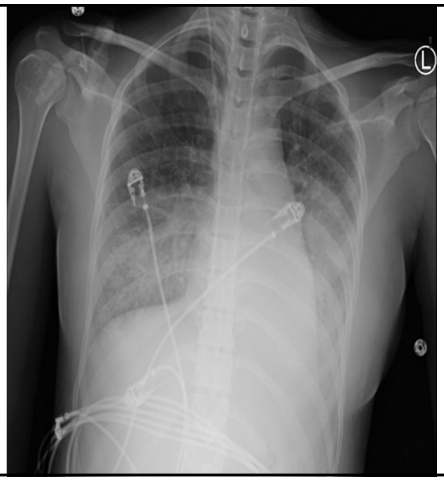
Sepsis

Jessica Kynyk, MD
Assistant Professor – Clinical
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
The Ohio State University Wexner Medical Center

Clinical Scenario

- **24 yo previously healthy female presents to ED with:**
  - **2 days of fevers, chills, headaches, and cough**
  - **Temp 101.8^{0}F, HR 132, BP 115/80, RR 18, O2 sats on 2L NC: 94%**
  - **WBC 7.8, Hgb 10, plt 132**
  - **Bicarb 19, lactate 2.2**
  - **INR 1.4**



Sepsis

Elliott Crouser, MD
Medical Director,
Intensive Care Unit at University Hospital East
Associate Professor
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
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Sepsis Background Information

- **Sepsis accounts for up to 50% of hospital deaths[1], and is the most expensive condition in US hospitals (~$20 billion/yr) [2]**
  - ***Most sepsis cases are admitted through the ED[3]***
  - ***Most sepsis cases identified during hospital stay were present on admission to ED[1]***

1. Liu et al. *JAMA* 2014; 312: 90-92.
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  - ***Most sepsis cases are admitted through the ED[3]***
  - ***Most sepsis cases identified during hospital stay were present on admission to ED[1]***
- **Early sepsis identification and treatment strongly influences sepsis outcomes[4]**
  - ***Sepsis screening & treatment in ED mandated in most hospitals***
  - ***Sepsis core measures are planned for CMS***

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Sepsis: Most Costly Disease

Table 1. Top 20 most expensive conditions treated in U.S. hospitals, all payers, 2011

Rank	CCS principal diagnosis category and name	Aggregate hospital costs, U.S. $, in millions	National costs, %	Number of hospital discharges, in thousands
1	Septicemia (except in labor)	20,298	5.2	1,094
2	Osteoarthritis	14,810	3.8	964
3	Complication of device, implant or graft	12,881	3.3	699
4	Liveborn	12,390	3.2	3,818
5	Acute myocardial infarction	11,504	3.0	612
6	Spondylosis, intervertebral disc disorders, other back problems	11,218	2.9	667
7	Pneumonia (except that caused by tuberculosis and sexually transmitted diseases)	10,570	2.7	1,114
8	Congestive heart failure, nonhypertensive	10,535	2.7	970
9	Coronary atherosclerosis	10,400	2.7	605
10	Respiratory failure, insufficiency, arrest (adult)	8,749	2.3	404
11	Acute cerebrovascular disease	8,361	2.2	597
12	Cardiac dysrhythmias	7,624	2.0	795
13	Complications of surgical procedures or medical care	6,850	1.8	529
14	Chronic obstructive pulmonary disease and bronchiectasis	5,700	1.5	729
15	Rehabilitation care, fitting of prostheses, and adjustment of devices	5,487	1.4	420
16	Diabetes mellitus with complications	5,380	1.4	561
17	Biliary tract disease	5,137	1.3	469
18	Fracture of neck of femur (hip)	4,866	1.3	316
19	Mood disorders	4,840	1.2	896
20	Acute and unspecified renal failure	4,668	1.2	498
Total for top 20 conditions		182,266	47.1	16,755
Total for all hospitalizations		387,272	100	38,591

Abbreviation: CCS, Clinical Classifications Software

Source: Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project (HCUP), Nationwide Inpatient Sample (NIS), 2011

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Severe Sepsis Acute Implications

- Global incidence ~19 million cases (1)
  - ~5 million related deaths (1)

