Session 1 | Saturday, August 21, 2021

Session Moderator: Dr. Masur
Session Panelists: Drs. Bell, Bennett, Boucher, Gandhi, Gilbert, Patel, and Winthrop

1 | 16S sequencing | Patel

A 50-year-old woman presents with fevers and general malaise of three weeks' duration. She was given a three-day course of amoxicillin, but her symptoms persisted.

On physical examination, a new murmur of mitral regurgitation is noted; subsequent echocardiography shows severe mitral regurgitation with a mobile 3 mm vegetation on her mitral valve.

- Three sets of blood cultures are negative after five days of incubation.
- Serologies for *Bartonella* species and *Coxiella burnetii* are negative.
- She undergoes mitral valve replacement.
- The valve is sent for diagnostic evaluation

In addition to histopathologic evaluation, which of the following is most likely to be helpful to perform on her valve?

A. *Bartonella* PCR
B. Fungal culture
C. **16S ribosomal RNA gene PCR/sequencing**
D. *C. burnetii* PCR
E. Mycobacterial culture

Correct answer: **16S ribosomal RNA gene PCR/sequencing**

This is a case of culture-negative endocarditis. The list of possible etiologies is extensive and includes HACEK organisms (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella* and *Kingella* species), *Coxiella burnetii* (agent of Q fever), *Tropheryma whipplei*, *Bartonella* species, *Abiotrophia* species, *Granulicatella* species, *Streptococcus* species, and many more.

Blood cultures are always the first microbiologic test for endocarditis, but in this case, they are negative (likely as a result of antecedent antibiotic treatment).

It is most important to perform histopathologic evaluation of the resected valve so that therapy can be properly directed: empiric therapy has obvious potential to omit activity against the actual pathogen given the broad range of possible etiologies.

16S ribosomal RNA gene PCR/sequencing is the next recommended test for the resected valve. Such PCR testing can amplify even a few copies of bacterial target DNA. When combined with sequencing, this approach can identify a specific organism to the genus and often species level. Molecular testing of excised valve material using PCR is optimally used in cases in which microbiologic diagnosis cannot be established by blood culture or serology. PCR is especially useful in blood culture-negative cases with a history of previous antibiotic exposure. Bacterial DNA persists even when organisms are nonviable or are present in numbers too low to be detected by culture. However, false positive results, often due to specimen contamination, can be a problem.

PCR specifically for *Bartonella* and *C. burnetii* could be performed on the valve, but would be of low value given the negative serologies. Moreover, the primers used to perform 16S ribosomal RNA gene amplification and sequencing should detect 16S ribosomal RNA gene of these organisms.

Fungal or mycobacterial endocarditis would be distinctly unusual (but may be suggested, if present, by the results of histopathology evaluation). Mycobacteria would be detected by 16S ribosomal RNA gene PCR/sequencing. Fungal pathogens require a different PCR/sequencing target.

A challenge with valvular testing is the limited amount of sample available, so testing should be prioritized based on the most likely and most useful approaches.

Bacterial culture of valves in blood culture-negative cases has low sensitivity and specificity (and is not a choice in this question).

2 | Cholangitis Rx | Boucher

A 79-year-old female with history of well-controlled non-insulin dependent diabetes mellitus (NIDDM) and hyperlipidemia is evaluated for abdominal pain and vomiting of 1-day duration. There is no known history of gallstone disease.

This patient has no exposure to health care facilities, no antibiotic exposure, and has had no acute illnesses in the past two years. She is an accountant and has not traveled out of the country.

On exam, the patient had temperature of 102 F, blood pressure 94/65, heart rate of 126 beats/min, icteric sclera, and tenderness to palpation in the right upper quadrant. WBC 18,000 cells/L with 23% bands, amylase = 100 (nl 23-85) U/L, lipase = 160 (nl 0-160) U/L, AST 55 (nl 10-40) U/L, ALT 80 (nl 7-56) U/L, ALK 650 (nl 20-140) U/L. TBili is 5.7 mg/dL, creatinine is 2.7 (baseline 1.0-1.3).

Abdominal ultrasound revealed dilated bile ducts with stones.

Which one is the following options is the most appropriate antimicrobial therapy for this patient?

A. **Piperacillin-tazobactam**
B. Ampicillin-sulbactam
C. Meropenem plus fluconazole
D. Plazomicin plus vancomycin
E. Cefepime plus clindamycin

Correct answer: **Piperacillin-tazobactam**

This patient presents with sepsis and the classic Charcot's triad (fever, abdominal pain, and jaundice) indicative of **acute cholangitis**. The most common pathogens for biliary tract infections are enteric gram-negative aerobic and facultative bacilli, as well as enteric streptococci. The choice of empiric antimicrobial therapy in this setting is dictated by the risk of infection with drug-resistant organisms.

Low risk patients (otherwise healthy patients with community acquired infection and mild-to-moderate severity of illness) can be treated with a cephalosporin (cefazolin, cefuroxime, or ceftriaxone) as monotherapy, followed by biliary drainage. Anaerobic coverage is not necessary in mild to moderate infections of the biliary unless there is history of biliary-enteric anastomosis.

