Syndromes in the ICU that Infectious Disease Physicians Should Know

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Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or "None"

Exam Blueprint: Critical Care Topics ~8-10%

- Critical Care Medicine
- Systemic inflammatory response syndrome (SIRS) and sepsis
- Ventilator-associated pneumonias
- Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])
- Bacterial pneumonias
- Viral pneumonias
- Hyperthermia and hypothermia
- E-cigarette or vaping product use–associated lung injury (EVALI)

Medical Content Category	% of Exam
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
Internal Medicine and Non-Infectious Syndromes	18%
	100%

Question #1

What proportion of patients in the ICU develop fever during their stay?

A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

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E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

Extreme Hyperpyrexia (T>41.5C)

All Potential Medical Emergencies

Heat Stroke

- Lack of hydration and/or inability to sweat
  - Exertional (football player in August)
  - Non-exertional (Elderly)

Drugs

- Cocaine, amphetamines, ecstasy, anti-parkinson, beta blockers, antipsychotics, anti-depressants, calcium channel blockers, etc.

Three Specific Syndromes You Should Recognize

Question #2

- You are called to the PACU to see a 29-year-old previously healthy male with a fever of 41.6°C who is 1 hour post-op from an arthroscopy for a rotator cuff injury.
- He initially did well post operatively except for some nausea that was treated.
- The patient is somnolent, flushed, diaphoretic, and rigid. His blood pressure has risen from 130/70 to 180/100 but is now dropping.
- He is given one ampule of Narcan but does not respond.

Which of the following would you give to reverse this syndrome?

A. Antihistamines
B. High-dose corticosteroids
C. Dantrolene
D. IVIG
E. Dilantin

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Malignant Hyperthermia

- **Syndrome – Rare (~700 cases/year) but 5-10% mortality**
  - Early signs: Steep rise in CO2, tachycardia, tachypnea, muscle rigidity/contraction (masseter spasm)
  - Late signs: Hyperthermia, acidosis, hyperkalemia, cardiac arrythmias
- **Genetic defect in the RYR1 or (less commonly) CACNAS1S gene**
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (Excessive calcium accumulation)
- **Triggers**
  - **Classic: Volatile anesthetics (halothane, sevoflurane, desflurane), succinylcholine**
  - **Usually < 1 hour after trigger (up to 10 hours)**
- **Management—Usually By Anesthesiologist/Intensivist**
  - Dantrolene-
    - **Muscle relaxant-inhibits calcium ion release necessary for muscle contraction**

Neuroleptic Malignant Syndrome (NMS)

- **Frequent trigger = haloperidol**
  - Any “neuroleptic” (antipsychotic)
  - Lead pipe rigidity
  - Antiemetics such as metoclopramide
  - Withdrawal of antiparkinson drugs (L dopa)
- **Onset variable: 1-3 days/within first 2 weeks**
  - Time of drug initiation
  - When dose changed
- **Management**
  - Dantrolene or
    - (Administer for up to 10 days)
  - Dopamine agonists (bromocriptine and others)

Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

What to Look for on the Exam

	Malignant Hyperthermia	NMS	Serotonin Syndrome
Trigger	Succinylcholine or inhaled halogenated anesthesia	Withdrawal of L Dopa in Parkinsons or Neuroleptic Drugs	SSRIs, Antiemetics, Linezolid, Lithium, Street Drugs
Onset	Rapid onset in perioperative period **(usually 1 hr)**	Subacute over **1-3 days**	**6-24 hours** of starting a drug or increasing dose
Exam	Masseter spasm, Lead pipe rigidity	Mental status change with dysautonomia, catatonia, mutism, stupor, coma	Shivering, myoclonus, n/v/d, hyper-reflexia, flush skin
Labs	Severe hypercarbia, **rhabdomyolysis**	**CK rise, rhabdomyolysis**	Nothing classic

Hypothermia: <35°C

- **Causative Drugs**
  - Beta blockers (metoprolol)
  - Alpha blockers (clonidine)
  - Opioids
  - Ethanol
  - Antidepressants
  - Antipsychotics
  - Aspirin
  - Oral hypoglycemics
- **Syndrome**
  - Hypotension due to fluid shifts
  - Consider adrenal or thyroid insufficiency
- **Treatment**
  - "ABC"s
    - Airway, Breathing, Circulation
  - Rewarming

*Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour

Question #3

- You are called to the medical ICU to see a 47 y/o woman with alcoholic cirrhosis
- Admitted 3 days ago for encephalopathy after missing lactulose doses
  - On HD#3 developed low grade fever, ARDS and Shock due to aspiration
    - Started on vancomycin and piperacillin-tazobactam
  - Daily fevers to 38.5°C and a persistent low-dose levophed requirement
    - Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
    - Micro: all cultures negative at 48 hours
    - Radiology: Chest Xray unchanged, Abdominal CT non-diagnostic

Which of the following would most likely contribute to reversal of shock and reduced time in ICU?

