The Hour-1 Sepsis Bundle:
Can Sepsis Be Sized Up in 60 Minutes?

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October 23, 2020

Learning Objectives

For Pharmacists:

1. Assess differences between sepsis definitions
2. Summarize current sepsis guideline recommended goals and therapy
3. Critique evidenced-based literature for the development of the sepsis bundle and its application to critically ill patients
4. Given a patient case, determine if use of the sepsis bundle is appropriate

For Pharmacy Technicians:

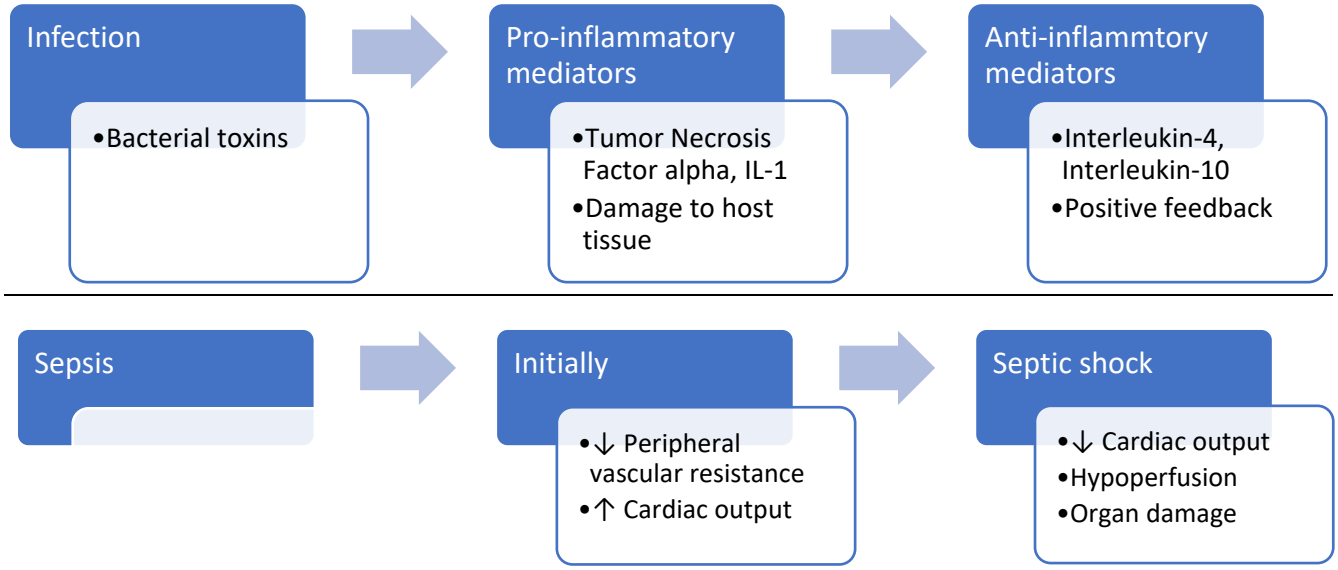
1. Review the differences between sepsis definitions
2. List current sepsis guideline recommended goals and therapy
3. Recognize appropriate timing bundles in sepsis treatment and their role in management of critically ill patients
4. Identify an appropriate patient scenario where sepsis bundle recommendations are appropriate

Epidemiology[1]

2016 Centers for Disease Control and Prevention estimates

- 1.7 million adult Americans develop sepsis each year
- 270,000 Americans die annually from sepsis
- 1 in 3 patients who die in a hospital have sepsis

Pathophysiology[2]



Causative Pathogen + Host Characteristics (immunosuppression + comorbidities) → Sepsis-Induced Inflammation

Acute Inflammatory State + Impaired lactate clearance + Non-oxidative phosphorylation lactate production → Hyperlactatemia

Sepsis Definition Evolution[3,4]

1991: Sepsis-1: initial systemic inflammatory response syndrome

2001: Sepsis-2: definitions revised to include threshold values for organ damage

2016: Sepsis-3: new definitions of sepsis, septic shock; introduction of qSOFA

<table>
<tr><th>Sepsis-1[5]</th><th>Sepsis-2[6]</th><th>Sepsis-3[7]</th></tr>
<tr><td>Sepsis = systemic response to infection, manifested by ≥2 SIRS criteria

Severe sepsis = sepsis + organ dysfunction, hypoperfusion or hypotension

Septic shock = sepsis-induced hypotension despite adequate fluid resuscitation + perfusion abnormalities

Bacteremia = presence of viable bacteria in the blood. Does not have to be present to have sepsis</td><td>Sepsis = documented or suspected infection + some general parameters of systemic inflammatory response
• Fever
• Hypothermia
• Heart rate >90 beats/min
• Tachypnea >30 breaths/min
• Altered mental status
• Significant edema or positive fluid balance (>20 ml/kg/24 hours)
• Hyperglycemia (glucose >100 mg/dL) in absence of diabetes

Severe sepsis = sepsis + organ dysfunction</td><td>Sepsis = life-threatening organ dysfunction caused by a dysregulated host response to infection

• Infection + acute increase of ≥2 sequential organ failure assessment (SOFA) points

Septic shock = subset of sepsis; underlying circulatory, cellular, and metabolic dysfunction are associated with a higher risk of mortality

• Sepsis + vasopressor therapy to elevate MAP ≥65 mmHg. Also, lactate ≥2 mmol/L despite adequate fluid resuscitation</td></tr>
<tr><td colspan="3">Objective Parameters Definitions</td></tr>
<tr><td>Systemic inflammatory response syndrome (SIRS)
• Temperature >100.4◦F or <96.8◦F
• Heart rate >90 beats per minute
• Respiratory rate > 20 breaths per minute or partial pressure of carbon dioxide < 32 mmHg
• WBC > 12,000/µL or < 4,000/µL or >10% bands</td><td>Inflammatory parameters
• WBC >12,000/µL or <4,000/µL or >10% bands
• C reactive protein >2x normal
• Procalcitonin >2x normal

Hemodynamic parameters
• Systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <70 mmHg, or a systolic blood pressure decrease >40 mmHg in adults
• Oxygen saturation >70%
• Cardiac index >3.5 L/min/m^2

Organ dysfunction parameters
• PaO_2/FiO_2 <300
• Urine output <0.5 ml/kg/h
• Creatinine increase ≥0.5 mg/dL
• INR >1.5
• Ileus present
• Platelet count <100,000/µL
• Total bilirubin >4 mg/dL

Tissue perfusion parameters
• Lactate >3 mmol/L
• ↓ capillary refill or mottling</td><td>Quick sequential organ failure assessment (qSOFA) scoring system
• Altered mental status (GCS score <15)
• Systolic blood pressure <100 mmHg
• Respiratory rate >22 breaths/min
+ if 2/3 of these criteria are met

