A Standardized Approach to Managing Severe Sepsis & Septic Shock

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I have no conflicts of interest

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Objectives

- Identify the stages of sepsis
- Design a treatment plan for initial resuscitation and antimicrobial management
- Justify the importance of implementing a standardized set of orders for sepsis management
- Discuss the role of the pharmacist in sepsis management

Stages of Sepsis

ACCP/Society of CC Medicine Consensus Panel Guidelines

- Systemic Inflammatory Response Syndrome (SIRS)
  Two or more of the following
  - Temperature of >38 °C or <36 °C
  - Heart rate of >90
  - Respiratory rate of >20
  - WBC count >12 x 10^9/L or <4 x 10^9/L or 10% bands
- Sepsis
  - SIRS plus evidence of infection
- Severe Sepsis
  - Sepsis plus organ dysfunction, hypotension, or hypoperfusion
- Septic Shock
  - Hypotension (despite fluid resuscitation) plus hypoperfusion

Multiple Organ Dysfunction Syndrome (MODS)

- The most commonly affected organs: Lungs, Heart, Kidneys, CNS, Hematologic/coagulation systems

Organ System	Mild Criteria	Severe Criteria
Pulmonary	Hypoxia/hypercarbia requiring assisted ventilation for 3-5 days	ARDS requiring PEEP* >10 cm H_2O and FiO_2† < 0.5
Hepatic	Bilirubin 2-3 mg/dL or other liver function tests more than twice normal, PT elevated to twice normal	Jaundice with bilirubin 8-10 mg/dL
Renal	Oliguria (< 500 mL/d or increasing creatinine) 2-3 mg/dL	Dialysis
Gastrointestinal	Intolerance of gastric feeding for more than 5 days	Stress ulceration with need for transfusion, acalculous cholecystitis
Hematologic	aPTT >125% of normal, platelets < 50-80,000	Disseminated intravascular coagulation
Cardiovascular	Decreased ejection fraction with persistent capillary leak	Hyperdynamic state not responsive to pressors
CNS	Confusion	Coma
Peripheral nervous system	Mild sensory neuropathy	Combined motor and sensory deficit

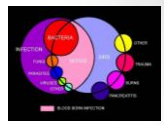
*Positive end-expiratory pressure

†Fraction of inspired oxygen

Epidemiology

- Incidence of sepsis in US is estimated to be 750,000 cases/year
- Approximately 40% may develop shock
- Mortality rates from severe sepsis = 30-50%
- Mortality rates from septic shock = 50-60%
- Severe sepsis kills ~1,400 people worldwide every day

Stages of Sepsis



- LR is a 73 yo male admitted 2 days ago due to CVA and is now transferred to ICU with suspected aspiration pneumonia.
- He is unresponsive with BP 74/30 and requires intubation.
- WBC 18, LA 8, AST 82, Cr 2.7 (1.4)
- IV bolus of NS 1000 mL x 2 and then NE started.
- He is responding to fluid resuscitation with a BP 90/58 (MAP 69) on NE at 40 mcg/min.

Which of the following best represents LR's stage of sepsis?

a) **SIRS**
b) **Sepsis**
c) **Severe Sepsis**
d) **Septic Shock**

Surviving Sepsis Campaign (SSC)/Institute for Healthcare Improvement

- An international guideline-based performance improvement program targeting severe sepsis
- Goals are to improve the diagnosis, survival, and management of patients with sepsis by addressing the challenges associated with it.
- Key is the ability to standardize care
  - Early recognition
  - Implementation of early goal directed therapy
    - Resuscitation Bundles
    - Management Bundles

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: Crit Care Med 2008

Surviving Sepsis Campaign/Institute for Healthcare Improvement: Sepsis **Resuscitation** Bundles

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer empiric antibiotics within 3hrs of ED admission and within 1 hour of non-ED admission
4. When hypotension or hyperlactatemia (≥4 mmol/L) is documented:
   - Treat hypotension and/or elevated lactate with fluids
   - Apply vasopressors for ongoing hypotension
5. For volume-refractory, vasopressor-dependent hypotension (septic shock):
   - Achieve a central venous pressure (CVP) ≥ 8 mmHg
   - Achieve a $ScvO_2$ ≥ 70%

