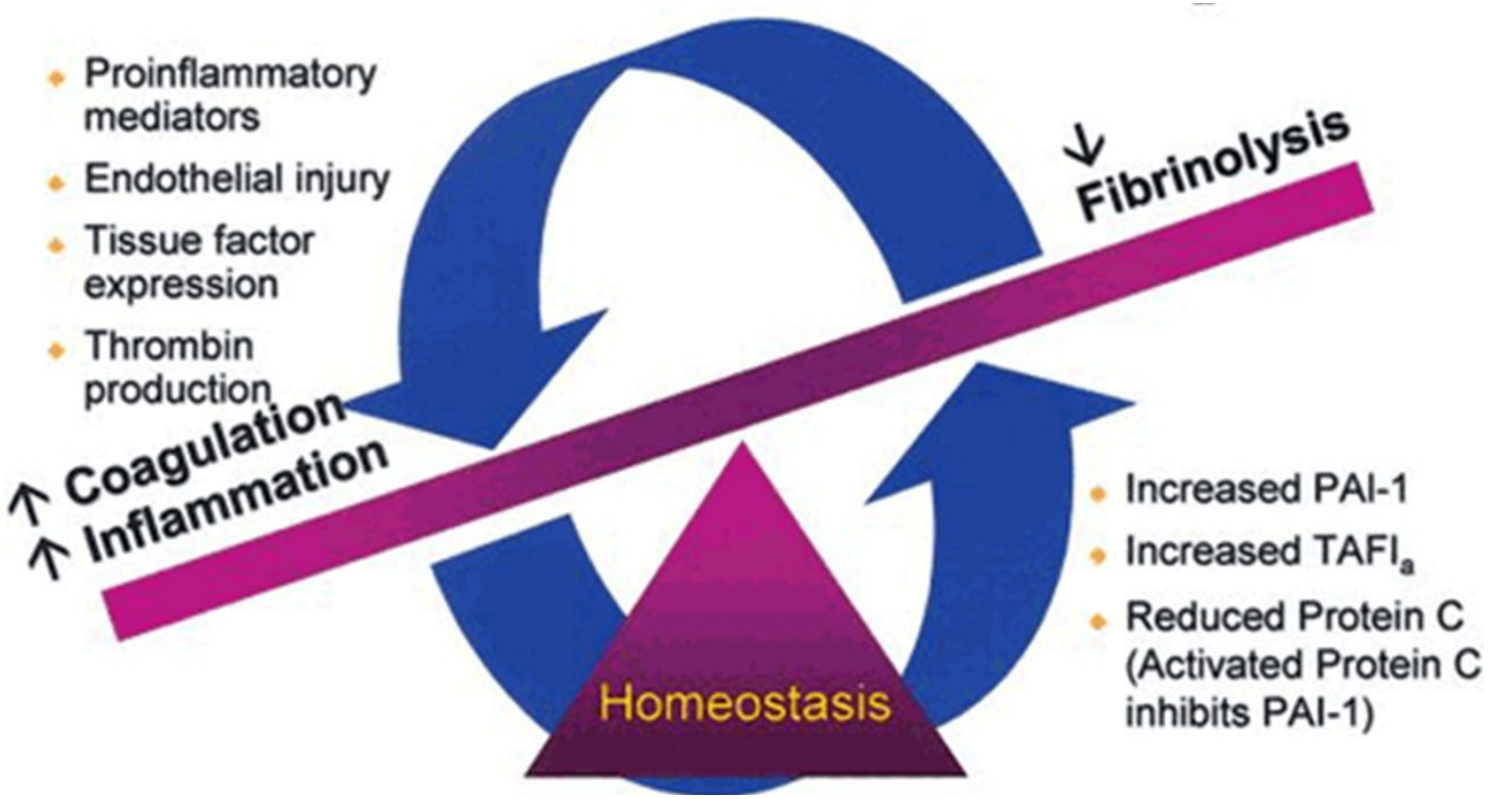
Malnourished

Organ transplant recipients

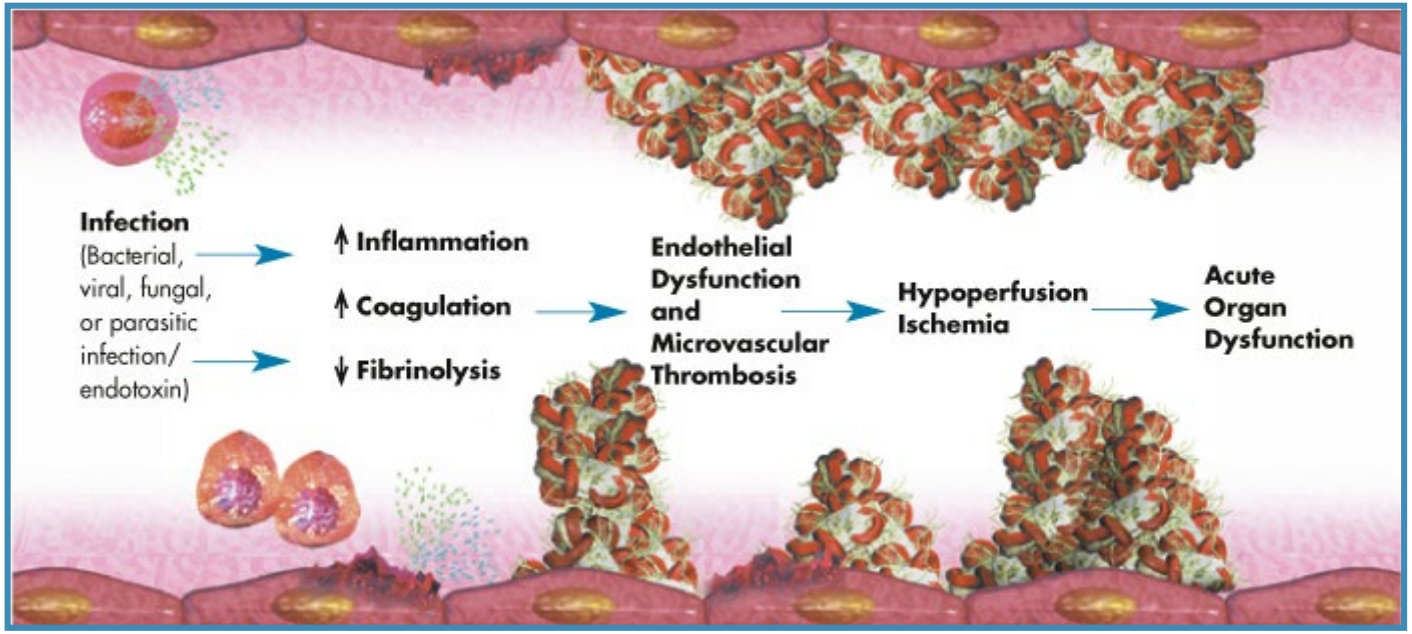


(Sepsis.org, 2019)

Pathobiology of Sepsis Syndrome



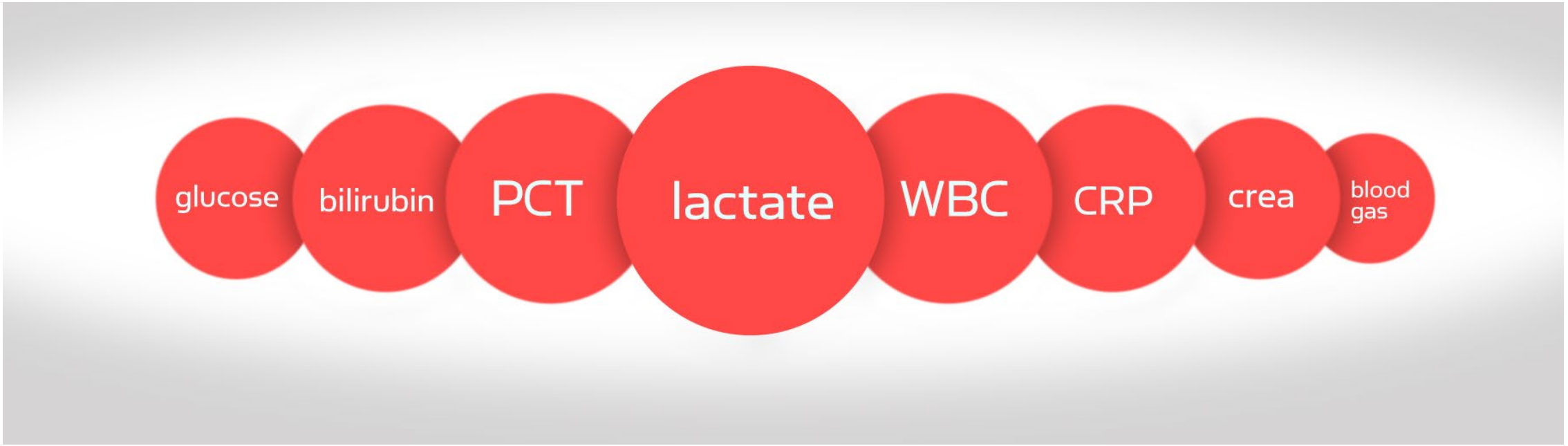
Pathophysiology of Infection



Reprinted with permission from the National Initiative in Sepsis Education (NISE).