SOFA score:
<table><tr><th></th><th>1</th><th>2</th><th>3</th><th>4</th></tr><tr><td>PaO_2/FiO_2 (mmHg)</td><td><400</td><td><300</td><td><200</td><td><100</td></tr><tr><td>Platelets $x10^3/mm^3$</td><td><150</td><td><100</td><td><50</td><td><20</td></tr><tr><td>Bilirubin (mg/dL)</td><td>1.2-1.9</td><td>2-5.9</td><td>6-11.9</td><td>>12</td></tr><tr><td>Hypotension</td><td>MAP <70</td><td>Dop ≤ 5 or any dob</td><td>Dop >5 or NE ≤0.1</td><td>Dop >15 or NE >0.1</td></tr><tr><td>GCS</td><td>13-14</td><td>10-12</td><td>6-9</td><td><6</td></tr><tr><td>Creatinine (mg/dL) or Urine output (mL)</td><td>1.2-1.9</td><td>2-3.4</td><td>3.5-4.9 or <500</td><td>>5 or <200</td></tr></table>MAP=mean arterial pressure; Dop=dopamine, dob= dobutamine, NE= norepinephrine, vasoactive medications administered for ≥ 1 hour and dopamine and NE units are µg/kg/min, GCS=Glasgow Coma Scale</td></tr>
<tr><td colspan="3">Cons</td></tr>
<tr><td>-A sepsis-like clinical picture may be observed without infection
-SIRS is overly sensitive and nonspecific in discriminating sepsis and non-complicated infection; not all infected patients will have sepsis</td><td>-No difference in diagnostic criteria compared with old definitions
-None of the parameters are specific for sepsis
-1 in 8 patients with sepsis were missed with application of SIRS criteria[8]</td><td>-Organ dysfunction is unclear since organs may have more than one function
-Inappropriate host response is hard to measure
-SOFA is valuable but not practical to use
-Lactate parameter is not widely used in other countries
-qSOFA needs validation before being used clinically</td></tr>
</table>

The current guideline recommended definitions accepted the recent Sepsis-3 definitions for sepsis and septic shock. However, qSOFA was not accepted or recommended as best practice, and SIRS along with all other specific clinical parameters of end-organ dysfunction were eliminated.[9]

SEP-1[10]

The Centers for Medicare and Medicaid Services issued core measures for the management of sepsis on October 1, 2015.

Sep-1 definitions	
CMS definition of severe sepsis: an infection or suspected infection with two or more SIRS criteria plus one sign of organ dysfunction (described below)	
CMS definition of septic shock: a patient with either SBP <90 mm Hg, a MAP <65 mm Hg, or a reduction in systolic blood pressure by >40 mm Hg from a previous measurement. Valid only after the patient has received 30 ml/kg crystalloid fluid resuscitation or when the initial lactate level is ≥4 mmol/L	
CMS evidence of organ dysfunction	
Lactate >2 mmol/L	INR >1.5 or aPTT >60 seconds
Platelet count <100,000 μ/L	Bilirubin >2 mg/dL
Creatinine >2 mg/dL	Urine output <0.5 ml/kg/hour x 2 hours
Acute respiratory failure by need for new invasive or noninvasive ventilation	Systolic blood pressure <90 mm Hg or MAP <65 mm Hg
Cons	
-CMS-definition-selected lactate values are below the threshold of widely accepted and studied lactate levels -Government-issued definitions are hard to abide by due to variable presentation of the disease state	

Guideline Directed Management

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016[7]

Initial resuscitation	• Sepsis and septic shock are medical emergencies, so treatment and resuscitation with crystalloids at 30 ml/kg should begin immediately • Target an initial mean atrial pressure (MAP) of 65 mm Hg in patients requiring vasopressors • Guide resuscitation to normalize lactate in patients with elevated lactate levels
Antimicrobial therapy	• Initiate intravenous (IV) antimicrobials as soon as possible after recognition and within 1 hour for both sepsis and septic shock
Source Control	• Emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock • Implement any required source control intervention as soon as medically and logistically practical
Corticosteroids	• Recommend against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability. • If not achievable, suggest IV hydrocortisone 200 mg per day

Common Treatment Agents

Crystalloids[11,12]								
Fluid	Na mmol/L	K mmol/L	Cl mmol/L	Mg mmol/L	Ca mmol/L	Buffer mmol/L	Osmolarity mOsm/L	pH
0.9% NaCl	154	0	154	0	0	0	308	5.7
Lactate Ringer's	130	4	109	0	3	Lactate 28	273	6.5
Plasma-lyte	140	5	98	3	0	Acetate 28 Gluconate 23	294	7.4

Vasopressors[13-19]					
Agent	Mechanism of Action	Admin	Ease of Access	Side Effects	Pricing (AWP)
Norepinephrine (Levophed)	Alpha and Beta agonist; ↑ mean arterial pressure through vasoconstriction, less effect on heart rate, stroke volume and cardiac output	0.1 to 3 mcg/kg/minute as a continuous infusion via an infusion pump	Stored at room temperature, protect from light	Cardiac arrhythmias, peripheral vascular insufficiency	1 mg/ml solution (per ml) $2.63-$6.00
Vasopressin (Vasostrict)	V-1 receptor agonist; ↑ systemic vascular resistance and mean arterial blood pressure, may ↓ heart rate and cardiac output	0.03 units/minute Non-titratable	Dilute prior to continuous IV infusion administration	Angina pectoris, atrial fibrillation, cardiac arrhythmia	20 units/ml (per ml) $215.75
Epinephrine (Adrenalin)	Alpha and Beta agonist; large doses produce constriction of skeletal and vascular smooth muscle	0.01 to 0.7 mcg/kg/minute	Continuous IV infusion, central line administration is preferred	Tachycardia, lactic acidosis, angina pectoris, atrial fibrillation, cardiac arrhythmias	1 mg/ml (per ml) $1.12-$17.50
Dopamine	Inotrope; Stimulates both adrenergic and dopaminergic receptors at various doses; ↑ MAP and cardiac output due to an increase in stroke volume and heart rate	Lower doses mainly dopaminergic Higher doses are both dopaminergic and Beta-adrenergic Large doses stimulate alpha-adrenergic receptors	May use in patients at low risk of tachyarrhythmias or with bradycardia Not recommended as renal protective strategy	Tachycardia, high risk of cardiac arrhythmias	40 mg/ml (per ml) $0.64
Dobutamine	Inotrope; Primarily beta-1 adrenergic agonist; some alpha-1 agonism; ↑ contractility and heart rate; may have vasodilation	20 µg/kg/min	May use in patients with low cardiac output on vasopressors or persistent hypoperfusion	Tachycardia, hypertension, hypotension	2 mg/ml (per ml) $0.06 - $0.17
Phenylephrine (Vazculep)	Pure alpha-agonist; produces systemic arterial vasoconstriction; Can decrease stroke volume	0.5 mcg/kg/minute Titrate to desired response	May use in patients with tachyarrhythmias	Hypertension, low cardiac output, peripheral vasoconstriction	10 mg/ml (per ml) $3.84-$7.20
Angiotensin II (Giapreza)	Vasoconstricts and increases aldosterone release	10-20 ng/kg/minute	No guideline recommendation May use as an adjunctive vasopressor	Thrombosis, tachycardia, peripheral ischemia, thrombocytopenia	2.5 mg/ml (per ml) $1,800

Adjunctive Therapies[7]