SSC Resuscitation Bundles

1. Measure Serum Lactate

- Indicator of oxygen transport and use by the tissues
- Lactic acid is generated by anaerobic metabolism/hypoxia
- Indicator of tissue hypoperfusion

- Surviving Sepsis Guidelines:
  - All pts with lactate >4 mmol/L should enter the early goal-directed therapy portion of the Severe Sepsis Resuscitation Bundle, regardless of blood pressure.
  - Turnaround time should be within minutes

SSC Resuscitation Bundles

2. Obtain blood cultures prior to antibiotic administration

- At least 2 blood cultures drawn 5 minutes apart
- At least 1 should be percutaneous
- At least 1 from each vascular access device in place >48 hrs

3. Administer broad spectrum antibiotics within 3 hrs of ED admission or within 1 hr of non-ED admission

- Bottom line = The earlier the better!

Empiric antimicrobial therapy

- Timing of Antibiotics
- Choice of Antibiotics
- Availability
- Re-evaluation
- Dosing

Time to broad-spectrum antibiotics

- Effective antimicrobial therapy initiated within 1 hour of documented hypotension associated with 80% survival rate
- Each 1hr delay in effective antibiotic therapy associated with an 8% decrease in survival
- Time to initiation of effective antimicrobial therapy was the single strongest predictor of patient outcome

Crit Care Med. 2006 Jun;34(6):1589-96

Choice of antibiotics

- Approached in a protocol-driven manner
- Evaluate patient risk factors
- If no HA risks, consider antibiotic-sensitive pathogens
- If immunocompromized or HA risk factors, must consider antibiotic-resistant pathogens
- Consider the source of infection

Additional considerations in Initial Antimicrobial Therapy

- Consider empiric antifungal therapy if:
  - Recent abdominal surgery
  - TPN therapy
  - Compromised immune system
  - Indwelling central venous catheters
- Consider empiric *C. difficile* therapy if:
  - Patient presents with diarrhea and recent history of antibiotic use

Empiric antimicrobial therapy

- Availability
- Re-evaluation
- Dosing

Incorporate into Hospital Severe Sepsis/Septic Shock Orders

Antibiotics:

1. Vancomycin 1gm IVPB every 12 hours. 1st dose STAT, then Pharmacy to dose. (DC vancomycin after 48 hours if cultures are negative for MRSA or MRSE).
2. Choose ONE antibiotic below -**REQUIRED**
   - ☐ Ceftriaxone 2 gm IV Q 24 hours, 1st dose STAT
   - ☐ Cefepime 2 gm IV Q12 hours, 1st dose STAT
   - ☐ Piperacillin/tazobactam 4.5 gm IV Q6 hours, 1st dose STAT FOR beta lactam allergic patients ONLY
   - ☐ Aztreonam 2 gm IV Q8 hours, 1st dose STAT
   - ☐ Levofloxacin 750 mg IV daily, 1st dose STAT
3. Choose ONE antibiotic below - **OPTIONAL**
   - ☐ Azithromycin 500 mg IV Q24 hours, 1st dose STAT
   - ☐ Tobramycin 7 mg/kg IVPB NOW, then pharmacy to dose
   - ☐ Levofloxacin 750 mg IV daily, 1st dose STAT
   - ☐ Fluconazole 800 mg IV day 1, then fluconazole 400 mg IV Q24 hours

Antimicrobial Recommendation:

- GM is a 37yo F with no significant PMH other than recent URI that was treated w/levofloxacin. She now presents to the ED with suspected CAP. She is alert and oriented with the following VS & test results:
  - T 102.7 F (39.3 C), P 102, RR 24, BP 74/40
  - Cxray: consistent w/pneumonia
  - WBC 21.3 x 10^3 cells/mm^3
  - Lactate 4.8 mmol/L
- Aggressive fluid resuscitation is started and blood cultures drawn.
- She is not responding to fluids and has become increasingly confused.

