University of Pittsburgh Emergency Medicine

www.emergencymedicine.pitt.edu

Early Septic Shock Care – Phenotypes and How We Got Here

Donald M. Yealy, MD

Chair, Department of Emergency Medicine;

Professor of Emergency Medicine, Medicine, and

Clinical and Translational Sciences,

School of Medicine, University of Pittsburgh

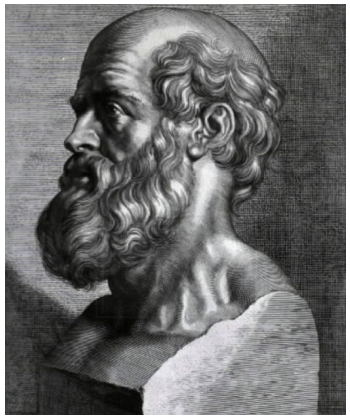
Financial disclosures

- Deputy Editor, *Annals of Emergency Medicine*
- My external funding past 36 months
  - NHLBI – **PETAL Network (PI); T32 Research Training Grant**
  - NIGMS - **RO1 ProACT (procalcitonin in LRTI)**
  - Royalties from three texts (*Tintinalli's Study Guide*; *The Trauma Manual*; *ED Critical Care*) and *UpToDate* (not sepsis related)
- **Expert opinions - civil**

Learning Objectives

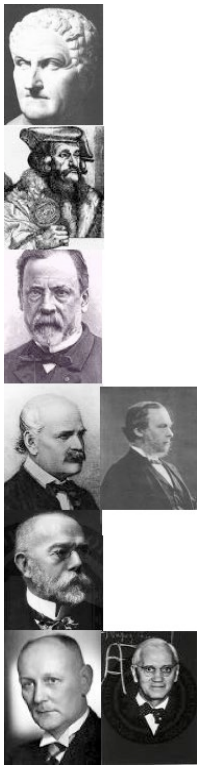
- **List** three reasons for the ProCESS and other two non-US trials
- **Note** two main outcomes
- **List** two similarities in design and outcome with the more recent trials
- **State** how different sepsis phenotypes exist and could influence actions and assessments.

Origins of sepsis



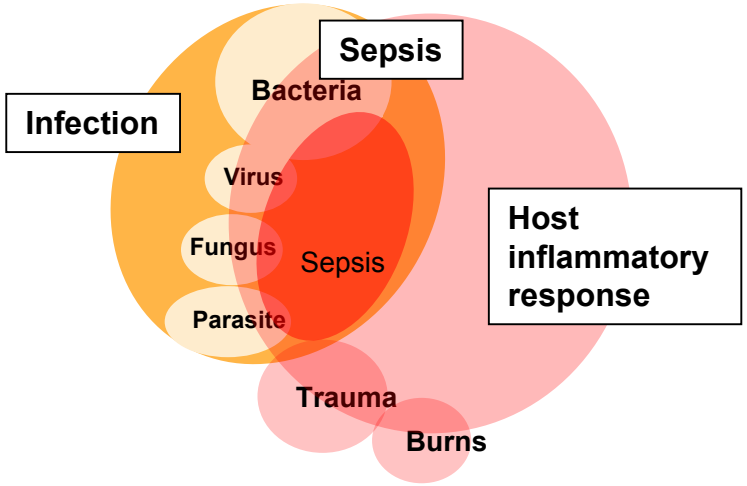
- **Hippocrates (BC ~460-370)**
  - Sepsis (σῆψις)
    - The process by which flesh rots, swamps generate foul airs at night, and wounds fester
    - It is rank, disease-producing, and evil

The 2000 year evolution of ‘germ theory’



- **Fracastoro (1478-1553)**
  - Passage of minute bodies from one person to another
- **Pasteur (1822-1895)**
  - Confirmation of the germ theory; vaccination
- **Semmelweis (1818-1865) and Lister (1827-1912)**
  - Antiseptic control
- **Koch**
  - Scientific basis for interrogation of mechanism of action
- **Domagk, Fleming, et al (20th century)**
  - Modern era of antibiotics

What do we think sepsis 'is'?



