28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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 then 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
- Near-drowning and *Scedosporium* and *Pseudallescheria* infection

General internal medicine
- Malignancies
- Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome)
- Noninfectious inflammatory disorders (e.g., vasculitis, lupus, inflammatory bowel disease)
- Dermatologic disorders
- Hematologic disorders
- Noninfectious central nervous system disease
- Bites, stings, and toxins
- Drug fever
- Ethical and legal decision making

Question 2

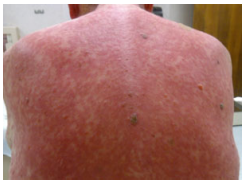
IDBR INFECTIOUS DISEASE BOARD REVIEW 2022 PREVIEW QUESTION

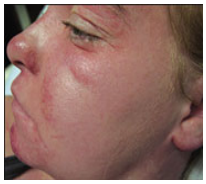
- **You are asked to see a 35 year-old woman with a history of seizure disorder admitted to the ICU with a fever to 40°C, hypotension, and a maculopapular rash**
- **She is being empirically treated with vancomycin and piperacillin-tazobactam. Blood, urine, and sputum cultures (taken prior to antibiotic 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)

Morbilliform 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

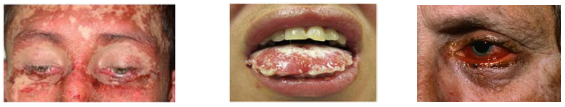
- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

SJS/TEN	AGEP	DRESS
• Severe blistering • Mucosal involvement common • SJS: <10% BSA • TEN: >30% BSA	• Rapidly spreading (hours) pustular lesions • Mucosal involvement rare • Common ddx: psoriasis	• > 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

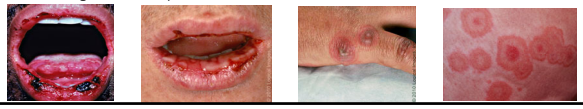
Stevens Johnson and Toxic Epidermonecrolysis



- "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
    - 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 Pyrexic 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?:

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

Malignant Hyperthermia

- Syndrome - Rare (~700 cases/year) but 5-10% mortality
  - Muscle contraction (masseter spasm)
  - Cardiovascular instability
  - Steep rise in CO2
- Genetic defect
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (excessive calcium accumulation)
- Triggers
  - Usually < 1 hour after trigger (up to 10 hours)
  - Classic: Halothane, 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 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	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?:

A. Broader spectrum antibacterial treatment
B. Stress dose corticosteroids
C. Dantrolene
D. IVIG
E. Antifungal therapy

Differential Diagnosis of Shock

Ohm's Law

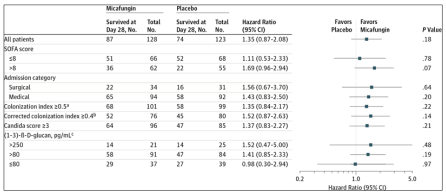
MAP = CO x SVR

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

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



	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	P Value
All patients	87	128	74	123	1.35 (0.87–2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53–2.33)	.78
>8	36	62	22	55	1.69 (0.96–2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67–3.70)	.64
Medical	65	94	58	92	1.43 (0.83–2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84–2.17)	.22
Corrected colonization index ≥0.4[b]	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→3)-ß-D-glucan, pg/mL[c]						
>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	0.98 (0.30–2.94)	.97

JAMA. 2016;316(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?

A. Early and effective antibiotics
B. Albumin as the preferred resuscitation fluid
C. Measuring serum lactate
D. 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

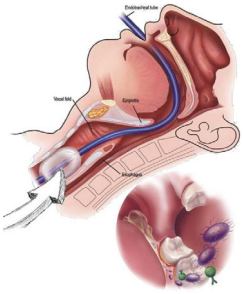
Antithrombosis (Activated Protein C)

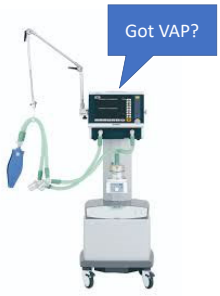
- Taken off the market

Surviving Sepsis Campaign Bundles

3 Hour Bundle	6 Hour Bundle
- Measure lactate level - Draw blood cultures - Administer broad spectrum antibiotics - Administer 30 cc/kg IV crystalloid	- Start vasopressors if MAP <65 despite fluid resuscitation - Reassess volume status if hypotension persists after fluid resuscitation or if initial lactate ≥ mmol/L

Ventilator Associated Pneumonia





Institute for Healthcare Improvement Ventilator Care Bundle Components

- Head of bed elevation to 45°
- Daily awakening trials and assessment of extubation readiness
- Chlorhexidine oral care
- Stress ulcer and DVT prophylaxis

www.IHI.org/topics/VAP
O'Grady. JAMA 2012
Weavind. Curr. Anesth 2013

Ventilator Associated Pneumonia National Healthcare Safety Network

Pathogen	% of Isolates
Staph aureus	24.7%
Pseudomonas aeruginosa	16.5%
Klebsiella	10%
Enterobacter	8.%
E. Coli	5%

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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	FQs, 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

Question

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.

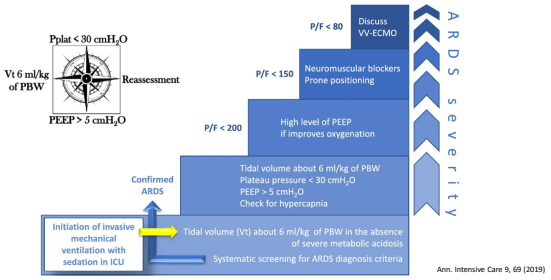
Which of the following is the most likely cause of her respiratory illness?

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

Eosinophilic Pneumonia

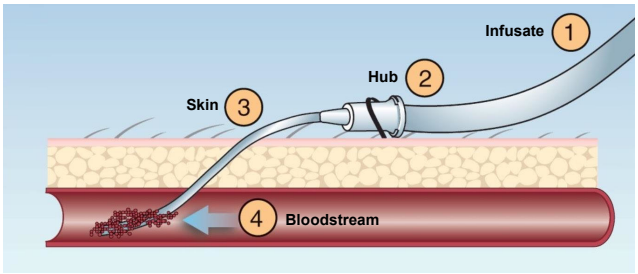
- Rare disorder characterized by eosinophil infiltration of the pulmonary parenchyma
- Often associated with peripheral eosinophilia
- Many drugs linked: daptomycin, nitrofurantoin, amiodarone, ACE-i's, etc.
- Daptomycin-induced EP: precise mechanism unknown but believed to be related to daptomycin binding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

ARDS Management



Ann. Intensive Care 9, 69 (2019)

CLABSI



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)

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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
  - Proprionibacteria
  - Pseudomonas aerug
  - Bacillus species
  - Malssezia
  - Micrococcus

Antibiotic Impregnated Catheters and Hubs Plus Antibiotic Lock Solutions

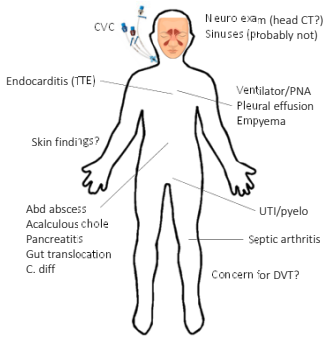
- Not likely testable on the boards
- They have a role, but not well defined

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
- Pyrexic syndromes



Thank You

- Good luck!
- Please give feedback
- Contact
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