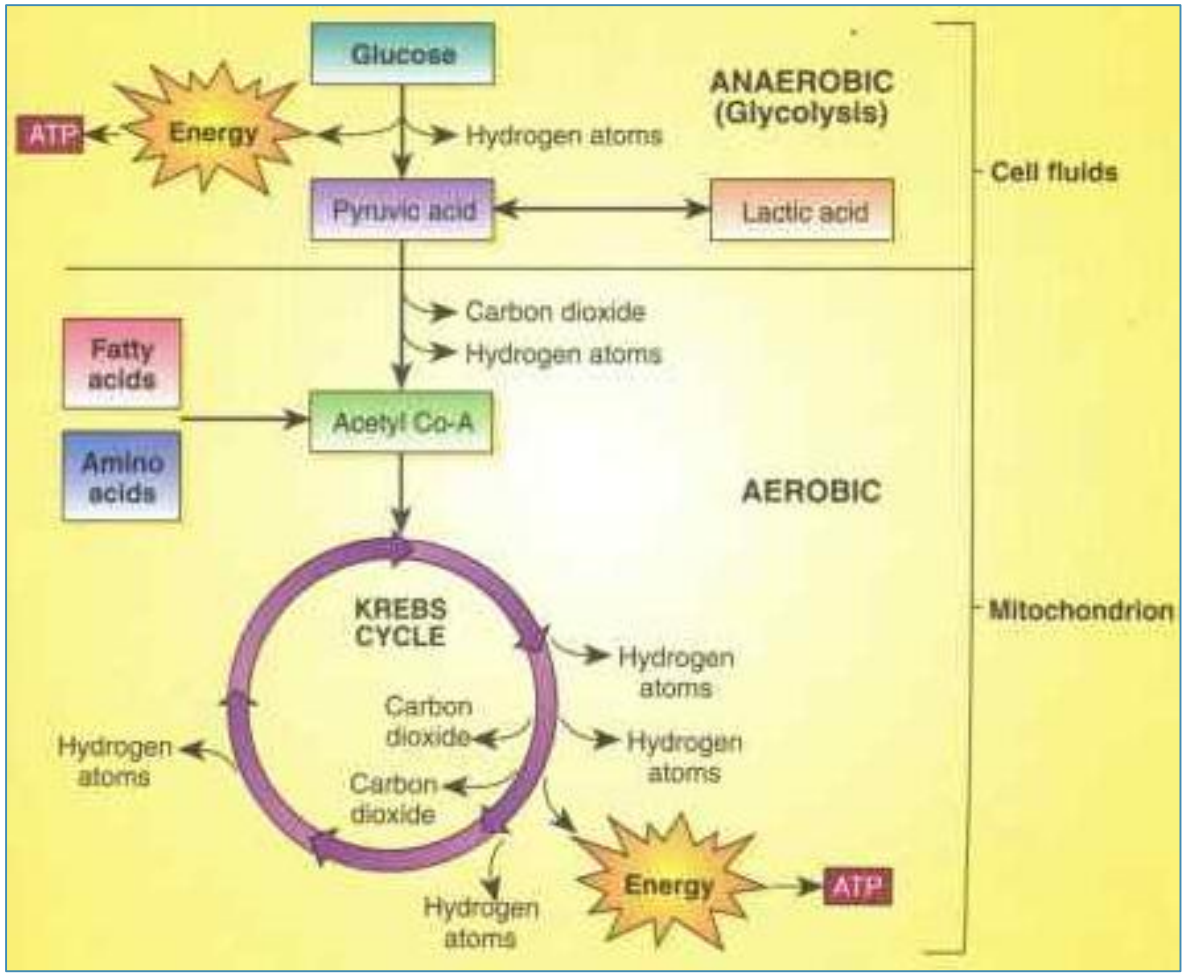
(Kaplow & Hardin, 2007)

There is No Blood Test to Detect Sepsis



20-30% of patients will not have increased lactate levels – COPD & Heart Failure are in this group (Harborview Medical Center, 2019)

Glycolysis produces 4 ATP‘s, but uses 2 ATP's in the process for a **net** of 2 ATP



Net Energy Production from Aerobic Respiration: 36 ATP!

Risk Stratification Based on Lactate Level

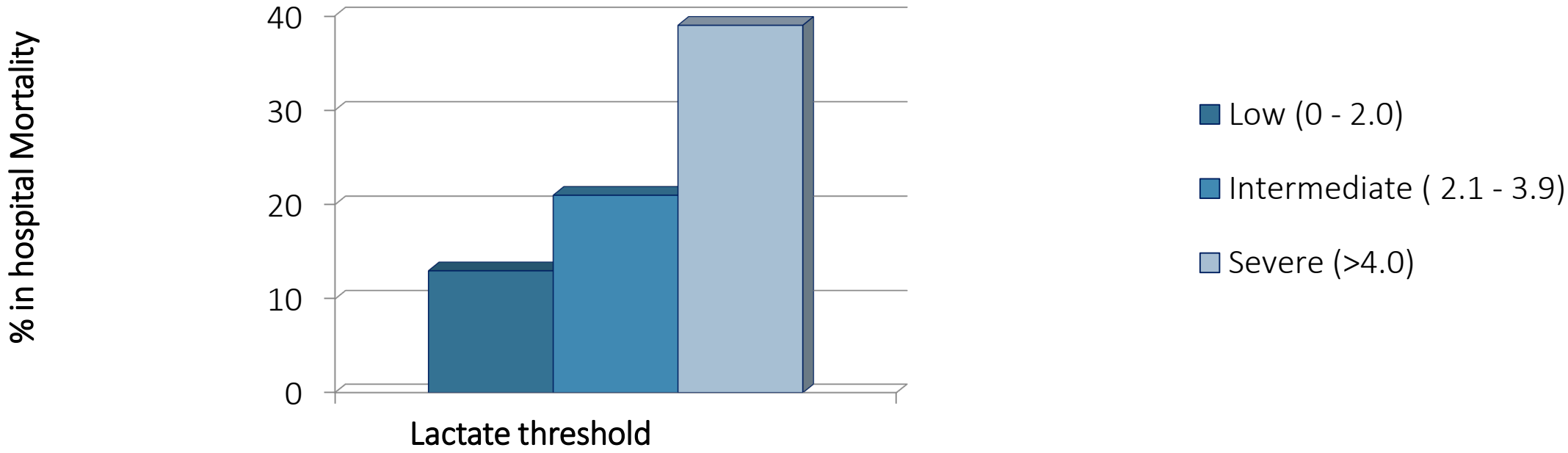


Image retrieved from https://phil.cdc.gov/Details.aspx?pid=23257

Methods to Detect Sepsis

- ✓ MEWS
- ✓ qSOFA
- ✓ SIRS

So What is the Problem?

