Gompf's ID Pearls

~ The Living Pearls ~

A Learning Tool about Pestilence & Contagion, for the Infectious Diseases Fellow…
&
Anyone Else with a Morbid Interest in the Peculiar

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GOMPF'S ID PEARLS – The Living Edition

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First ePrinting: 2017

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FRONTMATTER

THE LOGO:

the blue lotus - Perfection, knowledge
, eternal rebirth, perseverance

the pearls - Droplets of wisdom, or perhaps, chains of cocci?

the arrangement of the pearls - evokes the "gesture of discussion", or the Vitarka mudra, a hand gesture wherein the right thumb and forefinger are brought together, with the other fingers straightened. It signifies discussion and teaching in Buddhist traditions.

a "g" in "American Typewriter" font - In honor of the original typed pages of the "ID pearls".

HOW TO USE THIS DOCUMENT:

This document was initiated several years ago as a 20-page handout of teaching points by Dr. John T. Sinnott. Around 2000, I picked it up, transcribed it into electronic form, and began attaching more pearls and board-relevant information, along with bits of knowledge gleaned from the literature that I have found to be of clinical use. It is meant to be a tool for study and review. On occasion, I use it on rounds as a reference.

The Pearls is by no means an exhaustive overview of the subjects it covers, nor is it meant to be. It is "peer-reviewed" by my (brilliant) ID fellows and colleagues. I have tried to provide the evidence behind the Pearls as much as

possible in the References. Some of it is just plain attending experience that you won't find in a textbook (the true "pearl" and the Art of medicine).

This tool is a "living document", so if you should find an error, your comments will be most appreciated. Please include any relevant references to back you up. Any suggestions as to format and organization are also welcome.

ACKNOWLEDGEMENTS & IN MEMORIAM

Philip Thomas Gompf
August 5, 1999 to August 17, 2009

The University of South Florida Foundation Philip T. Gompf Memorial Fund was established by Dr. John T. Sinnott, Chair of Internal Medicine, to honor my son, Philip, and his aspirations to better the world. The fund supports educational efforts in Infectious Diseases throughout the Florida community, educational institutions, and online. It has supported scholarships for medical students with outstanding achievement in the field of Infectious Diseases.

I offer my humble appreciation to Dr. John T. Sinnott, who has been my dear friend and mentor for many years, and to Drs. John Toney, Richard Oehler, John Greene, Margarita Cancio and Frederick Heinzel. All have played roles in starting and/or perpetuating this teaching tool, as well

acting as my ongoing sources of wisdom (both personal and clinical).

To my contributing editors, Dr. Elvis Castillo, and medical students Laura Blood and Christian Perez, I offer my gratitude, as well as my admiration for your intellectual curiosity and generous desire to share knowledge with others. The obligation and joy of the doctor (from the verb "docere" in Latin), is to teach the Art, after all.

I offer humble gratitude for my middle child, Philip T. Gompf, who battled fulminant infection and lost. My beautiful, brilliant boy died of amoebic meningitis in 2009, at the age of 10, after tubing in a central Florida lake in summer. May my life and work and every breath that I take honor Life in your name, my cherished son, and your dear siblings, who deeply miss you. You are always present in my days.

I offer deepest gratitude for my husband, Dr. Timothy Gompf, a man of singular integrity, sensitivity, and remarkable patience. He is my anchor and my harbor from every storm we have ever faced.

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THE INFECTOLOGIST'S DICTUM

Seek and you will find it. That which goes unsought will go undetected.

Sophocles, 496-406 BC

ANTIBIOTICS

What is the First Law of Antimicrobial Use?

Antibiotics are not antipyretics. If you wish to treat a fever, use something else.
~ Larry Lutwick, MD, Dr. Schmeckman's Ten Commandments of Antimicrobial Use

Four considerations when choosing an antibiotic:

TASC
Toxicity
Activity
Spectrum
Cost

Causes of antibiotic-related acute renal insufficiency:

- Aminoglycosides - acute tubular necrosis (ATN), non-oliguric renal failure
- Amphotericin B - distal renal tubular acidosis, micro-ischemia, medullary necrosis - hypocalcemia, hypomagnesemia
- Acyclovir/sulfas - intratubular obstruction by crystals-HYDRATE patients first

- Nafcillin/oxacillin - acute interstitial nephritis, leukopenia
- Trimethoprim - artifactual, reduces creatinine excretion = Cr elevation/high K+
- Vancomycin - non-oliguric renal failure (uncommon unless peak levels > 50)
- Colistimethate (colistin) - oliguric renal failure

What is the mechanism of action, microbial spectrum, and resistance mechanism of povidone-iodine?

- Mechanism of action:

Iodophors release negatively charged free iodine (I^-). Free iodine electrophilically binds to enzymes in the respiratory metabolic chain and cell wall proteins in bacteria and fungi (direct killing); it binds hemaglutinins in viruses (prevents binding and infection of cells). More specifically, free iodine substitutes covalently for hydrogen in any available –OH, -SH, -NH, and –CH moieties.

Kills most pathogens within 15 seconds to 3 minutes of continuous contact. Drying of the solution on skin permits extended microbicidal action. It may be used in wounds, however, iodine toxicity may occur with extensive area of coverage.

- Microbial spectrum:

Broad—many bacteria, fungi, protozoa, Mycobacteria, Nocardia, and viruses. Includes Clostridia, but requires several hours of contact to kill them.

- Resistance mechanism:

None known, as the mechanism of action is not specific to a single metabolic action, and even low concentrations of free iodine are microbicidal.

Note: I^- may react with many substrates, and the presence of protein, sulfur compounds (e.g. silver sulfadiazine in a wound), and chlorhexidine may interfere with the effectiveness of povidone iodine. Don't mix them.

A patient in the postoperative/recovery unit is difficult to extubate. Which antibiotic is most likely to blame?

- Gentamicin/aminoglycoside - impairs Ca^{++} release at myoneural junction, thus may cause neuromuscular blockade either alone or in combination with neuromuscular blocking agents like succinyl choline
    - Give Ca^{++} intravenous to reverse
- Colistimethate/colistin, erythromycin, and clindamycin can do the same.

Which antibiotics may exacerbate myasthenia gravis?

- Aminoglycosides
- Flouroquinolones (inhibit GABA receptor interactions)
- Colistimethate/colistin

- Erythromycin
- Clindamycin

Which antibiotics produce otoxicity? What is the mechanism and manifestation?

- Vancomycin
- Aminoglycosides
- Macrolides

Irreversible cytotoxicity to sensory hair cells of the cochlea and vestibular apparatus. The initial manifestation is high frequency hearing loss or tinnitus, progressing to complete hearing loss unless drug is discontinued early. Imbalance is also common.

Risk factors include advancing age, renal impairment, and high dosage, but damage may occur at therapeutic drug levels. As drug accumulates in the cochlear fluid, ototoxicity may manifest up to 6 months after discontinuation.

[Williams JD. Int J Antimicrob Agents 2001;18:Suppl 1:S77-S81; Rubinstein E. Int J Antimicrob Agents 2001;18:Suppl 1:S71-S7; Selimoglu E. Curr Pharm Des. 2007;13(1):119-26; Forouzesh A, et al. Antimicrob. Agents Chemother. 2009;53(2): 483-486.]

Which drugs may crystallize in urine and cause renal

failure if the patient becomes dehydrated?

- sulfadiazine (treats toxoplasmosis)
- acyclovir (treats HSV & VZV)
- atazanavir (HIV protease inhibitor)

Your patient is receiving daptomycin for MRSA osteomyelitis, currently in week 4, as well as fluconazole that he started last week for thrush. He comes into clinic complaining of shortness of breath and fever the last 2 days. What adverse effect might he be having, and what is the culprit?

Eosinophilic pneumonitis.
Daptomycin is associated with an eosinophilic pneumonitis that may develop 2 or more weeks into therapy. Symptoms include dyspnea, fever, and pulmonary infiltrates that have a diffuse appearance like pulmonary edema. Diagnosis may be made by finding high serum IgE, or eosinophils in BAL fluid, lung biopsy, or even pleural effusion. Treatment is discontinuation of Daptomycin and a steroid taper. Pulmonary fibrosis may develop but the syndrome is mostly reversible.

What is Drug Rash with Eosinophilia & Systemic Symptoms (DRESS) syndrome? When do you suspect it?*

DRESS is an uncommon but severe and insidious drug hypersensitivity syndrome with 10% mortality. Antibiotics implicated include *vancomycin* (commonest in recent surveys—probably because of common use), sulfonamides, beta lactams, quinolones, and tetracycline (but any drug may cause hypersensitivity). It begins as a morbilliform eruption similar to commoner drug rashes, often days to weeks after starting the drug, but with the triad of fever, rash, & systemic findings: eosinophilia is common but may be absent, as well as atypical lymphocytosis, transaminitis and/or renal injury. It may mimic hemophagocytic lymphohistiocytosis.

Interestingly, reactivation of herpes simplex viruses, especially human herpes virus 6 (HHV6) but also EBV and CMV, has been associated with DRESS. A genetic component is also suspected.

DRESS may progress to multiorgan involvement and exfoliative dermatitis if the offending agent is not stopped. Hepatitis is common in half of cases (liver failure may cause death), followed by nephritis, lymphadenopathy (DRESS was reported as a pseudolymphoma reaction to anticonvulsants in 1959), pneumonitis, myocarditis. Stoppage of the offending agent and initiation of corticosteroids is life-saving.

*[This Pearl is dedicated to the memory of Izzy Tollaver, whose case advances medical knowledge of DRESS and is described in Prusty BK, et al. NPJ Genom Med. 2018 Sep 5;3:25. http://www.doi:org/10.1038/s41525-018-0064-5 . Her mother, Tasha, generously shared her story and taught be about the association of HHV6 with this syndrome. Learn more about Izzy and her mother Tasha's mission to

make clinicians more aware of DRESS: https://www.ivanhoe.com/medical-breakthroughs/making-drugs-safer-izzys-story.]

When do you use clindamycin vs. metronidazole in covering anaerobic infections?

The old rule of thumb that clinda = "above the diaphragm" and metro = "below the diaphragm" is still helpful.

- Clindamycin covers both Gram positive anaerobes such as Peptostreptococcus, Prevotella, Actinomyces, and Clostridial spp other than Clostridium difficile, as well as Gram negative anaerobes such as Bacteroides spp. (may not cover in up to 25% of cases, or strains with MIC ≥ 8 mcg/mL), Veillonella and Fusobacterium
- Metronidazole covers Gram – anaerobes such as Bacteroides fragilis and all Clostridia; it should not be used as monotherapy in aspiration pneumonia --- failure rate of about 50 percent--& not in serious head & neck infections. It will cover gut anaerobes.

[Incidentally, most beta-lactamase + Bacteroides is covered by beta lactam/beta lactamase inhibitors, so adding metronidazole isn't necessary with agents like piperacillin-tazobactam.]

What are the most common side effects of linezolid?

- Thrombocytopenia after 1 week (neutropenia possible)
- Polyneuropathy
- Optic neuritis

Which class of medications should be monitored closely while using linezolid and why?

Serotonin reuptake inhibitor antidepressants (SSRIs). Linezolid is a monoamine oxidase inhibitor (MAOI), like aged cheeses, red wine, beer, fermented foods, etcetera. MAOIs may interact with foods containing high levels of tyramine and increase biologic amines such as serotonin—i.e. due to serotonin syndrome. This may produce

- hypertensive crisis (with possible myocardial infarction or stroke), or
- delirium.

Which vancomycin-resistant Enterococcus is intrinsically resistant to quinipristin-dalfopristin?

Enterococcus faecalis, which is the commonest clinical isolate and more associated with endocarditis.

Which Enterococci are *intrinsically* resistant to vancomycin, why, & what's their epidemiologic/infection control significance?

E. gallinarum and E. casseliflavus/E. flavescens have intrinsic low-level vancomycin resistance due to vanC genes. Typical vancomycin MICs range from 2 – 16 μg/ml. VanC genes are not transferable, and these species have not been associated with outbreaks. So they are not considered "VRE" requiring infection control isolation precautions.

Which Enterococci are of epidemiologic importance and why?

E. faecalis and E. faecium acquire vancomycin resistance due to transferable vanA (high level resistance, MICs >128 μg/ml; serious infections) & vanB (lower level, MICs 16-64 μg/ml). These transferable genes are those associated with "VRE" spread in institutions, and "VRE" isolation precautions are targeted at these species when they are found to be vancomycin resistant.

Which antibiotics are bacteriostatic against Enterococci?

Vancomycin (bactericidal against Staphylococci)
Linezolid (static against Staphylococci)
Tigecycline/minocycline (static against Staphylococci)

Which antibiotics have little or no activity against Enterococci?

Cephalosporins
Nafcillin/oxacillin/ticarcillin
Ertapenem
Macrolides
Trimethoprim-Sulfamethoxazole (Enterococci can use exogenous folic acid if its own production is blocked)

Which beta lactam + beta lactam combination of antibiotics is effective against Enterococcus faecalis & why?

Ampicillin + ceftriaxone or ceftaroline
This combination works because the cephalosporin & ampicillin target different penicillin binding proteins and thus synergize to lower the MIC to ampicillin.

It is as effective as ampicillin + gentamicin in endocarditis, while sparing the kidneys. The gentamicin is performing the same function in this combination.

Which antibiotic synergizes with daptomycin against Enterococci & how?

Killing is enhanced by ceftaroline (best), ampicillin, ceftriaxone, and ertapenem. Their binding of multiple peniciclin binding proteins seems to enhance binding of daptomycin to the cell membrane, thus lowering MIC. Mechanism is unclear.

When considering the use of dapsone on a patient, which test is recommended, who is at risk, and why?

G6PD level.
G6PD deficiency is the commonest human mutation in the world and affects those of Mediterranean, South Asian, and African descent. Fava or broad beans have been known to trigger hemolysis (favism) in certain individuals since ancient times.

Aside from dapsone, what else is known to induce hemolysis in G6PD-deficient individuals?

- Infections
- Primaquine
- Fava beans, with or without a nice chianti :)

How are inhaled aminoglycosides & colistin (colistimethate) dosed?

- Tobramycin 320mg IV solution nebulized Q8 hours
- Amikacin 500mg IV solution nebulized Q12 hours
- Colistin 75-150mg IV solution nebulized Q12 hours
    - Monitor serum levels in renal insufficiency or if concomitant IV use.

How are once-daily aminoglycosides dosed?

- Amikacin or Streptomycin 15 mg/kg IV Q24H
- Gentamicin or Tobramycin 5 mg/kg IV Q24H
    - Above dose is for normal creatinine clearance over 80 cc/min; adjustments are needed for lower creatinine clearance.
    - Trough level is checked after 1st does, it should be~ zero.

How are intravenous colistin and polymixin dosed?

- IV colistin 2.5-5mg/kg/day ÷ Q6-12 hours
- IV polymixin B 1.5-2.5mg/kg/day ÷ Q6-12 hours

How is trimethoprim/sulfamethoxazole dosed intravenously and orally, and what doses are used for which conditions?

Dosing IV dosing is based on the trimethoprim component:
TMP/SMX IV solution = 16 mg TMP/mL(5 ml ≈ 50 mg)

- DS TMP/SMX = 160 mg TMP/800 mg SMX
- SS TMP/SMX = 80 mg TMP/400 mg SMX

- UTI, mild skin & soft tissue infection (SSTI)
    - 5mg/kg/day IV TMP ÷ Q6-8 hours ≈ TMP/SMX 10mL (100 mg) IV Q8 hours
    - DS 1 tablet (or 20mL suspension, 160 mg) PO BID
- Moderate SSTI, nodular lymphangitis
    - 10mg/kg/day IV TMP ÷ Q6-8 hours ≈ TMP/SMX 15mL (150 mg) IV Q8 hours
    - DS 2 tabs (or 40mL susp, 320 mg) PO BID
- Pneumocystis jirovici pneumonia, pulmonary Nocardia
    - 15mg/kg/day IV TMP ÷ Q6-8 hours ≈ TMP/SMX 20mL (200 mg) IV Q8 hours
    - DS 2 tabs (or 40mL susp, 320 mg PO TID
        - Pneumocystis jirovici pneumonia (21 days)
        - Pulmonary Nocardia (4 wks then

15mL IV Q8 hours or DS 2 tabs PO TID x 6 months; serum sulfonamide levels need to be 100-150 microG/mL 2 hrs after DS tabs dose)

Which antibiotics are bacteriostatic?

In sepsis, restore **V**olume with a **L**iter of **ST**AT **NML** (normal) saline.

Vancomycin in Enterococcus
Linezolid
Sulfas/trimethoprim
Tetracyclines/**T**igecycline
(at)
Nitrofurantoin
MLs group – clindamycin/macrolides/(streptogramins—these are bactericidal)

Everything else is bactericidal & probably better for sepsis and serious infections!
Note bene: Clindamycin might be an adjunct for Staph or Strep toxic shock, severe streptococcal cellulitis or suspected necrotizing infection; it halts protein synthesis—i.e stops production of toxins that mediate severe inflammation, necrosis, and toxic shock. Many Staphylococcus aureus strains carry inducible clindamycin resistance genes, so I suggest having susceptibilities available before relying on clindamycin alone for this pathogen.

BACTERIA

What's in a Gram stain and what does each reagent do?

A Gram stain, developed by Hans Christian Gram in the 1800s, is a serial staining method differentiating types of bacteria under the microscope. "Gram positive" bacteria have higher peptidoglycan and lower lipid content in the cell wall than "Gram negative" bacteria, therefore taking up various reagents differently and permitting them to be easily distinguished when viewed under microscope.

- Crystal violet – purple – binds peptidoglycans
- Iodine – mordant forms crystal violet-iodine complex to prevent the stain being washed away with the solvent step, next

- Acetone/ethanol – decolorizes/removes excess crystal violet, fixes it to the Gram positive cells (they dehydrate & shrink), & washes it out of Gram negative cells & removes lipids, which opens them up to take up the next dye.

- Safranin (or fuschin) – pink – taken up by the now-porous Gram negatives, which can now be seen under the microscope

What does it mean when Microbiology reports a "Gram variable" bacterium to you, what causes this

stain pattern, and which bacteria should you cover?

Bacteria may inherently take up less crystal violet, or undergo membrane changes with age that may change their uptake. Or you have overdecolorized your specimen (techs usually repeat to make sure). Anaerobes are often Gram "variable".

- Characteristically Gram positive/variable organisms
    - Bacillus, Corynebacterium – often contaminants
- Some Gram negative organisms
    - Acinetobacter (coccobacillus), less often Enterobacter/Klebsiella (patients on antibiotics)
- In CSF, consider Listeria that has been overdecolorized.

Which Gram negative bacilli may poorly take up safranin on Gram stain?

- Legionella
- Hemophilus
- Fuschin may stain these better.

What is the HACEK (or HACEK, BBQ) group?

Gram negative bacteria which are uncommon causes of intravascular infection and are difficult to culture (hold cxs 10 days with current micro systems).

- **H**emophilus spp
- **A**greggatibacter acetomycetamcomitans
- **C**ardiobacterium
- **E**ikenella
- **K**ingella

- **B**rucella
- **B**artonella
- **Q** fever (Coxiella burnetti)

What is the ESKAPE group?

The group of bacteriae that increasingly "escape" antibiotic therapy due to rising antimicrobial resistance, and which produce serious hospital- associated infections such as pneumonia, bacteremia, and urinary tract infections. New preventive and therapeutic approaches are necessary against these pathogens.

- **E**nterococcus faecium
- **S**taphylococcus aureus
- **K**lebsiella pneumonia
- **A**cinetobacter baumanii
- **P**seudomonas aeruginosa
- **E**nterobacter species (E. cloacae or E. aerogenes are perhaps the most common)

For which human pathogens are humans the only existing reservoir outside the lab?

- Mycobacterium tuberculosis
- Polio
- Malaria
- Syphilis
- Gonorrhea
- Meningococcus
- HIV
- Varicella zoster virus
- Herpes simplex
- Measles
- Mumps
- (And before it was eradicated in the wild, Smallpox)

What are the SPICE/SPACEK organisms & why are they significant? What is the preferred treatment for them?

Serratia
Pseudomonas/indole + **P**roteus
Acinetobacter
Citrobacter
Enterobacter/**E**. coli

Klebsiella

[SPICE – older; **S**erratia **P**seudomonas **I**ndole + Proteus **C**itrobacter **E**nterobacter/E.coli]

These organisms may all demonstrate resistance to beta lactams and may require carbapenem treatment. These organisms may produce inducible chromosome-based broad-spectrum beta lactamases as part of the Enterobacteriacae group, and resistance/failure may be induced during beta lactam treatment, even though they initially test susceptible. Preferred treatment in serious infection is a carbapenem (Primaxin/Merrem).

E. coli and Klebsiella are the most common extended spectrum beta lactamase (ESBL) producers, so many labs screen those isolates if MIC for ceftazidime is ≥ 2 microG/mL. Just remember that most Enterobacteriaceae should be suspect for ESBLs, & may require carbapenem treatment.

Remember that Klebsiella also has a constitutive (or inherent) chromosome-based beta lactamase that confers resistance to ampicillin/ticarcillin, so these drugs are never a good choice for this bacterium.

What are CRE and KPC organisms, and what is their significance?

CRE stands for carbapenem-resistant Enterobacteriaceae, which are often resistant to multiple other classes or may be pan-resistant. Of this family, Klebsiella and E. coli are

commoner CRE, but others may also harbor carbapenemases, and these genes are often spread on mobile genetic elements. KPC refers to Klebsiella pneumoniae carbapenemase. New Delhi Metallo-beta-lactamase-1 (NDM-1) is highly resistant. Verona Integron-Mediated Metallo-beta-lactamase (VIM) has been reported in Pseudomonas species.

[Note bene: Carbapenems and the monobactam, aztreonam are beta lactams, as they all have a beta lactam ring. This may be confusing initially when you read about beta-lactam resistance and recommendations to use a beta lactam (carbapenem); many references gloss over this, and clinically we often use carbapenems as if they're a completely different class.]

What is important to know about Acinetobacter baumanii complex bacteria? What is/are the antibiotics of choice?

In addition to being one of the inducible beta-lactamase producing "SPACEK" group above, Acinetobacter is intrinsically resistant to many antibiotics, especially all beta lactams and macrolides.

Acinetobacter exists in soil and water, as well as healthcare facilities. Multi-drug resistant strains have been commonly isolated from military causualties in Iraq and Afghanistan; some isolates have been susceptible to meropenem, but not to imipenem.

Antibiotics most often effective:

- Meropenem
- Colistin/Polymyxin B
- Amikacin
- Rifampin
- Minocycline
- Tigecycline

Which bacteria are typically gas producers?

- Anaerobes / Clostridia
- E. coli
- Klebsiella

What organisms do you think of with waterborne infection?

- Yersinia (untreated drinking water)
- Aeromonas (trauma, reptile bites)
- Vibrio (salt water)
- Pseudomonas (hot tub folliculitis)
- Legionella (aerosols from air conditioning units, drinking water, sources of standing water in institutions, plumbing)
- Leptospirosis (hunting trips, swimming in untreated fresh water, Hawaii)
- Atypical mycobacteria (pneumonia due to aerosols

from hot tubs, shower heads, faucets)
- Streptococcus iniae (cellulitis from whole tilapia fish)
- Naegleria fowleri (warm fresh water, hot springs, tap water/neti pots/plumbing)
- Balamuthia mandrillaris (soil, still water, Hispanic ethnicity)
- Acanthamoeba (contact lens solution, lakes)
- Cryptosporidiosis (untreated drinking water)
- Cercarial dermatitis (avian schistosomes/allergic reaction)
- Schistosomiasis/bilharzia (Puerto Rico/Caribbean)

What are the 2 commonest pathogens in the Nocardia genus & drug of choice?

- Nocardia asteroides (lung/brain)
  - trimethoprim/sulfamethoxazole
  - imipenem

- Nocardia brasiliensis (lymphangitis/madura foot)
  - trimethoprim/sulfamethoxazole
  - resistant to imipenem

Which pathogens cause significant recreational water illness in the U.S., and which is chlorine-tolerant?

- Cryptosporidium (chlorine-tolerant, may live for days even in properly chlorinated pools, commonest cause of l illness related to water recreation, 200% rise from 2004-2008)
- Norovirus (resistant to alcohol-based disinfectants; killed by 10% minimum sodium hypochlorite [bleach] solution).
- E. coli 0157:H7
- Giardia (chlorine-tolerant, requires longer contact with chlorine than commoner pathogens)
- Shigella (preschool ages)
- Naegleria fowleri (chlorine-tolerant, requires longer contact with chlorine than commoner pathogens; rare but may be underdiagnosed, rapidly fatal, 100% mortality; this organism, found in warm fresh water, hot springs, rain collecting systems, & underchlorinated splash pads or recreational pools, may be an increasing risk with warming global temperatures.)

Name the diseases caused by Listeria monocytogenes, common sources, and drug of choice.

- Gastroenteritis
- Meningoencephalitis
- Granulomatosis infantisepticum (spontaneous abortion/stillbirth due to disseminated Listeria; widespread micro abscesses/granulomas in the liver and spleen; abundant bacteria on Gram stain of meconium)
- Neonatal sepsis/meningitis - transplacental

infection from maternal enteritis/bacteremia

- From unpasteurized dairy products, soft cheeses, cold cuts/hot dogs/sausages-heat until steaming.

- Treatment: Ampicillin, trimethoprim/sulfamethoxazole

Stenotrophomonas is resistant to which antibiotics, and what are the resistance mechanisms?

- Resistant to most antibiotics:
- Carbapenems - intrinsic resistance due to impermeability of outer membrane; imipenem resistance is due to zinc-containing penicillinase
- Beta-lactams/Monobactam - inducible L1 & L2 beta lactamases, intrinsically impermeable outer membrane
- Quinolones - induced reduced permeability & efflux pumps
- Aminoglycosides, Tetracyclines (not doxycycline, tigecycline) - unclear

- What antibiotics are most reliable for Stenotrophomonas infections?
- Trimethoprim/sulfamethoxazole
- Tigecycline/doxycycline
- Ticarcillin-clavulanate

- (Ceftazidime, minocycline, quinolones sometimes)

Name clinically important members of Enterobacteriaceae. Which are lactose fermenters?

KEEPS fermenting lactose.

Klebsiella
E. Coli
Enterobacter
Providencia
Serratia

All these are lactose fermenters.

The Micro lab calls you to tell you that a blood culture you ordered yesterday is positive and the Gram stain reveals a "non-lactose fermenting, oxidase positive, Gram negative bacillus". Which pathogen should you make sure you are covering with your antibiotics, pending final identification?

Pseudomonas.

Can you name the gene cluster associated with vancomycin resistance in both Enterococcus and S. aureus?

The vanA gene cluster.

Can you name the gene cluster associated with oxacillin (methicillin) resistance for methicillin-resistant S. aureus (MRSA)?

MecA confers methicillin resistance.

Which gene is related to S. aureus toxin-associated virulence?

Panton-Valentine leukocidin or PVL gene.

Your patient has endocarditis with methicillin-resistant S. aureus (MRSA). He is persistently bacteremic and/or febrile after 3 days IV vancomycin. What could be causing his failure to improve?

- An undrained focus of infection
- Valve ring abscess
- Septic emboli to lungs, spleen, joints, brain may

organize into abscesses early or a few weeks into therapy
- Infected vascular devices (i.e. pacer wires)
- Vancomycin "creep" (see next question)

What are the MIC ranges for vancomycin susceptibility and resistance in Gram positive organisms?

Staphylococcus aureus
Vanco MIC 0.5-2.0 mcg/mL = Susceptible
MIC 4.0-8.0 mcg/mL = Intermediate/VISA
MIC ≥ 16 mcg/mL = Resistant/VRSA

Enterococcus faecalis/faecium
Vanco MIC ≤ 16 mcg/mL = Susceptible
MIC 16.0-128.0 mcg/mL = Resistant (mod)
MIC > 128 mcg/mL = Resistant (high)

Note: Moderately resistant Enterococcus (VRE) usually are vanB genotypes; highly resistant VRE are vanA genotypes; vanA & vanB are transferable resistance genes & usually E. faecalis/faecium & of infection control relevance. vanC genotypes (E. gallinarum/casseliflavus/flavescens) are intrinsically resistant & non-transferable, so these are not labelled as "VRE".

Describe "vancomycin creep" and when to suspect it.

Vancomycin has served humanity for over 20 years (!) in the battle against resistant Gram positive organisms. However, there is evidence that serious MRSA infections may not respond to treatment as expected when MIC is at the higher end of the accepted susceptible range of up to 2.0 mcg/mL.

Optimal antistaphylococcal activity of vancomycin requires an area under the curve (AUC)/MIC of at least 400 in S. aureus pneumonia and blood stream infections, and this concentration may not be safely achievable at MIC of 2.0 or greater.

"Vancomycin creep" refers to a gradual small increase in automated culture systems MICs to vancomycin in S. aureus strains. The clinical failure may be more significant than this small increment might suggest, as it may represent "heteroresistance" or the presence of a small population of vancomycin-intermediate S. aureus (VISA). Broth microdilution may not detect an elevated MIC. SCCmec II genotyping may be a better predictor of VISA strains with clinical relevance (Khatib R et al. J Antimicrob Chemo 2011;66:1594-99). Vanco creep remains controversial (see next Pearl), and If the clinical situation correlates, suspect "vancomycin creep" if:

- MRSA MIC to vancomycin ≥ 2.0 mcg/mL or greater (or even ≥ 1.5)
- Persistent bacteremia, fever, or other signs of delayed control of MRSA infection, especially in the absence of undrained foci—Suspect the presence of infective endocarditis.

What can you do to confirm "vancomycin creep" and help guide antibiotic treatment?

Ask the Microbiology lab to perform an Epsilometer test (E-test) for vancomycin. Generally, E-test MIC = 1 dilution higher than Vitek/automated MIC; .i.e.,

> E-test vancomycin MIC 2.0 = Vitek 2 vancomycin MIC 1.0 mcg/mL = susceptible

2017 & 2018 data suggest that E-test MIC level does not correlate with adverse outcomes like 30-day mortality; as always, underlying comorbidities may trump MIC in this regard (Hos NJ et al. J Infect 2017;74:248-59; Diaz R et al. Clin Micro Infect 2018;24:97-104)). However, E-test MIC > 1.5 does seem to be associated with infective endocarditis in those with catheter-associated bacteremia, regardless of empiric antibiotic or catheter removal (San-Juan et al. J Antimicrob Chemother 2017, 72:2102-09).

Pneumococcal meningitis is associated with what risk factors?

- Sinusitis
- Otitis media
- Skull fractures / Facial fractures
- CSF leaks/post neurosurgery
- Cochlear implants

What pathogens are associated with reactive arthritis/Reiter's syndrome?

- Chlamydia trachomatis
- Yersinia enterocolitica/Y. pseudotuberculosis
- Campylobacter
- SS – Salmonella, Shigella

Ask about day care/changing diapers (Shigella), sexual exposures (Chlamydia; Shigella in men who have sex with men), exposure to raw/undercooked poultry, eggs or pork (Salmonella, Campylobacter), undercooked or contaminated food and water.

Who is at risk for invasive pneumococcal disease (ENT, CNS or lung)?

- Sickle cell
- Hyposplenia (including polysplenia)
- Hypogammaglobulinemia
- Multiple myeloma
- Diabetics
- Alcoholics/cirrhotics

What are the hypervirulent strains of Clostridium difficile, and why are they important?

North American pulsed-field type 1 (NAP1) - the first strain to appear in 2004 in Canada; so named because it is typed by pulsed-gel electrophoresis. Other NAP types and strains have been identified by researchers.

These strains produce more severe colitis with higher morbidity and mortality than commoner strains and are spreading across North America and Europe. Commercial assays for C. difficile do not distinguish between hypervirulent and less virulent strains, thus treatment guidelines increasingly suggest hypervigilance and more aggressive treatment early into suspected colitis.

What organism causes Whipple's disease, and what are its hallmarks?

Tropheryma whipplei

Remember Mr. Whipple and his unfortunate compulsion? In case you are too young to recall, which you undoubtedly are, Mr. Whipple chastises shoppers squeezing the toilet tissue, only to get caught squeezing the irresistibly ultra-fluffy Charmin himself. ☺

Thus, confirming that
All **A**ctive **A**mericans **M**ush **C**harmin

Abdominal pain
Adenopathy
Arthritis
Malabsorption - anemia, weight loss, diarrhea
Confusion - cognitive dysfunction, oculomasticatory & oculo-facial-skeletal myorhythmia are pathognomonic

Treatment: Initially doxycycline + hydroxychloroquine, then doxycyline indefinitely with therapeutic drug monitoring (TMP-SMX has had significant failures. J Antimicrob Chemother 2014;69L219-227))

How is Whipple's disease diagnosed? What other infectious agent is it related to?

- Periodic Acid Schiff (PAS) stained material (the bacilli themselves) in the lamina propria of small bowel/duodenum.

- CSF cytology (& if available, PCR) should be performed if neurologic symptoms. (PCR of saliva & stool, though not sensitive for localized Whipple's infection, is available in Europe & in research settings.)

- It is in the same Family as Actinomyces.

General guidelines for managing Staphylococcus aureus bacteremia:

Try to find removable/drainable focus:

- CT abdomen/pelvis
- 2D Echocardiogram/Transesophageal Echocardiogram
- Remove intravenous catheters & culture tips
- Look for prosthetic devices
- Look for recent (non-epithelialized) vascular grafts

Is there a removable focus?

- NO: 4-6 weeks antibiotics
- YES, is there a murmur (some would add prosthetic devices & vascular grafts)?
    - NO: 2 weeks intravenous antibiotics
    - YES: 4-6 weeks intravenous antibiotics

What are classic features associated with Staphylococcus aureus infections?

- Golden yellow pus (aureus = "gold")
- Desquamation of palms and soles
- Toxic shock / severe illness
- Predilection for embolic seeding of
    - Lines
    - Devices
    - Valves
    - Joints & abnormal bone (arthritis, scar) – & it may occasionally coexist in bone with TB/atypical mycobacteria!)

Which Gram positive pathogens are intrinsically resistant to vancomycin?

- Leuconostoc
- Lactobacillus
- Pediococcus
- Erysipelothrix

(Enterococcus gallinarum/casseliflavus/flavescens have intrinsic low-level resistance but aren't common pathogens & don't share their resistance gene.)