- **Patients still die DESPITE effective antibiotics**
- **Sepsis is a host response to infection gone awry!**
  - A case of harm by friendly fire
- **When organs fail, the sepsis is called 'severe'**
  - 1992 and 2003 International Consensus Definition

Bone et al. Ann Intern Med 1992; Levy et al. CCM 2003

Research Letter | July 2, 2014

Hospital Deaths in Patients With Sepsis From 2 Independent Cohorts FREE

Vincent Liu, MD, MS[1]; Gabriel J. Escobar, MD[1]; John D. Greene, MA[1]; Jay Soule[2]; Alan Whippy, MD[2]; Derek C. Angus, MD, MPH[3,4]; Theodore J. Iwashyna, MD, PhD[5]

JAMA The Journal of the American Medical Association

- Sepsis accounted for 36-55% of all hospital deaths
- #1 cause of hospital deaths in the US

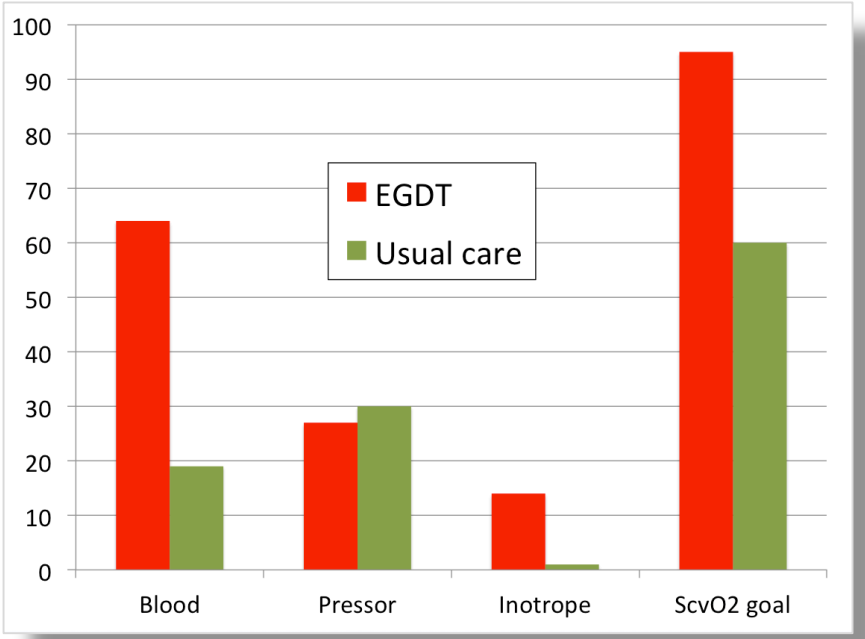
Background

The New England Journal of Medicine

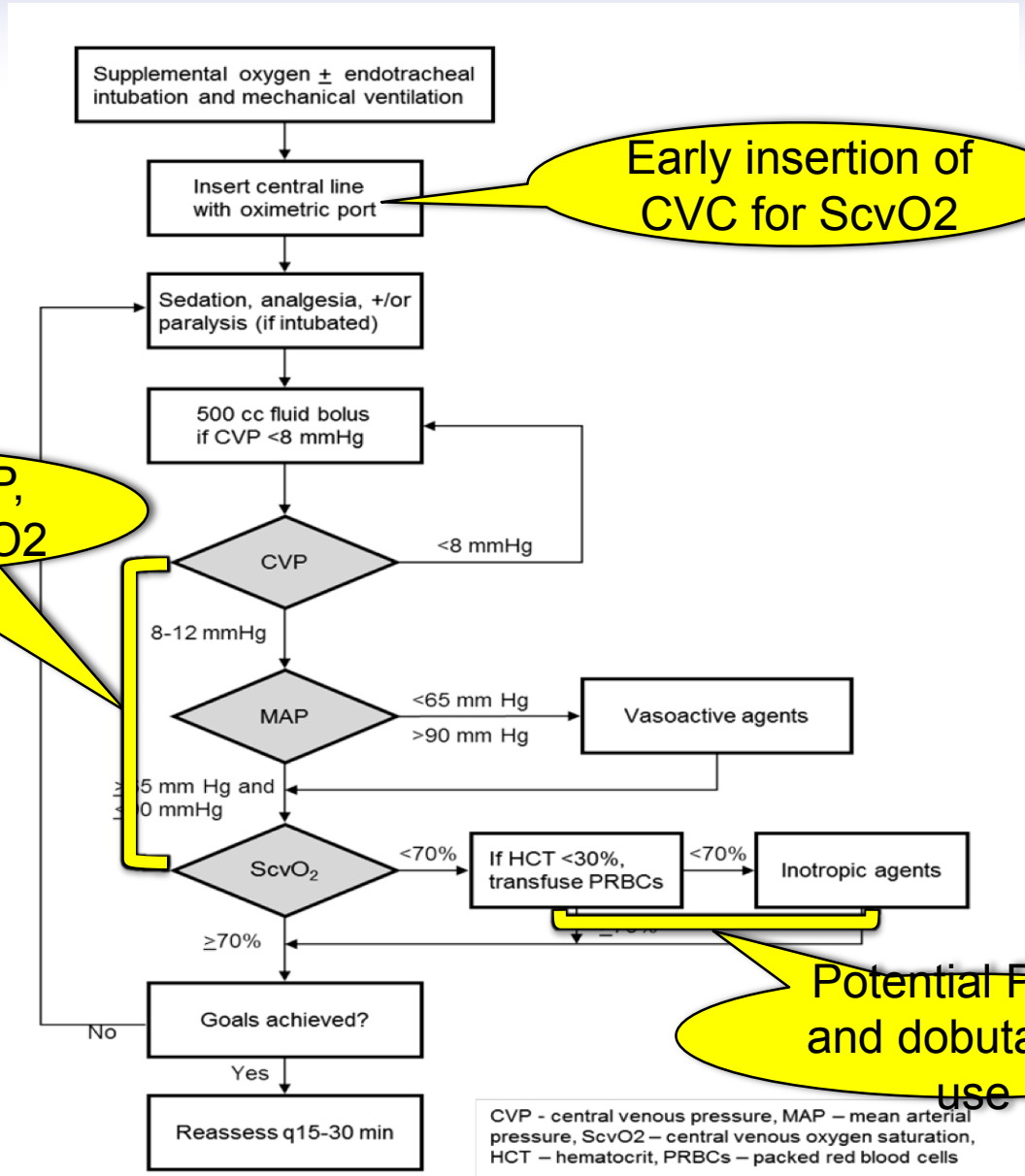
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

- **Landmark – 11k (!!)** citations on Google Scholar
- **Single center study**
  - N=263
- **Protocolized EGDT vs. usual care *after* early detection/fluid bolus**
- **16% absolute mortality reduction**
  - 30% vs. 46%
  - Exp arm: 5L (vs 3.5 L IVF), more blood, dobutamine



Protocol-based EGDT



Residual questions

- **Is the difference due to the act of 'protocolizing' or attention only to resuscitative care *after* early/better identification of shock?**

- **Are all elements of the protocol necessary?**
  - Early central venous catheterization in all patients
  - CVP guided initial fluid therapy
  - $ScvO_2$ monitoring to guide therapy, notably red cell transfusion and dobutamine

- **Are the results generalizable?**
  - Now?
  - In broader multicenter setting
  - Follow-up EGDT studies often used "off/on" design with limited CVC/protocol adherence – testing *attention* instead of protocol?

The ProCESS trial

- **Early** septic shock in the **Emergency Department**
- **Randomization** to one of 3 arms for 6 hours of resuscitation
  - **Protocol-based** 'Early Goal-directed Therapy'
  - **Protocol-based** standard therapy
  - **Usual** care
- **Two sequential hypotheses …**
  - Is protocol-based resuscitation superior to usual care?
  - If so, is EGDT superior to protocol-based standard therapy?

Where 'standard' therapy does **NOT** include

- Central venous pressure and oxygen monitoring
- Latter guiding blood or dobutamine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

