Chapter 138 – Sepsis Syndromes

Episode Overview:

1. Define SIRS, Sepsis, Severe Sepsis, and Septic Shock
2. Describe Early Goal Directed Therapy
3. What is Sepsis 3.0
4. Discuss the Surviving Sepsis Guidelines
5. List doses and indications for commonly used vasoactive medications
6. Describe empiric Abx regimens for typical sources of sepsis
7. Define ARDS
8. Describe the ED approach to managing ARDS

Wisecracks

1) Outline key priorities in diagnostic workup and management of the septic patient during the first 6 hours of emergency care.
2) What is HLH?

Key Points:

- ❑ Sepsis is a progression of disease due to a dysregulated inflammatory cascade, leading to organ dysfunction and circulatory compromise in severe cases.
- ❑ Sepsis is subtle and often difficult to detect, so the emergency clinician should maintain a high index of suspicion when assessing patients in the ED.
- ❑ Older adults, immunocompromised and neutropenic patients, and patients with multiple comorbidities are at increased risk for the development of sepsis syndromes.
- ❑ A thorough history and physical examination should guide the diagnostic evaluation.
- ❑ Early treatment should focus on appropriate identification, improvement of tissue perfusion (through administration of fluids and vasopressor medications), improvement of tissue oxygenation (through administration of oxygen and positive-pressure ventilation), administration of antibiotics, and early identification of infections requiring surgical management.
- ❑ Prompt administration of antibiotics is essential and should be based on the suspected source of infection.

Rosen's in Perspective

Sepsis is a continual changing field in emergency medicine. The definitions and our approach will continue to rapidly develop.

Even though we have the shiny new 9th edition of Rosen's, even it is 5 years behind (the reference the 2012 Surviving sepsis guidelines for example.

So for the sake of your clinical knowledge and exam purposes, we will rely heavily on the Giants of FOAM. Specifically, we use the wonderful knowledge that FOAMCAST and EMCRIT Project have been pumping out for years. So go straight to those sources for the knowledge goodness.

1) Define SIRS, Sepsis, Severe Sepsis, and Septic Shock

Bacteremia – Presence of viable bacteria in the blood, as evidenced by positive blood cultures

SIRS – At least two of the following:

- Oral temp >38°C (100.4°F) or <35°C (95°F)
- Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mmHg
- Heart rate >90 beats/min
- Leukocyte count > 12,000/dL or <4000/dL; or >10% bands

Sepsis – SIRS that has a proven or suspected microbial source

Multiple organ dysfunction syndrome (MODS) – Dysfunction of more than one organ, requiring intervention homeostasis

From UptoDate:

SIRS and Severe Sepsis (old terms)
"The use of systemic inflammatory response syndrome (SIRS) criteria to identify those with sepsis has fallen out of favor since it is considered by many experts that SIRS criteria are present in many hospitalized patients who do not develop infection, and their ability to predict death is poor when compared with other scores such as the SOFA score [29,37,38].

SIRS is considered a clinical syndrome that is a form of dysregulated inflammation. It was previously defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count [25]. SIRS may occur in several conditions related, or not, to infection. Noninfectious conditions classically associated with SIRS include autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, or surgery.

The term severe sepsis, which originally referred to sepsis that was associated with tissue hypoperfusion (eg, elevated lactate, oliguria) or organ dysfunction (eg, elevated creatinine, coagulopathy) [25,33], and the term systemic inflammatory response syndrome (SIRS (table 1)) are no longer used since the 2016 sepsis and septic shock definitions include patients with evidence of tissue hypoperfusion and organ dysfunction.

Sepsis and Septic shock
a constellation of clinical, laboratory, radiologic, physiologic, and microbiologic data is typically required for the diagnosis of sepsis and septic shock.

Big take home point:

A 2016 SCCM/ESICM task force has defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection" Uptodate.

So, it's nice a simple now:

1. You need an infection (suspected or confirmed)
2. You need organ dysfunction

Then you have sepsis!

