

Critical Care: Diagnosis and Management of Sepsis

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Learning Objectives

- Recognize the signs of sepsis
- Discuss the treatment of sepsis
- Provide guidance regarding proper documentation of sepsis.



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Sepsis Statistics

- 10th leading cause of death in US, most common cause nonmalignant death in oncology
- 750,000 cases/year; 250,000 deaths/year
- Severe sepsis occurs in 14% oncology patients
- Mortality from severe sepsis and/or septic shock 30-40%
- Early recognition saves lives
- Sepsis can present with atypical signs and symptoms in patients with cancer.
- Early and astute care by bedside clinicians can make the greatest difference in patient outcome

<http://www.bing.com/videos/search?q=sepsis+alliance+video&FORM=VIRE2#view=detail&mid=D1B58A028C89F931111CD1B58A028C89F931111C>



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Definitions

SIRS

- Systemic Inflammatory Response Syndrome (SIRS) is two or more of the following: Temp $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, Heart Rate (HR) >90 , Respiratory Rate (RR) >20 , WBC >12 K/cu mm or <4 K/cu mm or $>10\%$ bands

SEPSIS

- Is two SIRS criteria PLUS a known or suspected bacterial, viral, or fungal infection

SEVERE SEPSIS

- Sepsis + at least one sign of end organ dysfunction, such as altered mental status, decreased urinary output, thrombocytopenia, lactate >2 , systolic blood pressure (SBP) <90 or mean arterial pressure (MAP) <65 , prior to fluid resuscitation

SEPTIC SHOCK

- Hypotension and elevated lactate ≥ 4 may be signs of hypoperfusion/ septic shock
- Septic shock is persistent hypotension despite adequate fluid resuscitation (30 mL/kg)

Dellinger et al. Crit Care Med 2013



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Audience Response Question

Are you ready to answer?



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Audience Response Question #1

- What term would you use for a patient with < 500 neutrophils/ mm^3 and the following vital signs: T- 38.6°C , HR-94, RR-20, BP-110/60?
 1. Febrile neutropenia
 2. Sepsis
 3. Severe sepsis
 4. Septic shock



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Where does febrile neutropenia fit?

Even though this uses 38.3°C, oncology resources^{1,2} recommends 38.0°C X 2 within one hour

SIRS

- Temp >38.3°C or <36°C, HR >90, RR >20, WBC >12 or <4 K/cu mm or >10% bands

SEPSIS

- SIRS + Infection

SEVERE SEPSIS

- Sepsis + End Organ Damage or SBP <90 or MAP <65, prior to fluid resuscitation

SEPTIC SHOCK

- Severe Sepsis → Hypotension refractory to fluids

Patients with neutropenia are escalated to at least sepsis

¹ Baden, Bensinger, Angarone,... Wilson, 2015
² Flowers, Seidenfeld, Bow, Karten, Gleason, Hawley, ...Ramsey, 2013

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MAGNET RECOGNIZED

Audience Response Question

Are you ready to answer?

40

vista 40
audience response system

Welcome

reality

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Audience Response Question #2

- In my practice I currently evaluate blood pressures in the following manner:
 1. Use systolic/ diastolic BP to make decisions
 2. Use the mean pressure (MAP) to make decisions



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Blood Pressure *Concerns for Practice*



- Non-ICU settings use Systolic/Diastolic BP, not Mean arterial pressure (MAP)
- Low diastolic BP most common in early, warm (febrile) sepsis- *low diastolic BP lowers mean (perfusing) pressure.*
 - $MAP = 2D + S / 3$
 - $90/50 = (50 \times 2) + 90 / 3$
 - $190/3 = 63 \text{ mm Hg}$
 - Normal mean BP is $> 65 \text{ mm Hg}$



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Organ Dysfunction (new onset)

- Signs/ Symptoms
 - Altered mental status
 - Low urine output
 - Capillary refill > 3 seconds
 - Mottling
 - Weight gain > 20 mL/kg- ~ 2 kg previous 2 days
- Laboratory Abnormalities
 - Bilirubin > 2 mg/dl
 - Creatinine > 2.0 mg/dl
 - Glucose > 140 mg/dl absence diabetes
 - Hypoxemia requiring BiPAP
 - INR \geq 1.5
 - Lactate > 2mmol
 - Platelets < 100,000/mm³



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Common Findings in Sepsis: Mottling