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B. Add antifungal therapy
C. Stress dose corticosteroids
D. Dantrolene
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Acute Adrenal Insufficiency

- Patients with chronic adrenal insufficiency typically have normal or low body temperature
- Fever can occur during adrenal crisis, in the absence of infection:
  - Mechanism: the loss of cortisol's suppressive effect on inflammatory cytokines leading to fever and other systemic symptoms
  - Therapy:
    - Hydrocortisone 100mg bolus followed by 240mg/24 hrs in 4 doses or contin infusion
    - Rapid fluid resuscitation: Normal Saline: 1000 ml initially and then PRN
    - Management of glucose and electrolytes

Differential Diagnosis of Shock

Ohm's Law

$$MAP = CO \times SVR$$

Cardiogenic (flow)
- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)
- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- Adrenal insufficiency

Question #4

A patient with end stage renal disease on dialysis through a tunneled hemodialysis catheter is admitted to the medical ICU with altered mental status, hypotension (BP 80/50 mmHg), and fever.
- On exam he has obvious purulence at the catheter site.
- The line is replaced to a different site
- The patient is given a single initial bolus dose of vancomycin and a single initial bolus dose of piperacillin-tazobactam.

Which of the following is an evidence-based intervention to improve survival?

A. Serial lactate measurements q-1-h to assess adequacy of resuscitation
B. Serial procalcitonin levels to determine adequacy of antimicrobial regimen
C. Serum Beta D Glucan to determine whether micafungin should be added to initial antimicrobial regimen
D. Prolonged infusion of subsequent doses of piperacillin-tazobactam
E. Continuous (24 hr/day) infusion of vancomycin

Question #4

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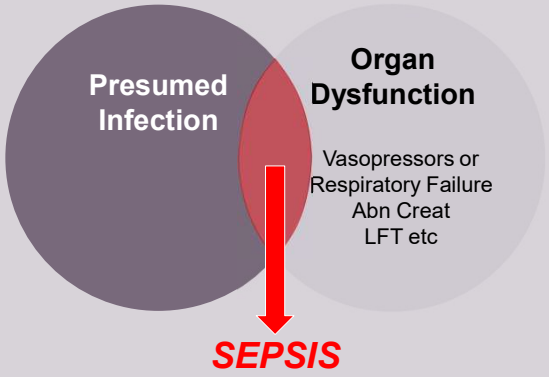
Question #4: Rationale

- Answer: Prolonged infusions of beta lactam drugs
- A meta-analysis has reinforced the 2021 Surviving Sepsis recommendation for prolonged infusion of beta lactam drugs compared to intermittent boluses
  - Reduction in short-term mortality
  - Increase in days alive out of the ICU and out of the hospital

Abdul-Aziz MH, et al.. JAMA. 2024;332(8):638-648

Definition of Sepsis



Surviving Sepsis Guideline Recommendations: What Do You Need to Know

- Few recommendations based on strong evidence
- Most ID related recommendations are common sense

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- **Mean Arterial Pressure >65 mm Hg by continuous monitoring**
  - Invasive or non-invasive
- **Timing of Antibiotics**
  - Septic Shock-Within 1 Hour
  - Sepsis without Shock-Within 3 Hours
- **Blood cultures before antibiotics**
- **Pathogen Specific Rapid Diagnostic Tests**
  - Multiplex nucleic acid amplification tests to identify blood culture isolates
  - Nucleic acid amplification tests to identify antibiotic resistance genes in blood culture isolates

*With a few modifications!

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- **Norepinephrine as Pressor of Choice**
  - Add Vasopressin if inadequate response
- **Prolonged infusion of beta-lactams for maintenance----Not initial dose**
  - Higher efficacy for organisms with higher MICs-suspected or confirmed
  - Especially for antipseudomonal beta lactams e.g. piperacillin-tazobactam, meropenem,, cefepime, ceftolozane-tazobactam. Ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol
- **Crystalloids for Resuscitation (e.g., Ringers Lactate) rather than Normal Saline**
- **PK/PD monitoring for selected antimicrobials**
- **Hydrocortisone for severe community acquired pneumonia**
- **Hydrocortisone for septic shock**
  - Shock reversal better documented than survival benefit

*With a few modifications!