In addition to gentamicin, which of the following is best to add to her antibiotic regimen?

a) Azithromycin
b) Cefepime
c) Ceftriaxone and Vancomycin
d) Cefepime and Vancomycin

SSC Resuscitation Bundles

4. When hypotension or hyperlactatemia (≥4 mmol/L) is documented:

- Treat hypotension and/or elevated lactate with fluids
- Apply vasopressors for ongoing hypotension

5. For volume-refractory, vasopressor-dependent hypotension (septic shock):

- Achieve a central venous pressure (CVP) ≥ 8 mmHg
- Achieve a ScvO2 ≥ 70%

Hemodynamic Parameters

- Cardiac output (CO) – amount of blood pumped per minute
- Cardiac index (CI) – CO standardized for BSA
- Central venous pressure (CVP)

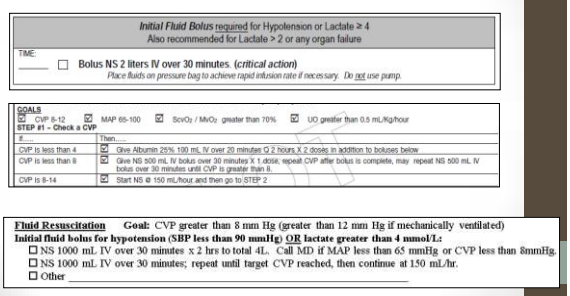
Hemodynamic parameter goals

- Goal is to optimize intravascular volume and organ perfusion
  - CVP 8-12 mmHg (12-15 if intubated)
  - MAP ≥ 65 mmHg
  - Urine output ≥ 0.5 ml/kg/hr
  - ScvO2 ≥ 70%

Intravascular volume resuscitation

- Goal is to achieve hemodynamic stabilization within the first 6 hours and reverse tissue hypoperfusion
- Early Goal Directed Therapy/SSC Recommendations
  - Rapid bolus of 20-30 mL/kg of NS or LR over 10-15 minutes
  - Continue in aliquots of 500-1000mL over 30 minutes
- Monitor CVP at baseline and after each fluid bolus
- Cardiac output is optimized at a CVP of 8-12 mmHg in non-intubated and 12-15 mmHg in ventilated patients
- Initiate vasopressor therapy if sustained hypotension despite aggressive fluid resuscitation

Incorporate into Hospital Severe Sepsis/Septic Shock Orders



Initial Fluid Bolus required for Hypotension or Lactate ≥ 4
Also recommended for Lactate > 2 or any organ failure

TIME:

☐ Bolus NS 2 liters IV over 30 minutes. (*critical action*)
Place fluids on pressure bag to achieve rapid infusion rate if necessary. Do not use pump.

GOALS
☑ CVP 8-12 ☑ MAP 65-100 ☑ $ScvO_2$ / MvO_2 greater than 70% ☑ UO greater than 0.5 mL/Kg/hour
STEP #1 – Check a CVP

If....	Then....
CVP is less than 4	☑ Give Albumin 25% 100 mL IV over 20 minutes Q 2 hours X 2 doses in addition to boluses below
CVP is less than 8	☑ Give NS 500 mL IV bolus over 30 minutes X 1 dose, repeat CVP after bolus is complete, may repeat NS 500 mL IV bolus over 30 minutes until CVP is greater than 8.
CVP is 8-14	☑ Start NS @ 150 mL/hour and then go to STEP 2

Fluid Resuscitation **Goal:** CVP greater than 8 mm Hg (greater than 12 mm Hg if mechanically ventilated)
Initial fluid bolus for hypotension (SBP less than 90 mmHg) OR lactate greater than 4 mmol/L:
☐ NS 1000 mL IV over 30 minutes x 2 hrs to total 4L. Call MD if MAP less than 65 mmHg or CVP less than 8mmHg.
☐ NS 1000 mL IV over 30 minutes; repeat until target CVP reached, then continue at 150 mL/hr.
☐ Other _____

Vasopressor Support

- Norepinephrine or Dopamine
- Titrate to an initial MAP goal of 60-65 mmHg
  - Minimum MAP of 60 mmHg needed to perfuse organs
- Tissue oxygenation should also be assessed
  - Measure the ScvO2 (goal ≥ 70%)
  - If low despite fluid and vasopressor therapy:
    - Begin inotropic therapy (e.g., Dobutamine) if low CI suspected
    - Transfuse if HCT < 30%

Vasopressin vs Norepinephrine in patients with septic shock (VASST)