What is characteristic about the manifestations of tuberculosis (TB)/Mycobacteria?

- Chronic presentations

- Cold abscesses/painless pus (monocytic, granulomatous inflammation, not neutrophils)
- Sterile pyuria (renal TB)

Most of the non-tuberculous mycobacteria are resistant to which anti-tubercular agent?

Pyrazinamide (PZA)

Can you name the Mycobacterium species that are "rapid growers"?

- M. fortuitum
- M. abscessus
- M. chelonae

Cultures may be positive within 1- week with newer culture techniques, so "rapid grower" is increasingly an historical term.

What is BCG & why is it important?

- BCG (Bacille-Calmette-Guerin) bacillus is used to immunize infants/young children in developing

countries to prevent TB meningitis.

- It does not protect against TB infection, and latent infection with TB will occur regardless of BCG status.
- But for 5-10 yrs after vaccination, the PPD is + & there is much confusion about what it means.
- Prior BCG vaccination does not cause a PPD > 20mm—that is very likely latent TB.
- A + PPD in the setting of prior BCG vaccination must be treated as if the patient never had a BCG (i.e., BCG status is irrelevant) because you cannot rule out latent TB infection.

What are the manifestations of extrapulmonary TB?

- CNS
  - meningitis (basilar meningitis, CN palsy, chronic process)
- ENT
  - laryngeal (HIGHLY contagious!)
  - chronic/painless otitis
  - adenopathy: cervical/SC/axillary adenitis (Scrofula)
- Chest
  - fibrosing mediastinitis/SVC syndrome (mimics Histoplasmosis)
  - constrictive pericarditis
- GI
  - enteritis
  - peritonitis
  - mesenteric adenitis (mimics Crohn's,

Yersinia)

- GU
  - sterile pyuria/renal
  - prostatitis
  - uterine
- Bone
  - osteomyelitis/septic arthritis --especially TB co-infection with Staphylococcus aureus
  - vertebral osteo (Pott's disease)
- Skin
  - erythema induratum (Bazin's disease-back of leg)
  - prosector's wart

How many organisms must be present on a sputum specimen for the acid-fast bacillus (AFB) smear to be +?

10,000/cc sputum

How many TB organisms must be inhaled for infection to occur?

10-100

A patient with negative sputum AFB smears whose AFB cultures later grow TB is infectious. True/False?

False.
Three consecutively negative AFB smears generally is accepted as indicating that a patient is not coughing up enough AFB to be infectious & can come out of isolation.

What are the standard first-line anti-tubercular agents and which are available intravenously (IV)?

- Isoniazid (INH) - IV
- Rifampin - IV
- Ethambutol
- Pyrazinamide
- Streptomycin – IV

What are the second-line anti-tubercular agents, IV availability, and unique features?

- Rifabutin – similar to Rifampin with longer half-life, less interaction with antiretrovirals & cyclosporine
- Cycloserine –bacteriostatic, central nervous system toxicity /seizures limits use
- Ethionamide – bacteriostatic

- Para-aminosalicylic Acid (PAS) – inhibits folic acid pathway/bacteriostatic
- large oral dose, poor GI tolerance
- Clofazamine – bacteriostatic – fatty tissue deposition/orange skin
- Quinolones – inhibits DNA gyrase/replication, IV or oral, risk of arthropathy/tendon rupture & poor absorption with concurrent calcium intake/antacids
- Other aminoglycosides (kanamycin, capreomycin) – IV only, nephrotoxicity
- Linezolid

What are the mechanisms of action, phase of activity, and possible delivery mechanisms of the anti-tubercular drugs: rifampin, isoniazid (INH), ethambutol, and pyrazinamide (PZA)?

- Isoniazid (INH) – inhibits mycolic acid/cell wall synthesis – active replication phase- bacteriCIDAL
- Rifampin – inhibits DNA-dependent RNA polymerase/RNA synthesis – slow or intermittent replication phase – bacteriCIDAL
- Ethambutol – inhibits glucose incorporation/cell wall synthesis – replication phase – bacterioSTATIC, prevents resistance when given with INH and Rifampin
- Pyrazinamide – inhibits ribosomal protein S1 (RpsA), which acts during ribosome-sparing protein –translation, i.e. permits killing of intracelluliar organisms that are not actively replicating & in acidic environment – early replication

phase/nonreplicating phase - bacteriCIDAL

- Streptomycin – aminoglycoside, inhibits protein synthesis – active replication in EXTRAcellular organisms – bacteriCIDAL

What must you NEVER do when considering changes to an anti- tubercular regimen that is clinically failing?

- NEVER add a single agent to a failing regimen (selects for resistance).
- NEVER fail to address adherence to therapy—the patient should receive directly observed therapy (DOT), which may require flexibility & accommodations to make this possible, while allowing the patient to work, etc, so that other factors contributing to TB infection do not worsen (such as money for food, housing, etc)

VIRUSES

Can you name the mutation involved in acyclovir resistance in herpes simplex?

Thymidine kinase-deficiency.

Name 5 CNS-related varicella zoster complications.

- Ramsey Hunt syndrome (zoster of the geniculate ganglion presenting as vesicles in the internal or external ear or palate or tongue associated with cranial nerve VII or Bell's palsy)
- Transverse myelitis
- Encephalitis
- Small vessel disease encephalitis (HIV infected patients)
- Large vessel vasculitis (granulomatous arteritis; acute stroke weeks or months after zoster ophthalmicus)

What is the differential diagnosis of acute bilateral cranial nerve palsy (one or multiple cranial nerves)?

- Botulism – esp descending paralysis (clues: home canned foods, potlucks, canned products from farmers markets)
- Miller Fisher variant (descending form of Guillain-Barre Syndrome; clue: viral syndrome in recent weeks)
- HIV (test everybody, regardless of admitted risk factors—trust me)
- Cavernous sinus thrombosis (clues: fever, ENT or dental infection, proptosis)
- TB basilar meningitis (clues: residence in endemic area, HIV+, TNF alpha inhibitors)
- Neurosyphilis clue: (anyone, but especially HIV+)
- EBV (recent mononucleosis-like syndrome or "strep throat")

What is the difference between encephalitis and meningitis (pathologically and clinically)?

Meningitis – inflammation of meninges; fever, headache, photophobia (esp viral)

- Nuchal rigidity or opisthotonus
- **B**rudzinsky sign = passive anterior flexion of neck causes hips & knees to **bend** (meningeal irritation)
- **K**ernig's sign = hamstring resistance to passive extension of the **knee**, when the hip & knee are flexed at 90 degrees (meningeal irritation)
- Fever with stiff neck = rule out meningitis!

Encephalitis – inflammation of cerebral parenchyma

Fever

- Delirium/mental status change
- Focal neurologic (stroke-like) findings on exam, i.e. Fever with stroke-like symptoms = rule out encephalitis!

Both are medical emergencies and require prompt empiric treatment for suspected pathogens, regardless of whether lumbar puncture is performed

Name 1 antiviral agent indicated for the treatment of novel Influenza virus H1N1.

oseltamivir

Which virus loves the temporal lobes?

HSV 1 or 2, depending on prevailing epidemiology—recently, HSV-1 has overtaken HSV-2 in causing genital herpes. Herpes simplex virus 1 is most likely older children and adults (neonates suffer from 2 more often).

Which virus causes Mollaret's recurrent aseptic meningitis?

Herpes simplex virus 1 or 2

Which virus is notorious for causing persistent arthralgias or arthritis weeks or even month after infection?

- Chikungunya virus
- Mimics dengue virus in early stages

Can you name two diseases associated with HHV-8?

- Kaposi's sarcoma
- Primary effusion cell lymphoma

What childhood vaccination (other than varicella) is important to update (give a booster) in adults?

Measles, mumps, rubella (MMR) vaccine

- In adults born after 1957 or who may have received an ineffective killed vaccine between 1963 and 1967 and never got another booster.
- The latter group is at risk for atypical measles

infection.

- Adults born before 1957 are presumed to have been exposed to measles and have long-term immunity.
- Give 2 doses of MMR to
    - Women of childbearing age
    - Healthcare workers
    - Travelers who don't have proof of immunization after 1967

Update Tetanus-diptheria every 10 years

- Update all adults: TdaP once

What is atypical measles?

A syndrome of hypersensitivity polyserositis as a result of the formation of non-protective measles antibodies in adults born after 1957 who received ineffective killed MMR vaccine

What are the complications of measles and how often do they occur?

30% of measles cases develop one or more complications:

- Ear infections - 1 in 10 measles cases, permanent loss of hearing may occur.
- Pneumonia -1 in 20 children, often cause of death

- Encephalitis – 1 in 1000 children (siezures, deafness, brain damage)
- Death – 1-2 in 1000 children
- Subacute sclerosing panencephalitis (SSPE)
    - 4-11 cases of SSPE per 100,000 (U.S. outbreak 1989-1991); risk correlates with younger ages of measles
    - Progressively fatal, degenerative neurologic disease
    - Begins 1 month – 27 years after infection (average 7 years)
    - Average survival 1-2 years
    - Brain tissue of SSPE patients + wild-type measles virus.
    - There is no evidence that measles vaccine strains can cause SSPE.

What noninfectious diseases are associated with HTLV-1 infections?

- Adult T cell leukemia/lymphoma
- Tropical spastic paraparesis or HAM (HTLV-1 associated myelopathy)
- Sjögrens
- Polymyositis
- Uveitis

What infectious diseases are associated with HTLV-1 infections?

- Crusted (Norwegian) scabies
- Strongyloides hyperinfection
- Tuberculosis
- Extensive tinea corporis

Lab test to diagnose HTLV-1 infections:

- HTLV-1 Ab
- Western blot with RIPA

How is HTLV-1 transmitted & where is it endemic?

It's a retrovirus like HIV, endemic to SE Asia

- Blood products
- Sexual contact
- Vertical transmission (breast milk)

Manifestations pf Tropical Spastic Paraparesis include

- Lower extremity weakness

- Ataxia
- Bladder dysfunction
- Spasticity of lower extremities
- Increased knee & ankle reflexes

What 6 diseases does Adenovirus produce?

- Pharyngoconjunctival fever (pools)
- Epidemic conjunctivitis/keratitis (pools)
- Acute respiratory disease (severe, epidemic URI-boot camp)
- Acute hemorrhagic cystitis (boys < 15 years old, self-limited)
- Gastroenteritis/? associated with intussusception
- Adenoviral infection/FUO in transplant patients

What physical finding is pathognomonic of Adenoviral conjunctivitis/pharyngoconjunctival fever"

Pre-auricular lymphadenopathy

(Gonococcal/chlamydial conjunctivitis do this also, but less commonly & associated with sexual activity)

With what active infections may adenovirus also be cultured?

- Epstein Barr Virus infection in immunocompromised individuals
- Bordetella pertussis (whooping cough)

Significance of the association is unclear, but co-infection might contribute to hemorrhagic features in gastroenteritis.

Which viruses produce hemorrhagic cystitis?

- Adenovirus (commonest in healthy boys, self-limited)
- BK virus (post-transplant)

For which conditions does Yellow Fever Virus pose a serious risk?

- Thymus-related disorders
    - Myasthenia gravis
    - DiGeorge syndrome
    - Thymoma
    - Thymectomy
- HIV disease, symptomatic OR CD4 <200/mm3 or <15%
    - If travel to a yellow fever–endemic area cannot be avoided by a person, a medical

waiver should be given, and the patient counseled on protective measures against mosquito bites.

- Primary immunodeficiencies
- Secondary immunodeficiency due to medications or immunomodulatory treatment
- Malignancy
- Solid organ or hematologic transplantation

What 6 diseases does Parvovirus B-19 cause?

- Erythema infectiosum/Fifth disease
- Abortion, fetal hydrops
- Chronic infection in the immunosuppressed
- Arthropathy (commonest manifestation in adults)
- Anemia in Sickle Cell disease
- Possibly chronic fatigue/FUO (+blood PCR)

Diagnosis: IgM, 4x rise in IgG drawn 2 weeks apart; Giant Pro- normoblasts on bone marrow biopsy

What diseases does HHV-6 cause?

- Exanthem subitum or Roseola infantum - high fevers in a generally comfortable child, followed by defervescence and a rash
- Fever in post-bone marrow transplant patients

What does JC virus cause and what are the typical findings that suggests it?

Progressive multifocal leukoencephalopathy (PML) in AIDS

- (progressive dementia, neurologic decline, death within 1 year)
- HIV disease with absolute CD4 < 100 cells/mL
- Focal parieto-occipital signs, insidious over weeks & progressive, similar to stroke
- gait abnormalities
- aphasia
- diplopia

What disease processes is Epstein-Barr virus associated with?

- Acute infectious mononucleosis (primary EBV infection; fevers, exudative pharyngitis, splenomegaly, lymphadenopathy, hepatitis, profound fatigue-which may be the most salient symptom in adults, resolves in several weeks)
- X-linked Lymphoproliferative Syndrome (fatal mono in genetically predisposed boys)
- Oral hairy leukoplakia (in AIDS)
- Exceedingly rare: "Chronic" EBV infection (usually immunosuppressed) [EBV does not cause chronic

fatigue syndrome.]

What malignancies are associated with EBV?

- B-cell lymphoblastic lymphomas
- Burkitt's lymphoma
- AIDS-related B cell lymphoma
- Nasopharyngeal carcinoma
- Post-transplant lymphomas (esp after OKT3, antilymphocyte therapies)
- Some T-cell lymphomas
- ? Hodgkin's lymphoma

Is acyclovir or other antivirals useful in EBV-associated diseases?

NO. Because disease manifestations of EBV, including acute mono, are related to immune activation (B-cell and T-cell activation). By the time symptoms begin, much of viral replication has resolved.

What virus causes rabies, how is it transmitted, and what tissue finding is diagnostic?

- Viruses of the genus Lyssavirus.
- Contamination of wounds or mucosa by the saliva of a rabid (encephalitic) animal.
- The "Negri body", or viral inclusion of rabies, is seen in the cytoplasm of neurons on brain biopsy.
- Rabies virus antibody appears in blood within approximately 2 weeks of infection.

What species are most likely to transmit rabies in the United States? Elsewhere in the world?

- Wild - Bats, raccoons, skunks, foxes
- Domestic – unvaccinated cats and dogs
- World: Unvaccinated dogs, foxes

What symptom heralds rabies while it is still treatable, before the onset of rabies encephalitis?

- NONE. Rabies is almost 100% fatal at the first symptom, pain or paresthesias at the original site of inoculation. Prior to symptoms, however, it is almost 100% curable by vaccination and immune globulin.
- It is never too late to vaccinate and give rabies immune globulin, unless symptoms have begun, in which IG treatment may worsen outcome.
- Rabies may incubate without symptoms for months

to a year typically, but cases have documented 6 years, rarely up to 20 years.

How is rabies prevented?

- Pre-exposure prophylaxis with rabies vaccine.
- Post-exposure prophylaxis with rabies vaccine and rabies immune globulin.

Who should receive rabies vaccine pre-exposure?

- Veterinary or animal care professionals and students
- Spelunkers
- Laboratory workers who may work with rabies virus
- Travelers from the U.S. to areas where rabies is endemic, especially if visiting areas where exposure is likely, or if staying 30 days or more

How is rabies post-exposure prophylaxis determined?

- WASH VIGOROUSLY with soap & water, to

reduce the inoculum

- If never vaccinated
    - Primary rabies vaccine series (refer to manufacturer recommendations for the vaccine formulation)
    - Human Rabies IG (as much as possible at and around the bite/exposure site)

- If prior vaccine BUT no booster in past 2 years
    - Booster series (refer to vaccine formulation)
- If prior vaccine & regular boosters every 2 years
    - None necessary, continue boosters as scheduled

What animal bite poses a low risk for rabies?

- No mammalian bite is risk-free.
- However, squirrels are not associated with rabies transmission.
- And opossums are relatively immune to rabies, because their body temperature is too low for the virus to replicate.
- Non- mammals are not infected by and thus cannot transmit rabies.

If an animal bite is provoked, then the risk of rabies is probably low. True or false?

False! A human being is not a good judge of what is provocative to a wild animal, or even a domestic animal to whom the human is a stranger.

Further a rabid wild animal may often be quite tame and docile at times, and is more likely to enter human habitats in its confusion than a healthy wild animal. Healthy wild animals do their best to avoid human activity.

A fox, raccoon, skunk, or bat that is roaming human habitats in daylight should be considered rabid.

A bat only transmits rabies if it bites. True or false?

Not clear. Several cases of documented rabies have occurred with only a history of exposure to a bat without a recalled or visible bite. An encephalitic bat may land on a sleeping human and bite painlessly, because bat teeth are exceedingly small and sharp. A bat bite may never be noticed.
There is also data to support aerosolization of rabies in caves and experimentally. A history of a bat discovered in a room with a sleeping person should be considered a rabies exposure regardless of a recalled bite.

What is tetanus?

Tetanus is a toxin-mediated disease due to toxin-producing Clostridium tetani contaminating a wound.

- It is characterized by severe and painful tetanic spasms of skeletal muscles of the entire body, unfortunately with a clear sensorium.
- Spasms begin in the masseter muscles of the jaw ("lockjaw"), and may progress to be so severe as to cause opisthotonus, tear muscles, or break bones.
- Drooling and loss of bowel and bladder continence is common.

Unless reversed by treatment, death occurs by anoxic brain damage due to asphyxia/airway obstruction during prolonged spasms, pneumonia/sepsis due to aspiration, and cardiac failure.

Tetanus is an agonizing disease that kills 25% of its victims, more in the setting of infancy.

Tetanospasmin enters the neuromuscular junction via blood and lymphatics, and reaches the central nervous system by retrograde axonal transport. It blocks release of gamma butyric acid (GABA) at the synapse, such that there is no inhibition of neuronal reflexes and spasm occurs unimpeded with even minimal stimulus.

Which wounds are at risk for tetanus?

- Last tetanus vaccine over 5 years ago AND
- Burns
- Bites
- Frostbite

- Irregular wounds, such as blunt object, crush, blast, tear or avulsion
- Wounds contaminated with foreign matter, especially soil
- Wounds over 6 hours old
- Wounds deeper than 1 cm

In the developing world, where mothers are not vaccinated, neonatal tetanus is caused by contamination of the umbilical stump, especially with cutting of the cord with unsterile instruments; neonatal mortality is 14% due to tetanus.

How is tetanus prevented?

- Pre-exposure prophylaxis is given as part of childhood primary vaccinations in the U.S., and is followed every 10 years with booster vaccine throughout adulthood.
- If a tetanus-prone wound occurs (see above), and over 5 years has passed since last vaccine, tetanus booster vaccine is given.
- If primary series was never received (there is a disturbing trend toward non-vaccination in developed countries where these scourges are not in the public consciousness), then tetanus IG should be given, as well as primary vaccination series.
- Neonatal tetanus is unknown in developed countries because mothers are vaccinated/immune, and because of attention to aseptic and sterile techniques at delivery.

How are tetanus and rabies similar?

- Drooling
- Generally clear sensorium in quiet periods
- Violent episodes ("furious" phase) in rabies, tetanic spasm in tetanus
- Incubation may last weeks or several months from the time of exposure, which may not be recalled
- Preventable by post-exposure prophylaxis before onset of illness
- May be associated with bites

FUNGI

What fungal organisms are associated with iron overload states, & desferoxamine use?

Mucormycosis (Rhizopus) -ALSO associated with diabetes

Describe the microscopic appearance of Blastomyces (Blastomycosis) and name 4 organ systems it most often affects.

Micro - Broad-based budding yeast forms in tissue specimens.

- Lungs
- Skin
- GU-prostate, epididymis, testes
- Bone

Describe the microscopic appearance of Coccidiomycosis.

- **Spherules** containing many spores **in tissue** (yeast

form).
- "Barrel shaped" beads in filamentous chains in culture (mold form)
- Severe biohazard in culture, handle only under appropriate hood!

Describe the microscopic appearance of Histoplasmosis.

Grouped clusters of yeasts that appear nucleated, often in a histiocyte or macrophage, in tissue.

Describe the microscopic appearance of Cryptococcus.

Individual yeasts, occasional pinched buds, with a **fat capsule**, in tissue or fluid smears.

Describe the microscopic appearance of Sporothrix.

"Cigar-shaped" yeasts in tissue.

Describe the microscopic appearance of Paracoccidiodes.

Large yeast with multiple buds off one central cell (**"mariner's wheel"**) in tissue.

Describe the microscopic appearance of Aspergillus.

Acutely branching (45-degree angle) septate hyphae in tissue.

Describe the microscopic appearance of Mucor.

Broad asepstate hyphae branching at 90-degree angle in tissue.

Describe the microscopic appearance of phaeohyphomycoses (dematiaceous fungi - produce black lesions.)

Hyphae that look like **fat beads strung together**, or look pinched at intervals in tissue.

What is characteristic for fungal endocarditis?

- Large vegetations
- Large arterial emboli (e.g. cold pulseless foot in an intravenous drug user)

Fungal endocarditis is an absolute indication for valve replacement.
Treat with intravenous amphotericin B and surgery ASAP.

Who is at highest risk for fungal endocarditis?

- Intravenous drug user (20% of IVDU endocarditis is fungal) – Candida parapsilosis
- Immunosuppression - Aspergillus
- Post cardiac surgery – Candida species
- Burn patients

What are the most serious complications of Candida bacteremia?

- Endophthalmitis (watch for visual loss, examine for

retinal "cotton balls"- consult Ophthalmology STAT)
- Endocarditis/emboli

What fungal complication may occur soon after resolution of neutropenia related to chemotherapy, especially for hematologic malignancy?

Hepatosplenic candidiasis (a manifestation of immune reconstitution syndrome)

Name 3 body sites were Candida lives as a colonizer without causing obvious infection?

- Sputum/oropharynx
- Urine
- Stool

Describe the microscopic appearance of Fusarium.

Septate, non-pigmented (hyaline) hyphae **and sickle- or banana-shaped macroconidia with 3-5 internal segments**.

What should you suspect in a patient with AIDS and a history of travel to the Mid West/Ohio River Valley or Mississippi River Valley & how do you diagnose it?

Histoplasmosis

- Lymphadenopathy
- Hepatosplenomegaly
- Oral ulcers
- Toxic, septic
- Also travel to/living in Caribbean, S. America

Diagnosis: Histoplasma urinary or serum antigen

Treatment: intravenous amphotericin B for 2 weeks then itraconazole oral

Note: in normal hosts, Histo may also produce chronic indolent cavitary disease, lung nodules.

Which fungi cause the true systemic mycoses (not necessarily opportunists), what is their US geographic preference/association, & drug of choice?

- Histoplasmosis-bat guano/caves/pigeons; Ohio River & Mississippi River Valleys-Amphotericin B
- Coccidioidomycosis-soil/SW US-

fluconazole/itraconazole, Amphotericin B
- Blastomycosis - moist soil, Midwest US/SE US- itraconazole
- Paracoccidioidomycosis - soil, usually Latin America ("South American blastomycosis")- itraconazole

Which fungi cause infection in patients who are iron-overloaded or have diabetes?

Mucor/Rhizopus species.
If ferritin level is high without other explanation (remember that ferritin is an acute phase reactant, rule out inflammatory causes), this may indicate a risk for these fungi.

Which fungus causes Madura Foot? How is it diagnosed & treated?

- Madurella & Allescheria species
- Diagnose by sinus tract drainage
    - Black grains speak against Actinomycete bacteria (the other differential diagnosis)
    - Do not stain Gram positive; also speaks against Actinomycete bacteria
    - + Gomorri-Methenamine Silver
    - + Periodic Acid Schiff stain
- Treatment – Surgical debridement +/- combination

therapy with sulfa/dapsone/streptomycin

What are the antifungals and what organisms do they cover?

- Fluconazole = yeasts, Crypto, NOT C. krusei/glabrata Itraconazole = yeasts, Histo, Crypto, Aspergillus
- Voriconazole = yeasts, Histo, Crypto, Aspergillus, Fusarium, *Scedosporium* apiospermum/S. auranticum (add terbinafine if S. prolificans; NOT Mucor/Rhizopus
- Posaconazole = like vori + Mucor/Rhizopus
- Isuvaconazole + Aspergillus/Mucor/Rhizopus
- Caspofungin/Micafungin/Anidulafungin = yeasts, Aspergillus, NOT Crypto/Fusarium/Mucor/Rhizopus
- Amphotericin = all, +/- Fusarium, NOT C. lusitaniae/guillermondi, Trichosporon, Scedosporium species
- Terbinafine = dermatophytes, Scedosporium species combined with voriconazole, tinea, sporotrichosis

Which azole antifungals are antagonistic when combined with amphotericin?

- Itraconazole
- Ketoconazole

What drugs do azole antifungals interact with?

MANY.

High risks include several anti-rejection drugs, statins, and antiarrhythmics.

CAUTION especially in pro-arrhythmic states, QTc prolongation, heart disease. If prolonged treatment, may wish to consider baseline EKG for QTc interval & repeat every 2 weeks. Hold if QTc ≥ 490 mm2.

Develop a habit of using drug interaction software tools, mobile application, or textbook, if you do not have access to an electronic ordering system that automates this process.

What formulations of amphotericin B are available and how are they dosed?

- Conventional amphotericin B 1 mg/kg/day
- Liposomal amphotericin B 3-5 mg/kg/day IV
    - Treat rigors with meperidine 25-50mg IV x 1
    - Hydrate with 500mg NS before & after, if

creatinine rising

- Conventional amphotericin B bladder irrigations:
    - 5 mg/100mL D5W given via bladder irrigation catheter at 42mL/hour x 48 hours
- Nebulized liposomal amphotericin B solution (50mg in 12mL sterile water, stable for 7 days
    - Given as 25mg via jet nebulizer every 2-7 days depending on condition being treated; few instances of lipid accumulation/lipoidal pneumonitis.
    - Liposomal formulation yields higher and more persistent levels in bronchiolar secretions, up to 14 days.

PARASITES

Malaria is a "FAST" disease. Name its 4 hallmarks.

- Fever
- Anemia
- Splenomegaly
- Travel within past year to endemic area

"Black water fever" refers to black/dark urine occurring during hemolysis periods of P. falciparum, especially with quinine/quinidine.

Which Plasmodium is the worst to have?

P. falciparum causes "malignant" malaria

- banana-shaped gametocyte
- parasitizes >4% of the RBC's (that's a lot!!).
- >1 trophozoite per oil immersion field on a thick blood smear suggests 10% parasitemia-that's P. falciparum!
- Multiply parasitized RBCs-that's P. falciparum!
- Peripheral or surface trophozoites-P. falciparum!
- No Schuffner's dots-P. falciparum!

Treatment: Chloroquine or mefloquine (usually P. falciparum is chloroquine resistant except in Haiti); atovaquone/proguanil (Malarone) also approved for prophylaxis/treatment of P. falciparum. Always refer to most recent recommendations of the U.S. Centers for Disease Control or the World Health Organization.

How does P. falciparum cause death?

- Hyperparasitemia (>250,000 RBCs parasitized/microL of blood on a thick smear), especially in travelers who have never been exposed to malaria.
- People who live in endemic areas are "semi-immune" & less likely to have hyperparasitemia/serious complications.
- Hyperparasitemia and the inherent stickiness or "knobbiness" of the trophozoites causes sludging in arterioles, capillaries--massive hemolysis.
- Diffuse cerebral ischemia is most life-threatening.
- Watch for severe anemia, hypoglycemia, lactic acidosis (trophozoites use anaerobic glycolysis, which produces lactate; quinine derivatives stimulate islet cell insulin also), renal failure, hypoxia, also get diarrhea, late pulmonary edema/cardiac ischemia, etc.

What are the complications of P. vivax/ovale?

- Severe anemia.
    - These trophozoites aren't sticky & only parasitize young RBCs, so they don't produce the other complications of P. falciparum, they reproduce every 48 hours (thus fever occurs every 48 hrs as disease progresses, & they reproduce at a lower rate).
- Splenic rupture 2-3+ months after resolution (even with palpation on abdominal exam—be very gentle).

What are the complications of P. malariae

Immune complex glomerulonephritis.
This is a low level parasitemia with few acute complications that may not be picked up for many years. Immune complexes are anti-parasite antibodies & P. malariae antigens.

Which group of semi-immune individuals is at a similar risk of complications as non-immune individuals?

Primagravidas.

How do you estimate the level of parasitemia (parasite density)?

Parasite density per microL = [Count # parasites/200 WBC in smear] X [Total WBC from CBC/200]

- Estimate is done on a thick blood smear, which is viewed under oil immersion.
- Blood smear should be spread just thin enough to read newsprint through it.
- It takes 20 minutes to adequately review blood smears!

- P. falciparum = >250K parasites/microL
    - Parasitizes all ages of RBCs
    - >1 trophozoite per oil immersion field
- P. vivax/ovale = < 50K/microL
    - Parasitizes younger RBCs
- P. malariae = < 10K/microL
    - Parasitizes older RBCs

How else do you tell the Plasmodiae apart?

- P. falciparum: banana shaped gametocytes
- P. vivax/ovale: red Schuffner's dots in RBCs
- P. malariae: band-like gametocytes that stretch across the RBC

How does sickle cell trait protect against P. falciparum?

Malaria in the African continent is the predominant reason that sickle cell trait has persisted in humans, as an evolutionary advantage. The parasitized RBCs are sequestered in peripheral circulation and sickling there produces low oxygen, which inhibits P. falciparum growth.

[Sickle cell trait also protects against Burkitt's lymphoma, which is endemic to equatorial Africa, in that chronic malaria also predisposes to Epstein Barr Virus infection. Brilliant!]

Which Plasmodia may relapse up to 5 years after infection and why?

- P. vivax/ovale may manifest malaria several months after initial infection, due to a persistent hepatic cycle (non-replicating dormant stage—hypnozoite) after inadequate treatment during the initial phase.
- Primaquine is added to other therapy in order to cure the hepatic phase, otherwise it may persist for up to 30 years despite treatment.

What are the vector, the manifestations, diagnostic

tests, and treatment of leishmaniasis?

- Phlebotomine sandflies (Texas S. Asia/Middle East/Latin America)
- Cutaneous leishmaniasis - raised, pizza-like (red base, yellow exudates) lesions-destruction of central face (espundia, Latin America, L. brasiliensis)
    - Biopsy the border for amastigotes.
- Visceral leishmaniasis (kala azar) - incubation period 3-8 months, fever/massive hepatosplenomegaly/wasting
    - Biopsy the liver/spleen/BM for amastigotes
- Treatment:
    - Amphotericin B for cutaneous
    - If mucosal involvement/face, intravenous pentavalent antimony/stibogluconate; fluconazole 8 mg/kg/day demonstrated 100% cure of 28 patients at 4-6 weeks (Sousa AQ. CID 2011;53)

What is Chaga's disease, the vector, diagnostic tests, and treatment?

Chaga's disease (Trypanosoma cruzi)

- C-shaped trypomastigotes in blood
- Acutely: Romaña's sign (periorbital edema), fever, myocarditis

- Chronically: fever, hepatosplenomegaly, achalasia/megacolon, cardiomyopathy

Vector: Reduviid (triatomid) bugs (Latin America/Texas)

Diagnosis: acute (blood smear for trypomastigotes), chronic (ELISA)

Drug of choice: Nifurtimox, benznidazole

What are the 2 forms of African sleeping sickness, vector, diagnosis, and treatment?

- Trypanosoma brucei rhodesiense (East African form)-EMERGENCY
    - Days to weeks: sudden high fever, myalgia, headache/somnolence/chorea, painless chancre at bite
    - Coma/death without prompt treatment
    - Increasing in travelers/safari vacations
- T. brucei gambiense (West African form)
    - Indolent
    - Weeks-months
    - Somnolence/chorea/Parkinson's-like
    - Prominent post cervical nodes (Winterbottom's sign), hepatosplenomegaly

Vector: Tse tse fly (African safari)

Diagnosis: thick & thin blood smear for trypomastigotes

Drug of choice: Suramin, pentamidine (arsenic agents:

melarsoprol/tryparsamide if CNS-get from CDC)

What is important about Strongyloides infections?

S. stercoralis can persist in the host for decades via an autoinfection cycle: larvae that hatch in the intestine reenter the bloodstream, enter lungs, are coughed up & swallowed, mature in GI tract, lay eggs, hatch larvae—and cycle repeats; interestingly, the larvae may also be excreted & have a fully independent life cycle in soil.

The normal host usually has mild or asymptomatic intestinal infection with unexplained peripheral eosinophilia—in the U.S., this finding is most likely due to asthma/atopy or Strongyloides—look for it! If heavy burden, wheezing/pneumonia (Loeffler's syndrome) may occur, as well as diarrhea, malabsorption, urticaria.

In immunocompromised hosts, *Hyperinfection Syndrome* occurs:

- meningitis
- Gram negative sepsis (from gut penetration with larvae)
- diffuse lung infiltrates
- abdominal pain
- often NO eosinophilia

Diagnosis: Think of this in the patient who is immunosuppressed, has features of the above, & has lived in the rural U.S. South (**Appalachias, coal miners**) or tropics. In hyperinfection syndrome, organism is found in

blood, CSF, sputum/BAL, urine.
Strongyloides EIA antibody is 90% sensitive.

Strongyloidiasis stool O&P X 3 or more is much less so in the normal host, because eggs and larvae are few & intermittent. Duodenal string test or Enterotest may have higher yield.

Treatment: thiabendazole x 2 d (2-3 weeks if hyperinfection). Best treatment for hyperinfection is avoidance by treating it before immunosuppression.

Describe the 3 major nematodes acquired by fecal-oral ingestion.

- Ascaris: (foot-long pig roundworm), rural US/SE
    - malabsorption/steatorrhea, likes to obstruct biliary tree/small bowel
    - easy to see on stool Ova & Parasite exam--large egg with rough coat
- Trichuris: (whipworm), rural SE US/Puerto Rico
    - iron deficiency, bloody diarrhea/rectal prolapse
    - O&P: football-shaped with plugged ends
- Enterobius: (pinworm) common in all social classes/children
    - extremely hardy in environment/sheets/dust, nocturnal perianal itching/nightmares
    - use clear tape on perianal area at night--small thready worms & oval eggs
    - treat entire family

Which parasite can be carried by the above nematodes and cause concurrent infection with diarrhea, bloating, and abdominal pain?