However, for patients with more severe illness, advanced age, immunocompromise, or healthcare associated infections, broader antimicrobial therapy is recommended. IDSA guidelines for intra-abdominal infections are being updated, but based on the 2010 recommendations options for monotherapy include piperacillin-tazobactam or a carbapenem. Combination therapy with cefepime or a quinolone plus metronidazole are also appropriate choices, although with increasing resistance among *E. coli* to quinolones this option is only recommended if local susceptibility testing suggests ≥90% sensitivity among community isolates.

Ampicillin-sulbactam is no longer recommended as empiric therapy for cholangitis because of high rates of resistance among community-acquired *E. coli.*

Meropenem would be a reasonable option for monotherapy, but empiric antifungal treatment is not recommended for patients with community-acquired infection.

Plazomicin is an aminoglycoside that has been developed to treat gram negative infections, including carbapenemase-resistant enterobactericiae (CRE). There is still limited data on its clinical efficacy, but it appears to be comparable to meropenem for complicated urinary tract infections. Aminoglycosides have no gram positive or anaerobic activity, and due to nephrotoxicity are not recommended for empiric therapy. While combination therapy with vancomycin would provide activity against enteric streptococci, this agent is overly broad as MRSA or enterococci are not significant pathogens for community-acquired biliary tract infections.

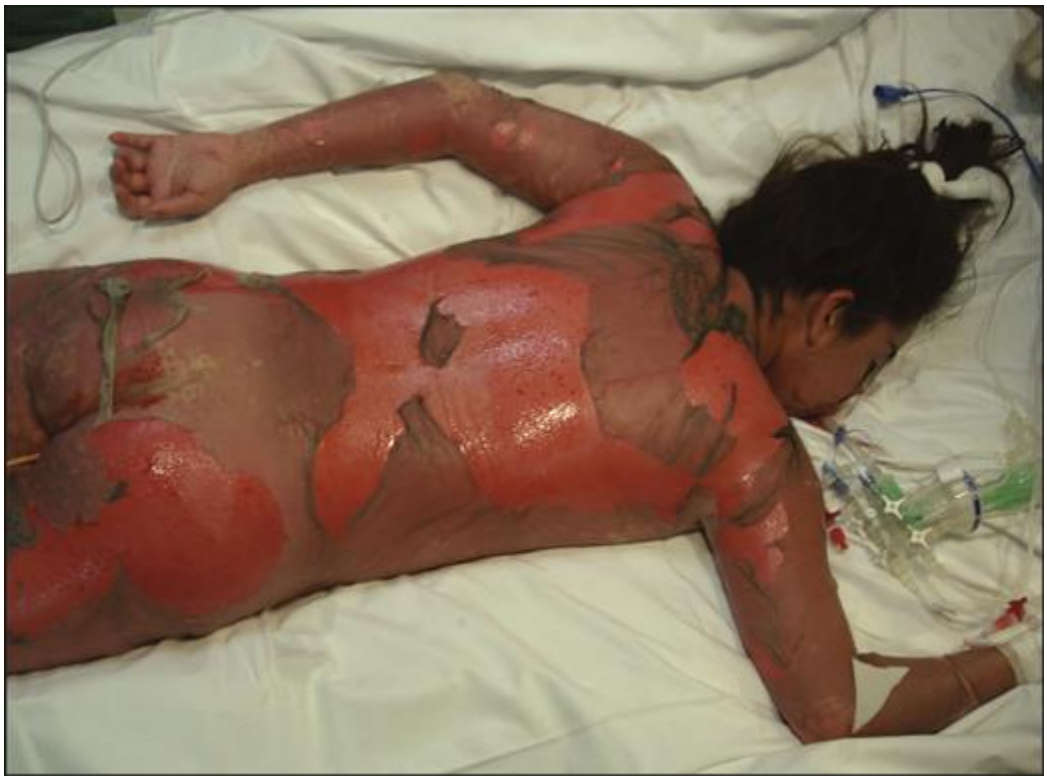
Metronidazole is preferred to clindamycin when anaerobic therapy is indicated due to high rates of resistance among *Bacteroides fragilis* to this latter agent.

3 | TEN | BELL

A 36-year-old woman presented with a fever and skin eruption two weeks after starting lamotrigine for depression. She had also had a mild, nonproductive cough for about ten days preceding the initiation of lamotrigine for which she was given trimethoprim-sulfamethoxazole by her family physician.

On examination, she has a temperature of 38.3C, oral ulcers, and ulcerating skin lesions over 75% of her body. Her conjunctiva are inflamed.

Her lungs are clear, as is her chest radiograph. Her CBC shows a slight leukocytosis.



Arch Dermatol. 2008;144(6):724-726

The most likely diagnosis is:

A. Erythema multiforme
B. Stevens Johnson syndrome
C. **Toxic epidermal necrolysis**
D. Scalded skin syndrome
E. Disseminated herpes simplex

Correct answer: **Toxic epidermal necrolysis**

Stevens-Johnson syndrome and toxic epidermal necrolysis are severe mucocutaneous reactions, usually triggered by medications started within the past 3 weeks. Patients have extensive necrosis and detachment of the epidermis. Mucosal and ocular involvement are characteristic. This patient likely had this reaction to either the trimethoprim-sulfamethoxazole or the lamotrigine.

SJS and TEN are variants of a disease continuum, which are distinguished by severity as measured by body surface area involved. They present with fever and malaise before the skin and mucous membrane lesions become apparent.