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Evidence Summary

Evidence Review: sepsis best practices, sepsis bundle interventions, febrile neutropenia, nurse managed

MedLine, EMBASE, Cochrane, CINAHL

Filter for duplicates
Title review
Abstract review
Full article review
Additional articles from hand searching

Final inclusion

Implementation strategies (69)
Risks, prognosis (15)
Fever and neutropenia (59)
Nurse-managed (37)
SIRS criteria & cancer (1)
Sepsis/ septic shock cancer (1)

Key Evidence Summary

Level I- 3, Level II- 25, Level III- 30,
Level IV- 1, Level V- 10

Specific bundled interventions (High)
Education (Moderate)
Protocols and algorithms (Moderate)
Electronic orders (Moderate)
Rapid response teams, Champions, Integrated monitoring alarms (Low)
Combining interventions (Moderate)

Literature universally supported implementation of Surviving Sepsis recommendations



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Surviving Sepsis Campaign

- Initial EBP recommendations 2001 United Kingdom
 - Endorsed by organizations internationally
 - Goal- reduce sepsis mortality 25% in 5 years
- Published sepsis guideline bundles- 2004
- Revised; separation of bundled interventions (2008)
 - Early goal directed therapy [EGDT] (3 and 6 hr interventions)
 - First 24 hrs
- Revised; performance measures, emphasis on continuous screening, establishment of “time zero”- 2012
- CMS Core measure 2015
- Joint Commission Safety Goal- future



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Surviving Sepsis Recommendations: 1st 6 hours

3 hours

- Screen for sepsis at first encounter/ triage or defined intervals
- Obtain blood cultures and lactate if positive screen
- Assessment of organ function
- First antimicrobial dose within 60 min of triage
- Oxygen if O₂ sat < 90%
- Initial fluid bolus *at least* 30 mL/kg if hypotensive

6 hours

- Assessment of source
- CVP line- goal 8-12 mm Hg unless mechanically ventilated- then 12-15 mm Hg
- MAP ≥ 65 mm Hg
- Central venous oxygen saturation (ScvO₂) ≥ 70% [obtained via blood gas from central line]
- Urine output ≥ 0.5 mL/kg/hr

Dellinger et al. Crit Care Med 2013



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Surviving Sepsis Recommendations: 1st 24 hours

- Indications:
 - Severe sepsis or septic shock OR
 - Persistent hypotension OR
 - Hyperlactemia (≥ 4.0 mmol/L)
- Low volume ventilation or maintain plateau pressures < 30 mm
- Glucose goal < 180 mg/dl
- Gastric Ulcer prophylaxis
- Venous thromboembolism (VTE) prophylaxis
- Low dose steroids for patients with hypotension*



* Exact methodology/ indications/ length of therapy is variable

Dellinger et al, Crit Care Med. 2013



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Implementing Sepsis Bundle Interventions: Challenges in Evaluation

- Excluded from most studies (*Claessens, Aegerter, Boubaker, Guidet, Cariou, & Cub Rea Network, 2013*):
 - Congestive Heart Failure (35%)
 - Cancer patients (30%)
- Bundle variability among Quality Measurement Organizations (*Fong, Cecere, Unterborn, Garpstad, Klee, & Devlin, 2007*).
 - The Joint Commission (TJC)
 - Institute for Healthcare Improvement (IHI)
 - Voluntary Hospitals of America (VHA)



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Generalizability of Sepsis Bundle Interventions

- Initial landmark study showed 7% mortality reduction if bundle elements completed 37% of time (Rivers et al, 2001)
 - Unclear which interventions most important
- Patients do not receive same care in all settings
 - “Time zero” recently revised- problematic since many interventions are time sensitive
 - Variables affecting timely antimicrobials- initially a different diagnosis, waiting for cultures to be obtained, younger patients, women, care by non-ED physician (Cullen, Fogg, Delaney, 2013; Madsen & Napoli, 2014)
 - Prompt sepsis management activation systems not consistently available



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Key Take Home Message...