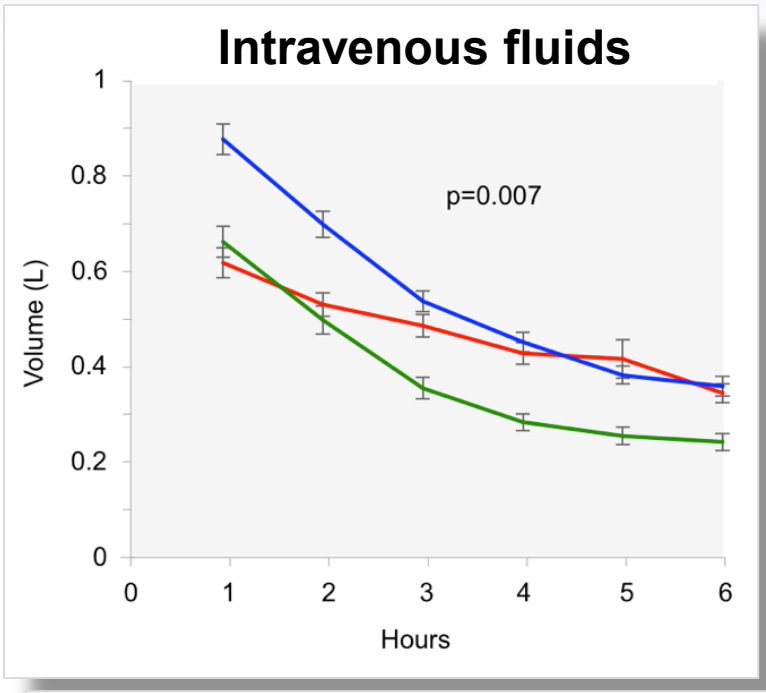
ABSTRACT

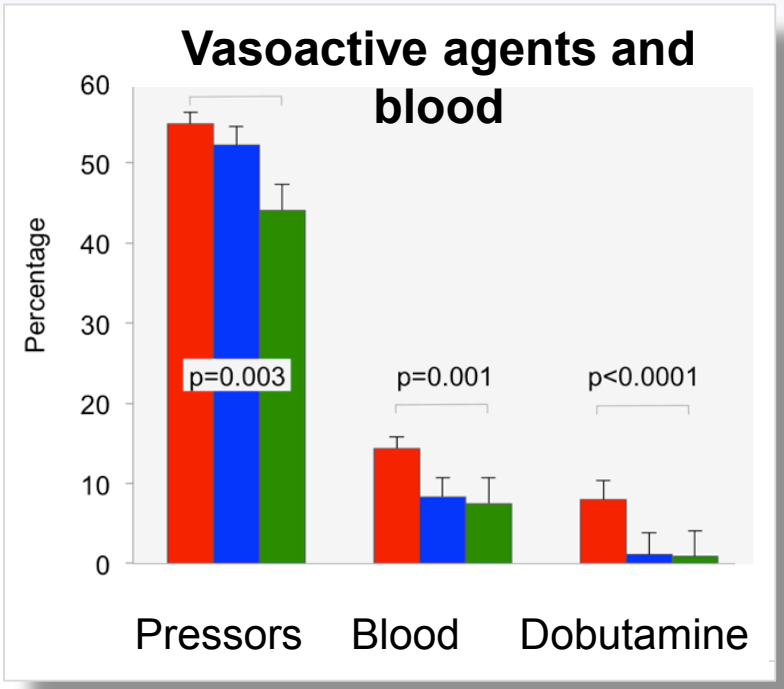
BACKGROUND

In a single-center study published more than a decade ago involving patients presenting to the emergency department with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT), in which intravenous fluids, vasopressors, inotropes, and blood transfusions were adjusted to reach central hemodynamic targets, than among those receiving usual care. We conducted a trial to determine whether these findings were generalizable and whether all aspects of the protocol were necessary.

The members of the writing committee (Donald M. Yealy, M.D., John A. Kellum, M.D., David T. Huang, M.D., Amber E. Barnato, M.D., Lisa A. Weissfeld, Ph.D., and Francis Pike, Ph.D., University of Pittsburgh, Pittsburgh; Thomas Terndrup, M.D., Ohio State University, Columbus; Henry E. Wang, M.D., University of Alabama at Birmingham, Birmingham; Peter C. Hou, M.D., Brigham and Women's Hospital, Boston; Frank LoVecchio, D.O., Maricopa