SJS: skin detachment is <10 percent of the body surface

Mucous membranes are affected in over 90 percent of patients, (ocular, oral, and genital).

TEN involves detachment of >30 percent of the body surface area. Mucous membranes are involved in over 90 percent of patients.

The drugs that most commonly trigger this are the following, with reactions occurring in the first 8 weeks of drug use.

- Allopurinol
- Anticonvulsants
- Sulfonamides
- Lamotrigine
- NSAIDs

Mycoplasma pneumoniae infection is the most common infectious trigger of SJS and TEN. This patient has a history that could be compatible with mycoplasma, and this infection could trigger either SJS or TEN, or erythema multiforme, but these lesions are not erythema multiforme (see below)

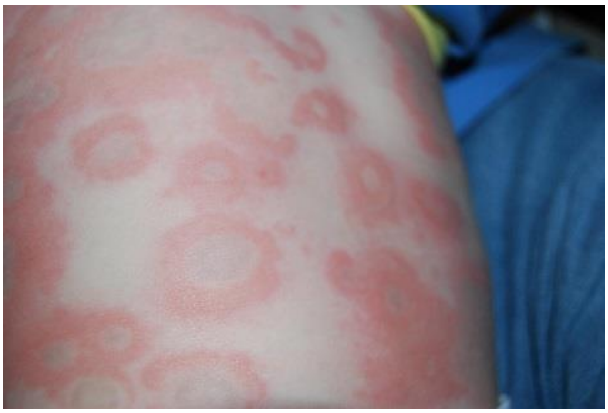
SJS and TEN skin lesions typically begin with ill-defined, coalescing erythematous macules with purpuric centers, although many cases of SJS/TEN may present with diffuse erythema. Lesions are tender and skin pain can be prominent and out of proportion to the cutaneous findings. They start on the face and thorax and do not usually involve the palms and soles.

Patients are often described as showing Nikolsky sign (gentle pressure on the skin loosens the epidermis). Mucosal involvement and ocular involvement occur in 90 percent of cases of SJS, and oral mucosa and the vermilion border are almost invariably involved.

Treatment is supportive with emphasis on fluid and electrolytes, avoiding infection, and treating promptly any infections that occur.

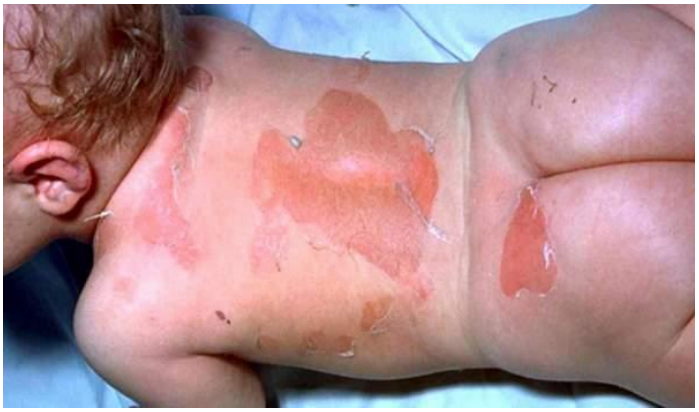
IVIG and corticosteroids have not been demonstrated effective although some clinicians use them.

This is not erythema multiforme. **Erythema multiforme (below)** usually presents with typical target lesions. Bullae and epidermal detachment are usually limited and involve less than 10 percent of the body surface area.



This is not **Staphylococcal scalded skin syndrome** (below). Staphylococcal scalded skin syndrome is caused by epidermolytic toxins produced by certain strains of Staphylo cocci but is usually seen in neonates and young children. This presents with generalized erythema followed by the development of blisters and desquamation. The mucous membranes are not involved.

Scalded skin histology reveals sloughing of only the upper layers of the epidermis, in contrast with the subepidermal split with full thickness epidermal necrosis observed in SJS/TEN.



http://www.bestonlinemd.com/scalded-skin-syndrome/

4 | Erysipelothrix | Gilbert

A 56-year-old commercial crab fisherman on the Chesapeake Bay is seen for a painful, red hand.

Three days ago he noticed a red dot on his index finger that was became increasingly painful. The lesion progressed to a red-purple involvement of his entire index finger, his middle finger, and most of the dorsum of his hand looking like a cellulitis.

He is afebrile and says the involved area is quite painful but only slightly tender to the touch.

He says the finger joints feel stiff although there is no joint swelling on exam.

Which one of the following is the most likely cause of his problem?

A. ***Erysipelothrix rhusiopathiae***
B. *Mycobacterium chelonae*
C. *Sporothrix schenckii*
D. *Aeromonas*
E. *Pseudomonas aeruginosa*

Correct Answer: ***Erysipelothrix rhusiopathiae***

Persons in contact with shellfish, pigs or occasionally other animals are at risk for erysipeloid, a subacute cellulitis due to inoculation with this Gram-positive bacillus that can persist for long periods on the surface of shellfish or cause chronic infection in the skin or pigs and some other domestic animals.

Erysipeloid, a subacute infection of the skin that begins with a painful red dot and progresses over days to a red-purple discoloration of the skin with minimal swelling and pain often out of proportion to the visible lesion. Bacteremia is uncommon but when it occurs is usually associated with aortic valve endocarditis.

None of the other entities fit this background or clinical picture. Nontuberculous mycobacteria, such as M. marinum, cause a much more indolent course.

