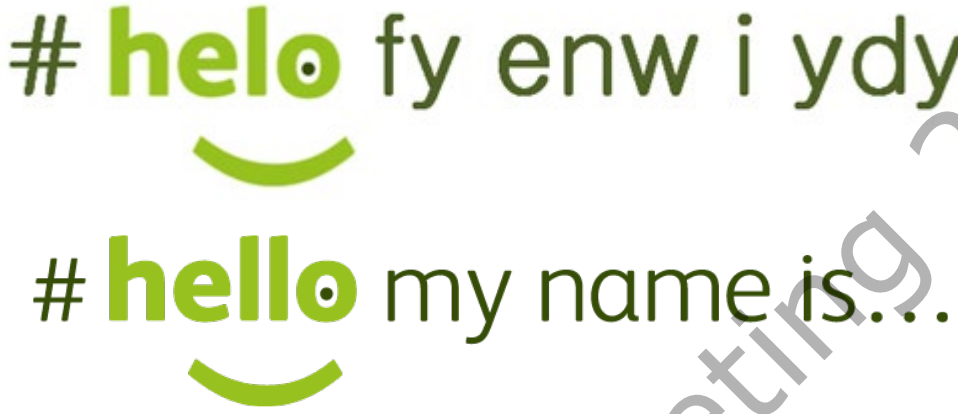

Dr. Paul Morgan
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Declaration of Interest

- Lead Volunteer for Wales, UK Sepsis Trust

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Sepsis – the latest?

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Lung Cancer

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Sepsis Kills and Maims

- Sepsis kills **52,000** people each year in the UK

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How many cases of sepsis?

- Increasing numbers of cases of acute deterioration being recognised
- 2012 – 102,000 cases
- 2015 – 150,000 cases
- 2017 – 260,000 cases???

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Avoidable deaths, avoidable harm

- Many of the sepsis deaths are unavoidable, but many - possibly >25% - should be avoidable
- Medium to long term morbidity affects > 20% of sepsis survivors

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Sepsis Survival

- Physical problems
- Psychological problems
- Recurring infections and risk of further sepsis
- Overlap with ICU survivor morbidities

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What Is Sepsis????

- Cannot measure it without defining it
- Cannot know whether care/outcome is improving without measuring it
- A definition is therefore essential!

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Sepsis Definitions - old and new

- No agreed definition of sepsis until 1992
  - "Bone" Criteria, aka "Sepsis 1.0"
  - Linked SIRS + infection
- 2002 – "Sepsis 2.0" added little except hyperglycaemia and altered mental state
- SIRS is problematic
  - Highly (?Overly) sensitive
  - Poor specificity
  - 1 in 8 patients in ICU with organ failures subsequent to infection don't meet 2 or more SIRS criteria

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The Problem with SIRS…

SIRS Sensitivity

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

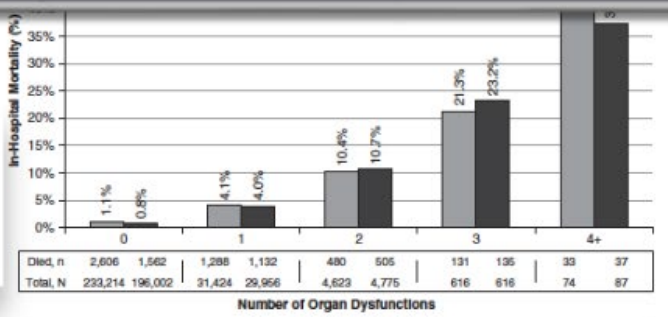
Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

N Engl J Med 2015;372:1629-38.

SIRS is an *appropriate* response to infection – or any other stimulus that activates inflammation

Am J Respir Crit Care Med 2015; 192:958-964

Conclusions: Almost half of patients hospitalized on the wards developed SIRS at least once during their ward stay. Our findings suggest that screening ward patients using SIRS criteria for identifying those with sepsis would be impractical.



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SIRS negative sepsis

- Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis
- N Engl J Med 2015 April 23; 372 (17):1629-38
- One in eight patients in ICU with sepsis did not have 2 or more SIRS criteria.

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Sepsis 3.0

- 2016 International Consensus Definition (JAMA February 23rd)
- “Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection”

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- In lay terms, sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs

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- Septic shock is a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase mortality

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- “For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than **10%**.”

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- “Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate level > 2 mmol/l despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of **40%**”

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What's changed?