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  - The trend is rising (2)
- 20-30 % 90 day mortality
  - The trend has been favorable over past 10 years (3)
- Implications for health care:
  - #1 most costly hospital Dx (4)
    - $20,000 per case
    - $24 billion/year in US alone!
  - >9 Days in ICU on average (1)

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~215,000 deaths a year in US

Photo: Robert J. Fisch

~590 Deaths Every day

~4100 Deaths Every Week

Severe Sepsis Chronic Implications

- One year mortality ~50% (1,2)
- Greater use of healthcare facilities (~100%) (2)
- Fewer days spent at home (~50%) compared to non-septic matching critically ill controls (2)

1. Puskarich MA, et al. Crit Care 2009; 13:R167.
2. Prescott HC, et al. Am J Respir Crit Care Med 2014; 190:62-9.

Evolution of Sepsis Diagnostic Criteria

- Initially based upon the observed changes in physiological and immune cell parameters reflecting transition from a localized to ***systemic inflammatory response***:

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  - Physiological Variables:
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Evolution of Sepsis Diagnostic Criteria

- **Initially based upon the observed changes in physiological and immune cell parameters reflecting transition from a localized to *systemic inflammatory response*:**
  - **Physiological Variables:**
    - **Tachycardia**
    - **Tachypnea**
    - **Hyperthermia**
  - **Immunological features:**
    - **Leukocytosis**
    - **Leukopenia (in some cases)**

1st International Consensus Taskforce 1991

Table 1. Criteria for SIRS, sepsis, severe sepsis, and septic shock based on the 1991 ACCP/SCCM Consensus Conference

Term	Criteria
SIRS*	2 out of the 4 following criteria:
	Temperature >38 °C or <36 °C
	Heart rate >90/min
	Hyperventilation evidenced by respiratory rate >20/min or arterial CO_2 lower than 32 mmHg
	White blood cell count >12 000 cells/μL or lower than 4000 cells/μL
Sepsis	SIRS criteria with presumed or proven infection
Severe sepsis	Sepsis with organ dysfunction
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation

Note: *SIRS, systemic inflammatory response syndrome.

Epidemiology of severe sepsis, Florian B Mayr , Sachin Yende , Derek C Angus Virulence Vol. 5, Iss. 1, 2014

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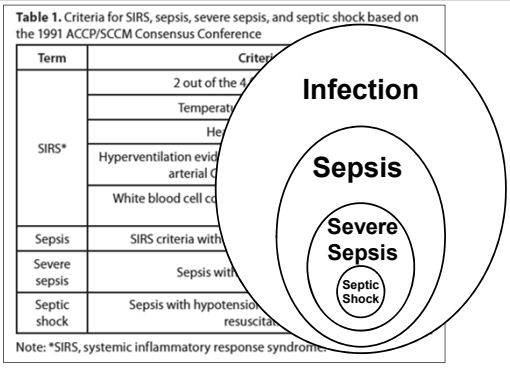

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2nd International Consensus Taskforce 2001

Table 2. Criteria for sepsis based on 2001 SCCM/ACCP/ATS/ESCIM/SIS Consensus Conference

Term	Criteria
Sepsis	Documented (or suspected) infection with any one of the following clinical or laboratory criteria
General parameters	Fever, hypothermia, tachycardia, tachypnea, altered mental status, arterial hypotension, decreased urine output, significant peripheral edema, or positive fluid balance
Inflammatory parameters	Leukocytosis, leukopenia, hyperglycemia, increased C-reactive protein, procalcitonin, or creatinine, coagulation abnormalities, increased cardiac output, reduced mixed venous oxygen saturation
Hemodynamic parameters	Hypotension, elevated mixed venous oxygen saturation, elevated cardiac index
Organ dysfunction parameters	Arterial hypoxemia, acute oliguria, increase in creatinine level, elevated international normalized ratio or activated partial thromboplastin time, ileus, thrombocytopenia, hyperbilirubinemia
Tissue perfusion parameters	Hyperlactatemia, decreased capillary refill, or mottling

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3rd International Consensus Taskforce 2016

Sepsis = "life-threatening *organ dysfunction* due to a dysregulated host response to *infection*.

