SEPSIS!

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Family Medicine Residency Program
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Objectives

1. Understand the Epidemiology
2. Understand how sepsis is defined
3. Understand the Pathophysiology of Sepsis & Septic Shock
4. Understand Clinical Presentation & Diagnosis
5. Understand How to Treatment
6. Know the Prognosis of Sepsis

Take Home Points

1. Early dx and tx improves outcomes
2. Early source-directed, broad-spectrum abx
3. Fluids, fluids, fluids!
4. Source Control

“Hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat.”
Niccolo Machiavelli (1469–1527)

Epidemiology

Epidemiology

Where does sepsis occur?

Globally

Little data available from developing countries

What's the yearly incidence of sepsis in the U.S?

About 750, 000 cases / yr. in the U.S. alone.

About 200,000 sepsis-related deaths / yr. in the U.S.

About 20% deaths in mild to moderate sepsis

Up to 60% in patients with septic shock.

Each sepsis case costs ~ 50,000. Total cost = 17 billion in U.S. alone.

Source:Cecil Essentials of Medicine, 9th Edition, ch 89

Question:
Infections in which organ system are the most common cause of sepsis?

Epidemiology

Most common sources of sepsis

Most Common infection Sources that cause Sepsis

- ✓ Respiratory system. Causes 50% of all cases of sepsis and septic shock.
- ✓ GU and abdominal sources are 2nd most common source.

Which microorganisms cause sepsis?

- ✓ Any microbe can cause sepsis. Bacteria, viruses, fungi, parasites, etc.
- ✓ However, bacteria are the most common.
- ✓ Of bacteria, Gram positive > Gram negative as causes of sepsis
- ✓ Pathogens often found in blood stream infections are: staph, group A strep, E. Coli, Klepsiella, Enterobacter, and Pseudomonas.

Question:
What are the risk factors for sepsis / severe sepsis?

Epidemiology

Risk Factors For Sepsis/Severe Sepsis

- ✓ **ICU patient:** "At any given moment, approximately 50 percent of ICU patients have a nosocomial infection and, therefore, are at high risk for sepsis" Uptodate.com
- ✓ **Bacteremia**: Patients with bacteremia often develop systemic consequences of infection.
- ✓ **Extremes of age:** Advanced Age (Age>65) & premature infants. Age is an independent predictor of mortality due to sepsis. 60-85% of all sepsis occurs in people 65 or older.
- ✓ **Breaks in the skin:** Pts with IV catheters, implanted devices, severe burns
- ✓ **Immunosuppression / Immunomodulation:** Things that depress host-defenses (e.g. cancers, chronic diseases. renal failure, hepatic failure, AIDS, asplenism) & immunosuppressant meds are common among patients with sepsis, severe sepsis, or septic shock.

Epidemiology

Risk Factors For Sepsis/Severe Sepsis, cont.