5 | Streptobacillus | Gilbert

A 57-year-old medical school research scientist is seen for a febrile illness. Four days ago he was bitten on his hand by a laboratory rat.

Last evening he had a fever, and today he has fever, chills, myalgias, and a painful left knee. On exam he is febrile. The bite wound is largely healed and has no evidence of infection.

His left knee is swollen with obvious effusion and some pain on both active and passive motion.

He has a petechial rash over both shins, and it is also present on the soles of his feet.

Which one of the following is the most likely cause of his illness?

A. *Leptospira interrogans*
B. *Spirillum minus*
C. ***Streptobacillus moniliformis***
D. Hantavirus
E. *Pasteurella canis*

Correct Answer: ***Streptobacillus moniliformis***

Rat-bite fever due to *Streptobacillus moniliformis* is one of the most common zoonosis associated with laboratory rats. While few cases are reported, it is estimated that 22,000 rat bites occur in the US annually, and that 10% are associated with rat bite fever. *S. moniliformis* has also caused waterborne outbreaks, called Haverhill Fever.

Patients have acute, systemic illness with fever that may be relapsing. Many patients have rash which may be morbilliform or petechial commonly occurring on the extensor surfaces of the extremities and may involve the palms or soles. Many patients have frank arthritis of one or more joints.

Given the severity of rat bite fever and the proposed frequency of this illness following rat bites, prophylaxis with 3 days of penicillin following the bite would be reasonable but is not known to be effective and is not a universally endorsed approach.

Spirillum minus, the other cause of rat-bite fever which occur in Asia, has an incubation period typically of 1-3 weeks and is associated with an ulcerative lesion at the site of the rat bite.

Leptospirosis is not associated with arthritis nor is hantavirus.

Pasteurella would be expected to have evidence of infection at the site of the bite.

6 | Port Infection | Bell

A 66-year-old patient in the ICU is day 6 post-operative following a pancreatectomy for pancreatic carcinoma.

He is recovering uneventfully with improving renal and hepatic function.

On the evening of his 6th post-operative day, he develops a fever of 38.5 C

The surgeons draw three cultures from an indwelling port that was placed preoperatively for chemotherapy that has not yet started. No other blood cultures were drawn. Piperacillin-tazobactam is started.

On Day 7 the patient remains intermittently febrile but is otherwise stable with no new findings.

Labs are remarkable only for a WBC that continues to decline following surgery and is now 7800 cells/uL with 70% neutrophils

An ID consult is requested because after 14 hours of incubation, all three blood cultures are growing Gram-positive cocci in clusters.

The patient has been stable but still has a low-grade fever. The port and the peripheral IV look fine, there are no other concerning physical findings or lab values. The organisms have been identified as Staphylococcus epidermidis with an oxacillin MIC of 1 mcg/ml. The surgeon is very eager to retain the port. Because the patient is stable and will be hospitalized for starting his chemotherapy, you ask for port and peripheral blood cultures. At 48 hours, the port cultures are positive but peripheral cultures are negative.

You recommend stopping the piperacillin-tazobactam. What else would you recommend?

A. Vancomycin should be started, and the port should be removed
B. Nafcillin or oxacillin should be started, and the port should be removed
C. **Start vancomycin through the port**
D. Start nafcillin or nafcillin through the port
E. Remove port. No antibiotic needed

Correct answer: **Start vancomycin through the port**

This patient likely has a port infection due to Staphylococcus epidermidis.

This catheter has a high likelihood of being salvaged. About ten days of therapy through the port should be sufficient. If blood cultures through the port remain positive, the port can be removed later.

Although removing the port (against the surgeon's wishes) might be sufficient treatment, the possibility of a metastatic infection or an unrecognized deep suppurative thrombophlebitis around the port catheter may need treatment after port removal.

An oxacillin MIC of 1 mcg/ml would be susceptible for Staph aureus and S lugdunensis but is considered resistant for coagulase negative staphylococci.

7 | Nafcillin Neutropenia | Boucher

A 57 y/o man presents with 1 week of fever, chills, and low back pain.

A transesophageal echocardiogram shows a 6 mm mobile mass on the mitral valve. MRI of the spine shows evidence of discitis between the 3rd and 4th lumbar vertebrae.

Admission blood cultures are positive for *S. aureus* resistant only to penicillin.

He is treated with nafcillin 2 gm IV every 4 hours with resolution of fever but little change in his back pain. Follow-up blood cultures form hospital days 4 and 5 are negative.

The white blood cell count, 18,000/mm^3 with 90% neutrophils on admission, but on hospital day 10, the white blood cell count is 3,000/mm^3 with 30% neutrophils. Renal function is normal.

Which of the following options is most appropriate for this patient?

A. **Cefazolin 2 gm IV every 8 hours**
B. Ceftriaxone 2 gm IV every 12 hours
C. Linezolid 600 mg IV every 12 hours
D. Nafcillin 1 gm IV every 4 hours
E. Vancomycin 1 gm IV every 12 hours

Correct answer: **Cefazolin 2 gm IV every 8 hours**

The neutropenia is due to bone marrow maturation arrest due to nafcillin and necessitates discontinuing this antibiotic.

Reducing the dose of nafcillin might resolve the neutropenia, but would provide subtherapeutic levels if 1 g IV q 4h were administered, as described in the answer above. Thus, this is not a good strategy.