JAMA 2016; 315(8):762-774

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Organ Dysfunction Criteria (At least 2 of these)
Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)
PaO_2/FiO_2 ratio
Glasgow Coma Scale score
Mean arterial pressure, mm Hg
Administration of vasopressors with type/dose/rate of infusion
Serum creatinine, mg/dL, or urine output, mL/d
Bilirubin, mg/dL
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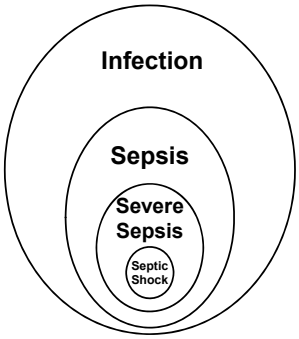
Alternative qSOFA approach

- **Respiratory Rate >22**
- **Any change in mental status (GCS <15)**

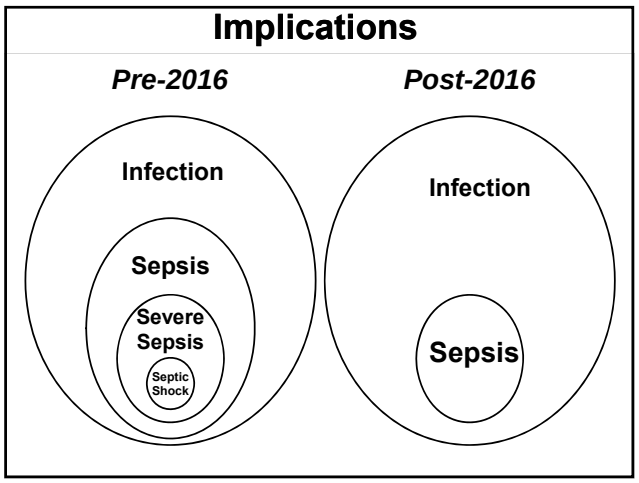
JAMA 2016; 315(8):762-774

Implications

Pre-2016



Implications



Sepsis: *Pathogen Profile*

Table 3. Types of organisms in culture-positive infected patients and associated risk of hospital mortality (modified from reference 32)

	Frequency (%)	OR (95% CI)
Gram-positive	46.8	
Staphylococcus aureus	20.5	0.8 (0.6–1.1)
MRSA	10.2	1.3 (0.9–1.8)
Enterococcus	10.9	1.6 (1.1–2.3)
S. epidermidis	10.8	0.9 (0.7–1.1)
S. pneumoniae	4.1	0.8 (0.5–1.4)
Other	6.4	0.9 (0.7–1.2)
Gram-negative	62.2	
Pseudomonas species	19.9	1.4 (1.2–1.6)
Escherichia coli	16.0	0.9 (0.7–1.1)
Klebsiella species	12.7	1.0 (0.8–1.2)
Acinetobacter species	8.8	1.5 (1.2–2.0)
Enterobacter	7.0	1.2 (0.9–1.6)
Other	17.0	0.9 (0.7–1.3)
Anaerobes	4.5	0.9 (0.7–1.3)
Other bacteria	1.5	1.1 (0.6–2.0)
Fungi		
Candida	17.0	1.1 (0.9–1.3)
Aspergillus	1.4	1.7 (1.0–3.1)
Other	1.0	1.9 (1.0–3.8)
Parasites	0.7	1.3 (0.5–3.3)
Other organisms	3.9	0.9 (0.6–1.3)

OR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*

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Virulence Vol. 5, Iss. 1, 2014

Sepsis Source

Site of Infection	Frequency (%)		Mortality (%)	
	Male	Female	Male	Female
Respiratory	41.8	35.8	22.0	22.0
Bacteremia, site unspecified	21.0	20.0	33.5	34.9
Genitourinary	10.3	18.0	8.6	7.8
Abdominal	8.6	8.1	9.8	10.6
Device-related	1.2	1.0	9.5	9.5
Wound/soft tissue	9.0	7.5	9.4	11.7
Central nervous system	0.7	0.5	17.3	17.5
Endocarditis	0.9	0.5	23.8	28.1
Other/unspecified	6.7	8.6	7.6	6.5

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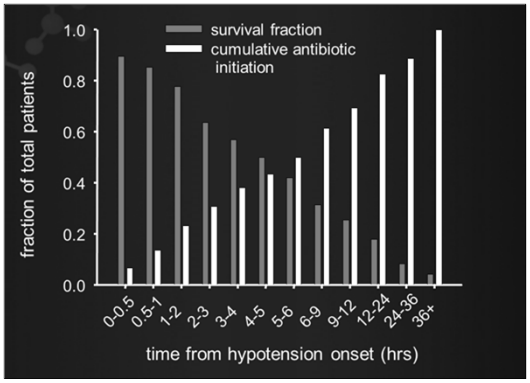
Kill the Infection!!