Organ dysfunction = Two or more points on the qSOFA score. ”

Source: FOAMCAST

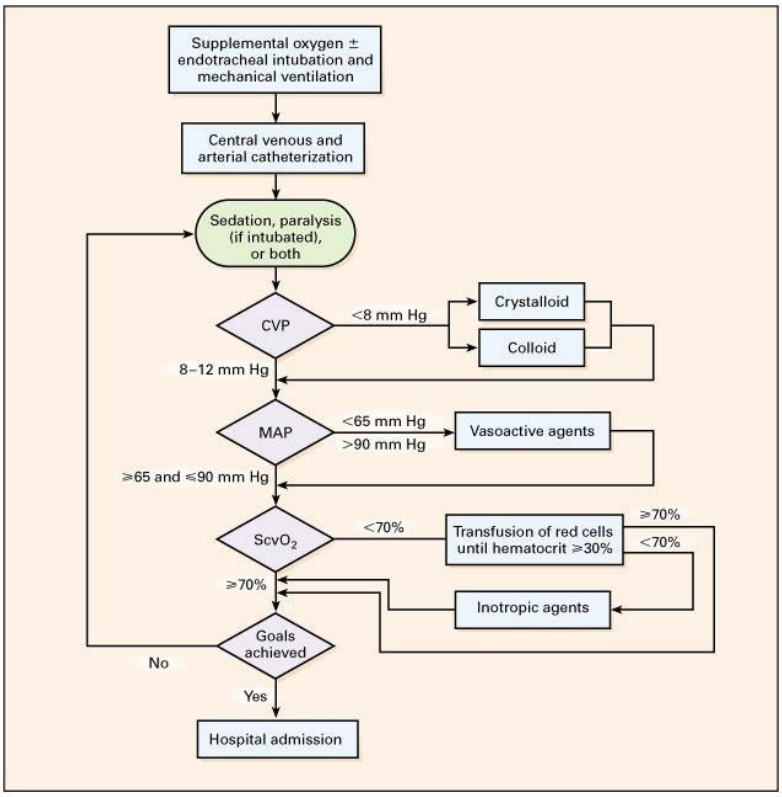
2) Describe Early Goal Directed Therapy

We won’t spend too much time on River’s, although we will give him major props for changing how we all care for sepsis patients EGDT! But the current trends have moved away from this fluid heavy protocol.

Comes down to the following parameters:

- ❏ CVP 8-12 mmHg
- ❏ MAP 65 – 90 mmHg
- ❏ Urine output >0.5 ml/kg/hr
- ❏ Mixed venous oxygen saturation >65% / ScvO2 >70%
- ❏ Haematocrit >30%

Source: The original Rivers paper



3) What is Sepsis 3.0

Check out this FOAMCAST post for the best summary you could ask for

Our understanding of sepsis is changing.

Now its thought of as:

"Sepsis is a clinical syndrome that has physiologic, biological, and biochemical abnormalities caused by a dysregulated inflammatory response to infection. Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death."
- UptoDate

Sepsis 3.0 with using the above definition, stops depending on SIRS and pickup on qSOFA.

	OLD	NEW
SEPSIS	SIRS + Suspected Infection	SUSPECTED/DOCUMENTED INFECTION + Rise in SOFA score by 2 or more
SEVERE SEPSIS	Sepsis + SBP <90 mmHg or MAP < 65 mmHg lactate > 2.0 mmol/L INR >1.5 or a PTT >60 s Bilirubin >34 µmol/L Urine output <0.5 mL/kg/h for 2 h Creatinine >177 µmol/L Platelets <100 ×109/L SpO2 <90% on room air	———
SEPTIC SHOCK	SEPSIS + HYPOTENSION after adequate fluid resuscitation	SEPSIS + VASOPRESSORS needed for MAP >65 mmHg + LACTATE >2 mmol/L after adequate fluid resuscitation

Singer M, Deutschman CS, Seymour CW, et al: The Sepsis Definitions Task Force The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
@FOAMpodcast

Source: FOAMCAST

- ❑ qSOFA failed to be validated in Chicago patients as published in 2016 (see the excellent PULMCRIT post on this)
- ❑ Follow-up multicentre European trial shows qSOFA outperformed SIRS for picking up SEPSIS patients that need ICU level care (see this post for more FOAMCAST)

Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department
JAMA. 2017;317(3):301-308.

quick SOFA: Hypotension SBP <100 mmHg, Altered Mental Status, Respiratory rate 22+
proposed by Sepsis 3.0 as a tool to "prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken.... positive qSOFA criteria should also prompt consideration of possible infection in patients not previously recognized as infected."