Patients require close, consistent monitoring

Providers can easily miss the insidious, gradual signs of sepsis

The definition of sepsis is in dispute amongst experts

Muddied use of treatment guidelines

Lack of care for patients whose symptoms do not fit the standard checklist for a sepsis diagnosis

Screening methods also in dispute amongst experts

ALL treatment interventions fall under the scope of advanced practitioners only without physician direction

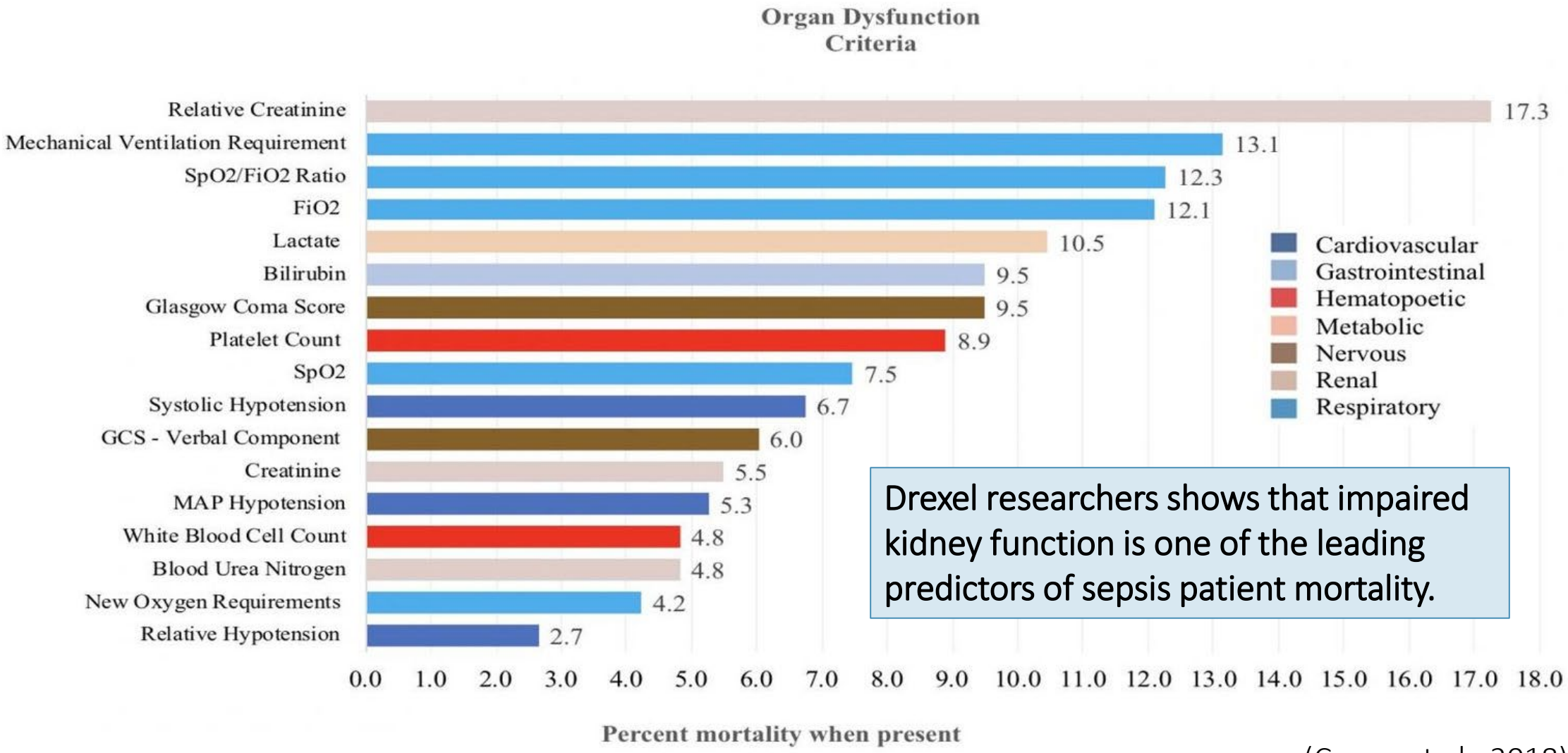
Using patient records from 210,289 hospital visits between 2013 and 2016, Drexel University researchers have identified the specific symptoms that put patients at the greatest risk of dying from sepsis

"We now have large-scale evidence that many of these organ system failures that are typically underappreciated - particularly the renal and respiratory systems - actually have the highest association with death," said study co-principal investigator Ryan Arnold, MD, an emergency medicine doctor and faculty member at Drexel College of Medicine.

"That means that symptoms related to these systems need to be raising a red flag for doctors. We're saying, 'Hey, this is the type of patient you need to be paying more attention to.'"

(Capan et al., 2018)

Study Identifies Sepsis Symptoms That Lead to Death



Drexel researchers shows that impaired kidney function is one of the leading predictors of sepsis patient mortality.

(Capan et al., 2018)

Low blood pressure was linked to lower mortality rates in the study

"That likely speaks more to the health care providers' response to the symptom, than the low blood pressure itself actually being a protective factor," Arnold added. "With sepsis, patients generally don't fall off of a cliff. Instead, it's a day by day, gradual deterioration. Maybe someone has a small increase in creatinine today, and tomorrow it's a little worse. Those subtle changes that don't get detected, we found, lead to death."

(Capan et al., 2018)

The ACCP/SCCM consensus conference committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992.

SIRS

- Widespread inflammatory response
- Two or more of the following
  - Temp>38 C or <36 C
  - Heart Rate >90 bpm
  - Tachypnea, RR>20 or hyperventilation $PaCO_2$ <32 mmHg
  - WBC >12,000 or <4000 or presence of >10% bands, immature neutrophils.

Sepsis=SIRS + definitive source of infection

Severe Sepsis=Sepsis + organ dysfunction, hypoperfusion, or hypotension

Septic Shock:

- Sepsis + hypotension despite fluids
- Perfusion abnormalities
  - Lactic acidosis
  - Oliguria

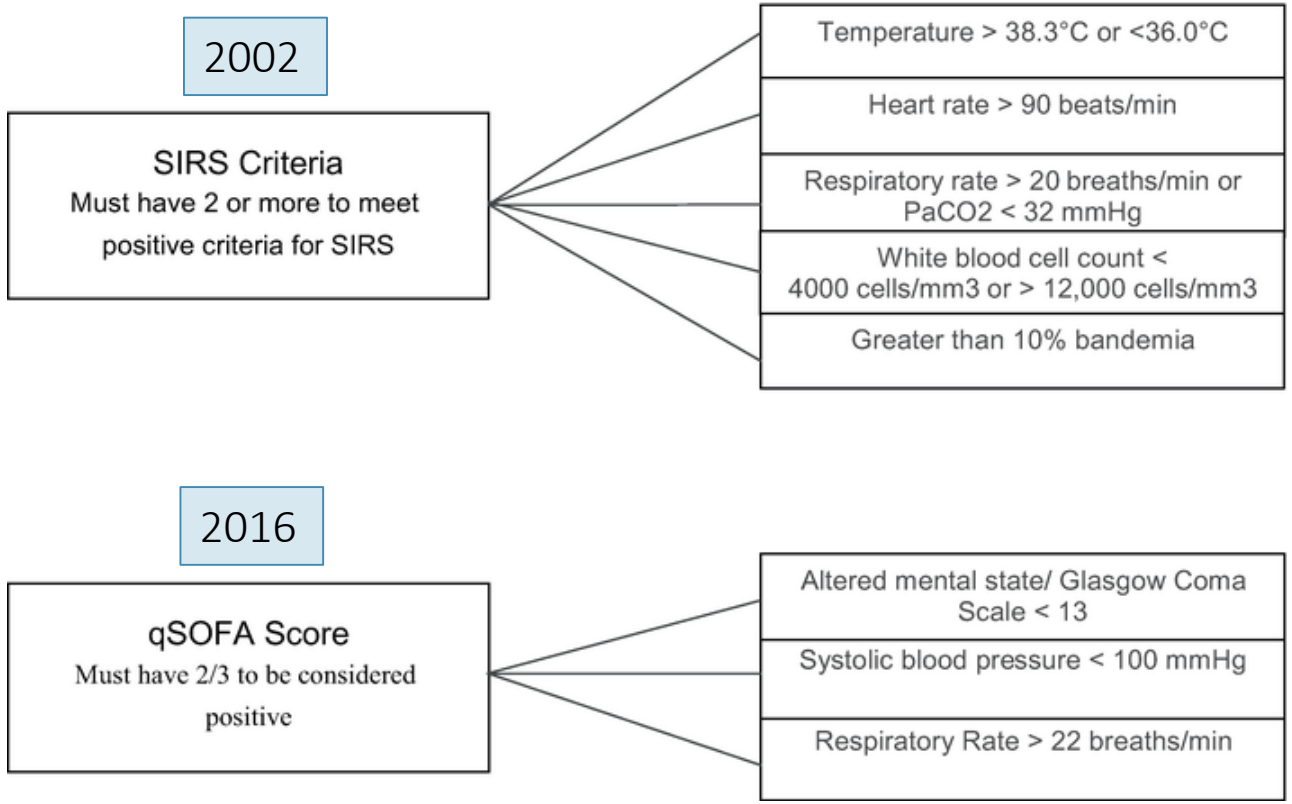
- Multiple Organ System Failure: Abnormal function of two or more organs such that homeostasis cannot be achieved without intervention.

Systemic Inflammatory Response Syndrome

Use for age 10+

Pediatric population adjust heart & respiratory rates for age

Maternal adjusted based on normal physiologic changes occurring during pregnancy



SIRS vs qSOFA

Worldwide diagnostic criteria adopted through professional consensus and endorsed by over 50 health professional groups.