·Every hour delay of appropriate antibiotics = 7.6% lower survival[1]

1. Kumar et al. *Crit Care Med* 2006; 34: 1589-96.

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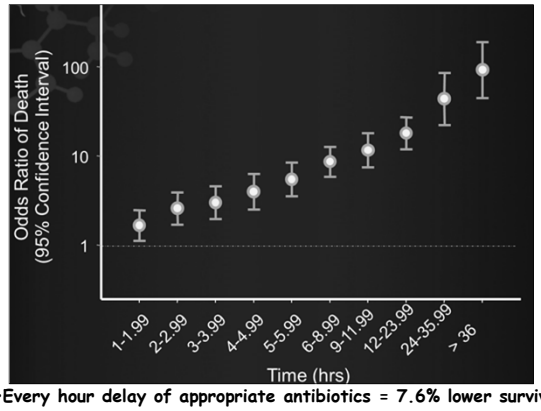

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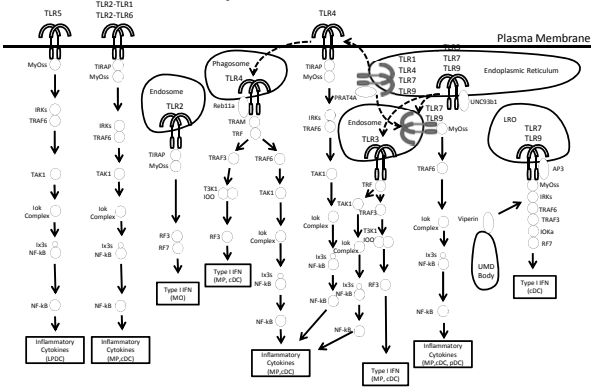
Immune Response to Infections 101



Pathogenesis: A Battle of Host vs. Pathogen

PAMP Detection by TLRs and Other PRRs

Species	PAMPs	TLR Usage	PRRs Involved in Recognition
Bacteria, mycobacteria	LPS	TLR4	
	lipoproteins, LTA, PGN, lipoarabinomannan	TLR2/1, TLR2/6	NOD1, NOD2, NALP3, NALP1
	flagellin	TLR5	IPAF, NAIP5
	DNA	TLR9	AIM2
	RNA	TLR7	NALP3
Viruses	DNA	TLR9	AIM2, DAI, IFI16
	RNA	TLR3, TLR7, TLR8	RIG-I, MDA5, NALP3
	structural protein	TLR2, TLR4	

T Kawai and S Akira *Immunity* 2011; 34:637-50.

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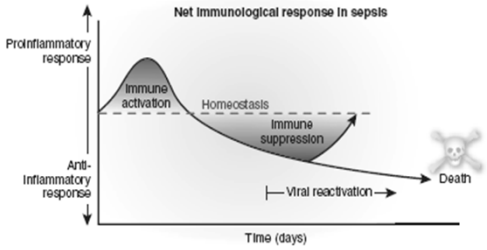
Species	PAMPs	TLR Usage	PRRs Involved in Recognition
Fungus	zymosan, β-glucan	TLR2, TLR6	Dectin-1, NALP3
	Mannan	TLR2, TLR4	
	DNA	TLR9	
	RNA	TLR7	
Parasites	tGPI-mutin (Trypanosoma)	TLR2	
	glycoinositolphospholipids (Trypanosoma)	TLR4	
	DNA	TLR9	
	hemozoin (Plasmodium)	TLR9	NALP3
	profilin-like molecule (Toxoplasma gondii)	TLR11	

T Kawai and S Akira *Immunity* 2011; 34:637-50.

