Ministry of Health

University Teaching Hospital Antibiotic Guidelines

Table of Contents

Glossary

Term	Definition
ADA	Adenosine deaminase
ALT	Antibiotic lock therapy
AMI	Acute myocardial infarction
Antibiogram	A list of antibiotics to which a cultured bacterium is susceptible, intermediate, or resistant
BC	Blood culture
BD	Twice daily
Beta-lactam antibiotic	Antibiotic class containing a beta-lactam ring that inhibits bacterial cell wall synthesis. Includes penicillins, cephalosporins, carbapenems, and monobactams.
BNP/Pro-BNP	Brain natriuretic peptide/ Pro-hormone Brain natriuretic peptide
CA	Community-acquired
CAP	Community acquired pneumonia
CIED	Cardiovascular implantable electronic device
Cleaning solution	Antiseptic for hand hygiene, including 0.5% chlorhexidine in 70% alcohol and iodine-based solutions
Community-acquired (CA) infection	Illness starts prior to, or within 48 hours of admission
CoNS	Coagulase-negative Staphylococcus
CRB-65 score	A clinical prediction rule for mortality in community-acquired pneumonia. The score is an acronym for individual risk factors as follows: **C**onfusion of new onset **R**espiratory rate ≥ 30 breaths per minute **B**lood pressure < 90 mmHg systolic or < 60 diastolic **65** years or older A single point is assigned to each risk factor.
CRE	Carbapenem resistant Enterobacterales
cTnI	Cardiac Troponin I
CXR	Chest X-ray
CVA	Cerebrovascular accident
CVP	Central Venous Pressure
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESBL	Extended spectrum beta lactamase producing organism
FTA-ABS	Fluorescent treponemal antibody absorption
Health care associated infection (HCAI)	Any patient with a new infection starting ≥ 48 hours after admission and was not apparent at the time of admission, or any catheter or line-associated infection irrespective of time of insertion. The following factors increase risk: • Admission to an acute care hospital within 90 days of the current presentation • Resident of a nursing home or long-term care facility • Recent intravenous antibiotic therapy, chemotherapy

Term	Definition
	or wound care within the past 30 days of the current presentation • Patients attending a haemodialysis clinic
HCAP	Health care associated pneumonia
ICD	Implantable cardioverter-defibrillator
IPC	Infection prevention and control
IM	Intramuscular
IV	Intravenous
MDR-TB	Multidrug-resistance tuberculosis – resistance to the two first-line medications isoniazid and rifampin.
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin sensitive Staphylococcus aureus
MSSE	Methicillin sensitive Staphylococcus epidermidis
MRSE	Methicillin resistant Staphylococcus epidermidis
OD	Oral daily
po	Per os (oral)
PPM	Permanent pacemaker
PWID	Persons who inject drug
Rx	Treatment/therapy
SSI	Surgical site infection
SSTI	Skin and soft tissue infection
TEE	Transesophageal echocardiogram
TOE	Trans-oesophageal echocardiogram
TTE	Trans-thoracic echocardiogram
VDRL	Venereal Disease Research Laboratory
VRE	Vancomycin resistant enterococci
XDR TB	Extensively drug-resistant tuberculosis – resistance to isoniazid, rifampin, and any fluoroquinolone as well as at least one additional drug (i.e linezolid and bedaquiline)

Foreword and Introduction

Foreword

Zambia has joined the rest of the global community in the fight against Antimicrobial Resistance (AMR), a major global public health challenge of the 21st century and a tragedy of commons that threatens the very existence of humankind.

In line with the core objectives of the Global Action Plan (GAP) on AMR, Zambia developed a multisectoral National Action Plan (NAP) on AMR which sets out priority actions and strategies to address the factors influencing development and spread of AMR in the local Zambian context. A key area recognized in Zambia's AMR NAP is the need to put in place mechanisms to optimize the use of antimicrobial medicines in health care settings.

To actualize this objective, Zambia's antimicrobial resistance coordinating committee (AMRCC) through the Zambia National Public Health Institute (ZNPHI) partnered with University of Maryland (UMB)/ Institute of Human Virology (IHV)/ Center for International Health, Education, and Biosecurity (Ciheb) and Action on Antibiotic Resistance (ReAct) Africa to implement several initiatives including strengthening antimicrobial stewardship activities in Health care settings. This partnership foresaw the development, review, finalization and launch of these antimicrobial prescription guidelines for the Adult University Teaching Hospital (UTH). The process was informed by local antimicrobial susceptibility data through a series of physical and virtual workshops, which incorporated expert participants from key departments including Infectious Diseases, Internal Medicine and Surgery, Pharmacy, and Microbiology at AMRCC, ZNPHII, ReAct Africa, UTH, and University of Maryland Baltimore (UMB)/.

These guidelines are vital as they will standardize clinical practice and will enable us to promote prudent use of antimicrobials and achieve the goals set out in Zambia's AMR NAP without negatively affecting patient outcome. I therefore call on each and every prescriber in our institution to adhere to these antimicrobial prescription guidelines as we all work together in preserving the effectiveness of antimicrobial therapy.

Dr Charles Mutemba
Senior Medical Superintendent
University Teaching Hospital

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Finally, we would like to thank the following people who contributed to the formation of these guidelines:

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Introduction to Guidelines

Antimicrobial resistance (AMR) has become a growing concern globally, receiving attention as deaths are being attributed to it. In low- and middle-income countries (LMICs), trends in AMR are poorly documented, and surveillance networks are non-existent. Zambia has started building a surveillance network for AMR and strengthened teams to build antimicrobial stewardship programs to optimize use of antimicrobials in health facilities.
There has been concern about rising resistant infections in the facilities and community alike. This can put more people at risk, make spread more difficult to identify and contain, and threaten the progress made to protect patients in these healthcare settings. The emergence and spread of new forms of resistance remains a concern.
To optimize antimicrobial usage and thus curtail the spread and emergence of antimicrobial resistance, development of guidelines and standard operating procedures is important. Furthermore, streamlining the use of these drugs is important. It is with this agenda that the University Teaching Hospitals in line with Zambia National Multisectoral Action Plan on AMR has embarked on developing these guidelines.

Having an antibiotic guideline is one way of addressing this global challenge. The aim of this guide is to give practical information needed to perform antibiotic stewardship in an algorithmic manner, which mimics the day-to-day experience of the prescriber. This will help overcome the threat of antimicrobial resistance by optimizing the use of existing antimicrobial agents and prevent the transmission of drug-resistant organisms through infection control.

Disclaimer
The recommendations given in this guide are meant to serve as treatment guidelines. They should never replace clinical judgment or Infectious Diseases consultation when indicated. The recommendations were developed for use at the University Teaching Hospitals in Lusaka, Zambia. They may not be appropriate for other settings and may need adjustment. The information was correct at the time of printing but changes to best practices may occur because of new research or data. Also, note that these guidelines contain antibiogram information that is confidential.
These guidelines were adapted from University of Maryland Medical Center 'Antibiotic Guidelines; Treatment Recommendations for Adult Inpatients' and special circumstance paediatric cases managed in units covered by infectious disease consultants.

ID Consults

Many patients with severe or difficult to treat infections will benefit from a consultation by the Infectious Disease service. ID consultation is recommended for all situations below. Primary teams should call as soon as these infections are suspected.

- Septic shock
- Blood stream infections, especially those involving catheters, Staphylococcus aureus, or Candida spp.
- Endocarditis
- Meningitis
- Encephalitis
- Brain abscess
- Trypanosomiasis
- Necrotizing skin and soft tissue infections
- Osteomyelitis
- Prosthetic joint infections
- Fever of unknown origin
- Infections in transplant patients
-Fever in a returning traveller
- Resistant organisms, e.g., MRSA, VRE, or Gram negatives resistant to 3rd generation cephalosporins or carbapenems
- MDR or XDR TB
- Concern for treatment failure in HIV, or review of nonstandard regimens
- Atypical, refractory, or difficult to treat infections
- Infections with high risk of transmission to others (Cholera, Typhoid fever, viral haemorrhagic fever, Neisseria spp., Rabies)
- Suspected outbreaks
- Questions on Pre- or Post-Exposure Prophylaxis
- Need for restricted / less available antimicrobials (e.g., vancomycin, imipenem, meropenem, etc.)
-Antibiotic durations (e.g., uncertainty on antibiotic start and stop)
- Any other infectious disease needs!

UTH Infectious Disease physicians are also available to see patients in the outpatient clinic (**7040**) for any infectious disease needs. Common consults include HIV, any infection above, and travel/tropical medicine (pre- and post- travel management).

General Prescribing

Principles for rational antibiotic prescribing

1. Decide if an antibiotic is indicated: does the patient have a bacterial infection?

a. Fever
b. Leucocytosis with neutrophilia
c. Raised inflammatory markers
d. Specific organ disfunction (such as tachypnoea, dysuria, inflamed skin etc).

2. Perform cultures before administering antibiotics in hospitalized patients or in outpatients with recurrent infections. This does not preclude administration of empirical antibiotics where necessary, including in situations where culture is not available.

3. Choose an appropriate empiric antibiotic:
    a. Target the most likely pathogen(s) for the site of infection
    b. Assess likelihood of antibiotic resistance
    c. Review potential contraindications
    d. Choose drug (s) with adequate target tissue penetration
    e. Aim for a single drug with the desired spectrum of activity

4. Ensure correct dose and route of administration.

5. Start the appropriate antibiotic rapidly in severe infections.

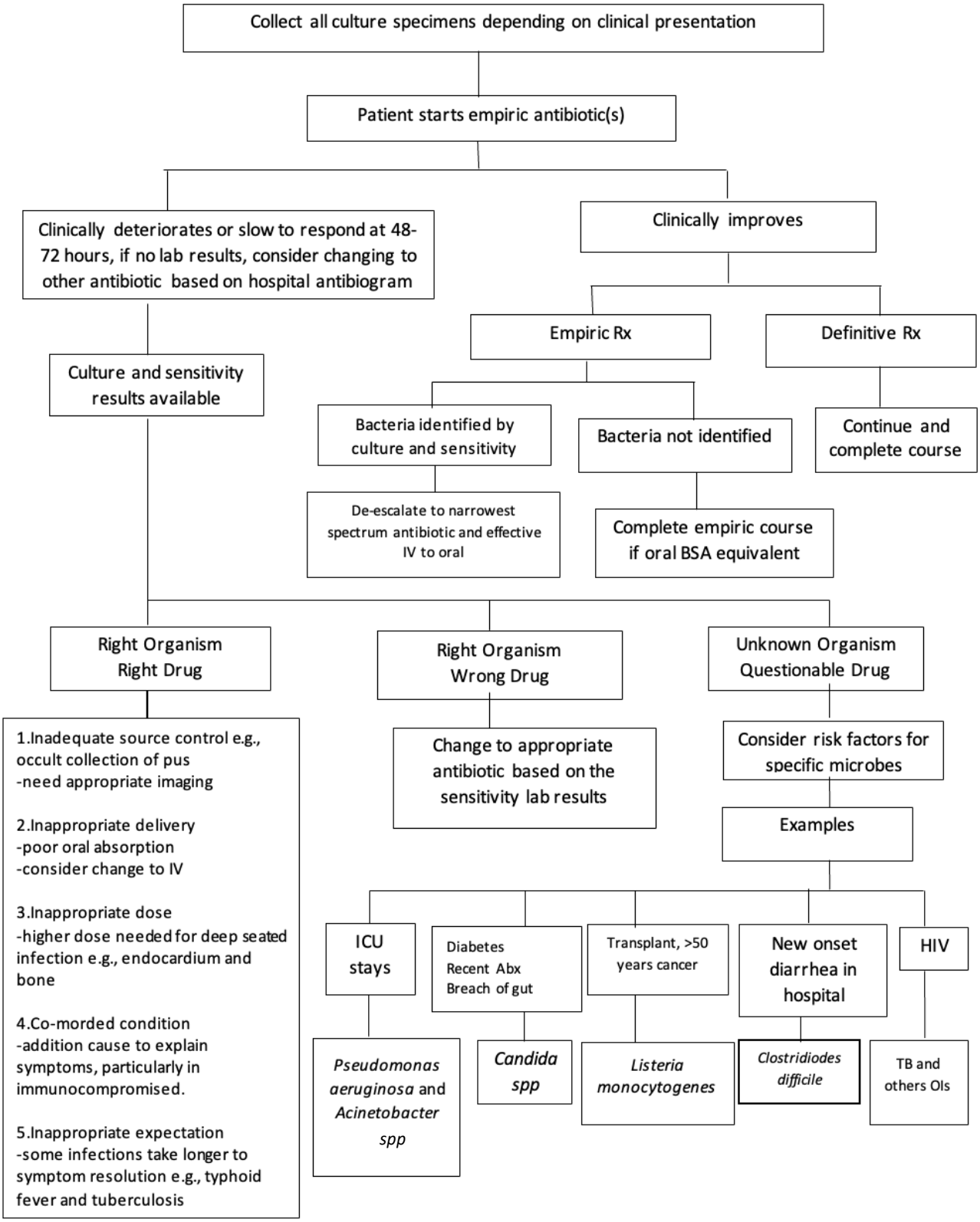
6. Practice early and effective source control. Search for and remove any persistent foci of infection such as an abscess.

7. Evaluate antibiotic appropriateness every day:
    a. **D**elivery - Always aim for oral/enteral. Switch from IV to oral as soon as patient is able to tolerate orally.
    b. **D**ose - Weight, eGFR, correct intervals
    c. **D**uration – Consult guidelines for recommended duration by infection type
    d. **D**e-escalation - Switch to a narrow spectrum based on culture results

Changing Antibiotics

Once antibiotics have been initiated, the decision to change or stop therapy depends on the patient's clinical response and culture results (**see algorithm on next page**)

Antibiotic Choice Algorithm



Durations of therapy:

For many infectious syndromes, recent data indicates that shorter courses of therapy are adequate to cure the infection, which is advantageous compared to longer courses of therapy, as unnecessary antibiotic exposure contributes to adverse reactions, antibiotic resistance, and increased health care costs. The table below outlines recommended durations of therapy for common infectious syndromes for adult patients. While these general guidelines apply to most patients, there is a need to individualize and treat until the patient is clinically stable. These durations assume that source control has been achieved, if applicable.

Disease State	**Recommended Duration***
Asymptomatic bacteriuria	0, antibiotics not usually indicated
Bronchitis	0, antibiotics not usually indicated
Intra-abdominal infection with source control	4 days
Acute exacerbation of chronic bronchitis/COPD	$\leq$ 5 days
Acute bacterial sinusitis	5 days
Pneumonia, community acquired	5 days
Cellulitis	5 days
Pneumonia, hospital-acquired or ventilator-associated	7 days
Pyelonephritis	7 days
Uncomplicated gram-negative bacteremia (**most patients in this study had urinary source) – [uncomplicated meaning low inoculum infections such as urinary source or infection with source control and clinical improvement]	7 days
Gram-negative bacteremia	14 days
Uncomplicated gram-positive bacteremia (non-S. aureus or S. lugdunensis)	7 days
Infective endocarditis	4+ weeks
Osteomyelitis	6+ weeks

*see individual guideline sections for further information on treatment durations

Resources:

- Intra-abdominal infections: Sawyer R.G., et al. New Eng J Med 2015;372(21):1996-2005.
- HAP/VAP: Dimopoulos G, et al. Chest 2013;144(6):1759-67.
- CAP: Uranga A., et al. JAMA Int Med 2016; doi:10.1001/jamainternmed.2016.3633
- Gram negative bacteremia: Yahav D., et al. Clin Infect Dis 2018, doi:10.1093/cid/ciy1054

Microbiology

Microbiology

Micro Sampling

Correct techniques of microbiologic sampling

Optimal sampling is very important to increase yields and decrease contamination rates (see boxes below). Surgical specimens from abnormal structures such as abscesses should usually be collected at the time of operation. Once surgical drains are placed, they quickly become colonized with skin and environmental bacteria and culture results are not interpretable. **Pus swabs** collected outside of theatre are discouraged, as it is extremely rare for them to yield information that will change patient management. Document clinical information on laboratory request form.

Box 1: Correct technique for collecting mid-stream urine specimens

Females:

- Wash your hands
- Clean the vulva front to back with sterile gauze and sterile water
- Spread labia with fingers
- Void and collect urine mid-flow

Males

- Wash your hands
- Retract foreskin and wash glans with sterile gauze and sterile water
- Void and collect urine mid-flow

Box 2: Correct technique for collecting urine specimens from a catheter (use fresh catheter)

- Use aseptic technique with sterile gloves and apron
- Clamp tubing just distal to sampling port
- Wait for urine to collect above clamp
- Wipe sampling port with cleaning solution
- Remove urine with a small gauge sterile needle and syringe
- Transfer urine to sterile container
- Clean port again
- Unclamp tubing

Box 3: Correct technique for performing a pus swab

- Wounds with slough, necrotic tissue, or dried exudate should first be debrided
- Wash the wound with sterile saline
- If the wound is dry moisten the tip of the swab with sterile saline
- Move swab tip across the wound surface in a zig-zag motion at the same time as being rotated between the fingers
- Apply gentle pressure to release fluid from the base of the wound
- Aim to include as much of the area of the wound as possible but avoid intact skin around the wound
- Transfer to laboratory as soon as possible

Box 4: Correct technique for performing a blood culture **(Sterile technique is essential to proper interpretation)**

1. Verify the patient's identity and obtain verbal consent.
2. Assemble the correct materials required for blood culture:
    - Blood culture bottle(s)
    - Syringe (10 ml or more)
    - Needle (22 gauge or more)
    - Sterile gloves
    - Tourniquet
    - Adhesive strip
    - Cleaning solution*
    - Sterile pack containing cotton/gauze swabs, sterile paper x2 and waste bag
    - Patient labels
    - Sharps waste disposal bin
3. Apply tourniquet and select a suitable vein
4. Wash hands and apply sterile gloves
5. Clean the puncture site with cleaning solution using aseptic technique and allow 30 seconds for the disinfectant to dry
6. Place green sterile cover with opening over site for blood culture
7. Collect 10ml of blood per bottle from adults
8. Release tourniquet and remove needle
9. If not using the vacutainer system, disinfect the top of the blood culture bottle before inoculating blood
10. Do not change needles between blood sample collection and inoculation of blood culture bottle
11. Always fill blood culture bottle before filling vials for other tests
12. Label the blood culture bottle making sure not to cover the bar code label or the bottom of the bottle
13. Complete a laboratory request form in full
14. If there is a delay in getting the sample to the laboratory, do not refrigerate the bottle; rather leave it at room temperature
15. Document in the notes, the date and time that the blood culture was taken

Microbiology

Interpreting test results

Non culture-based tests

Non culture-based tests such as urinary dipstick, peripheral white cell count (WBC), and C-reactive protein (CRP) confirm the presence of inflammation, but do not differentiate bacterial from non-bacterial causes. However, presence of nitrites on urine dipstick, high neutrophil count with left-shift and CRP >10 mg/L all suggest bacterial infection. Negative results are generally good at excluding inflammation and therefore bacterial infection.

Procalcitonin (PCT) is more specific for bacterial infection than CRP or WBC but 10 times more expensive. There is high quality evidence for its use in a limited number of infections and its use should be limited to these indications. Specifically, low PCT safely excludes bacterial infection such that antibiotics can be withheld in meningitis, and acute exacerbations of chronic obstructive pulmonary disease (see later sections for details). PCT has no value in differentiating bacterial infection from tuberculosis and has very limited value in sepsis. Its price generally excludes its use in serial measurements to determine when to stop antibiotics, although some evidence in ICU settings alone, exist.

Cultures

Does this positive culture represent infection, colonization or contamination?

Infection = the presence of one or more microorganisms with an inflammatory response (raised WBC)

Colonization = the presence of microorganisms without significant inflammation (mostly skin flora)

Contamination = the accidental introduction of microorganism in culture (not originated from the intended anatomical site of collection)

Sterile sites

Normally sterile sites are CSF, pleural fluid, pericardial fluid, synovial fluid, peritoneal fluid, urinary tract, and blood. Bacteria cultured from these sites are likely to be causing infection but still sometimes represent colonization or contamination.

Finding bacteria in a sterile site is abnormal and most likely represents an infection. If specimen is not properly collected, certain organisms that colonize the skin such as coagulase negative Staphylococci may cause contamination of sterile sites. Colonization of urinary tract can occur without causing infection. If the organism tallies with the clinical scenario and inflammatory response (e.g., raised WBC) then this should be considered to be a cause of infection.

Non-sterile sites

Non-sterile specimens include sputum (as it must pass through the mouth), pus swabs from skin, GI tract, and vagina. Specimens from these sites are expected to culture bacteria (unless growth is inhibited by laboratory techniques). Interpretation therefore depends on the organism(s) being compatible with the clinical scenario.

Cultures from non---sterile sites are often much harder to interpret and usually of less value.

Microbiology

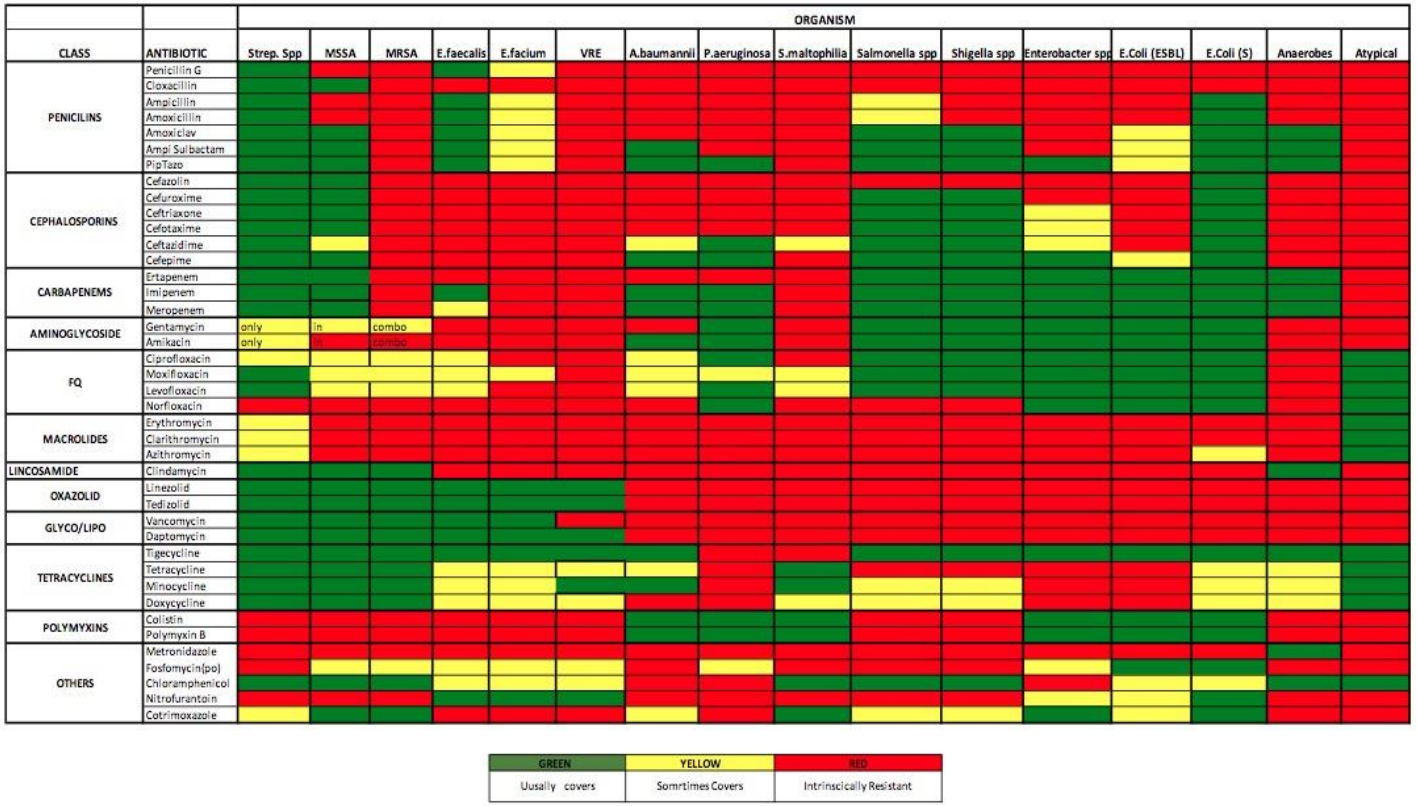
Organisms and Spectrum

Table 1: Bacterial Types

Gram Positive	Gram Negative	Anaerobes	Atypical
• Strep, Group A, B, C, G • Streptococcus pneumoniae • viridans Streptococci • Streptococcus milleri • Enterococcus faecalis • Enterococcus faecium • Staphylococcus aureus • Staphylococcus epidermidis • Corynebacterium jeikeium • Listeria monocytogenes	• Neisseria gonorrhoeae • Neisseria meningitidis • Moraxella catarrhalis • Haemophilus influenzae • E. coli • Klebsiella spp. • Enterobacter spp. • Serratia marcescens • Salmonella spp. • Shigella spp. • Proteus mirabilis • Morganella morganii • Citrobacter spp. • Acinetobacter spp. • Pseudomonas aeruginosa • Legionella pneumophilia	• Actinomyces spp. • Bacteroides fragilis • Prevotella. melaninogenica • Clostridium difficile • Peptostreptococcus spp.	• Chlamydia spp. • Mycoplasma pneumoniae

Table 2: Typical spectrum of activity

The table below displays the typical activity of select antibiotics against different groups of organisms. Individual patient cultures and susceptibility should guide definitive treatment selections.


ORGANISM
CLASS
ANTIBIOTIC
Strep. Spp
MSSA
MRSA
E.faecalis
E.facium
VRE
A.baumannii
P.aeruginosa
S.maltophilia
Salmonella spp
Shigella spp
Enterobacter spp
E.Coli (ESBL)
E.Coli (S)
Anaerobes
Atypical
PENICILINS
Penicillin G
Cloxacillin
Ampicillin
Amoxicillin
Amoxiclav
Ampi Sulbactam
PipTazo
CEPHALOSPORINS
Cefazolin
Cefuroxime
Ceftriaxone
Cefotaxime
Ceftazidime
Cefepime
CARBAPENEMS
Ertapenem
Imipenem
Meropenem
AMINOGLYCOSIDE
Gentamycin
Amikacin
only
in
combo
FQ
Ciprofloxacin
Moxifloxacin
Levofloxacin
Norfloxacin
MACROLIDES
Erythromycin
Clarithromycin
Azithromycin
LINCOSAMIDE
Clindamycin
OXAZOLID
Linezolid
Tedizolid
GLYCO/LIPO
Vancomycin
Daptomycin
TETRACYCLINES
Tigecycline
Tetracycline
Minocycline
Doxycycline
POLYMYXINS
Colistin
Polymyxin B
OTHERS
Metronidazole
Fosfomycin(po)
Chloramphenicol
Nitrofurantoin
Cotrimoxazole
GREEN
Uusally covers
YELLOW
Somrtimes Covers
RED
Intrinscically Resistant

Infection Control and Prevention

Infection Control and Prevention

Healthcare associated infections

Healthcare associated infections are related with increased patient morbidity, mortality, and cost. Healthcare workers are expected to be role models in preventing infection to patients. The most important tools to prevent spread of infection are hand hygiene and sterile technique for procedures.

Hand Hygiene

- Hand hygiene is required:
  - Before entering and when leaving patients wards and rooms.
  - Before donning and after removing gloves, for both sterile and non- sterile activities.
  - After contact with inanimate objects in patient's environment
  - As a reminder, there may be additional times at the bedside where hand hygiene is appropriate (e.g., after changing wound dressing)
  - Always wash/sanitize hands after glove use
- Hand sanitizer or soap and water are acceptable means of hand hygiene
- Soap and water for hand hygiene must be used for the following:
  - After caring for patients with diarrhoea
  - If hands are visibly soiled
  - After using the restroom or eating
  - If hands are contaminated with body fluids
- Indications for gloves
  - Patient interactions that involve exposure to blood, mucous membranes or non-intact skin
  - Suspected or proven infectious diarrhoea

Standard Precautions

- Personal protective equipment (PPE), such as masks, gowns, gloves and eye shield, should be used for your protection any time there is the potential for blood or body fluid exposure. PPE is to be removed after use.
- Eating or drinking is prohibited in work areas and patient care areas where patients or lab specimens may be present.

Transmission Based Precautions

Isolation precautions (use of side wards)

- Patients with antibiotic-resistant bacteria such as carbapenem-resistant Enterobacterales (CRE) (i.e., organisms resistant to imipenem)
- Burn patients
- Patients with infectious meningitis such as Neisseria spp.
- Hand hygiene is necessary prior to donning and upon removal of gloves

Enhanced contact precautions (gloves and soap and water for hand hygiene)

- Used for diarrhoea, likely infectious
- Suspected or confirmed C. difficile or Norovirus

Airborne precautions (N-95 mask for healthcare providers and visitors)

- Used most for suspected / confirmed TB
- Also used for possible disseminated varicella, measles
- Requires isolation room, patient should wear surgical mask

Safe Injection Practices

- Needles and syringes are single use devices. They should not be used for more than one patient or reused to draw up additional medication.
- Do not administer medications from a single-dose vial or IV bag to multiple patients.
- Limit the use of multi-dose vials and dedicate them to a single patient.

IV line associated bacteraemia prevention

Line Insertion:

- Perform hand hygiene and ensure aseptic technique.
- When inserting a central line, maximal barrier precautions (mask with face shield, cap, sterile gown, sterile gloves, and a large drape) are needed.
- Chlorhexidine-alcohol skin prep should be used to clean the skin during line insertion
- A chlorhexidine dressing needs to be placed over all central and arterial line exit sites, having maximum contact with the skin for optimal antimicrobial effect.

Maintenance

- **Daily, assess whether the line is still needed; promptly remove when no longer necessary.**
- Evaluate any IV medications for potential PO conversion
- **Evaluate continued need of other IVs such as fluids, nutrition, contrast dye, heparin, etc.**
- Evaluate line daily for signs of IV site inflammation
- Replace any line, as soon as possible, if inserted in an emergent situation where sterility could have been compromised.
- Notify nursing of damp/loose/soiled/unlabelled line dressings
- Do not routinely use central lines for obtaining blood cultures: catheter colonization likely leads to false positive blood culture results when obtained from central lines

Catheter-associated urinary tract infections

- Insert urinary catheters only when necessary, and remove them at earliest opportunity
- Insertion should be a sterile procedure
- The **appropriate indications** for a urinary catheter are as follows. **If patient does not have these conditions, then the patient should not have a urinary catheter**.
    - Acutely ill patients requiring monitoring of urine output
    - Acute retention (obstruction or neuropathy)
    - Immobilization required (trauma/surgery), e.g., unstable spine
    - Peri-op: Prolonged (>2hr) procedure
    - Peri-op: Intra-op urine out-put monitoring
    - Sacral/perineal wound with incontinence
    - Urological/GU surgery/bladder injury
    - End of Life/Comfort Care (urine cultures are usually not obtained)

- Perform daily review of catheter, document presence and need in progress note

- Foley maintenance:
  - Do not clean the meatal area with antiseptics after insertion
  - Do not screen for asymptomatic bacteriuria
  - Do not use antibiotics for prophylaxis of CAUTI
  - Do not irrigate catheters routinely
  - **Keep collecting bag below level of the bladder and suspend off the floor**
  - Collaborate with nursing staff on foley indication and plan for foley catheter removal

  Consider alternatives to a urinary catheter: intermittent catheterization, bedpan, bedside commode as a measurement for intake / output.