Neutropenia is a well-recognized toxicity of nafcillin in particular, and not a contraindication for use of cephalosporins or other beta-lactam antibiotics. The neutropenia often occurs with relatively high doses after weeks of therapy, i.e., it is time and dose dependent.

Cefazolin is recommended second line for treatment of invasive MSSA infections, including bacteremia and endocarditis, and is preferred over both vancomycin and ceftriaxone. This drug would be a good option since neutropenia is not a common adverse effect of cefazolin.

Ceftriaxone is a poor choice due to its marginal activity against MSSA, high level of protein binding, absence of any controlled trials of its use in the treatment of *S. aureus* osteomyelitis or bacteremia, and observational studies suggesting that it is less efficacious than cefazolin or anti-staphylococcal penicillins, particularly endocarditis.

Linezolid should not be used to treat endocarditis. It is a static drug, and long courses cause bone marrow suppression. There are no data showing this drug to be highly effective for endocarditis and thus, along with its long-term toxicity, linezolid is a poor option.

8 | MAC Lung | Winthrop

A 72 y/o US born, white female reports a history of needing antibiotic therapy for repeated respiratory infections over the last 12 months. With each treatment she improves to near her baseline, but within several weeks her cough has worsened again, became more productive, and she complains of fatigue.

Overall, she notes a decline in exercise capacity, 10 lbs weight loss, and progressive fatigue the last 6 months. She is a life-long non-smoker and has no risk factors for tuberculosis. She is otherwise healthy and takes no medications.

Her chest radiograph is normal, but a chest computed tomograph (CT) reveals right middle lobe bronchiectasis with scattered tree-bud infiltrate, mucous plugging, and a small right upper lobe cavity with a fungus ball present within the cavity.

The most likely cause of her syndrome and progressive decline is:

A. Mycobacterium gordonae
B. Chronic necrotizing aspergillosis
C. Mycobacterium tuberculosis
D. **Mycobacterium avium complex**
E. Nocardia farcinica

Correct answer: **Mycobacterium avium complex**

In this case, the patient has both symptoms, history, and radiographic features suggesting chronic pulmonary non-tuberculous mycobacterial disease. The fungus ball is a consequence of her lung disease, not a cause.

The overwhelming majority of NTM disease in the US is caused by M. avium complex. It frequently co-exists with bronchiectasis and causes all of the radiographic features mentioned above. This patient's condition has been called "Lady Windermere's syndrome", *M. gordonae* is a non-pathogenic NTM except in very rare or extreme circumstances, and it should be regarded as a contaminant.

Nocardia is much more rarely a cause of chronic invasive pulmonary disease, and is often a colonizer of bronchiectatic airways. Similarly, chronic necrotizing aspergillus is unusual and appears in patients with severe underlying lung disease.

M. tuberculosis should be considered in the differential, but is much less common in the US, unlikely to be confined to the right middle lobe, and unlikely to occur in an individual lacking TB risk factors.

9 | ESBL | Gilbert

A 72-year-old man develops fever, abdominal pain, and unstable blood pressure after a subtotal colectomy for carcinoma of the colon.

Empiric therapy with piperacillin-tazobactam and vancomycin is initiated.

Within hours, the Clinical Microbiology laboratory reports that the patient's blood cultures are positive for enteric Gram-negative rods, preliminarily identified as *Klebsiella pneumoniae*.

In vitro, the *K. pneumonia*e is:

- Susceptible to: piperacillin-tazobactam, meropenem, cefepime, and colistin
- Resistant to: ciprofloxacin, ceftriaxone and aztreonam

Which one of the following antibiotics would you recommend for specific therapy?

A. Continue piperacillin-tazobactam
B. Ceftazidime-avibactam
C. Gentamicin
D. Cefepime
E. **Meropenem**

Correct answer: **Meropenem**

Klebsiella pneumoniae is the most common pathogen to carry plasmids encoding extended spectrum beta-lactamases (ESBLs).

The pattern of *in vitro* resistance to extended spectrum cephalosporins (e.g., ceftriaxone), and aztreonam with preservation of susceptibility to piperacillin-tazobactam and meropenem is a common laboratory marker of production of an ESBL.

A carbapenem is the treatment of choice.

In vitro piperacillin-tazobactam is active. However, in a prospective controlled study comparing piperacillin-tazobactam with meropenem, meropenem was superior. This discordance is believed the result of an inoculum effect (i.e., low *in vitro versus* high clinical inoculum).

Ceftazidime-avibactam has efficacy vs many carbapenem-resistant K pneumonia isolates but would not be indicated in this case (meropenem is susceptible).

Aminoglycoside monotherapy is not preferred therapy for Gram negative bloodstream infections except some zoonoses.

10 | Cryptosporidiosis | Masur

A 26-year-old male with HIV infection (CD4=50 cells/uL, Viral Load 500,000 IU/mL) presents with severe right upper quadrant pain, nausea, vomiting and low-grade fever that suddenly occurred over the past 2 days.

The patient has not been adherent to his antiretroviral therapy over the past several years. He has had diarrhea (6 watery stools per day) for 8 months, and has lost 20 lbs during that period. The stools are brown, without blood or obvious mucous.

He lives in Washington, D.C., works as a tour guide, and eats often at a variety of downtown food carts. He has multiple sex partners and is not consistent about safe sex practices. He intermittently uses methamphetamines.