Dramatic Changes in Immune System During Sepsis and Related Complications



Hotchkiss et al. Nat Med 2009

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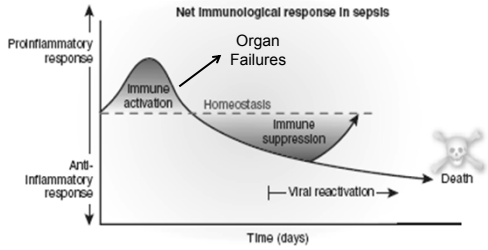

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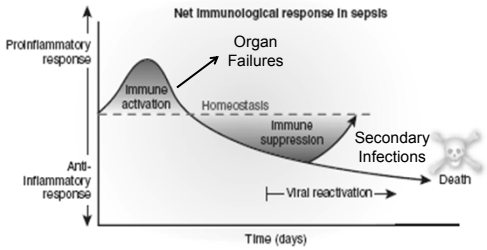

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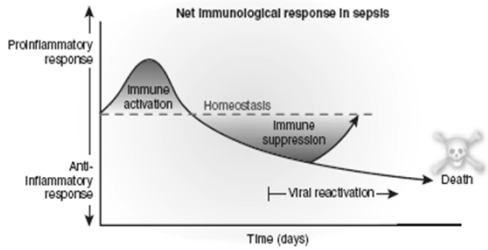
Treatment Implications of Immune Response?



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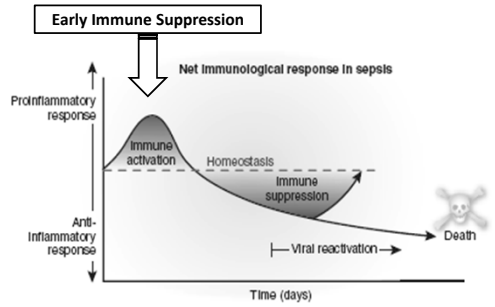

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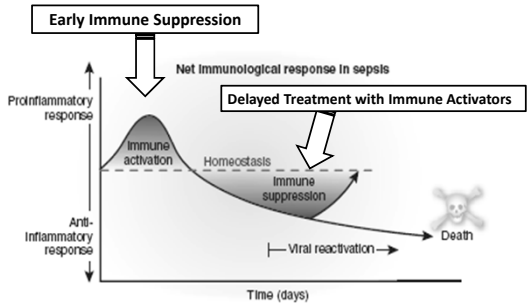

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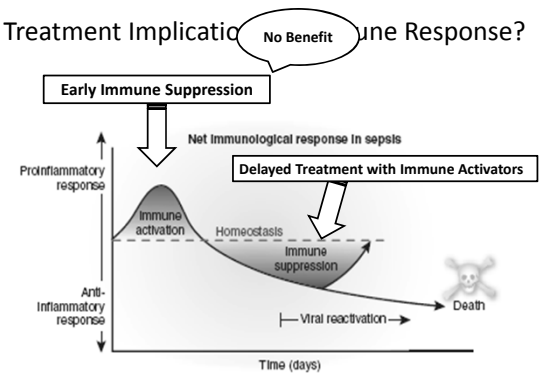

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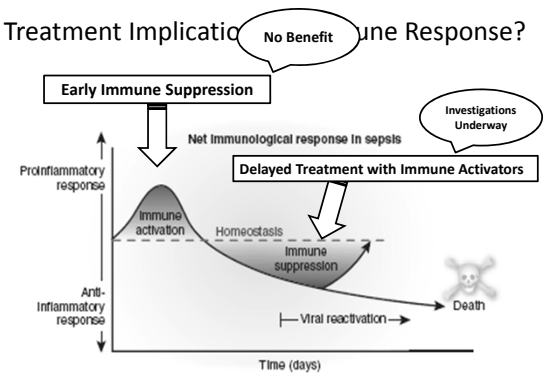

Summary

- Sepsis is a leading cause of morbidity and mortality

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Summary

- Sepsis is a leading cause of morbidity and mortality
- Sepsis is a leading healthcare cost
- Early and effective antibiotic treatment!
- Immune modulation therapies?
- Organ failure management

Sepsis

Jessica Kynyk, MD
Assistant Professor – Clinical
Department of Internal Medicine
Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
The Ohio State University Wexner Medical Center

What is sepsis?

- Sepsis represents a syndrome
  - No 1 diagnostic test
    - Variability in identification
  - Various manifestations at presentation
    - Variability in identification by providers
  - No process to operationalize the definition
    - Variability in incidence and mortality rates

What is sepsis?

- Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection
  - Utilization of SOFA score
    - More defined diagnostic criteria
- Septic shock: sepsis +
  - Persistent hypotension requiring vasopressors for MAP ≥ 65 mmHg and
  - Serum lactate > 2 mmol/L despite resuscitation

Recognizing Sepsis

- Increase awareness of signs/symptoms among healthcare providers
  - Assessment of EMR tools to aid in diagnosis
  - Evaluation of Sepsis alerts / rapid response teams
- Increase community awareness of sepsis

MEWS

Modified Early Warning Score (MEWS)

- a single-weighted "risk " score
  - 5 parameters: HR, SBP, RR, Temp, RASS

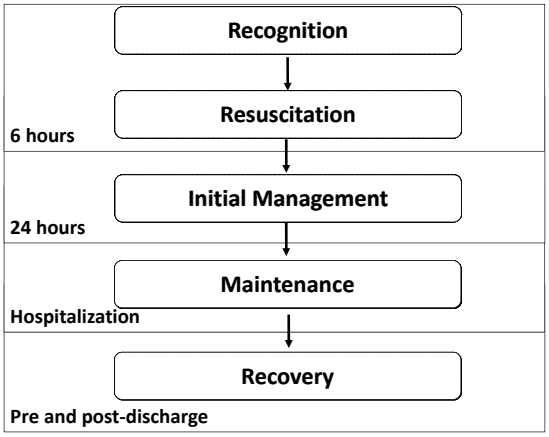
Score	3	2	1	0	1	2	3
Systolic BP	<70	71-80	81-100	101-199		>200	
Heart rate (BPM)	—	<40	41-50	51-100	101-110	111-129	>130
Respiratory rate (RPM)	—	<9	—	9-14	15-20	21-29	>30
Temperature (°F)	—	<95	—	95-101	—	>101.3	—
RASS	-	-	-	+3 to 0	-1 to -3	-4	-5

MEWS and sepsis recongition

- Evidenced-based proactive identification for clinical deterioration[1]
- Most adverse events preceded by early warning signs of clinical instability
  - MEWS shown predictive
    - ICU admission within 72hrs, ERT call within 72hrs, cardiac arrest, hospital mortality
- MEWS does not replace Clinical Judgment
- Ongoing research using MEWS for sepsis screening

[1] Maupin, Janice.. AHRQ Health Care Innovations Exchange, Nov. 23, 2011

Treating sepsis



Optimal sepsis treatment

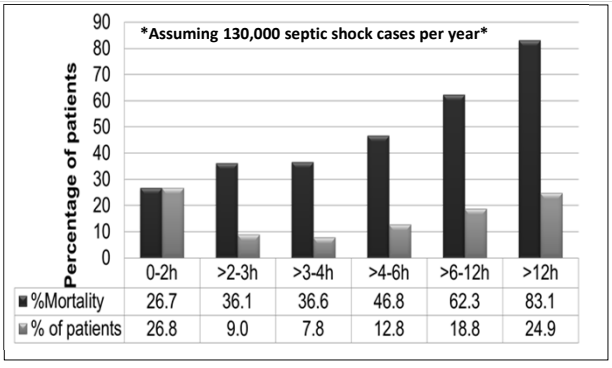
- Utilization of protocolized treatment / sepsis bundle
  - Resuscitation
  - Diagnostic procedures
  - Antimicrobial treatment
  - Source Control
  - Infection Prevention

Surviving Sepsis Campain. Crit Care Med 2013:41;580

Within 3 hours of presentation

- Measure lactate
- Obtain blood cultures (ideally prior to antibiotics)
- Administer broad spectrum antibiotics
- Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol?l

Septic shock mortality in relation to time to effective antibiotic from onset of shock



	0-2h	>2-3h	>3-4h	>4-6h	>6-12h	>12h
%Mortality	26.7	36.1	36.6	46.8	62.3	83.1
% of patients	26.8	9.0	7.8	12.8	18.8	24.9

Adapted from Kumar et al. *Crit Care Med* 2006; 34: 1589-96.