Resuscitation from randomization to 6h





Protocol-based EGDT Protocol-based Standard Therapy Usual care

Intravenous fluids		
EGDT protocol	2.8 L	p<0.001
PST	3.3 L	
Usual care	2.3 L	

Intravenous antibiotics		
EGDT protocol	97.5%	p=0.90
PST	97.1%	
Usual care	96.9%	

Outcomes

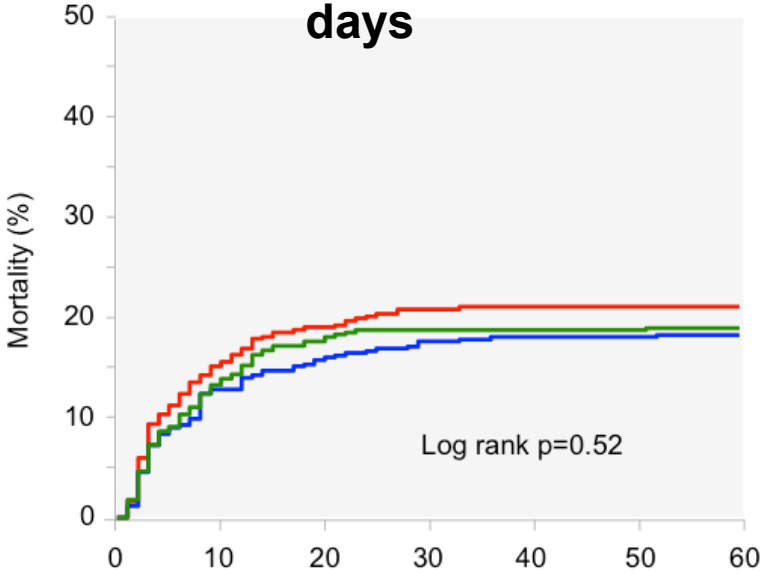
Table 2. Outcomes.*

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92

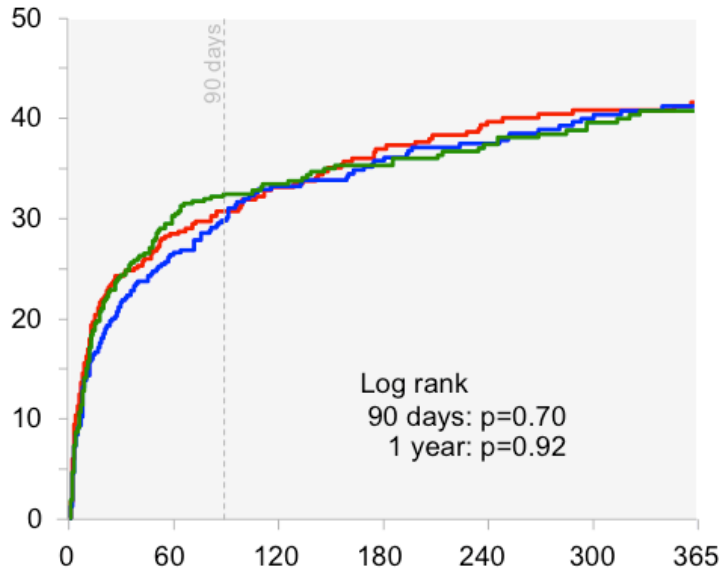
- **No difference in mortality**
  - Results unchanged when adjusting for potential site heterogeneity
  - Higher dialysis-dependent renal failure in protocol-based Std Rx arm

Mortality over time

In-hospital mortality up to 60 days



Mortality up to one year



Number at risk							
EGDT protocol	439	373	356	348	347	347	347
PST protocol	446	389	376	368	366	366	365
Usual care	456	396	376	371	371	371	370

439	289	217	194	175	156	145
446	308	212	196	179	158	142
456	285	211	199	181	164	139

Protocol-based EGDT Protocol-based Standard Therapy Usual care

Secondary outcomes

Table 2. Outcomes.*	EGDT	PSC	Usual	
Use of hospital resources				
Admission to intensive care unit — no. (%)	401 (91.3)	381 (85.4)	393 (86.2)	0.01
Stay in intensive care unit among admitted patients — days	5.1±6.3	5.1±7.1	4.7±5.8	0.63
Stay in hospital — days	11.1±10	12.3±12.1	11.3±10.9	0.25
Discharge status at 60 days — no. (%)				
Not discharged	3 (0.7)	8 (1.8)	2 (0.4)	0.82
Discharged to a long-term acute care facility	16 (3.6)	22 (4.9)	22 (4.8)	
Discharge to another acute care hospital	8 (1.8)	2 (0.4)	5 (1.1)	
Discharged to nursing home	71 (16.2)	93 (20.9)	88 (19.3)	
Discharged home	236 (53.8)	227 (50.9)	235 (51.5)	
Other or unknown	13 (3.0)	13 (2.9)	18 (3.9)	
Serious adverse events — no. (%)¶	23 (5.2)	22 (4.9)	37 (8.1)	0.32