DESIGN	prospective observational cohortstudy			
POPULATION	consecutive patients presenting during a 4 week period to one of 30 European EDs between May and June 2016 with suspected infection			
OUTCOME	Inpatient mortality (overall 8%) qSOFA score < 2 had 3% mortality (95% CI, 2%-5%) qSOFA score 2+ had 24% mortality (95% CI, 18%-30%)			
CHARACTERISTICS	AUROC qSOFA 2+ 0.80 (0.74-0.85) SOFA 2+ 0.77 (0.71-0.82) SIRS 0.65 (0.59-0.70)	Sensitivity qSOFA 70% (59-80) SOFA 73% (61-83) SIRS 93% (85-98)	Specificity qSOFA 79% (76-82) SOFA 70% (67-73) SIRS 27% (24-31)	+ LR qSOFA 3.40 (2.80-4.17) SOFA 2.40 (2.00-2.90) SIRS 1.29 (1.17-1.37) -LR qSOFA 0.37 SOFA 0.39 SIRS 0.25
LIMITATIONS	Excluded 20% of cohort, including patients who were: Retrospectively adjudicated to not have an infection (6%) or Had missing qSOFA identifiers (14%) This study assessed mortality, in line with the Sepsis 3.0 definition of sepsis. However, just because a patient doesn't die in the hospital, it doesn't mean they don't benefit form aggressive care or have sepsis like pathophysiology.			

Source: FOAMCAST

4) Discuss the Surviving Sepsis Guidelines

SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS		
	2012	2016
SEPSIS DEFINITION	Systemic manifestation of infection + suspected infection Severe sepsis: sepsis + organ dysfunction	Life threatening organ dysfunction caused by dysregulated response to infection No severe sepsis category
INITIAL RESUSCITATION	at least 30 cc/kg in first 3 hours Crystalloid fluid (no recommendations on 0.9% NaCl vs balanced solution) Albumin if patients require "substantial" fluids (weak)	
	Protocolized care including CVP ScVO2 Normalize lactate	Use dynamic resuscitation markers (passive leg raise) Target MAP of 65mmHg Reassess hemodynamic status to guide resuscitation Normalize lactate
VASOPRESSORS	target MAP of 65 mmHg 1. Norepinephrine 2. Epinephrine if not at target MAP OR vasopressin to reduce norepinephrine requirement 3. Avoid dopamine in most patinets	
STEROIDS	Only indicated for patients with septic shock refractory to adequate fluids and vasopressors	
ANTIBIOTICS	One or more antibiotics active against presumed pathogen Combination therapy (double coverage) for neutropenic patients and pseudomonas	Initial broad spectrum antibiotics (ex: vancomycin + piperacillin-tazobactam) Against combined therapy (i.e. do not double cover pseudomonas) May use procalcitonin to guide de-escalation
SOURCE CONTROL	Achieve within 12 hours, if feasible	Achieve as soon as medically and logically feasible
VENTILATOR	6 cc/kg tidal volume prone patients with severe ARDS (P/F <150 in 2017 guideliens)	
	no recommendation	Against high frequency oscillatory ventilation (HFOV)
	weak recommendation for noninvasive ventilation in select patients with sepsis induced ARDS	Unable to make recommendation on noninvasive ventilation

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med [Internet] 2017;1.

Source: FOAMCAST

5) List doses and indications for commonly used vasoactive medications

Sepsis
- ❑ 1st line Norepinephrine
- ❑ 2nd line Vasopressin
- ❑ 3rd Line epi if not reaching MAP

Cardiogenic Shock

- ❑ Epinephrine
- ❑ Dobutamine
- ❑ Milrinone

Neurogenic shock
- ❑ Epinephrine
- ❑ Dopamine

Table 130.2 – Dosing of Vasoactive Therapy

Drug	Dosing
Dobutamine	5 – 15 µg/kg/min
Dopamine	2 – 20 µg/kg/min
Epinephrine	5 – 20 µg/min
Norepinephrine	5 – 20 µg/min
Phenylephrine	2 – 20 µg/min

6) Describe empiric Abx regimens for typical sources of sepsis

When in doubt, go big!

Piptazo + Vanco

Or Mero + Vanco

See Rosen's Table 130.3 for suggested initial antibiotic management by source

REMEBER:

Super Bug coverage:

ESBL coverage : FatCAT
- ❑ Fosfomycin
- ❑ Carbapenems (imipenem vs Meropenem)
- ❑ Aminoglycosides (gentamycin / Tobramycin)
- ❑ Tigecycline

VRE Coverage
- ❑ Linezolid
- ❑ Dapto
- ❑ Tigecycline
- ❑ Chloramphenicol
- ❑ high-dose ampicillin or ampicillin/sulbactam
- ❑ nitrofurantoin