- Mechanical ventilation: use lung protective ventilation
- Sedation and analgesia: target appropriate pain control and a light sedation goal using validated scoring tools
- Venous thromboembolism prophylaxis: prophylaxis with unfractionated heparin or low-molecular weight heparin in the absence of contraindications. Low-molecular weight heparin is preferred.
- Stress ulcer prophylaxis: using either proton pump inhibitors or histamine-2 receptor antagonists
- Nutrition: early enteral nutrition in patients who can be fed enterally

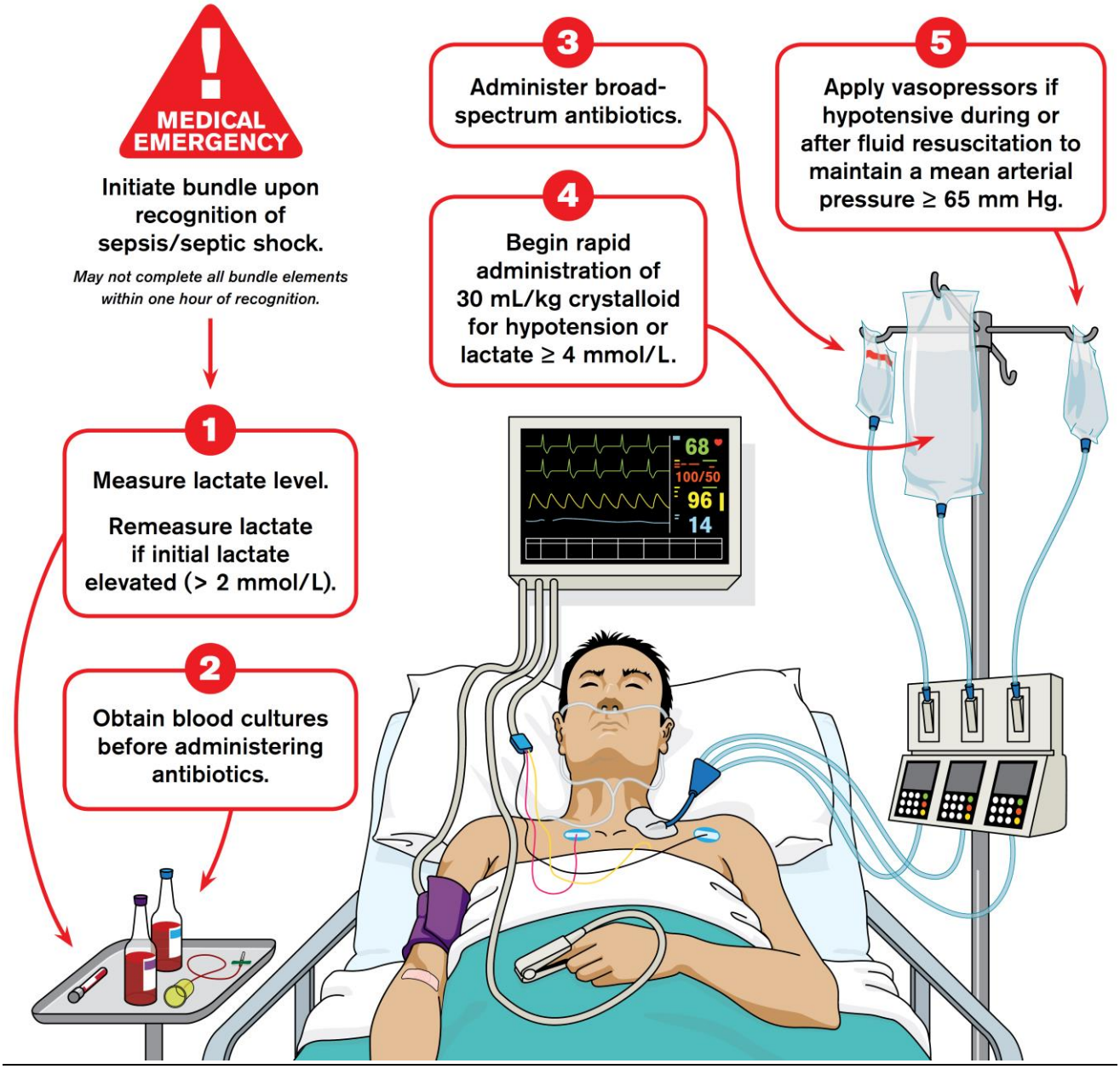
Treatment Summary	
Initial Resuscitation	• Sepsis and septic shock are medical emergencies that need immediate treatment and resuscitation • Target an initial mean arterial pressure of 65 mmHg
Antibiotics	• Broad spectrum IV antimicrobials initiated as soon as possible after recognition and within 1 hour
Fluids	• 30 ml/kg of crystalloids initially • Frequent assessment of volume status
Vasopressors	• Initial: norepinephrine • Second: vasopressin or epinephrine

Is Early Goal Directed Therapy (EGDT) The Answer?[20-23]

Rivers et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock
263 patients with severe sepsis or septic shock
Randomized into two cohorts: early-goal directed therapy (n=130) or standard of care (n=133) in a single center in Detroit. EGDT protocol consisted of several sequential goals started in the ER 6 hours prior to ICU admission: Central venous pressure 8-12 mm Hg, achieved with fluid boluses Mean arterial pressure >65 mm Hg, achieved with vasopressors if necessary ScvO2 >70%, achieved with packed RBC transfusion or dobutamine Urine output >0.5 ml/kg/hr
Standard therapy maintained: Central venous pressure 8-12 mm Hg Urine output >0.5 ml/kg/hr Mean arterial pressure 65-90 mmHg with either vasopressors or vasodilators
Primary outcome: in-hospital mortality 30.5% EGDT vs 46.5% standard (RR 0.58, 95% CI 0.38-0.87; 0=0.009) NNT=6

No difference in mortality using EGDT
• PROCESS 2014 (EGDT vs protocol-based standard therapy vs usual care) ○ Among patients with early septic shock, no difference in all-cause in-hospital mortality at 60 days with EGDT. Primary outcome: all-cause in-hospital mortality at 60 days: 21% vs 18.2% vs 18.9%; p=0.31 to 0.89 • ARISE 2014 (EGDT vs usual care) ○ Among patients with severe sepsis or septic shock presenting to an emergency department, EGDT did not reduce all-cause mortality at 90 days: 18.6% vs 18.8% (RR 0.98; 95% CI 0.80-1.21; p=0.90) • ProMISE 2015 (EGDT vs standard therapy) ○ EGDT did not improve mortality at 90 days compared to standard therapy including IV fluids and vasopressors: 29.5% vs 29.2% (adjusted HR 0.95, 95% CI 0.74-1.24; p=0.73)
These studies have disproven early goal directed therapy as the answer for sepsis therapy

Hour-1 Bundle[7]



SEP-1 Bundles "all or nothing measures"[9]	Hour-1 Bundle[7]
Severe sepsis: within 3 hours - Initial lactate measurement - Blood cultures - Broad-spectrum antibiotics - Repeat lactate within 6 hours if initial was elevated	Initiate bundle upon recognition of sepsis/septic shock - Measure lactate level - Remeasure if initial lactate elevated >2 mmol/L - Obtain blood cultures before antibiotics - Administer broad-spectrum antibiotics - Begin rapid administration of 30 ml/kg crystalloid for hypotension and lactate ≥4 mmol/L - Vasopressors if hypotensive to maintain a MAP ≥65 mm Hg
Septic shock: adds 3 additional requirements - 30 ml/kg of IV fluids within 3 hours - Vasopressors within 5 hours - Repeat volume assessment within 6 hours	

Concerns?