Miscellaneous topics

- If you have a bloodborne pathogen exposure, please refer to the HIV Guidelines and Hepatitis B Guidelines for post-exposure prophylaxis recommendations or consult infectious diseases.

Surgical Prophylaxis

Surgical Prophylaxis
Clinical pearls

- Appropriate antibiotic surgical prophylaxis is a key resource to preventing surgical site infections
- All antibiotics should be given **within 1 hour** prior to surgical incision (**EXCEPTIONS:** vancomycin and fluoroquinolones should be given within 2 hours prior to surgical incision).
- The antibiotic should be re-dosed during the procedure if the procedure lasts for greater than two half-lives of the antibiotic or there is blood loss of greater than 1500 mL and it is not returned to the patient with cell savers.
- **To prevent the development of resistant organisms, prophylactic antimicrobial agents should be discontinued within 24 hours of surgery.** There is NO data suggesting that prolonged prophylaxis further reduces infection. For most procedures, there is no evidence for continued postoperative antimicrobial administration.
- Some patients may already be receiving antimicrobials with the same or similar spectrum as those used for surgical prophylaxis. When this is identified, it should be clearly noted within the patients' medical record as the reason no additional prophylaxis is indicated.
- Drug Allergy
    - The presence of a true drug allergy is based on the presence of a positive patient response to one or more of the following signs/symptoms: respiratory difficulty (trouble breathing, shortness of breath, chest tightness), hypotension (low blood pressure, fainting), rash, hives, emergency room visit / emergent visit to the doctor's office.
    - In the absence of these findings, the patient likely experienced an adverse effect (e.g., gastrointestinal upset) but NOT an allergic reaction to the antibiotic. An antibiotic of the same class may be used for surgical prophylaxis. Contact pharmacy for assistance with allergies.

Surgical site infections
Prior to surgery:

- Treat any infection remote from the surgical site and postpone elective surgery until infection has resolved
- Patient should shower or bathe with an antiseptic soap on the night before and morning of surgery
- Remove hair only, if necessary, use clippers **NOT** razors

At the time of surgery:

- Use OR checklist to ensure compliance with critical processes for patient safety / infection prevention.
- Skin prep using alcohol + chlorhexidine solution (unless contraindicated). Allow prep to dry before incision.
- Preoperative antibiotics administered <u>within 60 minutes</u> prior to incision, agent appropriate for anticipated pathogens, dosed and re-dosed per UTH protocol.
- <u>Limit traffic</u> in the OR: Keep doors closed except as needed for passage of essential equipment, personnel, and the patient.

Dosing, Redosing, and Infusion Times for Select Antibiotics						
	Ampicillin/ Sulbactam	Cefazolin‡	Clindamycin	Gentamicin	Metronidazole	Vancomycin
Dose	3g	≤120 kg: 2g >120 kg: 3g	900 mg	5 mg/kg	500 mg	≤70 kg: 1g 71-109 kg: 1.5g ≥110 kg: 2g
Intra-op Redosing	Every 2 hours	Every 4 hours	Every 6 hours	N/A	N/A	N/A
Infusion Time	30 min	30 min (can give IV push over 3 min)	60 min	30 min	60 min	60-120 min
Redosing may be required sooner if large blood loss occurs [estimated as 6 units of blood or 1.5 liters (hemodilution)]. Redosing may not be warranted in patients in whom the half-life of the antimicrobial agent is prolonged (e.g., patients with renal failure). *Gentamicin dosing is dependent on the patient's bodyweight. For obese patients, the adjusted body weight (AdBW) should be used to determine dose. AdBW = IBW + 0.4(TBW-IBW) ‡ If Cefazolin is not available can substitute with Ceftriaxone 2g IV stat (Ceftriaxone does not require redosing)						

RECOMMENDED ANTIMICROBIAL SELECTION FOR PREVENTION OF SURGICAL SITE INFECTION IN ADULT PATIENTS		
Procedure	**Drug(s) of Choice**	**Intra-op Redosing**
Colorectal	Cefazolin + Metronidazole	4 hours (Cefazolin only), none for Metronidazole
Gastro-duodenal Surgery – including biliary procedures	Cefazolin	4 hours
Gastro-duodenal Surgery – if obstructed or perforated bowel	Cefazolin + Metronidazole	4 hours (Cefazolin only), none for Metronidazole
Gynecologic Surgery	Hysterectomy: Cefazolin C-section: Cefazolin + Azithromycin Miscarriage: doxycycline	4 hours for Cefazolin, N/A for others
Head and Neck Surgery	Clean: Prophylaxis not indicated Clean-Contaminated: Cefazolin + Metronidazole	4 hours (Cefazolin only), none for metronidazole
Neurosurgery – Brain and Spine Procedures	Cefazolin	4-hours
Orthopedic Surgery	Cefazolin	4-hours
Cardiac surgery	Cefazolin	4 hours
Thoracic Surgery	Cefazolin	4 hours
Urologic Surgery – clean-contaminated-High or low risk	Cefazolin + Metronidazole Alt: Ciprofloxacin + Metronidazole	None
Renal transplant	Cefazolin	4 hours

***Ceftriaxone can be used in the absence of cefazolin; however, ceftriaxone is excessively broad and contributes to antimicrobial resistance, thus cefazolin is highly preferred**

References:

- Clinical practice guidelines for antimicrobial prophylaxis in surgery. Bratzler DW, Dellinger EP, Olsen KM, et al. Am J Health-Syst Pharm 2013; 70:195-283.
- Antimicrobial Prophylaxis for Surgery: An advisory statement from the National Surgical Infection Prevention Project. Bratzler DW and Houck PM. Clin Infect Dis 2004;38:1706-1715.
- Antibiotic Prophylaxis for Gynecologic Procedures. ACOG Practice Bulletin #74: Obstetrics and Gynecology 2006;108.

Allergies

Type of Drug Reactions

- **Type A reactions** are pharmacological, dose dependent, and predictable from the known pharmacologic properties of a drug (e.g., gastritis from NSAIDs, diarrhoea from antibiotics, nephrotoxicity from aminoglycoside use).
- **Type B reactions** which are allergic or hypersensitivity reactions to antimicrobials are pharmacologically unpredictable, non-dose dependent, and often immune mediated.
- Type B reactions are further classified as types 1 through 4.
    - Type 1: IgE mediated – classic anaphylaxis with itching, hives, tongue swelling, wheezing, vasodilation, etc.
    - Type 2: cytotoxic – e.g., haemolysis
    - Type 3: immune complex mediated – e.g., serum sickness
    - Type 4: delayed/T cell mediated – e.g., Mantoux skin test, drug fever (see below), severe cutaneous adverse reactions (see below)
    - **Type 1 allergic reaction is the only type for which a patient can be safely re-challenged or desensitized.** Patients who have experienced type 2-4 reactions should never again receive a drug in that class.

Drug Fever

- Fever is defined by a body temperature of above 38 degrees C (100.4 degrees F).
- Drug Fever is a Type 4, delayed / T cell mediated hypersensitivity reaction.
- Drug Fever = fever coinciding with administration of a drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident.
- Drug fever takes an average of one week to develop but can occur at any time during therapy. After stopping the medicine, fever should resolve within 72 hours.
- When drug fever is suspected, the offending agent should immediately be stopped.
- **Fever often leads to empiric treatment for suspected infection, leading to overuse of antimicrobials, adverse effects, and antimicrobial resistance.**
- The drugs most commonly associated with drug fever include the penicillins, cephalosporins, antituberculars, quinidine, procainamide, methyldopa, and phenytoin.
- Severe and potentially fatal forms of drug fever include serotonin- syndrome, malignant hyperthermia, and neuroleptic malignant syndrome.

Drug Rash

- Included within type 4 are the severe cutaneous adverse reactions (SCARs) – Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), SJS/TEN overlap, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).
- Other types of drug rash include exanthematous rashes, hives, photosensitivity, and erythroderma which can all be caused by antimicrobials.
- Exanthematous rashes are generally benign. They are symmetric, often truncal, can be macular or papular and occasionally pustular or vesicular, and may be mildly pruritic.
- Photosensitivity occurs when certain medications make a person more sensitive to UV light. Examples include doxycycline, sulfa drugs and voriconazole. Patients should be advised to avoid exposure to direct sunlight while taking these medications.
- Erythroderma is a condition of diffuse erythema and pruritis and can cause scaling and eventual desquamation. It can be life threatening if not stopped.

Penicillin or Beta-Lactam Hypersensitivity

- Globally, approximately 10% of patients report an allergy to penicillin; only about 10% of those patients have a true allergy upon skin testing. Various 'reactions' to antibiotics are frequently inaccurately diagnosed as allergies.
- Even with a well-documented allergy, hypersensitivity often does not persist over time (80% 'resolve' over 10 years).
- Risk of cross-reactivity with cephalosporins (particularly 3rd and 4th generation) and carbapenems is very low.

TMP/SMX or Sulfa Hypersensitivity

- In patients with HIV, rates of adverse reaction to TMP-SMX are high (20% to 85%).
- Common adverse effects are rash (30% - 55%, including Stevens-Johnson syndrome), fever (30% - 40%), leukopenia (30% - 40%), thrombocytopenia (15%), azotemia (1-5%), hepatitis (20%) and hyperkalemia.
- Rashes often can be treated with antihistamines. Nausea and fever can be controlled with antiemetics and antipyretics respectively.
- Sulfa drugs are contraindicated in patients who have experienced type 2-4 adverse drug reactions.
- Be aware of other commonly used sulfa/sulfa- like drugs: sulfasalazine, sulfadiazine, dapsone, hydrochlorothiazide, furosemide.

Allergy History to Obtain

- What medication did you have a reaction to? If unknown, what was the medication given for?
- How long ago was the reaction? How long after taking the medication did the reaction occur?
- What was the reaction?
    - Was there any wheezing, throat or mouth swelling or urticaria?
    - Did a rash occur? Where was the rash and what did it look like?
    - Did you have to seek medical care, go to hospital, go to ICU, or have intubation/ventilator support?
- Patient's full allergy history with above details, should be documented in the medical record

Management of select reactions

Type 1/IgE mediated allergic reaction, immediate treatment:

- Adrenaline: 0.1mg IV x 1 every 3 minutes up to 3 times
- Steroid: hydrocortisone 200mg IV stat, then 50 mg IV q8h as needed
- Histamine blocker: chlorpheniramine 4mg q8h or cetirizine 10mg OD or loratadine 10mg OD
- Beta agonist if respiratory signs or symptoms: salbutamol inhaler or nebulizer
- Observation: monitor closely for signs of cardiovascular collapse or respiratory compromise.

TMP/SMX Desensitization:

- Refer to Zambian HIV Guidelines

Bacteraemia

Bacteraemia
Clinical pearls

- In patients with positive blood cultures, underlying source of infection will guide antibiotic selection and duration

- For example, for patients with bacteraemia from a urinary source, refer to the urologic infection guidelines for treatment recommendations.

- Most bacteraemia represents clinically significant infection; however, certain organisms can represent contamination. If multiple cultures are drawn and only a single culture is positive for coagulase negative staphylococcus, this is likely a contaminant and the decision to treat should be based on patient specific factors (e.g., presence of implanted hardware or critical illness without other possible sources of infection).
- *S. aureus* and *Candida spp*. never represent contamination in blood cultures and ID should always be consulted for these cases due to difficulty in treatment and high mortality.
- Complications of bacteraemia include sepsis and septic shock or seeding of other potential sites of infection (e.g., heart valves - infective endocarditis and endocardial abscess, lung abscess, renal abscess, bones and joint). Timely antibiotic therapy is the cornerstone of management.
- The latest University Teaching Hospital Microbiological data **(please see app for most up-to-date detail)** indicate coagulase negative staphylococcus (CoNS), Enterobacterales (*Klebsiella spp, E.coli, Enterobacter spp.*), and *Staphylococcus aureus* (MSSA and MRSA) as the most common pathogens isolated from blood.

Diagnosis

- When bacteraemia is suspected, at least **2 blood cultures** should be drawn **promptly before antibiotics**, **from separate sites**.
- Evaluate for underlying source of infection. Common sources include urinary tract infections (particularly for Enterobacterales), intravascular catheters or other implanted hardware, joint infections, skin and soft tissue infections, pneumonia, and endocarditis, although a source may not be obvious in all cases.
- For MSSA or MRSA bacteraemia, an echocardiography should be done (TTE or TOE).

Treatment

- Empirical management of bacteraemia should include coverage for gram positive organisms especially *Staphylococcus aureus*. Organism culture and susceptibility should guide antibiotic selection.
- Antibiotics that achieve high serum levels are preferred for management of bacteraemias. Antibiotics that are not recommended for treatment of bacteraemias include tetracyclines (e.g., doxycycline), macrolides (e.g., azithromycin), and oral beta-lactams (e.g., cefpodoxime) due to low serum levels or low bioavailability.
- Duration of therapy should be guided by underlying source (7 to 10 days) – see individual sections and duration sections.
- For *Staphylococcus aureus* bacteraemia the duration therapy is determined by several factors.
  - (I) uncomplicated bacteraemia defined as being without endovascular complications; defervescence within 72 hours; negative repeat blood cultures done 24-48 hours; no vascular lines, then the duration of therapy is 14 days from last day of negative culture.
  - (II) Complicated bacteraemia which is defined as not meeting the criteria of uncomplicated then duration of therapy is continued for 4-6 weeks.
- For Catheter related blood stream infection, see separate section in guidelines.

Catheter Related Bacteraemia

Catheter Related Bacteraemia

Clinical pearls

- CR-BSI is defined as bacteraemia or fungemia in a patient who has an intravascular device and >1 positive blood culture obtained from a peripheral vein, AND a positive semiquantitative (>15 CFU/ 5cm-catheter segment) culture where the same organism (species and susceptibilities) is isolated from the catheter segment and peripheral blood. In addition, the patient has clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for bloodstream infection (except for the catheter).

- Long-term catheters include tunnelled central venous catheters (CVC), haemodialysis catheters, PICCs, and medi-ports (for chemotherapy). Short-term catheters include peripheral IVs, arterial catheters, temporary CVCs.
- Common organisms include CoNS, *Staphylococcus aureus, Candida spp*., and Enterobacterales.

Diagnosis

- Diagnostic approach depends on the status of the line: retention vs removal, for indications refer to catheter management.
- When CR-BSI is suspected, at least 2 blood cultures should be drawn, equal volumes inoculated at same time, collected from the line and peripheral. Time to positivity between the two blood cultures of 2hrs supports the diagnosis. **AT LEAST ONE** (preferably >1) set should be from a peripheral site.
- With removal of line, catheter tip with organism isolated >15 cfu and same organism isolated on peripheral blood culture collected at time of CVP removal confirms the diagnosis.
- If a blood sample cannot be drawn from a peripheral vein, 2 blood samples should be drawn through different catheter lumens.
- Blood cultures should be drawn **prior** to the administration of antibiotics. Do not delay antibiotics by more than 2-3 hours while awaiting blood cultures.
- The utility of cultures of the catheter tip itself is not well defined and should only be sent when there is a clinical suspicion of infection, not routinely when lines are removed. They must be accompanied by two sets of blood cultures obtained as described above.
    - Technique of catheter tip cultures: The exit site should be cleaned with alcohol or alcoholic chlorhexidine solution. The catheter should be grasped a few centimetres proximal to the exit site.
    - A 5 cm segment of catheter including the tip should be cut off with sterile scissors and placed in a sterile container.
- When a CR-BSI is associated with catheter dysfunction, consider the possibility of suppurative thrombophlebitis. A definitive diagnosis requires the presence of positive blood culture results plus the demonstration of a thrombus by CT or US.

Treatment

Catheter Management

- If there is more than minimal erythema or ANY purulence at the exit site, the catheter is likely infected, and it should be removed and replaced at a different site if still needed.
- Short-term catheters should be removed from patients with any bloodstream infection due to gram-negative bacilli, *S. aureus, enterococcus spp*., and fungi.
- Long-term catheters should be removed from patients with bloodstream infection associated with any of the following conditions:
    - Severe sepsis or septic shock (see Sepsis section)
    - Suppurative thrombophlebitis
    - Infectious endocarditis (see Endocarditis section)
    - Infections due to *S. aureus, P. aeruginosa*, or fungi. Catheter removal in patients with CR-BSI due to other Gram-negative bacilli may prevent recurrence of CR-BSI and this decision should be made on a case-by-case basis.

- Persistent BSI caused by any organism despite 72 h of anti-infectives to which the pathogen is susceptible.
- Catheter tunnel infection or port abscess.

- For CR-BSI due to organisms that may be contaminants (e.g., *Bacillus spp., Micrococcus spp*., *Corynebacterium spp*., *Propionibacterium acnes* (now *Cutibacterium acnes*), CoNS catheters should generally be removed if blood cultures are persistently positive or positive in multiple bottles, suggesting a true BSI. At least one blood culture should be drawn from a peripheral vein.
- Central lines may be re-inserted when the last set of blood cultures has been negative for ≥ 48 hours.

Catheter Salvage: Antibiotic Lock Therapy (ALT)

- Catheters associated with tunnel infections CANNOT be salvaged.
- Catheter removal is STRONGLY recommended for infections with *S. aureus, Pseudomonas spp*., and fungi given the high risk of recurrent and metastatic infection.
- Catheter salvage may be attempted in patients with uncomplicated CR-BSI where removal of central line is not feasible and long-term IV access is necessary for survival, such as: patients undergoing haemodialysis, patients with short-gut syndrome, absolutely no alternative IV access for medication or chemotherapy administration, hemodynamic instability with removal of central line.
- Antibiotic lock therapy (ALT) is indicated for patients with CR-BSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the only option.
- For CR-BSI, ALT should NOT be used alone; instead, it should be used in conjunction with systemic antimicrobial therapy, with both regimens administered for 7–14 days.

Empiric Antibiotics

- If patient is critically ill, refer to severe sepsis & septic shock guideline.
- If patient has neutropenic fever (NF) refer to NF guideline.

Gram Stain from Blood Culture	Empiric Treatment	Empiric Treatment if Penicillin Allergic	Notes

Gram positive cocci in pairs/chains or clusters	Vancomycin (Alternative Linezolid)	Vancomycin	Empiric therapy should cover MRSA until further speciation and susceptibilities return. Doxycycline has inadequate serum concentrations for bacteraemia treatment
Gram negative rods	Piperacillin/Tazobactam OR Meropenem (if history of MDR GNRs)	Mild reaction: Meropenem Anaphylaxis: Ciprofloxacin +/- Amikacin	Consult ID if history of MDR GNRs and unsure of empiric therapy. If critically ill, consider adding a 2nd gram-negative agent, such as a single amikacin dose.
Yeast	Echinocandin (e.g., Micafungin, Caspofungin) Alternative: Fluconazole if echinocandin unavailable	Echinocandin (e.g., Micafungin, Caspofungin) Alternative: Fluconazole if echinocandin unavailable	Use for septic patients with: TPN use, prolonged antibiotics, hematologic malignancy, transplant patient, femoral catheterization, or colonization (Candida at multiple sites). Refer to Candidemia Guideline

Definitive Antibiotics

- Blood culture is the gold standard (peripheral avoid drawing from the catheter).
- Catheter tips may also be sent for culture.
- In instances where the blood and catheter tip are cultured at the same time and the blood cultures are negative, but the catheter tip culture is **positive**, antibiotics are generally not recommended, even for patients with valvular heart disease or immunosuppression.
    - **Exception: catheter tips growing *S. aureus* should be treated with 5–7 days of antibiotics**.
- Day 1 is the first day with negative blood cultures.
- Suppurative thrombophlebitis with CR-BSI:
    - Patient should receive a minimum of 3–4 weeks of antimicrobials
    - Surgical resection of the involved vein should be limited to purulent superficial veins, infection extending beyond the vessel wall, and failure of an appropriate antimicrobial regimen.
    - Given limited data for management, ID consult recommended.
- **See table below for suggested regimens.**

Suggested Antibiotic regimens for Catheter-Related Bloodstream Infection (CRBSI)

Organism	Contaminant?	Treatment	Duration	Notes
Coagulase negative Staph	Possibly Single positive culture likely contaminant. Do not treat unless patient is immunosuppressed, critically ill, or has implanted hardware.	Vancomycin 1g q12h	3–5 days if catheter removed (preferred) Otherwise,10–14 days (use antibiotic lock therapy)	With single positive culture, treatment can be started but repeat cultures should be sent PRIOR to first dose of antibiotics to confirm the diagnosis. ***S. lugdenensis* should be treated like S. aureus.**
MSSA	Never	Cloxacillin 2g q6h Mild penicillin allergy: cefazolin 2g 8hrly Anaphylaxis to Penicillin: Vancomycin	4-6 weeks unless meets exclusion criteria listed below	**Vancomycin is inferior to Cloxacillin or cefazolin for MSSA.** If catheter tip cx positive but peripheral blood cx negative, can remove catheter and treat for 5-7 days Cloxacillin: use 3g 6 hrly for endocarditis, prosthetic heart valves, meningitis, and osteomyelitis
MRSA	Never	Vancomycin (adjust dose according to creatinine clearance, see appendix) Alternative: Linezolid (No dose adjustment required, monitor for anemia and thrombocytopenia)	4-6 weeks unless meets exclusion criteria listed below.	If catheter tip cx positive but peripheral blood cx negative, can remove catheter and treat for 5-7 days Vancomycin loading dose 25-30mg/ kg advised in severe or critically ill patients. **Linezolid not recommended for endocarditis or other endovascular infections**
E. faecalis	Unlikely	Ampicillin 2g IV 4hrly Alternative: linezolid	7-14 days	Patients with endocarditis require combination therapy,

Organism	Contaminant?	Treatment	Duration	Notes
				options include gentamycin and ceftriaxone Note: Ceftriaxone lacks activity against enterococcus spp and is only used for synergy with ampicillin in endocarditis **Please consult infectious disease for further guidance**
E. faecium	Unlikely	Vancomycin Alternative: Linezolid, Daptomycin	7-14 days	
Gram-negative bacilli	Never	Antibiotic selection based on organism and susceptibilities	7-14 days	Catheters less commonly source of infection; however, remove catheter if possible
Candida spp.	Never	Preferred for suspected candidemia if azole resistance is suspected: Echinocandin- Caspofungin 70mg loading dose then 50mg daily PO Micafungin 100mg PO daily Alternative: Fluconazole 800mg loading dose then 400mg daily IV/PO	5 days then transition to azoles up to 14 days	***C. krusei, C. auris* and *C. glabrata* can be resistant to azoles.** Note: Documentation of clearance is important Duration of treatment determined from first negative serial culture i.e., 14 days from documented clearance Empiric Fluconazole only indicated in clinically stable patients with no history of prior antifungal therapy exposure

Use of Transoesophageal Echocardiography in Bloodstream Infection

- TOE/TTE should be done for patients with CR-BSI within 5-7 days of the onset of bacteraemia who have ANY of the following:
  - Prosthetic heart valve, pacemaker, or implantable defibrillator
  - Persistent bloodstream infection
  - Fever >72 h after initiation of appropriate antibiotic therapy and catheter removal
  - Any case of *S. aureus* CR-BSI in which duration of therapy less than 4–6 weeks is being considered, or clinical concerns for endocarditis (murmur, new heart failure symptoms, septic emboli etc.)

Staphylococcus aureus Treatment Notes

- Remove catheter. Relapse rates are high when catheters are not removed.
- Vancomycin is inferior to cloxacillin or cefazolin for treatment of MSSA.
- Patients with *S. aureus* BSI should have TTE or TOE to evaluate for endocarditis. They should also have careful evaluation to rule out metastatic sites of infection.
- Patients should receive 4-6 weeks of therapy based on the extent of infection and ID consultants should be involved in the management
- Blood culture done after 72 hrs. on appropriate treatment and source control achieved determines the duration of treatment and indicates presence of complications.
- 14-day course of therapy instead of 4-6 weeks may be appropriate if ALL the following apply AND ID consult team agrees.
  - Patient is not diabetic, neutropenic, or immunosuppressed
  - Source control has been obtained
  - Infected catheter is removed
  - The patient has no localizing signs or symptoms of metastatic staphylococci infection
  - Endocarditis has been excluded with TOE (preferred); high quality TTE may be adequate.
  - The patient has no prosthetic intravascular device (e.g., pacemaker) and no implanted prostheses
  - Fever and BSI resolve within 72h of starting appropriate antimicrobial
  - Follow-up blood cultures (2-4 days after initial cultures) are negative

Prevention

- Use the sterile technique for CVC Insertion
  1. Use appropriate hand hygiene.
  2. Use an alcoholic chlorhexidine antiseptic for patient skin preparation.
  3. Use maximal sterile barrier precautions (mask, sterile gown, sterile gloves, and large full-body sterile drapes) during insertion.
  4. Avoid the femoral vein as an access site (subclavian > internal jugular > femoral)
  5. Assess the need for continued central venous access on a daily basis. Remove unnecessary catheters.
- Other interventions to prevent CR-BSI include reducing unnecessary access to ports, disinfecting catheter hubs, needleless connectors and injection ports accessing the catheter, maintaining an intact dressing, and daily chlorhexidine bathing for ICU patients.
- TPN ports should be designated and used for TPN only where possible.

Resources:

- CLBSI Prevention Guidelines: Marschall J. Infect Control Hosp Epi 2014;35:753-771.
- Catheter Related Infections Guidelines: Mermel LA. Clin Infect Dis 2009;49:1-45.
- Catheter Related Infections Prevention Guidelines: O'Grady NP. Clin Infect Dis 2011;52:e162-93.
- Perencevich EN, Johnson S, Jablonover M. Rowen L, Schreibman D, Rock P. Preventing Central Line-Associated Bloodstream Infections (CLABSI): A Unit-Based Collaborative Approach. UMMC White Paper. 2009 April 22.

Bone and Joint Infections

Bone and Joint Infections

Clinical pearls

Bone and joint infections account for significant morbidity and mortality. Common infections include osteomyelitis (including vertebral), septic arthritis, spinal infections, epidural abscess, diabetic foot infections/osteomyelitis, TB spinal infection (refer to TB guidelines), prosthetic joint infections (PJI) and implant induced /foreign body osteomyelitis. Pathogenesis of osteomyelitis is via hematogenous route or through contagious soft tissue infections including abscess, and through direct inoculation during surgery or as a result of trauma, injection, etc.

Osteomyelitis may be classified as acute and chronic osteomyelitis and will have implications. *Staphylococcus aureus* accounts for most bone and joint infections in the developed nations. Some bone and joint infectious are a result of hospital-acquired infections.

Chronic Osteomyelitis

- Chronic osteomyelitis usually occurs in adults following trauma or surgery.
- Implies a long-standing infection and the presence of dead bone.
- Valid cultures are necessary to guide treatment options; **empiric therapy not recommended**.
- Common causative organisms: *Staphylococcus aureus, Enterobacterales, Pseudomonas aeruginosa, Streptococcus spp.*

Diagnosis

- Imaging is the mainstay for diagnosis:
  X-rays and CT scan play an important role. MRI can provide early diagnosis. Bone scans are rarely necessarily but maybe diagnostic e.g., blood cultures, pus and deep tissue culture are positive in osteomyelitis.
- **Bone biopsy is the gold standard for diagnosis**. Margins from amputated bone must be evaluated by a pathologist for evidence of infection. Presence of clean margins can significantly shorten treatment duration. Surgical specimen must be sent to pathology AND microbiology laboratories (send margin to pathology laboratory, and clearly infected bone to microbiology laboratory). Bone culture is imperative for choosing correct antibiotics. **In a stable patient, antibiotics should be delayed increasing yield of cultures if bone biopsy is performed**. If bone biopsy is not performed initiate antibiotics.
- Obtain aerobic cultures in all patients. Add anaerobic culture in shoulder infections and suspected polymicrobial infections. Some also add AFB and fungal culture for chronic infection, immunocompromised patients, treatment failure, or when aerobic and anaerobic cultures are negative in strongly suspected cases of vertebral osteomyelitis.
- Superficial wound cultures are to be avoided, except in cases of sinus tract drainage. If multiple cultures from a sinus tract are consistent with the same organism, they likely are representative of the pathogen infecting the bone.
- Blood cultures should be collected if the patient is systemically ill or has fever. New bone or joint pain (often in knee or spine) in the setting of *S. aureus* bacteraemia should always be investigated, as hematogenous seeding of bone/joint is common. If acute osteomyelitis had clear hematogenous source with positive blood cultures, bone culture is not needed.
- Leukocytosis and elevated ESR and CRP may be present. ESR and CRP are used for monitoring response to therapy over time but are imperfect markers. Obtain baseline values prior to treatment.

Treatment

- Treatment should be tailored to microbiological evidence. Empiric treatment must be based on suspected organisms and local antibiogram. Osteomyelitis cannot be cured unless dead bone is surgically removed, bone is covered by soft tissue, and the area has adequate vascular supply. In addition, any foreign implants may need to be removed to achieve cure.
- Intravenous antibiotics or oral antibiotics with excellent bone penetration can be used i.e., Linezolid, TMP-SMX, doxycycline, metronidazole, fluoroquinolones, and rifampicin have good bone penetration, but all require monitoring and ID oversight for prolonged courses.