MEWS Tools

Stratify patients through numerical scores to quantify physiologic findings

Scores trigger color-associated algorithms based on numerical values, thus prompting uniform clinical collaboration

Addresses human error and standardizes a systematic approach to identify and trigger interventions for patients at-risk for deterioration

(Roney et al., 2015)

qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU

30,677 patients in ED and wards at University of Chicago who were suspected of having infection (defined as any anyone cultured and started on IV antibiotics).

Electronic records were retrospectively analyzed to calculate SIRS, qSOFA, and two risk-stratification scores (MEWS and NEWS).

These scores were compared to a primary outcome of in-hospital mortality and a combined outcome of mortality or ICU admission.

MEWS and NEWS are risk-stratification scores, designed and validated to identify patients at risk for deterioration.

(Churpek et al., 2016)

	SIRS	qSOFA	MEWS	NEWS
Temperature	✓		✓	✓
Heart rate	✓		✓	✓
Blood pressure		✓	✓	✓
Respiratory rate	✓	✓	✓	✓
Oxygen saturation				✓
Use of supplemental oxygen				✓
Mental status		✓	✓	✓
Leukocyte count	✓			

(Churpek et al., 2016)

Modified Early Warning Scoring Systems (MEWS)

Differ internationally, but generally lack incorporation of all SIRS and qSOFA criteria. Risk stratification scores to supplement clinical judgement.

Accuracy in Predicting Mortality or ICU Transfer

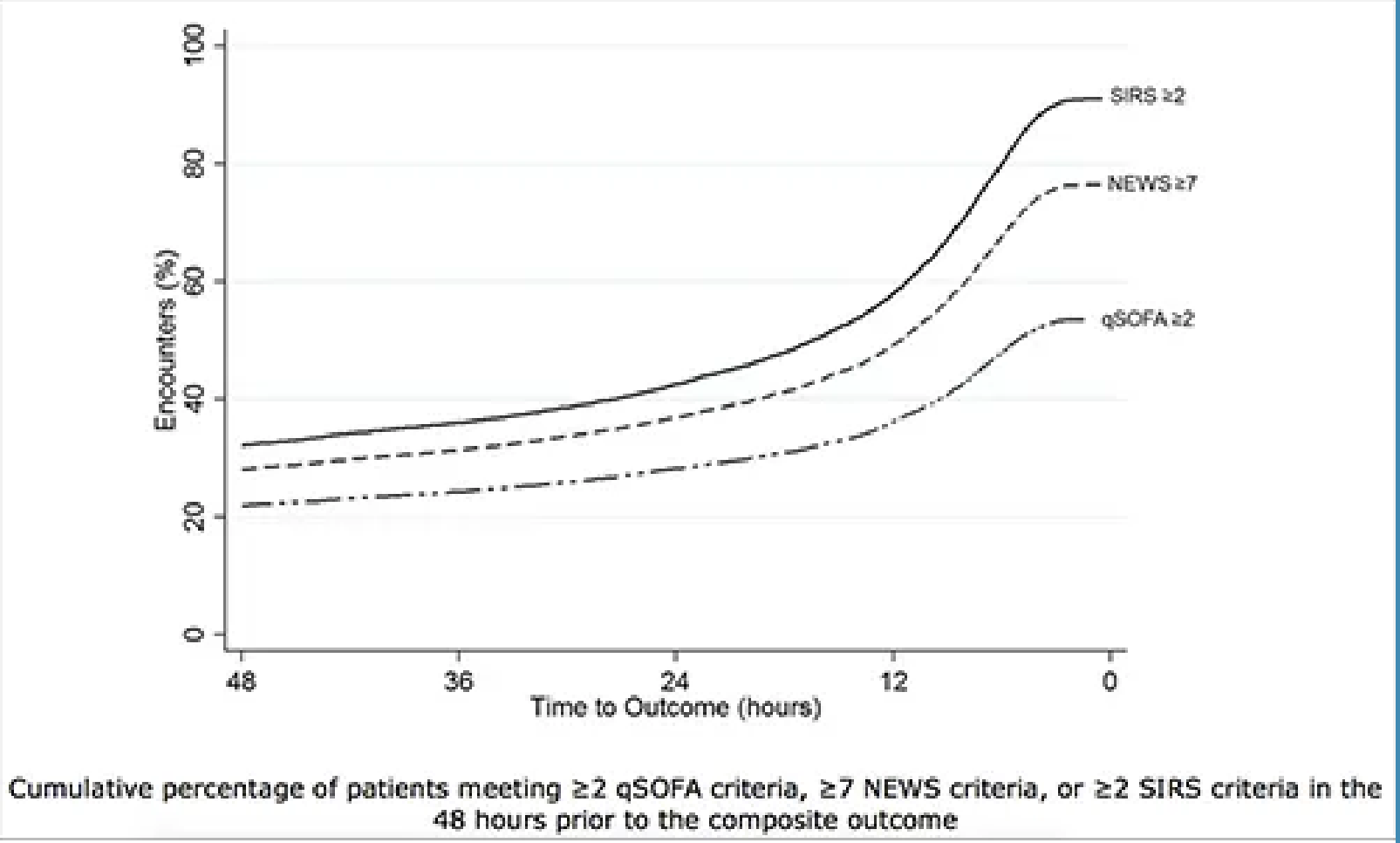
NEWS achieved a sensitivity that was 13% higher than qSOFA

	SIRS	qSOFA	MEWS	NEWS
Temperature	✓		✓	✓
Heart rate	✓		✓	✓
Blood pressure		✓	✓	✓
Respiratory rate	✓	✓	✓	✓
Oxygen saturation				✓
Use of supplemental oxygen				✓
Mental status		✓	✓	✓
Leukocyte count	✓			

Select cutoffs to predict mortality or ICU transfer

	Sensitivity	Specificity
SIRS ≥ 2	91%	13%
qSOFA ≥ 2	54%	67%
NEWS ≥ 7	77%	53%
NEWS ≥ 8	67%	66%
NEWS ≥ 9	54%	78%

(Churpek et al., 2016)



Cumulative percentage of patients meeting ≥2 qSOFA criteria, ≥7 NEWS criteria, or ≥2 SIRS criteria in the 48 hours prior to the composite outcome

(Churpek et al., 2016)

qSOFA is an insensitive and late indicator of deterioration

This study focused mostly on the highest test score before ICU transfer, rather than the test score at the point in time when infection was first suspected. For example, the sensitivity of a single test score will be lower than the sensitivity of the worst score before ICU transfer.

St George's University Hospitals NHS
NHS Foundation Trust

A retrospective cohort study of sepsis screening tools used in the Emergency Department for patients admitted to the Intensive Care Unit

Price J, Sivayoham N
Emergency Department, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom

Objectives and Background

Sepsis is a global health problem with increasing prevalence and mortality amongst both the developing and developed world[1].

Severe sepsis is responsible for 10% of all Intensive Care Unit (ICU) admissions and can carry a mortality rate of more than 20-30%[2]. Early recognition of sepsis and prompt intervention with intravenous fluids and antibiotics has been shown to improve outcome[3].

Screening potentially infected patients in the Emergency Department (ED) may enable earlier escalation of care to ICU. The aim of this study is to identify the most sensitive sepsis screening tool for identifying patients requiring ICU admission presenting to the ED with suspected infection. Utilisation of such a screening tool will enable earlier involvement of ICU physicians in the most high-risk patients and may improve clinical outcome.

Methods

We conducted a retrospective cohort study of patients admitted to ICU with a focus of infection over 12 months (September 2014 – August 2015) at an urban teaching hospital in London, UK. Patients who were transferred directly to ICU or were admitted to ICU within 7 days of admission were included. Intra-hospital transfers and patients with a primary diagnosis of malignancy were excluded.

The first set of ED observations and laboratory results were used to score patients utilizing the three most common sepsis screening tools: Systemic Inflammatory Response Syndrome Criteria (SIRS), Red Flag Sepsis (RFS) and the Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA).

We analysed the test characteristics of SIRS, RFS and qSOFA for all ICU sepsis admissions at identifying in-hospital all-cause mortality.

Results

178 patients were included over 12 months (Figure 1). Figure 2 illustrates the confirmed sources of sepsis with the 3 most common sources of sepsis being respiratory (38.2%), gastrointestinal (15.7%) and urinary (11.8%).

