

32 – Syndromes in the ICU that ID Physicians Should Know

Speaker: Taison Bell, MD



Syndromes in the ICU that Infectious Disease Physicians Should Know

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• Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question 1: What proportion of patients in the ICU develop fever during their stay?

- A. Less than 5%
- B. Between 15-25%
- C. Over 50%
- D. Everyone. Absolutely everyone

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 2

- You are asked to see a 35 year-old woman with a history of seizure disorder admitted to the ICU with a fever to 40°C, hypotension, and a maculopapular rash
- She is being empirically treated with vancomycin and piperacillin-tazobactam. Blood, urine, and sputum cultures (taken prior to antibiotic initiation) are negative
- Exam: Tachycardia with otherwise normal vital signs. Diffuse maculopapular rash with facial edema and sparing of the mucosal surfaces
- Labs are notable for elevated AST/ALT and peripheral eosinophilia
- Only home medication is lamotrigine, which was started two weeks prior to admission

Her clinical syndrome is most consistent with:

- A. Sepsis
- B. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
- C. DRESS (drug-induced hypersensitivity syndrome)
- D. Erythema Multiforme
- E. Neuroleptic Malignant Syndrome (NMS)

Morbilloform Rash with Facial Edema and Eosinophilia



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DRESS (drug-induced hypersensitivity syndrome)

| | |
|-----------------------------|---|
| Rash Characteristics | Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement |
| Onset | Usually 1-3 (up to 6) weeks after drug exposure |
| Other Features | Fever, LAD, other organ involvement in 80% (liver, kidney, pancreas, heart, lung), expansion of CD4/8 T cells → Herpesviridae reactivation (HHV6) |
| Lab Findings | Eosinophilia, lymphocytosis/lymphopenia, atypical lymphocytes |
| Classic Meds | Aromatic AEDs (highest with lamotrigine), Vancomycin, Raltegravir, Dapsone and other Sulfas, anti-TB RIPE |
| DDx | SLE, mycoplasma, viral hepatitis, mononucleosis |
| Treatment | Withhold offending agent, supportive care Steroids, CSA, IVig are controversial. Mortality is high |

Exanthematous drug eruptions

- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

| SJS/TEN | AGEP | DRESS |
|---|---|--|
| <ul style="list-style-type: none"> • Severe blistering • Mucosal involvement common • SJS: <10% BSA • TEN: >30% BSA | <ul style="list-style-type: none"> • Rapidly spreading (hours) pustular lesions • Mucosal involvement rare • Common ddx: psoriasis | <ul style="list-style-type: none"> • > 50% BSA • Facial edema • Infrequent mucosal involvement • Eosinophilia |

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

| | |
|-----------------------------|--|
| Rash Characteristics | Erosive mucositis of oral, urogenital, and ocular sites SJS: <10% BSA; TEN: >30% BSA |
| 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 | Aromatic AEDs, infection (mycoplasma), GVHD, HIV |
| Treatment | Withhold offending agent, supportive care Steroids and IVig are controversial |


Stevens Johnson and Toxic Epidermonecrosis



- “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
 - Others

Erythema Multiforme

- 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



Extreme Hyperpyrexia (T>41.5C)

- Heat Stroke
 - Exertional (football player in August)
 - Non-exertional (Elderly)
 - Lack of hydration and/or inability to sweat
- Drugs
 - Cocaine, ecstasy etc.
- The Pyrexia Syndromes

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Question 3

- You are called to the PACU to see a 29-year-old previously healthy male with a fever of 41.6°C who is 4 hours 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?:

- Antihistamines
- High-dose corticosteroids
- Dantrolene
- IVIG
- Dilantin

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 arrhythmias
- Genetic defect in the RYR1 or (less commonly) CACNAS1S gene
 - Ca⁺⁺ transport in skeletal muscle
 - Autosomal dominant
 - (excessive calcium accumulation)
- Triggers
 - Usually < 1 hour after trigger (up to 10 hours)
 - Classic: Volatile anesthetics (halothane, sevoflurane, desflurane), succinylcholine

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
 - (direct muscle relaxant for up to 10 days)
 - Dopamine agonists (bromocriptine and others)