Surviving Sepsis Guidelines* (2021 and 2026)
Strong Recommendations – Potentially Testable

- O2 Saturation Target: 90-96%
- Proton pump inhibitor if risk for stress ulcer bleeding
- Early enteral feeding (within 72 hours)
- Insulin therapy if glucose >180 mmols/L
- Venous thromboembolic prevention with low mol wt Heparin

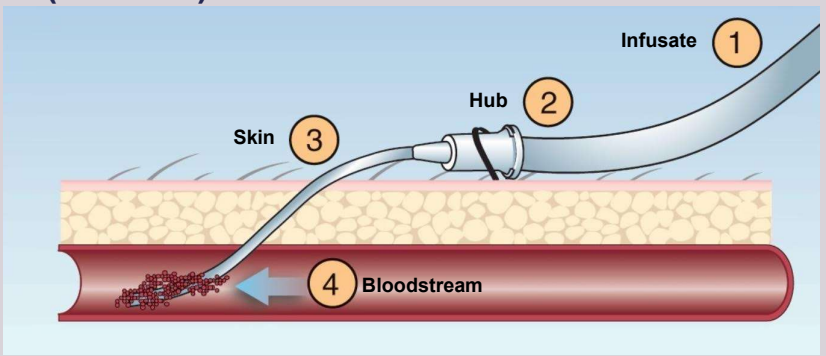
Watch For Questions About De-Escalation of Antimicrobials

- Use culture results to narrow spectrum
- Consider "shorter" courses if clinical response good and no major risk factors for poor outcome

Severe Community Associated Pneumonia Remember Therapy for Pseudomonas

- For severe CAP, if risk factors for Pseudomonas infection are present
  - CD4 count ≤50 cells/mm3, or Neutropenia, preexisting lung disease, use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in nursing home, chronic hemodialysis
- Treat with antipseudomonal beta-lactam (Mero, Pip Tazo, Cefepime) plus
  - Either ciprofloxacin (400 mg every 8 hours) or levofloxacin (750 mg/day)
- Treat with anti-MRSA agent
  - Only if risk factors present (e.g. influenza, recent antibiotics) and/0r
  - Nasal swab MRSA positive

Catheter Related Blood Stream Infection (CLABSI)



Antiseptic Techniques: Catheter Insertion
(See Michael Klompas Lecture)

Hand Hygiene	• **Soap/water or alcohol-based rub before/after insertion** • **Sterile gloves while inserting**
Skin Prep	• **Chlorhexidine solution before insertion and during dressing changes** • **Allow to fully dry before insertion**
Barrier	• **Maximum barrier protection: cap, mask, sterile gown, sterile gloves and full sterile drape**

CID 2011:52 (1 May)

Remove the Catheter!

- **On the Board Exam**
  - It's almost never wrong to remove/replace catheter
- **Syndromes Requiring Removal**
  - Septic shock
  - Septic thrombophlebitis/Venous obstruction
  - Endocarditis
  - Positive blood cultures>72 hrs after appropriate abx
- **Organisms Requiring Removal**
  - Staph aureus
  - Atypical mycobacteria
  - Candida species
  - Cutibacterium acnes
  - Pseudomonas aerug
  - Bacillus species
  - Malassezia
  - Micrococcus

Antimicrobial Lock Therapy & Impregnated Catheters

Catheter salvage: for long-term catheter CRBSI with line retained → antibiotic lock + systemic therapy ×10–14 days

Best evidence for uncomplicated CoNS; still remove line for S. aureus, PsA, or Candida

Prevention: prophylactic antimicrobial lock for long-term catheters with recurrent CRBSI (e.g. hemodialysis)

Antimicrobial-impregnated catheters: consider when CLABSI rates stay high despite basic prevention

Mermel et al., CID. 2009
Buetti et al., Infect Control Hosp Epidemiol. 2022

Life Threatening Rashes/Exfoliation

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Rash Characteristics	Erosive mucositis of oral, urogenital, and ocular sites SJS: <10% BSA; TEN: >30% BSA (body surface area)
Onset	4-28 days after drug exposure
Other Features	Fever, partial or full thickness injury with painful necrolysis, pulmonary and GI manifestations
Lab Findings	Leukopenia, no eosinophilia
Risk Factors	Anticonvulsants, infection (mycoplasma), GVHD, HIV
Treatment	Withhold offending agent, supportive care Steroids and IVIg are controversial