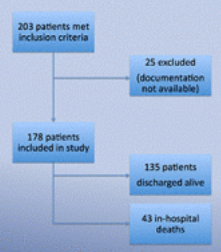


Figure 1: Consort diagram of patient flow

Confirmed source of Sepsis		
Source	**Number**	**Percent**
Chest	68	38.2%
GI	28	15.7%
Urinary	21	11.8%
Skin	11	6.2%
Liver and Biliary	11	6.2%
Unknown	10	5.6%
Abscess	9	5.1%
Other	20	11.2%

Figure 2: Sources of sepsis in patient group

Identification of the study population

The SIRS screening tool demonstrated the highest sensitivity for identifying septic patients in the study population (0.88 95% CI 0.83-0.93), followed by RFS (0.79 95% CI 0.73-0.85) and qSOFA (0.33 95% CI 0.26-0.40) (Figure 3). Combination of 2 screening tools demonstrated maximal sensitivity (SIRS and RFS, 0.94 95% CI 0.91-0.98).

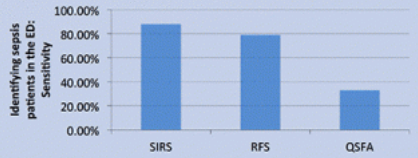


Figure 3: Sensitivity for identifying sepsis at triage

Identification of mortality

The mortality rate in the study population was 24.1%. RFS demonstrated highest sensitivity for mortality (0.81* 95% CI 0.67-0.92), SIRS (0.77 95% CI 0.61-0.88) and qSOFA (0.33 95% CI 0.19-0.49) (Table 1). The qSOFA screening tool demonstrated highest specificity (0.67** 95% CI 0.58-0.75), RFS (0.21 95% CI 0.15-0.29) and SIRS (0.08 95% CI 0.04-0.14).

	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
SIRS	0.77	0.61-0.88	0.08	0.04-0.14	0.21	0.14-0.28	0.52	0.30-0.74
RFS	**0.81***	0.66-0.91	0.21	0.15-0.29	0.25	0.18-0.33	0.78	0.62-0.90
QSFA	0.33	0.19-0.49	**0.67****	0.58-0.74	0.24	0.14-0.37	0.76	0.67-0.83

Table 1: Test characteristics of screening tools in identifying in-hospital mortality

Conclusion

The SIRS sepsis screening tool was identified as the most sensitive tool for identifying the most at-risk infected patients that may require ICU admission. Combination of SIRS and RFS achieves higher sensitivities. The qSOFA score is suboptimal for use as a screening tool in the ED.

Limitations

The retrospective study design led to missing data sets from a proportion of patients. This is likely due to poor documentation amongst clinicians but also partly a consequence of a lack of full electronic database in the organisation. Furthermore, we acknowledge that the generalizability of the results are limited, due to the single-centre nature of the study and also being conducted at a large urban teaching hospital in a developed country.

References
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3. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F et al: The PROCESS investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014, 370(18):1683-1693.

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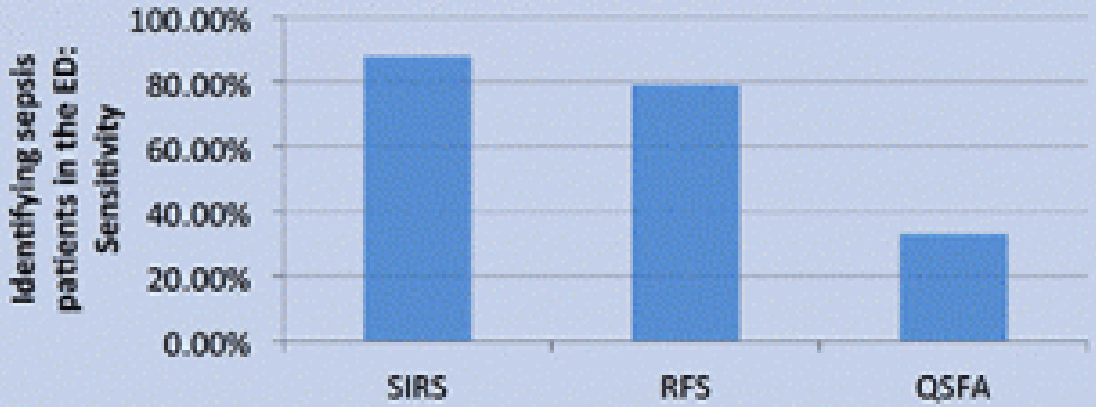

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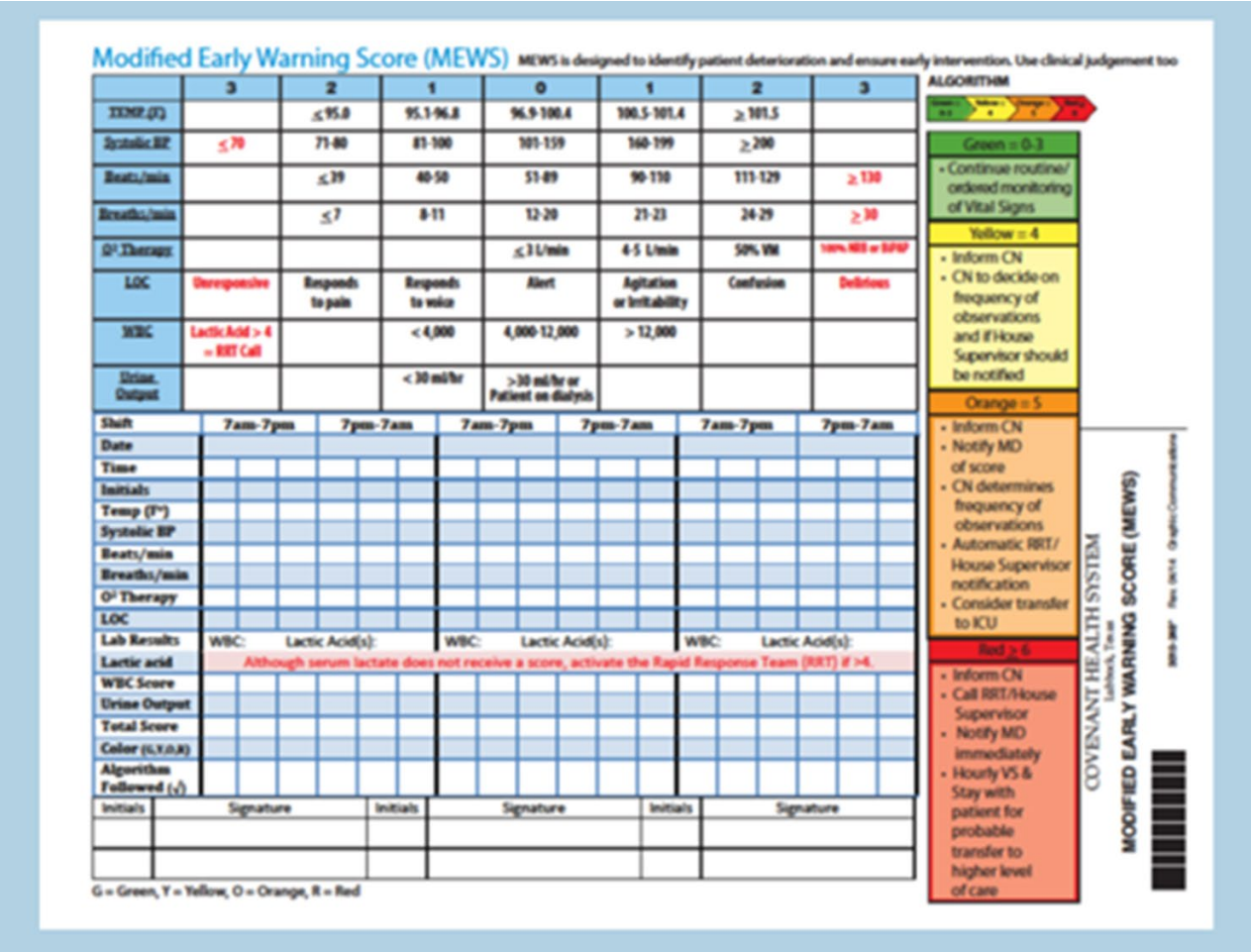
SIRS	0.77	0.61-0.88	0.08	0.04-0.14	0.21	0.14-0.28	0.52	0.30-0.74
RFS	**0.81***	0.66-0.91	0.21	0.15-0.29	0.25	0.18-0.33	0.78	0.62-0.90
QSFA	0.33	0.19-0.49	**0.67****	0.58-0.74	0.24	0.14-0.37	0.76	0.67-0.83

Table 1: Test characteristics of screening tools in identifying in-hospital mortality

"With sepsis screening recommended for early identification of septic patients prior to clinical worsening and MEWS tools advised for early identification of at-risk for deteriorating patients, one would anticipate MEWS tools 'physiological parameters would align with international sepsis screening benchmarks for heart rate, respiratory rate and temperature limits." (Roney et al. 2015)