On exam he has normal vital signs (no fever at the time of examination) but severe right upper quadrant pain that is worse with palpation.

CBC: WBC 4400, Platelets 270,000, Hct 43%

Chemistries: liver function tests were moderately elevated: AST 435 IU/L, ALT 530 IU/L, Alk Phos 561 IU/L, Total Bili 2.4 (mg/dl)

Urine toxicology screen positive for marijuana and amphetamines.

Stool PCR, cultures, and ova and parasite exams are pending.

MRCP (Magnetic resonance cholangiopancreatography) reveals of bile duct stricture and moderate ductal dilation with no masses or adenopathy. Ultrasound and CT scan revealed similar findings and also jejunal thickening and thickening of the gall bladder wall.

What is the most likely cause of this syndrome?

A. Methamphetamines
B. CMV
C. Lymphoma
D. **Cryptosporidiosis**
E. Calculous cholecystitis

Correct answer: **Cryptosporidiosis**

This patient has HIV associated cholangiopathy associated with cryptosporidiosis.

Cholangiopathy can occur due to a stricture, an obstruction, an enteric organism, or some combination of these disorders. Bile duct strictures are specifically reported in patients with HIV and low CD4 counts. The etiology is not known, but many of these patients also have biliary infections, often due to cryptosporidia, enteric bacteria, or a host of other bowel pathogens.

This patient's chronic diarrhea and jejunal thickening suggest an infectious syndrome although admittedly some patients with HIV associated biliary strictures have diarrhea without an identified pathogenic cause. The relatively low direct bilirubin is also more suggestive of HIV cholangiopathy than a bile duct obstruction or bacterial cholangitis.

Imaging did not show a biliary stone, a mass within the common duct, nor did imaging show a node or mass lesion extrinsically obstructing the common bile duct, and thus lymphoma or calculous cholecystitis seem unlikely.

Almost any enteric pathogen can cause cholangitis, so a thorough evaluation of stool is necessary with cultures, PCR, and parasitological examination.

From a pathologic perspective, patients with HIV cholangiopathy may have papillary stenosis, intrahepatic sclerosing cholangitis, or long (1-2 cm) extrahepatic bile duct strictures. They usually require a diagnostic ERCP (**Endoscopic retrograde cholangiopancreatography** (**ERCP**)and a sphincterotomy with or without a biliary stint.

A small bowel biopsy could be done to rule out CMV enteritis, but CMV cholangiopathy would be less likely than micro/cryptosporidiosis.

There is not specific therapy for cryptosporidiosis in this population. Trying to get the patient to adhere to his antiretroviral therapy is the best therapeutic strategy. Nitazoxanide is reported to be effective for cryptosporidia (and for giardia)in patients with normal immunity; for immunosuppressed patients nitazoxanide seems to have little effect although many clinicians would try this drug for lack of better options.

11 | Cocci Biohazard | Patel

Which of the following is considered a serious hazard to laboratory staff if not handled appropriately?

A. *Neisseria gonorrhoeae*
B. *Haemophilus ducreyi*
C. *Cryptococcus neoformans*
D. ***Coccidioides immitis***
E. *Corynebacterium diphtheriae*

Correct answer: ***Coccidioides immitis***

C. immitis/posadasii may be a risk for microbiology staff if worked with on an open benchtop (and not in a biological safety cabinet or "hood").

The other organisms listed do not pose risks if worked with on an open benchtop assuming they are handled appropriately.

Laboratory workers must be careful with other organism-types as well. For instance, *Neisseria meningitidis*, *Brucella* species, *Francisella tularensis, Yersinia pestis*, *Bacillus anthracis*, *Burkholdheria pseudomallei* and *Burkholdheria mallei* should be handled in a biological safety cabinet.

C. immitis/posadasii, along with *N. meningitidis*, *Brucella* species, *F. tularensis*, *Y. pestis, B. anthracis,* and *Burkholdheria* species may grow on routine bacteriology media, so the laboratory should be notified if these are suspected.

Laboratory workers who inadvertently work with these agents outside of a biological safety cabinet may require antimicrobial prophylaxis, serologic follow-up and/or symptom watch, depending on the organism, nature of the exposure and host. It is your responsibility to notify the laboratory if you suspect infection with any of these organisms to help protect those who provide a service for you.

12 | BCGosis | Winthrop

75-year-old male with diabetes mellitus and ankylosing spondylitis treated with prednisone 20 mg daily, admitted with 3 weeks of fevers to 39°C, lethargy, and weight loss of 10 lbs

He underwent transurethral resection of a bladder cancer three months prior, and recently completed a six-week course of intravesical Bacille Calmette Guerin (BCG) administered once weekly.

He lives in Tucson, Arizona. Urinalysis shows protein, nitrite, and leukocytes; routine bacterial culture is negative. Chest X-ray is normal. Chest CT scan shows innumerable tiny (1-4 mm) nodules.

What diagnostic procedure is most likely to reveal the diagnosis?

A. Bacterial blood culture
B. Silver stain of induced sputum
C. Ziehl-Neelsen stain of induced sputum
D. **Trans-bronchial biopsy**
E. Serum antibody testing for Coccidioides

Correct answer: **Trans-bronchial biopsy**

The presentation and history are most consistent with disseminated BCG infection as a complication of intravesical administration.