- **Higher ICU use with EGDT**
  - Possibly due to monitoring differences

A priori subgroup analyses

- **No interaction between treatment arm and …**
  - Age
  - Sex
  - Race
  - Source of infection
  - Type of shock
- **True for 60d hospital mortality, 90d mortality, and 1y mortality**
- **Process of care hour +6-72 – no difference (“catch up” or correcting gaps not evident)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND

Early goal-directed therapy (EGDT) has been endorsed in the guidelines of the Surviving Sepsis Campaign as a key strategy to decrease mortality among patients presenting to the emergency department with septic shock. However, its effectiveness is uncertain.

METHODS

In this trial conducted at 51 centers (mostly in Australia or New Zealand), we randomly assigned patients presenting to the emergency department with early septic shock to receive either EGDT or usual care. The primary outcome was all-cause mortality within 90 days after randomization.

RESULTS

Of the 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual-care group. Primary outcome data were available for more than 99% of the

The members of the writing committee (Sandra L. Peake, M.D., Ph.D., Anthony Delaney, M.D., Ph.D., Michael Bailey, Ph.D., Rinaldo Bellomo, M.D., Peter A. Cameron, M.D., D. James Cooper, M.D., Alisa M. Higgins, M.P.H., Anna Holdgate, M.D., Belinda D. Howe, M.P.H., Steven A.R. Webb, M.D., Ph.D., and Patricia Williams, B.N.) assume responsibility for the overall content and integrity of the article. Address reprint requests to Ms. Belinda Howe at the Australian and New Zealand Intensive Care Research Centre, Alfred Centre, Level 6 (Lobby B), 99 Commercial Rd., Melbourne, VIC 3004, Australia, or at anzicrc@monash.edu.

*The Australasian Resuscitation in Sep-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ABSTRACT

BACKGROUND

Early, goal-directed therapy (EGDT) is recommended in international guidelines for the resuscitation of patients presenting with early septic shock. However, adoption has been limited, and uncertainty about its effectiveness remains.

METHODS

We conducted a pragmatic randomized trial with an integrated cost-effectiveness analysis in 56 hospitals in England. Patients were randomly assigned to receive either EGDT (a 6-hour resuscitation protocol) or usual care. The primary clinical outcome was all-cause mortality at 90 days.

From the Clinical Trials Unit, Intensive Care National Audit and Research Centre (P.R.M., G.S.P., D.A.H., R.J., S.E.H., K.M.R.), Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine (M.Z.S., R.D.G.), and Faculty of Medicine, Imperial College London (D.B.), Department of Acute Medicine, Chelsea and Westminster Hospital NHS Foundation Trust (D.B.), and Bloomsbury Institute of Intensive Care Medicine, University College London

Put all 3 Together…..

Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

SEVEN-DAY PROFILE PUBLICATION

D. C. Angus
A. E. Barnato
D. Bell
R. Bellomo
C.-R. Chong
T. J. Coats
A. Davies
A. Delaney
D. A. Harrison
A. Holdgate
B. Howe
D. T. Huang
T. Iwashyna
J. A. Kellum
S. L. Peake
F. Pike
M. C. Reade
K. M. Rowan
M. Singer
S. A. R. Webb
L. A. Weissfeld
D. M. Yealy
J. D. Young

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

And put together again…..

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

ABSTRACT

BACKGROUND

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to

The members of the writing committee (Kathryn M. Rowan, Ph.D., Derek C. Angus, M.D., M.P.H., Michael Bailey, Ph.D., Amber E. Barnato, M.D., Rinaldo Bellomo, M.D., Ruth R. Canter, M.Sc., Timothy J.