Osteomyelitis

Acute osteomyelitis coverage

Infectious Pathogen	**Antibiotic**	**Comment**
Empiric Therapy	Vancomycin PLUS a third-generation Cephalosporin (such as Ceftriaxone, Ceftazidime)	Ceftriaxone for treatment of MSSA is not universally accepted; however, for osteomyelitis ceftriaxone 2g IV q12h is acceptable
Staphylococcus aureus, MSSA	• Cloxacillin 500 IV/PO q6h OR • Cefazolin 2g IV q8hrs	
Staphylococcus aureus, MRSA	• Vancomycin 20mg/kg loading dose, then 15-20mg/kg q8-12h • Linezolid 600mg PO/IV q12h	Vancomycin dosing used for most patients with normal renal function, monitor Vancomycin levels FBC should be monitored for use of Linezolid, risk of optic and peripheral neuropathy with long-term use
Gram-negative organisms	• Ciprofloxacin 750mg PO q12h or Ciprofloxacin 400mg IV q12h • Levofloxacin 750mg PO/IV daily • Ceftriaxone 2g IV q24h • Meropenem 1g IV q8h	FQ – monitor QTc, tendinopathy, monitor for disordered glucose regulation
Enterococcus spp.	• Aqueous crystalline PCN G 20-24 million units IV q24h • Vancomycin 20mg/kg loading dose, then 15-20mg/kg q8-12h	Vancomycin dosing used for most patients with normal renal function, monitor vancomycin levels
Streptococcus spp., if PCN sensitive	• Aqueous crystalline PCN G 20-24 million units IV q24h • Ceftriaxone 2g IV q24h • Vancomycin 20mg/kg loading dose, then 15-20mg/kg q8-12h	
Prosthetic joint infections	**Empiric therapy not recommended prior to obtaining culture results.** **Therapy guided by culture results:** **MSSA/MSSE:**	Three surgical options: Intraoperative inspection, debridement, and hardware retention. Appropriate if duration of symptoms < 3 weeks or implantation < 30 days;

Infectious Pathogen	Antibiotic	Comment
	Cloxacillin 500mg IV q6h+ Rifampicin 300mg PO q12h OR Cefazolin 2g IV q8h + rifampicin for 2-6 weeks followed by Ciprofloxacin 750mg po q12h or Levofloxacin 750mg po q24h + Rifampicin for 3-6 months **MRSA/MRSE:** Vancomycin 20mg/kg loading dose, then 15-20mg/kg q8-12h + rifampicin 300mg PO q12h for 2-6 weeks followed by ciprofloxacin 750mg po q12h or levofloxacin 750mg po q24h + rifampicin for 3-6 months **Streptococcus spp.:** PCN G 20-24 million units IV q24hrs ceftriaxone 2g IV q24h for 4-6 weeks **NOTE:** Poorer outcomes with retention compared with removal and exchange **Enterococcus spp:** **PCN-Sensitive: A**mpicillin 200mg/kg/kg IV in divided doses q6h or PCN G 20 million units/day IV in 6 divided doses x 4-6wks **PCN-Resistant:** Vancomycin 15-20mg/kg q12hr x 4-6wks	Otherwise, removal of prosthesis recommended if possible. 1st stage: direct exchange strategy 2nd stage: sequential debridement and prosthesis removal then later re-implantation Patients with prosthetic hardware should be given suppressive oral antibiotics, if possible, to prevent recurrence. Consider adjunct Rifampicin (to avoid resistance to Rifampicin – start rifampicin after patient has received several days of anti-staphylococcal therapy).

Cardiovascular Infections

Cardiovascular

Infective Endocarditis

Clinical pearls

- 'Infectious endocarditis' (IE) is not a single entity. IE can be left sided or right sided, affect native or prosthetic valve, be subacute or acute, be due to virulent or avirulent organisms, and be culture negative or positive. Each division carries different risk factors, treatments, complications, and prognosis.
- IE is a complicated disease with very high morbidity and mortality. **ID consult is highly recommended for every case**. Many cases will also warrant cardiac surgery evaluation for valve replacement, and other specialty consultation for metastatic sites of infection.
- Cerebral complications are the most frequent and most serious extracardiac complications.
- Common aetiologies include *S. aureus*, *Enterococcus spp*., Viridans streptococci, CoNS
  - Rarely HACEK organisms, *Enterobacterales*, and fungal.
- Risk factors: male gender, prosthetic valve, intracardiac device, unrepaired cyanotic congenital heart disease, history of IE, chronic rheumatic heart disease, age-related degenerative valvular lesions, haemodialysis, diabetes, HIV, and persons who inject drugs (PWID).
- If IE is suspected, the priority is **immediately collecting at least 2, ideally 3, blood cultures** from two different sites, and THEN starting empiric antibiotics. 2-3 sets of cultures should be repeated 12-24 hours later, and during active fever to increase yield. If blood culture bottles are unavailable, do not withhold antibiotics in patients with acute IE. If subacute presentation and supplies will be available within 24 hours, can hold antibiotics until culture.

Diagnosis

- Diagnosis of IE is based on Modified Duke Criteria as below. However, many patients with acute IE do not meet these specific definitions.
- <u>Definite IE</u>
  - Clinical criteria: 2 major Duke criteria **OR** 1 major and 3 minor **OR** 5 minor
  - Pathologic criteria: microorganisms on culture or histology of vegetation, embolized vegetation, or intracardiac abscess specimen
  - Evidence of IE found at surgery or autopsy (after antibiotic therapy for at least 4 days).

- <u>Possible IE</u>: 1 major and 1 minor **OR** 3 minor
- <u>Rejected IE</u>**:**
  - Resolution within <4 days antibiotics
  - Alternative diagnosis is made
- **Modified Duke Criteria**
  - **Pathological Criteria**

  Positive histology or culture from pathological material obtained at autopsy or cardiac surgery.

Clinical Criteria

Major Criteria

Blood culture criteria

- *S. aureus, S. gallolyticus* (*S. bovis* biotype 1), Viridans Streptococci, *Enterococcus spp*. , or HACEK organisms from at least 2 separately collected blood cultures, in the absence of alternate focus
- Other microorganisms in at least 2 sets of blood cultures drawn ≥12 hours apart **OR** 3 of 3 sets **OR** majority of ≥4 sets drawn ≥1hr apart
- Single positive blood culture for *Coxeilla burnetii* **OR** anti-phase 1 IgG titer >1:800

Endocardial involvement (from TTE or TOE)

- Oscillating intracardiac mass on valve or supporting structures, in path of regurgitant jet, or on implanted material without alternate cause **OR** abscess **OR** prosthetic valve dehiscence **OR** new regurgitation

Minor Criteria

- Fever
- Predisposing factors (i.e., PWID, predisposing heart condition)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, positive rheumatoid factor
- Microbiological evidence: positive blood culture that does not mean major criteria OR serological evidence of active infection with organism consistent with IE

Lab Evaluation

- **Immediately collect at least 2, ideally 3, sets of blood cultures** from different sites at first suspicion of IE. 2-3 sets of cultures should be repeated 12-24 hours later, and during active fevers to increase yield. Once the diagnosis is established, repeat blood cultures every 24-48 hours until negative.
- Subacute bacterial endocarditis is more likely to cause vascular and immune phenomena, including positive rheumatoid factor (RF) and glomerulonephritis. RF and UA can be useful in this setting if diagnosis is not certain based on other Duke criteria.
- Elevated ESR, CRP, and WBC are suggestive of systemic inflammation or infection.
- See culture negative IE section below also.

Physical Examination

- In addition to a complete standard physical examination, look specifically for cardiac murmurs, signs of CVA, visual acuity, ophthalmic complications, signs of septic pulmonary emboli, back or joint tenderness consistent with osteo-discitis or septic arthritis, Janeway lesions, Osler nodes, Roth spots, and poor dentition.

Cardiac Evaluation

- All patients with suspected IE need TTE for diagnosis and to evaluate for abscess, valvular complications, and embolic potential. Specificity of TTE and TOE is similar. False negative TTE and TOE are possible if a vegetation is small or has already embolized. The first TTE or TOE should be done within 12 hours of suspicion for IE.

- TOE should be pursued in patients with high suspicion of endocarditis not responding to treatment if TTE negative.
- TTE is not adequate to evaluate for left-sided valvular and peri-valvular complications and for left sided prosthetic valves. TOE is needed for all patients with permanent pacemaker (PPM) or implanted cardioverter device (ICD).
- TTE should still be done even if TOE is planned, because TTE can be used for comparison of post-treatment TTE.
- The decision to obtain TTE, TOE, or both can be complex. Discuss with ID and Cardiology if assistance is needed.
- All patients with suspected IE need an ECG to assess for conduction abnormalities. Conduction abnormalities such as AV block may signify periaortic abscess.
- Echocardiogram should be repeated at the end of therapy to establish a new baseline.

Evaluation for Metastatic Sites of Infection

- Metastatic sites of infection are common and lead to significant morbidity and mortality, especially in *S. aureus* IE. Evaluation for metastatic sites should be aggressively pursued.
- In right-sided IE this includes chest CT, only if presence of septic pulmonary emboli would help confirm diagnosis of IE or would alter treatment.
- In left-sided IE, imaging necessary is based on 1) suspicion for specific metastatic sites of infection and 2) pre-operative imaging needs. All patients with back pain (even mild and chronic) should have MRI spine. Patients with vision change need ophthalmologic examination. Other commonly needed imaging studies include abdominal CT for splenic abscess and MRI/MRA brain for cerebral septic emboli and mycotic aneurysm.

Culture Negative Endocarditis

- Classic culture negative IE is due to fastidious or intracellular organisms such as *Bartonella henselae, Brucella spp., Coxiella burnetii, T. whippelii*, and the HACEK group.
    - However, most 'culture negative' IE is due to receipt of antibiotics before blood cultures are collected. Always check medication records to see if any antibiotics were given. Even one dose within the previous 2 weeks can compromise chances of recovery for certain pathogens.
    - Remember also that non-infectious endocarditis exists. Libman-Sacks and non-bacterial thrombotic (or 'marantic') endocarditis should be considered in the differential diagnosis of endocardial lesions in the absence of positive cultures or symptoms consistent with infection.
- Blood cultures should be held by the lab for greater than 5 days if concern for HACEK group organisms given the difficulty in isolation.
- Molecular and serologic tests can aid in the diagnosis of other fastidious causes of IE, but epidemiologic factors should be considered before ordering.
- If valve excision is done, tissue should be examined for organisms by histopathologist. Special stains may be needed depending on suspected organism.

Treatment: Native Valve Endocarditis

- If patient has signs of systemic infection with suspicion for Gram-positive BSI or IE as a cause, it is appropriate to treat with **Vancomycin 15-20 mg/kg per dose** (dosing should be based on renal function). This is because most cases of IE at UTH are enterococcal or streptococcal species.

- If source is unclear and patient is hemodynamically unstable, refer to Severe Sepsis/Septic Shock guidelines.
- Treatment should be reviewed after 72 hours with a possibility of de-escalation based on isolated pathogens and susceptibility results.
- Repeat blood cultures daily until they have cleared. If blood culture bottles are in short supply, repeat cultures after 72 hours of therapy to assess for clearance.
- 'Day 1' of antibiotic course is the first day of negative blood cultures or day of valve replacement (if done), whichever is later.
- MSSA
  - First line: cloxacillin 2g IV q4h for at least 6 weeks
  - Beta-lactams are highly preferred over vancomycin.
- MRSA or CoNS
  - First line: vancomycin IV 15 mg/kg every 12 hours for at least 6 weeks
  - Alternative ONLY if vancomycin unavailable: linezolid 600 mg PO q12h.
  - Long-term linezolid use (>28 days) is limited by toxicities including thrombocytopenia, optic neuritis, and peripheral neuropathy.
- Viridans streptococci or *S. gallolyticus* (*S. bovis* biotype 1) with penicillin MIC ≤0.12 mcg/mL
  - First line: penicillin 3 million units IV q4h OR ceftriaxone 2g IV q24h for 4 weeks.
- Viridans streptococci or *S. gallolyticus* with penicillin MIC 0.12 to 0.5 mcg/mL
  - First line: penicillin 4 million units IV q4h for 4 weeks PLUS gentamicin 3 mg/kg IV q24h for the first 2 weeks of therapy, OR ceftriaxone 2g IV 24h alone
  - Severe penicillin allergy only: vancomycin 15 mg/kg IV every 12 hours
- *Enterococcus spp.,* viridans streptococci with penicillin MIC >0.5 mcg/mL or unknown MIC, and nutritionally variant Streptococcus (NVS- *Abiotrophia defectiva* and *Granulicatella adiacens*)
  - First line: ampicillin 2g IV q4h PLUS ceftriaxone 2g IV q12h for 6 weeks OR ampicillin 2g IV q4h PLUS gentamicin 1 mg/kg IV q8h for 6 weeks (ceftriaxone regimen preferred in older patients or patients at high risk of nephrotoxicity).
- **Other organisms: Consult ID for treatment recommendations**

Treatment: Prosthetic Valve Endocarditis

- Empiric therapy: vancomycin 15 to 20 mg/kg per dose plus gentamicin 1 mg/kg IV q8h plus rifampicin 300-600 mg q12h PO/IV (or rifabutin 300mg PO q8h).
- Medical treatment alone is rarely sufficient. See 'When to consider valve surgery.'
- 'Day 1' of antibiotic course is day of valve replacement (if done) or first day of negative blood cultures, whichever is later.
- MSSA
  - First line: cloxacillin 2g IV q4h PLUS rifabutin 300mg PO q8h for at least 6 weeks PLUS gentamicin 1 mg/kg IV q8h for the first 2 weeks
    - Beta-lactams are highly preferred over vancomycin
- MRSA or CoNS:
  - First line: vancomycin PLUS rifabutin 300mg PO q8h for at least 6 weeks AND gentamicin 1 mg/kg IV q8h for the first 2 weeks
  - Alternative if vancomycin unavailable: linezolid 600 mg PO q12h (maintain the gentamicin and rifabutin). These are second line options and should be changed to vancomycin as soon as supply is available.

- Cardiovascular implantable electronic device (CIED) infections affect PPM (permanent pacemaker) or ICD (implantable cardiac device) at generator pocket and/or along leads and can progress to involve cardiac valves and distant sites.
- Risk factors: diabetes, heart failure, recent replacement of device, renal dysfunction, long-term corticosteroid use, oral anticoagulant use, presence of 2 or more pacing leads, fever in 24 hours preceding implantation, use of pre-procedural temporary pacing, and early re-intervention.
- Bacteraemia, pain over generator pocket, redness/swelling over generator pocket, erosion of generator pocket, and/or fever should raise suspicion for CIED infection.
- Any patient with *S. aureus* bacteraemia who has a CIED has ~50% risk of device infection; rates are lower but not well defined for other pathogens.
- Common organisms: CoNS and *S. aureus*. Infection with other skin flora, GNR, and *Candida spp*. occur much less commonly.
- Consult ID early for assistance with diagnosis and management.

Diagnostic Evaluation

- Management depends on accurate diagnosis of extent of CIED and valve involvement.
    - All patients must have at least 2 **blood cultures** obtained **before antibiotics**, even if patient appears to have localized pocket infection.
    - Patients with bacteremia or negative blood cultures that were collected after even a single dose of antibiotics was given must have a **TOE**. TOE can show lead and valve vegetation.
- CT is sometimes used in patients with contraindication to TOE. It cannot be relied upon to exclude infection. May also help distinguish superficial from pocket infection.
- Do NOT aspirate a CIED pocket, as this can introduce infection.
- If a CIED is explanted, generator, leads, and tissue from pocket (not a swab) should be sent to microbiology for culture. In a pocket infection, a positive lead culture with negative blood cultures may not indicate infection of lead since leads are extracted through the pocket.
- Obtain repeat blood cultures after device is extracted to evaluate clearance.

Definitions

- Cellulitis or surgical site infection (SSI) over pocket: clinical signs of superficial infection overlying pocket, with negative blood cultures.
- Pocket infection: clinical signs of infection at pocket site or positive cultures from pocket when device explanted. Blood cultures are negative.
- Bacteraemia in setting of CIED: positive blood cultures but TOE does not show lead or valve vegetation, and cultures of explanted device (if removed) are negative.
- Lead infection (also called CIED related endocarditis): bacteraemia, and lead vegetation seen on TOE or lead cultures from explanted device are positive.
- Endocarditis: bacteraemia and valve vegetation seen on TOE.
- Complicated infection: any metastatic site of infection (e.g., osteomyelitis).

Treatment

- Empiric antibiotics: vancomycin
    - Alternative if vancomycin unavailable: linezolid 600 mg PO q12h.
- Definitive antibiotics: Adjust based on culture and susceptibilities.

- Device removal: Entire CIED (generator and leads) must be removed in proven or presumed pocket infection, lead infection, and endocarditis.
  - *S. aureus* bacteraemia in setting of CIED usually warrants CIED removal, especially if no alternate source is identified. BSI with other pathogens warrants consideration for CIED removal.
  - Superficial infection overlying pocket does not require CIED removal.
  - **Patients with contraindications to CIED removal require long-term suppressive antibiotics.**
- Antibiotic duration and timing of re-implantation: see table below
- CIED is usually re-implanted on contralateral side. Epicardial leads have lower rates of infection and are sometimes used after CIED infection to decrease risk of recurrence.

TIMING OF CIED REIMPLANTATION AND DURATION OF ANTIBIOTICS

Site of infection	When to re-implant CIED	Antibiotic route, duration
Overlying pocket	N/A	IV/PO, 7-10 days
Pocket	Blood cultures negative for ≥ 72 hours following CIED explantation and adequate debridement of pocket	IV/PO, 7-10 days if device erosion without inflammation IV/PO, 10-14 days all others
Bacteremia in setting of CIED	Blood cultures negative for ≥ 72 hours following CIED explantation	IV, 4 weeks for *S. aureus* IV, 2 weeks for all others
Lead	Blood cultures negative for ≥ 72 hours following CIED explantation	IV, 4 weeks
Endocarditis	Blood cultures negative for ≥ 14 days following CIED explantation	Treat per endocarditis guidelines
Complicated	Blood cultures negative for ≥ 72 hours following CIED explantation and source control of other infection achieved	Treat according to both site of CIED infection and site of metastatic infection

Prevention

- Perioperative anti-staphylococcal antibiotics at time of CIED placement (see surgical prophylaxis section., p.24). Postoperative antibiotics not recommended.
- Antibiotic prophylaxis for dental or other invasive procedures not recommended.

Resources

- AHA Guidelines on ICD Infections. Baddour LM. Circulation 2010; 121:458-477.
- PET/CT for diagnosis. Sarrazin JF. .J Am Coll Cardiol 2012;59(18):1616-1625.

Rheumatic Fever

Acute Rheumatic Fever

Clinical pearls

Non-suppurative immunologic sequelae 2-4 weeks after group A streptococcal pharyngitis.

Diagnosis

Revised Jones criteria:

There must be evidence of recent strep infection plus 2 major criteria, or 1 major + 2 minor criteria.

- **Evidence of group A beta-haemolytic streptococcal infection:**
  - Positive throat culture (but this is usually negative by the time symptoms of rheumatic fever appear)
  - Rapid streptococcal antigen test positive
  - Elevated or rising streptococcal antibody titre (e.g., ASO or DNase B titre)
  - Recent scarlet fever
- **Major Criteria:**
  - Carditis
  - Migratory large joint polyarthritis
  - Chorea
  - Subcutaneous nodules
  - Erythema marginatum
- **Minor Criteria**
  - Fever
  - Raised ESR or CRP
  - Arthralgia
  - Prolonged PR interval
  - Previous rheumatic fever

Treatment

- **Primary Regimens**
  - Relief of symptoms (fever, arthritis, arthralgia):
    - Aspirin 80-100 mg/kg/day (paediatric), 4-8 gm/day (adult)
    - May add prednisone 2 mg/kg po q24h
    - Cochrane review found no evidence of benefit of corticosteroids or IVIG compared to aspirin
  - Eradication of group A streptococcus:
    - Child: penicillin V 250 mg po tid x 10 days
    - Adult: penicillin V 500 mg po tid x 10 days

- **Alternative Regimens**
  - Eradication of group A streptococcus

    Child:
    - Benzathine penicillin G
      - Wt. > 27 kg: 1,200,000 units IM x 1 dose
      - Wt.< 27 kg: 600,000 units IM x1
    - Cephalexin 25-50 mg/kg/day po in 2-4 divided doses x 10 days
    - Azithromycin 10 mg/kg (max dose 500 mg) po day 1, then 5 mg/kg (max dose 250 mg) po q24h for days 2-5

    Adult:
    - Benzathine penicillin G 1.2 million units IM x1
    - Cephalexin 500 mg po bid x 10 days

- Azithromycin 500 mg po x 3 days

- **Secondary Prophylaxis**
  - Is indicated for previous documented rheumatic fever or those with rheumatic heart disease, specifically mitral stenosis.
  - Penicillin V250mg/12h PO. Alternatives: sulfadiazine 1g daily (0.5g if <30kg) or erythromycin 250mg twice daily (if penicillin allergic).
  - **Duration:**
    - If carditis + persistent valvular disease, continue at least until age of 40 (sometimes lifelong).
    - If carditis but no valvular disease, continue for 10 years.
    - If there is no carditis, 5 years prophylaxis (until age of 21) is sufficient.

Resources

- Anti-inflammatory treatment for carditis in acute rheumatic fever. Cilliers A, Adler AJ, Saloojee H. Cochrane Database Syst Rev. 2015 May 28;(5):CD003176.
- Acute rheumatic fever. Carapetis JR, McDonald M, Wilson NJ. Lancet. 2005 Jul 9-15;366(9480):155-68.
- The spectrum of group A streptococcal joint pathology in the acute care setting Mignemi ME, Martus JE, Bracikowski AC, Lovejoy SA, Mencio GA, Schoenecker JG.. Pediatr Emerg Care. 2012 Nov;28(11): 1185-9.

Myocarditis

Clinical pearls

- Myocarditis is an inflammatory disease of the myocardium
- Presents as acute, subacute, and chronic myocarditis.
- Clinical manifestation is highly variable from subclinical disease to fatigue, chest pain, heart failure, cardiogenic shock, arrhythmias, and sudden death.
- Caused by both infectious and noninfectious like cardiotoxins (alcohol), hypersensitivity reactions, systemic disorders, autoimmune causes, and radiation.
- Common pathogens
  - Viral (most common cause; lymphocytic myocarditis): HIV, HHV6, hepatitis B/C, parvovirus, adenovirus, mumps, varicella zoster, vaccinia (smallpox vaccine), CMV, EBV, etc.
  - Bacterial: Streptococcus spp., Staphylococcus spp., Haemophilus influenzae, Legionella spp., chlamydia spp. , diphtheria, Neisseria spp. , Mycobacterium spp.
  - Fungal: candidiasis, cryptococcosis, blastomycosis
  - Parasites: Plasmodium spp., Trypanosoma rhodesiense, Entamoeba histolytica, Toxoplasma gondii, Leishmania spp., Echinococcus spp., Ascariasis lumbricoides, filariasis, Schistosoma spp.
  - Others: Treponema pallidum (syphilis), Leptospia spp., Norcardia spp., Coxiella burnettii (Q-fever)
- Mostly is caused by viruses and does not warrant a viral panel evaluation unless it will change the course of patient care.

Diagnosis

Based on combination of clinical presentation and noninvasive diagnostic findings

- Typical symptoms include the following:
  - Excessive fatigue, chest pain, S3, S4, or summation gallop
  - New onset or worsening heart failure
  - Cardiogenic shock, acute pericarditis, sudden cardiac death
  - Unexplained sinus tachycardia, atrial or ventricular arrhythmia, partial or complete heart block, new-onset bundle branch block
  - Abnormal TTE/TOE
  - New cardiomegaly on chest x-ray
  - Rise in cardiac biomarkers (cTnI), ECG changes of AMI, arrhythmias, pericarditis, or abnormal cardiac function on Echo: with/without cardiac signs/symptoms
  - Unexplained cardiac abnormalities: HF, cardiogenic shock, arrhythmias
  - LV systolic dysfunction without apparent aetiology
  - AMI in patients with no cardiovascular risk factors and normal angiogram
  - with/without history of viral infection, rash, eosinophilia, history of new drug use or vaccine
- Histological types: lymphocytic myocarditis (viral), eosinophilic myocarditis (malignancy, parasites, hypersensitivity reactions), giant cell myocarditis (autoimmune), cardiac sarcoidosis
- Lab testing
  - Blood, urine cultures: usually normal
  - Viral panel if identification of the virus will alter management of patient
  - Cardiac biomarkers: cTnI, BNP/Pro NT-BNP
    Endomyocardial biopsy: Dallas criteria (histology, immunohistochemical, and detection of viral genomes by molecular techniques-PCR).
- Imaging
  - CXR: normal or enlarged cardiac shadow
  - ECG: nonspecific ST segment changes
    TTE/TOE: diffuse or regional wall motion abnormalities
  - Cardiac magnetic resonance

Treatment

- Lymphocytic myocarditis: consult ID for treatment plan.

Monitoring & Follow-up

- Clinical examination for persistent or recurring S3 or S4 gallop
- Cardiac biomarker, ECG, TTE/TOE
- Call ID when infectious cause is suspected, and patient is not improving with standard myocarditis therapy.
- Vaccination against rubella, measles, mumps, influenza, and poliomyelitis prevents myocarditis caused by these viruses.

Resources

- IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER, File TM Jr; Infectious Diseases Society of America. Clin Infect Dis. 2012 Apr;54(8): e72-e112.

- Clinical manifestations and diagnosis of myocarditis in adults. Cooper LT Jr. UpToDate 2018

Pericarditis

The principal manifestations of pericardial disease are pericarditis (acute, subacute, or chronic fibrinous process) and pericardial effusion, as well as long-term complications such as cardiac tamponade and constrictive pericarditis.

Clinical pearls

- Pericarditis can be caused by infections, radiation, post cardiac injury syndrome, drugs and toxins, metabolic diseases, malignancy, collagen vascular disease and idiopathic.
- The most common causes are MTB, neoplasia, nontuberculous infection, and collagen vascular disease.
- Idiopathic pericarditis is frequently presumed to be viral.

Risk factors for purulent pericarditis

- Immunosuppression (e.g., HIV)
- Alcohol abuse
- Chest trauma
- Malignancy
- Chronic kidney disease
- Primary infections such as pneumonia and endocarditis

Common pathogens

- Any infectious organism can infect the pericardium and the infection can be confined to the pericardium but sometimes can be extrapericardial.
- Common infectious causes include:
  - **Viral**: HIV, coxsackie virus (types A and B), echovirus, herpes viruses (HSV 1, HSV 2, VZV, EBV, CMV, VZV, HHV6, HHV-7, HHV-8.
  - **Bacterial**: *Staphylococcus spp., Streptococcus spp, Haemophilus spp*., and *M. tuberculosis*.
  - F**ungal**: Histoplasma in immunocompetent patients; *Aspergillus spp., Candida spp*., and *Coccidioides immitis* in immunocompromised patients.
- Others include:
  - *Rickettsia rickettsii, Chlamydia psittaci, Borrelia burgdorferi, Treponema pallidum, Tropheryma whippelii, Actinomyes spp., Ureaplasma spp., Nocardia spp*. and *Mycoplasma pneumoniae/hominis*.

Diagnosis

- Pericardial disease can present as "dry" pericarditis or with pericardial effusion.
- Presents in four ways: acute and recurrent pericarditis, pericardial effusion without major hemodynamic compromise, cardiac tamponade, constrictive pericarditis.
- Usual symptoms/signs: cough, dyspnea, chest pain (usually pleuritic), pericardial friction rub/knock, distant heart sounds, elevated jugular venous pressure (JVP), tachycardia, fever, night sweats.
- Pericardial fluid: hemorrhagic or serous effusions
  - Serous effusion: normal pericardial cavity contains 15-50mL of serous fluid. Serous effusions exceed 50mL
  - Purulent pericarditis: gross pus in the pericardium or microscopic purulence (>20 wbc/hpf)

- Hemorrhagic: Malignancy or tuberculosis in areas in with high risk of TB infection.

- **A triad of pleuritic pain, pericardial rub and widespread ST segment elevation on ECG is diagnostic of acute pericarditis.**

Lab testing

- Obtain pericardial fluid if present and safe to do so; othwerwise aim diagnostic evaluation at most likely causes of pericarditis.
- Pericardial fluid analysis: aerobic culture, microscopy, gram stain, acid fast stain and culture, Xpert MTB/RIF, adenosine deaminase, fungal stain, cytology, and biochemistry.
- Protein concentration is high and glucose levels are less than 35 mg/dL (2 mmol/L).
- Pericardial fluid leukocyte counts generally are elevated: 6000 -240,000/µl.
- Pericardial tissue biopsy: detection of tubercle bacilli or caseating granulomata is consistent with TB
- ECG: widespread ST segment elevation

Imaging

- TTE/TOE: may demonstrate presence of pericardial effusion
- CXR: may show cardiomegaly, pulmonary infiltrates, pleural effusions, mediastinal widening
- MRI: pericardial thickening and effusion

Treatment

- Treatment for purulent pericarditis consists of pericardial drainage and antimicrobial therapy
- Immunosuppressed patients / healthcare setting include coverage for both gram-positive and gram-negative bacterial pathogens
- Preferred:
  - Preferred Regimen: vancomycin (30 mg/kg) plus ceftriaxone (2 g IVq24h) plus fluconazole (200 to 400 mg IVq24h)
  - Alternative Regimen: vancomycin (30 mg/kg) plus piperacillin-tazobactam (4.5 g q6h or ampicillin-sulbactam (3 g IV q6h) plus fluconazole (200 to 400 mg IVq24h)
  - If MSSA is recovered from cultures of the blood/pericardial fluid, de-escalate to nafcillin or oxacillin (2 g IVq4)
  - Abx regimen in case of beta-lactam allergy: vancomycin
  - TB pericarditis: anti-tuberculous therapy
- Duration of therapy: usually 2-4 weeks of therapy
  - Therapy should be continued until fever and clinical signs of infection have resolved and until the white blood cell count is normal
- Adjunct therapy
  - Pericardial drainage or pericardiotomy in large pericardial effusion, hemodynamically significant pericardial effusion, suspicion of a bacterial or neoplastic aetiology, or evidence of constrictive pericarditis
  - NSAIDS and colchicine are the mainstay of treatment irrespective of the aetiology
  - Glucocorticoids (prednisolone 0.5-1 mg/kg/day) when refractory to NSAIDs /colchicine and NSAID contraindications and in tuberculous pericarditis
  - Specific cause for the pericarditis has been excluded before steroids use
  - Most cases of acute pericarditis in immunocompetent patients are due to viral infection or idiopathic are treated presumptively with NSAIDS and colchicine

Monitoring & Follow-up

- Monitoring: CRP levels, Echo
- ID should be involved as soon as pericarditis is suspected

Resources

- IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER, File TM Jr; Infectious Diseases Society of America. Clin Infect Dis. 2012 Apr;54(8):e72-e112.
- Clinical manifestations and diagnosis of myocarditis in adults. Cooper LT Jr. UpToDate 2018

Central Nervous System Infections

Central Nervous System

Overview

Symptoms of central nervous system (CNS) infections overlap significantly. Distinguishing the exact site of CNS infection will guide empiric treatment, based on common pathogens for each site.