- SIRS out
- Severe sepsis – gone
- qSOFA is in...
- .....or is it?

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SOFA and qSOFA

- SOFA = serial organ failure assessment
- Used in some ICUs to retrospectively categorise patients by severity of illness
- qSOFA (quick SOFA) focuses on just 3 aspects
  - Systolic BP < 100 mmHg
  - Respiratory rate ≥ 22/min
  - Altered mental status

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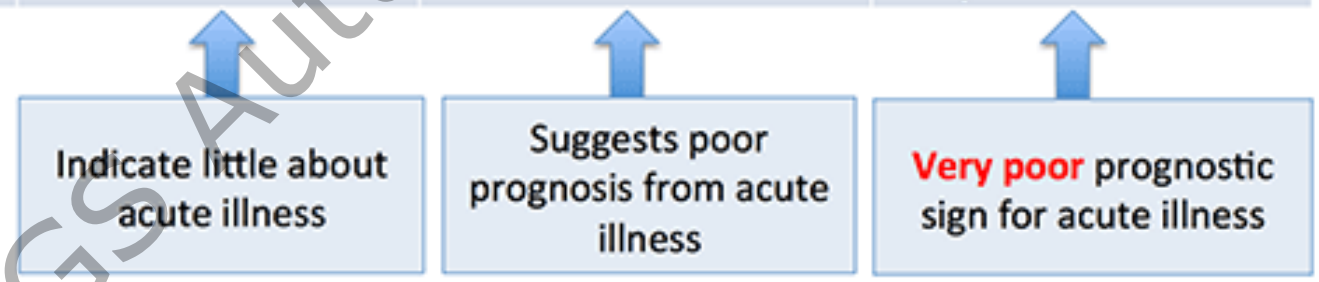
A note of caution...

qSOFA criterion	Spurious abnormality	Primary abnormality	Secondary abnormality
SBP ≤ 100	- Low baseline Bp	- Spontaneous AF with RVR - Myocarditis - Type-1 MI	- Septic shock - Hemorrhage
Altered mentation	- Dementia - Received procedural sedation	- Sedative intoxication - Stroke - Encephalitis	- Shock (any type) - Hypoxemia - Hypercapnia
RR ≥ 22	- Anxiety - Pain	- Pneumonia - Asthma - COPD	- Resp compensation for metabolic acidosis - Septic shock



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NEWS (NEWS-2) and qSOFA

- Systolic BP ≤ 100 = 2 points
- Respiratory Rate ≥ 22 = 2 points
- Altered mental state or new-onset confusion on “CAVPU” = 3 points.
- qSOFA ≥ 2 therefore <u>minimum</u> NEWS = 4

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RCEM, UK Sepsis Trust and NICE

> *For these reasons, we (UKST, RCEM and NICE) do not currently recommend the use of qSOFA as the primary bedside test for sepsis in the U.K. It is likely to be a useful and important redundancy to the proposed screening strategy in organizations benefiting from electronic observations and clinical prompts.*

"Since the minimum NEWS compatible with a qSOFA score of 2 (the recommended trigger threshold) is 4, UKST, RCEM and NICE believe it reasonable to propose that the existing NEWS escalation recommendations of an aggregate score of 3 or higher be used as a trigger to screen for sepsis. An aggregate score of 3 has been demonstrated recently to carry almost a 93% sensitivity and 77% specificity for a (Sepsis-2) diagnosis of severe sepsis or septic shock."

Emergency Medicine Journal 2016; 2016; 33: 37–41

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Sepsis Treatment – time is tissue!

- Time to Treatment and Mortality during Mandated Emergency Care for Sepsis
- NEJM May 21, 2017DOI: 10.1056/NEJMoa1703058
- New York State Department of Health, community-acquired sepsis requiring sepsis protocol initiation with 6 hours of ED presentation
- Mortality at time points based on delivery of treatments according to the Surviving Sepsis Campaign 3 hour initial treatment bundle

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- 49,331 eligible patients in the emergency department at 149 hospitals
- 40,696 patients (82.5%) had the 3-hour bundle completed within 3 hours
- Median time to completion of the 3-hour bundle was 1.30 hours (interquartile range, 0.65 to 2.35)
  - administration of broad-spectrum antibiotics 0.95 hours (0.35 to 1.95)
  - initial bolus of intravenous fluids 2.56 hours (1.33 to 4.20)