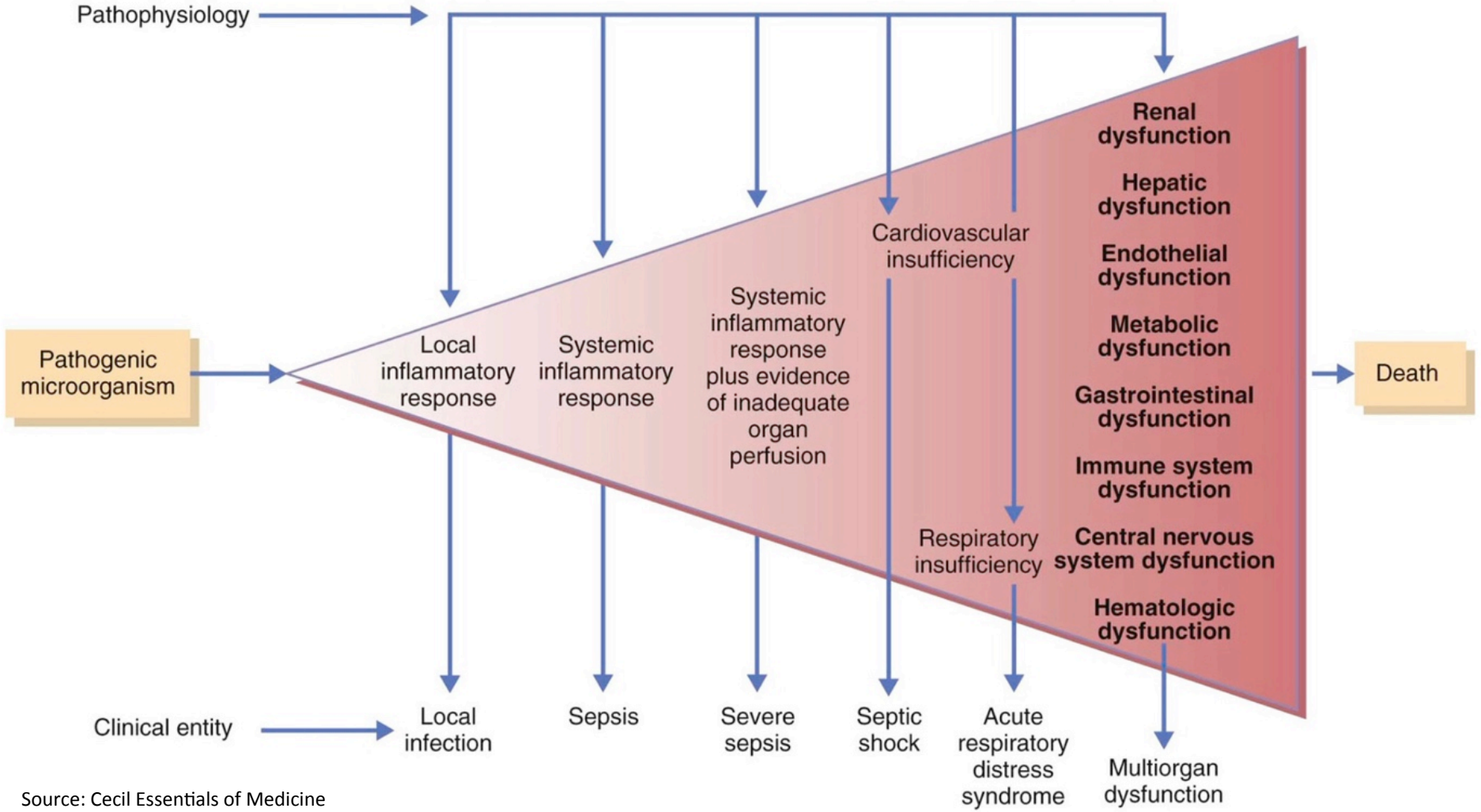
- ✓ **Diabetes and Cancer:** DM and some CA may alter the immune system > elevated risk of developing sepsis and increase risk of nosocomial sepsis.
- ✓ **Community Acquired Pneumonia:** Severe sepsis developed in about 50% of pts with CAP and septic shock developed in about 5 % of pts with CAP
- ✓ **Previous hospitalization:** Induces an altered human microbiome, particularly in pts tx with abx. Previous hosp > x3 increase in risk of developing sepsis in subsequent 90 days
- ✓ **Genetic factors increase risk of infection. E.g.** Sepsis is highest among African-American males.

MICROORGANISMS COMMONLY IDENTIFIED IN SEPTIC PATIENTS BASED ON HOST FACTORS

HOST FACTOR	ORGANISMS TO CONSIDER
Asplenia	Encapsulated organisms, particularly Streptococcus pneumonia, Haemophilus influenza, Neisseria Meningitidis, Capnocytophaga canimorsus
Cirrhosis	Vibrio, Salmonella, Yersinia species, encapsulated organisms, other gram-negative rods
Alcohol abuse	Klebsiella species, S. pneumoniae
Diabetes	Mucormycosis, Pseudomonas species, E. Coli, Group B Strep
Neutropenia	Enteric gram-negative rods, Pseudomonas, Aspergillus, Candida, Mucor species, Staphylococcus aureus, streptococcal species
T-cell dysfunction	Listeria, Salmonella, Mycobacterium species, Herpes viruses (including herpes simplex, cytomegalovirus, varicella-zoster virus)
Acquired Immune Deficiency Syndrome (AIDS)	Salmonella species, S. aureus, Mycobacterium avium complex, S. pneumoniae, Group B Strep, PCP