Probably not all interventions confer the same value, but research clarifying the most beneficial interventions is still in progress



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Audience Response Question #3

- The most likely intervention to statistically effect outcomes among the bundled sepsis intervention recommendations is:
 - Identifying the patient early
 - Identify the infection source
 - Broad spectrum antimicrobials
 - Adequate fluid resuscitation
 - Endocrine control



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Evidence: Antimicrobials within One Hour

Citation	Methods	Results
Gaieski, Pines, Band, Mikkelsen, Massone, Furia, Shofer, Goyal, 2010	Single center, retrospective cohort, 161 pts with severe sepsis and septic shock from 2005-2006	Median time to antimicrobials was 119 min Significant association between antimicrobial administration > 1 hr to increased mortality <u>Mortality increased 7.6% for every hour delay in antimicrobial administration</u>
Fletcher, Hodgkiss, Zhang, Browning, Hadden, Hoffman, Winick, McCavit, 2013	Single center, retrospective cohort, 1628 pediatric febrile neutropenia admissions (653 pts) from 2001-2009	Adverse outcomes 11.1%, 0.7% mortality, 4.7% PICU admission, 10.1% fluid resuscitation Time to antibiotics associated with adverse outcomes as composite <u>Two times greater risk adverse outcomes > 60 minutes until first antimicrobial</u>
Ali, Baqir, Hamid, Khurshid, 2013	Single center, retrospective cohort, 81 adult and pediatric cancer pts (mostly heme malignancy pts 64%) with FN in ED after PI intervention to improve time to antimicrobial	Mean time to antimicrobials was 45 min <u>Nine patients longer than 60 min, and included the only three that developed severe sepsis</u>
Ko, Ahn, Lee, Kim, Lim, Lee, 2015	1001 FN episodes mostly solid tumor pts (80%) from 2011-2014	Mean time to antimicrobials was 140 min <u>Time to antimicrobial did NOT influence incidence of severe sepsis, septic shock or mortality</u>
Mokart, Saillard, Sannini, Chow-Chine, Brun, Faucher, Blache, Blaise, Leone, 2014	Single center, retrospective cohort, 118 pts admitted to ICU with severe sepsis or septic shock from 2008-2010	<u>Multivariate analysis showed most important predictor for mortality was time to antibiotic greater than 1 hr</u>

Antimicrobials

Every hour delay
beyond the first 60
minutes, increases
mortality about
7.6%



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Challenging Value of Selected Interventions

(ProCESS Investigators, 2014)

- Randomized controlled trial
- Compared three arms management of severe sepsis/ septic shock
 - Bundled Early Goal-Directed Therapy
 - Protocol-based care without central venous catheter, ScvO₂, inotropes or transfusions
 - Usual care in a practice setting trained in bundle interventions
- Setting: 1341 patients, 31 Emergency departments
- Outcome measurement: 90 day mortality, 1 year mortality, need for organ support
- Results: No mortality differences at 90 days/ 1 year, no differences in organ support



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Central Venous Pressures (CVP)

Unclear if CVP
measurements or
CVP guided therapy
enhances outcomes



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Corticosteroids in Sepsis

*Volbeda, Wetterslev, Gluud, Zijlstra, van der Horst & Keus,
2015, Int Care Med, 41, 1220-1234*

- Cochrane methodology
- Randomized clinical trials evaluating corticosteroids for sepsis in adults
- 35 trials; 4682 patients
- Outcomes:
 - Mortality
 - Serious adverse effects (SAE)
- All trials except two had high risk of bias
- Findings:
 - No statistically significant effect of any dose steroids versus placebo on mortality or SAE
 - Low risk bias trials confirmed findings
 - No difference in steroid dose on outcomes
 - No difference in days of treatment on outcomes



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Corticosteroids

No established best practice
for steroid use in sepsis
despite recommendations
from Surviving Resuscitation



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The MD Anderson Experience

Hanzelka, Yeung, Chisholm, Merriman, Gaeta, Malik, Rice, 2013; Support Care
Cancer 21: 727-734.

- Purpose: Compare baseline and post-protocol (orders, algorithm) for Early Goal-Directed Therapy sepsis management
- Setting: Emergency setting, single center, NCI Designated comprehensive Cancer Center
- Methods:
 - Sample (n= 355): 100 pts severe sepsis or septic shock prior to intervention, and at least 100 randomly selected severe sepsis or septic shock post intervention
 - Modified screening criteria:
 - Fever and/or hypotension plus another SIRS
 - Neutropenia NOT included
 - Heart rate modified to 100/min
 - No measurement of central venous pressure related interventions
- Outcome measures:
 - 28 day mortality
 - ICU length of stay (LOS) / hospital LOS
 - Goal mean arterial pressure and urine output at 6 hours
 - Time to lactic acid measure
 - Appropriateness and timeliness of antimicrobials
- Significant Results:
 - Mortality significantly reduced (20% vs 38%)
 - Patients reaching goal BP (74% vs 90%)
 - Patients reaching goal urine output (79% vs 96%)