"MEWS out-predicts SIRS & qSOFA for deterioration detection" (Evans, 2019)



Modified Early Warning Score (MEWS) MEWS is designed to identify patient deterioration and ensure early intervention. Use clinical judgement too

	3	2	1	0	1	2	3
TEMP (F)		≤95.0	95.1-96.8	96.9-100.4	100.5-101.4	≥101.5	
Systolic BP	≤70	71-80	81-100	101-159	160-199	≥200	
Beats/min		≤39	40-50	51-89	90-110	111-129	≥130
Breaths/min		≤7	8-11	12-20	21-23	24-29	≥30
O² Therapy				≤3 L/min	4-5 L/min	50% VM	100% NRB or BiPAP
LOC	Unresponsive	Responds to pain	Responds to voice	Alert	Agitation or Irritability	Confusion	Delirious
WBC	Lactic Acid > 4 = RRT Call		< 4,000	4,000-12,000	> 12,000		
Urine Output			< 30 ml/hr	>30 ml/hr or Patient on dialysis			

Shift	7am-7pm	7pm-7am	7am-7pm	7pm-7am	7am-7pm	7pm-7am
Date						
Time						
Initials						
Temp (F°)						
Systolic BP						
Beats/min						
Breaths/min						
O² Therapy						
LOC						
Lab Results	WBC: Lactic Acid(s):		WBC: Lactic Acid(s):		WBC: Lactic Acid(s):	
Lactic acid	Although serum lactate does not receive a score, activate the Rapid Response Team (RRT) if >4.					
WBC Score						
Urine Output						
Total Score						
Color (G,Y,O,R)						
Algorithm Followed (✓)						

Initials	Signature	Initials	Signature	Initials	Signature

G = Green, Y = Yellow, O = Orange, R = Red

ALGORITHM

Green = 0-3
- Continue routine/ ordered monitoring of Vital Signs

Yellow = 4
- Inform CN
- CN to decide on frequency of observations and if House Supervisor should be notified

Orange = 5
- Inform CN
- Notify MD of score
- CN determines frequency of observations
- Automatic RRT/ House Supervisor notification
- Consider transfer to ICU

Red ≥ 6
- Inform CN
- Call RRT/House Supervisor
- Notify MD immediately
- Hourly VS & Stay with patient for probable transfer to higher level of care

COVENANT HEALTH SYSTEM

MODIFIED EARLY WARNING SCORE (MEWS)

(Roney et al., 2019)

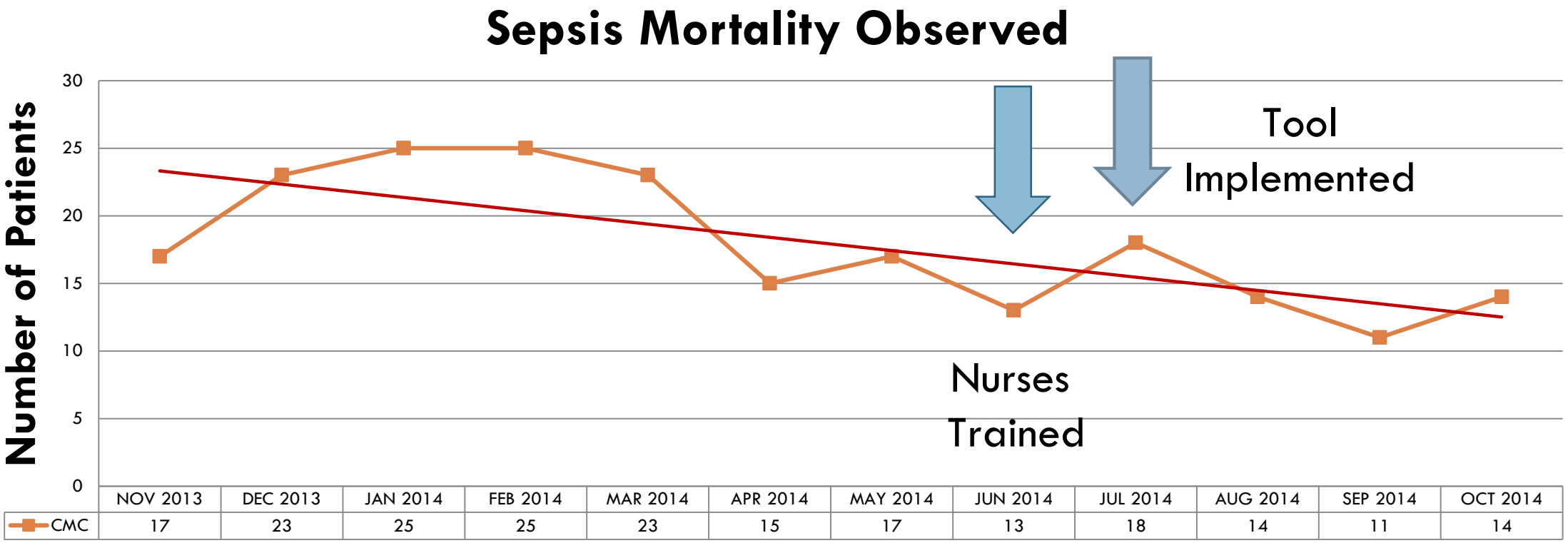
Covenant Health Developed MEWS

Temperature, respiratory rate, & heart rate were adjusted to match SIRS parameters

Oxygen saturation was changed to “oxygen flow rate”,

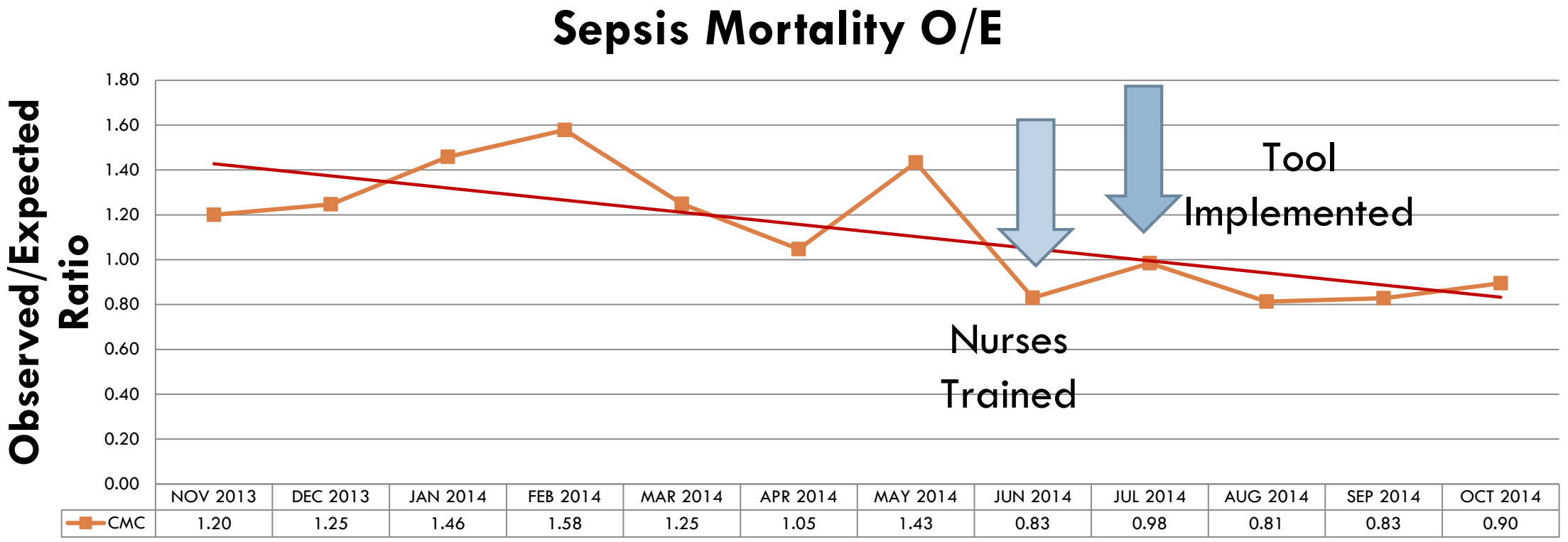
Lactic acid & white blood cell count were added

Sepsis mortality observed rate decreased from 17-25 to 11-18 patient deaths monthly after implementation of the MEWS-Sepsis screening tool.



(Roney et al., 2019)

Sepsis risk-adjusted mortality rates decreased from an observed/expected (O/E) monthly rate of 1.05-1.58 to 0.81–0.9 after implementation of the MEWS-Sepsis screening tool.