MRSA Coverage
PO
- ❑ Septra
- ❑ Doxy
- ❑ Clinda
- ❑ Linezolid

IV
- ❑ Vanco
- ❑ Linezolid
- ❑ Daptomycin
- ❑ Tigecycline

PSEUDOMONAL COVERAGE
(puncture wounds, post surgical wounds, Sickle cell anemia)

PO
- ❑ Cipro

IV
- ❑ Ceftazidime for cefepime
- ❑ Tobramycin
- ❑ Piptazo
- ❑ Meropenem

ANTIPSEUDOMONAL CEPHALOSPORIN = Ceftazidime for cefepime
ANTIPSEUDOMONAL aminoglycoside = Tobramycin

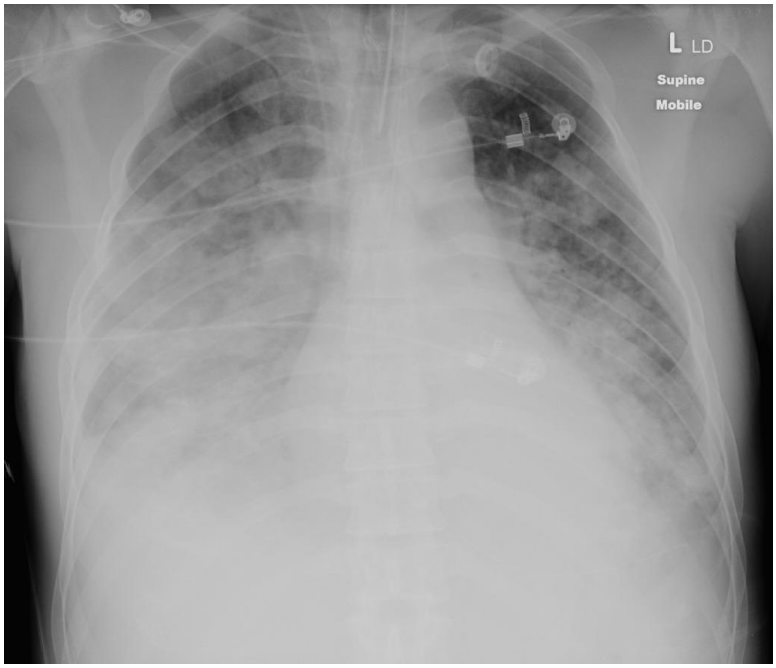
7) Define ARDS

Acute Respiratory Distress Syndrome

Complex interplay between (1) pulmonary oedema from damage to the alveolocapillary barrier; (2) inflammatory infiltrates; (3) surfactant dysfunction

According to LITFL:

ARDS is (The Berlin Definition (2013)
- ❑ Acute, with onset over 1 week or less
- ❑ Bilateral opacities consistent with pulmonary edema must be present; they may be detected on CT or chest radiograph
- ❑ PF ratio <300mmHg with a minimum of 5 cmH20 PEEP (PaO2 / FiO2 eg PaO2 80 / FiO2 0.80 = 100)
- ❑ Must not be fully explained by cardiac failure or fluid overload, in the physician's best estimation using available information — an "objective assessment" (e.g. echocardiogram) should be performed in most cases if there is no clear cause such as trauma or sepsis.



Source: Case courtesy of Dr. Craig Hacking, Radiopaedia.org, rID: 53759

ARDS is categorized as being mild, moderate, or severe:

ARDS Severity	**PaO2/FiO2***	**Mortality****
Mild	200 – 300	27%
Moderate	100 – 200	32%
Severe	< 100	45%

*on PEEP 5+; **observed in cohort

RISK FACTORS

Direct
- ❑ pneumonia (46%)
- ❑ aspiration of gastric contents (29%)
- ❑ lung contusion (34%)
- ❑ fat embolism
- ❑ near drowning
- ❑ inhalational injury
- ❑ reperfusion injury

Indirect
- ❑ non-pulmonary sepsis (25%)
- ❑ multiple trauma (41%)
- ❑ massive transfusion (34%)
- ❑ pancreatitis (25%)
- ❑ cardiopulmonary bypass

8) Describe the ED approach to managing ARDS

In essence this is a problem for our Colleagues in Critical Care, but we can HELP BIG TIME to prevent lung injury in the early hours of mechanical ventilation