- Meningitis – inflammation of the meninges
  - Subdural empyema – focal collection of purulence in subdural space; sequelae of meningitis
- Encephalitis – inflammation that is inside the brain, diffuse process.
- Meningoencephalitis – inflammation of the meninges and the brain.
- Brain abscess – organized stage of focal necrosis surrounded by fibrotic capsule
  - Cerebritis – focal inflammation in the brain that precedes brain abscess

Meningitis and Encephalitis distinction

- Meningitis is characterized by fever, altered mental status (often depressed mental status), neck stiffness, and new headache
- Encephalitis is characterized by fever, altered mental status (often confused, cognitive deficits, or bizarre behaviour), focal neurological signs, and/or seizures

Meningitis

Clinical pearls

- Common isolated pathogens at UTH include gram-negatives (e.g., *E. coli, Klebsiella spp., Pseudomonas spp., Acinetobacter spp*.) largely in neonatal population. Common pathogens in adults at UTH include Cryptococcus neoformans and Mycobacterium tuberculosis, in addition to common pathogens below.
- Bacteria
  - 2-50 years: *Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*
  - >50 years and immunocompromised: *Streptococcus pneumoniae*, *Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes*
  - Post neurosurgical and penetrating trauma: Streptococcus pneumoniae (if CSF leak), *Staphylococcus aureus*, CoNS, *Cutibacterium acnes* (formerly *Propionibacterium acnes*), *Enterobacterales* (e.g., *E. coli, Klebsiella spp*.), *Pseudomonas spp., Acinetobacter spp*.
  - Basilar skull fracture: *Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes* (group A strep)
  - *Mycobacterium tuberculosis*
  - Others include spirochetes (*Treponema pallidum, Borrelia burgdorferi), Nocardia spp. Actinomyces spp.*
- Viruses - Enterovirus group, HSV-2 (aseptic and Mollaret's meningitis), HSV-1 (rare, usually causes encephalitis), HIV, mumps
- Fungi – *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Candida spp.*
- Parasites – *Plasmodium species, Toxoplasma gondii* (more encephalitic), amoeba, helminths
- Noninfectious – drug induced (e.g., TMP/SMX, isoniazid, NSAIDs, IVIG), malignancy, connective tissue disease
- Test for HIV in all patients of unknown status presenting with meningitis

Pathogenesis

- Infectious organisms gain entry to the subarachnoid space and cerebrospinal fluid (CSF): Most commonly by bacteraemia, gaining entry through the large venous channels; alternatively, by nasopharyngeal spread through a CSF leak caused by a cribriform plate defect or basilar skull fracture; or direct spread from a brain abscess or air sinus infection.
- Rapid growth occurs in the CSF because the blood-brain barrier blocks entry of immunoglobulins and complement. Inflammation damages the blood-brain barrier, increasing permeability, allowing entry of serum protein, and impairing glucose transport**.** Progressive cerebral oedema, increased CSF pressure, and decreased cerebral blood flow lead to irreversible ischemic damage.

Diagnosis

- Fever, neck stiffness, altered mental status, and new headache should raise suspicion for meningitis, though only 44% of patients with bacterial meningitis have the first three. Most will have at least two out of these four signs/symptoms. Supporting features are photophobia, vomiting, blanching or purpuric rash (in *N. meningitides*).
- Lumbar puncture (LP) should be performed in all patients if safe.
    - LP is contraindicated in severe cardiorespiratory compromise, evidence of abnormal bleeding, or skin infection directly over lumbar puncture site.
    - In patients with suspected TB meningitis, intracranial pressure may be elevated and thus imaging should be done first to ensure LP is safe.
- CT should be performed prior to LP for patients >60 years old, immunocompromised, history of CNS disease (including CVA), seizures in preceding week, focal neurological deficits (such as hemiparesis or dysphagia), depressed mental status, or papilloedema, or suspected TB meningitis due to risk of LP causing herniation from elevated intracranial pressure.
    - If CT is consistent with possible increased intracranial pressure, do not proceed with LP **(unless cryptococcal meningitis (CM) is suspected, as LP should be done in setting of CM with elevated intracranial pressure).**
    - If CT excludes findings consistent with increased intracranial pressure, proceed with LP.
    - If CT is not available, decision to perform LP versus start antibiotics without LP should be based on assessment of risks and benefits of both. ALL cases discuss with neurology and/or ID. If no LP is performed, obtain blood culture.
- Obtain CSF for cell counts, CSF culture (includes Gram stain and aerobic culture), protein, glucose, and HSV PCR (pending availability). Obtain blood culture in all patients. Additional studies should be based on patient risk factors (e.g., AFB culture and smear and GeneXpert if TB risk factors present, CSF Cryptococcal Ag in HIV, etc.
- If encephalitis is being considered, send CSF studies to evaluate for encephalitis also (see encephalitis section).
- Bacterial meningitis is suggested in the presence of:
    - More than 90% polymorphonuclear leukocytes (except with Listeria)
    - Elevated CSF protein (usually 150–1000 mg/dL)
    - Low CSF glucose [less than two-thirds of the serum value (less than 25 mg/dL is prognostic of poor outcome)].
    - When performed before the initiation of antibiotics, Gram stain of CSF is positive in more than 75% of cases (except 25% with Listeria).
    - Blood and CSF cultures allow for antibiotic sensitivity testing.

- Evaluation and institution of antibiotic therapy should occur within 30 minutes if bacterial meningitis is being strongly considered. In cases in which a focal neurologic deficit is evident or papilledema is found, empiric antibiotic therapy should be instituted before sending the patient for CT scan.

Treatment

- Antibiotics should be given within 30 minutes if bacterial meningitis is suspected. Maximal doses of antibiotics must be given because of limited passage through the blood-brain barrier.
- Each hour delay in administering antibiotics is associated with 12.6% increase in mortality
- **DO NOT WAIT FOR CT SCAN OR LP RESULTS TO INITIATE ANTIMICROBIALS; IF LP MUST BE DELAYED, OBTAIN BLOOD CULTURES (if available) AND START THERAPY IMMEDIATELY.**
- **All patients should be isolated until after 48 hours of initiation of antibiotics.**

Empiric Antibiotics

- Vancomycin 25mg/kg loading dose followed by 15 mg/kg q8-12h, ceftriaxone 2g IVq12h and acyclovir 10 mg/kg Ideal body weight IVq8h
- Meropenem 2g IV8h or imipenem 500mg q6h or 1g q8h
    - Add acyclovir 10 mg/kg Ideal body weight IVq8h if suspicion for HSV encephalitis
    - Post neurosurgery or penetrating trauma: use meropenem 2g IVq8h or imipenem 500mg IVq6h or 1g q8h plus aminoglycoside (amikacin) if *Acinetobacter spp*. suspected
    - Age >50, alcohol abuse, or immunocompromised: add ampicillin 2g IVq4h to cover *Listeria monocytogenes*
    - Consider dexamethasone 10mg IVq6h (with first dose of antibiotics) if suspicion for *S. pneumoniae*. Antibiotics should not be delayed to give dexamethasone.
    - Review antibiotics in 72 hours de-escalate based on sensitivities. Stop empiric antibacterial coverage if CM or TB is confirmed.
    - **Severe penicillin allergy:** vancomycin + levofloxacin 750mg OD +/- TMP/SMX 5 mg/kg IVq8h
    - Aminoglycosides, erythromycin, clindamycin, tetracyclines, and first-generation cephalosporins should not be used to treat meningitis, because these drugs do not cross the blood-brain barrier.

Definitive Antibiotics and Duration

- Based on pathogens isolated and susceptibility results:
- *Streptococcus pneumoniae*:
    - Penicillin G 2.4 million IU or ampicillin 500 IV q6h if penicillin MIC < 0.1. µg/ml
    - Ceftriaxone 2g IVq12h if penicillin MIC 0.1-1.0 µg/ml (or unknown)
    - Add vancomycin if ceftriaxone MIC >1 µg/ml
    - Treat for 10-14 days
    - Dexamethasone 10 mg IV q6h x 4 days should be continued only if blood/CSF grows *S. pneumoniae.*
- *Neisseria meningitides*: ceftriaxone 2g iv 12-BD for 7 days.
    - Chemoprophylaxis is indicated for close contacts of patients with *N. meninigitidis* (household contacts, contact with respiratory secretions, etc.). Drug of choice is ciprofloxacin 500mg once.
- *Haemophilus influenzae*: ceftriaxone 2g IVq12h for 7 days.
- MSSA: cloxacillin 2g IVq4h (do NOT use cefazolin due to poor CNS penetration)

- MRSA and CoNS: vancomycin (consult pharmacy for dosing) for 10-14 days
- *Listeria monocytogenes*: ampicillin 2g IVq4h for 21 days
- *Streptococcus agalactiae*: ampicillin for 2g Ivq4h for 14 days
- *Pseudomonas spp.*: meropenem 2g IVq8h for 21 days
- *Cryptococcus spp*.: Refer to Zambia National HIV Guidelines and World Health Organisation guidelines cyptococcal meningitis guidelines. if HIV negative, anti-fungal treatment is longer.
- Tuberculosis: Standard fixed four drug combination for at least 2 months, then INH/RIF only for 7-10 more months for susceptible organisms. Add dexamethasone – see details in brain lesions section (page 49).
- Droplet isolation (Face mask, gowns, and gloves) is ideal empirically. Once *N. meningitides* and *H. influenza* are ruled out, only standard precautions are needed.

Consider Infectious Disease Consult if:

- Failure to improve in 48-72 hours
- Suspected atypical infection based on history
- Resistant pathogen detected
- Tuberculous meningitis suspected

Adjuvant Therapies

- Dexamethasone is indicated in children with *Haemophilus influenza*. Evidence from Malawi suggests no additional benefit of glucocorticoids in adults being treated for acute bacterial meningitis (ABM).
- Other supportive measures include maintenance of ventilation, careful rehydration with at least 2L of fluids in the first 24hours.
- It is also imperative to maintain normal blood pressure, glycaemic control, urine output, electrolyte balance and thermoregulation. Anti-seizure medication is indicated after the first seizure.

Complications

- Mortality remains high in patients with bacterial meningitis. *L. monocytogenes* is associated with the highest mortality, 26%; followed by *S. pneumoniae*, 19%; and *N. meningitidis*, 13% mortality.
- *H. influenzae* meningitis tends to be less severe, associated with an average mortality of 3%.
- Mortality is higher in very young and elderly individuals.
- Neurologic sequelae in surviving patients are common. The young patient whose brain is developing often suffers from intellectual disability, hearing loss, seizure disorders, or cerebral palsy.
- Older patients may develop hydrocephalus, cerebellar dysfunction, paresis, a seizure disorder, and hearing loss.

Tuberculous meningitis (TBM)

Clinical pearls

- TBM now accounts for 8-44% of all cases of meningitis in sub-Saharan Africa (SSA) depending on the local HIV and TB prevalence
- It usually develops during miliary tuberculosis; however, no pulmonary disease is evident in 25% of cases
- Risk factors include HIV, exposure to person with pulmonary TB, travel to high TB prevalence areas
- Tuberculous Meningitis is clinically similar to other forms of meningitis. HIV-infected persons and children are at highest risk.
- Presentation: subacute or chronic lethargy, fever, seizures, change in mental status, and confusion.
- Advancing infection - Deficits of the third, fourth, and sixth cranial nerves are common, focal deficits, and non-communicating hydrocephalus a possibility. Development of coma is a poor prognostic sign.

Diagnosis

- Culture should use large volumes of CSF; smear for AFB is positive in only one-third of cases; Gene Xpert in CSF is a more sensitive test.
- CSF profile classically lymphocytic-mononuclear pleocytosis (10-500 cells/mm^3), CSF proteins 100-500mg/dL range, CSF glucose approx. < 45mg/dL
- CSF adenosine deaminase (ADA) has a sensitivity of 60-80%, specificity 90-100%
- CT head: tuberculomas are discrete, ring-enhancing lesions of the brain with perilesional edema that may be single or multiple.

Treatment

- Empiric treatment should not be delayed due to high mortality
- Treatment entails standard fixed four drug combination for drug sensitive TB for a period of initial 2 months intensive phase
    - Isoniazid (INH) 300mg PO daily or 5mg/kg (administer with pyridoxine 50mg daily)
    - Rifampicin 600mg PO daily (approx. 10mg/kg)
    - Pyrazinamide 1500-200mg PO daily or 15-30mg/kg/day and
    - Fourth agent (ethambutol, streptomycin, levofloxacin or ethionamide)
- Followed by prolonged continuation phase of 10 months with two drugs
    - INH and rifampicin given daily for a total 12 months
- Adjuvant dexamethasone have been shown to reduce mortality in TBM; give for a total duration of 6 weeks (advisable to start within the first 6 weeks).
    - Dexamethasone 0.3 to 0.4 mg/kg/day IV for 2 weeks, then 0.2 mg/kg/day IV week 3, then 0.1 mg/kg/day IV week 4, then 4 mg per day orally and taper 1 mg off the daily dose each week; total duration approximately 8 weeks.
    - Hydrocephalus may develop during treatment. Perform head CT if deteriorating or new symptoms and consult neurosurgery if symptoms.

Other CNS Tubercular Infections

- Tuberculoma of brain: granulomatous focal conglomerate of tubercules; can occur without meningitis
    - Often clinically silent and depending on location and size clinical symptoms can vary from subclinical to focal neurological deficits. Can also present as a clinically apparent mass lesion of the brain in the absence of meningitis.
    - Lumbar puncture should be avoided if lesion is obstructive or concern for elevated intracranial pressure. CSF is usually culture negative and normal.
- Spinal arachnoiditis (spinal cord tuberculoma): may present with focal pain and/or cord compression signs and symptoms

Cryptococcal meningitis

Clinical pearls

- Cryptococcal meningitis (CM) is transmitted by pigeon excreta which are then inhaled in order to infect the lungs, blood stream and eventually the brain and meninges.
- CM is a thick capsuled yeast that commonly causes disease in patients who are immunosuppressed. The symptoms are known to wax and wane, hence delaying the diagnosis.
- Symptoms begin over a period of one to two weeks with headache being the most common symptom.
- The patient may develop personality change and confusion as disease progresses, as well as defects in the third, fourth, fifth, sixth and eight cranial nerves. Neck stiffness is uncommon.
- Disseminated disease is suggested if there is also cough, dyspnoea, and skin rash.
- Common in advanced HIV disease and can occur in HIV seronegative individuals (most common cause are glucocorticoid therapy, some tyrosine kinase inhibitors (e.g., ibrutinib), or biologic modifiers among other causes.

Diagnosis

- Physical exam may be notable for lethargy or confusion with associated fevers. Laboratory studies are nonspecific.
- LP is required for diagnosis and is also therapeutic, CSF pressure commonly elevated
- Expected CSF findings: white blood cells (WBCs) 20-200/mm^3, with a predominance of mononuclear cells, mildly elevated protein, and moderately depressed glucose
- India ink is sensitive in 25-50% of cases, and serum and CSF cryptococcal antigen (CrAg) sensitive in approximately 90% of cases. Positive CrAg in CSF strongly supports diagnosis of cryptococcal meningoencephalitis.
- In patients with AIDS and suspected cryptococcal meningitis, serum and CSF CrAg have comparable sensitivity and is a useful diagnostic in patients who cannot receive a lumbar puncture.
- CrAg titres correlate with initial organism burden and prognosis.
- Culture usually positive in 5-7 days. CT or MRI with contrast may show hydrocephalus, cerebral edema, and ring-enhancing lesions (cryptococcomas). Elevated intracranial pressure is an indication for urgent LP.

Treatment

- Induction phase (at least 2 weeks): amphotericin B (AmB) 0.7-1mg/kg/day in saline used in combination with flucytosine 100 mg/kg/day, for the first two weeks of infection (HIV positive) or 6 weeks (HIV negative). Alternative regimens include using amphotericin B with high dose fluconazole 1200mg po daily during the induction phase.
- Consolidation phase: fluconazole 400 mg po daily for 8-10 weeks
- Maintenance phase: fluconazole 200 mg po daily for duration of 12 months.
- AmB and flucytosine have been shown to be the most effective regimen with the highest early fungicidal activity in the CSF; alternative regimens are available.
    - Maintenance phase with low dose fluconazole for secondary prophylaxis is continued until the CD4 is greater than 350cells/ml in HIV + or for life in those who were immunocompetent at initiation of therapy.
- Mortality for cryptococcal meningitis is 25–30% in patients who do not have AIDS. Poor prognostic factors include a positive CSF India ink preparation, a CSF CrAg titer in excess of 1:32, a CSF WBC count below 20/mm3, elevated CSF opening pressure, and extraneural infection.
- HIV negative patients consult ID for management.

Encephalitis

Clinical pearls

- Encephalitis is characterized by fever, altered mental status (often confused, cognitive deficits, or bizarre behaviour), focal neurological signs, and/or seizures
- HSV encephalitis classically causes bizarre behaviour
- The majority of infections causing encephalitis cannot be treated with antimicrobials. HSV, VZV, and neurosyphilis are the exceptions.
- ID and Neurology can be consulted for assistance with diagnosis and management.

Diagnosis

- Most infectious encephalitis is viral in origin, but infection due to bacteria, parasites, or fungi, and non-infectious causes do occur. A careful history detailing host factors, vaccination status, time of year, travel history, recreational activities, occupational exposures, and insect and animal exposures should be elicited.
- Definitive aetiology is not found in most cases. Though most infections causing encephalitis cannot be treated, exact aetiology may provide prognostic and epidemiologic information. Diagnosis may have implications for prophylaxis in close contacts or for public health.
- Diagnostic evaluation should be individualized based on possible exposures; all patients should have LP (unless contraindicated – see meningitis section) with CSF collected for HSV and VZV PCR (pending availability)
    - PCR for HSV should be repeated in 3-7 days if suspicion remains high and initial testing was negative
    - See STI section for information on diagnosis of neurosyphilis.
    - If meningitis is being considered, send CSF studies to evaluate for bacterial meningitis also (see meningitis section)
- MRI could be performed in all patients if available (CT if MRI contraindicated), as imaging findings may suggest specific aetiology. Temporal lobe enhancement suggests HSV encephalitis.

Treatment

- Immediately start acyclovir 10 mg/kg IDEAL BODY WEIGHT IVq8h in all patients with suspected encephalitis to cover HSV and VZV. Oral acyclovir is not effective. Therapy should be continued until HSV/VZV ruled out by initial and repeat PCR, or an alternate diagnosis is reached.
- Ensure adequate hydration to prevent crystal nephropathy from acyclovir
- Treatment duration for HSV encephalitis is 14-21 days based on clinical response
- Treatment duration for VZV encephalitis is 10-14 days based on clinical response
- See STI section for treatment of neurosyphilis
- If meningitis is being considered, treat empirically for bacterial meningitis also (see meningitis section)
- Supportive care, often in the ICU, is the main management strategy in most cases

Resources

- IDSA. The management of encephalitis. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ; Clin Infect Dis. 2008 Aug 1;47(3):303-27

Brain Lesions

Clinical pearls

- Headache, fever, altered mental status, focal neurological deficits, and seizure are the most common clinical signs and symptoms
- Microbiology depends on route of infection and host factors
    - Contiguous spread
        - Penetrating trauma or neurosurgery: *S. aureus, S. epidermidis, Streptococcus spp., Enterobacterales* (e.g., *E. coli, Klebsiella spp*.), *Clostridium spp.*
        - Otitis media or mastoiditis: anaerobes, *Streptococcus spp., Enterobacterales*
        - Paranasal sinusitis: *Streptococcus spp., S. aureus, Enterobacterales, Haemophilus spp.*, anaerobes
    - Hematogenous spread
        - Lung abscess, empyema, or bronchiectasis: anaerobes (including *Fusobacterium spp.* and *Actinomyces spp*.), *Nocardia spp, Streptococcus spp*.
        - Bacterial endocarditis: *S. aureus, Streptococcus spp*.
        - Congenital heart disease: *Streptococcus spp., Haemophilus spp*.
        - Dental infection: anaerobes (including *Fusobacterium spp.* and *Actinomyces spp.), Streptococcus spp.*
        - Neurocysticercosis: pig exposure
    - Immunosuppressed (including HIV): *Toxoplasma gondii, Cryptococcus neoformans, Mucorales, Nocardia spp., Listeria monocytogenes, M. tuberculosis*
- **ID consultation is recommended in immunosuppressed hosts**

Diagnosis

- CT of the brain with contrast can identify the number and location of abscesses. MRI may be helpful in differentiating abscess from tumor.
- LP may be performed if there is a concern for meningitis or rupture into ventricular system AND there are no contraindications (i.e., risk for herniation or bleeding – see meningitis section for contraindications).

- In patients with suspected TB meningitis, intracranial pressure may be elevated and thus imaging should be done first to ensure LP is safe.

- Utilize imaging and focused history and physical examination to assess for contiguous and systemic foci of infection that may need surgical drainage.
- Microbiological diagnosis and directed antimicrobial therapy is dependent on obtaining sample of pus if possible. In some cases, this will also be therapeutic. Patients with HIV/AIDS are the exception to this rule and should be treated empirically for toxoplasmosis if serum IgG antibodies are present (or testing not available). Aspiration of abscess is only performed if they fail to respond to therapy for toxoplasmosis.

Treatment

Empiric Antibiotics

- Empiric therapy depends on predisposing conditions and local resistance patterns
    - Hematogenous spread: ceftriaxone 2g IVq12h + metronidazole 500mg IV/PO q6h + vancomycin (target trough 20 mcg/mL). If vancomycin not available, use linezolid 600mg po twice daily.
    - Post-neurosurgery: vancomycin 25 mg/kg x1 load then 15 mg/kg q12h + metronidazole 500mg IV/PO q6h + cefepime 2g IVq8h or meropenem 2g IVq8h. If vancomycin not available, use linezolid 600mg po twice daily. If using meropenem, do not give metronidazole.
    - **Weekly full blood count for patients on linezolid to monitor for thrombocytopenia, anemia, and leucopenia**
    - HIV infection:
        - Bacterial coverage: ceftriaxone 2g IVq12h + metronidazole 500mg IV/PO q6h + vancomycin dosed as above. If vancomycin not available, use linezolid 600mg po twice daily.
        - PLUS empiric treatment of toxoplasmosis as outlined in the definitive antibiotics section below

Surgical Treatment

- Consult neurosurgeons
- Samples must be sent from any surgical procedure/pus (aerobic bacterial culture, AFB stain and culture and GeneXpert). In general, pus swabs are inferior to actual biological specimen of pus in a sterile container.

Definitive Antibiotics

- Definitive therapy should be based on identification of organism, susceptibility, and discussion with ID. Therapy for anaerobes should be continued in polymicrobial or culture negative or neurosurgery-related brain abscess.
- Neurosurgical involvement crucial for diagnosis and treatment of complications (increased intracranial pressure, herniation, etc.)
- TB meningitis treatment (drug susceptible TB): [Please see link]
    - First 2 months: Isoniazid + Rifampicin + Ethambutol + Pyrazinamide (same dosing as pulmonary TB) + dexamethasone 0.4 mg/kg/day

        - Dexamethasone taper: 0.4 mg/kg/day week 1, 0.3 mg/kg/day week 2, 0.2 mg/kg/day week 3, 0.1 mg/kg/day week 4, then tapered to stop over 3-4 weeks
    - Next 10 months: Isoniazid and rifampicin (same dosing as pulmonary TB).
    - Monitor for signs of elevated intracranial pressure and possible need for shunt.
    - For HIV-positive patients not currently on ART, delay initiation until 8 weeks of TB treatment is complete.
- Toxoplasmosis treatment:
    - First line: Pyrimethamine (200 mg po once, then 75mg po daily if >60kg or 50mg po daily if <60kg) PLUS sulfadiazine (1.5g po 6-hourly if >60kg or 1g po 6-hourly if <60kg (pending availability). Folinic acid must be given with pyrimethamine.
    - Alternative: TMP/SMX 5mg/kg of TMP component, po/IV q8h
    - Sulfa allergy, first line: Pyrimethamine (200 mg po once, then 75mg po daily if >60kg or 50mg po daily if <60kg) PLUS clindamycin 600mg iv q6h. Folinic acid must be given with pyrimethamine.
    - Sulfa allergy, alternative: Pyrimethamine (200 mg po once, then 75mg po daily if >60kg or 50mg po daily if <60kg) PLUS Azithromycin 1000mg po daily. Folinic acid must be given with pyrimethamine.
    - Duration of treatment is 4-6 weeks after complete resolution of clinical symptoms in addition to brain imaging (if available). Chronic suppression is needed in HIV positive patients.
- Neurocysticercosis treatment:
    - Parenchymal lesions: Albendazole 15 mg/kg per day (max 800 mg/day) + praziquantel 50 mg/kg per day for 10 to 14 days (it maybe longer). Albendazole alone adequate if only 1-2 cysts on MRI
        - Dexamethasone 0.1 mg/kg/day (beginning 1 day prior to antiparasitic drugs)
        - Taper steroids very slowly after at least 10 days
        - May need antiepileptic medications
    - Dead, calcified cysts: No antiparasitic treatment, may need antiepileptic medications

Antibiotic Duration and Follow up

- Duration of therapy depends on etiology and response to therapy, but usually at least 6-8 weeks for bacteria and much longer for *Nocardia spp.,* fungi, MTB, or parasites.
    - Immunocompromised patients with toxoplasmosis require 4-6 weeks of treatment, followed by prophylaxis (in HIV patients, refer to HIV guidelines regarding prophylaxis)
- Obtain serial CT scans to assess for shrinkage of abscess in response to therapy. New or worsening neurological deficits on therapy should prompt repeat imaging.

Resources

- Brain Abscess Review: Brouwer, MC. NEJM 2014;371:447-456.
- Brain Abscess Systematic Review & Meta-analysis: Brouwer MC. Neurology 2014;82:806-813
- IDSA & ASTMH Clinical Guidelines for Diagnosis and Treatment of Neurocysticercosis. White AC Jr, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, Garcia HH, Nash TE. Clin Infect Dis. 2018 Apr 3;66(8):1159-1163.

CNS Device Infections

Clinical pearls

- CNS device infections are also called 'ventriculitis', or 'device related meningitis'
- Most infections occur within one month of device placement
- CNS devices include external ventricular drain (EVD), ventriculo-peritoneal shunt (VPS), ventriculo-atrial shunt (VAS), and lumbar drains
- CoNS*, Staphylococcus aureus, Cutibacterium* acnes (formerly *Propionibacterium acnes*), viridans group streptococci, and Enterobacteriaceae*, Acinetobacter spp*., and *Pseudomonas spp*. are common pathogens

Diagnosis

- Fevers, altered mental status, or neck stiffness in a patient with recent (<1 month) CNS device placement should raise suspicion for CNS device infection
- Erythema, pain, swelling, or discharge at either end of a shunt may be seen, but less virulent organisms (CoNS*, Cutibacterium acnes/Propionibacterium acnes*) may not produce overt signs or symptoms of infection
- CSF culture is the basis for diagnosis but should be interpreted in the context of the overall clinical picture, as skin flora can be contaminants or pathogens
- Culture obtained from the shunt valve has a higher yield than from a lumbar puncture
- VAS infections have higher rates of bacteraemia than VPS infections
- Elevated CSF leukocyte and granulocyte count, elevated lactate, elevated protein, and low CSF-to-blood glucose level may be indicative of a CNS shunt infection, though CSF parameters can also be normal
- CT of the brain should be obtained to look for ventriculitis or CSF obstruction

Treatment

Empiric Antibiotic Therapy:

- Direct empiric antibiotics at likely pathogens, including *S. aureus* and *Pseudomonas spp*. and have adequate CNS penetration: vancomycin IV and meropenem (dosing below).

Definitive Antibiotic Therapy:

- Definitive antibiotic choice should be based on culture results. Ensure that chosen antibiotic has good CNS penetration, and that 'CNS dose' (see antimicrobial dosing for CNS infections) is used. ID consultation is recommended.
    - For internal shunts, the shunt should generally be removed and replaced with a temporary EVD until the infection clears
    - Intraventricular antibiotics are not routinely recommended and are generally limited to refractory cases
    - Infections are unlikely to clear without removal of the CNS device due to biofilm formation.

Antimicrobial doses for CNS Infections (For patients with normal renal function)

Antibiotics	
Ampicillin	2g IVq4h
Ceftriaxone	2g IVq12h
Cefepime	2g IVq8h
Cloxacillin	2g IVq4h
Ciprofloxacin	400mg IVq8h
Meropenem	2g IVq8h
Metronidazole	500mg IVq6h
Penicillin	4 million units IVq4h
Vancomycin	25 mg/kg loading dose then 15-20 mg/kg q8-12h
Antifungals	
AmBisome (Liposomal Amphotericin B)	5 mg/kg IVq24h (rounded to nearest 50 mg)
Amphotericin b deoxycholate	0.7-1 mg/kg IVq24h
Fluconazole	800 – 1200 mg IV/PO q24h
Flucytosine	25 mg/kg PO q6h

Neurosyphilis, Treponema pallidum

Clinical pearls

- Syphilis is known as 'the great imitator' and can have almost any clinical manifestation
- Syphilis infection predicts subsequent infection with HIV; syphilis diagnosis is an opportune time to discuss risk reduction strategies and order HIV screening test.

Diagnosis

Time Course and Definitions

- Infection: can occur from any skin contact with primary of secondary syphilitic lesion (usually sexually transmitted), or vertically.
- **Primary syphilis:** ~3 weeks after infection. Manifestation is single painless ulcer (chancre) at the site of infection.
- **Secondary syphilis:** ~6 weeks after primary lesion. Manifestations are due to dissemination and can include maculopapular rash (including palms and soles, rarely ulcerates), constitutional symptoms, condylomata lata, or lymphadenopathy. Lesions are highly infectious.
- **Latent syphilis:** asymptomatic, detected by serologic testing only.
  - Early latent: acquired within the preceding year. High rate of secondary syphilis recurrence.
  - Late latent: acquired more than one year prior or unknown duration.
- **Tertiary syphilis: ~**30 years after primary infection. Involvement usually of cardiac or neurologic systems, but gummatous lesions can occur anywhere.
- **Neurosyphilis:** may occur at any stage.
  - In primary or secondary syphilis, usually manifests as meningitis.
  - In later stages, can manifest as cognitive, psychiatric, motor, sensory, auditory, or neuro-ophthalmic deficits, altered mental status, or stroke.

Laboratory diagnosis

- Primary and secondary syphilis are usually clinical diagnoses. Direct testing of lesion with direct immunofluorescence antibody or darkfield microscopy can also be done. Indirect testing will be negative in early stages.
- For all other stages, indirect testing is used. Diagnosis requires positive RPR (nontreponemal test) AND FTA-ABS or TP-PA (Treponemal tests).
    - RPR alone has a high false positive rate. In very high titres, RPR can be falsely negative ('prozone' effect).
    - RPR with titre should be used for screening. If positive, FTA-ABS will be done reflexively in lab. Positive FTA-ABS confirms diagnosis. If FTA-ABS is negative, RPR is considered false positive.
    - A 'reverse screening algorithm' is used at some institutions because of decreased cost and laboratory technician time. The algorithm starts with FTA-ABS and reflexes to RPR if positive. Positive RPR confirm diagnosis. If RPR is negative, TP-PA is the tiebreaker.