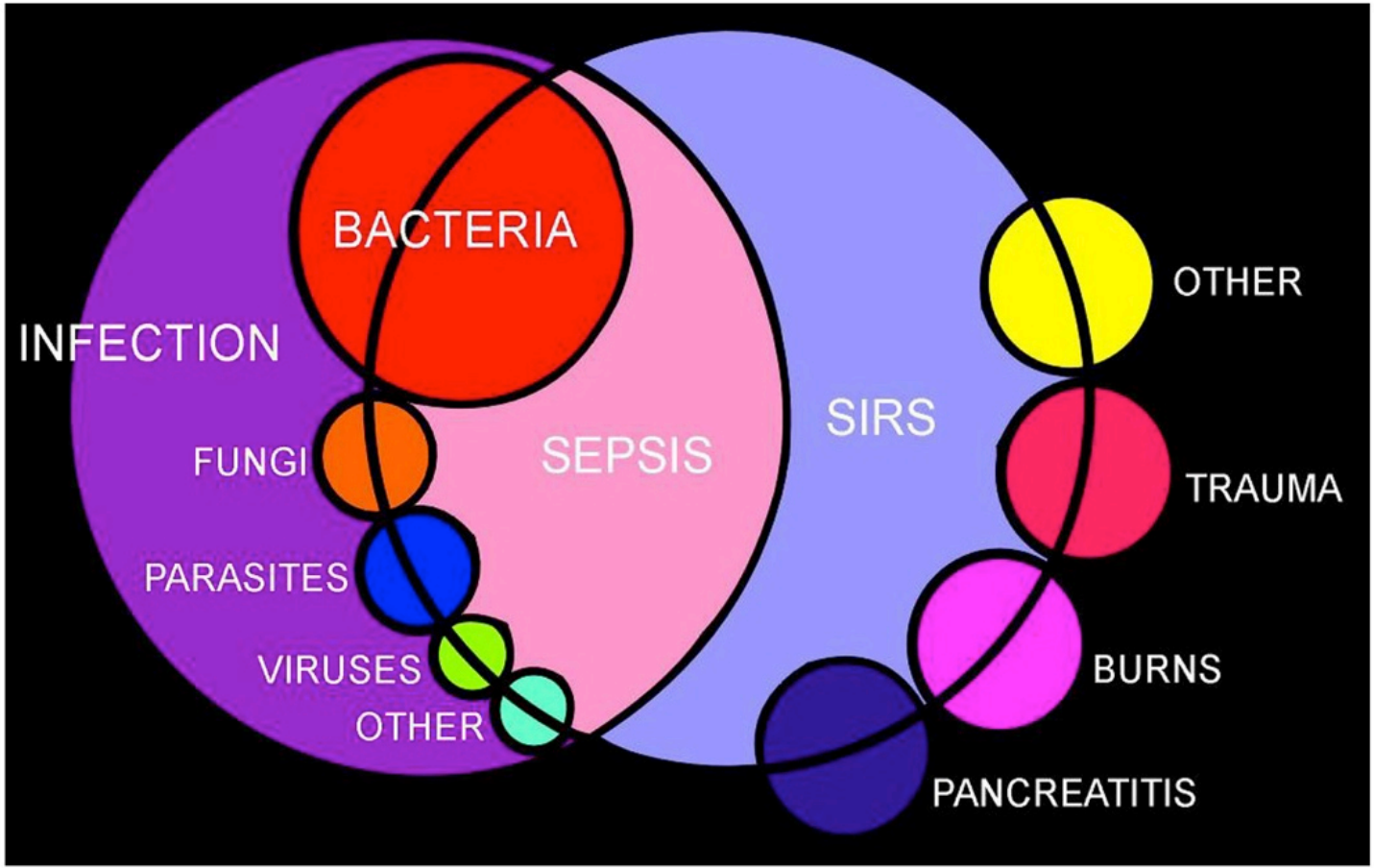
Source: Cecil Essentials of Medicine

Definition: What is sepsis?



Source: Cecil Essentials of Medicine

SIRS, INFECTION, AND SEPSIS



Source: Medscape.com

Definitions

Systemic Inflammatory Response Syndrome (SIRS)	2 or more of the following: ✓ Temp >38.3 or <36 ✓ HR>90 ✓ RR>20 or PaCo2 <32 ✓ WBC>12000 or <4000 or normal WBC with >10% bands
Sepsis	2 SIRS + confirmed or suspected infection
Severe sepsis	Sepsis + at least one sign of organ dysfunction, hypoperfusion, or hypotension. Signs of hypoperfusion may include lactate >2 mmol/L, oliguria, AMS
Septic shock	Severe sepsis + hypotension (BP <90/60) despite adequate fluid resuscitation or a serum lactate of ≥ 4.0 mmol/L
Multiple Organ Dysfunction Syndrome (MODS)	Evidence of ≥ 2 organs in dysfunction

SEPSIS STEPS

SIRS

T: >100.4 F
< 96.8 F
RR: >20
HR: >90
WBC: >12,000
<4,000
>10% bands
PCO2 < 32 mmHg

SEPSIS

2 SIRS

+

Confirmed **or** suspected infection

SEVERE SEPSIS

Sepsis +

Signs of End Organ Damage

Hypotension (SBP <90)