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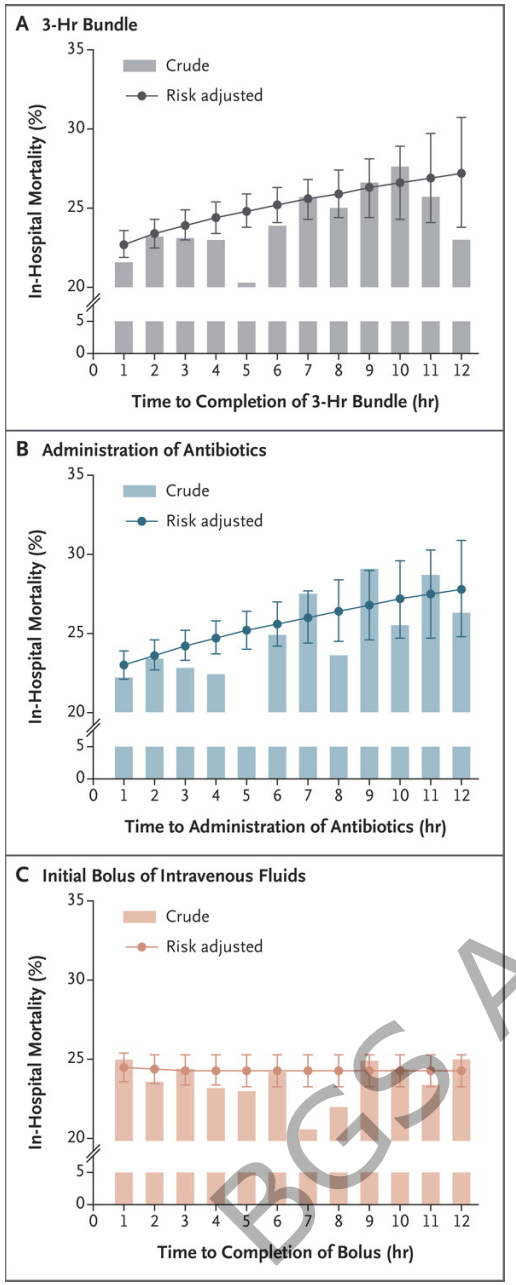

Crude In-Hospital Mortality and Predicted Risks of In-Hospital Death. Shown are the crude in-hospital mortality and predicted risks of in-hospital death, with adjustment for covariates across a range of time after protocol initiation, for the completion of the 3-hour bundle of sepsis care (Panel A), the administration of broad-spectrum antibiotics (Panel B), and the completion of the initial bolus of intravenous fluids (Panel C) in a typical patient. I bars represent 95% confidence intervals.

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- “Our statewide evaluation showed that the times to the completion of a 3-hour bundle and the administration of broad-spectrum antibiotics were associated with greater in-hospital mortality among patients with severe sepsis and septic shock in the emergency department. We found no association between the time to completion of the initial bolus of intravenous fluids and outcome. If the relationship is causal, prompt recognition and faster treatment of sepsis and septic shock in the context of emergency care may reduce the incidence of avoidable deaths.”

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Avoidable deaths?

- Many deaths occur in patients with sepsis, but how many of these deaths are directly, or even solely, attributable to sepsis?
- “Sepsis hysteria: excess hype and unrealistic expectations” Singer M, Inada-Kim M, Shankar-Hari M.
- Lancet, Volume 394, Pages 1513-1514
- “The high incidence of frailty and severe comorbidities makes most sepsis-related deaths neither attributable to sepsis, nor preventable through timely and effective health care.”

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- Kopczynska, M., Sharif, B., Cleaver, S. *et al.* Sepsis-related deaths in the at-risk population on the wards: attributable fraction of mortality in a large point-prevalence study. *BMC Res Notes* **11,** 720 (2018) doi:10.1186/s13104-018-3819-2
- 40/166 (24.1%) deaths directly or possibly related to sepsis
- Risk of death much higher with existing high clinical frailty

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Nevertheless…

- Many sepsis-related deaths occur
- Not all are in the clinically frail
- Sepsis treatment isn't just about those who die – many survivors (probably >25%) left with life-changing and life-limiting conditions
  - Amputations
  - Cardiac disease
  - Respiratory failure
  - Post-sepsis syndrome

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Sepsis Survival

- Post sepsis syndrome affects >25% of survivors
- Physical problems
- Psychological problems
- Recurring infections and risk of further sepsis
- Overlap with ICU survivor morbidities
- Can have problems for up to ~ 2 years

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Physical Problems

- Lethargy / excessive tiredness
- Poor mobility / muscle weakness
- Breathlessness / chest pains
- Swollen limbs (excessive fluid in the tissues)
- Joint pains
- Insomnia (due to pain / breathlessness)
- Hair loss
- Dry / flaking skin and nails
- Taste changes
- Poor appetite
- Changes in vision
- Changes in sensation in limbs
- Repeated infections
- Reduced kidney function

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Psychological Problems

- 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

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Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors

Shankar-Hari M, Harrison DA et al JAMA Netw Open. 2019 May; 2(5): e194900.