Conclusions

- **For patients presenting with early septic shock in the setting of …**
  - Prompt *recognition*
  - Prompt *intravenous fluid bolus* for hypotension
  - Prompt intravenous *antibiotics*

- **… there is *no superiority to routine*…**
  - *Protocol-based resuscitation* if other aggressive recognition/care exists
  - *Mandatory* central line placement in all patients
  - $ScvO_2$ monitoring, with triggers for blood transfusion and dobutamine

Impact

- **Looking early and hard, treating aggressively** with antibiotics and hemodynamic support, and rechecking **is more important than "how" support** is done
- ***"EGDT" vs 'egdt'*** (one set of specific goals vs. concepts)
- The durable message from Rivers through ProCESS – **septic shock is deadly, and early care matters.**
- **Not an anomaly** though still opportunity - outcomes match other reports (Jones *JAMA* 2010; Kakonen *JAMA* 2014)

So, buckets of volume then pressor, right?

- **Maitland (*NEJM* 2010) – those with more fluids did worse than rest**

- **Andrews (*JAMA* 2017) – same story**
  - Patients (children/acute and chronic illnesses)
  - Ancillary care (esp. ICU, ventilation)
  - Pathogens
  - Antimicrobial therapy

CLOVERS – NHLBI trial through PETAL network – RCT of early fluids vs early pressor in US sepsis care. All get @ 2L IV, then restrict/pressor or more fluids.

Antibiotics

- **All US/European/Australian trials gave early (inside hours)**
- **How early is early enough?**
- **Before resuscitation?**
  - Lab data conflict
- **Best human data – Seymour et al *NEJM*, NY state observational cohort**
  - Earlier matters – but crude measure (time to complete 3 hr bundle – better if done < 12 hrs)
  - Each hour delay increases mortality
  - Later giving sites do worse

Most Recent Data – Seymour et al

Research

JAMA | Original Investigation

Association Between State-Mandated Protocolized Sepsis Care and In-hospital Mortality Among Adults With Sepsis

Jeremy M. Kahn, MD, MS; Billie S. Davis, PhD; Jonathan G. Yabes, PhD; Chung-Chou H. Chang, PhD; David H. Chong, MD; Tina Batra Hershey, JD, MPH; Grant R. Martsolf, PhD, MPH, RN; Derek C. Angus, MD, MPH

IMPORTANCE Beginning in 2013, New York State implemented regulations mandating that hospitals implement evidence-based protocols for sepsis management, as well as report data on protocol adherence and clinical outcomes to the state government. The association between these mandates and sepsis outcomes is unknown.

OBJECTIVE To evaluate the association between New York State sepsis regulations and the outcomes of patients hospitalized with sepsis.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of adult patients hospitalized with sepsis in New York State and in 4 control states (Florida, Maryland, Massachusetts, and New Jersey) using all-payer hospital discharge data (January 1, 2011-September 30, 2015) and a comparative interrupted time series analytic approach.

EXPOSURES Hospitalization for sepsis before (January 1, 2011-March 31, 2013) vs after (April 1, 2013-September 30, 2015) implementation of the 2013 New York State sepsis regulations.

MAIN OUTCOMES AND MEASURES The primary outcome was 30-day in-hospital mortality. Secondary outcomes were intensive care unit admission rates, central venous catheter use, *Clostridium difficile* infection rates, and hospital length of stay.

Editor's Note page 250

Supplemental content

Results

- The mandated efforts improved outcomes – mortality and others
- Outcomes improved in non-mandated settings also, but not as much relatively
- Which parts are less clear – recognition and antibiotics still key, latter = sooner
- Who benefits the most from what? Phenotypes…

Newest Data – Seymour et al

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

IMPORTANCE Sepsis is a heterogeneous syndrome. Identification of distinct clinical phenotypes may allow more precise therapy and improve care.

OBJECTIVE To derive sepsis phenotypes from clinical data, determine their reproducibility and correlation with host-response biomarkers and clinical outcomes, and assess the potential causal relationship with results from randomized clinical trials (RCTs).

DESIGN, SETTINGS, AND PARTICIPANTS Retrospective analysis of data sets using statistical, machine learning, and simulation tools. Phenotypes were derived among 20 189 total patients (16 552 unique patients) who met Sepsis-3 criteria within 6 hours of hospital presentation at 12 Pennsylvania hospitals (2010-2012) using consensus *k* means clustering applied to 29 variables. Reproducibility and correlation with biological parameters and clinical outcomes were assessed in a second database (2013-2014; n = 43 086 total patients and n = 31 160 unique patients), in a prospective cohort study of sepsis due to pneumonia (n = 583), and in 3 sepsis RCTs (n = 4737).

EXPOSURES All clinical and laboratory variables in the electronic health record.