Lactate >4 mmol

SEPTIC SHOCK

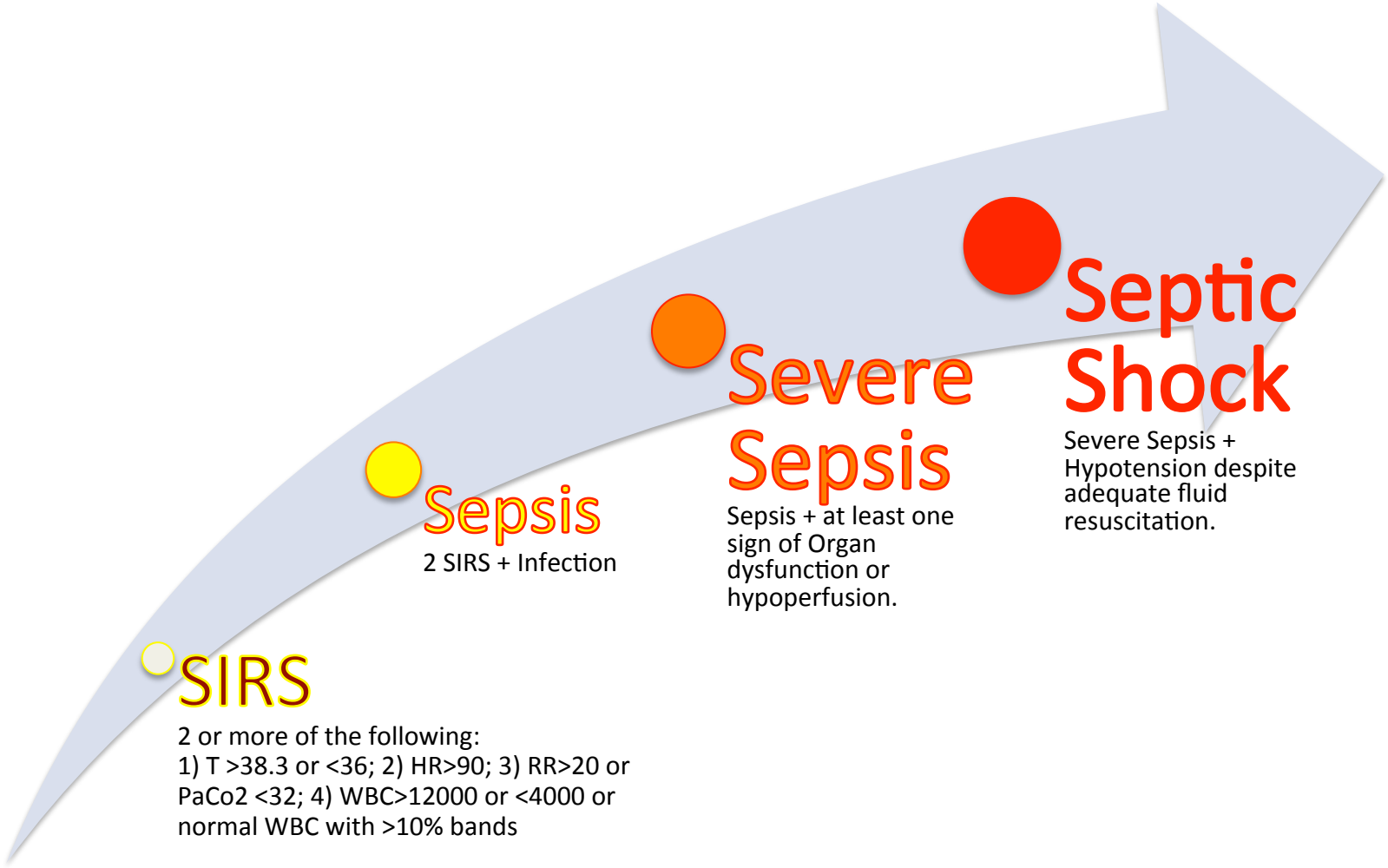
Severe Sepsis with persistent:

Signs of End Organ Damage

Hypotension (SBP <90)

Lactate >4 mmol

Slides Courtesy of Curtis Merritt, D.O.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2 or more of the following:
1) T >38.3 or <36; 2) HR>90; 3) RR>20 or PaCo2 <32; 4) WBC>12000 or <4000 or normal WBC with >10% bands
Sepsis
2 SIRS + Infection
Severe Sepsis
Sepsis + at least one sign of Organ dysfunction or hypoperfusion.
Septic Shock
Severe Sepsis + Hypotension despite adequate fluid resuscitation.

Diagnostic Criteria For Sepsis

Infection, Documented or Suspected and Some of the Following:

General Variables

- ✓ T >38.3 or <36ºC
- ✓ HR >90 beats/min or more than 2 SD above the normal value for age
- ✓ RR >20 (tachypnea)
- ✓ Altered mental status
- ✓ Significant edema or positive fluid balance (>20 mL/kg over 24 hours)
- ✓ Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Organ Dysfunction Variables

- ✓ Arterial hypoxemia (arterial oxygen tension [PaO2]/fraction of inspired oxygen [FiO2] <300)
- ✓ Acute oliguria (urine output <0.5 mL/kg/hr for at least two hours despite adequate fluid resuscitation)
- ✓ Creatinine increase >0.5 mg/dL or 44.2 micromol/L
- ✓ Coagulation abnormalities ([INR] >1.5 or [aPTT] >60 seconds)
- ✓ Ileus (absent bowel sounds)
- ✓ Thrombocytopenia (platelet count <100,000 microL–1)
- ✓ Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L)

Inflammatory Variables

- ✓ Leukocytosis (WBC count >12,000 microL–1) or leukopenia (WBC count <4000 microL–1)
- ✓ Normal WBC count with greater than 10 percent immature forms (bands)
- ✓ Plasma C-reactive protein > 2 SD above the normal value
- ✓ Plasma procalcitonin > 2 SD above the normal value

Tissue Perfusion Variables

- ✓ Hyperlactatemia (>1 mmol/L)
- ✓ Decreased capillary refill or mottling

Hemodynamic Variables

- ✓ Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or < 2 SD below normal for age)