- Examined whether adding vasopressin to NE would improve 28-day survival in septic shock
  - Vasopressin had a NE sparing effect the first 4 days
  - No difference in 28-day mortality
  - Lower than expected mortality rate (~37% in both groups)

VASST: Russel JA, NEJM 2008

Incorporate into Hospital Severe Sepsis/Septic Shock Orders

Vasopressors (Primary):

For hypotension (MAP less than 65 mmHg) not responding to initial fluid resuscitation (NOTE: It may be necessary to employ vasopressors early as an emergency measure in patients with septic shock):

- ☐ Norepinephrine 2 mcg/min (max: 30 mcg/min), titrate to a MAP of 65 – 90 mmHg
- ☐ DOPamine 5 mcg/kg/min (max: 20 mcg/kg/min), titrate to a MAP of 65 – 90 mmHg
- Continue fluid as described above during vasopressor therapy

Vasopressors (Adjunctive ONLY):

- ☐ EPINEPHrine 2-10 mcg/minute (start at 1 mcg/minute and titrate ONLY per physician order) NOT A FIRST LINE/MONOTHERAPY VASOPRESSOR AGENT

Transfusion / Inotrope therapy:

If ScvO2 is less than 65% despite CVP of 8 – 15 mmHg AND the addition of vasopressor therapy AND Hct is less than 30 gm/dL

- ☐ Transfuse one unit PRBC over _____ hours. H&H after infusion. May repeat PRBC as needed every _____ hours, to a maximum of _____ units.

If ScvO2 is less than 65% despite CVP of 8 – 15 mmHg AND the addition of vasopressor therapy AND Hct is greater than or equal to 30 gm/dL

- ☐ DOBUTamine 2.5 mcg/kg/min. Titrate until SvO2 is greater than or equal to 65% or maximum dose of 20 mcg/kg/min. Notify MD for persistent decrease in blood pressure and/or HR greater than 130.

SSC Resuscitation Bundles

- MS is a 92 year old female admitted to MICU with urosepsis and septic shock. She is living in a NH and has a PMH significant for MI, HTN, and HF.
  - BP is 72/44 mmHg. HR 120 BPM, O2 sat 99%
  - Labs are normal except for a BUN/SCr = 74/2.7
  - Empiric antibiotics were started.

Which one of the following therapies should be initiated next?

a) Dobutamine
b) Epinephrine
c) Normal saline
d) Norepinephrine

Surviving Sepsis Campaign/Institute for Healthcare Improvement Sepsis **Management** Bundles

1. Consider low-dose steroids administered for septic shock in accordance with a standardized ICU policy
2. Consider recombinant Human Activated Protein C (rhAPC) administered in accordance with a standardized ICU policy
3. Maintain adequate glycemic control (<180 mg/dL)
4. Inspiratory plateau pressures less than 30 cm H_2O maintained for mechanically ventilated patients

Corticosteroids in Septic Shock

- JAMA 2002: Hydrocortisone 50 mg IV q6h x 7 days significantly reduced mortality in patients with septic shock (hypotensive despite fluid resuscitation and vasopressors)
- CORTICUS 2008: Low dose hydrocortisone in patients w/Severe Sepsis x 7 days then tapered on days 6-11
  - No difference in mortality, ICU or Hospital LOS
  - ↑ Risk of Super-infections and Hyperglycemia
  - Similar results despite pts' adrenal responsiveness to corticotropin
- COIITSS 2008: The addition of oral fludrocortisone to low dose hydrocortisone did not improve mortality.

Corticosteroids in Septic Shock: 2008 SSC Recommendations

- Do not recommend routine testing for adrenal insufficiency with ACTH stimulation test – Grade 2B
- Consider corticosteroids in all patients with septic shock *poorly responsive to fluid resuscitation and vasopressor agents* – Grade 2C
- Hydrocortisone dose should be ≤ 300 mg/day – Grade 1A
- Wean and d/c steroid when vasopressors have been discontinued

Recombinant Human APC (rhAPC) in Severe Sepsis/Septic Shock

- PROWESS
- ADDRESS
- ENHANCE
- XPRESS

Absolute Contraindications for use of rhAPC – Drotrecogin Alfa (activated)