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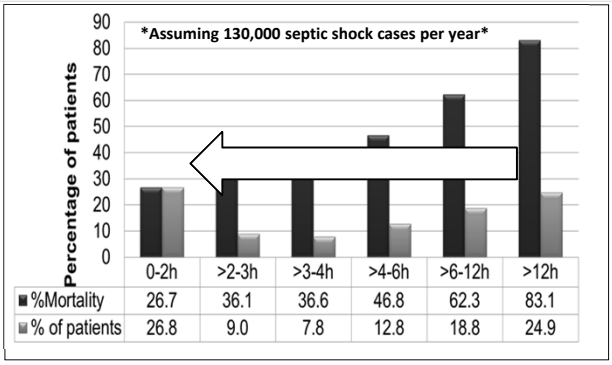

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Septic shock mortality in relation to time to effective antibiotic from onset of shock

By getting shock-to-antibiotic times of <2h
for ALL septic shock patients,
we would save
32,360 lives per year.
(89 people a day)
(3.7 people an hour)
(3.5 times the effect of STEMI intervention)

Adapted from Kumar et al. *Crit Care Med* 2006; 34: 1589-96.

Antibiotics and sepsis

- Effective antimicrobials within 1 hour of recognition:
  - Initial empiric anti-infective therapy with ≥ 1 drug with activity against all likely pathogens
  - Daily reassessment for potential de-escalation
    - Consider procalcitonin
  - Combination therapy recommended for:
    - Neutropenic patients
    - History of multidrug resistant organisms

Initial Resuscitation and Sepsis

- CVP 8-12 mmHg
- MAP ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg/hr
- Mixed venous oxygen saturation (Svo_2) ≥ 65%
  - SVC ≥ 70%

Surviving Sepsis Campain. Crit Care Med 2013:41;580

Assessment of resuscitation

- ProCESS trial
  - Compared Early Goal Directed Therapy protocol to protocolized standard therapy
    - fluid resuscitation followed by clinical reassessment (no CVP monitoring)
    - No protocolized transfusions
    - No defined inotropic role

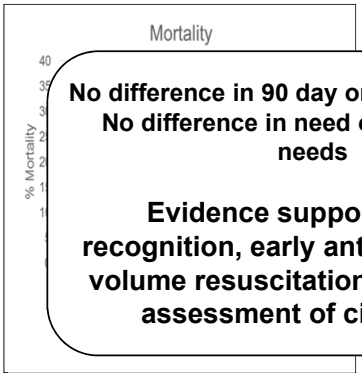
NEJM 2014;370:1683-1693

Process Trial

Usual care was associated with:
- Less PRBC transfusion
- Less dobutamine
- Less overall Vasopressor use

NEJM 2014;370:1683-1693

Process Trial



No difference in 90 day or 1 year mortality
No difference in need organ support needs

Evidence supports: early recognition, early antibiotics, early volume resuscitation, and clinical assessment of circulation

NEJM 2014;370:1683-1693

Initial Resuscitation and Sepsis

- Crystalloids as initial fluid of choice (1B)
- Albumin in patients who require substantial amounts of crystalloids (2C)
- Fluid challenge 30ml/kg of crystalloid (1C)

- But that was in 2012…

What is ideal resuscitation fluid

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

JAMA 2012;308:1566

What is ideal resuscitation fluid

Chloride-poor fluids use was associated with:

- **Less AKI (OR 0.52 [0.37-0.75] p<0.001)**
- **Less RRT (OR 0.52 [0.33-0.81] p<0.001)**
- **No difference in mortality or LOS**

Lactated Ringers (109 mEq) or Plasmalyte 148 (98 mEq)
(154 mEq in 0.9 NS & 120 mEq in 4% albumin)

ORIGINAL ARTICLE

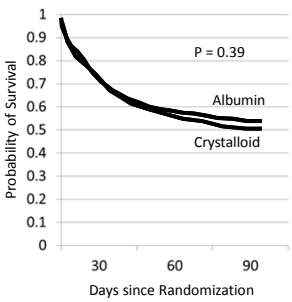
Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

ABSTRACT

NEJM online March 18, 2014

What is ideal resuscitation fluid?