(Roney et al., 2019)

Key New Evidence Driving Sepsis Treatment & Guideline Changes

Fluids, genetics, & recognition

Changes to Fluid Type & Amount

FLUID TYPE	AMOUNT
Isotonic crystalloids 0.9% sodium chloride Versus Balanced crystalloids	30 ml/kg Bolus Ideal body weight versus actual body weight

Normal Saline and Lactated Ringer's are recommended first-line fluid for sepsis resuscitation, but does selection matter?

- With 154 mmol/L each of sodium & chloride, NS is isotonic to extracellular fluid but contains a chloride concentration significantly higher than plasma
- Ringer's solution may be slightly hypotonic to extracellular fluid, but provides anions more closely matching plasma pH
- NS leads to a non-anion gap hyperchloremic metabolic acidosis & crystalloid chloride content regulates renal blood flow
- Human and animal trials demonstrate decreased renal flow, decreased urine output, and renal vasoconstriction associated with NS administration
- A meta-analysis found increased AKI with two other studies associating NS with higher chloride, mortality, acidosis, & inflammation

(Clin Chest Med. 2016 Jun; 37(2): 241–250. Published online 2016 Mar 4. doi: 10.1016/j.ccm.2016.01.007)

How much fluid should be given?

- Every liter after 5 liters led to a 2-3% increase risk in mortality on day one (Marik, 2017)
- Liu et al. (2019) demonstrated volume is beneficial to heart & renal failure patients
- Leismand article supports 30ml/kg ABW as beneficial in heart & renal patients

How much fluid should be given?

Guideline-directed fluid resuscitation was not associated with any increased risk in respiratory failure among patients with sepsis and heart failure, end-stage renal disease (ESRD), or cirrhosis, a study found (American College of Physicians, 2019)

Khan et al. (2019) found no differences were detected in the incidence of intubation in patients with sepsis and cirrhosis, end-stage renal disease, or heart failure who received guideline-recommended fluid resuscitation with 30 mL/kg compared with patients initially resuscitated with a lower fluid volume (American College of Chest Physicians, 2019)

What Research Tells Us About Fluid

CLASSIC, CLOVERS, & ARISE trials started fluid restriction debate in 2017

30-120 minute fluid initiation demonstrated no outcomes difference than <30 minutes (Leisman, 2017)

Bolus end time doesn't impact outcomes (Semour, 2017)

Excessive fluids administered when patient is not in shock increases incidence of ARDS (Seethala, 2017)

Saving $2,000-$5,000 per patient by getting bundle completed in 3 hours—every hour delay led to mortality increase of 4% (Semour, 2017)

Defending a mean arterial pressure in the intensive care unit: Are we there yet?

SSC guidelines recommend vasopressors be titrated to a MAP of at least 65 mmHg

Does a MAP of 65 mmHg ‘protect’ the patient from organ injury?

Or is this MAP of 65 mmHg the ‘one size fits all’ for all patients?

A landmark-randomized control trial has been performed

In the “Defend the MAP” study, 62% of patients had a MAP<65 mm/Hg for > 2 hours

- For every hour with a documented MAP of < 65 mm/Hg mortality increases by 5.1%

(Harborview Medical Center, 2019)

What Research Tells Us About MAP

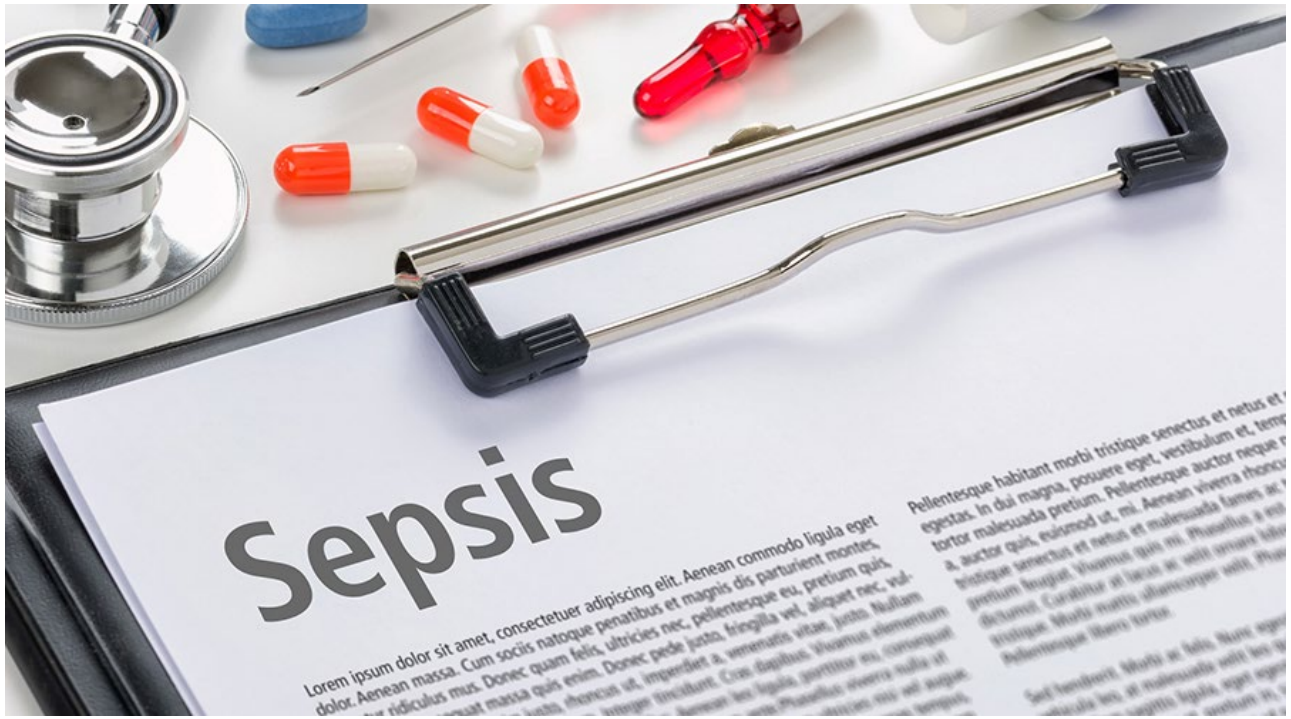
OVATION Trial recruited sample 24 hours into hospital stay and divided groups into two target groups:

- MAP 60-65 mmHg
- MAP 75-80 mmHg

Target identified as MAP of 70 mm/Hg

- >70 mmHg had increased arrhythmias (atrial fibrillation & supraventricular tachycardia)
- <70 mmHg resulted in increased acute myocardial infarction (AMI) & acute kidney injury (AKI)
- <65 mmHg demonstrated a increased incidence of AMI, AKI, & mortality

(Harborview Medical Center, 2019)



JAMA Novel Sepsis Phenotypes May 28, 2019

(Seymour et al., 2019)

Discovery follows study of nearly 64,000 EHRs

"Hopefully, by seeing sepsis as several distinct conditions with varying clinical characteristics, we can discover and test therapies precisely tailored to the type of sepsis each patient has," said first author Christopher Seymour, MD, MSc

Big Data Led to Genetic Sepsis Connection

University of Pittsburgh (UPMC) researchers mined electronic health records (EHRs) of almost 64,000 patients to derive four phenotypes of sepsis marked by demographics, lab values, and outcomes

- ❖ Analyzed 29 clinical variables in patient EHRs to identify the four phenotypes
- ❖ Developed & validated algorithm & findings in three patient groups
- ❖ Assessed reproducibility, biological parameter correlation, & clinical outcomes

20,000 sepsis patients within 6 hours of hospital arrival between 2010-2012
43,000 patients from 2013-2014
583 patients at 28 U.S. hospitals who developed sepsis due to pneumonia

(Seymour et al., 2019)

Genome Impact on Sepsis Syndrome

Sepsis phenotypes directly associated with cytokine profiles, thus genomics can be applied to sepsis care. The various phenotypes may explain differences in trial effects & patient outcomes.