- Rigid set of bundles that mandate specific interventions within fixed time frames
- Adopted by Centers for Medicare & Medicaid Services (government agency)
- Hasty management decisions
- Inappropriate fluid administration
- Indiscriminate use of broad-spectrum antibiotics
- Lack of evidence?!

Controversy: **What evidence is available to justify Hour-1 bundle recommendations?**

Item	Pro	Con
Bundles	Kahn et al.	Rhee et al.
Antibiotics	Kumar et al. & Whiles et al	Alam et al.
Fluids/Lactate	Chen et al.	Pepper et al.

Literature Review

Table 1. Pro for why the bundles exist[24]

Citation	Kahn JM, Davis BS, Yabes JG, et al. Association between state-mandated protocolized sepsis care and in-hospital mortality among adults with sepsis. *JAMA*. 2019;322(3):240-250. doi:10.1001/jama.2019.9021.	
Objective	To examine sepsis outcomes before and after implementation of the sepsis regulations in New York State and compare these changes with outcomes in other states that did not implement sepsis regulations during this time.	
Methods		
Study Design	• Retrospective cohort study • Funded by a grant from Agency for Healthcare Research and Quality (AHRQ) • Comparative time series study comparing data from the AHRQ Healthcare Cost and Utilization Project State Inpatient Database linked with the 2015 CMS Cost Reporting Information System for New York with 4 control states	
Population	Inclusion • Hospital admissions with sepsis using ICD-9 diagnosis and procedure codes for infection and organ failure	Exclusion • Patients <18 years • Admissions not identified in the Healthcare Cost Reporting Information System • Admissions with missing data for key covariates • Hospitals that were not classified as short-stay acute care hospitals by the Healthcare Cost Reporting Information System
Outcomes	• Primary outcome: 30-day in-hospital mortality • 4 secondary outcomes: intensive care unit admission rate, hospital length of stay, central venous catheter use, and *Clostridium difficile* infection rate	
Statistical Analysis	• Hospital characteristics compared between New York state and control states using chi squared test • A separate comparative interrupted time series analysis was performed for each outcome variable to account for the possibility that the association between the regulations and outcomes might change over time due to their staged implementation • All models were fit using linear regression with robust standard errors clustered at the hospital level • Secondary analysis was performed using sepsis administrative codes to see if the regulations were not associated with changes in administrative coding for sepsis	
Results		
Baseline Characteristics		

	New York State (n=163)		Control States: FL, MA, MD NJ (n=346)	
Admission Characteristics	Pre regulation (n=139,019)	Post regulation (n=186,767)	Pre regulation (n=289,225)	Post regulation (n=397,399)
Comorbidities, No. (%) ≥ 4	81,546 (58.7)	125,131 (67)	197,683 (68.3)	274,021 (69)

<table>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>30 Day In- Hospital Mortality, % (95% CI); p value</th><th>ICU Admission Rate, % (95% CI); p value</th><th>Hospital Length of Stay, d (95% CI); p value</th><th>Central Venous Catheter Use, % (95% CI); p value</th><th>Clostridium difficile Infection Rate, % (95% CI); p value</th></tr>
<tr><td>2015 Quarter 3</td><td>-3.2 (-5.4 to -1.0); 0.004</td><td>2.8 (-1.7 to 7.2); 0.22</td><td>0.50 (-0.47 to 1.47); 0.31</td><td>4.8 (2.3 to 7.4); <0.001</td><td>-1.8 (-2.6 to -1.0); <0.001</td></tr>
<tr><td>Joint test of significance</td><td>0.02</td><td>0.09</td><td>0.04</td><td>0.02</td><td><0.001</td></tr>
</table>
All models controlled for patient and hospital characteristics, seasonality based on calendar quarter, and preregulation temporal trends using a continuous time variable, implemented as quarters.
</td></tr>
<tr><td>Author's Conclusions</td><td>In New York, mandated protocolized sepsis care was associated with a greater decrease in sepsis mortality compared with sepsis mortality in control states that did not implement sepsis regulations.</td></tr>
<tr><td>Critique</td><td>
<u>Strengths</u>
Pragmatic trial
External validity
No defined inclusion criteria
Used data from before and after implementation of sepsis regulations against control states
<u>Limitations</u>
Trial design
Three landmark studies came out during this time which could have influenced outcomes
Baseline mortality rates higher in New York than control states
No post discharge follow-up
Hospitals in the NY group were more likely to be teaching hospitals and have smaller ICUs
May have included patients who did not have sepsis
</td></tr>
<tr><td>Summary</td><td>
Supports government-issued sepsis policy designed to incentivize quality improvement by mandating evidence-based care.
Similar policies adopted in Illinois and New Jersey, among other states
</td></tr>
</table>

<table>
<tr><th colspan="3">Table 2. Con for why the bundles exist[25]</th></tr>
<tr><td>Citation</td><td colspan="2">Rhee C, Filbin MR, Massaro AF, et al. Compliance with the national SEP-1 quality measure and association with sepsis outcomes: a multicenter retrospective cohort study. Crit Care Med. 2018;46:1585-1591. doi:10.1097/CCM.0000000000003261.</td></tr>
<tr><td>Objective</td><td colspan="2">To evaluate the association between SEP-1 compliance and patient outcomes considering patients' clinical characteristics.</td></tr>
<tr><th colspan="3">Methods</th></tr>
<tr><td>Study Design</td><td colspan="2">
Retrospective cohort study of sepsis cases submitted by seven hospitals to CMS for the SEP-1 measure from October 1, 2015 to September 31, 2017
Funded from Centers for Disease Control and Prevention (CDC) and Agency for Healthcare Research and Quality
</td></tr>
<tr><td>Population</td><td>
<u>Inclusion</u>
Met CMS criteria for severe sepsis when "time zero" occurred
</td><td>
<u>Exclusion</u>
Transfer from outside facilities
Documented goals of care precluding sepsis care
Hospital length of stay >120 days
</td></tr>
<tr><td>Intervention</td><td colspan="2">
Adherence was measured by quality staff who reviewed 20 randomly selected cases per month with ICD-10 codes for sepsis (as per CMS requirements)
One group was patients who met CMS criteria for severe sepsis when "time zero" occurred and completed sepsis bundles while the other groups were those who failed CMS criteria on any bundle component
Covariates from SEP-1 reporting included age, sex, race, specialty of discharging physician, and presence of septic shock (defined by initial lactate ≥ 4 mmol/L or persistent hypotension despite fluid bolus ≥ 30 cc/kg)
</td></tr>
<tr><td>Outcomes</td><td colspan="2">
Primary: in-hospital mortality
</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">
Compared characteristics of cases that passed versus failed SEP-1 using Wilcox rank sum test for continuous variables and chi-square statistic for categorical variables.
Univariate logistic regression to assess individual covariates and in-hospital mortality; multivariate analysis of covariates with p<0.20 on univariate analysis
</td></tr>
</table>