- Indications for LP: any suspicion for neurosyphilis, HIV (if late latent, unknown duration, or CD4<350), late latent, tertiary, RPR > 1:32, treatment failure. Some experts advocate evaluation and/or treatment for neurosyphilis in every patient with syphilis.
    - Test: CSF VDRL, cell count, glucose, and protein.
    - Laboratory testing is helpful in supporting a diagnosis of neurosyphilis, but diagnosis is rarely clear-cut. In a patient with neurologic symptoms/signs, a positive CSF VDRL is diagnostic for neurosyphilis.
    - Elevated CSF protein sometimes helps in the diagnosis of neurosyphilis, but this can be misleading in HIV patients who might have elevated CSF protein in the absence of neurosyphilis.
    - If CSF VDRL is negative but clinical suspicion is still high, check CSF FTA-ABS.
    - Many patients will be treated empirically if suspicion is high or there is neurological abnormality in a patient with syphilis.
- **Consider ID consult for assistance in diagnosis of any stage of syphilis, especially in HIV.**

Treatment

- **Primary, secondary, and early latent syphilis**
    - Benzathine Penicillin G 2.4 million units IM once
    - Penicillin allergy
        - Doxycycline 100mg PO BID for 14 days
        - Ceftriaxone 1 gram IM/IV Q24H x 10-14 days
- **Late latent and tertiary syphilis**
    - Benzathine penicillin G 2.4 million units IM weekly for 3 weeks
    - Penicillin allergy: doxycycline 100mg PO BID for 28 days
- **Neurosyphilis (any optic involvement treated as neurosyphilis**)
    - Aqueous crystalline penicillin G 4 million units IV q4h or continuous infusion for 14 days.
    - Other regimens such as ceftriaxone 2 gram IV or IM q24h x 14 days can be used but are associated with high failure rates.

- All pregnant women who report penicillin allergy must be desensitized and treated with penicillin There are no safe alternate options and vertical transmission must be prevented.
- Watch for Jarisch-Herxheimer reaction, which occurs within 24 hours of treatment. Symptoms can mimic sepsis and can include fever, chills, rigors, tachycardia, hypotension, flushing, headache, and myalgia. Treat symptomatically. Patients should be warned about this reaction.

Follow up

- Repeat RPR titre in 6 to 12 months to follow treatment response.
- A 4-fold drop in titre in 6 months (divide by 4, e.g., 1:64 to 1:16) or an 8-fold drop in 12 months (e.g., 1:64 to 1:8) is an appropriate response.
- Failure of titres to decrease as expected can be due to inadequate treatment (including failure to diagnose neurosyphilis) or reinfection (4-fold rise in titre usually seen).
- After treatment and over time, RPR will usually revert to non-reactive.
- Patients with persistently positive RPR are referred to as 'serofast.' This is common in HIV infected patients. Titres are usually low.
- Treponemal tests remain positive for life. Will also be positive in infection with other spirochetes. Once positive, there is no need to repeat this test.
- Sexual partners of patients with syphilis should be evaluated.
    - Sexual contact within 90 days of patient with primary, secondary, or early latent syphilis: Check baseline RPR; treat regardless of result.
    - Sexual contact greater than 90 days of patient with primary, secondary, or early latent syphilis: check RPR. Treat if positive.
    - Long term partners of patients with late latent syphilis: check RPR. Treat if positive.

Resource

- CDC Sexually Transmitted Diseases Treatment Guidelines: MMWR 2015; 64:1-140.

Eyes, Ears, Nose and Throat Infections

Eyes, Ears, Nose, and Throat Infections

Overprescribing of antibiotics for ears, nose, and throat (ENT) and upper respiratory tract infections (URTIs) is a major driver of bacterial resistance in the community. URTIs include three clinical syndromes depending on the site of infection: pharyngotonsillitis (sore throat), acute otitis media, and acute sinusitis.

Conjunctivitis

Clinical pearls

- Most commonly caused by viruses and self-limiting do not require antibiotics.
- Bacterial conjunctivitis causes a thick purulent discharge, typically caused by *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis*. *N. gonorrhoeae* can cause a severe conjunctivitis that can progress to keratitis.
- Allergic conjunctivitis is usually bilateral and accompanied by itching.

Treatment

- Bacterial, non-gonococcal: Fluoroquinolone eye-drop preparation 1-2 gtts q2h while awake for the first 2 days, then q4 -8h up to 7 days.
- Alternative:
    - Polymyxin/bacitracin/neomycin ointments
    - Azithromycin 1% ophthalmic solution 1 drop twice a day for 2 days; then one drop daily x 5 days
- Systemic treatment is generally not recommended except for extremely severe cases of bacterial conjunctivitis. Meta-analysis has revealed that although bacterial conjunctivitis is self-limiting, topical antibiotics are of clinical benefit with regard to shortening the clinical manifestations of the infection and reducing the possibility of person to person spread.

Orbital and Periorbital Cellulitis

Clinical pearls

- **Preseptal cellulitis (periorbital cellulitis)**
    - Infection of soft tissue anterior to orbital septum
    - Symptoms can include eyelid erythema, soft tissue swelling, and fever
- **Postseptal cellulitis (orbital cellulitis)**
    - Severe infection involving the orbit, with high risk of complication
    - Symptoms can include eyelid edema, soft tissue swelling, fever AND orbital pain, headache, rhinorrhoea, eyelid tenderness to palpation, chemosis, proptosis, visual loss, limitation of ocular movements, or pain with ocular movement
    - Complications include osteomyelitis, subperiosteal abscess, and cavernous sinus thrombosis
- Common organisms: *Streptococcus spp., H. influenza, M. catarrhalis, S. aureus*, anaerobes. Invasive fungal infection should be considered as a cause in immunocompromised hosts (e.g., malignancy, uncontrolled diabetes mellitus).

Diagnosis

- Preseptal cellulitis is a clinical diagnosis. If there is any concern for postseptal cellulitis based on exam, CT is recommended to delineate preseptal from postseptal cellulitis, and to evaluate for complications. If cavernous sinus thrombosis is possible based on exam, MRI is warranted.

Treatment

- **Preseptal cellulitis:** oral therapy as below
- **Postseptal cellulitis:**
  - **Initial IV therapy:**
    - Primary regimen: ceftriaxone 2g IV daily plus metronidazole 500 mg PO/IV q8h
    - Severe penicillin allergy: levofloxacin 750 mg PO daily
    - History of MRSA colonization/infection, abscess, bone involvement, orbital trauma, recent eye surgery, or severe infection: Add vancomycin IV (see appendix, page)
  - **Oral step down** (no evidence of bony involvement or cavernous sinus thrombosis):
    - Amoxicillin/clavulanate 1g PO q12h
    - Severe penicillin allergy: levofloxacin 750 mg PO daily
- Urgent ENT consult for surgical intervention for abscess, vision loss, or ophthalmaplegia
- Duration: 7 -14 days for pre- or post-septal cellulitis. Course extended to 6 weeks if evidence of bony involvement
- Response time usually 24-48 hours

Acute Otitis Media

Clinical pearls

- Symptoms of acute ear pain, aural fullness, decreased hearing +/- fever
- Common organisms isolated at UTH: Group A strep, *Pseudomonas spp., M. catarrhalis*. Also consider *S. pneumoniae, H. influenzae*.
- Complications can include perforation of the ear drum and mastoiditis (infection of mastoid process within skull temporal bone)

Diagnosis

- Most often the diagnosis is made clinically, should see a red and bulging tympanic membrane which may be draining pus
- Cultures not routine or obtainable unless spontaneous tympanic membrane rupture occurs

Treatment

- For mild to moderate disease, hold antibiotics and initially use analgesics only. Decongestants do not help with symptom improvement and just contribute to side effects.
- Antibiotics should be given if febrile or symptoms do not start to within 48 hours
  - Primary regimen: levofloxacin 750 mg PO QD
  - Alternative: amoxicillin/clavulanate 1g PO TID
  - Penicillin allergy (mild): cefuroxime 500 mg PO BD
- Nasal decongestants, NSAIDs
- **Duration:** 7-10 days

Acute Otitis External

Clinical pearls

- Symptoms include rapid onset painful and/or itchy ear with otorrhea, often with a history of minor local trauma, eczema, or water exposure
- Common organisms*: Pseudomonas aeruginosa, S. aureus*, often polymicrobial
- Risk factors: swimming (particularly freshwater), eczema, seborrhoea, local trauma, cerumen accumulation
- Complications can include conductive hearing loss, narrowing of the external auditory canal and rarely malignant otitis externa where the infection extends beyond the canal invading soft tissues and/or bone.

Diagnosis

- Physical exam findings (diffuse ear canal erythema and/or oedema, possible drainage), pain induced by pinna or tragus manipulation, and compatible history
- CT only needed to assess for malignant otitis externa or concern for osteomyelitis

Treatment

- For uncomplicated otitis externa, topical therapy can be used
  - Neomycin + polymyxin + hydrocortisone 4 drops TID
  - Ciprofloxacin otic solution 3-4 drops BID
  - Antibiotics should be given for severe infection
  - Ciprofloxacin 500-750 mg PO BID
- **Duration:** 10 days

Acute Rhinosinusitis

Clinical pearls

- Symptoms include fever, focal facial (maxillary or frontal sinus or maxillary tooth) pressure or pain, nasal congestion or discharge, reduced sense of smell
- Risk factors: environmental allergies, anatomical defect, smoking, dental infection
- Most cases (90-98%) are viral and do not require antibiotics
- Consider bacterial aetiology only in the following scenarios:
  - >10 days of symptoms of sinusitis without improvement
  - Fever (>39°C) with purulent nasal discharge or facial pain lasting > 3-4 days
  - New onset fever, headache, or increase in nasal discharge approximately 5-6 days into a viral URI, after a period of initial improvement. Referred to as “double-sickening.”
- Common organisms: *S. pneumoniae, H. influenzae, M. catarrhalis*. Rarely, *S. aureus*, Enterobacterales, or fungi in immunocompromised patients
- Complications: orbital infection, meningitis, brain abscess, cavernous sinus thrombosis – all rare!

Diagnosis

- Most often the diagnosis is made clinically, but sinus CT can corroborate mucosal wall thickening and find complications of sinusitis (i.e., orbital cellulitis and abscess)
  - Note: mucosal wall thickening can be seen incidentally on CT in patients without infection, so findings should be correlated clinically

Treatment

- Primary regimen: amoxicillin/clavulanate 1g PO TID
- Penicillin allergy (mild): Cefuroxime 500 mg PO BD
- Penicillin allergy (severe) Levofloxacin 750 mg PO QD (pending availability) or doxycycline 100 mg PO BD
- Intranasal saline irrigation and intranasal steroids are recommended as adjuncts for symptomatic relief. Antihistamines and decongestants are not.
- ID consult suggested for:
    - Persistent infection despite trials of at least 2 different antibiotic classes
    - Evidence of bone destruction
    - Immunocompromised patient
- **Duration**: 5 days for uncomplicated infection
- If there is no clinical improvement after antibiotic therapy consider coverage for fungal infections particularly in immunocompromised patients (diabetes mellitus, HIV).

Resources

- IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, Pankey GA, Seleznick M, Volturo G, Wald ER, File TM Jr; Clin Infect Dis. 2012 Apr;54(8):e72-e112.

Acute pharyngotonsillitis (sore throat)

Clinical pearls

- Acute inflammation of the pharyngeal walls and tonsils
- Most commonly viral (EBV, RSV, adenovirus, etc) in etiology
- If bacterial, most common organisms include beta-hemolytic streptococci (Group A, C and G), *Fusobacterium spp., Arcanobacterium haemolyticum*
- Viral and bacterial acute pharyngitis are self-limiting
- Primary reason to consider antibiotic therapy is to prevent acute rheumatic fever caused by *Streptococcus pyogenes* (group A strep), which most commonly occurs in children ages 5-15 years

Diagnosis

- Typical symptoms: sudden onset pain with swallowing, fever +/- headache, nausea, vomiting, abdominal pain (GI symptoms more common in children)
- Rapid strep antigen test (RADT) – 80-90% sensitive and >95% specific (pending availability)
- Centor clinical criteria – tends to over-diagnose Group A strep compared to microbial diagnostic methods but helpful when RADT unavailable
    - Score criteria:
        - Fever
        - Tonsillar exudates
        - NO cough
        - Tender cervical lymphadenopathy
    - Patients get 1 point for each of the above (subtract 1 point if age >45). Risk of group A strep based on Centor score:

        - 1 - 5-10%
        - 2 - 11-17%
        - 3 - 28-35%
        - 4 - 51-53%
    - Patient with score of 4 should be considered for empiric antibiotics, if <4, RADT or culture recommended first

Treatment

- Only consider antibiotics if (+) rapid strep antigen or high suspicion of bacterial infection based on clinical criteria
- Preferred:
    - Penicillin VK 500 mg BD for 10 days
    - Benzathine PCN 1.2 million units IM x1
    - Cephalexin 500 mg BD x 10 days (mild penicillin allergy)
    - Clindamycin 300 mg PO TID x 10 days (severe penicillin allergy only)

Resources

1. Periorbital cellulitis review: Bering DE. Clin Otolaryngol 2011;36:57-64.

Gastrointestinal Infections

Gastrointestinal Infections

Infections in the abdomen can be divided into the following main groups:

1. Infections of the biliary system, including cholecystitis and cholangitis
2. Infections of the bowel, including appendicitis and diverticulitis
3. Intra-abdominal collections or abscesses
4. Peritonitis, including bowel perforations and spontaneous bacterial peritonitis (SBP) related to liver disease

General clinical pearls

- Most intra-abdominal infections (IAIs) are diagnosed by history and physical, +/- imaging
- Upright abdominal X-ray for free air should be done immediately if there is suspicion of perforation
- CT is the imaging modality of choice to determine presence of IAIs and localize source
- Bedside ultrasound can be used in patients who are unstable/unable to travel for CT
- Complicated intra-abdominal infection is defined as infection that extends beyond a single organ (i.e., localized or diffuse peritonitis)
- Uncomplicated IAIs are often treated with antibiotics OR surgery
- Complicated IAIs are generally treated with antibiotics AND surgery
- For any IAIs, source control is imperative, ensure surgical consult. This includes drainage of abscess (percutaneous > surgical when feasible), resection, and control of peritoneal contamination.
- Patients with peritonitis or hemodynamic instability generally require emergent surgery; surgery should not be delayed waiting for imaging in cases of obvious peritonitis
- Hemodynamically stable patients without organ failure generally require urgent surgery (within 24 hours) if close monitoring and empiric antibiotics are available
- See individual sections below for specific information on each infection
- Antibiotic duration depends on source control, can often stop antibiotics ~4 days after completion of source control

Appendicitis

Clinical pearls

- Classic symptoms: periumbilical pain early (visceral) with later migration to right lower quadrant (parietal), nausea, vomiting, anorexia, fever
- Atypical symptoms: indigestion, flatulence, bowel irregularity, generalized malaise
- Physical exam signs: McBurney's point tenderness, Rovsing's sign, psoas sign, obturator sign, rectal or vaginal tenderness
- Common organisms: Enterobacterales, anaerobes, viridans streptococci

Diagnosis

- Generally made from the history and clinical examination

Modified Alvarado score for appendicitis

Description	Score	Interpretation

○ migratory right iliac fossa pain ○ anorexia ○ nausea/vomiting ○ rebound tenderness, ○ temperature >37.3C ○ Neutrophils >75%	1 point each	○ ≤4: unlikely ○ 5-6: possible ○ 7-8: probable ○ 9-10: definite Good for 'ruling out'; over-predicts likelihood in women and children (> 4 points, Sensitivity: 93%, Specificity: 55%, + LR: 2.07, - LR: 0.13)
○ tenderness in the right iliac fossa ○ WBC> 10,000	2 points each	

- CT is not always necessary but can be considered to evaluate for other causes of abdominal pain when diagnosis of appendicitis is not clear

Treatment

Surgery

- Appendicectomy is treatment of choice, open or laparoscopic approach acceptable
- Non-operative approach should be reserved for specific patients in whom surgery is contraindicated, because antibiotic therapy alone has not been shown to be equivalent to appendicectomy and results in significant rate of recurrence (~30% in 1 year).
- Patients with peri-appendiceal abscesses require percutaneous image-guided drainage. Interval appendectomies are not routinely necessary unless symptoms recur.

Empiric Antibiotics

- **Stable patient:**
  - **Uncomplicated:** A single preoperative dose of cefazolin 2g IV (ceftriaxone 1g IV if cefazolin unavailable) and metronidazole 500mg IV for surgical wound prophylaxis prior to appendicectomy is adequate. **Do not continue post-operatively.**
  - **Complicated (perforated or gangrenous appendicitis):** ceftriaxone 1g IVq24h AND metronidazole 500mg IV/PO q8h
  - **Severe penicillin allergy:** levofloxacin 750mg IV/PO q24h AND metronidazole 500mg IV/PO q8h; meropenem 1g IV q8h can be considered as well
- **Unstable or ICU patient:** meropenem 1g IVq8h or piperacillin-tazobactam 3.375mg IVq6h. Consider addition of antifungal (e.g., fluconazole) if prolonged hospital or antibiotic course, and hemodynamically unstable
  - **Severe penicillin allergy:** levofloxacin 750mg IVq24h PLUS amikacin 15 mg/kg IVq24h AND metronidazole 500mg IVq8h
- **Duration**: 4-7 days if source control achieved, longer if no source control or remains unstable
- Note, coverage for fungi and Enterococcus spp. is not necessary or recommended

Resource: Nonoperative Management of Uncomplicated Appendicitis Among Privately Insured Patients. JAMA Surg. 2019; 154(2): 141-149

Acute cholecystitis and cholangitis

Clinical pearls

- Cholecystitis
  - Signs/symptoms: RUQ or epigastric pain, nausea, vomiting, anorexia, fevers, chills
  - ~90% of cases are caused by obstruction of the cystic duct by gallstones or biliary sludge. Acalculous cholecystitis (inflammation without stones) is seen primarily in critically ill patients (5-14%).
  - Risk factors: female, hormone replacement therapy, hypertriglyceridemia, sickle cell disease, obesity, obesity surgery, weight loss, and gallbladder cancer
- Cholangitis
  - Signs/symptoms: fever + RUQ pain + jaundice = Charcot's triad. Charcot's triad + septic shock + altered mental status = Reynolds' pentad
  - Occurs in the setting of biliary stasis or obstruction (e.g., gallstone, primary sclerosing cholangitis (PSC), benign biliary stenosis, stricture of biliary anastomosis, stenosis due to malignancy)
- Common organisms: Enterobacterales, anaerobes. *Enterococcus spp*. and *Candida spp*. are sometimes cultured but pathogenic roles are not well defined.

Diagnosis

- Cholecystitis
  1. Local signs (Murphy's sign, RUQ pain/tenderness) PLUS
  2. Systemic signs (fever, leukocytosis, or elevated CRP) PLUS
  3. Imaging (US initially or CT)
- Cholangitis
  1. Cholestasis (jaundice, total bilirubin >2, ALP or GGT > 1.5 x ULN, AST or ALT >1.5 x ULN) PLUS
  2. Systemic signs (fever, leukocytosis or leukopenia, elevated CRP) PLUS
  3. Imaging (biliary dilatation, stricture, stone, stent, or other cause of obstruction seen on US, CT, MRCP, or ERCP, as available)
- Blood cultures should be obtained in patients with evidence of sepsis. Biliary cultures should be obtained at the time of gallbladder drainage when the gallbladder is not removed but are not needed in uncomplicated cholecystitis with cholecystectomy.

Treatment

- The mainstay of therapy for biliary tract disease is biliary drainage. Antibiotics prevent and treat sepsis associated with biliary obstruction.

Surgery

- Relief of biliary tract obstruction is crucial for antibiotics to reach the gallbladder
- Cholecystitis
  - Early cholecystectomy (within 24-72h) is generally the treatment of choice
  - In critically ill patients, IR guided percutaneous cholecystostomy is effective as temporizing measure until patient recovers sufficiently to undergo cholecystectomy if available
  - In severe acute cholecystitis, delayed cholecystectomy is recommended
- Cholangitis

- Biliary decompression is often urgently required. All patients should have prompt surgical evaluation. Endoscopic, percutaneous, and open drainage are options. Endoscopic drainage via ERCP is favored when possible if available.

Empiric Antibiotics

- Mild to moderate: meropenem 1g IVq8h
  - **Severe penicillin allergy:** levofloxacin750mg OD IV PLUS metronidazole 500mg IVq8h
- History of biliary tract procedures or bilio-enteric fistula or anastomosis: Use regimen for above PLUS doxycycline 100 mg PO q12h PLUS metronidazole 500mg IVq8h
- **Coverage for fungi and Enterococcus spp. not usually required except in bile duct to bowel anastomosis or fistula or healthcare associated biliary infection**

Duration

- Following uncomplicated cholecystectomy in a stable patient, empiric antibiotics should be continued for up to 24h only unless there is evidence of infection beyond gallbladder. Alternatively, there is evidence to support stopping antibiotics after cholecystectomy has been performed.
- Several small studies show non-inferiority of de-escalating or stopping antibiotics when fever and white blood cell count have normalized. Optimal duration is not known, but a short course (4 days) is probably sufficient in patients with quick recovery following source control.
- Patients with bacteremia to IAI should be treated for at least 7 days beyond source control

Diverticulitis

Clinical pearls

- Classic symptoms - acute onset of LLQ abdominal pain and change in bowel habit. Less commonly can present with RLQ pain, palpable mass, and nausea.
- Predominantly seen in older patients
- Common organisms: Enterobacterales, *Enterococcus spp*, viridans streptococci, anaerobes
- Types: simple (75%); complicated (25%) – abscess, fistula, obstruction, peritonitis, or sepsis

- **Hinchey classification** determines stage and directs surgical approach

Stage:	**Description:**
Stage I	inflammatory phlegmon
Stage II	paracolic abscess
Stage III	perforation with purulent peritonitis (OR finding)
Stage IV	perforation with feculent peritonitis (OR finding)

Diagnosis

- Diagnosis often based on history and physical exam. CT helpful for Hinchey staging.

Treatment

Empiric Antibiotics

- Some patients with uncomplicated diverticulitis may be monitored without antibiotics. A recent large, randomized trial and Cochrane review suggests that antibiotics may not be necessary in patients with uncomplicated disease.

- Outpatient, mild: amoxicillin/clavulanate 1g PO BD for 7-10 days
    - Severe penicillin allergy: ciprofloxacin 500mg PO q12h AND metronidazole 500mg PO q8h for 7-10 days
- Inpatient
    - Mild-moderate: levofloxacin 750 mg PO q24h AND metronidazole 500mg PO/IV q8h
        - Duration: 4 days after source control
    - Severe: meropenem 1g IVq8h or piperacillin/tazobactam 3.375g IVq6h
        - Severe penicillin allergy: ciprofloxacin 400mg IV q8h AND metronidazole 500mg PO/IV q8h
        - Duration: 4 days after source control

Surgery

- Image-guided percutaneous drainage is usually the most appropriate treatment for stable patients with large diverticular abscesses (≥ 4cm), if available. Antibiotics alone can be used for smaller abscesses.
- Following percutaneous drainage of pelvic abscesses, surgical intervention is usually recommended due to poor long-term outcomes with drainage and antibiotics alone. Minor mesocolin abscesses, however, do not typically require surgery.
- The decision to pursue elective sigmoid colectomy after recovery from uncomplicated acute diverticulitis should be individualized.
- Immunocompromised patients have higher rates of failure, recurrence, and mortality with antibiotics alone; have a low threshold for surgical intervention (consult surgery for management).
- Urgent sigmoid colectomy is required for patients with diffuse, feculent, or purulent peritonitis, or for those in whom non-operative management fails. Laparoscopic resection can be used in select patients, and laparoscopic peritoneal lavage can be used for purulent peritonitis.

Acute Pancreatitis

Clinical pearls

- Signs/symptoms: severe epigastric or periumbilical pain with radiation to back, chest, or flanks, nausea and vomiting, abdominal distension
- Predisposing conditions: gallstones, alcohol abuse, hypertriglyceridemia (level >1000 mg/dl), medications (corticosteroids, opioids, valproate, others), and malignancy. 10-25% are idiopathic.
- Pancreatitis warrants consult or management by surgical service, especially if complicated (pseudocyst, necrosis, infected pseudocyst or necrosis)
- Pancreatitis is rarely infectious, and only complicated by infection in severe cases
- Infectious pathogens causing pancreatitis are often opportunistic or atypical
- Common organisms in infected pancreatic pseudocyst or infected necrosis: anaerobes, Enterobacteriaceae. *Candida spp., Enterococcus spp*., and *Staphylococcus spp*. can occur in patients on antibiotics, especially long courses.

Diagnosis

- **Acute pancreatitis:** 2 of these 3 findings – characteristic abdominal pain, amylase or lipase ≥3x upper limit of normal, characteristic findings on ultrasound.
    - All patients with suspected pancreatitis should have abdominal ultrasound. Reserve CT for cases with unclear etiology of abdominal pain or failure to improve within 48-72 hours inpatient

- Lipase level does not correlate with severity
- ALT >150 units/L is suggestive of gallstone pancreatitis
- Lipase/amylase ratio >2 is suggestive of alcohol related pancreatitis
- If cause is not clearly alcohol or gallstones, triglyceride level should be checked
- Category:
    1) mild – no organ failure or complications
    2) moderate – organ failure for <48h or local or systemic complications
    3) severe – organ failure for >48h and local or systemic complications

- **Pancreatic pseudocyst:** fluid collection with well-defined inflammatory wall and minimal or no necrosis on CT. May need MRI or US to confirm absence of solid content. Fluid will have elevated amylase and lipase. Usually occurs > 4wks after onset of pancreatitis.
    - Infected pseudocyst: Fever, leukocytosis, and development of gas in a pseudocyst on CT raise suspicion for infection. Positive cultures are confirmatory.
- **Sterile necrotizing pancreatitis**: lack of pancreatic parenchymal enhancement and/or presence of findings of peripancreatic necrosis on CT. Necrosis develops after several days so may be absent on initial CT.
    - Infected necrosis: Either 1) extraluminal gas in the pancreatic or peripancreatic tissues on CT, OR 2) positive cultures (aerobic, anaerobic, fungal) from CT guided fine-needle aspiration.
    - Suspect infected necrosis if persistent or worsening symptoms or if evidence of abdominal infection, usually after 7-10 days of illness. Fever and leukocytosis typical.

Treatment

Surgery

- All patients with complicated pancreatitis should be evaluated by a surgical team.
- In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open laparotomy. Examples include laparoscopy, US or CT guided percutaneous drainage, video-assisted or small incision-based left retroperitoneal debridement, and transgastric or transduodenal endoscopic drainage.
- Asymptomatic necrosis and asymptomatic pseudocysts do not warrant intervention
- In stable patients with infected necrosis, drainage should be delayed allowing for development of a wall around the necrosis (consult surgery for further management).

Other Management

- See referenced guidelines for information on classifications and definitions, hemodynamic and fluid management, biliary tract management, nutrition, prognostic scores, imaging, utility of various surgical interventions, and timing of intervention

Prophylactic Antibiotics

- Prophylactic antibiotics are **not** recommended in pancreatitis, including severe acute pancreatitis, pseudocysts, and sterile pancreatic necrosis. Use of antibiotics in these situations does not improve morbidity and mortality and will alter the microbial flora from enteric gram-negative bacteria to gram-positive bacteria and fungi.

Empiric Antibiotics

- Empiric antibiotics are indicated only in these circumstances:
  - Infected pancreatic necrosis
  - Infected pancreatic pseudocyst
  - Septic shock
- Native belly (i.e., no previous surgeries or instrumentation), community acquired, not septic: piperacillin/tazobactam 3.375g IVq6h.
- Sepsis or risk factors for MDRO (recent hospitalization, antibiotic use, or abdominal surgery, HD, etc.): meropenem 1g IVq8h. Check CT abdomen in 48 hours.
  - Organized fluid collection on US or CT: aspirate ASAP, continue meropenem, and adjust antibiotics based on culture of aspirated fluid.
  - No organized fluid collection on US or CT, blood cultures negative, AND hemodynamically stable: stop antibiotics even if SIRS continues
  - If apparent response to meropenem, continue x 1 week then repeat US or CT
- Fungal coverage should **not** be given empirically

Definitive Antibiotics

- Definitive antibiotics should be based on culture results, with duration guided by clinical response

Peritonitis

- Peritonitis is generalized inflammation of the peritoneal cavity. Types include:
  - Primary: primary infection of the peritoneum, usually due to spontaneous bacterial peritonitis (SBP)
  - Secondary: secondary infection of peritoneum from perforation or disruption of abdominal or pelvic organs, usually due to trauma, infection, or ischemia
  - Tertiary: persistent or recurrent peritonitis after adequate initial therapy
  - Peritoneal dialysis associated
- Distinguishing between SBP and secondary peritonitis is of the utmost importance for determining appropriate management (i.e., antibiotics vs. surgical intervention)
- See below for management of select types of peritonitis

Spontaneous Bacterial Peritonitis (SBP)

Clinical pearls

- SBP is the most common cause of peritonitis in cirrhotics, but secondary peritonitis should be considered in the differential diagnosis also
- Infection is due to intestinal translocation of pathogenic bacteria into ascites fluid; this occurs due to alterations in the gut microbiome, increased intestinal permeability, and impaired immunity in the setting of cirrhosis and ascites
- Signs/symptoms: ESLD patient with ascites can present with fever, chills, abdominal pain, nausea, vomiting, and AMS. Up to 1/3 of patients are asymptomatic.
- Risk factors: ESLD with low ascites fluid protein (<1 g/dL), high serum bilirubin (> 2.5 mg/dL), acute liver failure, active variceal bleed

- Common organisms (usually monomicrobial): Enterobacterales*, S. pneumoniae, Enterococcus spp.* Presence of other organisms on culture suggests possibility of secondary peritonitis.

Diagnosis

- Paracentesis is indicated in new onset ascites, suspicion for SBP, any hospitalized patient with ascites, and variceal bleed. Low clinical suspicion for SBP does NOT exclude SBP.
- Diagnosis of SBP and similar entities is dependent on collection of ascites fluid BEFORE antibiotic administration. Also obtain blood cultures prior to antibiotics.
- Evaluation for SBP includes cell count and differential, and culture
- Ascites fluid LDH, glucose, total protein, alkaline phosphatase can help differentiate between SBP and secondary peritonitis
    - Likelihood of secondary peritonitis is increased if 2 of the following are present: glucose <50, LDH > ULN, total protein >1
- Correct for hemorrhagic ascites (> 10,000 RBC/mm^3) by subtracting 1 PMN per 250 RBCs

	Ascites PMN >250/ ul	**Ascites culture**
SBP	+	+ (monomicrobial)
Culture negative neutrocytic ascites (CNNA)	+	-
Non-neutrocytic bacterascites (NNBA)	-	+ (monomicrobial)
Secondary peritonitis	+	+ (polymicrobial)

Treatment

Empiric Antibiotics

- Start empiric antibiotics if ascites fluid analysis is consistent with SBP or CNNA. Treat NNBA empirically only if patient clinically appears infected.
- First line: ceftriaxone 2g IV q24h for 5 days or cefotaxime 2g q8h
- Severe penicillin allergy: levofloxacin 750 mg PO q24h (ciprofloxacin 500 mg PO BD if levofloxacin unavailable)
- Albumin in addition to antibiotics has been shown to decrease mortality significantly. Use albumin (25%) 1.5 g/kg on day 1 and 1 g/kg on day 3 (rounded to nearest 12.5g) in patients with SCr >1 mg/dL, BUN >30 mg/dL or total bilirubin >4 mg/dL

Definitive antibiotics

- Choose definitive therapy based on culture data. Continue first line therapy if patient is clinically improved. Duration is 5 days.
- Repeat paracentesis at 48 hours may be warranted if patient is not clinically improving.
    - Consider broadening therapy based on suspected patterns of resistance. Consider covering for *Enterococcus spp*.