Source: Surviving Sepsis Campaign

Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

- ✓ Sepsis-induced hypotension
- ✓ Lactate above upper limits of laboratory normal
- ✓ Urine output <0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation
- ✓ Acute lung injury with PaO2/FiO2 <250 in the absence of pneumonia as infection source
- ✓ Acute lung injury with PaO2/FiO2 <200 in the presence of pneumonia as infection source
- ✓ Creatinine >2 mg/dL (176.8 micromol/L)
- ✓ Bilirubin >2 mg/dL (34.2 micromol/L)
- ✓ Platelet count <100,000 microL–1
- ✓ Coagulopathy (INR >1.5)

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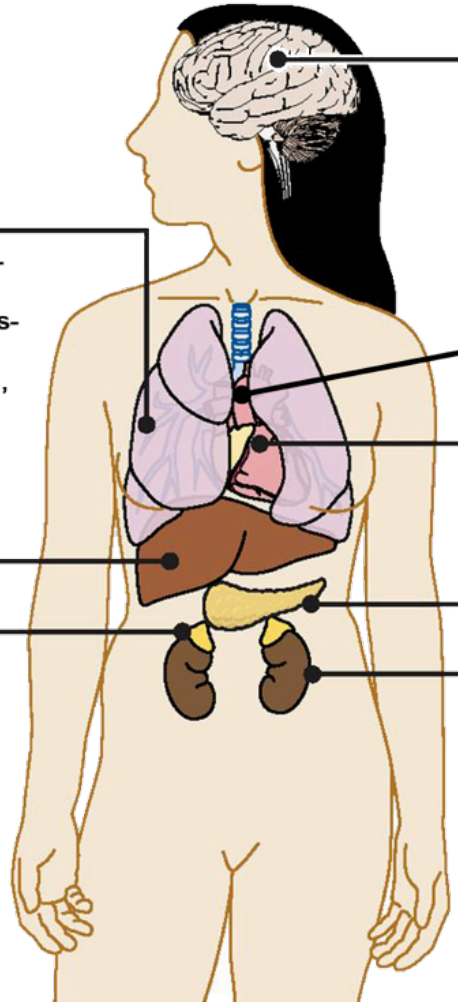
ORGAN DYSFUNCTION IN SEPSIS



CNS*
Confustion, Delirium, AMS, Cognitive loss

Metabolic
Lactate above upper limits of lab normal
Lactate >2 for DRMC & most other labs

Hematologic
INR > 1.5 or aPTT ≥ 60 secs
Platelet count < 100,000

Cardiovascular
Sepsis-induced hypotension:
SBP <90 mmHg or MAP <65 mmHg
SBP decrease of > 40 mmHg from baseline

Pancreas*
Ischemia
Decrease insulin production
Hyperglycemia

Kidneys
Cr > 2 mg/dL (34.2 micromol/L); OR
Cr increase of >0.5 from baseline; OR
UOP < 0.5ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation.

Lungs
ALI with PaO2 / FiO2 < 250 in the absence of PNA as source of infection
ALI with PaO2 / FiO2 <200 in the presence of PNA as source of infection
Edema, Diffuse alveolar damage, ALI, ARDS