See LIFTL

Mechanical Ventilation

- ❑ ARDS Network protective lung ventilation strategy (from the ARMA study)
- ❑ Controlled mode of ventilation
- ❑ TV 6mL/kg
- ❑ Avoid overstretch (volutrauma) and inadequate recruitment (atelectrauma)
- ❑ PEEP
- ❑ Plateau pressure <30 cmH20 (higher than this contributes to VILI from overstretching and hyperinflation of the functional 'baby lung')
- ❑ Mode of ventilation: generally no difference
    - ❑ PCV tends to be used c/o plateau pressure approximates peak pressure, with VC plateau pressure needs to be measured
- ❑ Oxygenation target: SpO2 > 90%, PaO2 >60mmHg
- ❑ Carbon dioxide target: ARDSnet aimed for a normal CO2 -> but lung is exposed to repeated tidal stretch, ideally hypercapnia should be minimised but there isn't compelling data to suggest it is harmful unless there is an obvious reason (raised ICP, pregnancy).

Other Tx

- ❑ Proning
- ❑ Sedation to ensure vent synchrony and lower O2 consumption
- ❑ <48 hrs of neuromuscular paralysis if PF ratio <150
- ❑ Start feeds
- ❑ Nitric or Prostacyclins controversial
- ❑ VV ECMO

Wisecracks

1) Outline key priorities in diagnostic workup and management of the septic patient during the first 6 hours of emergency care.

From UptoDate: ***"Therapeutic priorities include securing the airway, correcting hypoxemia, and establishing vascular access for the early administration of fluids and antibiotics.*** *Simultaneously obtaining the following is preferable (within 45 minutes) but should not delay the administration of fluids and antibiotics: routine laboratory studies, serum lactate, arterial blood gases, blood cultures (aerobic and anaerobic) from two distinct venipuncture sites and from indwelling vascular access devices, cultures from easily accessible sites (eg, sputum, urine), and imaging of suspected sources."*

1. Rapid identification
2. MOVIE + Airway
3. Fluids - RL or NS: 3 L in 3 hours
4. Empiric Antibiotics
    a. Probably at least two agents
    b. Ideally one given within the first hour of presentation
    c. Thorough HEAD TO TOE; GUMS TO BUMS; FOLD TO FOREIGN BODY assessment to help guide your empiric therapy

5. Investigations
    a. Assessment of end-organ function
    b. Cultures
    c. Imaging
6. Reassessment + consideration of inopressors
    a. MAP > 65-70
    b. U/O minimum 0.5 ml/kg/hr
7. Source control - ideally within 12 hours
8. Roll into AT's tender care → the ICU

General Guidelines to aim for in the resuscitative phase are:

- MAP > 65 mmHg
- HR < 100/min
- Adequate tissue perfusion as assessed by clinical examination
- CI > 2.2 l/min/m2
- CVP < 8 mmHg

2) What is HLH?

See LITFL and PULMCRIT

According to Dr. Josh Farkas:

"What is hemophagocytic lymphohistiocytosis (HLH)? (a.k.a., hemophagocytic syndrome, macrophage activation syndrome) HLH is a clinical syndrome resulting from immunological hyperactivation centered around macrophages. It involves a proinflammatory cytokine storm with high levels of many cytokines (e.g., IL-1, IL-6, and IL-8). The histological signature of this process is activated macrophages phagocytizing other cells."

Now thought to be a Sepsis and HLH overlap syndrome, or "SHLHOS"

Clinically =

- ❑ Fever
- ❑ Shock
- ❑ capillary leak
- ❑ Thrombocytopenia
- ❑ Delirium
- ❑ disseminated intravascular coagulation
- ❑ multiorgan failure

Need AT LEAST 5 of following:

- ❑ Fever
- ❑ Splenomegaly
- ❑ Cytopenia in at least two cell lines
    - ❑ Hemoglobin < 9 mg/dL (Hb <90 g/L)
    - ❑ Platelets < 100 billion/L (platelets <100 x 10E9/L)
    - ❑ Neutrophils < 1,000 / microliter (neutrophils <1 x 10E3/L)
- ❑ Hypertriglyceridemia and/or hypofibrinogenemia
    - ❑ Triglycerides >265 mg/dL
    - ❑ Fibrinogen < 150 mg/dL

- ❏ Hemophagocytosis in bone marrow, spleen, or lymph node biopsy
- ❏ Ferritin >500 ng/ml (>10,000 highly specific, > 50,000 high chance of mortality)
- ❏ Low natural killer-cell activity
- ❏ Soluble CD25 (i.e. soluble IL-2 receptor) > 2,400 U/ml

Basically super hard to diagnose, but likely very common in those sepsis patients that die in ICU.

Possible roles of interleukin-1 receptor antagonists (anakinra) and STEROIDS