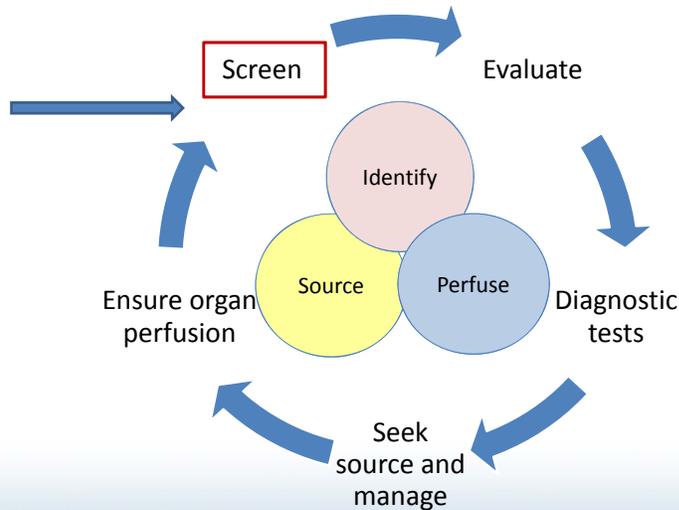


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Sepsis Management Algorithm



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Sepsis Core Measure

- The new Sepsis Core Measure began Oct 1, 2015
- Mirror Surviving Sepsis recommendations but with some variations
- Goal to perform **all** recommended interventions as indicated for patients with severe sepsis or septic shock within defined timeframes
 - Pass or fail based on completeness and timeliness
 - No clear medical exceptions (e.g. fluids and heart failure)
- Impacts all clinical areas across the hospital managing patients 18 years or older



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Test yourself

- Ms. MK- 66 year old woman with multiple myeloma 2 weeks after cycle two of dexamethasone, bortezomib, lenalidomide presenting to ED at 1240 with somnolence.
 - Vital signs in triage 1242: T- 35.6°C, HR- 102, RR- 20, BP 100/60 (MAP 73.3)
 - Provider assessment states in note 1300 “possible urinary tract infection”.
 - Labs drawn 1315- CBC, metabolic panel, lactate, blood cultures, urine cultures
 - Labs resulted 1334- lactate 2.2, Glucose 156
 - Labs resulted 1355- BUN/Creat 45/ 2.1, Bilirubin 1.5, INR 1.2, WBC 3.5, ANC 2.0, Platelets 60,000
- Time SIRS positive
 - 1240
 - 1242
 - Time SIRS plus risk infection
 - 1240
 - 1242
 - 1300
 - Time Severe Sepsis
 - 1242
 - 1300
 - 1315
 - 1334
 - 1355

Which labs are likely to be baseline abnormal for the core measure?



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Severe Sepsis Time Zero

- Mr. LP: Glioblastoma receiving temozolamide and radiation; corticosteroids for cerebral edema
 - To ED at 1410- worsening aphasia; right sided weakness
 - Vital signs 1415: T- 38.2°C, HR 122 (irregular), RR- 24, BP 90/50 (MAP 63.3), oxygen sat 88% room air
 - Glucose check 1420 is 330
 - Provider exam 1500
 - Slowed capillary refill, cool extremities
 - Note names “severe sepsis”
- Time zero for severe sepsis is:
 - 1410
 - 1415
 - 1420
 - 1500
 - Problems with defining severe sepsis in this patient:
 - Neurologic changes may be tumor-related
 - Fever borderline
 - Glucose possibly due to steroids



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Documentation of Volume Status and Tissue Perfusion (within 6 hours of septic shock)

- Documented exam (all five elements) by a MD/NP/PA
 - Vital signs (all four)
 - Cardiopulmonary (heart AND lungs)
 - Peripheral pulses: Radial/DP/PT (1+, 2+, absent)
 - Capillary refill (brisk, >2 seconds)
 - Skin findings (mottled, not mottled)
- **OR two of the following**
 - Bedside cardiovascular ultrasound
 - Measure ScvO₂
 - Measure CVP
 - Passive leg raises documented by a MD/NP/PA



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Audience Response Question

Are you ready to answer?