Stevens Johnson and Toxic Epidermonecrolysis



- "Positive Nikolsky sign"
  - Slight rubbing of the skin results in exfoliation of the outermost layer
  - NOT specific for Stevens Johnson and TEN
    - Staph scalded skin syndrome (mostly children, no mucosal involvement)
    - Pemphigus
    - Graft vs Host
    - Paraneoplastic syndromes

DRESS: Morbilliform Rash with Facial Edema and Eosinophilia


DRESS (Drug Induced Hypersensitivity Syndrome)

Rash Characteristics	Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement
Onset	1-3 (up to 6) weeks after drug exposure
Other Features	Fever, Lymphadenopathy, other organ involvement in 80% (liver, kidney, pancreas, heart, lung) Herpesviridae reactivation (HHV6)
Lab Findings	Eosinophilia, lymphocytosis/lymphopenia, atypical lymphs
Classic Meds	Anticonvulsants (esp. lamotrigine), Vancomycin, Raltegravir, Dapsone, other Sulfas, anti-TB RIPE
DDx	Mycoplasma, viral hepatitis, mononucleosis, SLE
Treatment	Withhold offending agent, supportive care Controversial: Steroids, CsA, IVIg. Mortality is high

Acute Generalized Exanthematous Pustulosis (AGEP)

- Acute diffuse pustular skin eruption starting on face
  - T cell-mediated neutrophilic inflammation
  - Arises suddenly hours or days after initiating new drug
    - Starts on face and spreads to extremities with facial edema
    - Fever, mild leukocytosis and eosinophilia
    - Mucosal involvement unusual
  - Often caused by antimicrobials
    - Often: Sulfonamides, Chloroquine, Ampicillin, Quinolones
    - Occasionally: Mycoplasma, Viruses
- Treatment
  - Supportive +/- Corticosteroids

Febrile Exanthematous Drug Eruptions

SJS/TEN	AGEP	DRESS
• Severe blistering • Mucosal involvement	• Pustular lesions • Rare Mucosal	• Facial edema • Rare mucosal • Eosinophilia
• Fever	• Fever	• Fever
• Steroids • IVIG controversial	• Steroid rx controversial	• Steroid rx controversial
• SJS: <10% BSA • TEN: >30% BSA	• Common ddx: psoriasis	• > 50% BSA

Erythema Multiforme: Rarely Life Threatening

- Immune mediated
- Distinctive target lesions that are usually asymptomatic
  - Febrile prodrome in some cases
- Often associated with oral, ocular, and genital mucosal lesions
- Less severe than DRESS or SJS or TEN
- Causes: Infection > Drugs
  - Infections: HSV, Mycoplasma, many others
  - Cancer, autoimmune, drugs, etc.
- Self Limiting in 10-14 days




Two Topics Specifically Mentioned on ABIM ID Blueprint

Near Drowning/Submersion Injuries

- Prophylactic Antibiotics
  - Not indicated unless water grossly contaminated
  - Steroids not indicated
- Etiologic Agents
  - Water borne organisms common
    - Pseudomonas, Proteus, Aeromonas
- Therapy for Pneumonia
  - Directed at identified pathogens

E-cigarette or Vaping Product Use Associated Lung Injury (EVALI)

- Primarily associated with e-cigarettes and vaping products, particularly THC-containing compounds
- Clinical presentation similar to community acquired pneumonia
- Exact cause believed to be related to direct lung injury → inflammatory response
- Treatment: supportive care, cessation of e-cigarette use

MMWR. 2019;68(46):1076

Summary: What To Look For on Exam

- **Hyper-pyrexia syndrome**
  - Use of dantrolene
- **Prevention of CLABSI, VAP, UTI, Surgical wound infection**
  - See Klompas lecture
- **Apparent Septic Shock**
  - Non-infectious cause-adrenal insufficiency, thyroid storm, anaphylaxis, neurogenic
- **Management of Septic Shock**
  - Time to antibiotics
  - Prolonged infusion of beta lactams
- **De-escalation of Antibiotics**
  - Based on culture results or MRSA screening
- **E-cigarette and pulmonary infiltrates**
- **Near Drowning**
  - Use of antibiotics for prophylaxis or therapy

Thank You

- Good luck!
- Please give feedback
- Contact
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  - Twitter/X: @TaisonBell (but don't bother)