Dientamoeba fragilis. This amoeba was considered a commensal for some time. It is now clear that it requires a nematode co-pathogen or symbiont to successfully infect.

It is easily treated, however, it may cause unexplained relapses, because it will not clear until the underlying nematode infection is treated first.

Check 3 stools for ova & parasites x 3 consecutive days.

- If no travel & no + diagnosis, give mebendazole as for pinworm first (see preceding question).
- If a traveler, give longer course mebendazole (see preceding question).

Treatment for D. fragilis: metronidazole 500mg PO TID x 10 days or iodoquinol 650mg PO TID x 20 days

What are the hookworms & what do they cause?

Necator americanus & Ancylostoma duodenale.

- Penetrate skin of feet ("ground itch"), enter lungs/trachea, are swallowed, attach to small intestine where they suck (a lot of) blood & lay eggs.

- Major cause of iron deficiency anemia worldwide.
- Easy diagnosis by stool O&P. Treatment with mebendazole x 3 days.

Which roundworm/nematode causes periorbital edema & myalgias?

Trichinella spiralis

- ingested as a cyst from undercooked (still pink) pork, bear, walrus; cougar jerky.
- Diarrhea, vomiting, abdominal pain, then
- Orbital myalgia/periorbital edema/conjunctivitis
- Myalgias, myocarditis-prolonged muscle weakness.
- Eosinophilia/high CPK/low ESR
- Treat with thiabendazole, mebendazole, or albendazole (kills gut worms, not in muscle), otherwise supportive.

What are the cestodes/tapeworms of major clinical significance & why?

Echinococcus (liver echinococcosis)

- sheepdogs in SW US/worldwide
- surgical resection (do not spill cyst contents—may cause anaphylaxis); in liver, cyst contents may be aspirated & ethanol injected to kill daughter cysts)

Taenia solium (neurocysticercosis)

- CNS lesions/seizures/paraplegia
- diagnosis by MRI/serology
- treatment with surgical resection, +/- praziquantel, antiepileptics

What are the flukes/trematodes of major clinical significance?

- Avian schistosomiasis-"swimmer's itch" in Great Lakes, self-limited
- Schistosoma (spp. Mansoni, hematobium, japonicum)
    - Cercaria in water enter skin, blood/liver/lung-larvae migrate to
        - Small bowel/superior mesenteric veins (S. japonicum)
        - Large bowel/inferior mesenteric veins (S. mansoni)-"bilharzia"
    - Fever, stool eggs, hepatosplenomegaly, non-cirrhotic portal hypertension
    - Tissue biopsy, serology
    - Bladder/bladder vein plexus (S. hematobium);
    - +eosinophilia, fever, urine/bladder wall eggs, hematuria, hydronephrosis, UTIs, painful ejaculation, bladder cancer
    - Treatment with praziquantel x 1 day.

Which nematode can cause sudden severe abdominal

pain after a meal of undercooked fish or sushi?

Anasakis. It can be removed via upper endoscopy.

FEVER & SEPSIS

Dr. John T. Sinnott's mnemonic for formulating a differential diagnosis in fevers (or almost anything in medicine!):

CINEMA TV

Congenital
Infection
Neoplastic
Endocrine
Metabolic
Autoimmune
Toxic
Vascular

List 8 common sources of fever in an ICU patient:

- Lines
- Lung (infection, atelectasis)
- Wounds
- Urine (aka Wound, Water, Wind, Walk)
- Sinuses
- Prostate
- Candidemia
- Drugs

4 non-infectious causes of fever in an ICU patient:

DAMP

Drugs
Addison's
Myocardial infarction
Pulmonary embolus

What clues shout "Danger!" in the setting of fever?

- Petechiae/purpurae - never dismiss petechiae + fever! – think meningococcemia in the young, and Rocky Mountain Spotted Fever if possible tick exposure. These infections demand prompt evaluation and empiric treatment.
- Headache – think meningitis--do lumbar puncture
- Traveler – think malaria, east African trypanosomiasis (game park safaris), Rocky Mountain Spotted Fever (global)
- Rigors – think bacteremia/sepsis –get a blood culture
- Asplenia – think overwhelming postsplenectomy sepsis—JUMP on this!
- Hypogammaglobulinemia – r/o sepsis

What's the differential diagnosis for petechiae?

- Coagulation disorder
- Platelet disorder (e.g. TTP. ITP, chemo-related)
- Rocky Mountain Spotted Fever (DON'T WAIT for petechiae to appear—TREAT empirically: 23% mortality if treatment delayed > 5 days; other rickettsiae can cause petechiae, too)
- Meningococcemia/pneumococcal meningitis (high mortality)
- Endocarditis (acute/rapidly progressive, Staphylococcus aureus can be deadly)
- Fat/cholesterol emboli

Common causes of fever in burn patients:

CPPP
Suppurative **C**hondritis
Suppurative **P**arotitis
Prostatitis
Phlebitis

Endogenous pyrogens are soluble factors that induce fevers. Name 4 of these pyrogens.

- Cachectin (tumor necrosis factor)
- Interleukin-1
- Interferon-alpha
- MIP (Macrophage inflammatory protein)
- Prostaglandins are used as secondary mediators by these pyrogens and can be inhibited by PG inhibitors.

Define Fever of unknown origin (FUO). List common causes with frequency of occurrence.

FUO

- Classic: Temperatures of 101 degrees Fahrenheit for 3 weeks with no diagnosis after 1 week of intense evaluation.
- In areas with good healthcare access, any fever of unclear cause after basic workup for respiratory, urologic, and lung infection = FUO.
- In the early 21st century, usual causes:
  - Undiagnosed –50%
  - Collagen vascular/inflammatory (inflammatory bowel disease, temporal arthritis, polymyalgia rheumatica) – 25%
  - Infection (endocarditis, occult abscess, HIV, EBV, discitis, dental abscess, syphilis, TB, tickborne disease) –15%
  - Neoplasia (especially leukemias and lymphomas) –5%
  - Misc. (adrenal insufficiency, pheochromocytoma, Familial Mediterranean

Fever) < 1%

Causes of a relative bradycardia (also called pulse-temperature deficit or Faget's sign):

Defined as is failure to increase pulse by 10 bpm per 1 degree F above 98.6F in the setting of fever.

- Dengue
- Typhoid Fever (enteric fever, caused by Salmonella)
- Legionellosis
- Brucellosis
- Leptospirosis
- Yellow Fever
- Psittacosis
- Drug fever

Conduction disturbances* are also seen with:

- Acute rheumatic fever
- Lyme disease
- Viral myocarditis
- Infective endocarditis

*Remember to check the medication list for beta blockers

Common & overlooked causes of drug fever

- Anticonvulsants (Dilantin, Tegretol)

- Minocycline
- Other antibiotics (beta-lactams, sulfonamides and nitrofurantoin)
- Allopurinol
- Docusate sodium
- Heparin

What is Dr. John T. Sinnott's differential diagnosis for sepsis syndrome?

TAMPA

Tamponade
Adult respiratory distress syndrome
Myocardial infarction
Pulmonary embolus
Abdominal compartment syndrome

When do you see abdominal compartment syndrome & why?

- Increased pressure in a closed anatomic space threatens the viability of surrounding tissue and causes organ dysfunction. Failure to recognize the presence of intra-abdominal hypertension before ACS develops leads to hypoperfusion, multisystem organ failure, and mortality rates 40 - 100 %.

- Pulmonary capillary wedge pressure and central venous pressure increase with rising intra-abdominal pressure (IAP), despite reduced venous return and cardiac output.
- Abdominal compartment syndrome is seen with:
    - Massive volume resuscitation
    - Bowel obstruction
    - Pancreatitis
    - Massive ascites
    - Peritonitis
    - Intraperitoneal blood
    - Bowel distension or third spacing of fluids

How do you measure IAP?

- 50 mL of sterile saline is instilled into the bladder via the aspiration port of a Foley catheter with the drainage tube clamped.
- An 18-gauge needle attached to a pressure transducer is then inserted in the aspiration port, and the pressure is measured.
- ACS is not present with a pressure < 10 mmHg and usually present with a pressure > 25 mmHg.

What are the "great imitators" in infectious diseases?

- TB

- Syphilis
- HIV

What are the causes of aseptic meningitis & their clues?

Common:

- HIV (early infection, before HIV antibody + check viral load or p24 antigen; test for HIV)
- Enteroviruses (summer/fall)
- HSV (recurrent=Mollaret's)
- Partially treated bacterial meningitis (prior oral/intravenous antibiotics)

Less common:

- Chickenpox (active disease)
- TB (TB exposure/+PPD or interferon-gamma release assay)
- Brucella (goats/hooved mammals)
- Lymphocytic choriomeningitis virus (hamsters, rodents)
- Syphilis (STDs)
- Lyme/Human Monocytic Ehrlichiosis (ticks in endemic areas in NE/NCentral U.S.)
- Naegleria fowleri (summer lakes, hot springs, residential plumbing - neti pots, slip & slides)
    - 99% lethal
    - Negative spinal fluid Gram stain + classic signs of bacterial meningitis + untreated fresh water exposure = primary amoebic

meningoencephalitis until proven otherwise
- Examine routine CSF Wright-Giemsa stain or hematocytometry for trophozoites.
- CSF wet mount - look carefully for slowly moving pseudopodia of trophozoites (may mimic WBC; warm the slide or add distilled water to induce flagellation & motility)
- For diagnostic assistance, specimen collection guidance, specimen shipping instructions, and treatment recommendations, contact the U.S. Centers for Disease Control and Prevention Emergency Operations Center at 770-488-7100

What are the causes of recurrent aseptic meningitis?

- Mollaret's meningitis (classic, caused by herpes simplex virus)
- Vogt-Koyanagi-Harada syndrome (aseptic meningitis, uveitis, 8th cranial nerve deficits)
- NSAIDS (especially in young women with lupus)
- Behcet's syndrome

A black/necrotic lesion may be seen in:

- Mold infections
- Ecthyma gangrenosa (Pseudomonas or Gram negative bacillus sepsis in neutropenics)
- Cutaneous anthrax (surrounded by gelatinous edema)
- Rickettsia conorii (tache noire)
- Meningococcemia/severe pneumococcal sepsis
- Herpetic/zoster infections
- Cholesterol emboli

What organisms should you suspect with an exudative pharyngitis?

- Group A streptococcus (very common)
- Fusobacterium necrophorum (very common!)
- Epstein Barr Virus (infectious mononucleosis) – Group A Streptococcus can co-infect in acute mononucleosis
- Diphtheria (exudates grow together into a membrane that must be peeled off) - call your health department if suspected!

What organisms should prompt a search for an underlying GI neoplasm?

- Streptococcus gallolyticus (formerly S. bovis) (bacteremia/endocarditis/septic arthritis/discitis)
- Clostridium septicum (crepitant cellulitis without trauma or penetrating injury)

General principles of using vaccines and immunoglobulins (IG):

IG and non-live vaccines should be given in separate sites & syringes because the IG interferes with mounting of antibody response. The following can be given simultaneously postexposure, in different injection sites:

- Rabies vaccine & Rabies IG
- Tetanus vaccine & Tetanus IG
- Hepatitis B vaccine & Hepatitis B IG
- Smallpox vaccine & Vaccinia IG

IG and LIVE vaccines should be separated:

- MMR & varicella vaccine may be given > 3 months after any type of IG or blood product. (Or if given earlier, re-dose 3-6 months later.)
- IG may be given 2-3 weeks after MMR or varicella.
- Cholera & Yellow Fever vaccines must be separated by 3 weeks.

2 or more LIVE vaccines should be given simultaneously OR 4 weeks apart, except the following can be given at any time.

- oral polio
- oral typhoid

- Yellow Fever

Varicella IG is given post-exposure if an individual is non-immune & immunocompromised, or *pregnant*. Vaccine is then offered additionally postpartum or if /when immunosuppression resolves.

IG (aka, immune serum globulin, gamma globulin) contains specific amounts of antibody to measles, diptheria, and polio, variable amounts of hepatitis A & B, varicella, RSV, others. Disease-specific IGs include:

- Hepatitis B IG
- Varicella zoster IG
- Rabies IG
- Tetanus IG
- Vaccinia IG

BONE

List the 3 basic types of osteomyelitis, their common bacterial etiology and cure rate:

- Hematogenous – Staphylococcus* - 90% cure
- Contiguous - 50% cure - Gram negatives and Staphylococcus (Staphylococcus aureus: 50-60%)
- Neurovascular - Anaerobes - 10% cure

*Staphylococcus aureus coinfection with tuberculosis has been reported in several case reports of septic arthritis (including prosthetic joints) in the literature, with the result of delayed cure and joint destruction. Pearl: We recommend an AFB stain & culture on joint & discitis aspirates, and in any case of S. aureus of lung with risk factors for TB. [Most notable case report: Our very own Chair of Medicine! T. Sinnott, John. (1990). Tuberculous Osteomyelitis Masked by Concomitant Staphylococcal Infection. Archives of Internal Medicine. 150:1865.]

List specific underlying non-infectious conditions and the associated organisms that cause hematogenous osteomyelitis or septic arthritis.

- Rheumatoid arthritis – Staphylococcus aureus
- Gout – Staphylococcus aureus
- Sickle cell disease –encapsulated organisms

(pneumococcus, Salmonella)
- Systemic Lupus Erythematosis (SLE) – Neisseria gonorrhea
- Hemodialysis – S. aureus, Pseudomonas
- Diabetes mellitus –Group B streptococcus
- Colon cancer – Streptococcus gallolyticus
- Immunodeficiencies – Candida, atypical mycobacteria, Listeria (and Bartonella, especially in HIV)
- Post partum – Mycoplasma hominis, gonorrhea
- Terminal complement deficiency (C5-8) – Neisseria gonorrhea

What animal exposures are associated with specific organisms in hematogenous osteomyelitis?

- Cat or dog bite – Pasteurella multocida, Capnocytophagia
- Human bite (we're animals, no?) – Eikenella, Fusobacterium, oral anaerobes
- Rat bite – Streptobacillus moniliformis
- Hoofed mammals, goats -- Brucella

What are travel-associated causes of hematogenous osteomyelitis?

- Mediterranean, S. & C. America, E. Europe, Asia, Africa, Middle East – Brucella
- SE Asia – Burkholderia pseudomallei
- Many – Salmonella

What organism must be considered in an adult under 30 years of age, especially female?

Disseminated gonococcal infection. Especially during menses, pregnancy, or post partum. Diagnosis by culture of cervix (90%) > penile discharge/mouth.

List 4 complications of osteomyelitis:

- Non-union of fractures (pseudo-arthrosis)
- Limb shortening
- Gait disturbances
- Amyloidosis
- A-V fistulas
- Squamous cell cancer in sinus tracts persisting over 20 years

What imaging studies are best for diagnosing osteomyelitis?

- MRI & CT without contrast –Positive & Negative Predictive Value > 90%
- Indium & 3 phase bone scan < 70% PPV
- Plain films not + until 2 weeks post-infection – 50%
- Don't bother with gallium

What infection is most often associated with gouty arthritis flare?

Staphylococcus aureus septic arthritis, as well as septic bursitis, especially with tophaceaous gout.

Remember:
Crystals in joint fluid DO NOT exclude bacterial arthritis! Not treating septic arthritis leads to permanent joint destruction, especially if caused by S. aureus! Both gouty flare and infection cause fever, leukocytosis, and elevated sedimentation rate because monosodium urate crystals intensely activate neutrophils to produce inflammatory cytokines such as interleukin-1 (IL-1). **Tap that joint!**

[Yu KH, Luo SF, Liou LB, Wu YJ, Tsai WP, Chen JY, Ho HH. Concomitant septic and gouty arthritis--an analysis of 30 cases. Rheumatology 2003;42(9):1062-6; So A. [New knowledge on the pathophysiology and therapy of gout]. Z Rheumatol 2007;66(7):562, 564-7]

What are possible infectious complications of compound (open) fractures?

- Gas gangrene (call a surgeon!) or crepitant cellulitis (Clostridium perfringens spores from soil/gravel contamination)
- Acute (& often chronic) osteomyelitis

Define discitis, the most likely pathogen, and drug of choice:

- Discitis = inflammation or infection of an intervertebral disc space.
- Pathogen = Staphylococcus aureus in adults & children.
- Treatment = oxacillin/nafcillin (or cefazolin)

How is discitis diagnosed?

- Percussion tenderness over a vertebrum +/- fever = 90% likelihood
- MRI highly sensitive/specific: >90% Positive Predictive Value (PPV)
- CT guided aspirate for culture off antibiotics ~

50% sensitive (if nondiagnostic, repeat or consult neurosurgeon for open biopsy)
- Blood cultures

List physical findings as an epidural abscess enlarges:

- Localized pain/percussion tenderness –90%
- Distal weakness/sensory aberrations—saddle anesthesia
- Urinary retention/bowel incontinence, later overflow incontinence
- Paralysis

What organisms are fond of areas of bone abnormality or trauma?

- TB
- Staphylococcus aureus

Due to disrupted blood flow and relative ischemia in the bone.

What organisms are most commonly found in discitis?

- Staphylococcus aureus > coagulase negative Staphylocci

What organisms are especially associated with discitis in an IV drug user?

- Candida
- Pseudomonas
- Staphylococcus aureus

Septic arthritis in IV drug users is associated with which joints?

Fibrocartilaginous joints

- Supraclavicular joint
- Sacro-iliac joint
- Vertebrae

What serum markers are often used to monitor activity of osteomyelitis?

- Erythrocyte sedimentation rate (ESR)

- C-reactive protein (CRP)

Both are non-specific inflammatory markers. The ESR is more likely to be falsely elevated by anemia and in renal failure, but it is more likely to remain elevated while osteomyelitis is active. CRP declines about a week into treatment.

If a patient with a chronic ulcer overlying bone has an ESR in the 90-110 range, in the absence of acute overlying soft tissue infection, suspect osteomyelitis.

Conversely, if ESR fails to decline after resolution of cellulitis in a diabetic foot, consider underlying osteomyelitis.

[Michail M, Jude E, Liaskos C, Karamagiolis S, Makrilakis K, Dimitroulis D, Michail O, Tentolouris N. The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. Int J Low Extrem Wounds. 2013 Jun;12(2):94-9.]

What are the commonest organisms in prosthetic joint infection?

- < 3 months post-OP – S. aureus, coag-negative Staphylococci, streptococci, Gram negative bacilli
- 3-12 months post-OP – coag-negative Staph, Propionobacterium acnes, S. aureus
- >12 months post-OP – S. aureus, coag-neg Staph, P. acnes, Corynebacterium, Gram negative bacilli

What are signs and symptoms of prosthetic joint infection?

- Progressive and *constant* pain >90%
- Sinus tract if very prolonged ~30%

How is prosthetic joint infection best diagnosed?

Aspirate the joint 2 weeks off antibiotics.

- Synovial fluid culture > 80% +
- 3 + tissue/fluid/bone cultures ~95% likelihood of infection
- Negative Gram stain & cultures ~ 3% -- high NPV

Imaging is poorly sensitive overall and expensive, and aspiration will be necessary for definitive diagnosis regardless. Technitium WBC scan in particular is abnormal at least 6 months after arthroplasty. Save the patient's money.

How is prosthetic joint infection managed & what are the odds of success?

- 2 stage procedure = 95% successful
    - Debridement, prosthesis removal, IV antibiotics for 6 weeks, followed by 3 months oral
    - Aspirate culture 2 weeks off antibiotics
    - If culture negative, replace prosthesis
- 1 stage procedure = 70% successful
    - Debridement, prosthesis exchange, IV antibiotics for 6 weeks, followed by 3 months oral
- Simple aspiration & IV antibiotics = 10-60% success
    - < 3 weeks symptoms predicts success

What physical finding correlates with osteomyelitis in diabetic foot infections, what is the imaging of choice, and what is important to consider in treatment?

- A wound that probes to bone - ~90% PPV/high specificity
- Imaging of choice is MRI > 90% sensitive, high NPV
- Before debridement & extended IV antibiotics, the limb should be assessed for arterial flow
    - Ankle-Brachial Index (ABI) > 0.6 will heal (> 0.9 in diabetics)
    - ABI = dorsalis pedis systolic pressure (by ultrasound) ÷ brachial artery systolic pressure

GASTROENTERIC

List 5 bacterial agents causing GI disease by toxin production, and give drug of choice for each.

- Campylobacter fetus spp jejuni (Erythromycin/Quinolone)
- Clostridium difficile (metronidazole)
- Shigella (Quinolone)
- Salmonella typhi (Quinolone/ceftriaxone)
- Escherichia coli 0157:H7 (GIVE NO ANTIBIOTICS--may increase toxin production & risk of Hemolytic Uremic Syndrome!)

List 3 invasive bacterial pathogens and the drug of choice for each.

- Yersinia enterocolitica (Quinolone, Trimethoprim/sulfamethoxazole)
- Vibrio parahemolyticus (Quinolone--probably won't change course of illness)
- Vibrio vulnificus (cellulitis) (doxycycline & ceftazidime/cefepime)

List 3 physical findings of enteric fever, agent

responsible, and drug of choice for each.

- Enteric fever with Salmonella typhi = typhoid fever.
- Pulse rate lower than expected for degree of fever (Faget's sign)
- Rose spots on thorax
- Splenomegaly
- Agent: Salmonella typhi, less commonly S. paratyphi or S. choleraesuis
- Treatment: Quinolone/Ceftriaxone.
    - If shock, give Dexamethasone x 8 doses, starting before antibiotics to decrease mortality.

An elderly patient presents to the urgent care clinic with watery stool for 4 days. He has not eaten any new foods, eats only thoroughly cooked meats and fish, no cold cuts, no travel recently. He admits to having "bronchitis" a month ago, for which he took 3 days of amoxicillin that he had "left over" at home. He feels weak but denies abdominal pain. What blood test may be helpful to you in determining what to do with him right now?

Serum leukocytes.
Suspect Clostridium difficile-Associated Diarrhea (CDAD) in all cases of unexplained diarrhea and leukocytosis, especially severe Clostridium difficile if WBC over 20,000 or

trending upward.

The severity of today's Clostridium difficile may be under-appreciated even by ID clinicians. This risk is especially high in patients who cannot communicate discomfort, such as those with spinal cord injury or very elderly. Clostridium difficile has become a very virulent pathogen and causes many cases of rapidly progressive, life-threatening Clostridium difficile in our center. Keep a high level of suspicion.

Clostridium difficile should be considered in all cases where patients have received antibiotics within the prior 6 months.

Empiric treatment with metronidazole 500mg PO TID before test results are available is very appropriate in suspected Clostridium difficile.

Response to treatment may lag beyond 7 days, however keep a low threshold for escalation of treatment to begin IV therapy in suspected Clostridium difficile. Monitor patients for 7 days or until the patient is improving clinically.

What clinical sign warrants escalating treatment from oral to IV in Clostridium difficile, and what is the treatment?

- Abdominal tenderness (full-thickness colitis from the gut lumen to the visceral surface).
- Diarrhea may actually seem to resolve with progression to ileus. *
- IV metronidazole + PO vancomycin until WBC

declining and abdominal tenderness resolves, then stop IV metronidazole and continue PO vancomycin tapering schedule for 6 weeks (See "Bakken protocol" below).
- Consider adding PO rifaximin x 2 weeks, IV immunoglobulin, or tigecycline if very severe illness.

*Presence of a colostomy may delay consideration of Clostridium difficile. I find that many clinicians assume "the colon is gone", so Clostridium difficile isn't possible. Clostridium difficile often occurs in residual colon and rectum, as well as small bowel. The abdominal pain of colitis may be absent, & the output of an ostomy may not be recognized as "diarrhea".

What is the difference between Clostridium difficile EIA toxin assays and Clostridium difficile Polymerase Chain Reaction (PCR) assays? What are the uses and advantages of each?

Clostridium difficile EIA toxin assays
- Detects active toxin A or A+B production in virulent Clostridium difficile strains
- ~30-80% sensitive (variable), ~95% specific; if A only, will miss the 30% of cases caused by B toxin production
- Cheaper

Clostridium difficile PCR
- ~98-100% sensitive and specific

- High negative predictive value: If it's negative, it's not Clostridium difficile.
- Most efficient tool for screening suspected cases
- More expensive, but automated (less man-hours to pay for)

Your patient above has a leukocytosis of 17,000. Since he is not having orthostatic hypotension and is able to drink fluids, you send him home with 10 days empiric metronidazole orally. The next day, the laboratory reports that his Clostridium difficile EIA toxin assay is negative. Do you stop the metronidazole?

No. This question illustrates the difference in sensitivity between Clostridium difficile EIA toxin assays and Clostridium difficile Polymerase Chain Reaction (PCR).

You may choose to repeat the assay or order a C. difficile PCR assay, if those options are feasible, or simply complete the course without further laboratory confirmation if he is doing well and improving.

Your patient above returns to you for the 3rd time with watery diarrhea, confirmed last time as Clostridium difficile by PCR. What are your treatment options for recurrent/refractory infection?

It's wise to consult the Infectious Diseases Society of

America at www.idosociety.org (or other national ID expert recommendations available in your area) for the most recent evidence-based recommendations. There is variability in the literature. Regimens I find useful in my practice:

Vancomycin 250mg PO QID + rifaxamin 400mg PO BID x 14 days.

- Concurrent kefir 4-6 oz with meals TID + ad lib x 16 weeks. Kefir is a dairy product available in manyost major grocery chains. It offers ~15 live probiotic strains + Saccharomyces, vs. yogurts/probiotic supplements, which offer 1-3 at most.

- If the patient is lactose intolerant/cannot take dairy, consider Florastor (Saccharomyces boulardii) 1-2X daily x 3-4 months. Florastor is distributed without prescription at most U.S. drugstores & online merchants.

In the event of recurrence (+Clostridium difficile toxin + watery stools) after the above, consider one of the following:

Bakken's tapering combination therapy + kefir (dispense #80 PO vancomycin 125mg & #80 PO metronidazole 250mg):

- 4-6 oz kefir with meals TID + ad lib x 16 weeks
- Week 1 & 2: PO metro 250mg QID + PO vanco 125mg QID, then
- Week 3 & 4: PO metro 750mg Q3D + vanco 375mg Q3D (12 caps), then
- Week 5 & 6: PO metro 500mg Q3D + vanco 250mg Q3D, then

- Week 7 & 8: PO metro 250mg Q3D + vanco 125mg Q3D, then STOP

OR

Vancomycin taper: (dispense #84)

- 125mg QID x 2 weeks, then
- 125mg BID x 1 week then
- 125mg QD x 1 week then
- 125mg on MWF x 1 week then
- 125mg Q3D x 15 days.

[Kelly CP et al. NEJM 2008;359:1932-40; Cohen SH et al. Inf Cont Hosp Epid. 2010;31(5); Johnson S et al. CID 2007;44:846; Bakken JS. Minnesota Med 2009:38-40; personal communications with Bakken JS.]

Other thoughts include fecal bacteriotherapy ("fecal transplant"), or longterm suppression with vancomycin 125mg PO daily in the rare patient with recurrence that will not remit.

What is scombroid and how do you diagnose it?

Histamine intoxication that includes flushing, itching, urticaria, angioedema, wheezing, vomiting, diarrhea (anaphylactoid reaction). Bacteria on the surface of improperly cooled fish degrade histidine to histamine. Usually tuna, mackerel, mahi, bonito, & kingfish, but also others.

The fish tastes odd, "peppery".

100 mg histamine/100g fish = scombroid (Usually clinical findings + history of fish ingestion are diagnostic)

Treat with antihistamines & H2 blockers, epinephrine SC if severe.

What are the major neurotoxic shellfish poisonings?

- Paralytic shellfish poisoning
  - clams, mussels, shellfish
  - Alaska, Maine, Pacific Northwest
- Neurotoxic shellfish poisoning
  - Florida, Gulf, mid-Atlantic coasts
  - Brevetoxin from "red tide" algal blooms
  - oysters, clams
  - Paresthesia, reversal of hot and cold temperature sensation,
  - Vertigo, ataxia, dilated pupils
  - Cough, shortness of breath, bronchospasm
  - Bradycardia
- Ciguatera
  - Florida, Hawaii
  - Neurotoxin related to ingesting reef fish, such as barracuda, grouper, snapper, jack.
  - Abdominal pain, vomiting, diarrhea
  - Headache, vertigo
  - Paresthesias, intense itching
  - Reversal of hot & cold sensation
  - Perioral paresthesias - sensation of loose teeth

What organisms are associated with chronic liver disease and iron-overload states & what are likely sources?

Think "liver": LYVAR

- Listeria (unpasteurized dairy products, any soft cheese, cold cuts/hot dogs/processed meats)
- Yersinia (fresh water, diary, meats)
- Vibrio vulnificus (warm sea water, shellfish)
- Aeromonas (fresh water, alligator bite)
- Rhizopus/Mucor (gardening, uncontrolled diabetes, projectile injury with wood/tornado victims)

Name 9 viral causes of hepatitis:

- Hepatitis A
- Hepatitis B
- Delta virus in (coinfection with Hepatitis B is required)
- Hepatitis C
- Hepatitis E (esp fulminant hepatitis in pregnant women)
- CMV
- Varicella (primary or disseminated)

- Epstein Barr (EBV)
- Yellow fever

What is the significance of Hepatitis G (HGC or HGV) in HIV?

It may slow the progression of HIV. The data does not demonstrate improvement of mortality in HGV-HIV co-infection.

What are the risk factors for Hepatitis E (HEV)?

- Travel to endemic areas (Africa, Afghanistan)
- Contaminated water/lack of water treatment
- Not person-person/sexually transmitted.

What condition predisposes to severe HEV?

Pregnancy increases risk of symptomatic hepatitis E ~10X (2□20%), especially 3rd trimester—fulminant hepatitis

Name 3 non-infectious causes of hepatitis in pregnancy.

- HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
- Hyperemesis gravidarum - early in Pregnancy
- Acute fatty liver of pregnancy - late in pregnancy

What is the clinical significance of core promoter mutation (pre- core mutation) in hepatitis B (HBV) infection?

- Chronic HBV infection usually produces HBeAg, which has been used for following response to treatment.
- HeAg + also heralds increased infectivity.
- However, pre-core mutant HBV cannot produce HBeAg & is HBeAb-negative.
- And mutant HBV is more severe, more progressive, & less responsive to therapy. Fortunately, mutant HBV is still not very common in the US, but the possibility should be borne in mind for the patient who may relapse after treatment or have severe disease, despite a negative HeAg.

How does Hepatitis D (HDV) differ in U.S. from

elsewhere?

Mostly occurs in intravenous drug users, blood transfusion
Rare here, common in Amazon

In what way is HCV similar to HIV?

Both are RNA viruses

Both are characterized by "antigenic variability", so that despite producing antibody, it is not protective. Billions of antibodies are produced in response to billions of virions produced daily with different protein coats. Antibody production simply fails to catch up. The body recognizes them each as different strains, or "quasispecies".

This is why HIV and HCV vaccine production has failed.

List 5 bacterial causes of hepatitis:

- Leptospirosis
- Gonorrhea
- Syphilis
- Salmonella
- Coxiella burnetti

Name a protozoan cause of hepatitis:

Toxoplasmosis

List the 3 types of infectious diarrhea, area affected, agents associated.

- Non-inflammatory: proximal small bowel; watery diarrhea; no neutrophils
    - Vibrio cholera, Escherichia coli, Giardia
- Inflammatory: colon; dysentery (blood, small volume); + stool neutrophils
    - Shigella, Vibrio parahemolyticus, Clostridium difficile
- Penetrating: distal small bowel; enteric fever; +/- 's
    - Yersinia enterocolitica
    - Salmonella typhi
    - Entamoeba histolytica
    - Clostridium difficile colitis

Name the causes of infectious gastroenteritis syndromes by incubation period (& note key features or exposures):

<6 hours

Heat-*stable* pre-formed toxin:

- Staphylococcus aureus (mayonnaise, cream not kept cold)
- Bacillus cerius (rice not kept hot)

>12 hrs

- Norovirus (vomiting; epidemic; daycare, school, nursing homes, cruise ships)
- Rotavirus (daycare; school)
- Clostridium perfringens (inadequate reheating; meats; potluck, buffet; heat-*labile* pre-formed toxin)
- Campylobacter (raw chicken)
- Salmonella (raw chicken, eggs)
- Shigella (bloody; men who have sex with men, especially proctitis; daycare; institutionalized people)
- Yersinia (raw dairy; pork; pigs; chitterlings/intestine)
- Listeria (salty cold cuts, dairy; pregnancy loss/neonatal sepsis)
- Enterotoxigenic E.coli/ETEC (travel)
- Vibrio parahemolyticus (sushi)
- Vibrio cholera (lack of latrines, sanitation; rice-water stool; lose several liters within hours; some vomiting)

> 7-10 days

- Giardia (drinking untreated fresh water)
- Cyclospora (water-borne—rinsed berries/vegetables)
- Hepatitis A
- Cryptosporidium (public pools;

daycare; MSM; resists chlorine)
- Order Microsporidia (Enterocytozoon, Encephalitozoon species; HIV)
- Entamoeba histolytica (fever, bloody stool in traveler from underdeveloped areas)

Which stool pathogens stain acid fast? How are they differentiated?

The parasites that start with C are aCid fast.

- **C**yclospora – largest, up to 30 microns
- **C**ycloisospora- ~10 microns ←glows under UV
- **C**ryptosporidium – smallest, ~5 microns ←glows under UV

Which is the smallest parasite that causes chronic diarrhea in immunocompromised hosts? How big is it, and what stains are commonly used?

Microsporidia species (Enterocytozoon, Encephalitozoon species)
- 1-4 microns

- Routine trichrome stain, Chromotrope, Calcoflour white

True or false: Diarrhea is always present in a person with hepatic amebiasis.

False. Liver abscess may occur without diarrhea or the presence of the amoeba in the stool. Fever, RUQ pain, and weight loss is most common. The organism enters the portal veins from the bowel to infect the liver. Diagnosis is usually by Entamoeba histolytica titers, occasionally by liver aspirate: "anchovy paste" pus.

True or false: Amebic abscess can be treated with one drug.

False. Asymptomatic cyst carriage may be treated with a luminal agent, such as diloxanide, paromomycin, or iodoquinol. Amebic colitis and liver abscesses must be treated with a trophozoite agent (metronidazole) AND a luminal agent x 10 days.

What are characteristics of amoebic colitis?