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Audience Response Question #4

- The correct way to do the passive leg raise test is:
 1. Start in supine position and raise legs, then check mean systolic BP
 2. Start in supine position and raise legs and check MAP
 3. Start in upright position, lie, flat, then raise legs and check pulse pressure
 4. Start in upright position, lie flat and check MAP

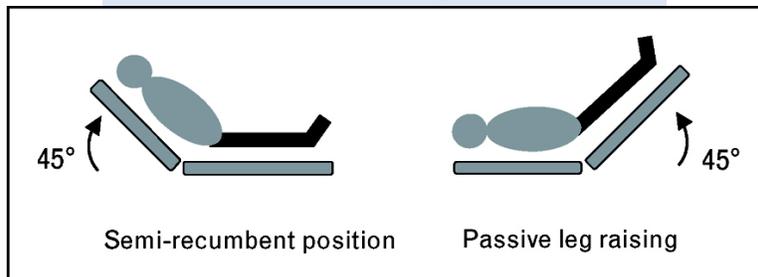


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Passive Leg Raise



- Start in head elevated position
- Lie head flat and leg raise 45°
- Measure pulse pressure 60-90 seconds after leg raise
- At least 10% increase pulse pressure (SBP- DBP) indicative of potential fluid responsiveness



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Challenges for Oncology

- Screening criteria
 - Overly sensitive
 - High screen positive rates for other reasons
 - Don't match febrile neutropenia literature
 - Not very specific- false positives
 - How to handle neutropenia
- Lactate
 - May be elevated for other reasons
- Fluid intervention
 - Only crystalloids count
 - Must be administered as bolus infusion



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Variations In Screening Criteria

*Invented Interpretations
I have heard*



- We decided that neutropenia should be omitted since most patients are neutropenic, therefore two other criteria must be met.
- Many of our patients have baseline heart rates greater than 90/min, so we changed the criteria to “complex tachycardia”.
- Patients are often beta blocked and so heart rate is not a reliable indicator.
- Since so many people meet criteria, we just call the RRT and tell them not to come because we have the situation in hand.
- Subnormal temperatures are common due to CRRT and therefore can't be reliable as a trigger criteria.



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Core Measure Inclusion / Exclusion

- All charts coded ICD10 Sepsis, Severe Sepsis, Septic Shock
- Inpatients 18 years or older
- Length of stay \leq 120 days
- Transfer from another acute care facility
- “Comfort care only”
- Death within 3 hours severe sepsis or 6 hours septic shock presentation
- IV antibiotics (broad spectrum) for > 24 hrs prior to onset



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Largest Threat to Effective Implementation

Recognizing the
septic patient early

BUT...

Oncology may require
revised screening processes
OR anticipate many false
positive alerts



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Evidence: How to Implement Sepsis Bundle Interventions

Strategy	Pro	Con
Focused Education	Easy answer Easy to perform	Knowledge retention inconsistent Staff turnover
Protocols, policies, algorithms	Summarization complex literature Familiar structure	Accessibility when and where needed Complexity
Structured pre-printed or electronic orders	Guide prescribers to choose correct EBP interventions	Requires recognition of need to activate May lead to over-treatment
Unit based Champions/ super-users	Solutions within the unit culture Peer to peer influence	Labor-intensive Champions may not always be present/available
Rapid Response activation with protocols	High activation rates (crying wolf) Standardization/frequent usage	Resource intensive
Combined interventions	Proven most effective Targets different learning styles/ locus of motivation	Resource intensive for integration

- Multiple methods to reinforce information is better than a single one.
- Multidisciplinary interventions more effective than single profession.
- Electronic forced templated actions without “opt out” options are highly effective to drive interventions.
- Documenting decisions in real-time not the current workflow for most providers.

Implementing Sepsis Best Practices



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Case Study: Elvira Adams

- 71-year-old female (from a rehabilitation facility) with rectal cancer and receiving daily radiation and capecitabine (treatment ongoing past 16 days)
- Admitted to the unit with progressive weakness and diarrhea X 2 weeks.
- Admitting Diagnosis: Dehydration



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Initial Assessment

- Assessment findings 0800: ABCs intact, alert/oriented X3, skin warm and dry, IV (22 g) infusing slowly in left hand
- History: skin rash X 2 weeks, treated with prednisone, type 2 DM, UTI 2 weeks ago treated with antibiotics
- VS: T-35.8°C, BP- 124/50 (MAP 73), HR-99, RR-20, 97% RA
- Does she have any “possible” SIRS signs or symptoms?