Results

Baseline Characteristics

Characteristic	Pass (N=281)	Fail (N=570)	P
Sepsis onset in ED, n(%)	232 (82.6)	421 (73.9)	0.005
Hospital-onset sepsis (>48 hr from presentation), n(%)	12 (4.3)	63 (11.1)	0.001
Septic shock	25 (8.9)	112 (19.7)	<0.001
Positive blood cultures, n(%)	75 (26.7)	160 (28.1)	0.672
Site on infection, n(%)			
Pneumonia	113 (40.2)	188 (33)	0.038
UTI	66 (23.5)	137 (24)	0.860
Intra-abdominal	50 (17.8)	105 (18.4)	0.824
Other	52 (18.5)	140 (24.6)	0.047
ICU length of stay (IQR)	3 (2-6)	4 (2-9)	0.030
Discharging service, n(%)			
Medical	206 (73.3)	407 (71.4)	0.560
Surgical	4 (1.4)	37 (6.5)	0.001
Other	71 (25.3)	125 (21.9)	0.277

Outcomes

- 281 sepsis cases passed SEP-1 (33%) and 570 (67%) failed
- SEP-1 failures more likely to have septic shock, hospital-onset sepsis, vague symptoms, and non-pulmonary infections
- Cases that failed SEP-1 had higher in-hospital mortality rates (18.4% vs 11% OR 1.82; 95% CI, 1.19-2.80;p=0.006) but this association was no longer significant after adjusting for differences in clinical characteristics and severity of illness (adjusted OR 1.36; 95% CI 0.85-2.18; p=0.205)
- Variables with a significant association with in-hospital mortality on multivariable analysis: age, non-white race, higher Elixhauser co-morbidity score, hospital-onset sepsis, septic shock, nonurinary source of infection, and vague presenting symptoms

Bundle Failure Reason	No. of failures (%) (Total n=570)
Initial lactate not drawn within 3 hours	112 (19.7)
Repeat lactate not drawn within 6 hours	116 (20.4)
Blood cultures not drawn within 3 hours or after antibiotics	86 (15.1)
Antibiotics not given within 3 hours	77 (13.5)
Inappropriate antibiotics	12 (2.1)
Inadequate crystalloids or not given within 3 hours	104 (18.3)
Vasopressors not given within 6 hours or persistent hypotension	8 (1.4)
Volume assessment not done within 6 hours	42 (7.4)

- Delays of >3 hours until antibiotics were significantly associated with death (adjusted OR 1.94; 95% CI 1.04-3.62; p=0.038)
- Failing SEP-1 for any other reason besides delayed antibiotics was not associated with death (adjusted OR 1.10; 95% CI 0.70-1.72, p=0.67)

Author's Conclusions

The all-or-nothing nature of SEP-1 fails to differentiate between vital factors such as early antibiotic administration vs secondary factors such as measuring lactate and documenting volume status

Critique

Strengths

- Explicit infectious symptoms were strongly associated with SEP-1 compliance, timely antibiotics, and survival rates

Limitations

- May be underpowered to detect an association of failing SEP-1 with mortality
- Unable to measure the relative contributions of different components of the SEP-1 bundle or percentage of total bundle compliance to patients' outcomes

Summary	• Early experience with SEP-1 demonstrates a high rate of SEP-1 failures and higher crude mortality rates in sepsis cases that failed versus passed but no differences in mortality after adjusting for clinical characteristics and severity of illness • Question the utility of SEP-1 as currently structured especially surrounding differentiating between explicit vs vague symptoms

Table 3. Pro Antibiotic Component[26]		
Citation	Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589-1596. doi:10.1097/01.CCM.0000217961.75225.E9.	
Objective	To examine the relationship between delay in initiation of effective antimicrobial therapy from initial onset of recurrent or persistent hypotension and survival in septic shock	
Methods		
Study Design	• Retrospective, multi-center review of three cohorts between 1989 and 2004	
Population	Inclusion • ≥18 years of age • Septic shock according to the 1991 SCCM/ACCP Sepsis Definitions	Exclusion • None
Intervention	• First cohort: all septic shock cases admitted to adult ICUs; identified using a local database where ICU admission and diagnosis are encoded by the attending • Second cohort: all cases of septic shock at a single institution; identified using same database • Third cohort: consecutive adult septic shock patients at 3 institutions; identified using a combination of internal ICU registries and/or ICD-9 codes	

Outcomes	• Primary: survival to hospital discharge, including discharges to chronic health care facilities
	• Primary independent variable: time to initiation of effective antimicrobial therapy relative to first occurrence of recurrent or persistent hypotension
	  ○ Effective antimicrobial therapy: antimicrobials with *in vitro* activity appropriate for the isolated pathogen or pathogens were received within 6 hours of the first new antimicrobial following onset of recurrent or persistent hypotension
	  ○ Defined persistent hypotension as hypotension that persisted from onset despite fluid (>2 L of saline or equivalent) administration	

Statistical Analysis	Logistic regression modeling used to examine survival to hospital discharge as a function of time delay to effective antimicrobial administration using interval data	
Results		
Baseline Characteristics	N=2,732 cases. Similar in terms of average APACHE scores, distribution of clinical infections, time to effective antimicrobial therapy following hypotension onset and outcome. 56 were moribund on admission. All were included in this analysis.	
Outcomes	• Initiation of effective antimicrobial therapy within the first hour following onset of septic shock-related hypotension was associated with 79.9% survival to hospital discharge • For every additional hour to effective antimicrobial initiation in the first 6 hours after hypotension onset, survival dropped an average of 7.6%	
Author's Conclusions	Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock.	
Critique	Strengths • Large cohort • Variety of considerations such as isolation of pathogenic bacteria, presence of bacteremia, clinical infection site, and epidemiologic etiology • Demonstrated the existence of substantial delays in delivery of effective antimicrobial therapy	Limitations • Trial design • Not unexpected outcomes • Temporal confounding with use of Sepsis-1 definitions • Primed to yield better outcomes with their definition of "appropriate antibiotics" • Minimal information about vasoactive drugs, fluid responsiveness/resuscitation
Summary	Landmark paper in critical care practice. Early and appropriate antibiotic therapy saves lives	

Table 4: Pro Antibiotic Component[27]

Citation	Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. *Crit Care Med*. 2017;45:623-629. Doi:10.1097/CCM.0000000000002262.
Objective	To determine if time to initial antimicrobial therapy is associated with progression of severe sepsis to septic shock

Methods

Study Design	• Retrospective, single-center study • Funding: Alpha Omega Alpha Honor Medical Society Research Fellowship	
Population	Inclusion • Adults admitted through the ED from 2007 to 2015 • ICD-9 diagnosis code for severe sepsis and/or septic shock • Administered an antimicrobial agent	Exclusion • ED triage or arrival time could not be determined • Initial antibiotic administered >24 hours after ED triage • Patients with septic shock in presentation, determined by receipt of the following vasoactive agents within 3 hours: epinephrine, norepinephrine, vasopressin, phenylephrine, dobutamine, or dopamine
Intervention	None	
Outcomes	• Primary: investigate the role of time to initial antimicrobial administration within the first 24 hours of severe sepsis	
Statistical Analysis	• Chi-square analysis used to compare proportional data between those who progressed to shock and those who did not progress	