- Bloody (or heme +) stool & fever in a traveler to the developing world.
- Flask shaped ulcers in the colon (biopsy the edge for trophozoites)
- Stool ova & parasite exam x 3 should be done to look for cysts and trophozoites containing ingested RBCs.

What are 3 causes of mesenteric adenitis?

- Crohn's disease
- Yersinia pseudotuberculosis ("pseudo-appendicitis", also mucosal ulcers in terminal ileum)
- TB

What are the sources of Yersinia enterocolitica infection?

- Raw pork intestines ("chitterlings") - pigs are major reservoir
- Raw poultry
- Raw dairy

What extraintestinal disease may follow Yersinia enterocolitica infection?

- Erythema nodosum
- Reactive arthritis/Reiter's syndrome

What GI pathogens are associated with reactive arthritis/Reiter's syndrome

- Campylobacter
- Yersinia species
- SS – Salmonella, Shigella

What are the sources of exposure for Campylobacter?

- All poultry, raw eggs (majority of U.S. cases)
- New ill puppies (classic scenario)
- Child day-care centers (outbreaks)
- Raw dairy (outbreaks)
- Anogenital intercourse
- Untreated/contaminated water (outbreaks)
- Usually NOT non-sexual, person-to-person contact

What may cause recurrent Campylobacter, especially

C. fetus?

- HIV infection
- Immunoglobulin deficiency
- Cell-mediated immune deficiency
- Gastric acid reduction (proton pump inhibitors, H2 blockers) - reduced acid may extend colonization with infective organisms beyond 3 weeks; consider extended duration of antibiotics

What is the pathophysiology of Campylobacter gastroenteritis?

- Toxin mediated watery or bloody/inflammatory diarrhea
- Immune-complex vasculitis with bloody diarrhea/pseudomembranes
- + leukocytes in stool

What extraintestinal disease may follow Campylobacter jejuni infection?

- Guillain-Barre syndrome (40% U.S. cases may be due to Campylobacter)
- Reiter's syndrome

What adjunctive treatment is best avoided with PO Vancomycin in the treatment of Clostridium difficile colitis?

Oral cholestyramine or colestipol. They bind the oral vancomycin.

Otherwise these resins are a useful adjunct to oral metronidazole in binding the toxin that causes the diarrhea & pseudomembranes. Probiotics such as lactobacillus preparations may help repopulate the bowel with more "normal" flora that out-compete Clostridium difficile. These are usually not "human" Lactobacillus species & the bowel will eventually repopulate with normal flora once antibiotic pressure is removed.

Any diarrheal problem may be treated with anti-spasmodic agents such as loperamide (Immodium®). True or False?

CAUTION! If the cause of diarrhea is likely to be severe infectious or toxin-related, AVOID anti-spasmodic agents. If watery stool is severe, try oral re-hydration and "water/toxin binders" such as colestipol or even psyllium, first. Remember that one function of diarrhea is to rid the bowel of the offending agent or toxin. If you slow this process down in the setting of severe Clostridium difficile

or an invasive pathogen such as Shigella, you may precipitate the disaster of toxic megacolon (or toxic colitis without megacolon), which may require urgent resection of the entire colon. Studies recently support that anti-spasmodics may be safely used in mild to moderate infectious colitis such as Clostridium difficile.

Other drugs that may precipitate toxic colitis include anticholinergics, opioids, and antidepressants.

What infectious agents may be associated with toxic colitis?

The inflammatory and/or invasive pathogens. Signs may include + fecal leukocytes, small bloody stools (dysentery), fever, leukocytosis:

- Clostridium difficile
- Salmonella, Shigella, Yersinia, Campylobacter
- Entamoeba histolytica
- Cytomegalovirus

What is the clinical picture of E. coli H7:0157, sources of infection, associated complications, growth media, and treatment?

- Afebrile watery, then bloody diarrhea
- Undercooked (pink) hamburger meat,

unpasteurized apple cider
- Hemolytic uremic syndrome (triad of acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia; children 5-10 & the elderly)
- Sorbitol-MacConkey (SMAC) agar (it is "sorbitol-negative"/requires sorbitol to grow)
- Supportive (antibiotics may increase toxin-production, increase risk of HUS)

What are the usual sources of a psoas abscess?

Local:
- Gut: diverticulitis, Crohn's disease (polymicrobial)
- GU: perinephric abscess (S. aureus, Gram negative bacillus)

Hematogenous:
- Blood: bacteremia from another focus (S. aureus)
- Bone: vertebral TB (Pott's disease) was once the commonest cause

GYNECOLOGIC & UROLOGIC

What is asymptomatic bacteriuria?

Growth at least 100,000 colony forming units/mL of bacteria in a urine culture in the absence of symptoms. It is not a urinary tract infection.

Asymptomatic bacteriuria (ASB) occurs in up to 2% of children and 5-10% of premenopausal women. 40% of those over 65 have it; % increases with age. Antibiotics do not kill nonreplicating bacteria, thus treatment does not eradicate ASB. But it does trigger resistance genes and increases adverse effects of antibiotics.

What is a urinary tract infection (UTI)?

Symptoms of GU infection + > 100,000 colony forming units/mL of bacteria in a urine culture.

- *Symptoms* are the defining feature of UTI, not level of pyuria or bacteriuria, not leukocyte esterase, or nitrites.
- No symptoms = no UTI

Symptoms most suggestive of UTI include:

- Fever (may be absent in advanced age or steroids) or rigors

- Burning on urination
- Frequent urination despite minimal urine
- Hesitancy on urination or perceived difficulty with voiding due to spasm
- Pelvic discomfort
- With ascending infection: costovertebral angle tenderness, flank pain, nausea/vomiting
- In dementia, look for new delirium/somnolence, new urinary incontinence, nausea/anorexia, physical exam signs of UTI.

How do you interpret pyuria in adults?

Pyuria or the extent of pyuria has not been shown to correlate with the presence of symptomatic UTI, incidence or onset of symptomatic UTI, or with morbidity/mortality associated with pyuria itself or symptomatic UTI.

Pyuria is common with advancing age in both genders. It does not indicate or warrant antibiotic treatment in itself.

Its utility is in the high negative predictive value of its absence: If your patient has no UTI symptoms and minimal pyuria, you may want to look for an alternative source of fever!

How is simple cystitis treated in a woman?

- oral trimethoprim-sulfamethoxazole for 3 days
- nitrofurantoin for 5 days
- fosfomycin for 1 dose

If ascending infection is initially suspected but nausea is not severe enough to preclude oral therapy, treatment may be extended to 7 days.

Avoid quinolones first line, due to risks of hypoglycemia, QTc prolongation, neurologic and tendinous adverse effects. And increasing resistance to them!

When does urinary tract infection (UTI) require further evaluation and perhaps longer treatment?

UTI in a male. Men have fewer UTIs due to a longer distance between the urethral meatus & the bladder. If a man presents with symptoms of UTI AND bacteriuria, 1 week of antibiotics may be given and evaluation for possible urologic impediments to flow, or stones, is warranted.

Recurrent symptoms of UTI in a male may also be associated with unrecognized chronic prostatitis that is undertreated by a course of antibiotics that would be sufficient for UTI.

The prostate is not well-vascularized and requires 6-8 weeks of antibiotic therapy for resolution of infection. In the absence of overt pain and acute illness or toxic appearance that is suspicious for acute bacterial prostatitis, check for a bogginess or tender prostate on examination. Chronic

prostatitis may require other urologic investigations and is best referred to a urologist.

Acute bacterial prostatitis is more obvious (VERY painful) & associated with bacteremia; if you suspect this, do NOT examine the prostate, due to risk of septicemia).

Which antibiotics have the best penetration into prostatic fluid?

- quinolones with Gram negative coverage
- trimethoprim-sulfamethoxazole
- fosfomycin

Causes of UTI in men include:

- Benign prostatic hypertrophy
- Nephrolithiasis
- Chronic prostatitis
- Instrumentation/catheterization
- Congenital/anatomical abnormalities of the urinary tract

What are causes of recurrent UTIs?

- Inadequate hydration due to poor thirst mechanism
- Inadequate antibiotic therapy/resistant organisms
- Congenital/anatomical abnormalities of the urinary tract
- Stones (urea-splitting Proteus/Klebsiella spp may produce large staghorn calculi; must eliminate colonized stones to clear infection, usually via lithotripsy)
- Uremia/azotemia/papillary necrosis (poor renal function does not allow adequate antibiotics into the kidney/urine)
- Perivesical abscess or colonic disease (cancer, Crohn's disease) with fistulas to bladder
- Benign prostatic hypertrophy
- Chronic prostatitis

What organisms may cause prostatitis other than the usual bacterial causes of UTI? Why?

- Tuberculosis/Mycobacterium bovis (after BCG treatment for bladder cancer) - granulomatous
- Fungi – Cryptococcosis, Blastomycosis, Coccidiomycosis

What do you do with asymptomatic bacteriuria and + urine culture in a woman?

If she is not pregnant, nothing.

Asymptomatic bacteriuria in pregnancy is considered to be a cause of pyelonephritis, miscarriage, and preterm labor and warrants immediate treatment with antibiotics. (This is being questioned and may change, but as of 2017, it stands.)

What do you do with asymptomatic bacteriuria in a male?

If the patient is about to undergo a urologic procedure that is expected to cause mucosal bleeding, then 1 preoperative dose of antibiotics should be given.

- Asymptomatic bacteriuria in this setting is associated with urosepsis
- PreOP antibiotics are beneficial

Asymptomatic bacteriuria need not be assessed or treated preOP for any other surgical procedure, including prosthetic devices. PostOP infection rate is not affected, nor is it reduced by treating + urine cultures with antibiotics.

Advancing age, obstruction (BPH, other), bladder catheterization, and spinal cord injury are associated with asymptomatic bacteriuria.

- No antibiotic treatment is warranted.
- However, this is a good opportunity to remove an unneeded catheter, assess for fixable obstructions

to urinary flow--enlarged prostate, stones, ureteral reflux--and get them fixed.

- UTI symptoms do lead to pyelonephritis and urosepsis when there is obstruction to flow and warrant antibiotics (remember: correct the flow).

What do you do with asymptomatic bacteriuria in a patient with a bladder catheter > 2 weeks?

Nothing.

- Change the catheter only when there is obstruction to flow or if there is a symptomatic infection (especially yeast).
- Bladder or catheter bag irrigations with peroxide, topical antibiotics to the urethral meatus, or routine catheter changes do not reduce infections.
- Breaks in the closed catheter system are KNOWN to produce infection.

List 4 common infectious causes of urinary tract infection or UTI. Which is associated with renal stones?

- Escherichia coli
- Enterococci (Group D streptococcus)
- Staphylococcus saprophyticus
- Proteus mirabilis (indole-negative) - associated with

struvite renal stones (staghorn calculi)

The nurse in the long-term care facility calls to report that Mrs. X has been having strong-smelling or cloudy urine, and requests an order for antibiotics. What questions do you have for her?

Is Mrs. X having symptoms of UTI (see above)? If she is chronically unable to express herself due to dementia, does she have signs of UTI (fever, chills, suprapubic tenderness)? Does she have other signs of infection in the elderly, especially new delirium, new somnolence, or anorexia?

UTI is a common cause of infection in the elderly who develop new mental status changes, but also keep in mind constipation, new medications, dehydration from poor thirst mechanisms, etc.

Changes in color, odor, concentration, or clarity DO NOT correlate with the presence of UTI, especially with catheters. But it seems a common misconception among the lay public, nursing, and allied health professions, and often leads to unnecessary antibiotics.

Bacterial vaginosis (BV) is an infection. True or false?

No. It is an imbalance of the vaginal flora from the usual predominance of Lactobacillus species to a polymicrobial

mix of anaerobes and gram-negative bacilli, including Gardnerella vaginalis, Bacteroides, viridans streptococci, Fusobacterium, Veillonella, Eubacterium, and Mobiluncus species. Mycoplasma hominis, Ureaplasma urealyticum, and Atopobium vaginae are also associated with BV. While mechanisms remain unclear, the organisms are felt to grow synergistically to outnumber the Lactobacilli. G. vaginalis also produces a biofilm in the vagina that may facilitate colonization by other organisms and resist metronidazole. Low pH tends to retard growth of many bacteria; thus, I speculate that once the pH rises, the environment progressively shifts to one that is friendlier to non-lactobacilli and promotes a cycle of bacterial overgrowth.

Normal vaginal pH is maintained in the range of 3.5 to 4.5 by peroxide- and lactic acid-producing Lactobacilli. When other species overgrow, the pH rises above 5. BV may occur in virginal individuals; however, it is highly associated with lifetime number of sexual partners, a new sexual partner, and male urethral colonization with Gardnerella. I speculate that sexual partners may simply introduce a greater variety of potentially colonizing flora into the vagina or perineum. Condoms may reduce the incidence. It seems feasible that hormonal shifts occurring throughout the lifetime may also alter vaginal chemistry.

[Verstraelen H. Cutting edge: the vaginal microflora and bacterial vaginosis. Verh K Acad Geneeskd Belg. 2008;70(3):147-74. PMID: 18669158]

Other than annoyance, what is the importance of BV?

BV in pregnancy is associated with a higher rate of miscarriage, early (preterm) delivery, and post-partum/post-abortion endometritis, so it is important for pregnant women to be tested and treated for bacterial vaginosis, even if asymptomatic.

What are the symptoms and clinical findings of BV?

- Thin, homogenous, white to grey discharge that coats the vaginal wall (biofilm?) and is annoying to the patient.
- Disagreeable fish-like odor, especially after intercourse.
- Vaginal fluid pH > 4.5 (highly sensitive) – use a pH strip.
- Positive "whiff test" (highly specific): Add a drop of 10% KOH solution to vaginal secretions on a slide. Sniff—a fishy odor indicates release of amines related to anaerobic products.
- Pathognomonic "clue cells" on a saline wet mount of vaginal secretions: Mix secretions with a drop of saline on a slide, add a coverslip, and view under a microscope. Epithelial cells covered with adherent bacteria (biofilm effect?) are the "clue".

Treatment of bacterial vaginosis:

According to the textbooks & board exams:

- Metronidazole 500mg PO BID x 7 days
- Metronidazole intravaginal gel 1 applicator-ful QHS x 5 days
- (Increasing resistance to metronidazole may be a problem, especially Atopobium vaginae species)
- Clindamycin 300mg PO BID x 7 days
- Clindamycin 2% vaginal cream 5g intravaginally QHS x 5 days
- Clindamycin ovules 100mg intravaginally QHS x 3 days
- Tinidazole 2G PO once

My anecdotal experience:
In the absence of pregnancy, broken mucosal barrier, or structural abnormalities that might obstruct outflow, peroxide 3% 10 cc intravaginally via bulb syringe daily x 5 days (may also dilute 50:50 with water, preferably distilled but tap is OK).

It's cheap, over-the-counter, no resistance. Minimal to no side effects, no need to stop sexual activity (the extra fluid will run back out in the commode; it may help to fully reach all areas if the patient lies flat for a couple of minutes after instilling the fluid.)

(Cardone A, et al. Utilization of hydrogen peroxide in the treatment of recurrent bacterial vaginosis. Minerva Ginecol. 2003 Dec; 55(6):483-92. Review. PMID: 14676737.)

Follow up with plain Stoneyfield or Dannon brand yogurt, or any brand of kefir (reliably acidic and consistently have active cultures—I have no financial relationship to disclose but I'm a pretty good yogurt & kefir maker.):

2-3 tablespoons (watered down with distilled water or saline if consistency is too thick) applied intravaginally QHS x 6 days

Also, cheap, over-the-counter, no adverse effects, no resistance, no need to stop sexual activity. Repopulation by lactobacilli may be facilitated by peroxide pre-treatment by restoring an environment favorable to them (they make peroxide). You will be a star to the woman who comes to you with her umpteenth BV episode fed up with antibiotics. In case of recurrence, which will be less often, just do it again.

CAUTION:
NEVER EVER put peroxide into a closed cavity or a space that does not easily drain, or inject into tissue or into or adjacent to a vessel. Don't apply it to inflamed or granulating, healing tissue. Peroxide is toxic to living cells other than unbroken mucosa. It also may release gas with unexpected force, and has been documented to produce lethal air embolism when instilled into abscess cavities, or adjacent to a blood vessel, for example. Pregnancy causes increased tissue vascularity, and there is no data using peroxide in pregnancy, so BV treatment is best managed with standard antibiotics.

EYE

What are the infectious causes of retinal vasculitis, any pathognomonic signs/associations, & diagnostics?

- Cytomegalovirus (CMV) – advanced HIV or other immunodeficiency with absolute CD4 <75
- Toxoplasmosis – immunocompetent; white focal lesions & severe vitreous inflammation
- Tuberculosis – primary active/miliary TB clinically and by chest X-ray, +PPD or interferon gamma release assay (IGRA, e.g. Quantiferon)
- Syphilis - + specific Treponemal test, e.g. FTA-Ab, Treponemal IGG (regardless of RPR or VDRL), may be the only other finding; HIV raises suspicion & likelihood; may or may not have Argyll-Robertson pupil or other manifestations neurosyphilis (eye is part of central nervous system!)
- Herpes simplex & zoster– chemotherapy-induced immunosuppression; white retinal infiltrates; zoster usually involves ocular division dermatome of trigeminal nerve
- Whipple's disease – All Active Americans Mush Charmin (abdominal pain/adenopathy/arthritis/gut malabsorption/confusion; PAS-positive macrophages on small bowel biopsy, +CSF PCR
- Lyme disease, late disseminated stage – months to years untreated, large joint intermittent pain/swelling, peripheral neuropathy, cognitive dysfunction; treat as for late disseminated Lyme; granulomatous iritis and vitreitis, neuroretinitis

reported

What are the manifestations of ocular herpes? What complications are associated? Best treatment?

- Dendritic keratitis – commonly seen in primary care offices, superficial cornea epithelial viral replication; classic branching appearance; may resolve spontaneously without sequela, but topical triflouridine or oral acyclovir is recommended
- Best managed by an ophthalmologist with topical, oral +/- corticosteroids:
    - Geographic ulcer – dendritic lesion that has enlarged, takes longer to heal, may scar
    - Stromal keratitis – uncommon, more likely with recurrent disease; deeper infiltrates due to antigen-antibody complexes most often; less commonly, necrotizing with active infection similar to progressive bacterial keratitis, risk of perforation
    - Uveitis, endothelitis, corneal perforation with recurrent disease

Oral acyclovir 400mg BID or oral valacyclovir 500mg daily x 1 year for suppressive therapy should be considered in recurrent disease or disease more severe than dentritic ulcer.

What is the differential diagnosis for bilateral periorbital edema that is not caused by cellulitis?

- Cavernous sinus thrombosis
- Epstein Barr Virus ("Hoagland sign")
- Trichinella spirallis (trichinosis)
- Hypersensitivity reaction
- Any cause of marked fluid retention or anasarca (hypo- or hyper-thyroidism, nephrotic syndrome, etc)

HEAD & NECK

Which cerebrospinal fluid (CSF) exam is underappreciated (& underutilized) but as useful as the Gram stain in determining the presence of bacterial vs. aseptic meningitis?

The CSF lactic acid level.

CSF lactic acid < 3 mmol = aseptic meningitis, 10 mmol = bacterial meningitis. 3-10 mmol usually is partially treated bacterial meningitis.

Unfortunately, few laboratories perform it despite several studies that support its reduction of costs and antibiotic overuse.

Bacterial meningitis initiates at the following sites in the following pathogens:

- Listeria - mild or asymptomatic gastrointestinal infection
- Pneumococcus - pneumonia/otitis media/sinusitis
- Hemophilus - otitis media
- Staphylococcus aureus - endocarditis
- Meningococcus - pharyngitis

Other than covering for pneumococcus and meningococcus, what organisms do you cover for in patients who are over 50 or pregnant? What do you add to the initial regimen?

Listeria (ampicillin or trimethoprim/sulfamethoxazole)

If the lab calls you about "diphtheroids" in your CSF sample, what do you think?

Listeria, Listeria, Listeria!

It's a Gram positive rod, like Bacillus & Corynebacteria, & may be mistaken for these skin contaminants.

What organism is important in causing meningitis in patients with neurosurgery, CSF leaks (clear rhinorrhea) or basilar skull fracture?

- Pneumococcus
- S. aureus
- Pseudomonas/Gram negative bacilli

What infectious agents may be associated with chorea or dystonia?

Classic:

- Group A streptococcus (post-streptococcal infection Syndenham's chorea)

Less often:

- Mycoplasma pneumoniae
- Legionella pneumophila

Others:

- Streptococcus viridans, Streptococcus pneumoniae
- Herpes simplex
- Borrelia burgdorferi
- ECHO virus
- Syphilis
- HIV
- Haemophilus
- Neisseria meningitidis
- Toxoplasma gondii
- TB
- Cryptococcus neoformans

Describe NMDAR encephalitis.

First described 2007.

Autoimmune N-methyl-D-aspartate receptor (NMDAR) antibody, which is produced by ovarian teratomas, is commoner than herpes, West Nile, varicella, in those under 30, commoner in young women. Has also been associated with acute Mycoplasma pneumonia.

NMDAR encephalitis mimics infectious causes (especially rabies) and neuroleptic malignant syndrome, with fever, delirium, seizures, and autonomic instability. Mild CSF pleiocytosis and mild CSF protein elevation may occur; CSF glucose is normal.

Diagnosis:

- Acute psychosis in s young woman or child
- + Anti-NMDAR titer
- Check CT chest/abdomen/pelvis for teratoma OR + acute rise in Mycoplasma titers
- Treatment: Resect the tumor

List infectious causes of encephalitis.

Viral:

- Herpes simplex 1 or 2
- Varicella zoster
- Powassan (ticks)
- West Nile Virus
- St. Louis
- LaCrosse
- Equine

- Rabies
- Polio
- Enterovirus-68 (California children with acute paralysis, 2014)

Bacterial:

- Lyme

Protozoan:

- Naegleria fowleri
- Acanthamoeba
- Balamuthia

List non-infectious causes of encephalitis.

- Anti-NMDAR encephalitis
- Behcet's
- Vasculitides
- Drugs/neuroleptic malignant syndrome
- Chemotherapy

West Nile encephalitis often presents with an ascending paralysis. How might you differentiate West Nile encephalitis from Guillain-Barre syndrome?

West Nile Virus:

- Confusion
- CSF pleiocytosis
- Elderly
- Fever

Guillain-Barre:

- Clear sensorium
- Normal CSF

Classical bacterial causes of pharyngitis and drug of choice for each.

- Group A streptococcus (penicillin/clarithromycin x 10d - there is increasing macrolide resistance)
- Fusobacterium necrophorum – (penicillin/clindamycin/metronidazole)
- Arcanobacterium haemolyticus (penicillin/macrolide)
- Mycoplasma pneumonia (doxycycline/macrolide/quinolone)
- Corynebacterium diphtheriae (erythromycin + antitoxin from Centers for Disease Control)

What causes epiglottitis?

Children < 5:

- Group A streptococcus (Hemophilus disappeared due to HiB vaccine),

Children > 5:

- Group A streptococcus

Adults:

- Almost always Group A streptococcus
- Hemophilus in older adults

What organism causes isolated uvulitis (inflammation of the uvula)?

Group A streptococcus

What else is in the differential diagnosis of uvular swelling?

- Trauma (intubation, aggressive suctioning during procedures)
- Angioedema/allergic reactions (pale uvula)

What are the immunologic sequelae of Group A streptococcal infections & how might they be prevented?

Acute rheumatic fever/rheumatic heart disease

- Streptococcus of throat only
- Penicillin is preventive, thus we always treat Strep throat to prevent rheumatic fever!!

Acute post-infectious glomerulonephritis

- Streptococcus of throat & skin/impetigo
- Penicillin does not prevent

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus)

- Autoimmune reaction – strep antibodies cross react with neural tissue
- Symptoms include Obsessive Compulsive Disorder, tics, and other neuropsychiatric symptoms

What symptoms/complications are associated with sinusitis of which sinuses?

- Frontal - epidural/subdural abscess - Pott's puffy tumor
- Maxillary - mild facial numbness (2nd branch of cranial nerve V/Trigeminal), tooth pain
- Ethmoid - watering eye, cavernous sinus thrombosis
- Sphenoid - retro-orbital/occipital headache, orbital cellulitis

How do you differentiate orbital cellulitis from cavernous sinus thrombosis?

Cavernous sinus thrombosis signs include

- papilledema
- bilateral eye involvement
- abnormal CSF
- 5th cranial nerve/trigeminal palsy

What is Parinaud's oculoglandular syndrome & what is the differential diagnosis?

Unilateral preauricular lymphadenopathy with an ipsilateral conjunctival granuloma.

Adenoviral conjunctivitis/pharyngoconjunctival fever
Bartonella henselae
Chlamydia trachomatis/GC conjunctivitis
Francisella tularensis
Paracoccidiomycosis
Yersinia species
Sporotrichosis

What are causes of periorbital edema?

Infectious

- Cat scratch fever

- Trichinosis (eosinophilia, elevated CPK, low ESR)
- Trypanosoma cruzi/Chaga's disease (acute = Romaña's sign)
- Cavernous sinus thrombosis due to bacterial meningitis or sinusitis
- Sporotrichosis
- Tularemia
- Rocky Mountain Spotted Fever
- TB dacrocystitis

Non-infectious

- Dermatomyositis (heliotrope rash)
- Acute obstructive hydrocephalus
- Lymphoma
- Nephrotic syndrome
- Anasarca
- Hypo- or Hyper-thyroidism

What are the infectious & noninfectious causes of parotitis?

Infectious

- Staphylococcus aureus
- Mumps
- HIV
- Epstein-Barr virus
- Adenovirus
- Influenza
- Common viral syndrome agents: Rhinovirus,

Enterovirus, parainfluenza virus, Human Metapneumovirus, others
- TB

Noninfectious
- Sjögren syndrome
- Hematologic malignancy
- Chronic autoimmune
- Recurrent of unknown cause
- Lymphoepithelial lesion of Godwin

What are the causes of acute otitis media?

- Streptococcus pneumonia
- Hemophilus influenza
- Moraxella catarrhalis
- Streptococcus pyogenes (Group A streptococcus)
- Sometimes Chlamydia pneumoniae
- Rarely Staphylococcus aureus, Pseudomonas
- Predisposers but not primary pathogens: Respiratory syncytial virus (RSV), influenza

What causes acute bullous myringitis (painful vesicles on the tympanic membrane)?

- Acute otitis media:
    - Streptococcus pneumonia

    - Influenza
    - Mycoplasma pneumonia*
- Shingles, or herpes zoster oticus
    - Reactivation of Varicella zoster along the auditory branch of the facial nerve. (See Ramsay Hunt syndrome)

*If the patient also has a sore throat, Mycoplasma is more likely.

What are the complications of chronic otitis media?

- Cholesteatoma
- Mastoiditis/mastoid osteitis
- Vth facial nerve paralysis (requires urgent myringotomy)
- Meningitis
- Epidural abscess
- Subdural empyema
- Bezold abscess, an abscess in the neck from mastoiditis

What is Ramsay Hunt syndrome?

Reactivation of shingles/Varicella/Herpes zoster along the auditory branch of the facial nerve. Vesicles appear in the auditory canal, on the tympanic membrane, and around the

external ear. Along with pain, nausea and vertigo may occur and may persist for weeks.

List the 10 leading causes of a chronic draining ear.

- Mastoiditis
- Foreign body
- Cholesteatoma
- Cancer - Histiocytosis X
- Syphilis (treat as neurosyphilis)
- TB
- Munchhausen's
- Pseudo-Munchhausen's
- Malignant otitis externa
- CSF leak (skull base fracture)

What are the classic associations and findings with malignant otitis externa?

- Otalgia, otorrhea, and granulation tissue in external canal in a diabetic
- Facial nerve palsy
- Complications include temporal bone osteomyelitis (check temporal bone CT), requires debridement
- Organism is Pseudomonas

4 bacterial causes of community-acquired meningitis and DRUG OF CHOICE:

- Pneumococcus – ceftriaxone (+ vancomycin if resistance suspected)
- Neisseria meningitidis – penicillin
- Listeria monocytogenes – ampicillin + gentamicin
- Hemophilus influenzae - ceftriaxone – older patients

Differentiate between CNS Toxoplasma, Cryptococcus, Herpes, and TB:

- Toxoplasmosis - multiple lesions in brain parenchyma, focal neurologic signs
- Cryptococcus - indolent, non-purulent meningitis, increased intracranial pressure, AIDS
- Herpes - <u>delirium</u>/<u>behavioral</u> change/focal neurologic signs (encephalitis), hemorrhagic CSF & hypoglycorrhachia (low CSF glucose), temporal lobe enhancement on MRI
- TB - CSF lymphocytosis with hypoglycorrhachia, basilar meningitis on MRI, increased intracranial pressure (needs steroids)

What are risk factors for meningitis and for which pathogen?

- CSF leak after head trauma/fracture of cribriform plate—pneumococcus
- Skull/sinus fractures, even distant—pneumococcus
- Unpasteurized cheese/soft cheeses/cold cuts—Listeria
- Hamsters/rodents—Lymphochoriomeningitis virus (may cause fetal loss in pregnancy also)
- Warm fresh water lakes/hot springs—Naegleria fowleri
- Soil/Stagnant water/Hispanic ethnicity—Balamuthia mandrillaris
- Contact lenses/warm fresh water lakes/HIV—Acanthamoeba

How do you tell if nasal fluid is cerebrospinal fluid (CSF) or not at the bedside, if CSF leak is suspected?

Check a drop of CSF with a glucose meter. If it's + for glucose, it's CSF.

What is known as the Meningitis Belt?

The equatorial region of Africa.
Meningococcus is spread easily on hot dry winds. Travelers to the area should receive meningococcal vaccine, especially during the crowded Hajj, the Muslim pilgrimage to Mecca.

What is the differential diagnosis for necrotizing lymphadenitis?

- Hodgkin's & non-Hodgkin's lymphoma
- TB (scrofula)/atypical mycobacteria (history of exposure to TB, gardening, etc)
- Toxoplasmosis (history of cat exposure)
- Sarcoidosis

Name 4 infections causing paralysis or weakness that must be distinguished from Guillain Barre, and their causative agents.

- West Nile virus encephalitis
- Botulism (Clostridium botulinum)
- Tetanus (Clostridium tetanus)
- Tropical Spastic Paraparesis (HTLV I)

Name 3 noninfectious causes of paralysis or weakness.

- Tick paralysis (toxin, removal of the tick is curative)
- Guillain-Barre
- Myasthenia gravis

What are 3 parasites are often on the Infectious Disease board examinations as a cause of eosinophilic meningitis?

- Angiostrongylus – rat lungworm – SE Asia/Pacific/Caribbean/Louisiana –raw freshwater snails/slugs/fish/crabs/frogs – resolves without treatment in 2 weeks
- Baylisascaris – raccoon roundworm – fecal oral – hepatomegaly/abnormal mental status – no diagnostic test – albendazole possibly effective
- Gnathostomiasis – raw freshwater fish/eel/frogs – SE Asia – migrating swellings under skin for months to years + eosinophilia

Head and neck infection syndromes:

- Ludwig's angina – infection spreading from a periapical abscess around lower molar tooth extending into the sublingual space. May spread to mediastinum.

- Vincent's angina - Necrotizing Gingivitis
- Lemierre's syndrome – Jugular vein septic thrombophlebitis after sore throat; septic pulmonary emboli may occur, as well as distant abscesses
- "Bull Neck" – Diphtheria infection of the posterior pharynx with white plaques over the tonsils, posterior oropharynx, uvula and contiguous structures.
- Lumpy jaw – cervico-facial actinomycosis

What are the commonest cause of chronically swollen or indurated soft tissue with a sinus tract? How do you differentiate & treat each?

Differentiate bacterial from fungal process first. Start by sampling the drainage for Gram stain, Gomorri-Methenamine Silver (GMS) and/or Periodic Acid Sciff (PAS), acid-fast bacillus (AFB) stains, as well as aerobic and anaerobic bacterial, fungal, AFB cultures.

Note that Mycobacteria, Actinomyces, Madurella, and Nocardia spread continguously and cross tissue planes readily (e.g. sinus tracts are common).

- Mycobacteria other than TB (MOTT)
    - Sinus tract
    - Not much inflammation – "cold abscess"
- Actinomyces species of bacteria
    - usually *yellow grains* in drainage
    - associated with *cervicofacial/dental disease*,

intrauterine device, extremities
    - Gram positive filamentous rods
    - Treat with surgery and/or combination treatment such as sulfa/dapsone/streptomycin
- Nocardia species
    - pale grains
    - associated with nodular lymphangitis, thoracic sinus tract
    - Gram positive long thin filamentous rods
    - +Acid fast stain
    - Treat with surgery and/or sulfa agents
- Madurella (Madura Foot), less often other fungi
    - *black to pale grains*
    - associated with extremities, hands, neck/back (from carrying firewood; bare feet)
    - + GMS, + PAS stain
    - Treat with surgery +/- itraconazole, amphotericin B

Note that bacterial superinfection is not unusual. Presence of Staphylococcus aureus in culture correlates with true soft tissue infection.

CARDIOVASCULAR

Which organisms should prompt line removal for central venous catheter infection? Why?

- Staphylococcus aureus
- Candida/fungi
- Pseudomonas aeruginosa
- Corynebacterium jeikeium ("JK")
- Bacillus
- Enterococcus faecalis/E. faecium
- Any organism if the blood cultures still grow 72 hours into antibiotics to which it is susceptible.

S. aureus and Candida very prone to embolic or "metastatic" hematogenous infections. The longer the focus of bacteremia remains, the more likely for the patient to later return with endocarditis, discitis, or septic arthritis. It's also "sticky" and very difficult to eradicate from biofilm; the latter goes for the other organisms, too. Watch for endophthalmitis within the following weeks.

List 4 common causes of infectious pericarditis:

- Viral - enterovirus, usually Coxsackie A and B, influenza A & B
- Bacterial - Meningococcus, S. aureus

- TB - constrictive pericarditis
- Fungal - Histoplasmosis, Aspergillus

Name predisposing factors for infective endocarditis:

- Previous endocarditis
- Damaged native valve*- congenital or rheumatic
- Prosthetic valves
- Idiopathic hypertrophic subaortic stenosis/Hypertrophic cardiomyopathy Ventricular Septal Defect

*S. aureus (& S. lugdunensis) can infect pristine native valves.