Prevention

- All patients with ESLD and active variceal bleed: ceftriaxone 1g IV q24h x 5 days (can transition to ciprofloxacin when patient able to tolerate PO)
- All patients with ESLD and prior SBP: lifelong ciprofloxacin 500 mg once daily OR Bactrim 1 DS tab PO daily
- Optional: patients with ESLD and ascites if ascites protein <1.5, impaired renal function (SCr >1.2, BUN >25, Na<130), or liver failure (Child score>9, bilirubin >3): lifelong ciprofloxacin 500 mg once daily or Bactrim 1 DS tab PO daily

Secondary Peritonitis

Clinical pearls

- Any perforation or disruption of abdominal or pelvic organs, usually due to trauma, infection, or ischemia, can cause peritonitis.
- Secondary peritonitis is a surgical emergency and requires urgent evaluation by surgical team.
- Common organisms: polymicrobial, with pathogens dependent on abdominal source of infection. Enterobacterales and anaerobes most common. Some patients are at risk for *Pseudomonas spp., Enterococcus spp*., or *Candida spp.*

Diagnosis

- Many patients, especially if critically ill, will require emergency exploratory laparotomy. Do not delay surgery to obtain imaging.
- Obtain CT A/P with IV contrast in patients not having immediate laparotomy, to delineate site of primary infection
- If SBP is also being considered as a cause, perform diagnostic paracentesis.
    - Both will have PMN>250. Likelihood of secondary peritonitis is increased if 2 of the following are present: glucose <50, LDH > ULN, total protein >1

Treatment

Surgery

- Urgent surgical consultation and intervention are of utmost importance

Empiric Antibiotics

- Mild to moderate, community acquired
    - First line: levofloxacin 750 mg IV/PO q24h PLUS metronidazole 500mg IV/PO q8h
- Critically ill, nosocomial/post-surgical
    - First line: meropenem 1g q8h or piperacillin/tazobactam 3.375 g IVq6h
- Empiric coverage of MRSA, *Enterococcus spp*., and *Candida spp*. not necessary except in multiple recent abdominal surgeries, recent antibiotic use, history of MDRO, or risks for MDRO

Definitive Antibiotics

- Definitive antibiotics should be based on culture data, but generally polymicrobial coverage should be continued
- Indications for *Enterococcus spp*. treatment: found in culture in the absence of polymicrobial infection, with concurrent bacteremia, or in critically ill.
- Indications for *Candida spp*. treatment: found in culture in the absence of polymicrobial infection, with concurrent candidemia, upper GI tract perforation, or in critically ill.

- First line: fluconazole 400mg IV/PO q24h
- Duration can be limited to 4-7 days with adequate source control and clinical improvement

Peritonitis associated with peritoneal dialysis

- Organisms: *Staphylococcus spp., Enterococcus spp*., gram-negative rods
- Peritoneal dialysate fluid should be sampled for cell count, differential, body fluid culture, and amylase
- Repeat cell count to ensure clearance of organism
- Empiric antibiotics
  - Mild to moderate – intraperitoneal therapy preferred
  - Severe illness - Provide gram positive coverage with vancomycin 15 mg/kg IV every 2-3 days and gram-negative coverage with meropenem 1g IVq8h or piperacillin-tazobactam 3.75mg IVq6h
- Definitive antibiotics: based on culture results. Duration 10-14 days.
- Catheter may need to be removed, especially for yeast, *S. aureus*, and *Pseudomonas spp*.

Helicobacter Pylori Infection

Clinical pearls

- H. pylori (HP) infection is associated with gastric inflammation, atrophic gastritis, gastric and duodenal ulcers, gastric cancer, and gastric MALT lymphoma. HP is considered a grade I carcinogen in humans.
- It is estimated that 50% of the world population is infected with HP
- The vast majority of infections are asymptomatic.

Diagnosis

- Testing for H. pylori (HP) is strongly recommended in current peptic ulcer disease (PUD), history of PUD who have never been tested/treated for HP, MALT lymphoma, persistent dyspepsia, after early gastric cancer endoscopic resection, initiation of chronic NSAIDs, chronic ITP, and unexplained iron deficiency anemia
  - Testing in patients with atrophic gastritis, GERD, non-ulcer dyspepsia, mild dyspepsia and family member has HP, risk for gastric cancer, aspirin use with PUD, PPI use, in 1st degree relatives of people with gastric cancer, and unexplained B12 deficiency, are recommended by some but not all sources
- If “red flags” are present, OGD is needed to evaluate for complicated ulcer, malignancy, and other pathology unrelated to HP. Otherwise medical treatment alone for HP is appropriate.
  - Red flags: dysphagia, early satiety, weight loss, abdominal mass, undifferentiated microcytic anemia, family history of gastric cancer, and onset of dyspepsia after age 45.
- Testing: positive result of any of the following tests is diagnostic
  - Does not require OGD
    - HP stool Ag (Helicobacter pylori Stool Antigen, send out test): **preferred test**
    - Urease breath test
  - Requires OGD with biopsy
    - Rapid urease test (Helicobacter pylori Urease): quick and reliable, **preferred test**
    - Pathology: invasive HP visible with special stains

- Upper GI bleeding (UGIB), and use of antibiotics, PPIs, and Histamine-2 blockers (H2B) cause tests for active infection to be falsely negative (serum Ab not affected). Tests for active infection can be done 2-4 weeks after stopping PPI or H2B, and 4 weeks after antibiotic use or UGIB.
- Serum H. pylori antigen test not recommended for diagnosis of active infection.

Treatment

- Any patient meeting indications for testing above should be treated if test is positive (stool or urease breath test)
- Patients who have previously received clarithromycin or metronidazole (ever) are more likely to be resistant to those antibiotics. Inquire about use and avoid regimens including those antibiotics if they have received them in the past.
- **Triple therapy:** 1st line regimen. Some use only if local clarithromycin resistance <15%
    - Clarithromycin 500 mg PO q12 h + tinidazole 500 mg PO q12h + esomeprazole 20 mg PO q12h X 7-14 days
    - Alternative: clarithromycin 500 mg PO q12h + amoxicillin 1 g PO q12h + esomeprazole 20 mg q12h X 7-14 days.
    - Note: Only 50-75% of patients treated are cured with triple therapy. Resistance to clarithromycin or tinidazole/metronidazole can cause treatment failure, as can difficulties with adherence due to pill burden and side effects.
- **Quadruple therapy:** Use in triple therapy failures. Some use as first line due to up to 50% failure rate of triple therapy.
    - Tetracycline 500 mg PO q6h, metronidazole 500 mg PO q8h, bismuth subsalicylate 525 mg PO q6h, + esomeprazole 40 mg PO q24h X 14 days.
    - Clarithromycin 500 mg PO q12h, amoxicillin 1 g PO q12h, metronidazole 500 mg PO q12h+ esomeprazole 40 mg PO q24h X 14 days.
- Substitutions: Do not substitute doxycycline for tetracycline or azithromycin for clarithromycin.
- For patients unable to take PO, consider ampicillin plus metronidazole. Switch to PO as soon as possible.
- Treatment failures: Consider consulting ID or GI if patient fails above regimen(s).
- Test of cure: Successful treatment should be confirmed 1-2 months after completion of therapy, with repeat HP stool Ag (or urease breath test if available). Serum Ab is not useful after treatment, and other methods require repeat EGD. Recall that receipt of H2B or PPI within 2-4 weeks can result in false negative stool Ag test.

Diarrhoea

Clinical pearls

- Acute diarrhoea is defined as abrupt onset of 3 or more loose stools per day for <2 weeks duration
- Common pathogens
    - Viral: norovirus, rotavirus, adenoviruses, astrovirus
    - Bacteria: *Salmonella spp., Shigella spp., Campylobacter spp*., Enterotoxigenic *E. coli, C. difficile,* bacterial toxins
    - Protozoa: *Cryptosporidium parvum, Giardia lamblia, Cyclospora cayatenensis, Entamoeba histolytica*
- Risk factors: contaminated food and water exposure, illness among close contacts, recent travel, HIV status, recent antibiotics

- Most episodes DO NOT require antibiotics
- Cholera (Vibrio cholerae), typhoid (Salmonella Typhi), non-typhi Salmonella– see individual sections
- Clostridiodes difficile: hospitalized patients exposed or currently on antibiotic develop diarrhoea

Diagnosis

- Diarrhoea requiring hospitalization or has blood mixed with the stool – send stool cultures, *C. difficile* toxin if recent antibiotics.

Treatment

- For HIV related diarrhoeal infections, reference HIV guidelines for treatment recommendations. However, optimization of ART is key.
- Consider antibiotics for patients with moderate to severe disease (moderate: defined as distressing or interferes >3-5 stools/24hrs or dysentery (bloody stool) with > 6-9 stools/24hrs, positive stool cultures and leukocytes in stool
- Preferred (enteric pathogens):
  - Azithromycin 500 mg PO q24h for 3 days
  - Alternative: ciprofloxacin 500 mg PO BD OR doxycycline 100 mg PO BD for 3-5 days
- For bloody diarrhoea – nalidixic acid 500 mg PO q6h, plus metronidazole 500 mg PO TID for 5 days
- Duration: 3-5 days (
- Adjunct therapy = symptomatic relief with oral rehydration and anti-diarrhoeal agents
- C. difficile
  - Mild to moderate (WBC </= 15,000 and SCr <1.5): vancomycin 125mg PO q6hrs x 10 days
  - Severe (WBC >15,000 and/or SCr >1.5): vancomycin 125 mg PO q6h
  - Severe, complicated (as above plus ileus or toxic megacolon): vancomycin 500 mg PO q6h plus metronidazole 500 mg IV q8h
  - Duration 10-14 days
  - **Do NOT give adjunct anti-diarrhoeal agents**
  - Recurrent *C. difficile* – consult ID
- Giardia lamblia
  - Metronidazole 400 mg PO TID for 7 days
- Entamoeba histolytica
  - Metronidazole 400 mg PO TID for 10-14 days

Monitoring & Follow-up

- If symptoms have not significantly improved in 72 hours, consider ID consult

Resources

- Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the SIS and the IDSA. Solomkin JS et al,.. Clin Infect Dis. 2010 Jan 15;50(2):133-64
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- Uncomplicated appendicitis: Park et al. Br J Surg 2017 104: 1785-1790.

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Pancreatitis:

- IAP/APA GLs: Pancreatology 2013;(13):e1-15.
- Step-up surgical management: Da Costa DW. Brit J Surgery 2014;101:e65-79.
- ACG GL: Tenner S. Am J Gastroenterol 2013;108:1400-15.
- Pancreatitis classifications: Banks PA. Gut 2013;62(1):102-11.

Peritonitis:

- AASLD SBP GL: aasld.org/practice guidelines/Documents/ascitesupdate2013.pdf
- CAPD peritonitis GLs: Li PK. Perit Dial Int 2010;30(4):393-423.
- RCT ABX Dx peritonitis. Piano S, et al,… Hepatology. 2016 Apr;63(4):1299-309.

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- Mastriicht IV Consensus Report: Malfurtheiner P. Gut 2012;61;646-664.
- US Seroprevalence: Everhart JE. J Infect Di. 2000;181(4):1359-63.
- American College of Gastroenterology GL: Chey WD. Amer J Gastroent 2017;112(2):212-239.

Neutropenic Fever

Clinical pearls

- Patients with acute leukemia or high-grade lymphomas have much higher risk of neutropenic fever (NF) than patients with solid tumor malignancies
- Low risk neutropenic patient (solid tumor) with fever can safely be treated as outpatients if MASCC risk index score is ≥ 21
- Early identification, triage, and appropriately collected specimens (i.e., 2 sets of blood cultures and urine cultures if indicated) **BEFORE** administration of antimicrobials, along with **PROMPT** delivery of antimicrobials are key to successful management of neutropenic fever. Do not delay antibiotics if cultures are not available.

Definition of Neutropenic Fever

- Neutropenia: absolute neutrophil count (ANC) < 500 neutrophils/µL (or <1000 but projected to decline to < 500 within 48 hours)
- ANC = WBC x [PMN/100 + bands/100]
- Fever:
  - Single temperature > 38.3 °C/101^0F
  - Two temperatures > 38.0°C/100.4^0F within one hour

- Any signs or symptoms of infection including hypotension, tachycardia, or subjective fever, chills, rigors, etc.

Empiric Antibiotics

- Patients become infected with bacteria and yeast that colonize their skin, mouth, and GI tract. Prior cultures should be considered when choosing empiric therapy.
- Septic patients should be treated according to the guidelines in the sepsis section or based on known site of infection.

Gram-negative and Gram-positive coverage

- Basic Initial regimen: piperacillin/tazobactam 4.5 g IVq6h (preferred choice) OR meropenem 1 g IVq8h
- Severe penicillin allergy: ciprofloxacin 500mg po BD OR levofloxacin 750 mg IV/PO QD PLUS amikacin (15mg/kg/day)
- Vancomycin should not be added to empiric coverage even in patients with central venous catheters in absence of increased risk for MRSA infection outlined below.

Resistant Gram-positive coverage

- Add vancomycin IV (see appendix for dosing) OR linezolid 600mg IV/PO BD to coverage above if: MRSA colonized, skin/soft-tissue infection, suspected Staphylococcus spp. bacteremia (Gram + cocci in clusters on Gram stain), sepsis. In patients with bone marrow transplant, also give if patient has mucositis.

Definitive Antibiotics

- Modification of initial regimen should be guided by culture and susceptibilities

Antibiotic Duration

- Antimicrobials are continued until ANC > 500 neutrophils/µL (consider de-escalation or stopping if the patient remains afebrile for at least 72hrs and all cultures are negative)
- Median time for defervescence is ~3 days
- If fevers are persistent, consider other causes
  - Infectious: resistant Gram-positive or Gram-negative infection, fungal sinusitis or pneumonia, disseminated candidiasis (See candidiasis for evaluation and treatment of disseminated candidiasis)
  - Non-infectious: fever from malignancy (more commonly seen with refractory malignancies), transfusion reactions, venous thromboembolism, drug fever (common with certain chemotherapy regimens)

Anti-Infective Prophylaxis in Cancer patients

Bacterial

Patients:

- Outpatient with expected ANC <100 for ≥ 7 days
- Inpatients receiving high dose steroid-containing chemotherapy AND expected ANC <100 for ≥ 7 days
- Regimen: levofloxacin 750 mg PO qday

Viral

Patients:

- Acute myelogenous leukemia, during periods of neutropenia
- Acute and chronic lymphocytic leukemia
- Lymphoma treated with high dose steroid-containing chemotherapy
- Solid tumor receiving high dose steroid-containing chemotherapy
- History of shingles, genital herpes, or frequent fever blisters
- Regimen: acyclovir 400-800 mg PO BD, famciclovir 500 mg PO BD, or valacyclovir 500 mg PO BD

Pneumocystis jirovecii

Patients:

- Acute and chronic lymphocytic leukemia
- Lymphoma treated with intense high dose steroid-containing chemotherapy or purine-based chemotherapy (e.g., fludarabine, cladribine)
- Regimen: trimethoprim-sulfamethoxazole 960mg PO QD, dapsone 50-100 mg PO QD, or inhaled pentamidine monthly (test for G-6-PD deficiency BEFORE patient receives first red blood cell transfusion).

Fungal

Patients:

- Acute myelogenous leukemia, while ANC<500 with induction and consolidation chemotherapy
- All leukemia patients, who were previously infected (confirmed or presumed) during previous periods of neutropenia
- Regimen: voriconazole 200 mg PO BD or posaconazole 300 mg PO QD
- Acute lymphocytic leukemia, while ANC<500 with induction and consolidation chemotherapy
- Regimen: fluconazole 400 mg PO QD

Resources

- Guidelines for antimicrobials in neutropenic cancer patients: Friefeld AG. Clin Infect Dis. 2011;52(4):e56-e93.
- NCCN Guidelines: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf.
- MASCC Risk Index**:** Klastersky J. J Clin Onc 2000;18:3038-3051.

Obstetrics and Gynaecological Infections

Obstetrics and Gynaecology

Pelvic inflammatory disease (PID)

Clinical pearls

- PID encompasses a spectrum of inflammatory disorders of the upper female genital tract including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis
- Wide variations in symptoms or lack of symptoms are common, making delays in diagnosis and treatment frequent

- Common organisms: *N. gonorrhoeae, C. trachomatis*, and vaginal flora (including anaerobes). *Mycoplasma spp., Ureaplasma spp*., and CMV may also be implicated.
- OB/GYN and ID consult should be considered in difficult cases

Diagnosis

- PID can be difficult to diagnose. Most cases are diagnosed by a combination of symptoms, physical exam findings, laboratory findings, and pelvic or transvaginal US. Advanced diagnostic modalities can include pelvic MRI, endometrial biopsy, or laparoscopy.
- 'Definitive' diagnosis is not required for treatment initiation, as sensitivity of any single test is not adequate, and the complications of untreated PID are unacceptable
- Suspect PID in any woman at risk for STI (i.e., sexually active) presenting with lower abdominal or pelvic pain without clear alternate diagnosis
    - Cervical motion tenderness, uterine tenderness, or adnexal tenderness on pelvic examination is sufficient to warrant empiric treatment

The following symptoms increase specificity:

- Fever
- Abnormal mucopurulent cervical discharge or cervical friability
- Abundant WBC on microscopy of vaginal fluid
- Elevated ESR or CRP
- Positive NAAT or microscopy/culture for *N. gonorrhoeae* or *C. trachomatis*
    - **A negative endocervical *N. gonorrhoeae/ C. trachomatis* NAAT does not rule out PID**
- Definitive diagnosis:
    - Endometrial biopsy with histopathologic evidence of endometritis
    - Pelvic or transvaginal US or pelvic MRI showing thickened, fluid-filled tubes with or without free pelvic fluid, or tubo-ovarian complex
    - Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
    - Laparoscopic findings consistent with PID

Treatment

- **Mild - moderate** (patients with temperature < 38^0c, WBC <11,000/mm^3, minimal evidence of peritonitis, active bowel sounds and can tolerate oral food): Treat outpatient
    - Ceftriaxone 250mg IM once + doxycycline 100mg PO BD for 14 days +/- metronidazole 500mg PO BD for 14 days
    - Alternative: Substitute cefixime 400 mg PO for ceftriaxone above
    - Women treated as outpatients must be able to return for re-evaluation in 3 days. Those who do not respond by then (no fever, less abdominal/pelvic pain less adnexal, uterine, and cervical motion tenderness), need hospitalization and reevaluation for PID and alternate causes.
- **Moderate - severe:**
    - Hospitalize women with: nausea or vomiting who are unable to tolerate oral regimen, no response to oral therapy, high fever, pregnancy, tubo-ovarian abscess, or if surgical emergencies (e.g., appendicitis) cannot be excluded
    - Ceftriaxone 1g IVq24h + doxycycline 100mg PO/IV q12h + metronidazole 500 mg PO/IV q8h
    - Severe penicillin allergy only: clindamycin 900mg IVq8h + gentamicin loading dose 2 mg/kg IV/IM followed by maintenance dose 1.5 mg/kg q8h

- May transition to oral therapy within 24-48 hours of clinical improvement
- If no clinical improvement (see above) within 72 hours, consider antibiotic change, additional diagnostic evaluation for PID and alternate diagnoses, and possible surgical intervention

- In women with intrauterine devices (IUD) who are diagnosed with PID, consider removing IUD if no clinical improvement noted within 72 hours of starting therapy
- Treatment of sex partners, avoidance of sex, and follow up testing as per Zambia STI treatment guidelines

Infections in Pregnancy

- **Seek specialist advice on the use of antimicrobials in pregnancy. Consult ID, OB & Gyn and Pharmacy.**

Pulmonary Infections

Bronchitis, Acute

Clinical pearls

- Acute bronchitis is defined as self-limited inflammation of the upper airways due to infection or irritants. It should be differentiated from small airway disease by the presence of airway obstruction.
- Most common presenting complaint is cough (can be productive or non-productive) that can be accompanied by sinus congestion, rhinorrhea and sore throat
- Most commonly caused by viruses e.g., rhinovirus, parainfluenza, human coronavirus (exception: SARS CoV-1 and SARS-CoV-2, the virus that causes COVID-19), and RSV.
- Less commonly, can be caused by atypical bacteria, including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, or non-infectious offenders (allergens, smoking, pollution)
- Rarely can be caused by other bacteria including Bordetella pertussis in non-immunized hosts. Presentation would be persistent, dry cough for 2-6 weeks or more with cough paroxysms, post-tussive emesis and rib pain.

Diagnosis

- Clinical diagnosis based on symptoms and lack of abnormal systemic or pulmonary findings
- Rule out pneumonia and consider chest Xray in patients with abnormal vital signs (P>100, T>38°C, RR>20), rales, or cough >3 weeks

Treatment

- **Antibiotics are not indicated. They will not be effective.**
  - Exception: pertussis, and acute exacerbations of COPD
- Supportive care, symptomatic management

Bronchiectasis

Clinical pearls

- Abnormal, irreversible dilation of the bronchi due to destruction of the bronchial walls. Often a consequence of pulmonary infections such as untreated bacterial pneumonia, TB, endemic fungal infections, structural lung disease, or mucociliary problems.
- Characterized by wet/productive cough +/- dyspnea, bronchospasm, clubbing, hyperinflation, recurrent infections lasting months to years
- Diagnosis of a flare should include 4 of the following:
  - change in sputum
  - increased dyspnea
  - increased cough
  - fever
  - increased wheezing
  - fatigue
  - worsened pulmonary function tests
  - new infiltrate
  - change in lung exam
- Bacterial causes are lung tissue colonizers such as *K.pneumoniae, S. pneumoniae, H. influenzae. P. aeruginosa* and *S. aureus* may be seen in antibiotic experienced patients
- Other organisms include non-tuberculosis mycobacteria, *Aspergillus spp.*

Diagnosis

- Chest X-ray with tram tracks due to non-tempering of the bronchioles; may appear as cylindrical, secular, or cystic
- CT: gold standard to secure diagnosis of bronchiectasis.
- Dilation of bronchi >1.5x nearby vessel, lack of tapering and dilatation may be more specific than bronchial dilatation alone, bronchial wall thickening, cysts
- Sputum culture should be obtained in all patients

Treatment

- Outpatient:
  - Empiric therapy in patients without previous culture data: levofloxacin 750mg PO QD
  - Severe disease or history of *P. aeruginosa*: levofloxacin 750mg PO QD or Ciprofloxacin 750mg PO BD
  - Adjust therapy based on cultures
  - Duration: 10-14 days
- Inpatient:
  - Piperacillin/tazobactam 4.5g IVq6h
  - Alternative: levofloxacin 750mg PO/IV OD
  - Adjust therapy based on cultures
  - Duration: 14 days
- Allergic bronchopulmonary aspergillosis: prednisolone 0.5-1 mg/kg/day and itraconazole 400 mg daily
- Adjunct therapy: nebulized saline or hypertonic (3%) saline may help facilitate airway clearance, reduce sputum viscosity, and improve expectation. No role for bronchodilators.

Prevention

- Consider for patients with >3 flares per year, persistent symptoms, or 2+ hospitalizations
  - Azithromycin 250 mg daily or 500 mg PO three times per week
  - Before commencing, ensure that non-tubercular mycobacterial infection has been ruled out
  - Duration 6-12 months

Acute Bacterial Exacerbation of COPD

Clinical pearls

- COPD is defined by persistent airflow limitation that is typically progressive in nature and associated with an inflammation of the airways due to noxious stimuli
- COPD exacerbation is defined as worsening of a patient's chronic respiratory symptoms beyond normal day-to-day variation, accompanied by a need for medication change
- COPD subtypes include emphysema, chronic bronchitis, and chronic obstructive asthma
- Pulmonary infections (bacterial and viral) trigger ~70% of COPD exacerbations; viruses are most common particularly in winter months
- Common organisms: *H. influenza, M. catarrhalis, S. pneumoniae*, rhinovirus, parainfluenza virus, influenza virus, and respiratory syncytial virus. Change in strain of colonizers can also trigger exacerbation. Pseudomonas spp. and Enterobacterales are rarer and mostly in patients with severe COPD and a history of antibiotic exposure.

Diagnosis

- Signs/ symptoms in exacerbation caused by infection:
  - Cough with or without Increased sputum production AND either increased sputum volume or increased dyspnoea at rest or exertion
- Patients requiring hospitalization, or non-invasive or invasive ventilation are presumed to have infection
- Sputum culture has low yield as similar organisms are recovered in patients before, during, and after exacerbation. Culture **does not** distinguish colonization from infection.
- If available, viral respiratory panels can aid in diagnosis

Treatment

- Several studies have shown that antibiotic therapy improves mortality in patients hospitalized for COPD exacerbations; benefit is less clear for outpatient exacerbations
- Indications for antibiotics in COPD exacerbation include increased sputum purulence, increased sputum volume or increased dyspnoea OR requiring mechanical ventilation.
- Outpatient or non-severe illness
  - **Uncomplicated** (low risk for poor outcome): no cardiac disease, <65y/o, <3 exacerbations per year, FEV1>50% predicted (if known)
    - Azithromycin 500mg PO QD OR cefuroxime 500mg BD OR doxycycline 100mg PO BD
  - **Complicated**: co-morbidities especially cardiac, age ≥65, severe COPD (i.e., FEV1≤50% predicted, if known), ≥3 exacerbations/ year
    - Amoxicillin/clavulanate 1g PO BID
- Inpatients, severe illness
  - Hospitalization ≥2 days in past 90 days, ≥4 courses of antibiotics in last year, severe COPD, previous *Pseudomonas spp*., systemic glucocorticoids: piperacillin/tazobactam 4.5 g IVq6h or meropenem 1g IVq8h
  - Alternative: levofloxacin 750 mg IV/PO QD
- Re-evaluate after 72 hours of therapy; if not improved obtain sputum culture
- Treatment duration varies from 3-7 days depending on rate of response to therapy

Resources

- Global Initiative for Chronic Obstructive Lung Disease Guidelines, 2016: http://www.goldcopd.org/

Pneumonia

Definitions

- Pneumonia is defined as inflammation of the lower respiratory tract secondary to infection with bacterial, viral, or fungal organisms. Community acquired pneumonia (CAP) is pneumonia in a patient without exposure to health care settings.
- Hospital-acquired pneumonia (HAP) is pneumonia that develops ≥48 hours after hospital admission (i.e., NOT present on admission).
- Ventilator-associated pneumonia (VAP) is pneumonia arising greater than 48-72 hours after endotracheal intubation and is caused by bacterial colonization of the oropharynx/stomach/sinuses coupled with aspiration of secretions or ventilator circuit condensate.

Clinical pearls

- Risk factors for pneumonia: Underlying lung disease (e.g., COPD, asthma), smoking, alcoholism, recent or current hospitalization, immunosuppression, and age ≤ 2 or ≥ 65
- Risk factors for VAP: Factors that increase risk of aspiration (e.g., acid suppressants, re-intubation, tracheostomy, laying supine, presence of NG tube, enteral nutrition), COPD, prolonged mechanical ventilation, and prior antibiotic exposure
- Common CAP organisms: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, atypical bacteria* (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella spp*.), viruses (rhinovirus, adenovirus, parainfluenza virus, influenza virus, SARS-CoV-2)
- Common HAP organisms: CAP organisms plus nosocomial pathogens including MRSA, *Pseudomonas spp., Acinetobacter spp.*, and Enterobacterales
- Common VAP organisms: nosocomial pathogens are likely; including MRSA, *Pseudomonas spp*., *Stenotrophomonas maltophilia*, *Acinetobacter spp.*, Enterobacterales.
- Other potential causes of pneumonia: TB, PCP (HIV-associated), and fungal (histoplasmosis, blastomyces)
- *Enterococcus spp*. and *Candida spp*. are often isolated from respiratory samples in hospitalized patients, but true infection is exceedingly rare. These should be considered colonizers and should NOT be treated.
- Diagnosis and management of pleural effusion are complex topics. Any effusion ≥ 1 cm or 10mm associated with pneumonia should be investigated with thoracentesis and appropriate laboratory testing based on clinical situation to rule out parapneumonic effusions and/or empyema.
- Aspiration pneumonia is usually caused by less virulent bacteria which are common constituents of the normal flora in a susceptible host prone to aspiration. This typically consists of oral anaerobes and streptococci. Occasionally, patients who have been hospitalized for an extended period of time may be infected with nosocomial organisms.
- Addition of anaerobic coverage is not needed for aspiration pneumonia; oral anaerobes are adequately covered by standard pneumonia therapy. Only add additional anaerobic coverage if lung abscess or empyema.
- Chemical pneumonitis is the aspiration of substances that are toxic to the lower airways, independent of bacterial infection; important to differentiate from aspiration pneumonia. Aspiration pneumonitis is typically more acute and fulminant than aspiration pneumonia. Happens rapidly and can occur with fevers. Does not require antibiotics for treatment.
- **Test for HIV and TB in all patients of unknown status presenting with pneumonia**

Diagnosis

- There are no definitive criteria that confirm or exclude a diagnosis of pneumonia in non-intubated patients
    - Generally, patients will have fever, cough with or without sputum production, dyspnea, and leukocytosis. **Must have opacities on CXR or CT**.
    - Patients may also have evidence of respiratory failure and/or sepsis
    - If clinical signs are concerning for pneumonia but initial chest imaging is unremarkable, it should be repeated in 2-3 days
    - Physical exam is less sensitive and specific than chest imaging
- Aspiration pneumonia has a more indolent course progressing over several days or weeks. Imaging typically shows involvement of the dependent pulmonary segments - lower lobes when aspiration

occurs in the upright position or the superior segments of the lower lobes or posterior segment of the upper lobes when aspiration occurs in laying down.

- For VAP, diagnosis requires new or worsened infiltrate on CXR or CT plus at least 1 of the following: fever, decreased respiratory function (increased minute ventilation or respiratory rate, decreased tidal volume, hypoxemia), increased thickness and/or quantity of respiratory secretions, leucocytosis, increased coarseness of breath sounds.
- The Modified Clinical Pulmonary Infection Score (CPIS) can help in diagnosis of VAP

	0 Points	1 Point	2 Points
Tracheal secretions	Rare	Abundant	Abundant + purulent
Infiltrate on CXR	None	Diffuse	Localized
Temperature (°C)	36.5-38.4	38.5-38.9	<36 or >39
WBC ($1000/mm^3$)	4 – 11	<4 or >11	<4 of >11 with >500 bands
PaO_2/FiO_2	ARDS or >240		Without ARDS and <240

CPIS Score <6 – VAP is unlikely, consider alternative diagnoses.