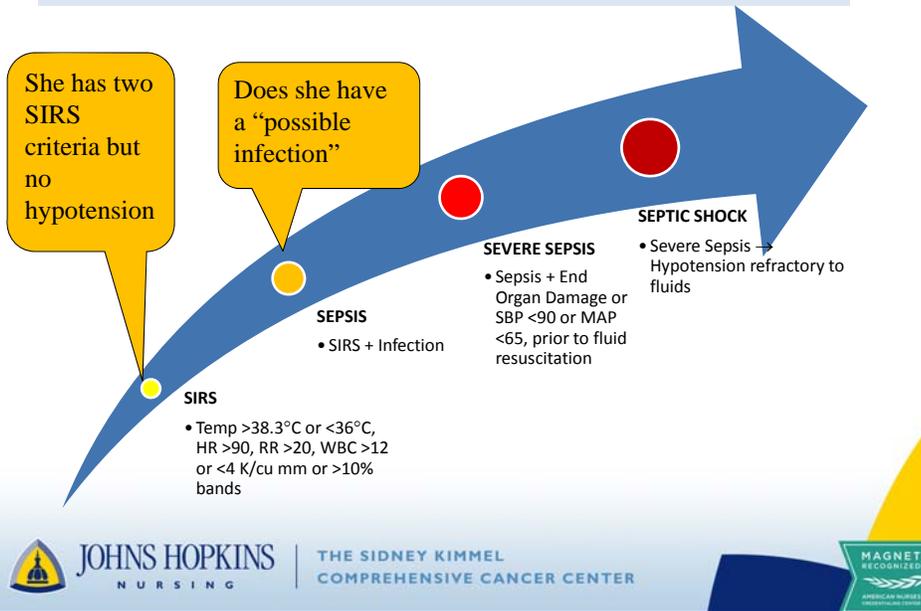


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Does Ms Adams have sepsis?



Are SIRS criteria met?

- SIRS criteria for Sepsis at this time:
 - Temp 35.8°C
 - Heart Rate > 90/minute
 - Check labs for WBC count (bands if appropriate), organ failure
- ➔
- Once two SIRS criteria are met, identify if sepsis is possible:
 - Assess for documented risk for infection/ sepsis (age, medications, hospitalized)
 - Assess for disorders that may commonly deteriorate into sepsis (recent infection)

Even if we are unsure if she has a refractory UTI, we know her risks suggest possible sepsis

What should you do?

Ms. Adams has two SIRS criteria and has a risk for sepsis

- Decide if infection likely or an alternate explanation for symptoms.
 - Not likely myelosuppression?
 - Can chemotherapy adverse effects mimic sepsis?
- Consider potential sources- decide if diagnostic evaluation is warranted
 - Excrement?
 - Physical evidence of possible infection to culture/ evaluate?
- Determine if antibiotics are indicated at this time.
 - Strong enough risk and likelihood of infection?



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Audience Response Question

*Are you ready to
answer?*



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Audience Response Question #5

- What would you do now?
 1. No immediate action required- observe and follow-up vital signs
 2. Identify that these signs/ symptoms are not likely to be sepsis
 3. Order CBC, blood and urine cultures
 4. Obtain CBC, chemistry, pan cultures, blood lactate, and request imaging to evaluate a source



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A few hours later... at 1000:

- You requested CBC, chemistry
- Vital signs 0945: T-38.8°C BP-107/50 (MAP 68), HR-106, RR-20, SaO₂ 96% on RA
- Labs results:
 - 09:45 AM
 - WBC: 16.5 (N 3.9-11.3)
 - Bands 24% (N 0-8)



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Audience Response Question

Are you ready to answer?



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Audience Response Question #6

- What would you do first?
 1. Obtain cultures and blood lactate
 2. Start antimicrobials
 3. Administer fluids 30 mL/ kg
 4. Check central venous pressure
 5. Perform a perfusion assessment



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Consider sepsis more strongly and order:

- Oxygen as needed
- Additional labs (blood cultures, lactate, urine and stool culture and sensitivity)
- Antibiotics?- if so, give **STAT** *after* blood cultures are drawn
- IV access adequate? Consider Fluids
- Frequent vital sign monitoring and trending
 - Watch for increases in HR, RR, decreases in BP, urine output
 - Change in mental status, signs of organ failure



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With 12 noon vital signs...