Results

Baseline Characteristics

Variable, n (%)	All patients, n=3,929	With progression to septic shock, n=984 (25%)	Without progression, n=2,945 (75%)	P value
Charlson Comorbidity Index	2.10 ± 2.40	2.34 ± 2.44	2.02 ± 2.38	<0.001
Total no. unique infection ICD-9	2.47	2.64	2.41	<0.001
First lactic acid mg/dL	2.64±2.01	3.05±2.52	2.50±1.79	<0.001

Outcomes

- Primary: 25% progressed to septic shock during their hospitalization
- Most common infection groups:
  - Respiratory and lung (38.2%)
  - Genitourinary (31.8%)
  - Intra-abdominal (7.5%)
- Patients who progressed to shock had:
  - ↑ hospital length of stay (18.7 ± 17.1 vs 9.66 ± 9.12 days; p<0.001)
  - ↑ ICU admission rates (95.3% vs 46.3%; p<0.001)
  - ↑ ICU length of stay (9.73 ± 11.6 vs 4.40 ± 4.95 days; p<0.001)
  - ↑ hospital mortality (30.1% vs 7%;p<0.001)
- Median time to initial antimicrobial administration among all patients was 2.95 hours
- Median time to initial antimicrobial agent among those with progression was 3.77 hours and without progression was 2.76 hours
- For each hour that passed with antimicrobial delay, the risk of progression to septic shock increased by 8%
- Intra-abdominal infections and Charlson Comorbidity Index were associated with increased time to receipt of antibiotics

Author's Conclusions	Early and broad-spectrum antimicrobial administration in patients with severe sepsis may decrease progression to shock and mortality	
Critique	Strengths • Novel study that investigated the association between progression of severe sepsis to septic shock and time of first antimicrobial	Limitations • Used ICD-9 diagnosis codes may provide a lower sensitivity for detection • Single center • Duration of severe sepsis is unknown

	• Confirmatory of previous findings	• Did not investigate appropriateness of antimicrobial coverage • Unable to investigate reasons for delay in antimicrobial administration • Unable to determine if patients received preadmission antimicrobial agents • Difficult to distinguish broad vs narrow spectrum antimicrobials
Summary	• Early antibiotic administration can decrease progression of sepsis to septic shock	

Table 5. Con Antibiotic Component (PHANTASi)[28]

Citation	Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicenter, open label, randomized trial. *Lancet Respir Med.* 2018;6(1):40-50. Doi:10.1016/S2213-2600(17)30469-1.	
Objective	To assess the effect of early pre-hospital antibiotic treatment after training EMS personnel in recognizing sepsis	
Methods		
Study Design	• Prospective, randomized, controlled, multicenter, open-label trial	
Population	Inclusion • ≥18 years of age • Diagnosed or suspected infection • Temperature ≥ 38°C or < 36°C • At least one other criterion of SIRS (HR >90 bpm or RR >20 per minute or both)	Exclusion • Known allergy to ceftriaxone or other beta-lactam antibiotics • Pregnant • Suspected prosthetic joint infections
Intervention	• Sepsis severity categorized into 3 groups after inclusion according to Sepsis-2 definitions • Randomly assigned (1:1) to intervention group or usual care group using block-randomization • Patients in intervention group received open-label ceftriaxone 2,000 mg IV in the ambulance + usual care vs usual care group received only usual care	
Outcomes	• Primary: all-cause mortality at 28 days • Secondary: number of misdiagnosis in patients enrolled in the study by EMS personnel, mortality during hospital stay and within 90 days, length of hospital stay, intensive care unit (ICU) admission, length of stay in the ICU, time to antibiotic in the emergency department for the usual care group and time to antibiotic before hospital arrival for the intervention group, microbiological data, adverse events, and quality of life 1 month after discharge	
Statistical Analysis	• The sample size calculation was based on the effect of training and prehospital administration of antibiotics on 28-day mortality by trained EMS personnel • The maximum required sample size to achieve 80% power was 2,144 patients (1,072 per group); assuming two-sided testing at an overall 5% significance level while incorporating formal interim analysis for efficacy after observing outcomes of the first 25%, 50%, and 75% of patients and using the O'Brien-Fleming alpha-spending function • Analyzed all data according to the intention-to-treat analysis • Subgroup analyses were done for the primary outcome for the following variables: age (<65 or ≥ 65 years), National Early Warning Score (NEWS [<5 or ≥5]), systolic blood pressure (≤100 or >100 mm Hg), and severity of sepsis (non-severe, severe, or septic shock) • In 2016, Sepsis-3 criteria were introduced, so a subgroup analysis was done after retrospectively categorizing the population according to qSOFA criteria (<2 or ≥2)	
Results		

Baseline Characteristics

	Usual care group (n=1,137) n (%)	Intervention group (n=1,535) n (%)
Age (years)	72.5 (14.1)	73 (13.6)
Urgency ambulance ride		
A1: life threatening	492 (43%)	659 (43%)
A2: urgent	561 (49%)	757 (49%)
B: non-urgent	71 (6%)	107 (7%)
Unknown	13 (1%)	12 (1%)
Patients already on oral antibiotics before randomization	255 (22%)	322 (21%)

	qSOFA score (in ambulance) <2 ≥2	 872 (82%) 181 (17%)	 1132 (78%) 318 (22%)
	Severity of sepsis Non-severe Severe Septic shock Other	 424 (37%) 657 (58%) 37 (3%) 19 (2%)	 579 (38%) 868 (57%) 66 (4%) 22 (1%)

Outcomes

- The intervention group received antibiotics a median of 26 minutes (IQR 19-34) before arriving at the emergency department
- At day 28, 120 (8%) patients had died in the intervention group and 93 (8%) had died in the usual care group (relative risk 0.95, 95% CI 0.74-1.24)
- 986 (64%) patients in the intervention group received fluids in the ambulance; mean volume of administered fluids was 447.1 ml (247.9) and 450.7 ml (185.8), respectively

	Usual care (n=1,137)	Intervention (n=1,535)	P value
28 day mortality	93 (8%)	120 (8%)	0.78
90 day mortality	134 (12%)	178 (12%)	0.87
Median time to antibiotics in ED (min)	70 (36-128)		
ICU admission	98 (9%)	155 (10%)	0.19
28-day re-admission	119 (10%)	102 (7%)	0.0004

Author's Conclusions

Training EMS personnel in early recognition of sepsis does seem to have benefits by improving care in the whole acute care chain for patients with sepsis. However, do not advise antibiotic administration in the ambulance to patients with suspected sepsis

Critique

Strengths

- Utilized standard of care in both treatment cohorts

Limitations

- Difficult to apply to different health-care settings
- More patients included in the intervention group secondary to trial being open label
- All patients received broad-spectrum ceftriaxone
- Diagnosis of sepsis in ambulance made using systemic inflammatory response syndrome criteria
- Overall lower mortality rate and only a small percentage had septic shock
- High rate of patients on PO antibiotics at baseline

Summary

Pre-hospital administration of antimicrobial therapy did not correlate with an improvement in 28-day mortality compared to standard of care

Table 6. Pro Lactate/Fluid Component[29]

Citation

Chen H, Zhao C, Wei Y, et al. Early lactate measurement is associated with better outcomes in septic patients with an elevated serum lactate level. *Crit Care.* 2019;23:351. Doi:10.1186/s13054-019-2625-0.