Serotonin Syndrome

| Clinical Characteristics of Serotonin Syndrome | |
|--|--|
| Pathogenesis | Excess Serotonergic Activity <ul style="list-style-type: none"> Therapeutic drugs, drug interactions, self poisoning |
| Triggers | <ul style="list-style-type: none"> Linezolid = MAO inhibitor SSRI inhibitors (Bupropion) Antiemetics (Granisetron) Tricyclic antidepressants (amitriptyline) |
| Clinical Manifestations | <ul style="list-style-type: none"> Acute onset (within 24 hrs of new drug/drug change) Hyper-reflexive-bradylreflexia Nausea, vomiting, diarrhea, tremors followed by shivering |
| Treatment | <ul style="list-style-type: none"> 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 | 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, myoglobinemia | 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
 - *Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour
 - Consider adrenal or thyroid insufficiency
- Treatment
 - Rewarming
 - "ABC's"
 - Airway, Breathing, Circulation

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Question 4

- You are called to the medical ICU to see a 47 y/o woman with a history of alcoholic cirrhosis with ARDS and shock
- Initially admitted to general medicine for encephalopathy in the setting of skipping lactulose doses
- On HD#3 developed ARDS, thought to be from aspiration
- Subsequently goes into distributive shock. Started on vancomycin and piperacillin-tazobactam
- Patient has daily fevers to 39°C and a persistent low-dose levophed requirement
- Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
- Micro: blood, urine, sputum, and ascitic fluid are benign
- Radiology: CXR with unchanged b/l multifocal opacities, RUQ USG benign, Abd CT benign

Which of the following would you give?:

- Broader spectrum antibacterial treatment
- Stress dose corticosteroids
- Dantrolene
- IVIG
- Antifungal therapy

Differential Diagnosis of Shock

Ohm's Law $\overline{\overline{\overline{\quad}}}$

$$MAP = CO \times SVR$$

Cardiogenic (flow)

- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)

- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- Adrenal insufficiency

Why not empiric antifungal? EMPIRICUS

- Multi-center RCT of 260 Adults in ICU
- Non-neutropenic
- Multorgan failure
- ICU-acquired sepsis
- On MV at least 5d
- At least 4d broad spectrum Abx in prior week
- Multifocal candida colonization

| | Micafungin | | Placebo | | Hazard Ratio (95% CI) | Favors | Favors | P Value |
|------------------------------------|-------------------------|-----------|-------------------------|-----------|-----------------------|------------|---------|---------|
| | Survived at Day 28, No. | Total No. | Survived at Day 28, No. | Total No. | | Micafungin | Placebo | |
| All patients | 87 | 128 | 74 | 123 | 1.35 (0.87-2.08) | | | 18 |
| SOF6 score | 51 | 66 | 52 | 68 | 1.11 (0.53-2.33) | | | 78 |
| >8 | 36 | 42 | 33 | 55 | 1.09 (0.96-1.24) | | | 07 |
| Admission category | | | | | | | | |
| Surgical | 22 | 34 | 18 | 31 | 1.56 (0.87-2.70) | | | 64 |
| Medical | 65 | 94 | 56 | 92 | 1.43 (0.83-2.50) | | | 20 |
| Colonization index >0.5* | 68 | 101 | 58 | 99 | 1.35 (0.84-2.17) | | | 22 |
| Corrected colonization index (CI)† | 52 | 76 | 45 | 80 | 1.52 (0.87-2.63) | | | 14 |
| Candida score ≥ 3 | 64 | 96 | 47 | 85 | 1.37 (0.83-2.27) | | | 21 |
| [1-10-B-galactase, pg/ml]‡ | | | | | | | | |
| >250 | 14 | 21 | 14 | 25 | 1.52 (0.47-5.00) | | | 48 |
| >80 | 58 | 91 | 47 | 84 | 1.41 (0.85-2.33) | | | 19 |
| >80 | 29 | 37 | 27 | 39 | 0.88 (0.30-2.19) | | | 97 |

Hazard Ratio (95% CI)

JAMA. 2016;314(15):1555-1564

Question 5

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, and fever. On exam he has obvious purulence at the catheter site.