- **Alpha**: The most common type (33%), with the fewest abnormal lab values, least organ dysfunction, and lowest in-hospital death rate (2%);
- **Beta**: Patients in this type (27%) were typically older and had the most chronic illnesses and kidney dysfunction;
- **Gamma**: These patients (27%) had elevated measures of inflammation, mostly pulmonary dysfunction, and the second-highest in-hospital death rate (15%);
- **Delta**: These patients (13%) typically were the sickest, often with liver dysfunction and shock. 85% were admitted to intensive care, and 32% died in hospital.

https://traffic.libsyn.com/jamaeditorsaudiosummary/novel_sepsis_phenotypes_effect_of_thrombomodulin_on_mortality_in_sepsis-associated_coagulopathy_effect_of_laparoscopic_vs_open_distal_gastrectomy_on_survival_in_gastric_cancer_and_more.mp3

Sepsis Genomes

Mutation	Genotype	Number of cases/controls	Association
−308 G/A	GA+AA	278/115	Risk of sepsis and septic shock[4]
	GA+AA	432/624	Susceptibility to severe sepsis, but not mortality[5]
	AA	1057/-	Increased mortality and ventilator duration[6]
	GA	490/610	Protection against ARDS* and sepsis mortality[7]
	GA	123/-	Predictor of ICU† mortality[8]
	AA	106/-	High survival rate[9]
	GA+AA	-/-	Associated with sepsis, but not mortality[10]
	GA+AA	306/-	Associated with sepsis[11]
	GA+AA	69/-	Increased mortality risk[12]
	GA+AA	173/-	Increases sepsis mortality, but did not affect sepsis development[13]
	GA+AA	159/-	Increased risk for severe sepsis[14]
	GA	197/214	Risk of sepsis and poor outcome[15]
−238 G/A	GA+AA	278/115	Risk of sepsis and septic shock[4]
	GA+AA	233/-	Increased mortality[16]
−376 G/A	GA+AA	278/115	Risk of sepsis and septic shock[4]
+489 G/A	GA+AA	278/115	Risk of sepsis and septic shock[4]
−863 C/A	CA	490/610	Risk for ARDS in sepsis patients[7]

*ARDS = Acute respiratory distress syndrome, †ICU = Intensive care unit

Septic Shock-Like Presentation

Hemophagocytic lymphohistiocytosis (HLH) is a primarily pediatric severe systemic inflammatory syndrome

- Most frequently affects infants from birth to 18 months of age
- Can sometimes occur in normal people with medical problems that can cause a strong activation of the immune system
- Hyper immune disorder that can impact adults with symptoms overlapping those of severe sepsis
- A lot learned from the pediatric population
- HLH patients do not extract oxygen, thus they require plasmaphoresis

(Harborview Medical Center, 2019)

HLH can cause all of the features of septic shock & regarded as a “sepsis mimic”

- Fever – 95%
- Splenomegaly – 89%
- Bicytopenia – 92%
- Hypertriglyceridemia or hypofibrinogenemia – 90%
- Hemophagocytosis – 82%
- Ferritin >500 mcg/L – 94%
- Low/absent NK cell activity – 71%
- Soluble CD25 elevation – 97%

Shock, Capillary leak syndrome,

ARDS, Cytopenias,

Disseminated intravascular coagulation (DIC),

Delirium, Seizure,

Lymphadenopathy,

Hepatomegaly,

Elevated inflammatory markers

Death

(Bergsten et al., 2017)

Diagnostic Criteria for HLH (at least five)

Fever

Splenomegaly

Cytopenia in at least two cell lines

- Hemoglobin < 9 mg/dL
- Platelets < 100 billion/L
- Neutrophils < 1,000 / microliter

Soluble CD25 (i.e. soluble IL-2 receptor) > 2,400 U/ml

Hypertriglyceridemia and/or hypofibrinogenemia

- Triglycerides >265 mg/dL
- Fibrinogen < 150 mg/dL

Hemophagocytosis in bone marrow, spleen, or lymph node biopsy (4)

Ferritin >500 ng/ml

Low natural killer-cell activity (5)

(Bergsten et al., 2017)

Case Study 1: Delay in Evaluation

Patient Details	Comorbidities	Presentation	Details
[redacted] 78 M **Admit Date** **9/24/16** Length of Stay 6 days	CHF, CKD, COPD, HTN, HypoTh, AKI, acute respiratory failure	@2307 – patient arrived in ED @2310 – patient triaged @0008 – patient seen by MD Patient presented with 24-36 hours of cough + shortness of breath **Initial VS:** 94/43, 93, 16, 97.0, and 94% on NRB mask. WBC = 13, Lactate = 1.85, Creatinine = 3.5	Pt admitted to ICU for septic shock secondary to PNA +/- UTI. Started on Levofloxacin + Meropenem and given IV fluids (1 liter bolus in ED + maintenance on the floor). Cultures later + for VRE and E. Coli HD 1 – Levophed initiated; lactate trending up (2.6 → 4.4). Fluids increased and over the next 24 hours patient given ~ 5 liters He gradually deteriorated over subsequent days despite aggressive + appropriate care. On 9/30 he had cardiopulmonary arrest.

Case Studies 2 & 3: Delay in Evaluation

Patient Info	Time Details	Presentation	Outcome
76 F	Arrived: 0952 Triaged: 1001 MD eval: 1130	Pt to ED s/p fall caused by AMS. RR 40s and patient requiring 3 liters nasal cannula. WBC 37.6 Pt met sepsis criteria via 2/3 qSOFA	On HD 0, patient developed VT arrest. Resuscitated + transferred to MICU. Treated for sepsis + VT. Ultimately deceased on HD 2
58 F	Arrived: 0937 Triaged: 0938 MD eval: 1131	Pt w/ ESLD presents with AMS + PNA. Afebrile, HR 102, + BP 108/95. WBC 27 + Lactate 2.4	Gradually decompensated and ultimately died on HD 8

Case Study 4: Under Resuscitation

Patient Details	Comorbidities	Presentation	Details
[redacted] 80 M **Admit Date:** **9/24/16** Length of Stay: 2 days	Sepsis, Septic Shock, Dementia, UTI, AKI, AHRF, PVD	Pt BIBA for SOB + concerns for aspiration. Non verbal on presentation Initial VS: Afebrile, 95, 98/54, 24, 91% (on 10 liters) Labs: -Hgb = 8.5 -Cr = 3.2 -Lactate = 3.62 UA c/w UTI	Patient in ED for ~ 4 hours and received 1L bolus of normal saline. Also started on Clindamycin + Levofloxacin. Admitted to MICU. Suspected source of sepsis = indwelling suprapubic catheter HD 0 – **in first 10 hours of hospitalization, the patient received ~ 1500 cc IVF.** HD 1 – worsening shock required initiation of Levophed. Goals of care discussion resulted in DNR HD 2 – patient made comfort care and died

Case Study 5: Volume Resuscitation & Trending Lactates

Patient Details	Comorbidities	Presentation	Details
[redacted] 68 F	Sepsis, UTI, A fib	Pt w/ history of recurrent Enterococcus UTI, transferred from SNF for evaluation of UTI. VS: 98.8, 81, 16, 135/73, 97% on room air WBC = 23.6 Lactate = 4.2 Started on Vancomycin + maintenance fluids	Despite significant elevation, lactate was not repeated for ~ 48 hours, when it was found to still be elevated ~ 2.5. In the first 24 hours of admission, the patient only received 320 cc IVF. Throughout admission, she had progression to septic shock and required intubation for respiratory failure. Family discussion led to decision to terminally extubate and withdraw care.
Admit Date: 7/12/16			
Length of Stay: 5 days			

Case Study 6 & 7: Under Resuscitation

Patient Info	Details	Comments
57 F	Pt with sepsis 2/2 PNA; initial lactate = 7.02. Given 1L in ED then maintenance @ 80/hour. Given 2800 cc IVF in 1st 24 hours	
72 F	Transfer w/ sepsis 2/2 UTI. SBP 70s and patient started on Dopamine en route. Admit note says to avoid boluses due to concerns for heart failure	**How does history of heart failure affect volume resuscitation?**
69 M	Pt admitted with UTI; sepsis not documented despite patient having 2/3 qSOFA (altered mental status + BP 98/46). Given antibiotics but fluids only @ 80/hour (no bolus).	Pt developed respiratory failure + required intubation. Decompensated and was ultimately made comfort care

Case Study 8: Opportunity for Palliative Care

Patient Details	Comorbidities	Presentation	Details
[redacted] 88 F **Admit Date: 9/3/16** Length of Stay: 9 days	Septic Shock, Cholangitis, Encephalopathy	Transfer from Clovis due to AMS + sepsis (secondary to cholangitis). Patient had DNR/DNI order noted at arrival in ED. Initial VS: 98.0, 106, 29, 106/56, + 98% (on room air) WBC = 75.7 Hgb 10.5 UA + Transaminitis	Admitted to ICU; started on Vancomycin + Zosyn. Given ~ 5L total IVF between Clovis + Covenant ED. Cultures ultimately + for VRE. HD 0 – patient started Levophed for worsening shock. Son decided to make patient full code again. Following this she requiring intubation for respiratory distress. She also underwent ERCP. Patient made no signs of improvement. Palliative care c/s on 9/9 and patient made DNR/DNI again and transitioned to comfort care.

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What Questions Do You Have for Me?