MAIN OUTCOMES AND MEASURES Derived phenotype (α, β, γ, and δ) frequency, host-response biomarkers, 28-day and 365-day mortality, and RCT simulation outputs.

Editorial page 1981

Supplemental content

CME Quiz at jamanetwork.com/learning

Findings

- 4 derived/validated phenotypes in > 60k episodes:
  - the **α phenotype** was the most common (n = 6625; 33%) and included patients with the lowest administration of a vasopressor;
  - in the **β phenotype** (n = 5512; 27%), patients were older and had more chronic illness and renal dysfunction;
  - in the **γ phenotype** (n = 5385; 27%), patients had more inflammation and pulmonary dysfunction;
  - and in the **δ phenotype** (n = 2667; 13%), patients had more liver dysfunction and septic shock

So what?

- In the derivation cohort, cumulative 28-day mortality was:
  - 287 deaths of 5691 unique patients (5%) for the α phenotype;
  - 561 of 4420 (13%) for the β phenotype;
  - 1031 of 4318 (24%) for the γ phenotype;
  - and 897 of 2223 (40%) for the δ phenotype.

- Across all cohorts and trials, 28-day and 365-day **mortality were highest among the δ phenotype** vs the other 3 phenotypes ($P < .001$).

Sepsis Phenotypes – what next?

- Are there genotypic or other patient based observations – at any level – that tie to these phenotypes? Can they be measured in a useful way?
- Are phenotypes stable, and when can one be assigned?
- How do the common interventions interact with outcome across phenotypes?
- What should we do when assessing quality or mandating care with phenotypic information?

SEP-3 : Third International Conference

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term *severe sepsis* was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused

Editorial page 757

Author Video Interview, **Author Audio Interview**, and **JAMA Report Video** at jama.com

Related articles pages 762 and 775

CME Quiz at jamanetworkcme.com and **CME Questions** page 816

SEP–3 and qSOFA

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

IMPORTANCE The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The performance of clinical criteria for this sepsis definition is unknown.

OBJECTIVE To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

DESIGN, SETTINGS, AND POPULATION Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706 399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

EXPOSURES Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) criteria, Logistic Organ Dysfunction System (LODS) score, and a new model derived using multivariable logistic regression in a split sample, the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score (range, 0-3 points, with 1 point each for systolic hypotension [≤100 mm Hg], tachypnea [≥22/min], or altered mentation).

MAIN OUTCOMES AND MEASURES For construct validity, pairwise agreement was assessed. For predictive validity, the discrimination for outcomes (primary: in-hospital mortality; secondary: in-hospital mortality or intensive care unit [ICU] length of stay ≥3 days) more common in sepsis than uncomplicated infection was determined. Results were expressed as

Editorial page 757

Author Audio Interview at jama.com

Related articles pages 775 and 801

Supplemental content at jama.com

SEP-3 and EM

- **No participation –** acute, early view under-represented
- **Benefits vs harm**
  - Simpler gradation – no "*severe sepsis*" any more
  - Septic shock now *only* with elevated lactate and vasopressor use (restrictive)
  - ? More reproducible
- **Sensitivity vs specificity, validation**
  - qSOFA robust
  - In ED – unknown performance vs "old way" (SIRS plus old definitions, or gestalt) – likely **limited sensitivity in early stages**
  - Overall effect (change # with "sepsis" and "septic shock", and deaths attributed – but will fewer die with infections?)

The “New one-hour bundle” from SSC

- **Released 2018**
- **Three from SSC group created this new bundle (even more selective)**
- **Targets one hour actions – notably volume + antibiotics**
  - Time 0 = arrival
  - Starting vs finishing
  - “Aspirational” and “we know the starting time is wrong”
- **Impact?**
  - Overuse
  - Use in non-sepsis
  - Is all sepsis the same?

Our take away

- **Sepsis kills,** still
- Key is looking ***early and often*** – not “one test/thing”.
  - The field and the ED matters
- **Use tools** to aid – order sets, complimentary tests
- ***Trying*** **matters – ATB and restoring perfusion (LR or pressors)** more than specific steps **– *assess and re-assess***
- **Sepsis** and care **has many faces** – soon, we will tailor care better – even the simple things like volume, antibiotics and pressors.


USC
HOME
GUEST
INNING
BALL
STRIKE

Questions ?