For the patient's syndrome, which of the following is NOT an evidence-based intervention?

- Early and effective antibiotics
- Albumin as the preferred resuscitation fluid
- Measuring serum lactate
- Fluid resuscitation with 30 cc's/kg crystalloid

FYI: Sepsis 3 Definition: Not Testable!

- Definition of Sepsis
 - "Life-threatening organ dysfunction due to a dysregulated host response to infection"
- Definition of Septic Shock: Sepsis
 - Absence of hypovolemia
 - Vasopressor to maintain mean blood pressure >65mmg
 - Lactate >2 mmol/L (>18 mg/dL)
- Predicting Outcome
 - Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
 - Quick Sofa is relatively specific but not very sensitive


Sepsis 3 Definition: For Background (Not Testable)!

| | Traditional Definition | Sepsis 3 |
|---------------|--|---|
| Sepsis | Suspected or known infection with ≥ 2 SIRS criteria | Life-threatening organ dysfunction due to a dysregulated host response to infection - SOFA score ≥2 points or positive qSOFA |
| Severe Sepsis | Sepsis + organ failure | N/A |
| Septic Shock | Severe sepsis + hypotension refractory to adequate fluid resuscitation or addition of vasopressors | Sepsis with adequate resuscitation with vasopressor requirement and lactate ≥ 2 mmol/L |

Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
Quick Sofa is relatively specific but not very sensitive

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Surviving Sepsis Campaign Managing Sepsis 

What's the Bottom Line?

- Some recommendations are plausible
 - Fluid resuscitation with 30 cc's/kg crystalloid
 - Vasopressors for MAP goal 65
 - But do not use Dopamine!
- Some are wrong
 - Early goal directed therapy
 - Tight glucose control. Better outcomes <180

- Two are unequivocally true
 - Early effective antibiotics
 - Source control



Surviving Sepsis Campaign Other Things 

Stress-dose steroids: conflicting data


- CORTICUS/ADRENAL
 - No change in mortality with hydrocortisone
 - **Quicker reversal of shock**
- Annane/APROCCHSS
 - Improved mortality with hydrocort/fludricort
 - **Quicker reversal of shock**

Antiendotoxin and Anticytokine therapy

- No benefit

Antithrombosis (Activated Protein C)

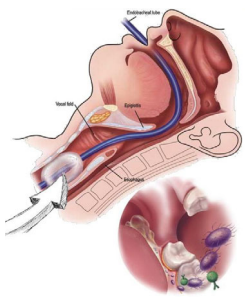

- Taken off the market



Surviving Sepsis Campaign Bundles

| 3 Hour Bundle | 6 Hour Bundle |
|---|---|
| <ul style="list-style-type: none"> - Measure lactate level - Draw blood cultures - Administer broad spectrum antibiotics - Administer 30 cc/kg IV crystalloid | <ul style="list-style-type: none"> - Start vasopressors if MAP <65 despite fluid resuscitation - Reassess volume status if hypotension persists after fluid resuscitation or if initial lactate \geq mmol/L |

Ventilator Associated Pneumonia

Ventilator Associated Pneumonia National Healthcare Safety Network

| Pathogen | % of Isolates |
|------------------------|---------------|
| Staph aureus | 24.7% |
| Pseudomonas aeruginosa | 16.5% |
| Klebsiella | 10% |
| Enterobacter | 8.8% |
| E. Coli | 5% |

IDSA VAP Treatment Guidelines

Cover for *S. aureus*, *P. aeruginosa*, and other GNRs in ALL patients (strong recommendation, very low-quality evidence)

| Clinical Question | Recommendation |
|-----------------------|--|
| MRSA coverage | Use vancomycin or linezolid |
| PsA and other GNRs | Pip-tazo, Cefepime, Ceftazidime, Levofloxacin |
| Double GNR coverage? | Only if >10% of isolates are resistant to the primary abx |
| Double coverage agent | FCs, aminoglycosides (no monotherapy), polymyxins |
| Procalcitonin | Do not use for diagnosis. Consider to aid in discontinuation |
| Duration of therapy | 7 days, consider longer or shorter based on clinical signs |

Clin Infect Dis 2016; 63: e61-e111

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Question 6

34 year-old woman with opiate use disorder is admitted to the medical ICU for acute respiratory distress syndrome requiring intubation. She has been receiving intravenous daptomycin through a PICC for tricuspid valve endocarditis for the past three weeks. Transthoracic echo is unchanged from prior and chest CT shows bilateral ground glass opacities with scattered areas of consolidation. Blood cultures are negative. Bronchial alveolar lavage shows a predominance of eosinophils with negative cultures.