- Ms. Adams tells the nurse: “I don’t feel well.”
- She is oriented only to self, confused and restless.
- Vital signs: T- 35.8°C, BP- 86/40 (MAP 55), HR-125, RR- 28, Oxygen saturation 90% (2 L n/c)

- Does she have any signs of organ failure (severe sepsis)?
 - Systolic BP < 90, MAP < 65 mm Hg
 - Change in mental status
 - RR > 20 and new oxygen requirement



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Audience Response Question

Are you ready to answer?



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Audience Response Question #7

- How would you administer fluids to this patient?
 1. Administer incremental 500 mL fluid boluses until response
 2. Administer 1000 mL fluid bolus
 3. Administer 20 mL/kg
 4. Administer 30 mL/kg
 5. Hesitate to administer fluids given new oxygen requirement and consider vasopressors instead



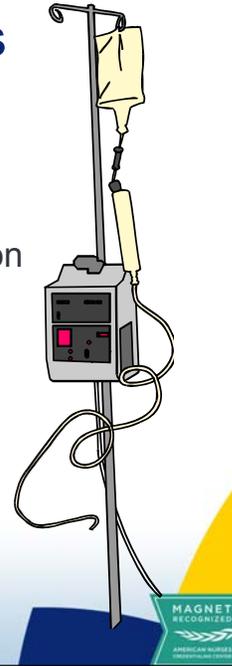
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Severe Sepsis Interventions

- Re-evaluate antimicrobials; broaden coverage if indicated
- Consider infection sources not addressed or controlled
- Supportive measures for organ dysfunction
- ↑ Lactate = hypoperfusion
 - Check central venous oxygen saturation (ScvO₂) - < 70% may be blood responsive
 - Check echocardiogram- may be dobutamine responsive
- Fluids 30 mL/kg reference/ actual weight
 - Consider more fluids
 - Consider vasopressors



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Ms. Adams deteriorates and meets criteria for septic shock

- Blood pressures persistently low with 60-70s systolic
- Heart rate 130+
- Respiratory Rate 24-28
- Cool clammy skin
- No urine output for past two hours
- Change in mental status



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Septic Shock



- Optimize anti-infective therapy
 - Change or add antimicrobials
 - More aggressive source control
 - Granulocyte transfusions
 - Immune support
- Enhance perfusion
 - Volume
 - Inotropy
 - Selective vasoconstriction
- Organ failure support
- Consider sepsis-induced adrenal insufficiency
- Consider hypothyroidism of critical illness
- Manage possible shock-induced vasopressin insufficiency



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

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, ...
Angus DC. JAMA, 2016 315(8), 801-810. doi: 10.1001/jama.2016.0287

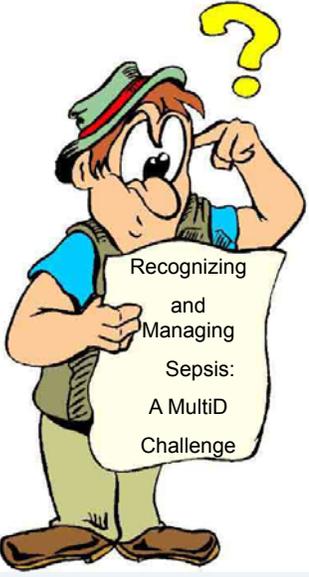
- Process
 - Task force of experts
 - Meetings
 - Delphi processes
 - Analysis of records
 - 31 organization endorsement
- Screening change
 - SOFA score increase 2 points in ICU
 - Quick SOFA (qSOFA) in non-ICU (any two)
 - RR > 22/min
 - Altered mentation
 - SBP < 100 mm Hg
- Sepsis and septic shock
 - Sepsis: life-threatening organ dysfunction
 - Septic shock: subset of sepsis patients requiring vasopressors to maintain a MAP > 65 mm Hg OR serum lactate > 2.0mmol/L in absence of hypovolemia



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Recognizing
and
Managing
Sepsis:
A MultiID
Challenge

Questions?

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 **MAGNET**
RECOGNIZED