Objective

To examine the relationship between early lactate measurement (within 1 hour after ICU admission) and the outcomes of septic patients with an elevated serum lactate level (>2 mmol/L), as well as to characterize the association of delays in initial lactate measurement and remeasurement with 28-day mortality

Methods

Study Design

- Retrospective, observational study
- Data extracted from an online international database, the Medical Information Mark for Intensive Care III (MIMIC-III)

Population

Inclusion

- Septic patients with an initial lactate level >2 mmol/L after ICU admission
- Used Sepsis-3 definitions

Exclusion

- Patients < 18 years old
- Patients in ICU <48 hours

Intervention

- Admitted patients were divided into two groups
  - Early lactate group (initial lactate level was measured within 1 hour after ICU admission)
  - Late lactate group (initial lactate level was measure more than 1 hour after ICU admission)

Outcomes

- Primary: 28-day mortality

	• Secondary: mechanical ventilation-free days and vasopressor-free days within 28 days after ICU admission, AKI stage, and the duration of ICU and hospital stays
Statistical Analysis	• Causal meditation analysis: method for separating the total effect of a treatment into direct and indirect effects. Used early lactate measurement as the treatment and time to initial intravenous fluids, time to initial antimicrobials, and time to initial vasopressors as mediator variables • Multivariate modeling of the association between early lactate measurement and 28-day mortality was performed with logistic regression • The variance inflation factor method was used to examine multicollinearity; variance inflation factor ≥5 suggested multicollinearity • Also investigated the delay in initial lactate measurement and a delay in remeasurement in the early lactate group and 28-day mortality by multivariate logistic regression

Results

Baseline Characteristics

Variables	Early lactate (n=738)	Late lactate (n=1,904)	P value	SMD
Male, n (%)	424 (57.5)	1020 (53.6)	0.079	0.078
SOFA score	7.8 (3.6)	7 (3.6)	0.002	0.136
Mechanical ventilation in 1st 24 h, n(%)	591 (80.1)	1410 (74.1)	0.001	0.144
Vasopressor use in 1st 24 h, n(%)	460 (62.3)	1099 (57.7)	0.034	0.094
Septic shock, n(%)	483 (65.4)	1167 (61.3)	0.053	0.086
Respiratory site of infection, n(%)	344 (46.6.)	740 (38.9)	<0.001	0.157
Initial lactate level (mmol/L)	3.6 (2.7-5.2)	3.1 (2.5-4.4)	<0.001	0.261

Outcomes

	EL group	LL group	P value
Time to initial vasopressor (hours)	2.6 (0.6-5.5)	4.2 (1-8.6)	<0.001
Time to initial antibiotics (hours)	1.6 (0.5-4.4)	2.2 (0.8-5.7)	0.014
Volume of IVF within 6 hours (L)	4.7 (1.4-9.1)	3.4 (1-6.7)	<0.001
28-day mortality (%)	22.2	27.5	0.026
Vasopressor-free days in 28 days	26.6 (24.8-27.4)	23.7 (21.6-24.3)	0.018
Ventilation-free days in 28 days	24.1 (17.4-27.2)	23.8 (18.4-27.3)	0.026

Author's Conclusions	Early lactate measurement is associated with a lower risk-adjusted 28-day mortality rate in septic patients with lactate levels >2 mmol/L. A shorter time to the initial vasopressor administration may contribute. Repeating lactate measurement within 3 hours after initial measurement is appropriate for patients whose lactate levels were measured within 1 hour of admission	
Critique	Strengths • Conclusion is consistent with current limited studies • Provides support for earlier action for initial lactate measurement and remeasurement	Limitations • Diagnosis of infection used from the database unclear • Recommendations for sepsis were changed during the study period • Unable to determine interventions before lactate measurement • Cause of elevated lactate is difficult to distinguish
Summary	In most acute illnesses, early lactate measurement in patients with elevated lactate levels is beneficial for their mortality. Difficult to say this is true for every case, but if the lactate is measured early and was elevated, repeating the measurement can also be beneficial.	

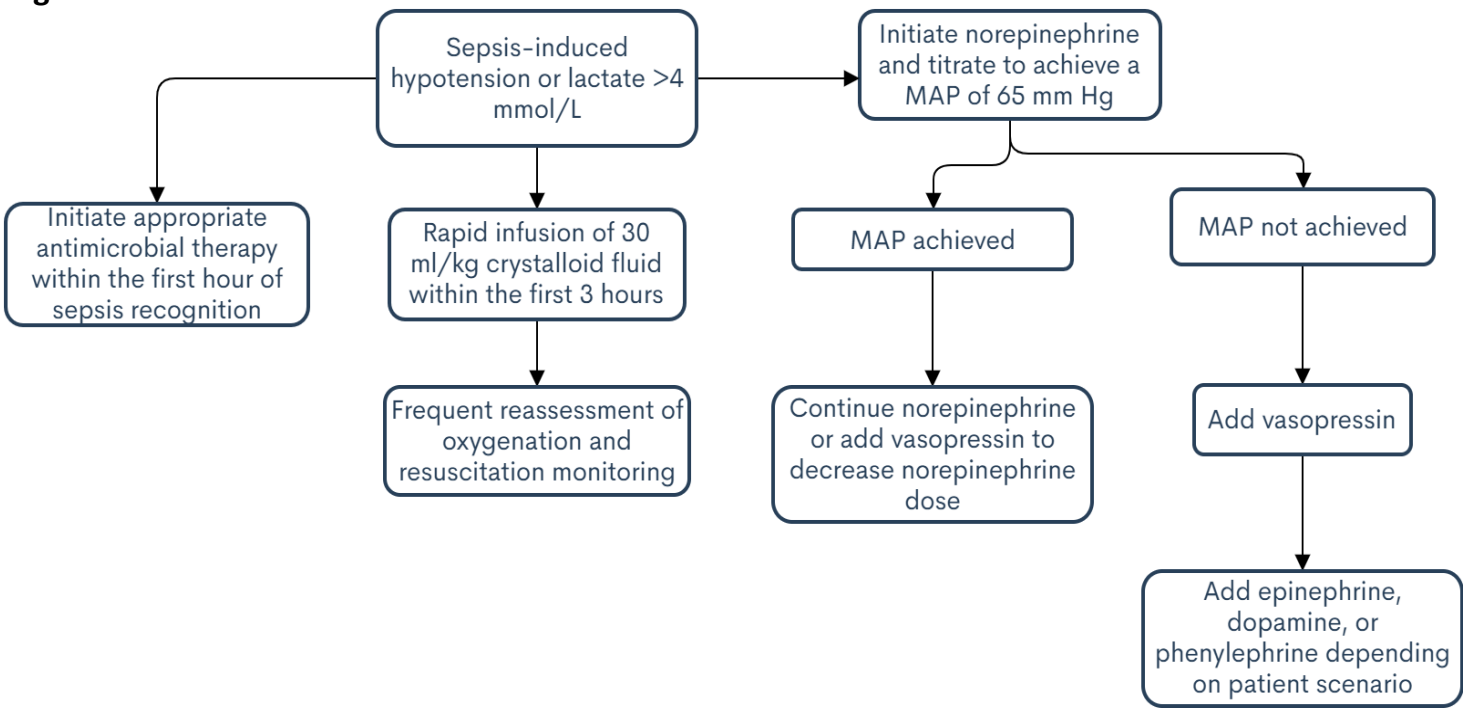
Table 7: Con Lactate/Fluid Component[30]

Citation	Pepper DJ, Sun J, Cui X, et al. Antibiotic and fluid focused bundles potentially improve sepsis management, but high-quality evidence is lacking for the specificity required in the Centers for Medicare and Medicaid Service's Sepsis Bundle (SEP-1). *Crit Care Med.* 2019;47:1290-1300. Doi:10.1097/CCM.0000000000003892.