Routine bacterial blood cultures are not incubated sufficiently long enough to detect growth of *Mycobacterium bovis* BCG. When mycobacterial infections present with a miliary pattern on chest imaging, the bacillary burden in respiratory secretions typically is very low; Ziehl-Neelsen staining of sputum has very poor sensitivity, and is not likely to be positive in this context.

Multiple respiratory specimens should be sent for mycobacterial culture, which is the most sensitive approach for microbiologic confirmation of mycobacterial disease, although sensitivity is less than 100% in miliary disease.

Pneumocystis jirovecii is in the differential diagnosis in this patient on corticosteroids, although a miliary pattern on chest imaging would be very unusual for PJP, and molecular nucleic acid amplification tests of induced sputum are substantially more sensitive than silver stains.

Coccidiomycosis is a consideration given the patient's residence in Arizona and it can present with a miliary pattern, usually in AIDS patients. However, serum antibody testing for Coccidioides can be falsely negative early in disease and in immunosuppressed patients. A positive EIA IgG serology might represent remote infection as the serology can remain positive for years.

13 | Clostridium | Gandhi

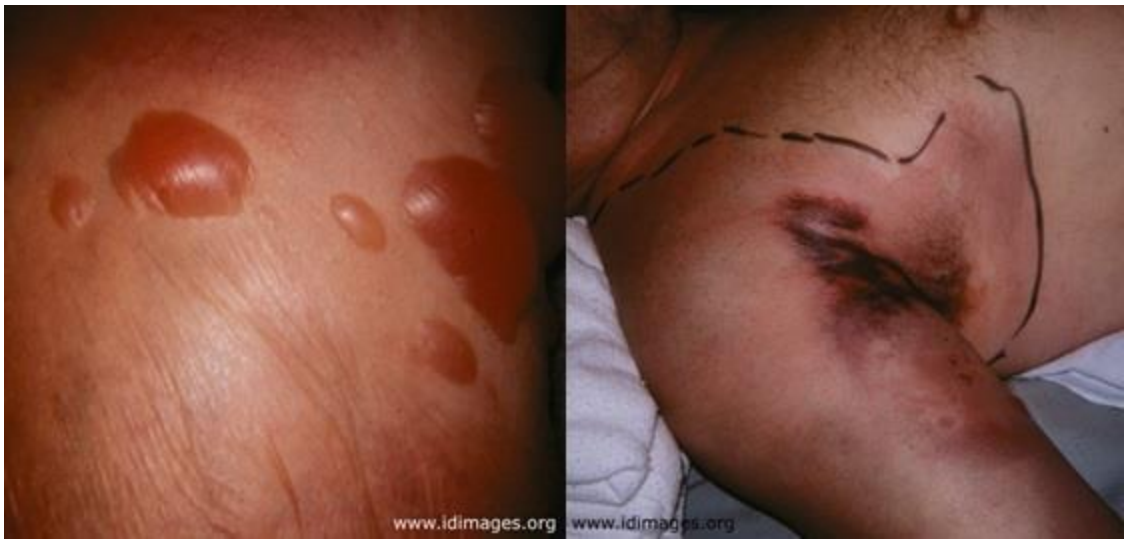
A previously healthy 60 y/o man presented with a few hours of severe pain in the right upper extremity. The exam was normal and he was discharged.

Over the next few hours, he developed progressive swelling of the right upper extremity. There was no history of trauma.

On exam, he appeared anxious, with cold and clammy skin.

BP55/30. The right upper extremity was diffusely swollen with a deep-red discoloration; there were several bullae (shown). No pulses were palpable in the right upper extremity.

WBC 8,900 (47% polys, 38% bands). An X-ray showed air in the soft tissues



The most likely diagnosis is which of the following:

A. Vibrio vulnificus
B. Group A streptococcal necrotizing fasciitis
C. Mixed aerobic/anaerobic necrotizing fasciitis
D. **Clostridial gas gangrene**
E. Ecthyma gangrenosa

Correct answer: **Clostridial gas gangrene**

Discussion: This patient has spontaneous gas gangrene. Surgical cultures grew *Clostridium septicum*. In retrospect, patient reported a several month history of bright red blood per rectum. Subsequent evaluation revealed an invasive colonic carcinoma.

Gas Gangrene (Clostridial myonecrosis) may present with acute onset of severe pain, sometimes without abnormal physical findings. The patient generally appears quite ill. There is subsequent rapid progression of skin discoloration, tense edema, crepitus and development of bullae containing thin, serosanguinous, or hemorrhagic fluid. Gram stain of fluid or surgical specimen demonstrates large gram-positive or gram-variable rods.

Traumatic gas gangrene is generally due to *C. perfringens,* and sometimes other Clostridial species. Spontaneous (non-traumatic) gas gangrene is most commonly due to *C. septicum.* Predisposing factors for spontaneous gas gangrene include intestinal disease (tumor, ulceration, inflammation) or systemic factors (malignancy, cirrhosis, neutropenia, diabetes mellitus). *C. septicum* infection is associated with malignancy: In one series, 81% of patients had malignancy and in 37% the cancer was occult. The most common cancers associated with *C. septicum* are colorectal and hematologic malignancies.