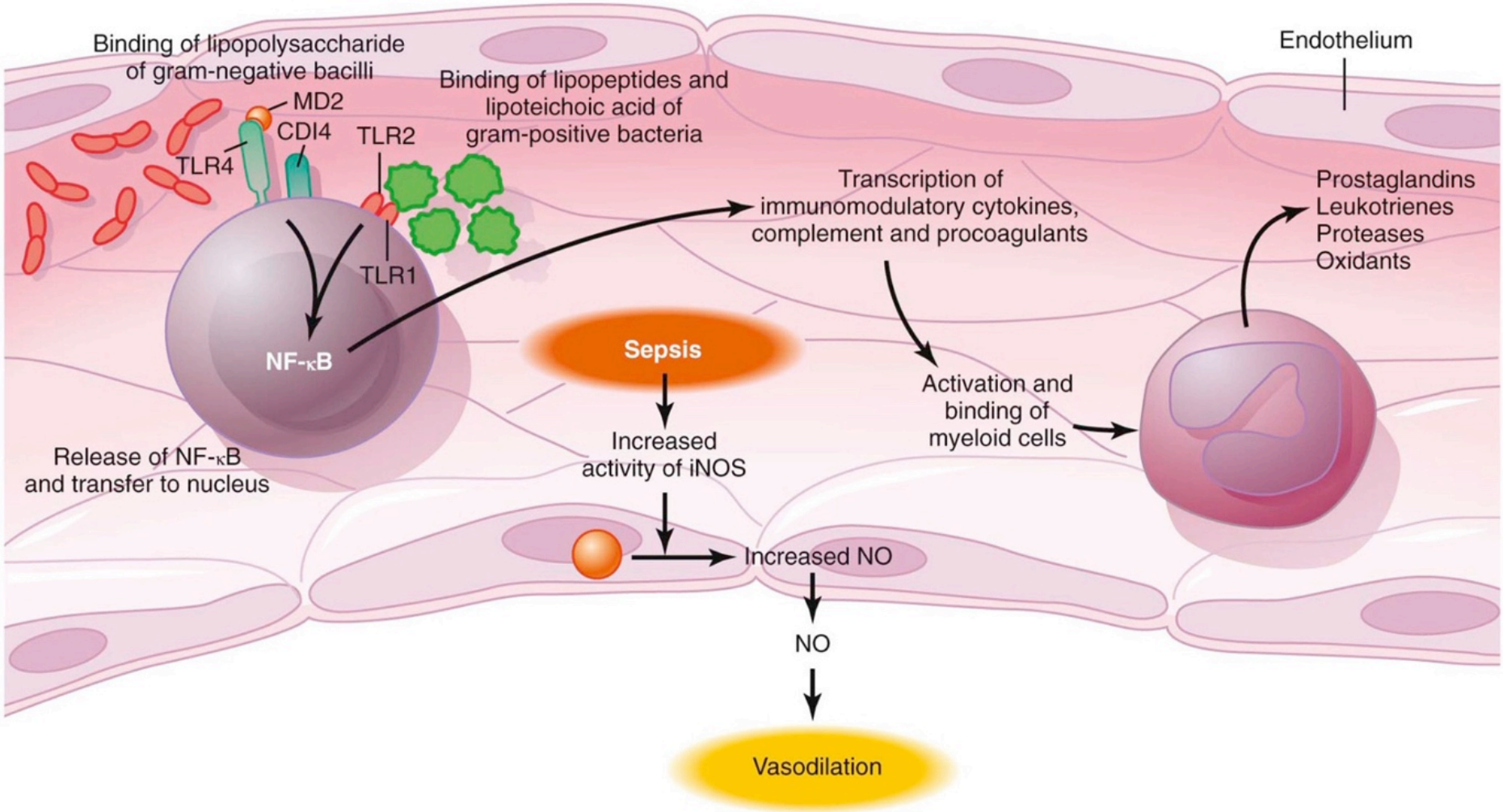
Liver
Bilirubin > 2mg/dL (34.2 mmol/L)

Adrenals*
Hemorrhage
Lipid depletion

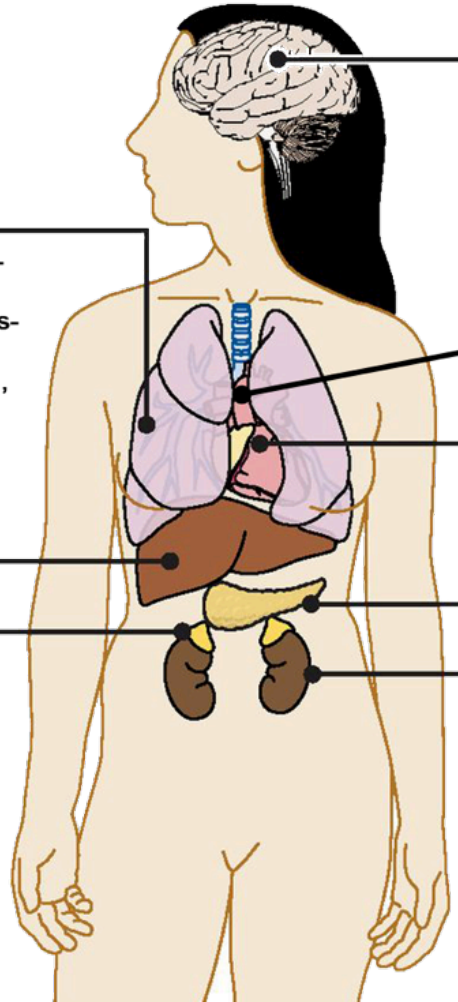
Definition: What is Sepsis?

1. Sepsis is a spectrum, not a single entity
2. Sepsis is a continuum from milder to more severe forms
3. Sepsis is not the same thing bacteremia
4. Bacteremia is the presence of viable bacteria in the blood.
5. Infection is the invasion of normally sterile tissue by organisms.

Pathophysiology of Sepsis & Septic Shock


Binding of lipopolysaccharide of gram-negative bacilli
MD2
CDI4
TLR4
TLR2
TLR1
Binding of lipopeptides and lipoteichoic acid of gram-positive bacteria
NF-κB
Release of NF-κB and transfer to nucleus
Transcription of immunomodulatory cytokines, complement and procoagulants
Endothelium
Prostaglandins
Leukotrienes
Proteases
Oxidants
Sepsis
Activation and binding of myeloid cells
Increased activity of iNOS
Increased NO
NO
Vasodilation

ORGAN DYSFUNCTION IN SEPSIS



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Clinical Presentation & Diagnosis

How do Patients with Sepsis Present Clinically & How is Diagnosis Made?