Name 2 types of noninfectious endocarditis:

- Liebmann-Sacks - associated with SLE (no infection, no emboli, no antibiotic)
- Marantic - associated with malignancy

List 6 peripheral stigmata of endocarditis:

- Petechiae (mucous membranes)

- Roth spots (retinal hemorrhages)
- Splinter hemorrhages (nail beds)
- Janeway lesions (flat, painless lesions on palms/soles)
- Osler's nodes (palpable, painful "nodes" on fingertips)
- Splenomegaly

NOTE: In the antibiotic era, these occur in ~1-10%. Absence does not rule out endocarditis. Check daily.

What are the infectious causes of culture-negative endocarditis, workup, & treatment for each?

- HACEK group of Gram negative bacilli – extended incubation of cultures unnecessary with modern automated systems; consult Micro re: possible special media vs. nucleic acid amplification tests or serology – ceftriaxone or ciprofloxacin 4-6 weeks
- Coxiella burnetti (Q fever) – Phase 1 C. burnetti IgG titer > 1:800 – doxycycline + hydrochloroquine OR levofloxacin x 1 ½ years
- Tropheryma whipplei (differs from Whipple's disease, which is systemic) – fever uncommon; + ECHO and + PCR for *T. whipplei* on valve or blood, PAS + macrophages in valve
    - doxycycline + hydrochloroquine x 1 year, then lifelong doxycycline, OR
    - ceftriaxone high dose 2 weeks then TMP-SMX DS (160mg TMP) BID x 1-2 years

For each special setting in which bacterial endocarditis occurs, list associated pathogens:

- Intravenous drug user - Staphylococcus aureus/Candida parapsilosis
- Prosthetic valves - Staphylococcus epidermidis, fungal
- Culture negative - Q-fever (Coxiella burnetti), HACEK group (see Antibiotics section), Tropheryma whipplei
- Colon cancer - Streptococcus gallolyticus (formerly S. bovis); Clostridium septicum

What are the Modified Duke Criteria for diagnosis of infective endocarditis?

- 2 major criteria, or
- 1 major criteria + 3 minor criteria, or
- 5 minor criteria

Major Criteria

- Continuous bacteremia with typical organisms, without another identifiable source (2 blood cultures + drawn 12 hours apart, or 3 blood cultures + drawn ½-1 hour apart)
- Viridans strep, Streptococcus gallinarum (formerly S. bovis)

- Enterococcus
- HACEK bacteria (see Antibiotics section)
- S. aureus
- + Echocardiogram:
- vegetation, perivalvular abscess
- new dehiscence of prosthetic valve
- new valvular regurgitation
- 1 or more blood cultures with Coxiella burnetti
- + Q Fever/C. burnetti titer >1:800
- [+ PCR for *T. whipplei* on valve or blood has not been added but should; Fenollar F et al. Tropheryma whipplei Endocarditis: A 28 Patient Series and Review. Emerg Infect Dis. 2013 Nov;19(11):1721-30.]

Minor Criteria

- History of rheumatic heart disease/predisposing condition/intravenous drug use
- Oral temperature > 38 Celsius/100.4 Fahrenheit
- Vascular/embolic phenomena (emboli, hemorrhagic CVA, nail hemorrhages, conjunctival hemorrhages)
- Immunologic phenomena (Osler's nodes, Roth's spots, glomerulonephritis, +Rheumatoid Factor)
- Two + blood cultures with other organisms than the above
- Echo suggestive of endocarditis (but no major criteria)

List complications of endocarditis:

- CHF
- Conduction defects (valve ring abscess)
- Mycotic aneurysms (not fungal, "mushroom-shaped")
- MI (secondary to coronary emboli)
- Glomerulonephritis - focal and diffuse
- Obstruction (valvular)
- Embolic stroke
- Embolic abscess/infection: brain/spleen (left-sided), lung (right-sided)

What are the usual pathogens in bacterial endocarditis?

- Streptococci 70% (Streptococcus viridians > Group D enterococci)
- S. aureus 20%
- Miscellaneous (Hemophilus influenzae, Pseudomonas, Gram negative bacilli, pneumococci)

What are 2 signs to alert one to the presence of infective endocarditis?

- Fever
- Murmur (85%)

Treatment of infective endocarditis:

According to the sensitivities of blood culture isolates. Duration is 4-6 weeks in general.

What is characteristic for fungal endocarditis?

- Large vegetations
- Large arterial emboli (e.g. cold pulseless foot in an intravenous drug user)

Fungal endocarditis is an ABSOLUTE indication for valve replacement. Treat with intravenous amphotericin B and surgery ASAP.

What fungi are associated with endocarditis in which individuals?

- IV drug use - Candida parapsilosis
  Immunosuppression - Aspergillus
- Post cardiac surgery - Candida spp.

According to the American Heart Association, what are the ONLY cardiac conditions that warrant endocarditis prophylaxis for dental procedures & why?

- Prosthetic valve
- Prior infective endocarditis
- Congenital heart disease
    - Unrepaired cyanotic heart disease including palliative shunts and conduits
    - Repaired congenital heart disease with prosthetic material, during first 6 months after surgery
    - Repaired congenital heart disease with residual endothelial defects adjacent to prosthetic material
- Post cardiac transplantation with development of valvular disease

Research demonstrates that bacteremia from regular activities such as chewing and dental hygiene far exceed dental procedures as a cause of bacteremia (up to 70%!). The highest risk of endocarditis results from valvular abnormality, not bacteremia. Antibiotics have not demonstrated significant preventive benefit.

LUNG

Bacterial causes of atypical pneumonia and drug of choice for each.

- Mycoplasma pneumoniae (Macrolide/Doxycycline/Quinolone)
- Chlamydia pneumoniae (Macrolide/Doxycycline/Quinolone)
- Legionella pneumophila (Macrolide/Quinolone)
- Chlamydia psittaci (Doxycycline)

Principle viral causes of pneumonia, and treatment for each.

- Influenza A (amantadine/neuraminidase inhibitor)
- Respiratory syncytial virus (RSV) (ribavirin)
- Adenovirus (none)

Name 8 organisms causing pneumonia.

- Pneumococcus
- Hemophilus influenza

- Klebsiella
- Mycoplasma
- Legionella
- Chlamydia
- Pneumocystis jiroveci (PCP, or Pneumocystis pneumonia)
- Viruses

What is CURB65, and how is it useful?

CURB65 is a simple severity-scoring tool published by the British Medical Society in 2003 for assessing the need for admission and IV antibiotics in patients presenting with community-acquired pneumonia. For each item below, a score of 1 is added.

- Confusion
- BUN > 19 mg/dL (7 mmol/L)
- Respiratory Rate ≥ 30
- Systolic BP < 90 mmHg or Diastolic BP ≤ 60 mmHg
- Age ≥ 65

0-1
Predicted 30-day mortality 0-3% - Low risk - May be managed safely as outpatient

2 or greater
Predicted 30-day mortality up to 30% - Hospitalize, consider ICU monitoring as score rises

[Lim W, M van der Eerden M, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003 May; 58(5): 377–382.]

What acute infections are associated with "diffuse ground glass" opacity on pulmonary CT scan?

- Pneumocystis pneumonia
- Influenza
- Respiratory Syncitial Virus
- Cytomegovirus
- Herpes simplex

What are acute non-infectious causes of "diffuse ground glass" opacity on pulmonary CT scan?

- Diffuse alveolar hemorrhage (DAH)
- Pulmonary edema - congestive heart failure or adult respiratory distress syndrome (ARDS; cytotoxic drugs, viridans streptococci bacteremia)
- Drug - cytotoxic drugs (cytarabine, cyclophosphamide, bleomycin, carmustine), amiodarone, gold salts, methotrexate, daptomycin
- Lymphoma/malignancy

What are chronic noninfectious causes of "diffuse ground glass" opacity on pulmonary CT scan?

- Fibrosis
- Interstitial lung disease
- Sarcoidosis
- Cryptogenic organizing pneumonia (COP)

What is the differential diagnosis of miliary lung nodules seen on computed tomography?

- Tuberculosis
- Histoplasmosis
- Viruses (& post viral changes)
- Nocardia
- Malignancy
- Sarcoidosis
- Pneumoconiosis
- Alveolar proteinosis

What may cause nodular pneumonia in the immunocompromised and what computed tomography pattern might provide clues?

- Fungal/molds – light halo around nodule (Aspergillus), reverse halo or atoll sign (Mucor)
- Tuberculosis – miliary nodules (primary), thick-walled cavities in upper lobes/apices (reactivation)
- Metastases
- Fibrosis - ground glass in peripheral lung
- Cryptogenic organizing pneumonia (COP)

Which infections common in immunocompromised patients can cause lung infection in immunocompetent patients as well?

Aspergillus

- Subacute necrotizing Aspergillosis (thin-walled cavities with infiltration into parenchyma over weeks)
    - Associated with chronic marijuana smoking
- Fungus ball in empysema cavities ("ball" moves on decubitus films)
    - Treatment indicated only if rare infiltration into parenchyma is seen
    - Risk factors for invasion: steroids, diabetes
    - Hemoptysis suggests bacterial superinfection or erosion—may be severe
- Nocardia
- Rhizopus/Mucor
- Cryptococcus (C. gatti, not C. neoformans)
- Histoplasmosis

Infectious causes of multiple pulmonary nodules:

- Septic emboli/bacteremia
- Recurrent aspiration with abscesses
- Fungi
- Cryptococcus
- Coccidioides
- Histoplasma
- Blastomyces
- TB/atypical mycobacteria
- Flukes & roundworms
- Paragonimus (Asia)
- Toxocara
- Ascaris

What may cause tree-in-bud bronchiolitis appearance on computed tomography of lungs?

- Tuberculosis/atypical mycobacteriae
- Respiratory Syncytial Virus
- Adenovirus
- Mycoplasma
- Aspergillus in immunocompromised

What is the differential diagnosis of a "halo sign" on computed tomography of lungs?

A halo sign is a nodular consolidation of lung surrounded by a diffuse area radiating out from it.

Classic association with Zygomycetes (mucormycosis) in lung. Zygomyces may break through in neutropenic patients receiving extended voriconazole prophylaxis.

[Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia. Clin Infect Dis. 2005; 40:770-1; Vigouroux S et al. Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. Clin Infect Dis. 2005; 40:e35-7; Kobayashi K, et al. Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis. Haematologica. 2004; 89:e42.]

What is the differential diagnosis of an "air crescent sign" on computed tomography of lungs?

An air crescent sign refers to the black "crescent" seen around a nodular area inside of a lung cavity.

- Fungus ball – Aspergillus
  - patient is asymptomatic– the "ball" changes position on lat decub film, thin walled cavity (under 15mm)

    - fungus ball is a noninvasive ball of hyphae

- Invasive Aspergillus – typically immunocompromised patient with fever & the air crescent-nodule represent infarcted lung due to angioinvasive fungus

- Lung abscess with necrotic sequestrum – examples include aspiration in demented patient, Klebsiella/currant jelly sputum in an alcoholic – usually systemically ill patient – the necrotic sequestrum doesn't move, thick walled cavity (over 15mm)
- TB
- Lung cancer
- Pulmonary vasculitides (example, Wegener's granulomatosis)

[David M. Hansell, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging Radiology March 2008 246:3 697-722.]

What is Cryptogenic Organizing Pneumonia (COP), causes, diagnostics, and management?

- Nonproductive cough, dyspnea on exertion
- Flu-like illness, chronic
- Foamy macrophages on open biopsy is gold standard
- Excessive small airways granulation

tissue/intraluminal plugs in alveoli/bronchioles
- Post infectious, drug, connective tissue disease, hypersensitivity
- Treat with corticosteroids

What is the infectious differential diagnosis for a solitary lung nodule ("coin lesion")?

- Endemic fungi (Cryptococcus, Coccidioides, Histoplasmosis)
- TB & atypical mycobacteria
- Dirofilaria (dog heartworm)
- Pneumocystis jiroveci pneumonia (PCP)

What are characteristics of Klebsiella pneumonia, what is the treatment, & who is at risk?

- "Currant jelly" sputum, hemorrhage/necrosis-pulmonary gangrene may rarely occur→cavity with dead sequestrum on CT, may look like a "fungus ball" that doesn't move with change in position, or a "crescent cavity" in a patient with K. pneumoniae)
- Bulging horizontal fissure
- Lobar infiltrate
- Treatment: double Gram negative coverage: antipseudomonal penicillins (imipenem if

severe/ICU)+ quinolone/aminoglycoside (remember: Klebsiella may be ESBL/rapidly becomes resistant)
- At risk: alcoholics, diabetics, COPD

Describe aspiration pneumonia, microbes and drug of choice.

- Patients with seizures and alcoholics aspirate vomited material and get a cavitary abscess in a lower lobe (acid-central lobular necrosis), usually not right away. (Fever, infiltrates with acute aspiration are due to chemical pneumonitis.)
- Anaerobes are responsible for infection.
- Treatment: penicillin/clindamycin

Name 3 organisms causing micro aspiration pneumonia, characteristic symptoms, and drug of choice.

- Pneumococcus
    - Abrupt onset, pleuritic pain, fever, chills and shaking; rust-colored sputum; "normal" patient - lobar pneumonia
    - ceftriaxone + azithromycin/clarithromycin or quinolone
- Hemophilus influenza

    - Associated with bronchitis in patients with chronic lung disease; COPD
    - ceftriaxone
- Klebsiella
    - Alcoholics, drug addicts, DM, COPD, elderly in nursing homes
    - "currant jelly" sputum, lung necrosis
    - 3rd or 4th generation cephalosporin, or carbapenem if critically ill (empiric coverage for Extended Spectrum Beta Lactamase-producing organisms)

What diseases are associated with asbestosis and silicosis?

- Asbestosis - cancer - squamous cell mesothelioma
- Silicosis - TB

What is the Ghon complex?

Healed primary TB infection of the lower lobe with associated calcified hilar node. The primary site of pulmonary TB infection.

What is Simon's focus?

TB infection of upper lobes. This is a secondary site of TB infection via blood/lymphatics from the primary Ghon focus. May cause upper lobe fibrotic changes prior to any active disease. This is the usual reactivation site, with typical TB pneumonia, years after primary infection.

OBSTETRICAL & NEONATAL

Causes of fever that must not be missed in the postpartum period by time onset:

- Within 24 hrs: Puerperal sepsis (childbed fever) - Group A streptococcus
- 24-48 hrs: Endometritis - associated with foul-smelling discharge
- 48-72 hrs: Pelvic thrombophlebitis - associated with septic pulmonary emboli

Common causes of postpartum fever in the first 24 hrs:

- Breast engorgement
- Aspiration/atelectasis (after emergent C-sections/general anesthesia)
- UTI
- Occasionally pelvic deep venous thrombophlebitis

List the three periods to be considered in fetal and neonatal infections and the associated viruses:

- Congenital
  - CMV
  - Rubella
  - HSV
  - VZV
  - Vaccinia
  - Hepatitis B
- Natal
  - CMV
  - HSV
  - Hepatitis B
  - Enterovirus
- Postnatal
  - CMV
  - Hepatitis B
  - Herpes
  - RSV
  - Enterovirus

List three causes of neonatal conjunctivitis and their times of onset:

- Gonococcal 3-5 days (heavily purulent)
- Chemical 0-3 days
- Chlamydia 5-14 days

What is TORCH syndrome?

- Toxoplasmosis
- Rubella
- Cytomegalovirus
- Herpes simplex 2 (&1)

Clinically similar congenital infections caused by Toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus, types 1 and 2 that are manifested in the neonate by cutaneous manifestations: petechiae, purpurae, jaundice, and dermal erythropoiesis ("blueberry muffin" rash).

Risk is greatest if maternal infection acquired in 1st trimester.

Name the main antibiotics to avoid in pregnancy:

Flagyl QUITS PREGnAnC

Flagyl (metronidazole) - 1st trimester
QUinolones
Interferon
Tetracyclines/doxycycline
Sulfas*, **Streptomycin**

PZA, **P**odophyllin
Ribavirin
Estolate of Erythromycin
Griseofulvin
Nitrofurantoin*

Aminoglycosides
n
Chloramphenicol

*These are now considered to be relatively safe in the 1st trimester if no alternatives available, and safe as first-line agents thereafter in pregnancy.
[Sulfonamides, nitrofurantoin, and risk of birth defects. Committee Opinion No. 494. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:1484–5.]

What do you do if a pregnant woman has a history of genital herpes?

- C-section, only if active lesions or prodrome of herpes outbreak are present at the time of delivery
- Avoid procedures that may lacerate neonatal skin and introduce HSV

Because mothers can shed HSV without active lesions, examination is performed on the newborn delivered vaginally for scalp or oral ulcers; surveillance vaginal HSV culture at delivery &/or culture of neonate's mouth can be done at delivery & at 48 hours. If positive findings, treat neonate for 21 days with acyclovir. Acyclovir given to the laboring mother or empirically to the neonate is not beneficial.

What is the risk to newborns born vaginally to a mother

with genital herpes?

Neonatal disseminated herpes, which can be fatal.

What do you do if a mother delivers within 5 days after developing chickenpox (primary varicella), or develops chickenpox up to 2 days after delivery?

- Give the baby Varicella IgG to prevent disseminated neonatal varicella.
- Women of childbearing age (esp healthcare workers) should be screened for antibodies and receive Varicella vaccine prior to pregnancy, if no history of chickenpox.

What is the most serious risk of adult chickenpox, highest for women in 3rd trimester pregnancy?

- Varicella pneumonia
- Give Varicella IgG if a non-immune mother is exposed during pregnancy
- Give her varicella vaccine after she delivers

A woman in her 1st trimester of pregnancy is exposed to rubella in her college dormitory. She doesn't recall her immunization history. What do you do?

This is why preconception vaccination is so important in women of childbearing age (especially at college entry & healthcare fields) & why pre-college physicals should cover this; dorms are a common way to get exposed to vaccine-preventable & other illnesses, since they may be an international "melting pot".

Check Rubella titers; if negative, she has 2 options:

- Generally recommended/standard-of-care: If she has been infected with rubella, the risk of severe congenital defects is 30-50%. If the mother will want to have an abortion instead of risking congenital defects, do NOT give IG. Repeat titer in 3 weeks; therapeutic abortion is offered if she seroconverts to + antibody.

If the mother will not want to have an abortion if she is infected, IG may be offered. IG is NOT usually given because it does not prevent fetal rubella infection very well, and will mask whether the mother has seroconverted. It may provide (unreliable) fetal protection. This is why therapeutic abortion is safer.

SKIN & SOFT TISSUE

Describe atopic dermatitis and its distribution.

- "The itch that rashes rather than the rash that itches" i.e., small papular lesion resulting in erythema, weeping, and scaling secondary to scratching.
- Located in flexural areas: neck, antecubital, popliteal folds, eyelids, wrists, behind ears.
- Dry weather is a common trigger

Describe seborrheic dermatitis and its distribution:

- Scaling patches, indistinct margins, moderate erythema, oily, often yellow.
- Located on scalp, retro-auricular, eyebrows, eyelids, nasolabial folds--extensor surfaces and distal extremities spared.

Describe contact dermatitis and its distribution.

- Can be allergic or irritant

- Located where the offending substance touched skin
- Thousands of causes and morphology possible
- Face and hands most common sites

Describe stasis dermatitis and its distribution.

Area of cyanotic erythema that is pruritic, painful, and lies over a distended vein that eventually results in ulceration. Most common initial site is area above medial malleolus. Verrucous, thickened skin may occur with prolonged stasis, due to microischemia from hydrostatic pressure in the tissues.

Describe nummular dermatitis and its distribution.

- Characteristic round or ringed lesions that do not change in size, ooze and itch, then crust and scale
- Affects older men and younger women
- Exacerbated by hot water
- Often located on extensor surfaces of extremities, posterior trunk, buttocks, and lower legs

Name the major soft tissue infections from superficial to deep, their bacterial causes, and tissues affected.

- Impetigo contagiosum - Group A streptococcus – epidermis (associated with glomerulonephritis)
- Erysipelas - Group A Streptococcus - dermis (sharp border; raised peau d'orange edema)
- Cellulitis - Group A streptococcus /Staphylococci - subcutaneous tissue (diffuse border & edematous)
- Fasciitis - Mixed flora - fascia Myositis - Clostridia - muscle Impetigo Bullosum – S. aureus

Describe wound infections caused by Staphylococci, Group A Streptococci and Pseudomonas.

Staphylococcus aureus - coagulation of plasma and necrosis of soft tissue; well-localized abscess, especially face, neck, groin, post-operative.

- Community-acquired MRSA (new culture of MRSA arising in a person who has not been institutionalized or had surgery within the prior 12 months, with no indwelling bladder catheter or device that breaks the skin barrier) is now prevalent in some communities on the order of 60% S. aureus admissions and a rising cause of deaths. Characterized by severe rapidly progressive soft tissue infection, including pyomyositis and necrotizing fasciitis.
- Virulence factor = Panton-Valentine leukocidin cytotoxin. A common presenting clue is the patient's report of a "spider bite", even when no

arachnid was seen, presumably because of the sudden onset of sharp pain and swelling that may suggest such an occurrence—think CA-MRSA. See Necrotizing fasciitis below.

- Treatment: trimethoprim/sulfamethoxazole or doxycycline/minocycline oral if mild (organism may demonstrate inducible resistance to clindamycin; have lab perform testing before relying on this agent); if systemically ill, tigecycline/vancomycin/daptomycin /linezolid IV or oral are much more expensive options.

Group A streptococcus GAS)/S. pyogenes

- Virulence factor = M protein; early onset; rapid invasion, rapidly evolving cellulitis; life- threatening bacteremia; "flesh-eating bacteria"
- Treatment: penicillin-G + (GAS remains highly susceptible to penicillin- G)/- clindamycin (clindamycin inhibits protein synthesis-stops M protein); consider a carbapenem in cases where polymicrobial necrotizing fasciitis is likely, such as Fournier's gangrene (scrotal infection in diabetic) or post intra-abdominal surgery.

Pseudomonas

- Usually mixed infections
- Burn patients, seriously ill patients, severe septicemia
- Large amount of necrotic tissue
- Musty sweet/foul odor (Pseudomonas smells like grape juice in pure culture), blue-greenish discoloration
- Virulence factor = Collagenases

- Treatment: burn wound - topical sulfamylon, silvadene and 0.5% silver nitrate; systemic - piperacillin-tazobactam + tobramycin/ciprofloxacin

Name and describe the 2 forms of crepitant cellulitis, as well as synergistic gangrene.

Necrotizing fasciitis

- Acute mixed infection – Bacteroides, anaerobic streptococci, Clostridium. Community-acquired-MRSA

Keys to necrotizing fasciitis

- PAIN (deep & often out of proportion to findings) + FEVER.
- "Woody" induration of the painful area
- Cutaneous anesthesia over the painful area (cutaneous innervation is picked off as the fascia dies)
- Violaceous bullae
- **50% of the time, necrotizing fasciitis does not present with clinical signs of infection over the painful area.**
- Treatment: Wide excision and extensive decompression; intravenous penicillin + clindamycin. Hyperbaric O2/intravenous IG may be helpful adjuncts.

Clostridial gangrene

- C. perfringens/C. septicum/C. sordelli sepsis
- Fever, severe pain, PLUS
- antecedent trauma/open fractures, OR
- post-abortion endometritisobstetric infection ("pink lady syndrome"—hemolysis), OR
- underlying colon cancer (esp. C. septicum)
- "Bronze cellulitis" or pinkish appearance of skin-massive hemolysis
- Alpha-toxin mediated 3rd-spacing or anasarca
- Systemic inflammatory response/sepsis

List which Gram negative organisms may cause cellulitis and describe the associated conditions.

Gram negative bacilli rarely cause cellulitis of unbroken skin, except in certain settings, especially:

- Any Gram-negative bacillus - neutropenic fever (absolute neutrophils < 500/mL), organ or hematologic transplantation, cirrhosis, other immune disorders
- Vibrio species – cirrhosis, iron over load states – exposure to salt or brackish water
- Pseudomonas, molds – eschar or trauma
- Aeromonas – fresh water, mud, "mud run" types of races
- Pasteurella multocida – cat or dog bite or lick in diabetic
- Hemophilus influenza – orbital cellulitis, elderly
- Salmonella – reptiles

- Clostridium septicum – colon cancer, open fracture/dirty trauma, septic abortion

What is Crislip's sign in streptococcal cellulitis?

Painful inguinal lymphadenopathy, which often precedes or heralds Group A streptococcal cellulitis in the individual with lower extremity lymphedema.
[Mark Crislip, MD, personal observation, Rubor, Dolor, Calor, Tumor blog post, 07:44 June 22, 2012; available at http://blogs.medscape.com/rdct]

(Check out Dr. Crislip's multimedia empire at http://edgydoc.com, where you can access his podcasts, A Gobbet o' Pus, QuackCast, Puswhisperer, and his comprehensive Infectious Disease Compendium. I receive no remuneration for this endorsement, it's just a shout-out to another #pusgeek who does this sort of thing for no money and, er,…fun!)

What is Meleney's progressive synergistic gangrene?

- Chronic progressive form of mixed infection, Streptococcus (nonhemolytic, microaerophilic) and Staphylococcus aureus
- Starts around wound edges/ostomies
- Lesion = pale red cellulitis with purplish center,

progressively turning gangrenous; ulceration with purplish, grayish, painful margins that extend.

- Treatment: wide excision, penicillin + erythromycin

What is pyomyositis?

Previously found mostly in the tropics, now frequently caused by community-acquired MRSA strains + for Panton Valentine Leukocidin toxin (PVL+). Sudden onset of

- Fever
- Severe muscle pain/deep infection, & abscesses, which may not always be readily apparent at the surface.
- Treat with aggressive surgical debridement and intravenous antibiotics to cover community-acquired MRSA (See Describe wound infections caused by Staphylococci, Group A Streptoccus and Pseudomonas earlier in this section).

Gas gangrene occurs only with some form of trauma? True or false.

False.
Clostridial (especially C. septicum) gangrene may occur spontaneously, especially in patients with bowel cancer or neutropenia. It may also recur (spores may persist in

previously infected tissue!!).

What is very important to remember when treating susceptible skin/soft tissue infections with cephalexin/1st generation cephalosporin given orally?

- It needs stomach acid to be absorbed.
- Many patients today are on acid reducers (prescribed or OTC).
- Avoid in patients who are on chronic H2 blockers, proton pump inhibitors, or use antacids frequently.
- Consider clindamycin or doxycycline in patients who are penicillin-allergic, as an alternative.

Causes of soft tissue gas:

- Clostridium perfringens/septicum
- Other anaerobes

What are the causes of nodular lymphangitis?

- Sporotrichosis (rose thorns, sphagnum moss, cats may transmit from skin lesions) – commonest in U.S.

- Nocardia (brasiliensis, especially)
- Mycobacterium marinum (fish tank granuloma; fresh or salt water); also M. chelonei/fortuitum (soil, vegetation)
- Cutaneous leishmaniasis (Leishmania brasiliensis; tropics)
- Francisella tularensis (ulceroglandular or glandular tularemia; rabbits/rodents, insect bites)
- Bartonella henselae (cat scratch fever)

What organisms are known to produce toxic shock syndrome?

- Staphylococcus aureus (endotoxin, TTS-1)
- Group A streptococcus (exotoxin, Streptococcus pyrogenic exotoxin A)

What is toxic shock syndrome & how might you distinguish Staph from Strep toxic shock?

Staphylococcus TTS is characterized by septic shock and diffuse erythematous rash like sunburn, & is associated with:

- Wounds (especially post-operative, even if they don't look infected)
- Highly absorbent vaginal tampons
- Nasal packing ("nasal tampon") for epistaxis (ENT docs usually give prophylactic antibiotics; blood

provides a perfect culture medium for Staphylococcus aureus, which normally colonizes the anterior nares)

Streptococcus TTS is characterized by septic shock and a deep soft tissue infection, esp. necrotizing fasciitis. Consider IVIG.

Name a pathogen causing purple facial cellulitis in elderly.

Hemophilus influenza (disappearing in children since HiB vaccine introduced)

Name the cause of erysipeloid & its treatment:

Erysipelothrix rhusiopathiae (raw fish/crabs, gefilte fish, raw chicken) - penicillin

What is the differential diagnosis of a painful ulcer associated with lymphadenitis:

- Plague – Yersinia pestis – Western half of U.S. – rodents/chipmunks/deer/fleas

- Tularemia – Francisella tularensis – Midwest/NE U.S. – rodents/rabbits/ticks/biting flies

Name 3 infectious causes of a red face:

- Toxic shock: Staphylococcus aureus (toxin)
- Scarlet fever: Group A strep
- Fifth disease: Parvovirus B-19

Which ectoparasite is a putative pathogen or co-pathogen in seborrheic disorders, such as rosacea? What is the proposed mechanism? What treatments have been reported successful in improving rosacea and ocular blepharitis?

Demodex folliculorum (and perhaps other species)

Support for the putative role of Demodex spp., until recently considered a harmless skin commensal, is increasing. It is believed to cause an inflammatory response in the follicles where it resides, and increase in skin or follicular concentration coincides with the age and onset of rosacea. It is strongly implicated in chronic blepharitis, and may play a role in seborrhea, acne, and even eosinophilic folliculitis in those with advanced HIV disease. Interestingly, Bacillus oleronius colonizes Demodex, and has been shown to produce systemic and local inflammatory responses.

Rosacea & blepharitis:

- Topical ivermectin daily x 12 weeks
- Oral ivermectin 0.2 mg/kg weekly x 2 +/- oral metronidazole 250mg TID x 2 weeks
- Low dose doxycycline daily

Blepharitis:

- Topical 50:50 ratio of tea tree oil to mineral oil; scrub eyelids weekly + daily 2.5% tea tree shampoo eyelid scrub
- Tobramycin/dexamethasone ocular ointment daily x 7 days

Name as many infection-associated skin conditions starting with E as you can and name the agent responsible:

- Erythrasma: Corynebacterium minutissimum - easily confused with fungal skin infection - pink under Wood's lamp. Infection seen in the groin area.
    - Treatment: Erythromycin
- Erythema infectiosum: Parvovirus B-19 - "Fifth disease" - "slapped- cheek" appearance to face in kids. Livedo reticularis on lower body.
- Erythema marginatum: rheumatic fever - Group A beta-hemolytic Streptococcus
- Erythema nodosum: All granulomatous disease - located on anterior shin - multifactorial infectious etiologies
    - OFTEN in HSV, Mycoplasma,

Histoplasmosis

- Erythema nodosum leprosum (ENL): painful nodular lesions on extremities in leprosy; Arthus reaction to leprosy
    - Treat with thalidomide.
- Erythema multiforme: Hypersensitivity reaction - macules, vesicles, on distal extremities; annular lesions on lips.
    - Associated with HSV, Mycoplasma.
- Erythema migrans: - "Lyme Disease" - bull's eye appearance - Borrelia burgdorferi

Name 4 drugs associated with Stevens-Johnson Syndrome or Erythema multiforme:

- Dilantin
- Phenobarbital
- Sulfonamides
- Fansidar (Pyrimethimine/Sulfadoxine) for chloroquine-resistant falciparum malaria.

What are the common infectious causes of Stevens-Johnson Syndrome or Erythema multiforme?

- Mycoplasma
- HSV
- EBV

- Measles

What are infectious causes of Erythema nodosum?

- HSV
- Mycoplasma
- Pneumococcus
- Group A Streptococcus
- Histoplasmosis
- Coccidiomycosis
- Blastomycosis
- Enteroviruses
- BCG (Mycobacterium bovis)
- M. tuberculosis
- Enterobacter
- Smallpox vaccination (cowpox-Vaccinia virus-is used in this vaccine)

What are non-infectious causes of Erythema nodosum?

Same as Stevens-Johnson: mostly drugs.

List 5 characteristics of a tetanus-prone wound:

- Depth at least 1cm
- Duration at least 6 hrs
- Dimension - puncture of stellate wound
- Dirty - contaminated/foreign body
- Devitalized tissue/burns

Easily confused diseases:

- Juvenile Rheumatoid Arthritis + Lyme disease
- Typhoid fever + Typhus
- Plague + Tularemia

What may cause recurrent episodes of cellulitis in cartilagous areas such as the ears and nose?

Relapsing polychondritis

Name the 3 infectious causes of saddle nose deformity/nasal cartilage perforation.

- Syphilis

- Lepromatous leprosy
- Mucocutaneous leishmaniasis (espundia)

Name 3 non-infectious causes of saddle-nose deformity/nasal cartilage perforation:

- Inhaled cocaine
- Wegener's granulomatosis/lethal midline granulomatosis
- Relapsing polychondritis

Name a mononucleosis-like syndrome with a systemic inflammatory disorder in adults characterized by high spiking fevers, arthritis, and (in most cases) an evanescent rash.

Still's disease

SEXUALLY TRANSMITTED DISEASES (STDs)

List 4 common STDs, causative agent, and drug of choice:

- Non-gonococcal urethritis (Chlamydia) - Azithromycin/Doxycycline
- Syphilis (Treponema pallidum) (hard chancre-painless) - penicillin Gonorrhea (GC) - Ceftriaxone
- Chancroid (Hemophilus ducreyi) (soft chancre-painful) - Azithromycin/ceftriaxone

Which STDs cause painful ulcers?

- Herpes simplex 2 (or 1)
- Chancroid (Hemophilus ducreyi)

Which STDs cause painless ulcers?

- Syphilis
- Granuloma inguinale (Donovanosis)
- Lymphogranuloma venereum

What is the differential diagnosis of proctocolitis related to receptive anal intercourse?

- Lymphogranuloma venereum (especially men who have sex with men)
- Herpes
- Syphilis

Can you name an emerging STD other than Chlamydia or gonorrrhea that may cause mild urethritis, cervicitis, and pelvic inflammatory disease?

Mycoplasma genitalum

What STD can cause reactive arthritis/Reiter's Syndrome? Describe the manifestations of this syndrome.

- Chlamydia trachomatis
- Conjunctivitis
- Heel swelling or enthesitis
- Sausage-like swelling of digits
- Oral ulcers
- Nail pitting

- Keratoderma blenorrhagica (hyperkeratotic areas on palms & soles)
- Circinate balanitis

What are ocular manifestations of syphilis?

- Argyll-Robertson pupil: Think "prostitute accommodates but doesn't react"
- "Gun barrel" (tunnel) vision: Think "shotgun wedding"

What are causes of a false + RPR or FTA?