- Microbiology: Commonly used tests include sputum culture, blood culture, viral respiratory panel. These tests are not needed in every patient.
  - Viral respiratory panel should be sent for all patients presenting with respiratory symptoms. Note that 20% of patients with viral PNA have bacterial superinfection. This association is especially strong with Influenza virus and *S. aureus*.
  - Patients treated as outpatients (includes those discharged from ED, see below for criteria for outpatient treatment), do not require any additional testing.
  - All in-patients with severe pneumonia should have blood cultures collected before antibiotics are given. Collect sputum for culture in inpatients with productive cough. However, antibiotics should not be delayed if there is delay in obtaining cultures.
  - All intubated patients should have lower respiratory tract cultures sent.
  - **Order MRSA surveillance culture in any patient that you plan to treat empirically for MRSA PNA**. **Negative predictive value is high and can aid in earlier antibiotic de-escalation.**
  - Additional testing for TB should be completed if patient is co-infected with HIV or if patient has other risk factors for TB; refer to TB guidelines

Treatment

- Treatment location (inpatient vs outpatient) for CAP: Use 'CURB-65' score or pneumonia severity index (PSI), plus clinical judgment to determine who can safely be treated in an outpatient setting
  - PSI: Demographic factors, comorbidities, physical exam, laboratory, and radiological findings can be entered into online PSI calculator (internalmedicine.osu.edu/pulmonary/cap/10849). Suggested site of care is based on estimated mortality.
  - CURB-65 score:
    1 point each is given for:
    - decreased **c**onsciousness,
    - increased blood **u**rea nitrogen (if available)

- **r**espiratory rate >30/min
- **B**P <90 systolic, and
- age > **65** years.
    - If BUN is unavailable, add one point

Score:	Mortality Risk:	Patient status:
0-1	1-2.7%	outpatient
2	6.8%	inpatient, or outpatient with close follow up
3-5	>14%	inpatient, possibly ICU

Outpatient CAP

- Healthy, no comorbidities, low concern for resistance
    - Amoxicillin/clavulanate 1g PO BD x 5 days
    - Doxycycline 100 mg PO BD x 5 days
- Comorbidities (COPD, diabetes, CHF, renal, asthma, etc.) or concern for resistance (recent antibiotics) select one from each group
    - Amoxicillin/clavulanate 1g PO qBD x 5 days PLUS azithromycin 500 mg PO daily x 5 days, OR
    - Cefuroxime 500 mg BD x 5 days PLUS azithromycin 500 mg PO daily x 5 days
    - If severe penicillin/cephalosporin allergy: levofloxacin 750 mg PO daily x 5 days

Inpatient CAP and aspiration pneumonia

- Non-ICU
    - Amoxicillin/clavulanate 2g PO BD OR ceftriaxone 1-2 g IV daily AND azithromycin 500 mg PO/IV q24h OR doxycycline 100 mg PO q12h
        - Severe penicillin allergy: levofloxacin 750 mg PO daily x 5 days
- ICU
    - Meropenem 1g IVq8h or piperacillin/tazobactam 4.5g IVq6h AND doxycycline 100 mg PO q12h or azithromycin 500mg PO/IV q24h
    - Severe penicillin allergy: levofloxacin 750 mg IV q24h
    - Necrotizing or cavitary pneumonia: add MRSA coverage
        - ADD Linezolid 600 mg PO q12h to above regimen (preferred)
        - Vancomycin can be used an alternative if linezolid unavailable
        - Doxycycline is not adequate to treat S. aureus pneumonia

Hospital Acquired Pneumonia (HAP), Ventilator Associated Pneumonia (VAP)

- Piperacillin/tazobactam 4.5 g IVq6h (or 3.375 g IV q4h) OR
- Meropenem 1g IVq8h

If suspicion of MRSA add:

- Linezolid 600 mg IV/PO q12h OR
- Vancomycin 15 mg/kg q12h

Definitive Antibiotic choice, Follow up, and Antibiotic duration

- Antibiotic coverage should always be narrowed as soon as culture results are available

- If MRSA surveillance cultures are negative, stop MRSA coverage. This has a high negative predictive value for MRSA pneumonia.
- If IV agents are started, switch to PO as soon as appropriate in stable patients
- If HAP or VAP is confirmed, treat for 7 days
- If CAP:
    - 5 days: minimum duration, should be afebrile for 48-72h and have no more than 1 sign of clinical instability (listed below)
    - Azithromycin 500 mg x 3 days is an adequate course for atypical coverage (unless suspected or confirmed Legionella pneumonia)
    - Consider longer durations (7-14 days) in patients with immunocompromised, structural lung disease, or slow clinical response
- Criteria for clinical stability: afebrile for ≥ 48 hours, requires no supplemental oxygen, and has ≤1 abnormal vital signs (HR >100, RR >24, SBP <90),
- Cough and chest imaging abnormalities may take 4-6 weeks to improve and should not be used as tests of cure
- If patients have not resolved after 3-5 days of antibiotic therapy, TB should be ruled out
- Patients being treated for aspiration pneumonia who defervesce rapidly (~24 hours) should get repeat imaging. If infiltrates and signs and symptoms have resolved, antibiotics should be discontinued as it is likely aspiration pneumonitis and not aspiration pneumonia
- In intubated patients, tracheal colonization may not be eradicated despite sterilization of lower airways. Therefore, follow up cultures should not be obtained unless there is clinical deterioration or suspicion for recurrent pneumonia.

Resources

- IDSA/ATS Guidelines for HAP/VAP: Kalil AC Clin Infect Dis 2016; 63 (5) e61-e111
- IDSA/ATS Guidelines for CAP: Metlay J. Am J Respir Crit Care Med 2019;200(7):e45-e67.
- Antibiotic duration in VAP: Chastre J. JAMA 2003;290:2588-98.
- Clinical pulmonary infection score: Fartoukh M. Am J Respir Crit Care Med 2003;168:173-9.

Lung Abscess & Empyema

Clinical pearls

- Lung abscess, necrotizing pneumonia, and empyema are usually consequences of aspiration of oral flora into the lung. Oral flora such as *Streptococcus anginosus* group, *Fusobacterium nucleatum*, *Bacteroides spp*., and *Peptostreptococcus spp*. are often implicated.
    - Predisposing conditions include those that lead to aspiration: CVA, seizures, esophageal dysmotility, gastro-oesophageal reflux, endotracheal intubation, altered consciousness, and intoxication
- Additional pathogens that may cause lung abscess or cavity include
    - Bacterial: *S. aureus* and *Streptococcus pyogenes* (particularly following influenza infection), *Klebsiella pneumoniae, Pseudomonas aeruginosa, Legionella spp., Nocardia spp., Actinomyces spp., H. influenza, Rhodococcus equi*
    - Mycobacterial: tuberculosis complex, kansasii, avium-intracellular complex, and abscessus
    - Fungi: *Aspergillus spp., Cryptococcus spp. , Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Fusarium spp. , Mucormycoses*
    - Parasitic: *Echinococcus granulosus, Paragonimus westermani*

Diagnosis

- Patients present with symptoms of pneumonia (cough, fever, purulent sputum, hemoptysis, pleuritic chest pain), plus putrid smelling sputum if lung abscess is due to aspiration of oral flora. Presentation may be protracted, with indolent signs of infection such as night sweats, weight loss, and fatigu Pulmonary e.
- On exam patient will have typical findings of pneumonia and may also have poor dentition and gingivitis
- Sputum culture will grow normal oral flora in cases of abscess from aspiration. Other pathogens noted above can be seen and should be tested for based on clinical suspicion (e.g., AFB or fungal cultures).
- Chest imaging is diagnostic
- Differential diagnosis should include malignancy, pulmonary embolus, and pulmonary vasculitis

Treatment

- Antibiotic regimen should cover typical community acquired pneumonia pathogens plus oral anaerobes.
  - Amoxicillin-clavulanate 1g PO BD
  - Ceftriaxone 1-2g IV OD plus metronidazole 500mg PO TID
- Alternate regimens:
  - Piperacillin-tazobactam 3.375g IV q8h
  - Meropenem 1g IV q8h
- Beta-lactam allergy: Levofloxacin 750 mg PO/IV daily
- Add coverage for MRSA if patient has severe necrotizing pneumonia, respiratory failure, or has pneumonia/abscess following possible influenza
  - Vancomycin 15 mg/kg q12h OR
  - Linezolid 600 mg IV/PO q12h
- Surgical intervention may be necessary to drain abscess
- Duration of treatment of 4-6 weeks
- **Extended duration of antibiotics is usually necessary and guided by resolution of abscess on imaging**

Empyema

Clinical pearls

- A diagnosis of pleural empyema should be made in older children and adults (Age > 5 years).
- Presents as either acute (usually parapneumonic) or subacute /chronic
- If blood, respiratory, or pleural fluid culture and Gram-stain are negative, treat as subacute (below)
- Drainage is almost always indicated
- Tuberculosis or tumor are considerations if epidemiological risk is present, presentation is subacute or chronic, and routine cultures are negative
- **Light's criteria:** fluid is exudative if pleural fluid to serum protein ratio >0.5 or pleural fluid to serum LDH >0.6 or pleural fluid LDH > 0.67 x upper limit of normal serum LDH
- Alternative, more specific criteria fluid is exudative if cholesterol is > 55 mg/dl, LDH > 200 U/L, or the ratio of pleural fluid to serum cholesterol is > 0.3

- **Differentiation:**
  - **Uncomplicated parapneumonic effusions**: small to moderate and free-flowing, pH > 7.20, glucose > 60 mg/dL, negative culture and Gram stain; tend to resolve on their own
  - **Complicated parapneumonic effusions**: large volume, loculated, thickened parietal pleura, pH < 7.20, glucose < 60 mg/d; often require drainage
  - **Empyema**: presence of pus, positive culture, or Gram-stain in addition to features of complicated effusion; requires drainage + decortication procedure or video-assisted thorascopic surgery (VATS) for loculated effusions with extensive pleural fibrosis
- If tuberculosis is suspected, do pleural biopsy with histology and culture for mycobacteria
- Staphylococcal empyema is usually a complication of S. aureus pneumonia and/or bacteremia

Etiologies

- **Acute:**
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*
  - *Staphylococcus aureus* (MSSA and MRSA)
  - *Haemophilus influenzae*
- **Subacute/Chronic:**
  - Anaerobic streptococci
  - *Streptococcus milleri* group
  - *Bacteroides spp*.
  - Oral Gram-negative anaerobes
  - Enterobacterales
  - *M. tuberculosis*

Primary Regimens

- Perform diagnostic thoracentesis; catheter or chest tube drainage for empyema (See Comments section below).
- Choice of regimen is determined by clinical presentation and etiology.
  - **Acute**
    - *Streptococcus pneumoniae* or *Streptococcus spp*. (Group A):
      - Ceftriaxone 2 gm IV q24h or Cefotaxime 2 gm IV q8h (where available)
    - *Staph. aureus:*
      - MSSA: Adult: Cloxacillin 2g IV q6h; Child: 50 mg/kg IV q6h
      - MRSA: Adult: Vancomycin 15-20 mg/kg IV q8-12h to achieve trough of 15-20 µg/mL); Child: 60-80 mg/kg/day in 3-4 divided doses or Adult: Linezolid 600 mg IV q12h; Child: 10 mg/kg q8h up to age 12)
    - *H. influenzae:*
      - Adult: Ceftriaxone 2 gm IV q24h; Child: 50 mg/kg IV q24h)
  - **Subacute or chronic**
    - Adult: Clindamycin 450-900 mg IV q8h; (Child: 7.5 mg/kg IV q8h) + Ceftriaxone 2 gm IV q24h; Child: 50 mg/kg IV q24h)

Alternative Regimens

Acute:

- S. pneumoniae, penicillin susceptible strains MIC < 2 µg/ml:

    - Adult: Penicillin G 12-18 million units IV divided q4h/day; Child: 150,000-300,000 units/kg/day IV divided q4-6h
    - Adult: Ampicillin 8-12 gm IV divided q4h/day; Child: 150-200 mg/kg/day IV divided q4-6h
- Strep. pneumoniae or Streptococcus pyogenes (Group A):
    - Penicillin G 12-18 million units IV divided q4h/day
    - Vancomycin 1 gm IV q12h; Child:40 mg/kg/day in 3-4 divided doses
- H. influenzae:
    - Adult: TMP-SMX (5-10 mg/kg/day as trimethoprim component) IV/po in 2-3 divided doses or Ampicillin-sulbactam 3 gm IV q6h; Child: 100-300 mg/kg/day IV divided q6h

Subacute/Chronic: (Empiric – of patient is clinically stable would recommend cefoxitin or ampicillin-sulbactam; if clinically unstable can empirically start meropenem or piperacillin-tazobactam while awaiting culture data.)

- Cefoxitin 2 gm IV q6-8h; Child: 80-160 mg/kg/day IV divided q6h
- Ampicillin-sulbactam 3 gm IV q6h; Child: 100-300 mg/kg/day IV divided q6h
- Meropenem 500mg IV q8h OR Imipenem-cilastatin 0.5 gm IV q6h; Child: 15-25 mg/kg/day [max dose 2 gm/day]) IV divided q6h (depending on availability)
- Piperacillin-tazobactam 3.375 gm IV q6h (or 4-hour infusion of 3.375 gm q8h); Child: 100 mg/kg IV q6h)

Antimicrobial Stewardship

- Can step-down to oral therapy once drainage has been established and the patient has responded; depending on the microbiology oral options include amoxicillin, amoxicillin-clavulanate, clindamycin, moxifloxacin, linezolid
- Duration of therapy ill-defined but 4-6 weeks is typical

Comments

- Vancomycin: traditional paediatric dosing of 45-60 mg/kg/day frequently does not achieve target AUC in term infants and older children with normal renal function. Use of AUC 24 closer to 400 µg/mL adequate for most non-CNS infections.
- Intrapleural tissue plasminogen activator (t-PA), 10 mg + DNase 5 mg administered via chest tube twice daily for 3 days improved fluid drainage, reduced the frequency of surgery, and reduced the duration of the hospital stay; neither agent was effective alone.
- Pros and cons of intrapleural fibrinolytics for complicated parapneumonic effusion
- Criteria for differentiating transudative (i.e., non-inflammatory) from exudative pleural effusion

Resources:

- Intrapleural use of tissue plasminogen activator and DNase in pleural infection. Rahman NM, et al,.. N Engl J Med. 2011 Aug 11;365(6):518-26.
- Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. Wilcox Meet al,.. JAMA. 2014 Jun 18;311(23):2422-31.
- Diagnostic approach to pleural effusion. Saguil A, et al... Am Fam Physician. 2014 Jul 15;90(2):99-104

Sepsis

Clinical pearls

- Sepsis is a life-threatening clinical syndrome that involves biologic and physiologic abnormalities that cause organ dysfunction due to the host response to infection
    - The 'quick' Sequential Organ Failure Assessment Score (qSOFA) can help identify early sepsis with three components. Patients would have at least 2 of:
        - Respiratory rate ≥22/min
        - Altered mentation
        - Systolic blood pressure ≤100 mmHg
    - Systemic inflammatory response syndrome (SIRS) criteria (at least 2) plus suspicion for infection can also indicate sepsis, although there are many non-infectious causes of SIRS.
        - Body temperature ≥38°C or <36°C
        - Heart rate >90/min
        - Respirations >20/min
        - White blood cell count >12 x 10^9/L
    - Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality compared to sepsis alone defined by need for vasopressor therapy to maintain MAP >65 mmHg and lactate >2 mmoL/L
- The latest University Teaching Hospital (UTH) Microbiological data (2020) indicate coagulase negative staphylococcus (CoNS), Enterobacterales (*Klebsiella spp, E.coli, Enterobacter spp*.), and *Staphylococcus aureus* as the most common pathogens isolated from blood. Previous studies at the institution have also shown tuberculosis to be one of the commonest causes of sepsis.
- For sepsis, refer to specific sections based on suspected source of infection (e.g., pneumonia, urinary tract infection). Use below empiric antibiotic recommendations for septic shock.
- Empiric therapy for septic shock (i.e., acutely ill patient with ICU level of care, suspected hospital acquired infections) should cover both MRSA and Pseudomonas spp.
- Prior microbiological data and antibiotic history should be reviewed, and antibiotics tailored to cover prior resistant pathogens.
- **Consult ID for all cases of septic shock**.

Diagnosis

- Collection of cultures prior to antibiotics is crucial for diagnosis and tailoring of antimicrobials.
- Antibiotics should be given within an hour of presentation and should not be delayed if cultures cannot be obtained.
- Complete a septic screen which should include at minimum obtaining 2 sets of blood cultures (one aerobic and one anaerobic from different sites within 1 hour, at least 30 minutes apart), urinalysis and urine culture, lumbar puncture with CSF for m/c/s, malaria slide, and chest imaging. In addition, screening for TB must be done through sputum AFB gene Xpert, urine LAM (HIV+, severely ill) and biopsy if indicated. Consider MTB blood culture.

Treatment

- Mortality increases with delays in antibiotic administration. Antibiotics should be given within **one hour** of recognition of sepsis or septic shock.
- Identification and control of infectious source is critical. For unstable patients, the least invasive methods (i.e., percutaneous drainage) are often preferable to surgery.

- Gram-negative/pseudomonal coverage **(give this agent first)**
  - Piperacillin-tazobactam 4.5g IV q6h OR Meropenem 1g IV q8h +/- Amikacin 25 mg/kg ideal body weight IV x 1
  - **Amikacin should be given as one-time dose only. Further doses require Infectious Diseases authorization and should only be used if cultures return with multi-drug resistant organisms.**
- Gram-positive/MRSA coverage
  - Vancomycin load with 30mg/kg, then 15 mg/kg slow IV q12h (**closely monitor renal function every 24 hours**)
  - Linezolid 600mg IV q12h (if vancomycin unavailable)
- Necrotizing fasciitis suspected: add clindamycin 600mg IV q8h (to block toxin production)
- Other source suspected (i.e., meningitis, skin/soft tissue): see individual sections for additional coverage needed
- Antibiotics should be narrowed based on culture results. MRSA coverage should generally be stopped if reliable cultures do not grow MRSA.
- Duration determined by identified source of infection – see those individual sections

Resources

- Surviving Sepsis Campaign: Rhodes A. Intensive Care Med 2017; 43(3):304-377.

Skin and Soft Tissue Infections

Skin and Soft Tissue Infections

Cellulitis and Cutaneous Abscess

Clinical pearls

- Differentiating between pyogenic (abscess), non-pyogenic (cellulitis), or both is the basis for determining if incision & drainage alone, antibiotics alone, or both are required.
- Common organisms
  - Cellulitis: beta-hemolytic *Streptococcus spp*. most common, also consider MSSA
  - Abscess: *S. aureus* most common
- Pathogens associated with specific exposures or hosts
  - Bite wounds: *Pasteurella multocida* (cat), *Capnocytophaga canimorsus* (dog), *Eikenella corrodens* (human), anaerobes, and skin flora (*S. aureus, Streptococcus spp*.)
  - Cat scratch: *Bartonella henselae*
  - Salt water: *Vibrio vulnificus*
  - Fresh or brackish water: *Aeromonas hydrophobia*
  - Immunosuppressed patients: fungi, *Nocardia spp.*, non-tuberculous mycobacteria, *P. aeruginosa*, other GNRs.
- Cellulitis may appear to worsen during first 24-48 hours of therapy as dying bacteria induce inflammation
- Failure to improve with first line antibiotics- consider resistant organisms, necrotizing infection, or secondary conditions that mimic cellulitis
  - Skin and soft tissue infection mimics: DVT, insect bites, fixed drug eruptions, stasis dermatitis, erythema multiforme, pyoderma gangrenosum, filariasis, lymphedema
  - Cellulitis is typically unilateral; bilateral is likely a mimic

Diagnosis

- Cellulitis and cutaneous abscess are diagnosed clinically

- **Do not obtain superficial wound swabs (actual pus collected in sterile bottle preferred). Superficial swabs exhibit low sensitivity, are prone to contamination and result may reflect colonization only and not infection.**
- Cultures should be collected from abscess if moderate-severe, recurrent, clinical failure, or systemic symptoms. No culture is needed for simple abscess with mild symptoms.
- **Deep tissue cultures should be obtained for patients undergoing surgical debridement**
- Blood cultures are not needed unless there is suspicion for systemic infection or if the patient is immunosuppressed or has post-surgical wounds. The yield of blood cultures in cellulitis in absence of systemic infection is extremely low.
- Punch biopsy is generally not necessary, and is reserved for patients with refractory or nosocomial infections or immunocompromising conditions
- Ultrasound can be used to detect deep abscess or exclude DVT
- Urgent CT scan and surgical consultation are crucial when there is any suspicion for necrotizing fasciitis (see necrotizing fasciitis section)

Treatment

- For all categories, empiric coverage is based on whether infection is pyogenic (cover *S. aureus*) or not (cover *Streptococcus spp*.). If patient is not improving with therapy directed at either pathogen, add antibiotic to cover the other.
- Bite wounds: amoxicillin/clavulanate 1g IV q12h
- Cellulitis, mild: cover for *Streptococcus spp*. with oral antibiotic
    - Cloxacillin 500 mg PO q6h OR
    - Cephalexin 500 mg PO q6h, OR
    - Severe penicillin allergy only: clindamycin 450 mg PO q8h
- Cellulitis, moderate-severe or unable to tolerate PO: cover *Streptococcus spp*. with IV antibiotic
    - Cefazolin 1 g IV q8h, OR
    - No access cefazolin: ceftriaxone 1g IV q24h
    - Expansion for MRSA coverage (e.g., add doxycycline to above regimen) is indicated in cases of cellulitis associated with penetrating trauma, prior MRSA infection or colonization, PWID, lack of clinical response to antibiotics not active against MRSA, athletes, children, prisoners, military recruits, and men who have sex with men
    - Switch from IV to oral therapy once patient is clinically stable
- Abscess, mild: incision & drainage only for simple abscess <5 cm
    - A short course (3-5 days) of antibiotics to cover MRSA should be added in cases of: surrounding cellulitis, multiple lesions, extremes of age (e.g., pediatrics or elderly), proximity to device, inadequate response to incision and drainage or immunocompromised hosts. A short course (3-5 days) of antibiotics may also reduce likelihood of recurrence.
        - Doxycycline 100 mg PO q12h
        - Alternative: Clindamycin 300-450 mg PO q6-8h

Duration

- Uncomplicated: 5-day course, but can extend if infection has not improved
- Hospitalized or complicated: 7-14 days depending on time to clinical improvement

Adjunctive therapy

- Elevate affected area
- Keep skin hydrated
- Treat associated conditions: tinea pedis, traumatic wounds, stasis dermatitis, lymphedema
- There is limited data showing quicker time to clinical improvement with the addition of NSAIDs or corticosteroids

Resources

- IDSA SSTI Guidelines: Stevens DL. Clin Infect Dis 2014: 59:10-52.
- Role of beta-hemolytic streptococci in cellulitis: Jeng A. Medicine (Baltimore) 2010;89:217-26.
- Cellulitis Review. Raff AB. JAMA 2016; 316 (3) 325- 337.
- Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess. Talan D. NEJM 2016; 374:823-832.
- A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. Daum RS, et al. NEJM 2017:376:2545-2555

Diabetic Foot Infection

Clinical pearls

- Diabetic foot infection (DFI) leads to serious morbidity and requires a multi-disciplinary approach for prevention and treatment. A multi-disciplinary team may include primary care, endocrinology, podiatry, orthopedic surgery, general surgery, ID, pharmacy, wound care, physical /occupational therapy, and others.
- DFI encompasses a spectrum of type and severity of infections, including superficial infection of an ulcer, cellulitis, abscess, osteomyelitis, gangrene, and necrotizing fasciitis
- Risk factors: diabetic patient with peripheral vascular disease, renal insufficiency, loss of protective sensation, traumatic foot wound, walking barefoot, ulceration present for >1-month, recurrent ulcers, able to probe to bone
- Common organisms: (see grading of severity under diagnosis)
    - Most DFIs are polymicrobial
    - Mild: Gram-positive organisms (MSSA, MRSA, CoNS, *Streptococcus spp*.)
    - Moderate to severe: above PLUS Enterobacterales, Enterococcus spp.
        - *Pseudomonas spp*. seen in <10% of DFI. Risk factors include water exposure, hospitalization for ≥ 2 days in last 90 days, or antibiotic use in last 90 days.
    - Necrotic or ischemic wounds: above PLUS anaerobes (e.g., *Bacteroides spp., Clostridium spp*.)
- MRSA can be seen in some patients with these risk factors: history of colonization with MRSA, recent or current prolonged hospitalization, PWID.

Diagnosis

- Clinical suspicion based on history and physical examination: Suspect DFI in any patients with risk factors noted above
    - Evidence of infection includes inflammation (erythema, warmth, swelling, tenderness, pain) and purulence, and may include additional signs (non-purulent secretions, friable or discoloured granulation tissue, undermined wound edges, malodour)
    - Assess for protective sensation and biomechanical problems
- Grading of severity:

Severity:	Description:
Mild	superficial, erythema < 2cm around ulcer
Moderate	cellulitis > 2cm around ulcer, proximal spread, deep tissue infection
Severe	above plus systemic signs of infection

- Suspect diabetic foot osteomyelitis (DFO) if a chronic, deep and/or large foot ulcer is present or if probe to bone test is positive
- **Cultures: The importance of appropriately collected deep surgical cultures cannot be understated in moderate or severe DFI. Lack of appropriate cultures leads to inappropriate antibiotic use, which leads to treatment failure and unnecessary side effects.**
  - Send deep tissue specimen after debridement or resection.
  - If there is suggestion of osteomyelitis on imaging, clinical suspicion for osteomyelitis, probe to bone test is positive, bone is in infected field, or bone appears abnormal during surgery, also send bone culture
  - If surgery is not planned and DFO is suspected, a bone biopsy should be obtained
  - Do not obtain culture in clinically uninfected wounds
  - Culture is generally unnecessary in cases of mild cellulitis
  - Do not obtain culture from superficial swabs
  - **In stable patients without SSTI but with suspected DFO, antibiotics can be held up to 7 days to pursue cultures**
- Pathology: If osteomyelitis is suspected, bone should also be sent to pathology for histological evidence of bony inflammation. Margins should be sent whenever possible to see if any infected bone remains after surgical intervention.
- Imaging: all patients with DFI should have foot x-ray to assess for bony erosion, foreign body, and soft tissue gas. Obtain MRI if there is concern for abscess or osteomyelitis
- Vascular assessment: assess for arterial and venous insufficiency
- See osteomyelitis section for additional information on osteomyelitis diagnosis

Treatment

- **When to hospitalize:**
  - severe DFI
  - moderate DFI in certain patients (PVD, poor social situation)
  - unable to comply with outpatient therapy
  - failing outpatient therapy.
- A safe discharge plan should be in place including glycemic control, wound care services arranged, offloading of affected area, and assurance that antibiotic is obtainable.

Multi-disciplinary Intervention

- Consult podiatry or surgery (general or orthopedic) to obtain specimen for culture and pathology, debride any callus or necrotic tissue
- For moderate to severe DFI, and for osteomyelitis, general or orthopedic surgery are sometimes involved, especially if patients require more proximal debridement or amputation

- Consult general surgery for patients with vascular insufficiency to assess for re-vascularization options. Consult should be obtained emergently in instances of critical limb ischemia.
- Any wound with necrotic tissue or surrounding callus should be debrided
- Wound care and off-loading of pressure (PT, orthotic devices) are also necessary.

Empiric Antibiotics

- Wounds without evidence of infection should not be treated with antibiotics
- **If patient has no systemic symptoms, it is appropriate to defer starting antibiotics until cultures can be obtained.** Peri-operative antibiotics can be given per protocol.
- If there are systemic symptoms, risk for progression to systemic infection, or cultures are not being obtained (mild skin/soft tissue infection only):
    - Mild: cover streptococci AND staphylococci
        - *Streptococcus spp*.: cloxacillin 500 mg PO q6h OR cephalexin 500 mg PO q6h
        - *Staphylococcus spp*.: doxycycline 100 mg PO BD clindamycin 150 to 300mg PO q6h
    - Moderate: cover Gram-negative, Gram-positive, and anaerobes
        - Doxycycline 100 mg PO q12h PLUS piperacillin/tazobactam 4.5g q6h IV PLUS metronidazole 500 mg IV/PO q8h
        - Severe penicillin allergy: doxycycline 100 mg PO BD PLUS ciprofloxacin 400 mg IV/PO q12h PLUS metronidazole 500 mg IV/PO q8h
        - If Pseudomonas spp. risk factors, treat as severe
    - Severe, ischemic, or necrotic:
        - Piperacillin/tazobactam 4.5 g IV q6h OR meropenem 1g q8h IV
        - Severe penicillin allergy: ciprofloxacin 400 mg IV q12h PLUS metronidazole 500 mg IV q8h
        - PLUS vancomycin 15 mg/kg q12h (alternative if vancomycin unavailable, doxycycline 100 mg PO q12h)

Definitive Antibiotics

- Definitive antibiotics must be based on appropriately collected deep cultures
- Switch from IV to oral therapy when patient is clinically stable and tolerating PO
- If patient is not colonized with MRSA and appropriately collected cultures do not grow MRSA, consider stopping MRSA coverage (ensure *Streptococcus spp.* coverage still present)
- If patient with severe DFI has clinically stabilized and appropriately collected cultures do not grow Pseudomonas spp., consider stopping pseudomonal coverage (ensure other Gram-negative coverage still present)
- Duration: SSTI is usually treated for 1-2 weeks, depending on clinical response. If osteomyelitis, treat for 6 weeks (See osteomyelitis section). In instances where debridement or amputation completely remove source of infection, and pathology shows negative margins, antibiotics can usually be stopped in 2-5 days.

Prevention

- Optimize glycemic control
- All patients at high risk for DFI should be followed closely by a podiatrist, endocrinologist, or general physician
- Patient education re: daily foot checks for lesions and appropriate footwear

Resources

- IDSA DFI Guidelines: Lipsky BA. Clin Infect Dis 2012;54:e132-73.