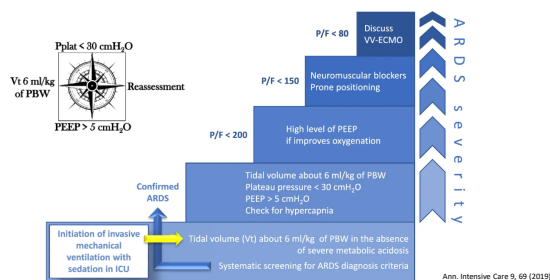
Which of the following is the most likely cause of her respiratory illness?

- A. Injection drug use
- B. Septic pulmonary emboli
- C. Daptomycin
- D. Sepsis

Eosinophilic Pneumonia

- Rare disorder characterized by eosinophil infiltration of the pulmonary parenchyma
- Often associated with peripheral eosinophilia
- Many drugs linked: daptomycin, nitrofurantoin, amiodarone, ACE-i's, etc.
- Daptomycin-induced EP: precise mechanism unknown but believed to be related to daptomycin binding to pulmonary surfactant leading to epithelial injury

ARDS Management



Question 7

A 22-year-old male presents to the ED with a three-week history of cough, shortness of breath, and low-grade fever. His past medical history is unremarkable. There are no sick contacts or recent travel. He went to an urgent care center one week ago and was prescribed levofloxacin but has not improved. ROS is notable for frequent use of e-cigarettes with THC-containing products. Physical examination reveals mild tachycardia, tachypnea, and decreased breath sounds bilaterally. His oxygen saturation is 88% on room air. A chest X-ray shows bilateral diffuse opacities. Laboratory studies reveal an elevated white blood cell count and elevated inflammatory markers.

What is the most likely diagnosis?

- A. Community acquired pneumonia
- B. Acute respiratory distress syndrome (ARDS)
- C. E-cigarette or vaping product use-associated lung injury (EVALI)
- D. Tuberculosis
- E. Pulmonary embolism

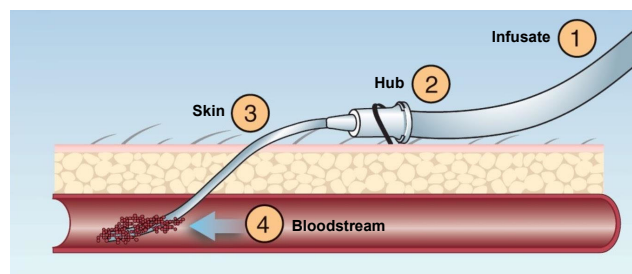
E-cigarette or vaping product use associated lung injury (EVALI)

- Primarily associated with e-cigarettes and vaping products, particularly THC-containing compounds
- Clinical presentation is very similar to community acquired pneumonia
- Exact cause not fully understood but believed to be related to direct lung injury → inflammatory response
- Treatment: supportive care, cessation of e-cigarette use



MMWR. 2019;68(46):1076

CLABSI



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Antiseptic Techniques: Catheter Insertion

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

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 | Pseudomonas aerug |
| • Atypical mycobacteria | Bacillus species |
| • Candida species | Malssezia |
| • Propionibacteria | Microcococcus |

Antibiotic Impregnated Catheters and Hubs Plus Antibiotic Lock Solutions

- Not likely testable on the boards
- They have a role, but not well defined

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

Approach

- Run med list
- Consider AI
- Pyrexia syndromes

Thank You

- Good luck!
- Please give feedback
- **Contact**
 - taison.bell@virginia.edu
 - Twitter/X: @TaisonBell (but not on it as much these days)