Many (any process that involves a strong humoral immune stimulus), such as chronic infections, recurrent bacteremia, recurrent exposures to antigens (blood transfusions, multiparity), etc.

Infectious Cause of a + Rapid Plasma Reagin (RPR)/negative FTA:

- Leptospirosis
- Relapsing fever

- Leprosy
- Rat bite fever (Spirillum minor)
- TB
- Pneumococcal pneumonia
- Mycoplasma pneumonia Chickenpox
- Sub-acute bacterial endocarditis
- Chancroid
- Scarlet fever
- Rickettsial disease
- Malaria
- Trypanosomiasis
- Vaccinia vaccine (live virus)
- Measles
- Lymphogranuloma venereum
- Hepatitis
- Infectious mononucleosis
- Early HIV infection

Noninfectious Causes of a +Rapid Plasma Reagin (RPR)/negative Fluorescent Treponemal Antibody (FTA):

- Intravenous drug use
- Any connective disease disorder
- Rheumatoid heart disease
- Systemic lupus erythematosis
- Blood transfusions (multiple)
- Pregnancy (especially multiparous women)
- "Old age"

- Chronic liver disease

Infectious Cause of a + FTA/negative Rapid Plasma Reagin (RPR):

Lyme disease

What constitutes a syphilitic emergency?

- Ocular syphilis (uveitis, optic atrophy/neuropathy, chorioretinitis)
    - Syphilitic otitis

Both may present with rapidly progressive, usually unilateral sight or hearing loss. Other manifestations of neurosyphilis may not be present. These progress to blindness/deafness if not urgently treated.

In what cases is a + FTA alone sufficient justification for treatment for syphilis with IV PCN-G?

In the case of ocular syphilis (uveitis, optic atrophy/neuropathy, chorioretinitis) and syphilitic otitis, both of which may present without other manifestations of

neurosyphilis and will progress to blindness/deafness if untreated. Both are often of longstanding duration and RPR, normally used for screening, may be negative.

Ophthalmology/ENT literature recommends treating both these syndromes as active neurosyphilis on the basis of a +FTA alone if no other cause is found: intravenous penicillin for 14 days.

For otitis, there is some data using steroids & more prolonged therapy.

CLUES TO NON-INFECTIOUS & INFLAMMATORY CONDITIONS

List infectious and noninfectious causes of high erythrocyte sedimentation rate (ESR) (>100*):

- Osteomyelitis
- Giant cell arteritis/Polymyalgia rheumatica
- Collagen vascular disease
- Inflammatory bowel diseases
- Multiple myeloma/Hodgkin's lymphoma
- Subacute Thyroiditis
- Tissue infarction/necrosis
- Acute myocardial infarction/thrombophlebitis/thrombosis
- Chronic renal failure
- Malignancy
- Pregnancy/hormone replacement/birth control pills
- Drug hypersensitivity reactions

*Note: Nephrotic syndrome & end-stage renal disease may be associated with ESR >100 in about 20% cases. Remember that anemia falsely raises ESR.

What may cause a low erythrocyte sedimentation rate (ESR)?

- Trichinosis – history of myalgias & eating undercooked pig, bear, game
- Very high leukocytosis
- Polycythemia
- Red blood cell abnormalities - sickle cell diseas, anisoctyosis, spherocytosis, acanthocytosis, microcytosis
- Protein abnormalities –hypofibrinogenemia, hypogammaglobulinemia, dysproteinemia with hyperviscosity state

Nice review by Brigden ML. Clinical utility of the erythrocyte sedimentation rate. Am Fam Physician. 1999 at http://www.aafp.org/afp/1999/1001/p1443.html

What are common non-infectious causes of a neutrophilic leukocytosis?

MITTT

Metabolic
- diabetic ketoacidosis
- gout

Inflammatory processes
- collagen vascular diseases/vasculitis
- pancreatitis, pericarditis, others

Tissue destruction
- burns, trauma/destructive tissue damage
- infarctions/ischemia/gangrene

- hemolysis/hemorrhage/hematoma/GI bleed
- Chronic myelogenous leukemia (CML)
- Chronic lymphocytic leukemia (CLL)
- carcinomatosis/cancers (tissue necrosis)

Thrombosis

- deep or superficial thrombophlebitis, pulmonary embolus
- chemical phlebitis due to peripheral IV infiltration

Toxic

- drugs; steroids (acute OR chronic), lithium, others
- heavy tobacco use

Which surgical procedures are most associated with needlestick injuries to healthcare workers?

General abdominal & oral surgeries, especially:

- Small/large bowel procedures
- Cholecystectomy
- Nephrectomy
- Thyroidectomy
- Dental extractions, root surgeries, gingival surgeries

Should healthcare workers with Hepatitis B, Hepatitis C, or HIV be restricted from work with patients? If so, which criteria are recommended?

Yes. Healthcare workers with these conditions should be

restricted from the above high risk surgical procedures if viral load is ≥

- HIV ≥ 500 copies/mL (or genome equivalents/mL)
- HBV ≥ 10,000 copies/mL (or genome equivalents/mL)
- HCV ≥ 10,000 copies/mL (or genome equivalents/mL)

How can you distinguish leukemoid reactions/severe neutrophilic leukocytosis (High WBC +/- high PLTs) from CML?

Chronic myelogenous leukemia

- Splenomegaly
- Low leukocyte alkaline phosphatase
- High uric acid
- T9,22 (Philadelphia chromosome)
- bcr/abl gene

Leukemoid reaction

- No splenomegaly
- HIGH leukocyte alkaline phosphatase
- Normal uric acid

What are 3 major causes of an elevated total protein?

- HIV
- TB
- Multiple myeloma

Due to elevated immunoglobulins.

What infections are most likely to cause nonspecific chronic fatigue?

- Chronic active hepatitis C (HCV), less often chronic hepatitis B (HBV)
- HIV (ALL individuals should be screened at least once in adulthood for HIV)
- EBV mononucleosis may produce residual fatigue for several weeks but not a year or more

What common drugs may be associated with unexplained lymphadenopathy?

- Allopurinol
- Atenolol
- Antibiotics (DRESS pseudolymphoma: vancomycin, beta lactams, trimethoprim/sulfamethoxazole, quinolones, tetracyclines)
- Captopril
- Carbamazepine Hydralazine

- Phenytoin
- Pyrimethamine
- Gold

What can give you a false + blood culture by the Bactec T/Alert system?

- Leukocytosis
- Red blood cells
- Coincident antibiotic use by the patient

Why? Bacteria growing in the medium produce CO2. Once the levels are high enough, CO2 crosses the semi-permeable membrane at the base of the Bactec bottle and produces a color change in the colorimetric CO2 sensor. The change is detected by a colorimetric scanner and the bottle is flagged. The micro tech then performs a Gram stain or acridine orange stain to determine whether bacteria are present, as well as a subculture to solid media. The culture is reported as + only if the stain and/or culture are +. RBCs may produce some background CO2, as will high WBC.

[Streptococcus pneumoniae sometimes may give a false negative. In culture, Streptococcus pneumoniae may lyse RBCs as well as itself ("chocolatizing" the medium), while producing CO2 & flagging +. The stains, and possibly the culture, may be negative because of lysis—it may look like a false + by Bactec alarm, but in reality be a false – by stain and culture.]

Besides leukocytosis, how can a complete blood count provide clues to an undrained abscess or developing abscess (phlegmon)?

Reactive thrombocytosis

Noninfectious causes (5) of acute pulmonary infiltrates:

- Aspiration
- Congestive heart failure
- Pulmonary embolus
- Hemorrhage
- Acute respiratory distress syndrome (ARDS)

List the causes of a monocytosis:

- Infective endocarditis (subacute)
- Disseminated TB
- Typhoid fever
- Malaria
- Visceral Leishmaniasis (kala azar)
- Collagen vascular diseases

- Myelodysplastic syndromes/malignancy
- Helicobacter pylori

List the causes of a lymphocytosis:

- Tuberculosis
- Toxoplasmosis
- Pertussis
- Viruses
- Epstein Barr Virus
- Cytomegalovirus
- Varicella zoster (Herpes zoster)
- Acute or Chronic Lymphocytic Leukemia
- Immunization, autoimmune diseases, graft rejection
- Hypothyroidism
- Relative lymphocytosis associated with granulocytopenia

List the causes of an eosinophilia:

- Helminths
- Strongyloides
- Visceral larva migrans (Toxocara)
- Hookworms
- Filariasis
- Gastroenteritis due to Isospora or Dientamoeba

(NOT other protozoa)
- Atopy/asthma/allergies
- Hematologic malignancies
- Drugs – many

List 6 acute phase reactants (increase with infection, trauma, inflammation, or malignancy):

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Ferritin
- Haptoglobin
- D-dimer
- White blood cells, especially immature forms/bands ("left-shift")
- Platelets

What non-infectious conditions may elevate CRP?

- Pregnancy or estrogen hormone therapy
- Splenectomy
- Collagen vascular disease
- Inflammatory bowel disease
- Hematologic or solid organ malignancy
- Acute graft vs host disease

Causes of thrombocytosis:

- Fe^{++} deficiency
- Reactive
    - inflammation
    - infection (undrained abscesses, especially splenic abscess; TB)
    - rebound
- Myeloproliferative disorders/myelodysplastic syndrome
- Post-splenectomy

What is PFAPA syndrome?

- Periodic Fever
- Aphthous stomatitis
- Pharyngitis
- Adenitis (cervical)

- Recurrence of the above symptoms every 3-6 weeks
- Onset before 5 years of age
- Inflammatory markers elevated: leukocytosis, erythrocyte sedimentation rate

Also referred to as Marshall's syndrome, for the clinician who first reported it. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and

aphthous stomatitis. J Pediatr 1987;110:43-46; Marshall GS, Edwards KM. PFAPA syndrome [letter]. Pediatr Infect Dis J 1989;8:658-659.

List conditions that should be ruled out when investigating Chronic Fatigue Syndrome (now known as Systemic Exertion Intolerance Disease)

- Hypothyroidism
- Adrenal insufficiency
- Anemia
- Rheumatologic disorder (e.g. RA, fibrositis/fibromyalgia, SLE)
- Depression
- Neurally mediated (orthostatic) hypotension
- 2nd or 3rd Stage Lyme Disease in endemic areas or exposure history to deer ticks in endemic areas

What about infectious conditions?

Chronic hepatitis, especially hepatitis C
Lyme

Name 3 hallmarks of each of the following diseases:

- Rheumatoid Arthritis - Serositis, Nodules, Vasculitis.
- Wegener's Granulomatosis - Sinusitis, Bronchitis, Nephritis
- Behcet's Syndrome - Genital & oral ulcers, Uveitis, Aseptic meningitis
- Amyloidosis - Macroglossia, Nephropathy (proteinuria), Peripheral neuropathy
- Sjogren's Syndrome - Keratoconjunctivitis sicca, Xerostomia, Parotitis

What conditions cause ascending aortitis and aortic branch vasculitis?

- Syphilis (tertiary) - the Great Imitator
- Takayasu's vasculitis (also pulmonary arteritis)
- Sarcoidosis (rarely but it happens)

What conditions cause pulmonary arteritis?

- Pulmonary artery stenoses on high-resolution CT
    - Bechet's (Hugh-Stovin syndrome, a variant of Bechet's)
    - Takayasu's
    - Giant Cell arteritis

- Acute focal lung hemorrhage (large pulmonary arteries)
    - Bechet's
    - Less often Takayasu's, Giant Cell arteritis
- Diffuse Alveolar Hemorrhage (DAH) (bilateral "ground glass" airspace disease sparing apices, anemia, +/- hemoptysis; hypoxia; capillaritis on path)
    - Wegener's or Granulomatosis with Polyangiitis (glomerulonephritis, +anti-neutrophil cytoplasmic auto-antibodies [ANCA])
    - Churgg-Strauss (+ANCA and asthma, eosinophilia >10%, neuropathy)
    - Systemic lupus erythematosus (immune complexes on lung biopsy)
    - Microscopic polyangiitis (glomerulonephritis on renal biopsy)

[Marten K, Schnyder P, Eckart S et al. Pattern-based Differential Diagnosis in Pulmonary Vasculitis Using Volumetric CT. AIR 2005;184(3):720-733.]

Name the 5 components of the CREST Syndrome.

- Chondrocalcinosis
- Raynaud's syndrome
- Esophageal dysmotility
- Scleroderma
- Telangiectasia

What joints of the hand do the following affect?

- Psoriasis – distal interphalangeal joint
- RA – proximal interphalangeal joint, metacarpophalangeals
- Hemochromatosis – metacarpophalangeals of the 2nd and 3rd fingers
- Osteoarthritis – all joints

Where are Heberdens's nodes?

- Dorsolateral and medial aspect of the distal interphalangeal joints of the fingers.
- They are associated with osteoarthritis.

Where are Bouchard's nodes?

- At the PIP joints.
- Also associated with osteoarthritis.

Give the 11 revised criteria for classification of systemic

lupus erythematosis (SLE):

SOAP BRAIN MD (John T. Sinnott, M.D.'s mnemonic)

Serositis - pleuritis, pericarditis
Oral ulcers - nasopharyngeal ulceration, usually painless
Arthritis - nonerosive with 2 or more peripheral joints - tenderness, swelling, effusion.
Photosensitivity - sunlight - rash
Blood disorders - hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia.
Renal - proteinuria or cellular casts
ANA (antinuclear antibodies)
Immunologic disorders: +LE cell prep or anti-dsDNA; false + Rapid Plasma Reagin
Neurologic disorders
Malar rash - fixed erythema over the malar eminences, spares nasolabial folds.
Discoid rash - erythematous, raised patches with scaling & follicular plugging; atrophic scarring may occur with old lesions.

Discoid & drug-induced lupus spare the kidneys.

Rheumatoid arthritis is a systemic illness that may present with fever during flares. What are the 3 components of this disease?

- Nodules on extensor surfaces
- Serositis

- Vasculitis

What syndromes are associated with HLA B-27?

- Ankylosing spondylitis/Inflammatory Bowel Disease spondylitis
- Anterior uveitis
- Reiter's syndrome
- Psoriatic arthritis

What syndromes are associated with HLA D types?

- Sjogren's syndrome
- Myasthenia gravis
- Addison's disease
- Celiac sprue
- Chronic Hepatitis
- IDDM
- Thyrotoxicosis
- Hodgkin's disease
- Multiple sclerosis
- SLE

Name 5 types of cytokines.

- Interferons (IFN)
- Interleukins (IL)
- Growth factors (GF)
- Tumor Necrosis Factor (TNF)
- Colony Stimulating Factor (CSF)

Name 3 types of interferon, an important source, and action.

- IFN-alpha – Leukocytes - Antiviral/antitumor via NK-cells and macrophages
- IFN-beta – Fibroblast - Same
- IFN-gamma - T-cells - Antiviral/antitumor and immunoregulatory, esp. via macrophages.

Describe the action of 6 interleukins.

LeT'S BBB
IL-1 **L**ymphocyte Activating Factor (T-cells)
IL-2 **T**-cell Growth Factor
IL-3 **S**tem cell Growth Factor (Colony Stimulating Factor)
IL-4 **B**-cell Growth Factor
IL-5 **B**-cell differentiation Factor

IL-6 **B**-cell Maturation Factor

Which interleukin is not produced primarily by T-cells?

IL-1 is produced by macrophages.

The production of which interleukin is directly blocked by cyclosporine?

IL-2

Name 5 types of growth factors.

- PDGF Platelet Derived Growth Factor
- FGF Fibroblast Growth Factor
- NGF Nerve Growth Factor
- EGF Epithelial Growth Factor
- TGF Tumor Growth Factor beta

Colony stimulating factors enhance the growth and differentiation of bone marrow stem cells. Name the 5 types of CSF's, and the stem cells they affect.

- G-CSF, Granulocyte
- SF, Macrophage
- GM-CSF, Granulocyte/Macrophage
- IL-3, Pluripotent stem cells
- Erythropoietin, Erythroid stem cells

IMMUNODEFICIENCY & CANCER

What is the commonest cause of immunodeficiency globally?

Malnutrition. Predisposes to gastroenteritis and pneumonia.

What are the commonest types of immunodeficiency in adults?

- Antibody defects or deficiency
- Complement deficiency

List infectious and non-infectious clues to immunodeficiency in adults:

- Infectious
- Frequent infections
- Unusual severity of infections
- Prolonged or refractory infections
- Unusual pathogens
- Family history of autoimmunity or malignancy
- Non-infectious

- Poor wound healing
- Poor dentition
- Bronchiectasis of undetermined cause

Patterns of infection, immunodeficiency, and pathogens of concern:

- Recurrent sinus, lung infections, meningitis, bacteremia
    - Immunoglobulin or Complement defect
        - pneumococcus
        - Hemophilus influenza
        - Neisseria meningitides
        - Campylobacter
        - Giardia

- Recurrent abscesses not related to apocrine areas, foreign bodie, S. aureus colonization
    - Neutrophil defect
        - Staphylococcus aureus
        - Gram negative bacilli
        - Aspergillus
        - Nocardia

- Opportunitistic viruses, fungi
    - T cell/cell mediated immunodeficiency
        - Candida
        - Cryptococcus
        - CMV, HSV
        - Molluscum contagiosum – atopy, eczema (low Th1)
        - Mycobacteria

- Respiratory tract infections
    - Job's syndrome/hyperimmunoglobulin E
    - look for IGE > 2000 IU/mL

- Hemolytic anemia with fava beans (favism) or sulfa drugs, recurrent pneumonia, severe skin/soft tissue infection
    - severe G6PD deficiency
    - usually <5-10% G6PD activity
    - confers some immunity to malaria (like sickle cell disease) by increasing splenic clearance of infected cells

- Recurrent Staphylococcus aureus furunculosis/boils
    - look for areas of S. aureus colonization other than nares & apocrine areas:
    - Untreated eczema, psoriasis
    - chronically abnormal skin such as dishydrotic eczema/pompholyx

List 3 types of B-cell deficiency.

- IgA deficiency (Most common immunodeficiency in developed nations.)
- Bruton's hypogammaglobulinemia
- Common variable immunodeficiency (CVID)

What diseases are associated with IgA deficiency & CVID?

Sinusitis, otitis and bronchitis, (pneumococcus).

Name 4 types of T-cell deficiency.

- DiGeorge Syndrome (neonatal tetany & thymus hypoplasia)
- Chronic mucocutaneous candidiasis (ketoconazole prophylaxis)
- SCID (Severe Combined Immunodeficiency)
- Wiskott-Aldrich Syndrome Ataxia-telangiectasia

What are 3 types of Severe Combined Immunodeficiency (SCID)?

- Adenosine deaminase deficiency (Treatment: 1 unit of blood on first day of life)
- Reticular dysgenesis (decreased neutrophils & T-cells)
- Swiss-type immunodeficiency (no B or T-cells)

What are the characteristics of Wiskott-Aldrich Syndrome?

It's a **MITE** found in **males**:
Males - excess bleeding of umbilical stump or circumcision site!
Immunodeficiency
Thrombocytopenia
Eczema

What heralds the presence of leukocyte adhesion disorder?

- Non-purulent infection of the umbilical stump
- Delayed separation of the umbilical stump.

What are the characteristics & treatment of Ataxia Telangiectasia?

- Characteristics: Ataxia, telangiectasias, & liver degeneration
- Treatment: Gamma globulin

What are the types of nonspecific immune defects?

Neutrophil defects = **COIN**

- **C**hemotaxis - as in lazy leukocyte syndrome
- **O**psonization (Pneumococcus, Hemophilus)
- **I**ngestion - intracellular killing - as in Chediak-Higashi Syndrome & chronic granulomatous disease. Characterized by intracellular inclusions & Staphylococcus abscesses in brain, liver, & lungs.

What infections suggest a terminal complement defect?

- Chronic/recurrent gonococcemia
- Meningococcemia in adult without meningismus
- Less severe disease, low CH50
- If >1 episode Neisseria in BLOOD, check for terminal complement defect!

[Terminal complement = C^{5-8}]

What are some secondary causes of immune impairment in adults that are not caused by HIV, drugs, or splenectomy? And what is the defect, if known?

- Diabetes mellitus
    - hyperglycemia causes decreased neutrophil

chemotaxis and phagocytosis, decreased opsonization by complement
    - vascular ischemia
- Cirrhosis
    - increased endogenous glucocorticoid causes deficient natural killer cell activity, decreased complement level/function
    - Cirrhosis-associated Immune Deficiency Syndrome (CAIDS)
    - sepsis, peritonitis
- Nephrotic syndrome
    - urinary losses/hypogammaglobulinemia
    - peritonitis is common
- Hemodialysis/uremia
    - mechanism not known but decreased T cell/neutrophil activity
- Peritoneal dialysis
    - complement & IG is removed with dialysate, causes reduced neutrophil function
    - peritonitis
- Autoimmune diseases
- Saphenous vein harvesting/venous stasis/chronic lymphedema
    - pooled lymph = culture medium
    - Streptoccus A
- Cancers
- Protein calorie malnutrition
    - decreased phagocytosis, T cell function, reduced specific antibody function
- Trauma/BURNS
    - necrosis releases large amounts of tumor necrosis factor/IL-1; add the loss of skin barrier/dermis with burns

Infectious diseases associated with immune defects:

- Measles
  - macrophage/antigen-presenting cell dysfunction
  - Gram negative bacillus pneumonia
- Cytomegalovirus
  - acute T cell dysfunction, reduced gamma globulin production
- Superantigen-producing bacteria (S. aureus, Group A streptococcus)
  - T cell anergy after cytokine storm/systemic inflammatory response
- Mycobacteria
  - organism deactivates the monocytes it infects
- Protozoa – trypanosomes, leishmaniasis, malaria*
  - macrophage/antigen presenting cell dysfunction

*Malaria induces cytotoxic T cell dysfunction in EBV-infected cells are predisposed to EBV-associated/Burkitt's lymphoma

Name the chemotherapy agents associated with the following side effect:

Hepatotoxicity
- Methotrexate (MTX)
- Asparaginase
- Mercaptopurine
- Adriamycin

Hemorrhagic cystitis - Cyclophosphamide
Neurotoxicity
- MTX
- Vincristine, vinblastine

Cardiotoxicity
- Adriamycin
- Doxo- & daunorubicin

Nephrotoxicity
- Platinum
- MTX
- Streptozocin

Cell mediated immunodeficiency - Fludarabine (esp with steroids)

Malignancies associated with/caused by infections and the associated pathogens:

1/3 of cancers in those over 50 is caused by infection!

Streptococcus bovis/gallolyticus and Clostridium septicum; possibly Fusobacterium necroforum (Recently found in 50% of tumors and their metastases. Tumor growth stopped in cells treated with metronidazole!)
- Colon cancer

Human papilloma virus (especially types 16, 18)

- Squamous cell cervical/vaginal/vulvar, penile, anal, head & neck

Hepatitis B, C

- Hepatocellular carcinoma

Chronic osteomyelitis/sinus tracts

- Squamous cell carcinoma

Epstein Barr Virus

- endemic type Burkitt's lymphoma (B cell lymphoma)

Helicobacter pylori

- gastric carcinoma
- mucosa-associated lymphoid tissue (MALT) lymphoma

HIV

- B cell lymphomas

Human herpes virus 8 (HHV8)

- Kaposi's sarcoma

Human T-cell Lymphotrophic Virus I

- Adult T-cell leukemia/lymphoma

Schistosoma

- Bladder carcinoma

Merkel cell polyomavirus

- Merkel cell carcinoma

Liver flukes

- Cholangiocarcinoma (especially Viet Nam veterans who consumed raw or undercooked fish during the service)

Brucellosis

- Medulloblastoma

Hematologic malignancies associated with increased infection risks:

Chronic lymphocytic leukemia (CLL)

- Hypogammaglobulinemia, neutropenia, reduced CD4
- Give IVIG if IgG levels low
- At risk for Pneumocystis, Listeria
- Add Pneumocystis prophylaxis if also on fludarabine (markedly drops CD4)

Acute lymphocytic leukemia (ALL)

- Steroids - risk for Pneumocystis - add Pneumocystis prophylaxis during therapy
- Intermediate-high grade non-Hodgkin's lymphoma (NHL)
- Treatment-related neutropenia
- Fludarabine - risk for Pneumocystis - add Pneumocystis prophylaxis during therapy

Multiple myeloma (MM)

- Hypogammaglobulinemia (<20% of normal, may need IGG replacement), reduced humoral response to antigen challenge, cell mediated immune deficiency
- Sepsis/pneumococcus
- Infection risk highest in 1st 2 months chemotherapy

Acute Myelocytic Leukemia (AML)

- High dose cytosine arabinoside (Ara-C, HiDAC regimen)-associated with substantial GI mucositis
- expect fevers during neutropenia, Gram negative bacillus sepsis

Chronic Myelocytic Leukemia (CML)

- Hypogammaglobulinemia, cell mediated immune deficiency

Myelodysplastic syndrome (MDS)

- Neutropenia

Hairy Cell Leukemia (HCL)

- 40% have under 500 cells/mm3 neutrophil count
- Poor intracellular killing
- Pyogenic infections are common

Lymphoproliferative disorders with "functional neutropenia" (poorly functioning neutrophils despite normal - high WBC):

- AML – able to phagocytize but poor intracellular killing
- ALL – poor intracellular killing
- CLL – mild-moderate neutropenia
- CML – poor phagocytosis, poor chemotaxis, blast crisis (high# WBC)
- Hairy Cell Leukemia - poor intracellular killing on top of absolute neutropenia

Define neutropenia, and describe a timeline for worrisome infections.

Absolute Neutrophil Count (ANC) = total WBC x (% neutrophils + % bands)

e.g. ANC = 7,000 cells/mm3 x (30% neutrophil + 5% blasts) = 7,000 x 0.35 = 2,450

Neutropenia = ANC under 1,500 cells/mm3

Per the classic reference: Bodey GP et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Int Med 1966; 64:328-40:

Under 500 cells/mm3 = increased risk for opportunistic/severe infections

- ANC < 1000/mm3 = 20% infection
- ANC < 500/mm3 = >35% infection
- ANC < 100/mm3 = >50% infection

Infection risk rises with duration and depth of neutropenia. Severe neutropenia (ANC < 100/mm3) over 3 weeks = 100% infection risk

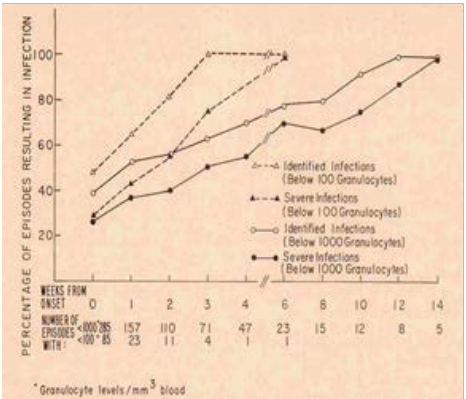

FIGURE 7. The effect of duration of granulocytopenia on the frequency of infection. The duration of granulocytopenia is plotted against the percentage of episodes resulting in infection. Along the abscissa are recorded the number of episodes of granulocytopenia (< 1,000/mm³) and severe granulocytopenia (< 100/mm³) for each time interval. The curves illustrate the percentage of episodes at both granulocyte levels resulting in any infection and in severe infection. The risk of developing infection increases the longer granulocytopenia is present and this risk is consistently greater at the lower granulocyte level.

Define the infection risk periods during febrile neutropenia, and the most likely sources/sites/types of

infections seen in each.

Day 0-7

- Skin, gut translocation, terminal ileitis/typhlitis
- Gram negative bacilli, anaerobes
- While on empiric anti-Pseudomonal/Gram negative bacillus coverage
    - S. aureus, viridians Streptococci (associated with ARDS), Corynebacterium – especially with central lines less than a week old

Day 7-14

- Gut translocation, line-associated bacteremia
- Gram negative bacillus, Gram positive coccus (MRSA/VRE), yeasts (especially while on broad-spectrum antibiotics), anaerobes

Day 14+ (prolonged neutropenia)

- Gut, skin, hospital-associated (lung/bloodstream/UTI—don't expect pyuria)
- Gram negative bacillus (include multidrug resistant), Gram positive coccus (include coagulase negative Staphylococcus, MRSA/VRE), Gram positive bacillus (Bacillus, Corynebacterium JK), yeasts
- Mouth/teeth, oral anaerobes (Clostridia, Capnocytophagia, Fusobacterium)
- Lung/SINUSES, molds (environmental exposure, especially during construction/remodeling in hospital)
- Reactivation: herpes simplex, varicella/zoster, CMV, adenovirus, BK virus

List 5 opportunistic organisms often causing pulmonary infection in immunocompromised patients. What stain is used histologically?

CPLANT
Cytomegalovirus – hematoxylin and eosin (H & E) stain
Cryptococcus – CNS-India Ink, lung-Gomori Methenamine Silver (GMS), Periodic Acid-Schiff (PAS)
Pneumocystis jiroveci - Gomorri methenamine silver
Listeria - CNS
Legionella pneumophila - Dieterle silver
Aspergillus - Gomorri methenamine silver), Periodic Acid-Schiff (PAS)
Nocardia - Modified acid fast
Toxoplasma gondii - Immunoperoxidase

Name the three post-solid organ/-hematologic transplant periods, and the associated infections:

EARLY PERIOD (0-30 DAYS)

-
- Community-acquired infections – UTI, pneumonia
- Nosocomial infections, incl central lines
    - Mucosal disruption – Strep viridans bacteremia (assoc with ARDS), Candida
- Reactivation infections – (from recipient or donor) HSV, VZV, TB

IMMUNOSUPRESSED PERIOD (30-180 DAYS)

- Humoral & cell-mediated immunodeficiency
- Opportunistic infections - CPLANT
- Fever of unknown origin/GI-CMV
- Adenovirus (multiple organ systems, hemorrhagic cystitis)
- BK virus (hemorrhagic cystitis only)
- HHV6- encephalitis, FUO
- Respiratory viruses – influenza, parainfluenza, human metapneumovirus, RSV, rhinovirus
-

LATE PERIOD (180 + DAYS)

- Immunity normalizes
- If chronic GVHD
    - Cell-mediated, humoral immunodeficiency persists
    - Functional asplenia due to GVHD
- Community-acquired infections

Name conditions and infections of concern in allogeneic bone marrow transplant recipients.

Post-engraftment period (new marrow cells being produced & no longer neutropenic)

- Cell mediated immune deficiency persists
- Graft vs. Host Disease (steroids & cytosine

arabinoside reduce immunity)
- Sinopulmonary molds remain a risk indefinitely
- CMV, herpes, varicella - acyclovir/ganciclovir prophylaxis, weekly CMV PCR
- BK virus - hemorrhagic cystitis
- HHV6
- Viral pneumonia with community respiratory viruses (RSV, influenza, parainfluenza, adenovirus, rhinovirus, human metapneumovirus)
- Diffuse alveolar hemorrhage

What infections, immune insults, & toxicities are associated with which immunosuppressive agents?

Cyclosporine/Cytosine arabinoside/ara-C/tacrolimus/cell mediated
- CMV bacterial pneumonias
- renal insufficiency
- tremor
- hepatotoxicity

Azathioprine (Imuran/cell mediated)
- pancytopenias
- pancreatitis/hepatitis
- skin cancers

Mycophenolate mofetil (Cellcept)/cell mediated
- CMV
- diarrhea

Cyclophosphamide (Cytoxan)/chlorambucil/cell mediated

- hemorrhagic cystitis
- bone marrow suppression
- Pneumocystis (with concomitant corticosteroids ≥ 20mg prednisone equivalent daily for over 30 days)

Methotrexate/mild lymphoid suppression/concomitant steroids (especially with rheumatic disease)

- Pneumocystis
- CMV
- Fungal
- Nocardia
- Hepatitis

TNF-alpha inhibitor drugs/cell mediated

- TB
- Histoplasma, Aspergillus, Coccidioides, others
- Pneumocystis
- Listeria
- Hepatitis B
- JC virus (progressive multifocal leukoencephalopathy or PML)

Purine analogs (fludarabine, cladribine, pentostat)/lymphopenia/CD4 suppression

- Pneumocystis
- S. aureus, Gram negative bacilli
- Listeria
- Disseminated VZV
- CMV
- Legionella
- Nocardia
- Monoclonal antibodies

Temozolomide plus radiotherapy

- Pneumocystis – while lymphopenic

Monoclonal antibodies (rituximab/alemtuzumab/natalizumab)/IgG & cell mediated

- CMV (alveolar hemorrhage/hemorrhagic pneumonitis), HSV
- Pneumocystis
- Aspergillus, Mucor, Cryptococcus
- Skin infections
- Otitis media
- PML
- HSV risk up to 12 months later
- With concomitant corticosteroids ≥ 20mg prednisone equivalent daily for over 30 days
- Pneumocystis

All: post transplantation B cell lymphomas (EBV) associated with

- Level of immunosuppression, especially antithymocyte therapies, OKT3
- EBV seronegativity

What are the important antimicrobial interactions with cytosine arabinoside (CyA), tacrolimus, sirolimus?

Reduces levels → PRECIPITATES REJECTION

- Rifampin, INH – remember "RIFAMPIN

REJECTS"

Elevates levels → increases antirejection drugs' toxicity

- renal, siezures, hypertension
- Azole antifungals
- Erythromycin/clarithromycin

What diseases does BK virus produce?

- Hemorrhagic cystitis
- Urethral stenosis
- Hepatic dysfunction, especially in bone marrow/neutropenic patients.

What are the reactivation rates for BK and JC viruses?

- BK - 50%
- JC - 5%

Name 2 types of post-transplant EBV disease and time of occurrence.

Young: 9 months post-transplant - viral illness

Old: 6 years post-transplant - tumor mass

Name 5 major types of immunosuppressive agents used in transplantation:

Corticosteroids

- most broadly acting
- block release of IL I-V
- decrease gamma –IFN
- decrease Ab production
- blunt inflammatory response by membrane stabilization

Cytotoxins

- Azathioprine
- purine analog
- interrupts DNA synthesis

Antilymphocytic Antibodies

- OKT3 - blind T-cell CD3 receptor FK506-associated with posttransplant lymphoma

Cyclosporine - inhibits proliferation of T-4 helper cells (blocks IL-S)

Radiation therapy

What microorganism is used in the treatment of bladder cancer & why?