<table>
<tr><td>Objective</td><td colspan="2">To address three controversial components in the Centers for Medicare and Medicaid Service's sepsis bundle for performance measures (SEP-1)
Performed a systematic review of sepsis bundles to examine overall effect of these bundle components on mortality as well as whether variation in the administration of the components altered the bundles' outcome</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">• Meta-analysis of studies of sepsis bundles like SEP-1</td></tr>
<tr><td>Population</td><td>Inclusion
• Studies comparing mortality between subjects receiving versus not receiving a focused sepsis bundle that included antibiotic and fluid administration, with or without vasopressors</td><td>Exclusion
• Studies evaluating prior SEP-1 interventions no longer required in the revised 2018 version</td></tr>
<tr><td>Intervention</td><td colspan="2">• None</td></tr>
<tr><td>Outcomes</td><td colspan="2">• Overall survival effects of bundles
• If survival effects differed stipulating differing antibiotic treatment times, 30 ml/kg fluid volumes vs other volumes, or obtaining vs not obtaining serial lactate measurements</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Outcome summary estimates for the included studies were provided using random-effects models adjusting for <20 studies with the Hartung-Knapp method
• For binary outcomes including survival or the proportion of patients receiving an intervention, odds ratios (OR) and their 95% Cis were calculated
• For time to a test or treatment or the amount of treatment, reported median and IQR values were converted to mean difference and standard error (SE) values
• Heterogeneity among studies was assessed using the Q statistic and I^2 value
• Two-sided p-values <0.05 were considered significant</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline Characteristics</td><td colspan="2">15 publications encompassing 17 studies were identified. All studies used observational designs
<table>
<tr><td></td><td colspan="2">No. of Patients</td></tr>
<tr><td>Reference</td><td>Control</td><td>Bundle</td></tr>
<tr><td>Austrian et al</td><td>838</td><td>1,306</td></tr>
<tr><td>Bhat et al</td><td>67</td><td>54</td></tr>
<tr><td>Bruce et al</td><td>62</td><td>75</td></tr>
<tr><td>De Miguel-Yanes et al</td><td>53</td><td>50</td></tr>
<tr><td>Ferreras Amez et al</td><td>222</td><td>222</td></tr>
<tr><td>Gao et al</td><td>49</td><td>52</td></tr>
<tr><td>Gatewood et al</td><td>137</td><td>83</td></tr>
<tr><td>Hayden et al</td><td>108</td><td>130</td></tr>
<tr><td>Kumar et al</td><td>55</td><td>71</td></tr>
<tr><td>Leisman et al 2012, 2014, 2015</td><td>4,769, 958, 5,124</td><td>1,050, 739, 2,115</td></tr>
<tr><td>Liu et al</td><td>5,942</td><td>6,544</td></tr>
<tr><td>Prasad et al</td><td>287</td><td>742</td></tr>
<tr><td>Ruangchan et al</td><td>70</td><td>158</td></tr>
<tr><td>Teles et al</td><td>46</td><td>121</td></tr>
<tr><td>Tse et al</td><td>31</td><td>33</td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td colspan="2">• Bundles were associated with increased odds ratio of survival in 15 of 17 studies (statistically significant in nine), but there was substantial heterogeneity overall (I^2=61%;0<0.01)
• Bundles associated with similarly increased survival (p-0.19) whether they specified antibiotic administration within 1 hour (1.92 [0.92-4]; I^2=57%; p=0.03, 3 hours (1.34 [1.11-1.61]; I^2= 56%;p=0.03), or without a specific time (1.21 [0.69-2.13]; I^2= 0; p=0.77). Two of the 1-hour antibiotic studies had survival effects on the side of harm.
• Bundles associated with increased survival using 30 ml/kg fluid infusions (1.23 [1.09-1.39]; I^2 = 38%;p=0.14), a volume other than 30 ml/kg (1.70 [0.94-3.05]; I^2 = 41%; p=0.13) or did not specify a volume (1.30 [0.17-10.13]; I^2= 77%;p<0.01)
• In the only bundle study requiring serial lactate measurements, survival (1.14 [1.03-1.27]) was no greater than all other (1.50 [1.20-1.87]; I^2= 58%; p<0.01)</td></tr>
</table>

Author's Conclusions	Emphasize the importance of early care for septic patients, flexibility is also necessary because it is unlikely there will ever be definitive data showing specific antibiotic time or fluid volume that fits all sepsis cases. Did not provide evidence that any specific time to antibiotic treatment or fluid volume was better or safer than any other tested	
Critique	Strengths • Evaluated heterogeneity • Used a random effects model	Limitations • All studies were observational non-RCT • No measurable relationship between bundle effects on time to treatments and improved survival • None of the studies analyzed reported or clearly investigated bundle-associated adverse events • Substantial heterogeneity across studies of the 1- and 3-hour antibiotic treatment times • Substantial variability in how they defined time zero
Summary	• Antibiotics for infection and fluids for cardiovascular resuscitation benefit care. Bundles had similar survival effects whether the required time to antibiotics was 1 or 3 hours or was not stated. • No evidence that serial lactate measurements increase the effectiveness of focused sepsis bundles; should be guided by providers' assessment	

Algorithm



Adapted from Dellinger RP, Schorr CA, Levy MM: User's guide to the 2016 Surviving Sepsis Guidelines

Conclusion and Recommendation

- Early goal-directed therapy initially showed a survival advantage, but was later disproven in large well-designed randomized controlled trials
- Both sepsis and septic shock are viewed as medical emergencies
- Sepsis is dynamic and diagnosis of sepsis is not as straightforward as other medical emergencies
- No "one size fits all picture" for treating patients with sepsis and septic shock despite the deceptively simple checklist that is required

	Guideline Recommendation	Literature Consideration
Antibiotics	Early and broad spectrum appropriate	Delayed time to antibiotic initiation correlates with numerous confounders
Lactate/Fluids	Early and aggressive resuscitation is life saving Initial goal of 30 ml/kg	Must consider the entire patient's hemodynamic stability
Bundle	Hour-1 Bundle used to guide resuscitation	Individual components of a bundle are proven mainstays of sepsis therapy Unclear if 1 hour is the right time frame for everything

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