1. The Presentation depends on what stage in the spectrum the patient is.
2. Remember the risk factors and epidemiology
3. Clinical diagnosis is based on history, symptomatic assessment, nonspecific labs, and hemodynamic criteria.
4. Patients who meet general SIRS criteria "should undergo thorough and prompt evaluation for a possible infection cause, including bacterial cultures of blood and (when indicated) other body fluids."
5. Localizing s/sx should lead to PE & imaging to ID a nidus of infection.
6. Defects of natural defensive barriers e.g. transcutatneous devises or IV catheters should be assessed for infection and removed if suspected.

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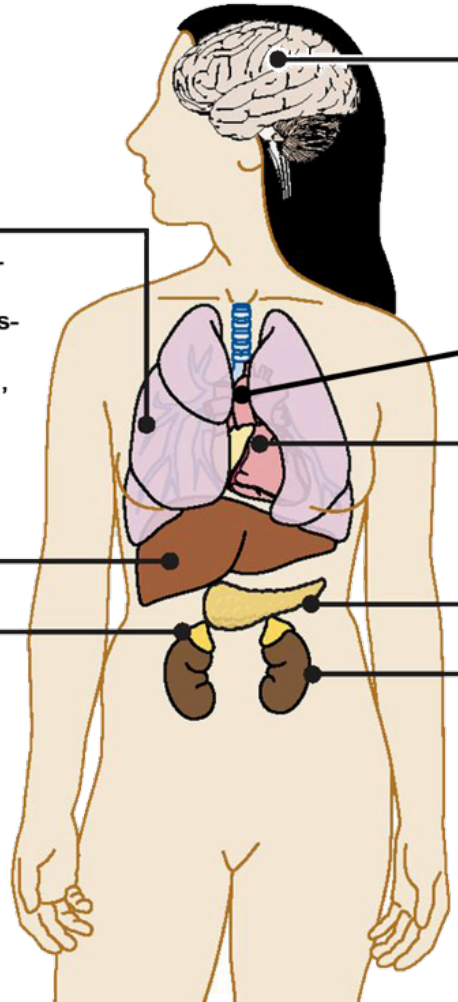

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Treatment


Surviving Sepsis
Campaign

2015 Updated SSC Bundles

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*

- ✓ Measure lactate level
- ✓ Obtain blood cultures prior to administration of antibiotics
- ✓ Administer broad-spectrum antibiotics
- ✓ Administer 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION

- ✓ Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
- ✓ In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
- ✓ Re-measure lactate if initial lactate elevated.

2015 Updated SSC Bundles

TABLE 1: DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER :

- ✓ Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- ✓ Measure CVP
- ✓ Measure ScvO2
- ✓ Bedside cardiovascular ultrasound
- ✓ Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

NB: Only the 6-hour bundle has been updated. The 3-hour SSC bundle is not affected.

SAMPLE SEPSIS PROTOCOL

Name

Hospital No

DOB

Adult Sepsis Management Pathway

(Non Neutropenic Sepsis)

Complete and Insert in Patient Notes

St Helens and Knowsley Teaching Hospitals NHS
NHS Trust

Time (Zero) Now: **Date:** **Bleep:** **Name:**

SEPSIS

Confirmed or Suspected Infection

☐ Chest ☐ Urinary ☐ CNS (Meningitis)
☐ Skin ☐ Abdomen ☐ Joint
☐ Unknown

&

At least **2 SIRS or General Variables**

☐ HR>90 ☐ T° >38° or <36°C ☐ Acute Confusion
☐ RR>20 ☐ WBC>12 or <4 ☐ Raised CRP
☐ BMs: >7.7 mmol/L in Non Diabetic

YES

Within 1st Hour of Diagnosis

☐ Lactate ☐ Stat Abx Time
☐ Antibiotic
☐ **Iv Access** ☐ **Blood Gases** ☐ **CXR**
☐ **Blood Cultures** – 2 sets (Ideally Prior to antibiotic administration)
☐ **Bloods**: FBC / U&E / LFTs / CRP / INR / BMs
☐ **BP**: Aim for urine output (UOP) of > 0.5ml / kg / hr
☐ **Oxygen**: Aim for SATS 88-92 in type 2 Respiratory failure or COPD and 94-98 in others ☐ **Hourly MEWS**

Now Check Below for any signs of Severe Sepsis

SEVERE SEPSIS

Any Features of Severe Sepsis? (i.e. End Organ Dysfunction)

Mortality 20 - 35%

☐ Lactate > 2
☐ Creatinine > 177 µmol/L or
☐ Creatinine of > 45 µmol/L over baseline
☐ Oliguria <0.5mls/kg/hr for >2hrs
☐ Altered Mental State
☐ Platelets<100
☐ BP Low<90 systolic
☐ Bilirubin>35 µmol/L
☐ INR>1.5
☐ Hypoxia pO2<8.0