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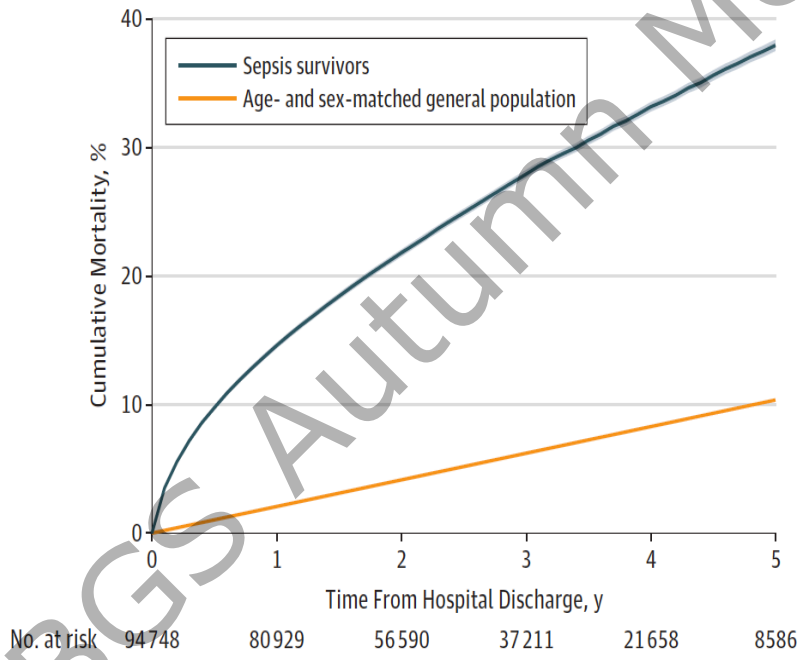
Figure 2. Cumulative All-Cause Long-term Mortality in Adult Sepsis Survivors Compared With Age- and Sex-Matched General Population



Cumulative all-cause long-term mortality in the entire cohort of sepsis survivors (as defined by the Third International Consensus Definitions for Sepsis and Septic Shock) compared with age-, sex-, and index sepsis admission year–matched general population expected probabilities of death in England, using relative survival framework (eTable 3 in the Supplement).

Long-term Host Immune Response Trajectories Among Hospitalized Patients With Sepsis

- JAMA Network Open. 2019;2(8):e198686.
- In this study, persistent elevation of inflammation and immunosuppression biomarkers occurred in two-thirds of patients who survived a hospitalization for sepsis and was associated with worse long-term outcomes.

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Long-term impact of sepsis on cardiovascular health