- Active internal bleeding
- Recent (past 3 months) hemorrhagic stroke
- Recent (past 2 months) intracranial or intraspinal surgery or severe head trauma
- Trauma with increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Warnings and Precautions for use of rhAPC – Drotrecogin Alfa (activated)

- Concurrent therapeutic dosing of heparin to treat an active thrombotic or embolic event
- Platelet count <30,000 x 10^6/L, even if it is increased after transfusion
- INR > 3
- Recent (past 6 weeks) GI bleeding
- Recent administration (past 3 days) of thrombolytic therapy
- Recent administration (past 7 days) of oral anticoagulants, antiplatelet agents, ASA > 650mg/day or GPIIb/IIIa inhibitors
- Recent (past 3 months) ischemic stroke
- Intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis
- Chronic severe hepatic disease
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

rhAPC in Severe Sepsis/Septic Shock: 2008 SSC Recommendations

- Consider rhAPC in adult patients at high risk of death (APACHE II $\geq$ 25 or sepsis-induced multiple organ failure) and no contraindications
  - Grade 2B (weak, moderate quality evidence)
  - Grade 2C (weak, low quality evidence) if w/in 30 days of surgery
- Adult patients with severe sepsis and low risk of death (APACHE II <20 or 1 organ failure) should NOT receive rhAPC
  - Grade 1A (strong, good quality evidence)
  - No mortality benefit, but increased risk for serious bleeding

Implementing the SSC Management Bundles

You are the CC pharmacist rounding in the ICU. You are approached by one of the Intensivists wanting your opinion about next steps in treating a patient in which he has initiated early goal directed therapy.

Which is the best rationale against the use of hydrocortisone in this patient?

a) SBP is volume-responsive with a MAP of 70 mmHg
b) Risk of hyperglycemia with steroids outweigh the potential benefit
c) First need to evaluate patient's adrenal function
d) The risk of infection with steroids outweighs the potential benefit

SSC Statement on Glucose Control in Severe Sepsis (June 2009)

- Patients w/severe sepsis and hyperglycemia who are admitted to ICU should receive IV insulin therapy (1B)
- Insufficient data to determine optimal target BG range in severely septic patients
- Based on results of the NICE-SUGAR trial, SSC recommends against IV insulin therapy titrated to keep BG in the normal range (80-110 mg/dL)
- Consider initiating insulin therapy when BG >180 mg/dL with a goal BG approximating 150 mg/dL

Justification for implementation of standardized order sets

- Standardized order sets:
  - Are the product of multidisciplinary team efforts
  - Represent an organized approach to implementing evidence based guidelines
  - Are customized to function well within your institution

ISMP's Guidelines for *Standard Order Sets* – Purpose:

- Communicate best practices
- Modify practice through evidence-based care
- Reduce variation and unintentional oversight
- Enhance workflow
- Reduce the potential for medication errors
- Reduce unnecessary calls for clarification

Barriers to Standardization

- Time and resources associated with the process
- Logistics in bringing together all necessary decision-makers
- Achieving final consensus
- Physician adoption

Evidence Supporting Standardized Orders

- Impact of a standardized order set for the management of bacteremic severe sepsis
- Compared 200 patients treated prior to and 200 patients treated post implementation
- **Results** – Compared w/Before, the After group:
  - Received more IV fluids in the 1st 12 hours after onset of hypotention (1627 mL vs 2054 mL, *p=0.04*)
  - Were more likely to be treated with an appropriate initial antimicrobial regimen (53% vs 65.5%, *p=0.01)*
  - Had significantly lower in-hospital mortality (55% vs 39.5%, *p<0.01)*
  - Had a shorter hospital LOS (28.7 days vs 22.4 days, *p=0.02)*
  - Has significantly lower rates of renal failure and were less likely to require vasopressors