- 20% albumin versus crystalloid in severe sepsis
  - Targeted serum albumin of 30 g/L
- No survival difference at 90 days

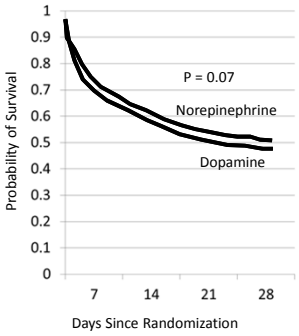
N Engl J Med 2014; 370:1412- 21

Within 6 hours of presentation

- **Start vasopressors if MAP < 65 mmHg despite IVF**
- **Re-measure lactate if initial lactate is elevated**
- **Reassess volume status**
  - **Focused exam <u>or</u> 2 or more of:**
    - **CVP**
    - **$ScvO_2$**
    - **Bedside ultrasound**
    - **Passive leg raise or fluid challenge**

Surviving Sepsis Campain. Crit Care Med 2013:41;580

Sepsis and Vasopressors



- N = 1,679
- MAP < 70 or systolic blood pressure < 100 despite > 1 L crystalloid or > 500 ml colloid and signs of hypoperfusion
- Excluded if on vasopressors for > 4 hr

N Engl J Med 2010; 362:799-89

	Dopamine	Norepinephrine	OR (95% CI)
ICU mortality	50.2%	45.9%	1.19 (0.98 – 1.44)
Hospital mortality	59.4%	56.6%	1.12 (0.92 – 1.37)
6 mo mortality	63.8%	62.9%	1.06 (0.86 – 1.31)
12 mo mortality	65.9%	63.0%	1.15 (0.91 – 1.46)
			P value
Vasopressor-free days	12.6	14.2	0.007
RRT-free days	12.8	14.0	0.07
ICU-free days	8.1	8.5	0.43
Arrhythmias	24.1%	12.4%	<0.0001
Skin ischemia	6.5%	4.1%	0.09
Arterial occlusion	2.7%	2.4%	0.12

NEJM 2010;362:799-89

Sepsis and hemodynamic support

- **Norepinephrine is vasopressor of choice**
  - **Epinephrine may be added to NE**
  - **Vasopressin 0.03 units/minute may be added to NE**
  - **Trial of Dobutamine in certain cardiac conditions**

Lactate and sepsis

- Check upon suspicious for sepsis
  - If elevated monitor for clearance
    - repeat in 4-6 hours
- Predictor of hospital mortality
  - LR 1.4-2 if ≥ 2.5mmol/L; 2.6-6.3 for > 4 mmol/L
  - Early normalization and clearance are predictors of survival (odds ratio 5.2 and 4 respectively)

Steroids and Sepsis

- Corticosteroids should NOT be given in absence of shock
- Do not use ACTH stim test to determine steroid use
- 200mg/day Hydrocortisone if unable to achieve hemodynamic stability with IVF and vasopressors

Supportive Phase

- Identify organ failures
- Customize antibiotics based on cultures/sensitivities
- Additional diagnostic testing
- Goals of care discussions
- Limited transfusions
  - Hgb ~ 7, Plt > 20 if bleeding otherwise > 10
  - No routinue use of FFP for coagulopathy

Supportive Phase

- Vent management in ARDS
  - 6ml/kg Vt
  - Plateau Pressure ≤ 30 cm H_2O
  - PEEP
  - Early consider for prone ventilation
  - SBTs

Supportive Phase

- Sedation interruptions (if sedation is needed)
- Glucose ≤ 180 mg/dL
- NOT using bicarb if pH ≥ 7.15
- DVT prophylaxis
- Stress ulcer prophylaxis
- Nutrition
- Mobility

Supportive Phase

- Sedation interruptions (if sedation is

Minimize additional harm to patient
Avoid nosocomial complications and new infections!

Clinical Scenario

- Was admitted and started on broad spectrum antibiotics
- Developed ARDS was intubated and underwent prone ventilation
  - Too hypoxic for initial bronchoscopy evaluation
  - Received empiric course of antibiotics and antivirals
  - Was extubated after 12 days
- Discharged to home with physical therapy after 21 hospital days

Summary

- Sepsis is common
- Sepsis is a life threatening organ dysfunction due to dysregulation in host response to infection
- Early recognition is crucial
- Early antibiotics decreases mortality
- A standardized process with re-evaluation is needed
- Norepinephrine is vasopressor of choice
- Prevent further harm