A live attenuated strain of Bacillus Calmette-Guerin (BCG), Mycobacterium bovis, is used as therapy for superficial bladder cancer. BCG stimulates potent macrophage-induced cytoxicity against bladder cancer cells.

What is an uncommon infectious complication of BCG treatments?

- Disseminated BCG with hypersensitivity response and granulomas, with or without culturable organism.
- Manifestation ranges from cystitis to sepsis syndrome.
- Treatment includes antitubercular agents and corticosteroids.

What is hyperammonemia syndrome?

- Hyperammonemia syndrome has been documented in transplanted and other immunocompromised patients as a progressive rise in serum ammonia (>1000) that leads to cerebral edema and death
- Ureaplasma urealyticum hydrolyses urea to produce ammonia. It has been documented by PCR in blood in these patients; culture requires special techniques.
- Empiric doxycline resolves the condition, but

watch for relapse.

-

List a differential diagnosis for non-infectious causes of pulmonary infiltrates in cancer patients.

- Congestive heart failure/fluid overload
  - coronary artery disease, IL-2 direct cardiotoxicity
  - Non-cardiogenic pulmonary edema
  - adult respiratory distress syndrome/ARDS, cytarabine, IL-2
- Pulmonary embolus
  - hypercoagulable state
- Neoplasm
  - metastasis, lymphangitic spread, leukemic infiltrates with WBC >100,000 cells/mm3 in AML/CML
- Diffuse alveolar hemorrhage (D)AH
  - Autologous/allogeneic bone marrow transplantation
  - Caused by cytotoxic drugs, ARDS, infections
  - sudden dyspnea, dry, fever, blood in BAL; give steroids
- Cryptogenic organizing pneumonia (COP)
  - post-BMT, esp with chronic graft-versus-host disease/GVHD); give steroids
- Drug-related
  - busulfan, bleomycin, carmustine, methotrexate

- less often: cyclophosphamide, mitomycin, 6-mercaptopurine, semustine, vinblastine, etoposide

Bacteremia with which organism is associated with adult respiratory distress syndrome (ARDS) in the neutropenic leukemic patient? How can you prevent ARDS in this setting?

- Viridans streptococci, especially Streptococcus mitis
- Corticosteroids given at the onset of bacteremia can prevent ARDS or ameliorate it if given at the onset of dyspnea. Aggressive cytotoxic drug treatment and streptococcal sepsis probably combine to exacerbate cytokine release with capillary leak.
- Viridans streptococcal bacteremia is probably related to increased mucosal injury with aggressive cytotoxic agents; quinolone prophylaxis during neutropenia may provide selective pressure toward Gram positive organisms.

What is "cord colitis"? Describe what it is, what patient population it occurs in, diagnostics/differential diagnosis, suspected etiologic agent, and treatment.

Cord colitis syndrome (CCS)

- Culture-negative, refractory diarrheal illness occurring in umbilical cord blood transplant recipients
- Presentation: Granulomatous inflammation of the upper and lower gastrointestinal tract
- Differential diagnosis: acute graft-versus-host disease
- Diagnostics:
- Endoscopic biopsy for granulomatous histopathology
- Special/immunohistochemical stains for infectious organisms are negative
- PCR for Bradyrhizobium enterica if available
- Treatment: Prompt response to ciprofloxacin and metronidazole. Therapeutic trial may help rule out GVHD.

[Gupta NK, et al. Am J Surg Pathol. 2013 Jul;37(7):1109-13; Bhatt AS, et al. N Engl J Med. 2013 Aug 8;369(6):517-28.]

What types of infection are associated with brain cancer?

Postoperative infections—surgical wound infections, subgaleal/subdural abscess, meningitis

What are risk factors for postoperative infection in brain cancer?

- CSF leak
- Prior neurosurgery
- Chemotherapy
- Radiation therapy (also radionecrosis, which can develop osteomyelitis) Prolonged steroids
- Prior surgical wound infection
- Prolonged operative time
- Gliadel chemotherapy wafer insertion into tumor cavity

What organisms cause infection in brain cancer?

S. aureus, Gram negative bacillus, Propionobacterium acnes, coagulase negative Staphylococci, anaerobic streptococci (especially post sinus surgery)

Interestingly, medulloblastoma has been associated with brucellosis.

What infections are associated with ENT cancers?

- Herpes reactivation, thrush
- Surgical site infection - 10-20% wound infection rate
- Saliva contains 108 CFU/mL bacteria (similar to 105 CFU/mL infected soft tissue)

- S. aureus, Gram negative bacillus, Candida, anaerobic streptococcus, herpes simplex

What risk factors are associated with infection in ENT cancers?

- Xerostomia - gingivitis, dental disease
- Mucositis - with chemotherapy/XRT
- Prolonged OR time
- Peri-operative blood transfusion
- Flap reconstructions
- Radionecrosis of the mandible - polymicrobial, osteomyelitis

What infections are associated with lung cancers? Which organisms?

- Pneumonia at any time, especially obstructive
- Broncho-pleural fistula (BPF)/Empyema post-operative
- Surgical wound infection post-operative
- S. aureus/MRSA, Gram negative bacillus, alpha streptococci, Candida (empyema due to BPF, not pneumonia), Legionella, non-TB mycobacteria

What infections may occur in the setting of colon

cancer?

Post-operative

- surgical wound infection
- perforation/intra-abdominal abscess (also pre-OP & with radiation colitis)
- mesh infections
- enterocutaneous fistulas (also with radiation colitis)
- With abdominal-perineal resections: perineal abscess, pre-sacral abscess, sacro-iliac osteomyelitis
- S. aureus, Gram negative bacillus, Enterococcus/VRE, Candida
- Sepsis, hematogenous infections due to Clostridium septicum or Streptococcus bovis/gallolyticum

Mr. X received 5-flourouracil for head and neck cancer. Watery diarrhea began a couple of days later and has been refractory through the neutropenic period. Three weeks after chemotherapy he is admitted with bloody diarrhea and shock. MRSA is cultured from stool and you are asked if this is relevant.

Indirectly. If the patient has dihydropyrimidine dehydrogenase deficiency, however, this may preclude metabolism and elimination of 5-FU, so that severe mucositis/colitis may occur after a few weeks. Shock may be associated with gut translocation, therefore, in this setting, it's probably wise to include coverage for the MRSA in the stool along with any broad-spectrum regimen

covering colitis and sepsis.

What properties of Streptococcus gallolyticus (formerly S. bovis) promote its association with colon cancers?

- S. gallolyticus antigens induce pro-inflammatory cytokines, angiogenesis, local vasodilation/capillary permeability
- S. gallolyticus adheres strongly to connective tissues, survives in bile acids/escapes hepatic reticuloendothelial system
- Thus, this organism is able to translocate easily from gut/biliary tree, adhere to colonic epithelium and endothelial sites of turbulent flow, and trigger neoplasia in the colonic tissues to which it adheres. This organism can be found colonizing colorectal tumors as well.
- This organism stimulates high levels of specific IGG in colonized persons. Some researchers have proposed that high SBG IGG may serve as an early marker for colorectal cancer risk.

[Abdulamir et al.: The association of Streptococcus bovis/gallolyticus with colorectal tumors: The nature and the underlying mechanisms of its etiological role. Journal of Experimental & Clinical Cancer Research 2011 30:11.]

Define myeloproliferative disorders and name 6:

Definition: Clinical condition resulting from uncontrolled expansion of all bone marrow elements.

PEACE

Polycythemia vera - inc. RBC's
Essential thrombocytosis
Agnogenic myeloid metaplasia (pancytopenia), acute myelogenous leukemia (AML)
CML - inc. WBC's
Erythroleukemia

Splenomegaly results from extramedullary hematopoiesis

Tumors associated with EBV:

- Burkitt's lymphoma
- Nasopharyngeal carcinoma
- B-cell lymphoma in immunosuppressed patients

Name the 6 tumors that often metastasize to bone:

Kidney
Thyroid
Lung
Prostate

Testes
Breast

What are risk factors for infection in breast cancer? What organisms are common?

- Surgical wound & drains
- Breast implant/expander
- Post-operative seroma
- Myocutaneous flaps
- Smoking - flap necrosis/infection
- Lymphedema
- Prior skin/soft tissue infection radiation therapy/XRT
- S. aureus/MRSA, beta streptococci, Gram negative bacillus, rapid growing Mycobacteria

What causes skin/soft tissue infections in cancer patients?

- Impaired lymphatic drainage, edema
    - Surgeries, tumor invasion, lymph node dissections
- Wound infections
- Surgeries
- Reduced if radiation therapy is delayed 3-4 weeks

post-operative
- Group A streptococci, S. aureus/MRSA, Gram negative bacillus, polymicrobial

What are the sources of infection in catheter-associated bacteremia?

Skin, followed by the catheter hub, then hematogenous source, and uncommonly, infusates
Wash your hands. :}

What is the most significant infectious complication related to radiation therapy (XRT) to head, long bones & spine?

Radionecrosis with resulting cellulitis and possibly osteomyelitis (infection of dead bone)

- Head - regional flora
- Long bone/spine - skin/hematogenous organisms

What is the most significant infectious complications related to radiation therapy (XRT) to the thorax?

- Community- & hospital-acquired respiratory pathogens, Aspergillus (esp with nodules/cavities)
- Radiation-damage esophagitis
    - Superimposed herpes simplex, CMV, yeast
- Radiation-damaged alveoli/radiation pneumonitis/fibrosis/pleuritis/COP
    - Recurrent pneumonia?
    - Think radiation tracheo-esophageal fistula with aspiration!

Does XRT have immune-associated effects other than local tissue damage?

Yes.
There is a small drop in chemotaxis of neutrophils for about 3 days after XRT.

- Early in XRT = epithelial cell death (mucositis, xerostomia, proctitis)
- Later (6 months+) = reduced fibroblasts, poor wound healing, fibrosis, reduced vascularity

What infections may be increased in Systemic Lupus Erythematosis and why?

- Salmonella bacteremia
- Shingles/Varicella
- CMV
- Parvovirus B 19

- Pneumococcus
- Nocardia (steroids)

- complement deficiency, CD4 lymphopenia,
- asplenia
- steroids
- Note that homozygous early complement deficiency (C1q,r,s; C2,C4) is associated with sinopulmonary disease, pneumococcal infections, and development of systemic lupus erythematosus. CH50 will be very low.

What pathogen may superinfect in Wegener's granulomatosis?

Staphylococcus aureus

List infectious agents that post-splenectomy patients are susceptible to. What is the mechanism?

Pneumococcus - #1
Neisseria meningitidis
Hemophilus influenza B
Klebsiella pneumonia
Pseudomonas aeruginosa
Capnocytophaga canimorsus (dogs)
Salmonella

Streptococcus Group B
Babesiosa microti

All of these bacteria are encapsulated organisms, meaning they have a polysaccharide capsule that impedes phagocytosis. It is, however, bound by antibody (opsonization), and the spleen plays a prominent role in defense by plucking them out of circulation. Babesia is an intro-erythrocyte parasite that damages or deforms red blood cells; a major function of the spleen is clearance of old or damaged red cells.

Absent the spleen, encapsulated bacteria can cause overwhelming sepsis.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

[HIV deserves its own book of Pearls. I have included here some absolute basics. Please look to more comprehensive sources for details.]

List the differential diagnosis of opportunistic infections in HIV by absolute CD4 count, and note prophylaxis, if any.

Absolute CD4 (cells/mL):

- Any CD4
- TB – screen for symptoms regularly; screen asymptomatic patients with CXR PA/lat & PPD or interferon gamma release assay (IGRA); treat + screening test x 12 months with isoniazid + B6
- EBV-related lymphoma (B cell)

<500

- Community acquired pneumonia

<250

- Coccidiomycosis – prophy if + IGM or IGG in endemic areas – azole antifungals

<200 (or %CD4 ≤ 14) ← This is the cut-off where most opportunistic infections begin to appear.

- Candida
- Pneumocystis jirovecii (PCP) – sulfa drugs, atovaquone, inhaled pentamidine, dapsone (doesn't cover Toxo)
- Cryptococcus

<150

- Histoplasma capsulatum – endemic areas or known occupational risk– azole antifungals

<100

- Mycobacterium avium Complex – 2/100 person-years & rises with lower CD4 – azithromycin or clarithromycin
- Cryptosporidium, Microsporidium
- Toxoplasmosis – screen new patients with Toxoplasma IGG; if negative, counsel on risk reduction; if +, initiate prophy at 100 cells/mL with sulfa drugs, pyrimethamine, or atovaquone (susceptibility variable)

<50

- Cytomegalovirus – negative IGG has high negative predictive value in evaluation for active disease – CMV viremia predicts active disease; prophy may improve mortality & prevent active disease, but is costly and may cause resistance, so consider pros and cons, patient adherence, etc.
- JC virus – progressive multifocal leukoencephalopathy (PML) – treat with 5-drug antiretroviral therapy (tenovofir-emtricitabine, ritonavir-boosted protease inhibitor, integrase inhibitor, & add efuvirtide for at least 6 months), may extend life but won't reverse damage; physical therapy may recover some functions
- Bartonella henselae

Remember: CD4 is a rough guide in differential diagnosis & starting prophylaxis, not a rigid cut-off for risk assessment; assess the patient and presentation, not a number. E.g. CMV disease may manifest at 75 or 100 cells/mL.

What's the differential diagnosis of intracranial lesions in HIV+ patients?

Lymphoma – often single lesions

- EBV PCR > 10,000 copies/mL in cerebrospinal fluid (CSF)
- CT/MRI: hypodense or hyperdense lesion that enhances in a nodular, homogeneous, or ring-enhancing with contrast
- SPECT Thallium-201: highly specific, increased uptake

Toxoplasmosis – usually multiple, white matter and basal ganglia,

- MRI T2-weighted imaging - target sign - concentric alternating zones of hypointensity and hyperintensity
- CT, ring-enhancing with IV contrast

JC virus/progressive multifocal leukoencephalopathy (PML) – may be unifocal or multifocal, fronto-parietal

- MRI T-2 weighted imaging - hyperintense lesions in periventricular or subcortical white matter
- May suggest ischemic lesions or event

Which drugs may crystallize in urine and cause renal failure if the patient becomes dehydrated?

- sulfadiazine (treats toxoplasmosis)
- acyclovir (treats HSV & VZV)
- atazanavir (HIV protease inhibitor)

Which co-infection may cause an unexpectedly high absolute CD4 count despite clinical evidence of immunosuppression? What should you think of when you see a high CD4 that doesn't "make sense"?

HTLV-1

Which live vaccines may & may not be given in the setting of HIV & when?

In general, live vaccines should be avoided in immunosuppressed individuals.

In the setting of HIV, the following vaccines can be given:

YES, if absolute CD4 > 200 cells/mL

- Measles-Mumps-Rubella vaccine (measles mortality is over 40% in HIV)
- Varicella vaccine for primary varicella
- Varicella vaccine for shingles
- Yellow Fever vaccine for travelers to, or traveling through, endemic areas (avoidance of such travel is best)

NO:

- Any live vaccine if CD4 < 200 cells/mL
- Inhaled attenuated influenza vaccine (pending

trials)
- Bacille-Calmette Guerin (BCG)
- Live oral polio vaccine (use inactivated injected polio vaccine)

Which vaccine(s) are contraindicated with myasthenia gravis? Why?

All live attenuated virus vaccines, if receiving immunosuppressing treatments.

- Yellow Fever Vaccine – significant increased incidence of yellow fever vaccine-associated viscerotropic disease in those with thymus disorders.
- Health-care providers should carefully consider the benefits and risks of vaccination for elderly travellers, and should ask about a history of thymus disorder or dysfunction, irrespective of age, including myasthenia gravis, thymoma, thymectomy, or DiGeorge syndrome, before giving yellow fever vaccine.
- If travel plans cannot be altered to avoid yellow fever-endemic areas, people with a history of thymus disease should consider alternative means of yellow fever prevention, including use of insect repellents, containing N, N-diethyl-metatoluamide (DEET) and permethrin, and other behaviours to reduce mosquito bites."

[Eidex RB. Lancet 364:936, 11–17 September 2004]

What adverse events are associated with Yellow Fever Vaccine, and who is at risk?

Immediate hypersensitivity reactions/anaphylaxis - 1.8 cases per 100,000 doses

Yellow fever vaccine–associated neurologic disease (YEL-AND) - meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, bulbar and Bell palsies

- Onset 3 - 28 days after vaccination
- Increased risk in
    - first time vaccine recipients
    - Age > 60
    - Exclusively breastfed infants

Yellow fever vaccine–associated viscerotropic disease (YEL-AVD) - similar to wild-type disease; vaccine virus causes disseminated disease, often with multisystem organ failure and death

- Onset 0 - 8 days after vaccination
- 0.4 cases per 100,000 doses, 1 or higher if age > 60
- Increased risk in
    - first time vaccine recipients
    - Age > 60

Yellow Fever Vaccine is contraindicated in:

- Immunosuppression
- HIV with symptoms or CD4 <200/mm3 or <15%
- Thymus disorders incl myasthenia gravis

Precaution is needed in those over 60, breastfeeding

mothers (risk to infant), pregnant women (variable immune response to vaccination/variable protection), & those with chronic medical conditions associated with variable immune defects: liver disease/chronic hepatitis, diabetes mellitus, chronic renal disease, collagen vascular disorders, etc.

[Always consult CDC's "Yellow Book", Health Information on International Travel on Yellow Fever risks and vaccination at http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014]

In patients co-infected with hepatitis C and possible concomitant HIV, which HIV medication should you avoid if using Ribavirin?

Didanosine (DDI) – serious mitochondrial toxicities/lactic acidosis

Which rare Mycobacterium can cause disseminated or localized red draining cutaneus nodules in HIV+ patients?

Mycobacterium haemophilum

Name some of the most common HIV mutations and

the associated nucleoside drug resistance?

- M184V = resistance to emtricitabine, lamivudine and abacavir. BUT hyper-susceptibility to zidovudine (AZT or ZDV) > tenofovir, & makes virus less fit.
- T215 = zidovudine resistance
- K65R = Cross resistance to tenofovir, abacavir, lamivudine, and didanosine
- L74V or I = resistance to abacavir
- Q151M = All nucleoside reverse transcriptase inhibitors (NRTI) except tenofovir
- K103N = resistance to the NNRTIs, efavirenz & nevirapine
- V179D+K103R = efavirenz & nevirapine
- Y181C+V179F = high level resistance to rilpivirine, etravirine
- 172K = may overcome resistance mutations to NRTIs & NNRTIs

Which HIV medication is Food and Drug Administration Category D (Positive Evidence of Fetal Risk) in pregnancy?

Efavirenz: It was changed from category C to D after 4 retrospective reports of neural tube defects in infants born to women with first trimester exposure to efavirenz, with 3 cases of meningomyelocele and 1 Dandy Walker Syndrome.

Pregnancy testing is advised prior to administration of this agent to women of childbearing age.
Contraception/avoidance of pregnancy is advised in those receiving this agent prior to pregnancy.

Which test is recommended before initiation of abacavir to assess the risk of a serious life-threatening hypersensitivity reaction?

HLA-B*5701 allele.

In a predominantly white population at low risk, testing has a negative predictive value of 100% and a positive predictive value of 47.9%.

(Mallal S et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med 2008;358:568-79.)

Which syndrome may develop soon after initiation of antiretroviral therapy in HIV+patients?

Immune Reconstitution Syndrome/IRIS
onset of opportunistic infections despite rising absolute CD4 or other markers of immune recovery
often these were simply smoldering and become clinically evident when the immune system recovers ability to mount an inflammatory response

When do you worry about neurosyphilis in a patient with HIV and + syphilis serology?

At any stage of infection, even primary active (chancre). Consider LP for CSF syphilis serology, especially if neurologic symptoms.

GENOMICS & INFECTION

[This Section is only a sample of what will is already an exponential growth in human understanding of how genetic polymorphisms or mutations in both human and pathogen genomes impact susceptibility or resistance to infection. I do not expect to be able to keep up with this section over time. One day, it may serve as a quaint example of the history of genomics in its infancy. :}]

Note one theme: Interferon Gamma is very important in the defense against mycobacteria. Hence the use of exogenous IFN G in treating some types of mycobacterial infections.

Which genotype is associated with possible predisposition or susceptibility to Creutzfeld-Jacob (prion) disease?

Valine 129 homozygous genotype

What genes are associated with susceptibility to TB?

In West Africa/African-Americans:

- Four NRAMP1 gene polymorphisms associated with higher risk of TB

- Individuals heterozygous with NRAMP1 /3' UTR allele = 4X greater incidence of TB
- May explain higher incidence of TB in these ethnic groups

In Vietnam:

- C allele variant of Toll-Like Receptor 2 (TLR2 variant) - associated with greater risk of pulmonary TB & TB meningitis due to Beijing genotype TB
- Beijing TB genotype also associated with Multi-Drug Resistance
- Deficiency of Vitamin D receptor - predisposes to TB

TIRAP CC-to-TT single-nucleotide polymorphism at 558 (SNP 558TT)

- decreased IL-6 production
- greater risk of TB meningitis

What polymorphism may protect against TB?

Interferon Gamma (IFN G) polymorphism with A-to-T substitution at 874

- protects against TB
- favors binding of transcription factor NFkappaB
- improved IFN G production?

What is CISH allele & why is it of interest?

CISH = Cytokine Inducible SRC Homology 2 domain protein)

- suppresses cytokine release, regulates IL-2
- 5 CISH polymorphisms affect risk of bacteremia, TB, malaria
- 1 polymorphism = 18% risk of infection
- 4+ polymorphisms = 80+% risk of infection

Which polymorphism is associated with disseminated Mycobacterium avium complex (MAC) infections?

IFN G Receptor 1 mutations

- absence of IFN G receptors on macrophage surface
- macrophage up-regulation of Tumor Necrosis Factor in response to IFN G is impaired

What 2 human genetic mutations have conferred evolutionary advantages by protecting against disease? Which disease and by what mechanism?

- G6PD deficiency
- Sickle cell trait

G6PD deficiency results in hemolysis during infections, which interferes with the lifecycle of malaria by lysing parasitized red blood cells.

Sickle cell trait causes more red blood cells to be sequestered or cleared by the spleen when parasitized.

ZOONOSES & INSECT-ASSOCIATED INFECTIONS

Key Animal Associations, Pathogen, Key Presentation, & Drug of Choice:

- **Goats**/cattle/unpasteurized dairy/feral hogs, hunters/elk & bison at Yellowstone National Park-**Brucellosis**-splenic abscess-doxycycline + gentamicin
- **Rabbits**/skinning rabbits-**tularemia**-lymphadenopathy-streptomycin
- **Placental exposure**/parturient animals/hoofed livestock-**Q fever**/Coxiella burnetti-pneumonia/splenomegaly-doxycycline
- **Dogs/cattle/rats (urine)/fresh water** contact-**Leptospirosis**-conjunctivitis/hepatitis/renal insufficiency-penicillin G
- **Cat bites**>dog bites-**Pasturella** multocida-cellulitis/osteomyelitis/sepsis-penicillin G
- **Cats**-**Bartonella** henselae - angiomatous lesions in AIDS-doxycycline or azithromycin
- **Dog bites**/licks-**Capnocytophagia** canimorsis (especially if asplenic)-amoxicillin/clavulanate or clindamycin; Pasturella-penicillin G
- **Reptiles/turtles**-**Aeromonas** (bites), **Salmonella** (just being around a reptile is a risk factor for the latter, due to stool carriage)-cellulitis/bacteremia-quinolone
- **Parrots/parakeets/pet shop**-**psittacosis**-pneumonia/splenomegaly--doxy
- **Guinea pigs-Salmonella**-as for reptiles
- **Hamsters/rodents-lymphocytic**

choriomeningitis virus-meningitis

- **Hoofed livestock-Bacillus anthracis**-widened mediastinum/septic shock/black gelatinous skin lesions-ciprofloxacin (+ clindamycin if sepsis)
- **Pork/wild hog/sausages/smoked cougar or BEAR meat-Trichinella spiralis**- myositis, eosinophilia, periorbital edema, low ESR--albendazole/mebendazole
- **Flying squirrels-Rickettsia prowazekii** (epidemic typhus)
- **Prairie dogs/Giant Gambian rats/monkeys-monkey pox**-acyclovir
- **Monkeys/primates – herpes B** (simian herpes)-acyclovir

Key Insect Associations, Pathogen, Key Presentation, & Drug of Choice
(* eschar @ bite site)

Ticks/outdoor activity:

- **Lyme disease (Borrelia burgdorferi)-**erythema migrans early, facial cranial neuritis, peripheral neuropathy, lymphocytic meningoencephalitis, less often myopericarditis/AV block, chronic arthritis) – doxycycline, ceftriaxone
- **Babesia microti**-protozoan like malaria; cattle/hooved livestock, deer; flu-like illness, hemolytic anemia/hemoglobinuria, hepatosplenomegaly, NE or NW US, Maltese cross (tetrads & pairs) in RBCs-- clindamycin + quinine or atovaquone + azithromycin – asplenics have high mortality
- **Rocky Mountain Spotted Fever (Rickettsia**

rickettsiae, RMSF)-flu-like illness, macular/petechial rash, SE or SCentral U.S./dog ticks, thrombocytopenia (~meningococcemia) 3-5 days into illness, edema hands & feet/periorbital – doxycycline ASAP (25% mortality if not treated)

- **Ehrlichiosis**-flu-like illness (**"spotless RMSF"),** thrombocytopenia, no edema hands/feet, human *monocytic* ehrlichiosis/morula in *monocytes* (buffy coat Wright stain), SE or SCentral U.S., white tail deer/deer tick – doxycycline; asplenics can be very sick
- **Anaplasmosis-** flu-like illness, sometimes macular rash, thrombocytopenia, no edema hands/feet, human *granulocytic* anaplasmosis/morula in *granulocytes* (buffy coat Wright stain), NE or NCentral U.S., dog tick - doxycycline
- ***African tick bite fever (R. africae)** - Sub-Saharan Africa-**multiple eschars**, fever, lymphadenopathy- doxycycline
- ***Boutonneuse fever, Mediterranean spotted fever (R. conorii)** - N. Africa- single **"tache noire"** eschar, fever, lymphadenopathy-Doxy
- **Q fever** (also via aerosols/placental exposure/livestock) – fever of unknown origin (FUO), splenomegaly, culture-negative endocarditis - doxycycline
- ***Tick-Borne Relapsing Fever (Borrelia hermsii & other species)** – staying in a cabin in NW U.S./rodents/*soft* ticks; eschar, flu-like illness, 3-5 relapses - doxycycline
- **Tularemia (also aerosols/rabbit blood**)-ulcer at bite, lymphadenopathy, typhoid-like illness, or pneumonia-streptomycin, gentamicin
- **Colorado tick fever ~ RMSF,** less

rash, biphasic illness, West US- doxycycline

- **Tick paralysis-Guillain-Barre like** (tick neurotoxin) that resolves within 12-24 hrs of tick removal-no treatment other than tick removal from scalp

Flea/rats:

- Yersinia pestis/SW US/chipmunks - pneumonia/buboes – doxycycline + gentamicin/streptomycin
- Murine typhus (Rickettsia mooseri) - flu-like, rash, rat infestations - doxycycline

Mice/mites:

- *Rickettsialpox (Rickettsia akari) - eschar, mild flu-like, maculopapular-vesicular rash, New York City/city parks - doxycycline

Chiggers:

- Scrub typhus (Orentia tsusugamushi)-fever, flu-like, vesicopustular rash, adenopathy - doxycycline

Body louse/homelessness/disasters/war:

- Trench fever, urban trench fever/endocarditis in homeless (Bartonella quintana) - doxycycline
- Epidemic typhus/flying squirrels /Brill Zinsser disease (R. prowazekii) - flu-like, rash; may recur years later as Brill-Zinsser - doxycycline
- Louse-borne Relapsing Fever (Borrelia recurrentis) - doxycycline

Sand fly:

- Leishmania-hepatosplenomegaly/fever (Latin America/Middle East), cutaneous ulcers (tropics) – amphotericin B, antimonial drugs/stibogluconate
- Bartonellosis-Oroya fever/verruga peruana - doxycycline/azithromycin

Black fly:

- Oncocerca volvulus-River blindness – ivermectin

Tse tse fly/African safari:

- Trypanosoma brucei rhodesiense (EAST AFRICAN)-sudden high fever, myalgia, headache, painless chancre at bite, wasting, coma, death unless prompt treatment)—EMERGENCY - suramin, pentamidine (melarsoprol)/arsenic if central nervous system disease- in U.S., call Centers for Disease Control
- T. b. gambiense (West African)-more indolent sleeping sickness, prominent post cervical nodes (Winterbottom's sign), hepatosplenomegaly, mental status decline-suramin, pentamidine

Reduviid bugs/Latin America:

- Chaga's disease (Trypanosoma cruzi-C-shaped trypanosomes in blood) - acutely, Romaña's sign (periorbital edema), fever, myocarditis; chronically, fever, hepatosplenomegaly, achalasia, megacolon, cardiomyopathy
- nifurtimox, benznidazole

Mosquitoes/Latin America/Asia/tropics:

- Malaria-fever, rigors, headaches, prostration, dark urine (hemolysis)
- Dengue-fever, headache, severe pain in joints/behind eyes with movement, prostration, +/- sunburn-like rash; complication: hypotension, if infected previously with same serotype→capillary leak/hemoconcentration/shock 2 days after fever drops, may be followed by hemorrhages
- Chikungunya- dengue-like fever with severe joint pain, possibly morbilliform rash; complication: arthralgia without arthritis persists after 2-5-day illness up to weeks or months
- Zika virus- dengue-like fever with morbilliform rash & joint pain, lasts 4-5 days; complication: microcephaly, Guillain-Barré syndrome

TRAVEL & GEOGRAPHICALLY-ASSOCIATED ILLNESS BY SYNDROME

What can you see on a blood smear for in a febrile traveler?

- Malaria!!
- African trypanosomiasis
- Relapsing fever/Borrelia recurrentis/hermsii/parkeri
- Bartonella
- Babesia
- Filariasis

What are the symptoms/signs/associations with brucellosis?

- Fever of unknown origin/FUO
- Chronic fatigue
- Osteomyelitis—sacroiliitis
- Hepatosplenomegaly—splenic abscess/infarct
- Epididymoorchitis
- Chronic meningitis

- Unpasteurized dairy—GOATS/hoofed mammals outside U.S., undercooked meats, farms

- Feral hogs, wild game hunters
- Wild reservoirs in U.S. - Elk, bison (Yellowstone National Park)

Common infections by incubation period in travelers returning to United States:
(Ryan ETet al. N Engl J Med 2002;347:505-16; Tolle MA. J Am Board Fam Med 2010;23(6):704-713.)

Under 2 weeks

- Malaria
- Dengue
- Zika virus
- Chikungunya
- Leptospirosis
- Typhoid fever
- Acute HIV
- Spotted fever (rickettsial infection)
- Scrub typhus (rickettsial infection)
- Leptospirosis
- Yellow Fever
- East African trypanosomiasis (EMERGENCY, days-weeks)
- Babesia
- Campylobacteriosis, salmonellosis, shigellosis

2-6 weeks

- Malaria
- Typhoid fever
- Leptospirosis

- Acute HIV
- Hepatitis A & E
- Giardiasis, Cyclospora
- Acute schistosomiasis (Katayama fever)
- Amebic liver abscess (Entamoeba histolytica)
- East African trypanosomiasis (EMERGENCY, days-weeks)
- Viral hemorrhagic fever viruses
- Visceral leishmaniasis
- Q fever/Coxiella burnettii
- TB
- Rabies

Over 6 weeks

- Malaria
- Tuberculosis
- Visceral leishmaniasis
- Lymphatic filariasis
- Schistosomiasis
- Amebic liver abscess
- Chronic mycosis
- Hepatitis A & E
- West African trypanosomiasis (months to years)
- Rabies

Why must you treat Rocky Mountain Spotted Fever within 5 days?

The mortality rises from 6-7% to almost 25% with delayed

treatment. Treat empirically based on geographic exposure (especially SE U.S.) & likelihood of tick exposure—rash will only appear several days into illness.

Differential Diagnosis by Syndrome:

Typhoidal illnesses (fever, splenomegaly, adenopathy, headache)

NO rash:

- SE Asia – melioidosis
- Latin America/Mediterranean coast/Arabian Gulf - brucellosis
- Peru/Ecuador - bartonellosis
- Nantucket/Martha's Vineyard/NE US – babesiosis, tularemia
- Non-Lyme borreliosis (see Relapsing Fevers below)
- Rabbits - tularemia
- Latin America/Middle East - visceral leishmaniasis

With rash:

- Developing nations/India/Asia - Typhoid fever/Salmonellosis (rose spots on trunk)

Spotted fevers (maculopapular rash, fever, thrombocytopenia; all transmitted by ticks, except Rickettsia akari, & Rickettsia prowazeckii)

Developing nations/crowding/war/disaster/refugees:

- Rickettsia prowazeckii
- flying squirrels

- 20-50 yrs later-recurrent disease is Brill-Zinsser, mild

Mediterranean/N. Africa/Black Sea:

- Rickettsia conorii/Boutonneuse fever/Mediterranean Spotted Fever
- 70% *single black eschar* - tache noire

Japan:

- Rickettsia japonica/Japanese Spotted Fever (similar to MSF)

E. coast Australia:

- R. australis - Queensland Tick Typhus

Sub-Saharan Africa:

- R. africae-African Tick Bite Fever
- common in travelers/safari history, mild
- *multiple* eschars

New York City/city parks/mouse infestations/mouse mites:

- R. akari-Rickettsialpox
- small crusted eschar, rash may be vesicular

Asia/Pacific Rim/Australia/chiggers/scrub vegetation/tourists:

- Orentia tsutsugamushi-Scrub Typhus
- high fever, intense headache
- multiple black eschars

<u>Flu-like syndromes (fever, aches)</u>

SE/South central United States, Rocky Mountain

states/Cape Cod/Long Island-Spring/Summer:

- R. rickettsiae / Rocky Mountain Spotted Fever
- headache, myalgia, nausea ~ viral syndrome
- ankles/wrists, edema hands/feet/trunk
- rash 3-5 days later
- thrombocytopenia/shock

SE/South central United States, Ehrlichiosis

- similar to RMSF except no rash, no edema hands or feet, morula in buffy coat monocytes (human monocytic ehlrichiosis)

NE/NW United States/Anaplasma

- similar to RMSF/Ehrlichia except +/- rash, no edema hands or feet, morula in buffy coat granulocytes (human granulocytic anaplasmosis)

Relapsing fevers (fevers that go away & come back):

United States

- Tick-borne Relapsing Fever –Borrelia hermsii - 4 or 5 week-long relapses, cranial neuritis
- Soft tick/rodent exposure/sleeping (night feeder) in a log cabin in NWest U.S.