Crit Care Med 2009; 37(3):818-24

Implementation of standardized order sets – Overcoming Barriers

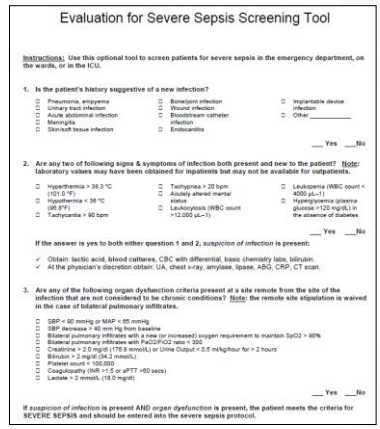
- Improve quality of care
- Enhance patient safety
- Aid in efficiency
- Reduce cost related to medication errors and hospital length of stay
- Meet TJC expectations and CMS's value-based purchasing targets

The Pharmacist's Role

- Development
- Implementation
- Evaluation
- Education
- Prevention

Strategies for successful implementation

- A high-profile awareness campaign
- Training workshops for nursing staff
- Academic detailing of medical staff
- Incorporation of the order set into CPOE/EMR



Evaluation for Severe Sepsis Screening Tool

Instructions: Use this optional tool to screen patients for severe sepsis in the emergency department, on the wards, or in the ICU.

1. Is the patient's history suggestive of a new infection?

☐ Pneumonia, empyema ☐ Bone/joint infection ☐ Implantable device infection
☐ Urinary tract infection ☐ Wound infection ☐ Other _____
☐ Acute abdominal infection ☐ Bloodstream catheter infection
☐ Meningitis ☐ Endocarditis
☐ Skin/soft tissue infection

___ Yes ___No

2. Are any two of following signs & symptoms of infection both present and new to the patient? Note: laboratory values may have been obtained for inpatients but may not be available for outpatients.

☐ Hyperthermia > 38.3 °C (101.0 °F) ☐ Tachypnea > 20 bpm ☐ Leukopenia (WBC count < 4000 µL−1)
☐ Hypothermia < 36 °C (96.8°F) ☐ Acutely altered mental status ☐ Hyperglycemia (plasma glucose >120 mg/dL) in the absence of diabetes
☐ Tachycardia > 90 bpm ☐ Leukocytosis (WBC count >12,000 µL−1)

___ Yes ___No

If the answer is yes to both either question 1 and 2, *suspicion of infection* is present:

✓ Obtain: lactic acid, blood cultures, CBC with differential, basic chemistry labs, bilirubin.
✓ At the physician's discretion obtain: UA, chest x-ray, amylase, lipase, ABG, CRP, CT scan.

3. Are any of the following organ dysfunction criteria present at a site remote from the site of the infection that are not considered to be chronic conditions? Note: the remote site stipulation is waived in the case of bilateral pulmonary infiltrates.

☐ SBP < 90 mmHg or MAP < 65 mmHg
☐ SBP decrease > 40 mm Hg from baseline
☐ Bilateral pulmonary infiltrates with a new (or increased) oxygen requirement to maintain SpO2 > 90%
☐ Bilateral pulmonary infiltrates with PaO2/FiO2 ratio < 300
☐ Creatinine > 2.0 mg/dl (176.8 mmol/L) or Urine Output < 0.5 ml/kg/hour for > 2 hours
☐ Bilirubin > 2 mg/dl (34.2 mmol/L)
☐ Platelet count < 100,000
☐ Coagulopathy (INR >1.5 or aPTT >60 secs)
☐ Lactate > 2 mmol/L (18.0 mg/dl)

___ Yes ___No

If *suspicion of infection* is present AND *organ dysfunction* is present, the patient meets the criteria for SEVERE SEPSIS and should be entered into the severe sepsis protocol.

Prevention

- Avoidance of invasive catheters or removal as soon as possible
- Appropriate prophylactic antibiotics in the perioperative phase
- Pneumococcal and Influenza Vaccinations
- INFECTION CONTROL

Justification for Standardization

An ED physician new to your organization was given your name to call and complain about the hospital's Severe Sepsis protocol being "too cookie cutter" and "doesn't allow me to call the shots"….

Which would be the best rationale to give Dr. ED for using the protocol?

a) The protocol is evidence-based
b) Use of the protocol should ↑ efficiency
c) Will help avoid unintentional oversight
d) All of the above

Objectives

- Identify the stages of sepsis
- Design a treatment plan for initial resuscitation and antimicrobial management
- Justify the importance of implementing a standardized set of orders for sepsis management
- Discuss the role of the pharmacist

Questions?

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