YES → **to be reviewed by SpR / Cons**

NO → **Observe Hourly Inform Senior if NOT improving**

Within 3 hrs of Diagnosis

☐ **Ensure** all above steps have been Completed **And**
☐ **Source Control**
☐ Consider **Urinary Catheterisation** △ Infection Risk
☐ **Fluid Resuscitate** with either Saline or Hartmans.
☐ Unless CCF / HF give 1st Litre as Stat and fluid boluses **30mls/kg/hr** of Crystalloid or equivalent if Hypotensive or Lactate > 4mmol / L
☐ **Repeat Lactate** in 1hr ☐ **Half Hourly MEWS**
☐ Refer to ITU / Critical Care if Lactate Not improving or deteriorating

Now Check Below for any signs of Septic Shock

SHOCK

Septic Shock

Mortality Very High 40-60%

As above and Profound Hypotension (BP less than 90 Systolic)
Hypotension Resistant to Fluid Challenges

☐ **Ensure all above steps have been Completed** &
☐ **Urgent referral to ITU / Critical Care**
☐ **Continue with aggressive Fluid Resuscitation**
☐ **Consider Central Venous Access**
☐ **Urinary Catheterisation**
☐ **15 min MEWS**

Treatment

- ✓ Early diagnosis and treatment of sepsis improves outcomes and decreases mortality. Time is Life!
- ✓ Treatment of the infection is the #1 cornerstone of sepsis tx.
- ✓ Three key components of antibiotic treatment are:
  - ✓ Right time: EARLY abx tx. Delaying them increases the risk of death.
  - ✓ Right antibiotic: Using the wrong abx = Delaying tx. Use source-directed broad-spectrum abx & de-escalate later when ID & susceptibility are known.
  - ✓ Right way: The correct dose & correct route (IV) matter.

Treatment

- ✓ Source Control is crucial
- ✓ Fluids, Fluids, Fluids is the #2 cornerstone of sepsis tx
- ✓ Patients with septic shock should be transferred to the ICU

INITIAL ANTIBIOTIC RECOMMENDATIONS FOR ADULT PATIENTS WITH SEPSIS

INDICATION	RECOMMENDED DOSAGES*
Empirical coverage (source unknown)	Vancomycin 15mg/kg q12h plus piperacillin-tazobactam[#a] 3.375g IV q6h or imipenem 0.5g IV q6h or meropenem 1.0 g IV q8h with or without an aminoglycoside (e.g., tobramycin 5mg/kg IV q24). [#b]
Community acquired Pneumonia (CAP)	Ceftriaxone 1g IV q24h plus azithromycin 500mg IV q24h or a fluoroquinolone (e.g. moxifloxacin 400mg IV q24h or levofloxacin 750mg IV q24h) [#c]
Community acquired urosepsis	Piperacillin-tazobactam 3.375g IV q6h or ciprofloxacin 400mg IVq12h
Meningitis	Vancomycin 15mg/kg IV q6h plus ceftriaxone 2g IV q12h plus dexamethasone 0.15mg/kg IV q6h x 2-4 days, preferably before antibiotics; add ampicillin 2g IV q4h if Listeria is suspected.
Nosocomial Pneumonia	Vancomycin 15mg/kg q12h plus piperacillin-tazobactam 4.5g IV q6h or imipenem 0.5mg IV q6h or meropenem 1g IV q8h or cefepime 2g IV q8h plus an aminoglycoside (e.g. amaikacin 15mg/kg IV q24h or tobramycin 5-7mg/kg IV q24h) or levofloxacin 750mg IV q24h. Some authorities substitute linezolid 600mg IV q12h for Vancomycin if MRSA is a significant concern or know to be the cause.
Neutropenia	Cefepime 2g IV q8h; add Vancomycin 15mg/kg IV q12h if a central line is present and infection is a concern. Add antifungal coverage with caspofungin 70mg IV x 1, then 50mg IV q24h if fever persists ≥ 5 days. For suspected or proven invasive aspergillosis, voriconazole 6mg/kg IV q12h should be used.
Cellulitis and Skin Infections	Vancomycin 15mg/kg IV q12h. Add piperacillin-tazobactam 3.375 IV q6h in diabetics and immunocompromised patients. If necrotizing fasciitis is suspected, add clindamycin 900mg IV; surgical debridement is crucial.

* Assumes normal renal function; dose adjustment are required with impaired creatinine clearance.
#a Substitute aztreonam 2g IV q8h if patient is allergic to penicillin
#b Monitor drug levels of aminoglycosides (i.e. peak and trough)
#c Substitute Cefepime or a cabapenem and azithromycin ± an aminoglycoside if the patient has severe CAP or health-care associated pneumonia

Prognosis

Prognosis

- ✓ Prognosis is bad in spite of medical advances.
- ✓ Risk of mortality depends on many patient specific factors.
  - ✓ 20 to 30% in healthy adults
  - ✓ ≥ 80% in elderly, immunocompromised patients and those with significant chronic medical comorbidities.
- ✓ Risk of mortality increases if patient is poorly managed.

Sepsis-3: New Definition

1. JAMA, 2/23/16
2. Sepsis = evidence of infection plus life-threatening organ dysfunction
3. SIRS criteria are eliminated

Objectives

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Questions?

SEPSIS!

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