Eurasia and North America

- Borrelia miyamotoi - may cause relapsing flu-like fever with 10% Lyme-like erytherma migrans; week-long illness with week-long remissions

Central/South America, Africa, Asia

- Malaria, especially Plasmodium vivax/ovale; every 2-3 days, more regular the longer person is ill

Middle East/Latin America/All areas with refugees/war/disaster/epidemics:

- Louse-borne Relapsing Fever—Borrelia recurrentis/mellitensis – lice – 7 day relapses separated by 7 days remission

Biphasic Fevers

Western United States:

- Colorado tick fever- mountains; saddleback fever—3 d viral syndrome, 3 days well, 3 days viral syndrome (3-3-3)

Tropical climates

- Leptospirosis – fresh water exposure, triathlons, heavy rain/flooding; flu-like illness/calf pain/conjunctival suffusion (septicemic phase); initial improvement, then may recur in a couple of days with severe headache/aseptic meningitis/multiorgan disease (immune phase)

Target-lesion rash

Eurasia and North America

- Borrelia miyamotoi - may cause relapsing flu-like fever with 10% Lyme-like erytherma migrans

NE/Upper Midwest United States (sporadic elsewhere)

Borrelia burgdorferi / Lyme Disease

- Ixodes tick nymph/adult female
- Hunting/camping/hiking

Early/Stage 1

- Erythema migrans
- precedes antibodies, thus serology is unhelpful (except in prior infection or vaccine)
- occurs 3 days to 1month post bite
- migrates/fades in 3-4 weeks

- Flu-like syndrome
- Diagnosis: erythema migrans rash, geographic location, and tick exposure; early on, rash may take 2-3 days to become clear

Disseminated/Stage 2

- Idiopathic Bell's palsy, carditis/fluctuating AV Block not due to ischemia, meningitis, arthritis
- 3d-6 weeks
- Diagnosis:
- 2-step testing with Lyme ELISA or IF antibodies (total or IgM + IgG), then Western Blot confirmation if + (Important: if pretest probability of Lyme is low, the likelihood of false positive is high. Test if truly suspicious.)
- Synovial fluid is inflammatory in arthritis; PCR if available & meticulously performed is + but not reliable enough to rule out infection.
- Bannwarth's syndrome – classic triad of acute neuroborreliosis:
    - lymphocytic meningitis
    - cranial nerve palsy
    - radiculoneuritis
    - Blindness may be seen, especially children, with increased intracranial pressure or neuropathy.

Late/Stage 3

- arthritis, polyneuropathy, rarely chronic encephalopathy; months to years
- Diagnosis
    - Clinical findings, geography, tick exposure
    - 4-fold rise in IgG, + IgM
    - Synovial PCR (75-85% sensitive) probably more reliable than other fluids; 30% of active Lyme cases have + PCR due to low number of spirochetes, non-standardized

test
    - Flow cytometric Borreliacidal Antibody (99% specific, 72% sensitive); rises with chronicity
- Obtain CSF if neurologic symptoms
    - <10% Culture +
    - >80% +Lymphocytic pleiocytosis & CSF IgM/IgG
    - CSF antibody + by 3-6 weeks, may persist indefinitely or be + without neuro symptoms
    - 4 of 5 criteria should be + for neuroborreliosis:
    - No history of neuroborreliosis
    - No alternative diagnosis
    - +CSF antibodies to B. burgdorferi
    - + anti-Borellia antibody Index (CSF-to-serum antibody ratio) >1.0

East Texas/ SE /entire East coast U.S.

Southern Tick-Associated Rash Illness (STARI)
Lone Star tick / Amblyomma – adult has white spot on dorsum; interestingly, its saliva kills Borrelia burgdorferi

- Etiologic agent unknown
- Target-lesion (bull's eye) within 7 days of tick bite, expands to 8 cm or more
- Flu-like symptoms
- Diagnosis: rash, geographic location, and tick exposure; no lab test
- Treatment: unclear but likely benefit from antibiotics, most doctors treat with doxycycline empirically

Heartland Virus Disease

- Lone Star tick / Amblyomma
- Heartland virus
- Flu-like symptoms, leukopenia, thrombocytopenia
- Diagnosis: Heartland virus PCR or 4-fold rise in titer (Call CDC)

Hemorrhagic fevers

SW United States

- Sin Nombre hantavirus
- inhaled dried rodent urine, deer mice
- acute respiratory distress syndrome/non-cardiacpulmonary edema after 4-5 d flu-like prodrome
- leukocytosis
- disseminated intravascular coagulation

Caribbean/Asia/equatorial tropics – Aedes aegypti mosquito territories

- Dengue - breakbone fever
- fever, sunburn-like rash, adenopathy, severe myalgias/arthralgias
- biphasic illness with 2nd rash/fever sparing palms/soles
- repeated infection may cause hemorrhagic/shock syndrome-fever, bleeding/DIC, edematous face/hands
- S. Florida/Keys residents have been found to have + antibodies

- Yellow Fever – especially sub-Saharan Africa where

Aedes aegypti control is poor
  - subclinical to icteric infection with hemorrhage, liver/renal/cardiac failure, jaundice, GI bleed (black vomit)
  - leukopenia, thrombocytopenia
  - IgM, 4-fold rise in IgG

Africa:
- Ebola Hemorrhagic Fever/Marburg-Zaire/Sudan, monkeys? /bats?
- Flu-like illness-N/V/diarrhea-diffuse hemorrhages/death
- Neutrophilia/severe thrombocytopenia
- IgM/4-fold rise of IgG; DFA/electron microscopy of tissue, culture-high level containment lab (BSL-4)

West Africa:
- Lassa Fever
- inhaled rodent excreta
- ribavirin

Congo, Russia/Balkans:
- Congo-Crimean hemorrhagic fever
- blood-borne
- ticks
- human to human

Rift Valley:
- Rift Valley Fever
- cattle/sheep
- mosquitoes

South America:

- Machupo-Bolivian hemorrhagic fever
- inhaled rodent excreta

How does STARI differ from Lyme disease?

- Lyme exposure is less likely in S.E. U.S.
- STARI syndrome is shorter onset, within 7 days of bite/tick exposure
- Tick bite is more often recalled with STARI
- Target-lesions are less often associated with flu-like symptoms in STARI
- Target-lesions are often more circular and centrally-clearing, fewer in number in STARI

Which larvae are most likely to be visible in stool in a returning traveler?

Strongyloides stercoralis
Hookworms

MISCELLANY

What are Gompf's Can't-Miss ID Differential Diagnoses?

In every differential diagnosis, you should include the

Likely
Reversible
Life-threatening/disabling

Bacterial

- Necrotizing skin/soft tissue infections:
  - Necrotizing fasciitis/Fournier's gangrene
  - gas gangrene/myonecrosis
- Look for underlying GI cancer with Strep gallolyticus bacteremia or septic arthritis
- Gram negative rod cellulitis – Aeromonas, Vibrio
  - water exposure, bites
  - high risk with liver disease, iron overload
- Strep/Staph Toxic Shock – find the focus – drain or remove it (many cases no focus found)
- Cavernous sinus thrombosis – complicates nasal/sinus/orbit infections
- Epiglottitis – acute airway obstruction/Ludwig's angina – mediastinitis

Tick exposure

Rocky Mountain Spotted
Fever/ehrlichia/anaplasma – history of hiking, landscaping, gardening in tick-infested areas

Animal bites/Person sleeping with a bat in room

- Rabies exposure – incubates > 20 years or more
- Virus travels up axons to CNS 1 inch/day – head bites most dangerous
- 99.99% lethal once pain begins at bite site
- 100% preventable – Rabies IG & vaccinate regardless of how long since the exposure

Vesicle on nose

- Hutchinson's sign heralds shingles with ocular involvement – involve eye specialist in care

Parasites/Travel

- Naegleria fowleri meningoencephalitis– untreated fresh water exposure + "bacterial meningitis with negative Gram stain"
    - Call CDC Emergency Operations 770-488-7700 (save to your Contacts list)!
    - Call hospital pharmacy for emergency miltefosine from Profounda Pharmaceuticals
- Malaria – cerebral malaria in returning traveler
- East African Sleeping Sickness (Trypanosoma rhodesiense) in returning traveler
- CNS tuberculosis

Otic/Ocular Neurosyphilis - progressive irreversible loss of vision/hearing

Invasive mold sinusitis - DKA, neutropenia, DM
Invasive mold skin/soft tissue infection – trauma with soil, natural disasters

Botulism – history of home canned food, home fermented fish

What is pasteurization & where is it most important why?

Emperor Napoleon III asked Dr. Louis Pasteur to investigate the diseases afflicting vineyards with economic losses to the wine industry. Pasteur demonstrated that wine diseases are caused by microorganisms that can be killed by heating the wine to 55deg.C for several minutes. Applied to beer and milk, this process, called "pasteurization", soon came into use throughout the world.

With HTST (high temperature short time) pasteurization, raw milk is heated to a minimum of 161 degrees F for 15 seconds, followed by immediate cooling. This method produces milk with a shelf life of 14-17 days. (This level of pasteurization can be performed on a stovetop at home.) With ultra pasteurization, milk is heated to a minimum of 280 degrees F. for two seconds and then immediately chilled. This method produces a shelf life of around 60 days, when unopened and refrigerated.

Remember: pasteurization ≠ sterilization. Organism numbers are simply reduced to safer levels. Contamination may also occur after pasteurization at many steps from processing to table. This is why milk will eventually sour due to bacterial overgrowth.

Which human pathogens, ordinarily killed by pasteurization, have been documented in raw milk, including outbreaks?

- M. bovis—one of the M. tuberculosis group which causes cow & human TB
- Rabies
- Brucella abortis & mellitensis
- E. coli/coliforms—including E. coli H7:0157 Listeria
- Salmonella, Yersinia, Campylobacter
- Staphylococci & their enterotoxins
- Group A streptococci & others
- Coxiella burnetti

Note bene: Rabies has been transmitted from rabid human mother to infant via breast milk. Rabies cases are rarely recorded from nonhuman milk, because in most societies where pasteurization is not mandated, people understand the risk of rabies, and they boil their milk. Further, in areas where raw milk is consumed for ritual or other purposes, rabies vaccination is mandatory when exposure to milk from a rabid cow has been confirmed. It is well-known that rabies is underreported in many areas. Rabies is 100% fatal upon becoming symptomatic and is a horrific death. It is also 100% preventable.

Which potential pathogen is NOT killed by pasteurization?

Mycobacterium paratuberculosis—a cause of Johne's disease in cows, which is very similar to Crohn's disease—is

there a link?

Which nematode is associated with inducing remission in inflammatory bowel disease?

- Porcine whipworm, Trichuris suis.
- Colonization with whipworms has been suggested as an effective, safe, and well-tolerated treatment for Crohn's and ulcerative colitis.

[Summers RW, et al. Am J Gastroenterol. 2003;98:2034-2041]

What other principles that we use daily did Dr. Pasteur elucidate?

The Germ Theory – in 1857, demonstrated that decay/fermentation occurred only on exposure to contaminated air. If germs could cause fermentation, they could well cause animal & human disease, and be transmitted.
Vaccine theory – he added to Jenner's work on vaccination, and developed anthrax and rabies vaccines

Who is the father of modern epidemiology?

Dr. John Snow, who in 1854, after interviewing victims' families, he traced a cholera epidemic to the Broad Street pump from which most had taken water. Convincing authorities to remove the handle, he halted the epidemic within 2 weeks. Workers at an adjacent brewery, allotted free beer daily, did not suffer from cholera! An adjacent pub has been named after Snow, a fact which would have dismayed him, as he abhorred alcohol.

Who is the father of infection control?

Dr. Ignaz Philippe Semmelwies, who noted that the patients of medical students were dying of puerperal sepsis/Group A strep after childbirth, whereas the midwives' patients did not. Noting that medical students performed autopsies (presumably on those who died of sepsis!) between deliveries, he had them wash with chlorinated lime after autopsies - mort 20% to 1%. The medical profession ridiculed him (denial being easier than guilt), and he died penniless & demented in an insane asylum. Common sense is so rarely appreciated in its own time.

Who furthered the principles of sanitation in healthcare facilities, nutrition in illness, and the application of mathematics to epidemiologic investigation?

Florence Nightingale. She is known for her kindness and comfort to soldiers as a nurse, but her contributions are far more extraordinary and intellectual. She developed the polar-area diagram to objectively demonstrate mortality associated with poor hygiene during the Crimean War. She pioneered tools for data collection, graphical display and analysis, and statistics in healthcare, and in so doing, reformed healthcare in her time. She did this under the tutelage of her father, who believed all of his children should be educated, in an era when women were not formally educated.

Who is the father of antibiotics?

Dr. Alexander Fleming, who noted that a penicillium mold had contaminated his cultures and that something was killing the bacteria around it. That substance was penicillin, and 25 years later, it was saving lives on the battlefield (& perhaps a few brothels) in WWII. Enter the Antibiotic Era!

What is Dr. Walter Reed's contribution to medicine?

Dr. Reed instituted mosquito (vector) control as a means of controlling yellow fever, which had decimated troops during the Spanish-American War and stymied completion of the Panama Canal & U.S. economic expansion. Mosquito control has eradicated yellow fever and malaria from this continent and remains the principal means of control

(although note that the vector mosquitoes are still endemic to Florida/SE U.S.—if these pathogens were to again become epidemic, mosquito control would be the key to control & these programs remain in place today).

Vector control is important in control of malaria, encephalitides (like West Nile), dengue, hanta virus, plague, etc.

What are the U.S. Centers for Disease Control transmission-based precautions for preventing transmission of infectious organisms in healthcare settings? Describe each and common pathogens that fall into each category.

- Contact - gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment
    - norovirus/enteric viruses
    - methicillin-resistant S. aureus (MRSA), vancomycin-resistant Enterococcus (VRE)
    - Clostridium difficile
    - Certain multidrug-resistant organisms, such as carbepenemase resistant Enterobacteriacae (CRE)
    - Vaccinia virus (smallpox vaccine in military personnel), herpes zoster or shingles
- Droplet precautions– (pathogens spread through close respiratory or mucous membrane contact with respiratory secretions) surgical-type mask for all interactions within 3 feet of patient
    - pertussis

    - influenza, adenovirus, rhinovirus
    - meningococcus, pneumococcus (for the first 24 hours of antimicrobial therapy)
    - group A streptococcus (for the first 24 hours of antimicrobial therapy)
- Airborne precautions – (pathogens agents that remain infectious over long distances suspended in air) Use of negative pressure isolation room, preferably 12 air exchanges per hour, as well as N-95 or higher fitted respirator.
    - TB
    - Chickenpox, disseminated shingles or herpes zoster (varicella-zoster virus)
    - Measles (rubeola virus)
    - SARS-coV, MERS-coV
    - Smallpox (Variola virus)

What kind of isolation does naturally occurring inhalational anthrax required?

Standard precautions only. There is no person-to-person spread.

What about pneumonic plague? Bubonic?

Droplet precautions for pneumonic plague until 48 hours on antibiotic therapy and improving.
Standard precautions for bubonic plague.

What about smallpox?

Airborne. Same as measles, the most infectious pathogen on Earth now that smallpox is gone.

What does Standard Precautions mean?

It combines the old "universal" precautions and blood and body fluid guidelines, and presumes that all patients admitted to a facility may be infected with potentially transmissible pathogens. Thus, it includes:

- Hand hygiene before and after patient contact.
- Personal protective garb as appropriate to the care or clinical situation, in addition to any transmission-based precautions.
- Specific precautions for invasive procedures that may not be covered under transmission-based precautions.

What are the forms of dermal TB?

- Bazin's disease: Papular, necrotic lesions

representing hypersensitivity reactions to deeper infection. Especially noted on back of lower legs.
- "Prosector's wart" occurs from direct inoculation.

What is classic Scrofula?

Cervical/facial TB

What is the source of massive hemoptysis in TB?

Rasmussen's aneurysm - erosion of a tuberculous granuloma into a pulmonary artery followed by rapid exanguination.

Describe major infectious & noninfectious causes of splenomegaly.

- EBV/CMV
- Endocarditis
- Tuberculosis
- Histoplasmosis
- Typhoid fever
- Syphilis
- Parasites

- Leishmaniasis (visceral)
- Malaria
- Schistosomiasis (non-cirrhotic portal hypertension)
- Toxoplasmosis
- Lymphoma/myelodysplastic disease
- Collagen vascular disease (rheumatoid arthritis, lupus)
- Portal hypertension (noncirrhotic or cirrhotic)
- Hereditary hemolytic anemias/polycythemia vera
- Sarcoidosis
- Metastases
- Amyloid

What infections are classically associated with splenic abscess?

C the Spleen above your BELT:

- **C**oxiella
- **S**pleen-**S**almonella/**S**. aureus/**S**treptococcus
- **B**rucellosis/**B**artonellosis
- **E**ndocarditis/**E**scherichia coli
- **L**emierre's syndrome (post-anginal sepsis with Fusobacterium necrophorum)
- **T**B

In travelers from Thailand/SE Asia, think Melioidosis.

Classic scenario for splenic abscess:

Unexplained thrombocytosis in a septic ICU patient with persistent left pleural effusion

Diseases that occur concurrently:

- Lyme disease + Babesiosis + Ehrlichiosis (same tick vector)
- Measles + Streptococcus
- Mono + Streptococcus (mono pharyngitis may mimic strep throat; strep throat may also be super-infecting-treat for Streptococcus throat to prevent rheumatic fever)
- Endocarditis + acute osteomyelitis

6 Childhood Diseases:

Measles (Rubeola)

- Prodrome - cough, coryza, conjunctivitis, Koplik's spots
- Rash - erythematous, maculopapular, 5 days post onset of illness; begins on head and spreads downward

German Measles (Rubella)

- Children - no prodrome
- Adults - malaise, fever, anorexia, posterior auricular, cervical, suboccipital lymphadenopathy
- Rash - maculopapular begins on face, then generalized

Roseola Infantum (Exanthum subitum)
Human Herpes Virus 6

- Abrupt fever, lasts for 1-5 days with no other physical findings.
- On 4th day, rash - macular or maculopapaular on trunk, and spreads peripherally, resolved within 24 hours.
- Child generally looks pretty well.

Varicella (chickenpox)

- Prodrome - malaise, fever, runny nose.
- Rash - Starts the same day as fever, pruritic, first on trunk, then peripherally; begins as red papules, develops into "tear drop" vesicles, becomes cloudy, breaks open, forms scabs, occurs in "crops".
- Remember: *Grouped vesicles on a red base in various stages of evolution*.

Erythema Infectiosum (Fifth disease)

- 3 stage rash – pruritic
- Marked erythema on cheeks, "slapped cheek"
- Livedo reticularis: Erythematous, maculopapular rash starts on arms, then to the trunk and legs.
- Lasts 2-39 days, fluctuation in severity of rash with environmental changes.
- Mainly arthralgias in adults.

Scarlet Fever

- Group A Streptococcus, fever, pharyngitis, rash
- Rash - erythematous, finely punctate, blanches with pressure, starts on trunk then generalized.
- Face is flushed, increased erythema in skin folds (Pastia's lines), circumoral pallor
- Skin may feel rough like sandpaper, strawberry tongue.

Name common conditions that may change urine color:

- Red or pink: blood, beets, porphyria
- Orange: pyridium, rifampin, sulfasalazine
- Blue or Green: methylene blue, amitriptyline, indomethacin, propofol, familial hypercalcemia (blue diaper syndrome)
- Purple: purple urine bag syndrome, which may indicate colonization or clinically significant infection/UTI. It is associated with several species of Enterobacteraceae, chronic urinary catheterization, and strongly alkaline urine. The chain of events includes metabolism of ingested tryptophan to indole; the latter is then metabolized and excreted as indoxyl, which is excreted and further metabolized by the urinary organisms to indirubicin and indigo. The only treatment required is changing of the catheter. As for any bacteriuria, antibiotic therapy is only indicated if the patient has symptoms or signs suggesting UTI.
- Brown: metronidazole, nitrofurantoin, methocarbamol, senna, chloroquine-primaquine;

rhabdomyolysis, bilirubinuria, acute tubular necrosis

[Credit for this pearl is given to my colleague, Daniel Poetter, MD. He declined to be added as contributing editor, however, his review has been invaluable in keeping several pearls relevant!]

What are the 2 commonest pathogens in the Nocardia genus & drug of choice?

- Nocardia asteroides (lung/brain) - trimethoprim/sulfamethoxazole, Imipenem + Amikacin
- Nocardia brasiliensis (lymphangitis/madura foot) - trimethoprim/sulfamethoxazole, Resistant to Imipenem

Name the diseases caused by Listeria monocytogenes, common sources, and drug of choice.

- Gastroenteritis
- Meningoencephalitis
- Granulomatosis infantisepticum* (spontaneous abortion/stillbirth due to disseminated Listeria; widespread micro abscesses/granulomas in the liver and spleen; abundant bacteria on Gram stain of meconium)

- Neonatal sepsis/meningitis*

* transplacental infection from maternal enteritis/bacteremia.

- From unpasteurized dairy products, soft cheeses, cold cuts/hot dogs/sausages-heat until steaming.
- Treatment: Ampicillin, trimethoprim/sulfamethoxazole

You should call your Microbiology laboratory if you are sending culture specimens that may contain organisms hazardous to the microbiologist (lethal or easily aerosolized, & readily grow on routine culture media)?

Coccidiodes
Francisella tularensis (tularemia)
Yersinia pestis (bubonic plague)
Bacillus anthracis (anthrax)
Neisseria meningitidis (meningococcal meningitis)
Brucella abortus
Burkholdheria
(If they are unaware to work under a biological safety cabinet, the staff may need prophylactic therapy.)

REFERENCES

Textbooks:

Greene JN, et al. Infections in Cancer Patients. Marcel Dekker, Inc., 2004.

Betts RF, et al. Reese and Betts' A Practical Approach to Infectious
Diseases 5th ed. Lippincott Williams & Wilkins, 2003.

Mandell G, et al. Principles and Practice of Infectious Diseases, 5th ed.,
Churchill Livingstone, 2003.

Sahn SA, et al. Infectious Disease Pearls. Hanley & Belfus, 1999.

Websites, electronic media:

Centers for Disease Control, http:/www.cdc.gov/.

CDC "Yellow Book", Health Information for International Travelers, http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014.

Public Health Image Library, http://phil.cdc.gov/phil/home.asp

eMedicine, http://www.emedicine.com/.
Johns Hopkins Infectious Diseases, http://www.hopkins-id.edu/.

Medscape Infectious Diseases, http://www.medscape.com/.

MDConsult, http://www..mdconsult.com .

UpToDate, http://www.uptodateonline.com.

The Gorgas Courses in Clinical Tropical Medicine, http://www.gorgas.org

Peer-reviewed literature:

Prusty BK, Gulve N, Chowdhury SR, et al. HHV-6 encoded small non-coding RNAs define an intermediate and early stage in viral reactivation. NPJ Genom Med. 2018 Sep 5;3:25. https://www.doi.org/10.1038/s41525-018-0064-5 .

Wolfson AR, Zhou L, Li Y, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. J Allergy Clin Immunol Pract 2018 (in press). Accessed on October 10, 2018. https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S2213219818305488.pdf?locale=en_US

Yang H-W, Su Y-J. Trends in the epidemiology of purple urine bag syndrome: A systematic review. Biomedical Reports. 2018;8(3):249-256.

Bullman S et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Science 2017 Dec 15;358:1442.

Moriyama, Y., Sono, Y., Nishioka, H. Tuberculous arthritis of the hip with Staphylococcus aureus superinfection. J Infect Chemo. 2016;22(11): 7.52-4

Bharat A et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Trans Med. 22 APR 2015 : 284RE3.

Arora AA, Krishnaswamy UM, Moideen RP, Padmaja MS. Tubercular and bacterial coinfection: A case series. Lung India : Official Organ of Indian Chest Society.

2015;32(2):172-174.

Epperla N, Kattamanchi S, Fritsche TR. Appearances are Deceptive:
Staphylococcus Superinfection of Clavicular Tuberculous Osteomyelitis. Clin Med Res. 2015 Jun;13(2):85-8. doi: 10.3121/cmr.2014.1247. Epub 2014 Dec 8.

Salem DA, El-Shazly A, Nabih N, El-Bayoumy Y, Saleh S. Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of Demodex folliculorum. Int J Infect Dis. 2013 May;17(5):e343-7.

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei Endocarditis: A 28 Patient Series and Review. Emerg Infect Dis. 2013 Nov;19(11):1721-30.

Lagier JC, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment ofclassic Whipple's disease: from in vitro results to clinical outcome. JAntimicrob Chemother. 2014 Jan;69(1):219-27.Epub 2013 Aug 14

Gupta NK, et al. Cord colitis syndrome: a cause of granulomatous inflammation in the upper and lower gastrointestinal tract. Am J Surg Pathol. 2013 Jul;37(7):1109-13

Bhatt AS, et al. Sequence-based discovery of Bradyrhizobium enterica in cord colitis syndrome. Engl J Med. 2013 Aug 8;369(6):517-28.

Jarmuda S, O'Reilly N, Zaba R, Jakubowicz O, Szkaradkiewicz A, Kavanagh K. Potential role of Demodex mites and bacteria in the induction of rosacea. J Med Microbiol. 2012 Nov;61(Pt 11):1504-10.

Manigandan G , Venkatesh C , Gunasekaran D , Soundararajan P Tuberculous otitis media and staphylococcus aureus coinfection in a five-year-old boy with miliary tuberculosis. Journal of Global Infectious Diseases [01 Jan 2013, 5(1):26-28

O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated Bacillus proteins and erythematotelangiectatic rosacea. Br J Dermatol. 2012 Nov;167(5):1032-6.

Szkaradkiewicz A, Chudzicka-Strugała I, Karpiński TM, Goślińska-Pawłowska O, Tułecka T, Chudzicki W, Szkaradkiewicz AK, Zaba R. Bacillus oleronius and Demodex mite infestation in patients with chronic blepharitis. Clin Microbiol Infect. 2012 Oct;18(10):1020-5.

O'Reilly N, Bergin D, Reeves EP, McElvaney NG, Kavanagh K. Demodex-associated bacterial proteins induce neutrophil activation. Br J Dermatol. 2012 Apr;166(4):753-60.

Schaumann R, et al. In Vitro Activities of Clindamycin, Imipenem, Metronidazole, and Piperacillin-Tazobactam against Susceptible and Resistant Isolates of Bacteroides fragilis Evaluated by Kill Kinetics. Antimicrob Agents Chemother June 2012;56(6):3413-3416

Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012 Apr;54(7):899-904.

Catherine de Martel, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis, The Lancet Oncology, Available online 8 May 2012 at http://www.sciencedirect.com/science/article/pii/S1470204512701377)hi

Shi W, et al. Pyrazinamide Inhibits Trans-Translation in Mycobacterium tuberculosis. Science 11 August 2011: 1208813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21835980?dopt=Abstract

Levy-Hara G et al. "Ten commandments" for the appropriate use

of antibiotics by the practicing physician in an outpatient setting. Front Microbiol. 2011 Nov 24;2:230. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3225075/

Lu Q et al. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by Pseudomonas aeruginosa.Am J Respir Crit Care Med. 2011 Jul 1;184(1):106-15. http://www.ncbi.nlm.nih.gov/pubmed/21474643

Rostagno C, et al. Surgical Treatment in Active Infective Endocarditis: Results of a Four-Year Experience. ISRN Cardiology Volume 2011, Article ID 492543.

Zhang B, Izadjoo M, Horkayne-Szakaly I, Morrison A, Wear DJ. Medulloblastoma and Brucellosis - Molecular Evidence of Brucella sp in Association with Central Nervous System Cancer. J Cancer 2011; 2:136-141. doi:10.7150/jca.2.136. http://www.jcancer.org/v02p0136.htm

Lee RA, et al. The Use Of Linezolid And Nebulized Amikacin In A Case Of Mycobacterium Chelonae/Mycobacterium Abscessus Pulmonary Disease. Chest 2010;138(4_MeetingAbstracts):86A-86A.

Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection, United States. MMWR 2010; 59 (No.RR-5)

Mayfield E. Charting the path from infection to cancer. Available at http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2009/092209/page5.

Nara T, Katoh N, Inoue K, Yamada M, Arizono N, Kishimoto S. Eosinophilic folliculitis with a Demodex folliculorum infestation successfully treated with ivermectin in a man infected with human immunodeficiency virus. Clin Exp Dermatol. 2009 Dec;34(8):e981-3.

Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, Collins A, Dengel A, Dalmau J, Glaser CA. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis. 2009 Dec;28(12):1421-9. doi: 10.1007/s10096-009-0799-0. Epub 2009 Aug 29.

Boucher HW, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jan 1;48(1):1-12.

Yahia Zayani CB, Daoued L, Tekaya R, Bouebdella M, Abdelmoula L, Kooli M, Chaabouni L, Zouari R. Tuberculous osteomyelitis masked by staphylococcal infection. Joint Bone Spine. 2009 Jul;76(4):429.

Patel R, Naik S, Melnikau B, Nagarajan V, George L, Lindenmayer AE, Colby S, Goldshteyn N. Clavicular tuberculosis following trivial trauma. South Med J. 2009Aug;102(8):848-51.

Forouzesh A, Moise PA, Sakoulas G. Vancomycin Ototoxicity: a Reevaluation in an Era of Increasing Doses. Antimicrob. Agents Chemother. 2009;53(2): 483-486.

Corcoran C, Rebe K, van der Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. J Clin Virol. Aug 2008;42(4):433-6.

Ehrmann S et al. Pharmacokinetics of high-dose nebulized amikacin in mechanically ventilated healthy subjects. Intensive Care Med. 2008 Apr;34(4):755-62. Epub 2007 Nov 29. http://www.ncbi.nlm.nih.gov/pubmed/18046534

David M. Hansell, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging Radiology March 2008 246:3 697-722. http://radiology.rsna.org/content/246/3/697.full

Rice LB. Federal funding for the study of antimicrobial resistance

in nosocomial pathogens : no ESKAPE. Comment in J Infect Dis. 2008 Apr 15;197(8):1082-3.

Verstraelen H. Cutting edge: the vaginal microflora and bacterial vaginosis. Verh K Acad Geneeskd Belg. 2008;70(3):147-74.

Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007;13(1):119-26.

Verdonck K, et al. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis. 2007 Apr;7(4):266-81.

Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007 Jan;61(1):25-36.

Leedom JM. Clinical Practice: Milk of Nonhuman Origin and Infectious Diseases in Humans. Clinical Infectious Diseases 2006 43:5, 610-615

Marten K, Schnyder P, Eckart S et al. Pattern-based Differential Diagnosis in Pulmonary Vasculitis Using Volumetric CT. AIR 2005;184(3):720-733.
http://www.ajronline.org/content/184/3/720.full#sec-4

Morris AJ, et al. Bacteriological Outcome after Valve Surgery for Active Infective Endocarditis: Implications for Duration of Treatment after Surgery. Clinical Infectious Diseases 2005; 41:187–94.

Oren I. Breakthrough zygomycosis during empirical voriconazole therapy in f e brile patients with neutropenia. Clin Infect Dis. 2005; 40:770-1.

Vigouroux S, Morin O, Moreau P et al. Zygomycosis after prolonged use of voriconazole in immunocompromised patients

with hematologic disease: attention required. Clin Infect Dis. 2005; 40:e35-7.

Eidex RB for the Yellow Fever Vaccine Safety Working Group. History of thymoma and yellow fever vaccination. The Lancet 364:936, 11–17 September 2004. http://www.sciencedirect.com/science/article/pii/S0140673604170177

Kobayashi K, Kami M, Murashige N et al. Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis. Haematologica. 2004; 89:e42.

Delahaye F, et al. Indications and optimal timing for surgery in infective endocarditis. Heart 2004;90:618–620.

Hallstrand TS, et al. Inhaled IFN-gamma for persistent nontuberculous mycobacterial pulmonary disease due to functional IFN-gamma deficiency. Eur Respir J 2004 Sep;24(3):367-70. http://www.ncbi.nlm.nih.gov/pubmed/15358692

Goldstein I, et al. Lung Tissue Concentrations of Nebulized Amikacin during Mechanical Ventilation in Piglets with Healthy Lungs. Am J Respir Crit Care Med. 2002;165(2):171-175 http://ajrccm.atsjournals.org/content/165/2/171.long .

Williams JD. Evaluation of the safety of macrolides. Int J Antimicrob Agents 2001;18:Suppl 1:S77-S81

Franco-Paredes C, Blumberg HM. Psoas muscle abscess caused by Mycobacteriumtuberculosis and Staphylococcus aureus: case report and review. Am J Med Sci. 2001 Jun;321(6):415-7.

Rubinstein E. Comparative safety of the different macrolides. Int J Antimicrob Agents 2001;18:Suppl 1:S71-S76

Brigden ML. Clinical utility of the erythrocyte sedimentation rate. Am Fam
Physician. 1999 Oct 1;60(5):1443-50.

http://www.aafp.org/afp/1999/1001/p1443.html

Ghauri, Rana Rahman et al. Optic Disk Edema with a Macular Star. Survey of Ophthalmology , Volume 43 , Issue 3 , 270 – 274.

Mass treatment of rabid cows of Humans Who Drank Unpasteurized Milk from Rabid Cows — Massachusetts, 1996-1998, MMWR Weekly, March 26, 1999 / 48(11);228-229.

Ryan ET, et al. Illness after international travel. N Engl J Med 2002;347:505-16.Dutta JK. Rabies transmission by oral and other non-bite routes. J Indian Med Assoc. 1998 Dec;96(12):359.

T. Sinnott, John. (1990). Tuberculous Osteomyelitis Masked by Concomitant Staphylococcal Infection. Archives of Internal Medicine. 150:1865.

Saltzstein S.L., and Ackerman L.V.: Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically and pathologically malignant lymphomas. Cancer 1959; 12: pp. 164-182.

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