Vibrio vulnificus can cause a rapidly progressive soft tissue infection but usually afflicts patients with liver disease, iron overload or an immunocompromising condition. Group A Streptococcal necrotizing fasciitis would not result in air in the soft tissues. Mixed aerobic/anaerobic necrotizing fasciitis often

occurs after trauma or surgery. Ecthyma gangrenosa would be rare in the absence of profound neutropenia or comparable immunosuppression.

14 | CRYPTO PROSTATE | GANDHI

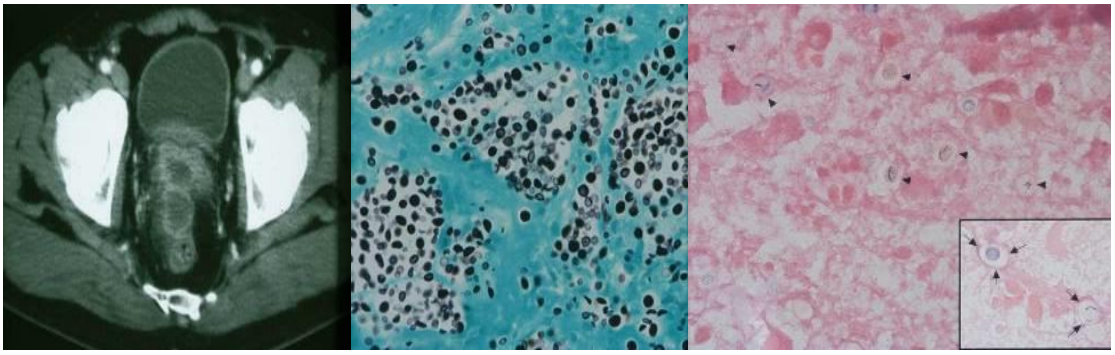
49-year-old man with AIDS (CD4 count 43, HIV RNA 225,000) presented with 4 weeks of pain on defecation.

His physical exam was notable for a tender, boggy prostate. The urinalysis showed 5-10 WBC/hpf. The urine culture was without growth.

A pelvic CT scan showed a prostate abscess.

Aspirate of the abscess revealed the findings below.

Pelvic CT Silver stain. 4-8 mM Hematoxylin and eosin stain



Which of the following is the correct diagnosis?

A. *Blastomyces dermatitidis*
B. *Pneumocystis jirovecii*
C. *Histoplasma capsulatum*
D. *Candida albicans*
E. ***Cryptococcus neoformans***

Correct answer: ***Cryptococcus neoformans***

Discussion: The prostate aspirate showed evidence for Cryptococcus:

On hematoxylin and eosin stain, there are yeast surrounded by a thick capsule (below).

H & E stain

Cryptococcus neoformans enters body via the respiratory route. The organism has a tropism for the central nervous system, and can cause meningitis. Other focal sites of infection may include the skin, bone, or prostate.

Cryptococcal prostate infection may be asymptomatic. The prostate may serve as a sanctuary from antifungal therapy; as a result, prolonged therapy may be required to cure the infection

Differential diagnosis

- *Blastomyces:* may involve prostate; yeast form usually has thick wall, broad-based budding
- Histoplasma: multipolar budding, sometimes with narrow buds
- *Candida albicans:* in tissues, yeast forms intermingled with pseudohyphae
- *Pneumocystis:* extrapulmonary disease may occur, but prostate involvement not typical

15 | Crypto Antigenemia | Bennett

A 38-year-old male with HIV is asymptomatic, but his clinic physician drew a serum cryptococcal antigen test, which has come back positive.

On evaluating the patient you find nothing remarkable by history or examination. The patient has not been willing to take any medicines for HIV infection but is now willing to start antiretrovirals.

Lab tests:

- Confirmatory assay: positive for HIV-1, negative for HIV-2
- CD4 count: 45 cells/mm^3
- HIV viral load: 400k copies/ml
- CBC: normal
- Chemistry panel: normal
- LP: 0 cells, normal protein, and glucose, negative Cryptococcal antigen

- Serum Crypt antigen: 1:32

For this patient, what would be the optimal approach for management regarding his cryptococcal antigen results?

A. No therapy: monitor serial crypt antigens
B. **Fluconazole**
C. Amphotericin B plus Flucytosine
D. Posaconazole
E. Caspofungin

Correct answer: **Fluconazole**

Most experts would treat asymptomatic cryptococcal antigenemia in a patient with a low CD4 count with oral fluconazole, but the duration of fluconazole therapy is debatable: the current recommendation is 12 months (assuming the patient is also started on effective antiretroviral therapy).

This patient does not have cryptococcal meningitis by either clinical criteria or laboratory criteria. Asymptomatic patients with positive cryptococcal antigen tests can be treated preemptively with fluconazole, whereas patients with cryptococcal meningitis must receive amphotericin B induction for 2 weeks.

The first choice is incorrect: the patient should receive some type of preemptive antifungal therapy.

Amphotericin B is not indicated in this patient who does not have cryptococcal meningitis.

There is no need to use posaconazole, and caspofungin has no activity against Cryptococcus.

Note that this question did not ask when ART should be started. This patient has no documented CNS involvement, and thus starting within 2 weeks of initiating fluconazole is reasonable. However, there is considerable controversy regarding when to start ART when there is documented CNS infection, and thus such a question would not be testable if the patient had cryptococcal meningitis - current recommendations are to wait until ~ 2 weeks after antifungal therapy is started.