- R. T. Mankowski, S. Yende and D. C. Angus
- Intensive Care Med (2019) 45:78–81

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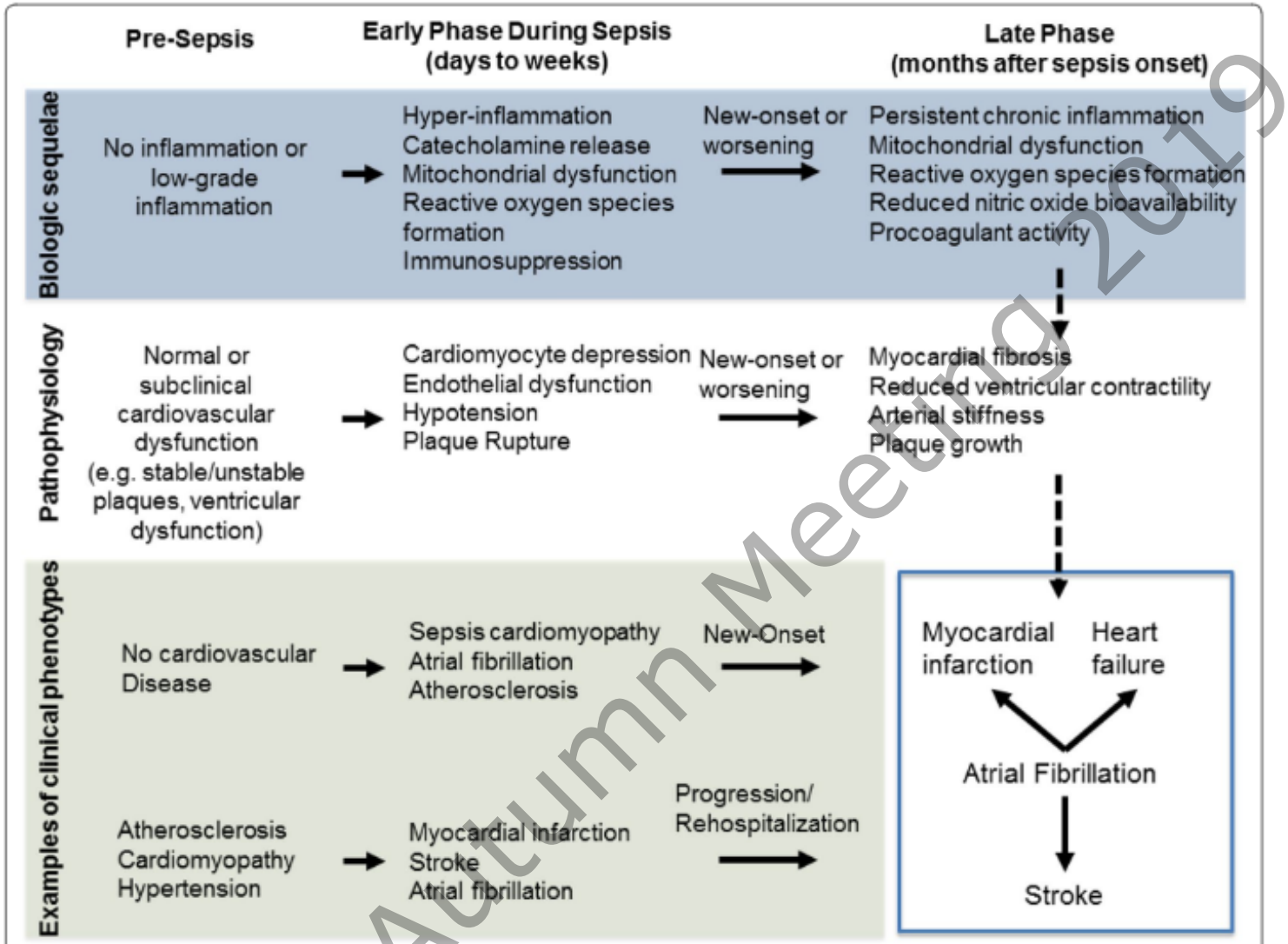

Fig. 1 Conceptual mechanistic model of the long-term impact of a sepsis incident on cardiovascular disease development and/or worsening of pre-existing dysfunction/disease. The figure presents the impact of a sepsis (early phase) on long-term (late phase) cardiovascular disease development in three domains: biologic sequelae due to sepsis (blue), pathophysiology of cardiovascular dysfunction (white), and examples of cardiovascular disease phenotypes (green). The magnitude of long-term cardiovascular disease risk is likely dependent on pre-sepsis health state and clinical or subclinical cardiovascular dysfunction/disease (pre-sepsis) and biological mechanisms and pathophysiologic changes during the episode of sepsis and recovery. Dashed arrows demonstrate how late biologic sequelae (deteriorating processes initiated or accelerated by a sepsis incident) may lead to the late clinical phenotypic changes. Over time, persistent systemic inflammation, progressive mitochondrial dysfunction, formation of reactive oxygen species, reduced nitric oxide bioavailability, and procoagulant activity (late phase biologic sequelae) may lead to dysfunctional cardiovascular remodeling, which contributes to the development/progression of cardiovascular disease. We also demonstrated that potential interactions between cardiovascular diseases such as development of atrial fibrillation might contribute to the development of stroke, MI, or heart failure

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Enough is Enough

- Unrealistic to prevent all sepsis morbidity and mortality
- Thousands of avoidable deaths
  - Chloe Christopher
  - Rachel Day
  - William Mead
- How many cases of avoidable harm?
  - Jayne Carpenter
  - Angela Burns
  - Tom Ray

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- Health Professionals must do better at early recognition and treatment
- Governments need to support efforts to reduce sepsis morbidity and mortality
- We must provide better support for sepsis survivors

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Any questions?

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- @drpaulmorgan

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