Necrotizing Soft Tissue Infections (NSTI)

Clinical pearls

- Rare entity but rising incidence related to heightened awareness and reporting, increasing bacterial virulence, and worsening antimicrobial resistance
- NSTIs are characterized by rapidly progressive necrosis of subcutaneous tissue, superficial fascia and muscle
- NSTIs can rapidly progress to systemic toxicity, shock, and organ dysfunction, resulting in major morbidity and mortality
- **Initial clinical findings of necrotizing soft tissue infections (NSTI) can be very subtle. Pain out of proportion is an early clue to the diagnosis.**
- Suspect necrotizing infection if: pain out of proportion to physical examination, anesthesia over cellulitic area, hemorrhagic skin bullae, skin necrosis, grayish skin discoloration, hard/ wooden feel of skin extending beyond the area involved, or 'dishwater-like' discharge. Crepitus is often not present until late.
- Two major categories:
    - Type I (polymicrobial, 80%): average of 5 pathogens, aerobic and anaerobic. Source is usually GI or GU tract. Often associated with decubitus ulcers, PWID, surgical procedures involving GI tract or spread from genital tract
    - Type II (monomicrobial, 20%). Frequently isolated causative organisms include *Streptococcus pyogenes* (Group A strep), anaerobic streptococci*, Staphyloccocus aureus*, *Clostridium perfringens, Bacteroides fragilis,* and *Vibrio vulnificus*. Predisposing conditions include diabetes mellitus, malnutrition, PWID, childbirth, obesity, peripheral vascular disease, venous insufficiency with edema and stasis, immunosuppression, recent surgery, and traumatic wounds. The cases which arise from trivial laceration, insect bite or varicella are usually due to *S. pyogenes*. 50% of patients with *S. pyogenes* infection report no portal of entry but infection develops at the site of bruise or muscle strain.

Diagnosis

- Diagnosis should generally be based on physical findings and operative findings
- Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score:

Parameter	Value	Points	Score
C-reactive protein (mg/L)	< 150 > 150	0 4	> 6 points should raise suspicion for NSTI. Score of > 8 points is strongly predictive (92%). Low scores cannot be used to rule out NSTI.
WBC (x1000/mm^3)	< 15 15-25 > 25	0 1 2	
Hemoglobin (g/dL)	> 13.5 11-13.5 <11	0 1 2	
Sodium (mEq/L)	> 135 < 135	0 2	
Creatinine (mmol/L)	< 0.089	0	

	> 0.089	2	
Glucose (mmol/L)	< 10 > 10	0 1	

- **Obtain blood cultures as soon as possible, without delaying surgery or antibiotics**
- CT and MRI are sensitive for the presence of soft tissue stranding and edema of the muscle and fascial layers and can demonstrate soft tissue gas. However, these findings are not mandatory for the diagnosis of NSTI and imaging should not delay surgery!
- Percutaneous needle aspiration can rapidly be performed to assess for the "dishwater-like" fluid of NSTI, with the sample then being sent for culture
- A small exploratory incision can be made in the suspected area; cultures and direct visualization of the area may aid in diagnosis
- The most important feature is the appearance of subcutaneous tissue and fascia at the time of surgery. Swollen and dull gray necrotic fascia, thin brownish exudate and extensive undermining of surrounding tissue is consistent with necrotizing fasciitis. Obtain culture from deep surgical specimens.

Treatment

Surgery

- **Early operative intervention is essential in NSTI and should involve wide debridement of all infected tissues. Amputations are often necessary and life-saving.**
- **Without prompt surgical control, mortality is extremely high**
- Indications for surgery:
  - Clinical findings as described
  - Failure of cellulitis to respond after a reasonable period of antibiotics
  - Profound toxicity or worsening during appropriate therapy
  - Skin necrosis with easy dissection along the fascia
  - Presence of gas in the soft tissues
- Surgical intervention needed every 24-36 hours until there is no more tissue to debride!
- Wound closure should only be performed when there is no longer evidence of infection, and the patient has been adequately resuscitated.
- Expect major fluid losses and aggressively hydrate

Empiric Antibiotics: Antibiotics are necessary but are adjunctive therapy

- **Start empiric antibiotics as soon as possible:**

  Crystalline penicillin G 4 million units q4h PLUS gentamicin 5 mg/kg IV x 1 PLUS clindamycin 600 mg IV q8h (substitute metronidazole 500 mg IV q8h if clindamycin unavailable)
  - Switch to vancomycin 15 mg/kg IV q12h + piperacillin/tazobactam 3.375 g q6h (alternative meropenem 1g IV q8h) + clindamycin 600 mg IV q8h once available before cultures return
  - Severe penicillin allergy: vancomycin as above + ciprofloxacin 400 mg IV q8h + clindamycin 600 mg IV q8h
- Vibrio infection *(V.vulnificus*) is suspected based on the following history: **predisposed host with exposure of a wound to salt or brackish water (estuaries, mangroves, marshlands) handling seafood, or recreational water activities**
  - For severe infections, use combination therapy with doxycycline 100 mg PO/IV q12h plus ceftriaxone 1 g IV q24h

- Monotherapy with levofloxacin 750 mg PO/IV q24h is an alternate option for patients with severe penicillin allergy
- Aeromonas is found in fresh or brackish waters and infection typically occurs on the extremities following traumatic aquatic injuries.
  - Empiric antimicrobial therapy recommendations include fluoroquinolone, third generation cephalosporin (e.g., ceftriaxone), or TMP-SMX.

Definitive Antibiotics

- Definitive antibiotics should be based on culture data
- Toxic shock syndrome caused by *Streptococcus pyogenes*: penicillin 4 million units IV q4h + clindamycin 600 mg IV q8h. Clindamycin suppresses bacterial toxin production. Linezolid is also an option for suppressing bacterial toxin production.
- Duration: consider stopping antibiotics when clinically improved and afebrile 72 hours

Resources

- LRINEC Score: Wong CH. Crit Care Med 2004;32:1535-41.
- IDSA SSTI Guidelines: Stevens DL. Clin Infect Dis 2014:200:1-43.

Surgical Site Infections

SSI categories:

- **Superficial incisional**: Involves subcutaneous space and occurs within 30 days of the surgery
- **Deep incisional**: Involves the fascia and muscle and occurs within 30 days of the surgery or within 90 days if a prosthesis was inserted
- **Organ/ space**: Involves any part of the anatomy (organs or spaces) other than the original surgical incision

Clinical pearls

- Microbiology and risk of infection are dependent on classification of wound (clean, clean-contaminated, contaminated, or dirty) and depth of wound (superficial, deep, organ/space):
- Clean: procedure did not enter a normally colonized viscus or lumen
  - Example: elective inguinal hernia repair
  - Organisms: skin flora (MSSA, MRSA, CoNS, streptococci)
  - Infection rate: low
- Clean- contaminated: procedure does enter a normally colonized viscus or lumen, but under controlled/elective conditions
  - Examples: elective intestinal resection, oropharyngeal procedure, gynecologic procedures
  - Organisms: endogenous flora from site of procedure
  - Infection rate: 4-10%
- Contaminated: procedure where gross contamination is present at the surgical site without obvious infection

- Examples: penetrating abdominal injury
- Organisms: endogenous flora from site of procedure
- Infection rate: over 10%

- Dirty: procedure at site of known/active infection
  - Example: exploratory laparotomy for peritonitis
  - Organisms: flora from primary infection
  - Infection rate: over 10%
- Risk of infection also increases with length of procedure
- Signs of systemic inflammation < 4 days after surgery are usually not due to a SSI
  - Exception: *Clostridium spp*. and Group A streptococci can cause early onset, severe SSI.
- Serious deep-tissue infections and infections that extend to the fascia should be treated as necrotizing fasciitis. Surgical team should be alerted at first suspicion of fasciitis.

Diagnosis

- Diagnosis is usually clinical, with pain, swelling, purulent discharge, or erythema noted on physical examination. Systemic signs of infection can also be present.
- Culture of abscess fluid or purulent drainage recommended. Do not collect superficial swabs from surface of wound. If a wound is explored, deep cultures can be helpful.
- Consider imaging (US, CT) to evaluate for deep infection, such as abscess or fasciitis (see necrotizing fasciitis section).

Treatment

Surgery

- Primary treatment is surgical. All SSIs should be treated with suture removal, incision, and drainage (I&D), and removal of any infected foreign material. Depth of infection should be assessed during wound exploration.
- A superficial wound without systemic symptoms should be treated by I&D alone
- Antibiotic therapy is indicated if the wound is deeper, temperature is > 38.5 C, HR > 110/minute or erythema extends beyond wound margin for >5cm

Empiric Antibiotics

- Clean wounds: Gram-positive coverage only
  - Cefalexin 500mg PO q8h PLUS doxycycline 100 mg PO q12h
- Clean-contaminated, contaminated, dirty wounds: **ADDS** Gram-negative + anaerobic coverage.
  - Piperacillin/tazobactam 4.5g IV q6h + metronidazole 500 mg IV/PO q8h
  - Alternative: levofloxacin 750 mg IV/PO q24h + metronidazole 500 mg IV/PO q8h
  - Add Vancomycin (or doxycycline if vancomycin unavailable) if known MRSA colonization, PWID, exposure to health care settings or antibiotics, hardware present at surgical site, or systemic symptoms
- Severely ill: piperacillin/tazobactam 4.5 g IV q6h (alternative meropenem 1g IV q8h) + vancomycin IV
  - Severe penicillin allergy: ciprofloxacin 400 mg IV q8h + amikacin 25 mg/kg ideal body weight IV x 1 + vancomycin IV

Definitive Antibiotics

- For clean wounds, definitive treatment can be adjusted for culture results
- Duration of antibiotics depends on severity of infection and response to therapy

Resources

- SSTI Guidelines: Stevens DL. Clin Infect Dis 2014:200:1-43.

Urologic Infections

Urologic Infections

Clinical pearls

- **Important to differentiate asymptomatic bacteriuria from true urinary tract infection (UTI) to prevent unnecessary use of antibiotics**
- Asymptomatic bacteriuria (ASB) = positive urine culture without clinical signs or symptoms
- ASB is common, especially among catheterized patients and the elderly, and treatment is not recommended
- ASB should only be treated in the setting of pregnancy, invasive urological procedures, recent renal transplant (particularly within 3 months post-transplant)
- Acute uncomplicated cystitis = symptoms localized to lower urinary tract (frequency, urgency, dysuria, suprapubic pain), with no structural or functional abnormalities. Haematuria is also observed.
    - Clinical diagnosis of acute uncomplicated cystitis also excludes fever (>37.7^{o}C), signs of systemic illness (i.e., rigors, fatigue, chills, flank pain, and costovertebral angle tenderness).
    - If any of these clinical features are present, they suggest extension of the infection beyond the bladder (i.e., pyelonephritis)
- Complicated UTIs = UTIs that have possibly extended beyond the bladder (i.e. fever or other systemic symptoms, in the presence of structural or functional abnormalities, or causative organism with increased resistance
    - Structural abnormalities – congenital, stents, stones, indwelling catheters, neurological deficits
    - Functional abnormalities – pregnancy, diabetes

- In immune competent patients, suspected UTI must meet one of the following criteria in order to pursue urine culture:
    1. Fever plus at least one urinary symptom
    2. Two or more urinary symptoms
    3. Sepsis or lethargy with no other identifiable source
- Common UTI organisms:
    - In patients with acute uncomplicated cystitis, infection with a single organism is common. Enterobacterales (especially *E. coli, Klebsiella spp.* and *Enterobacter spp*.) *Enterococcus spp*. and *S. saprophyticus* are also possible
    - Patients with urinary catheters, immunocompromised, or structural abnormalities (e.g., calculi, obstruction, neurogenic bladder) are also at risk for Pseudomonas spp. and resistant gram-negative rods.
    - Mycobacterium tuberculosis can cause urologic infection and will not grow on routine bacterial culture. Consider this diagnosis in setting of sterile pyuria.
    - *S. aureus* is not a uropathogen. If found in urine it originated from blood stream infection, and patient should be evaluated for bacteraemia/endocarditis (obtain blood culture)

- Yeast/Candida are **rarely** uropathogens, though frequently detected in urine, particularly in the setting of antibiotic use and critical illness
  - Only treat in consultation with Infectious Diseases in selected patients who are severely immunocompromised (e.g., neutropenic), have urologic hardware, or about to undergo urologic procedure

Diagnosis

- Diagnosis requires signs and symptoms of infection plus evidence of infection on urinalysis
- Urinary symptoms
  - No catheter: dysuria, urgency, flank pain or tenderness, shaking chills, new onset urinary incontinence, frequency, gross haematuria, suprapubic pain/tenderness
  - Catheterized patient: shaking chills, flank pain, or suprapubic pain or tenderness
  - Change in mental status without symptoms localized to urinary tract is not sufficient reasoning for urine culture
- Obtain urinalysis and urine culture in patients with suspected UTI who are admitted to the hospital (2 specimens sent to lab)
  - Most outpatients with classic uncomplicated UTI symptoms can be treated empirically without urinalysis or culture
  - Ideally, urine culture should be sent only after confirmation of pyuria on bedside urinalysis
  - For more information on appropriate use of UA and reflex urine culture please reference infection prevention section
- If pyuria is absent, UTI is unlikely and should not be treated even if urine culture has growth. Pyuria without bacteriuria (without recent antibiotic therapy) can also occur in prostatitis.
- Specimen collection: For more information on appropriate collection of UA and reflex urine culture please reference infection prevention section
- Urinalysis interpretation:
  - Pyuria (>10 WBC/hpf) is sensitive but not specific (i.e., in the presence of indwelling catheter, pyuria does not necessarily indicate UTI)
  - Urinary neutrophils with a negative urine culture (ie, sterile pyuria) should prompt workup for interstitial nephritis, renal tuberculosis, and nephrolithiasis
  - Leukocyte esterase also indicates that WBCs are present and is also not specific
  - Nitrites have good specificity for Gram-negative bacteriuria, but not necessarily for UTI
  - Presence of bacteria alone is not useful
- Urine culture interpretation:
  - Not catheterized: ≥100,000 colonies of no more than two species of microorganism can be consistent with UTI
  - Catheterized: ≥1,000 colonies of any organism can be consistent with UTI
  - ***S. aureus*** **growing on urine culture is consistent with bacteraemia as a source rather than UTI.** ***S. aureus*** **does not cause UTI.**

Treatment

Outpatients

Empiric Antibiotics

- Acute uncomplicated cystitis:
  - Nitrofurantoin 100 mg PO bid OR amoxicillin/clavulanate 1g PO TID OR cefuroxime 500mg po BD for 5 days

- This is the only situation where patients can be diagnosed based on classic symptoms alone. No need for urinalysis or culture.
- History of recurrent or drug resistant UTIs: empiric therapy based on prior cultures and susceptibilities. Obtain urinalysis and culture. Consider ID consultation.
- Reserve fluoroquinolones (ciprofloxacin, levofloxacin) for more severe disease (i.e., pyelonephritis) or resistance to other antibiotic options

Definitive Antibiotics

- For outpatients that had urine culture obtained, adjust antibiotics based on sensitivities. If patient fails to improve on antibiotics and no culture was obtained initially, check urinalysis and culture.

Inpatients

Empiric Antibiotics

- Uncomplicated cystitis:
  - Ciprofloxacin 500mg po q12h OR levofloxacin 500 mg PO q24h
- Pyelonephritis or complicated UTI:
  - Ceftriaxone/sulbactam 1.5 g IV q12h for nosocomial UTI OR recent antibiotic exposure
  - Amikacin 15mg/kg IV OD
  - Ciprofloxacin 400mg IV q12h OR levofloxacin 500 mg q24h
- UTI associated with sepsis:
  - Meropenem 1g IV q8h
  - Amikacin 15mg/kg IBW IV OD
  - Piperacillin-tazobactam 3.375 -4.5g IV q8h – if patient is clinically improving and culture data permits

Definitive Antibiotics

- Definitive antibiotic should be chosen based on culture and susceptibilities
- Choose the narrowest-spectrum effective antibiotic

Surgery and Catheter Management

- Role of surgery: if urinary tract stents, stones, or obstruction, may need urologic intervention. Stents and stones are assumed to be infected and will continue to be a source of infection until removed.
- Catheterized patients: remove/replace catheter in all. If stable and no upper urinary tract disease, observe without antibiotics. If upper tract disease or severely ill, treat as recommended above.
- Catheterized patients with positive urine cultures as part of evaluation for sepsis of unknown source, may have asymptomatic bacteriuria (colonization). If possible, remove/replace catheter and attempt to identify another source of fever. If bacteriuria and symptoms persist > 48 hours consider treating.

Antibiotic Duration and Follow up

- 3 days for non-pregnant women ≤ age 65 with acute uncomplicated cystitis or CA-UTI (assuming catheter removed) and no upper tract or systemic symptoms

- 5-7 days in those with prompt resolution of symptoms, or when treating with nitrofurantoin or oral beta-lactam
- 10-14 days for those with sepsis, pyelonephritis, or delayed response to treatment
- Repeating urine culture to document clearance of infection is not recommended; do not repeat urinalysis and urine cultures in patients who have clinically improved
- If patient is not improving by 48 hours, obtain urine culture again and consider imaging to look for peri-nephric abscess

Prevention

- Avoid/minimize use of indwelling urinary catheters. Please refer to infection prevention section
- Consider alternatives to indwelling urinary catheters when possible: bladder scan and intermittent straight catheterization, incontinence pads, barrier creams.

Resources

- IDSA Asymptomatic Bacteriuria Guidelines: Nicolle LE. Clin Infect Dis. 2005;40:643-54.
- IDSA CA-UTI Guidelines: Hooton TM. Clin Infect Dis. 2010;50:625-63.
- IDSA Uncomplicated UTI Guidelines: Gupta K. Clin Infect Dis. 2011;52:103-20.
- Diagnosis and management of urinary tract infection in older adults. Infect Dis Clin North Am. 2014 Mar;28(1):75-89.

Prostatitis, Acute

Clinical pearls

- Typically presents with fever, chills, myalgias, and abrupt onset of lower UTI symptoms such as dysuria, pelvic or perineal pain and cloudy urine
- Complications can include bacteremia, epididymitis, prostatic abscess, metastatic sites of infection (e.g., joints) or conversion to chronic prostatitis
- In patients <35 years of age, most common causes are *N. gonorrhoea* or *C. trachomatis*
- In patients >/= 35 years of age, most common causes are Enterobacterales (*E.coli* most common), *Enterococcus spp.*
- In patients with HIV, can be a reservoir for *Cryptococcus neoformans*
- Not all antimicrobials have the ability to penetrate the prostate; fluoroquinolones are recommended

Diagnosis

- Physical exam findings: prostate is very tender, tense, swollen and warm
  - Gentle digital rectal exam okay but do not massage prostate due to risk of disseminating infection
- Obtain pre-antibiotic midstream urinaylsis and urine culture
- Elevated PSA can provide corroborative data
- In patients at risk for STDs, test for gonorrhoea, chlamydia and trichomoniasis
- Imaging not indicated unless high suspicion for abscess

Treatment

- **Uncomplicated/risk of STD (Age < 35 years)**

- Ceftriaxone 500mg IM x 1 dose OR cefixime 400mg po 1 dose; then
- Doxycyline 100 mg PO q12h x 10 days
- If confirmed Chlamydial prostatitis: azithromycin 1g qweek for 4 weeks

- **Uncomplicated/low risk of STD**
  - Levofloxacin 750 mg PO q24h or ciprofloxacin 500 mg PO q12h x 10-14 days
- **Confirmed gonorrhoea**
  - Ceftriaxone 500 mg IM as a single dose OR
  - Cefixime 400 mg PO as a single dose
- Severe cases or delayed response to therapy warrant 4-6 weeks of antibiotics
- Use of adjunctive uroselective alpha-adrenergic antagonist (e.g tamsulosin, alfuzosin and silodosin) should be considered to reduce symptomatology)

Epididymo-orchitis

Clinical pearls

- Etiologies and treatment differentiated based on patient's age
- Midstream pyuria, dysuria, thickened epididymis, swollen testis, and scrotal pain, erythema, and edema. Testicular findings are usually unilateral.
- Rule out testicular torsion; ultrasonography is useful to distinguish torsion from epididymitis/orchitis)

Etiologies

- Age ≤ 35 years
  - *N. gonorrhoeae*
  - *C. trachomatis*
  - Enterobacterales (occasional)
- Age > 35 years
  - Enterobacterales
  - Less common causes: *Mycobacterium tuberculosis, Brucella spp., B. pseudomalle*i, mumps virus, BCG, fungal (histoplasmosis, coccidioidomycosis), Bechet's disease

Primary Regimens

- All: bed rest, scrotal elevation, and analgesics
- Age ≤ 35 years: ceftriaxone 500 mg IM x 1 + doxycycline 100 mg po BDx 10 days
- Age > 35 years: levofloxacin 750 mg IV/PO once daily for 10-14 days (see Comments)

Alternative Regimens

- Age ≤ 35 years: Levofloxacin 500 mg po once daily for 10 days
- Age > 35 years:
  - Ampicillin-sulbactam 3 gm IV q6h or amoxicillin-clavulanate 875/125 po BD
  - Ceftriaxone 2 gm IV q24h
  - Piperacillin-tazobactam 4.5 gm IV q6h or 4-hr infusion of 3.375 gm q8h

Antimicrobial Stewardship

- Increasing incidence of fluoroquinolone-resistant enteric organisms a potential concern
- If Enterobacterales are suspected, choice of agent should be guided by local antibiotic susceptibility patterns

Comments

- Do urine NAAT (nucleic acid amplification test) to ensure absence of *N. gonorrhoeae* with concomitant risk of fluoroquinolone-resistant gonorrhoeae or of chlamydia if using agents without reliable activity in patients age < 35 years
- If STI etiology documented or suspected, sexual partners within the past 60 days should be evaluated
- Review article of differential diagnosis of scrotal pain and masses: Am Fam Physician 89:723, 2014.
- Complete resolution of discomfort may take weeks after antibiotic treatment is completed, but swelling and tenderness that persist should be evaluated

Resources:

- Clin Infect Dis 61:S770, 2015; Eur J Clin Microbiol Infect Dis 37:1001, 2018.
- CDC STD Guidelines: MMWR 64(RR-3):1, 2015.

Fungal Infections

Aspergillosis, Allergic fungal sinusitis

Clinical pearls

- Relapsing chronic sinusitis can occur in nasal polyps without bony invasion, asthma, eczema or allergic rhinitis.
- Increased IgE levels and isolation of *Aspergillus spp*. or other dematiaceous moulds (*Alternaria spp., Cladosporium spp.,* etc.).
- Treatment is controversial

Treatment

- No antifungal therapy OR
- Itraconazole oral solution 2.5 mg/kg po q12h or 200 mg capsules po BD. Itraconazole may be steroid sparing
- Endoscopic surgical sinus drainage is warranted in sinus obstruction
- Goal of therapy is prevention or treatment of life-threatening haemoptysis; bronchial artery embolization an option for patients with haemoptysis and who are poor surgical candidates.
- Role of medical therapy is uncertain.

Aspergilloma

Clinical pearls

- Aspergilloma (or fungus ball): solid rounded mass, within a pulmonary cavity
- Imaging: Local pleural thickening is often present
- Lab findings: Positive galactomannan present in serum
- Clinical presentation typically includes haemoptysis

Primary regimens

- Surgical resection (optimal candidates are patients with single aspergilloma)
- No therapy if asymptomatic, stable, or single lesion, but monitor for progression radiographically.

Alternative Regimens

- Voriconazole 6 mg/kg IV/po q12h on day 1; then 4 mg/kg IV/po q12h OR
- Isavuconazonium sulfate (prodrug of Isavuconazole) 372 mg po/IV q8h x 6 doses and then 372 mg po/IV daily
- Itraconazole oral solution 2.5 mg/kg po q12h or 200 mg capsules po q12h
- Transthoracic, intracavitary instillation of Amphotericin B in poor surgical candidates

Aspergillosis, Allergic Bronchopulmonary

Clinical pearls

- Allergic bronchopulmonary aspergillosis (ABPA) is characterized by wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis
- Airway colonization is associated with increased blood eosinophils, increased serum IgE and increased specific serum antibodies.

Primary Regimens

- Corticosteroids + itraconazole oral solution 2.5 mg/kg po q12h or 200 mg capsules po q12h

Alternative Regimens

- Corticosteroids + voriconazole 200 mg po q12h

Comments

- Itraconazole given for 16 weeks has been demonstrated to be steroid sparing: decreases number of exacerbations requiring corticosteroids with improved immunological markers, lung function, and exercise tolerance.

Aspergillosis, Chronic Cavitary Pulmonary

Clinical pearls

- Chronic cavitary pulmonary aspergillosis is a chronic disease often with systemic symptoms.
- Imaging: Multiple cavities, with or without aspergilloma.
- Labs: Positive aspergillus antibodies in serum, positive culture of bronchopulmonary specimen
- Diagnosis: abnormal labs and imaging noted above.

Primary Regimens

- Voriconazole 6 mg/kg po/IV q12h x 1 day, then 4 mg/kg po/IV q12h

Alternative Regimens

- Isavuconazonium sulfate (prodrug of Isavuconazole) 372 mg po/IV q8h x 6 doses and then 372 mg po/IV daily
- Posaconazole (NOTE: different dosing delayed release tabs/IV vs. suspension, better levels achieved with delayed-release tabs)
    - Delayed-release tabs 300 mg po bid x 2 doses and then 300 mg po daily OR
    - Suspension 400 mg po BD
- Itraconazole oral solution 2.5 mg/kg po q12h or 200 mg capsules po BD

Comments

- Antifungal therapy is standard of care.
- Duration of therapy may be prolonged, 6-12 months. For response rates with Voriconazole see
- Surgical resection associated with high morbidity and mortality.

Resources:

- Pulmonary aspergilloma: clinical aspects and surgical treatment outcome. Passera E, et al, Thorac Surg Clin. 2012 Aug;22(3):345-61.
- Intracavitary aspergilloma: transthoracic percutaneous injection of amphotericin gelatin solution. Munk PL, et al.. Radiology. 1993 Sep;188(3):821-3.
- Voriconazole for chronic pulmonary aspergillosis: a prospective multicenter trial. Cadranel J, et al... Eur J Clin Microbiol Infect Dis. 2012 Nov;31(11):3231-9.

Aspergillosis, invasive

Clinical Setting

- Invasive pulmonary aspergillosis (IPA) is most common, but dissemination can also occur to CNS, skin, GI tract, etc.
- Risk groups: prolonged neutropenia (acute leukemia, myelodysplastic syndromes), allogeneic stem cell transplant (graft-versus-host disease), solid organ transplant, chronic granulomatous disease, and high-dose corticosteroids
- Diagnosis:
  - Imaging
    - Typical x-ray/CT lung lesions include halo sign, cavitation, or macronodules . Initiation of antifungal therapy based on halo signs on CT is associated with better response to treatment and improved outcome.
    - Vascular interruption on CT pulmonary angiogram plus contiguous focal lung lesion in a patient with suspected invasive aspergillosis supports the diagnosis; absence of this finding may also be useful in excluding the disease
  - Galactomannan antigen
    - Serum: Sensitivity of 78% (95% CI of 61-89%) and specificity of 81% (95% CI, 72-88%)
    - BAL fluid: Enhanced sensitivity over serum but reduced specificity
    - Improved manufacturing processes have eliminated previous false positive tests that occurred with patients receiving piperacillin-tazobactam and amoxicillin-clavulanate.
    - There are also false positives from cross-reactivity with other fungi (*Fusarium spp., Histoplasma capsulatum, Blastomyces dermatitidis,* and even some blood product conditioning fluids
  - 1,3 - Beta-D-glucan assay
    - Polysaccharide in cell wall of aspergillus and other fungi
    - Detected in serum with chromogenic quantitative enzyme immunoassay
    - High frequency of false positives; low sensitivity and specificity

Primary Regimens

- Voriconazole 6 mg/kg IV/po q12h on day 1; then 4 mg/kg IV/po q12h OR
- Isavuconazonium sulfate (prodrug of Isavuconazole) 372 mg po/IV q8h x 6 doses and then 372 mg po/IV daily

Alternative Regimens

- Liposomal Amphotericin B (L-AmB) 3-5 mg/kg/day IV OR
- Amphotericin B lipid complex (ABLC) 5 mg/kg/day IV OR
- Posaconazole (NOTE: different dosing delayed release tabs/IV vs. suspension, better levels achieved with delayed-release tabs).
  - Delayed-release tabs 300 mg po bid x 2 doses and then 300 mg po daily OR
  - Suspension 200 mg qid, then 400 mg po bid after stabilization of disease OR
  - Posaconazole IV 300 mg IV over 90 minutes bid x 1 day, then 300 mg IV daily

Comments

- Voriconazole:
  - Monitor serum concentrations to achieve target range of 1.0–5.5 mg/L (trough on day 4). This is associated with improved response rates and reduced adverse effects
  - Administration of IV voriconazole in patients with renal dysfunction was not associated with worsening renal function with up to 7 days of treatment; IV voriconazole may be less toxic than previously thought
  - In retrospective study of 196 pts, 37 (19%) harbored voriconazole-resistant infection which correlated with an increase in mortality. Hence, need for early testing for in vitro susceptibility
- Isavuconazole (prodrug isavuconazonium sulfate):
- A randomized control trial of Isavuconazole vs. Voriconazole for invasive aspergillosis demonstrated that Isavuconazole is non-inferior to voriconazole for the treatment of invasive aspergillosis. However, isavuconazole was associated with fewer side effects overall, (specifically skin, visual, and hepatobiliary)
- Liposomal Amphotericin B (L-AMB) or Amphotericin B lipid-complex (ABLC):
  - Preferred regimen when patient is intolerant to voriconazole
- 10 mg/kg no more efficacious but more toxic than 3 mg/kg doses of L-AMB
- Posaconazole:
  - 42% response rate in open-label trial of patients' refractory/intolerant to conventional therapy
  - Concern exists for cross-resistance with azole-non-responders
  - Measurement of serum concentrations advisable, better serum levels achieved with delayed-release tabs
- Attempt to achieve trough concentrations of > 1.0 µg/mL for treatment of disease
- Caspofungin:
  - Approximately 50% response rate in IPA, not recommended for use as monotherapy
- Combination therapy:
  - A randomized control trial of Voriconazole plus Anidulafungin vs. Voriconazole alone showed a trend towards reduced mortality in all patients with invasive aspergillosis in the combination therapy arm. Subgroup of patients with invasive aspergillosis whose diagnosis was established by radiographic findings and GM positivity had lower mortality with combination therapy. Combination therapy should be strongly considered although further data is needed to determine which patients would benefit the most. Some experts would recommend addition of echinocandin to amphotericin-based regimen or other azoles as well.

Resources:

- IDSA Practice Guidelines for the Diagnosis and Management of Aspergillosis. Patterson TF, et al.. Clin Infect Dis. 2016 Aug 15;63(4):433-42.
- ATS & ATSFWG Treatment of fungal infections in adult pulmonary and critical care patients. Limper AH, et al.. Am J Respir Crit Care Med. 2011 Jan 1;183(1):96-128.
- Aspergillus infections in the head and neck. Laury AM, Delgaudio JM. Curr Infect Dis Rep. 2010 May;12(3):217-24.
- The clinical spectrum of pulmonary aspergillosis. Kosmidis C, Denning DW. Thorax. 2015 Mar;70(3):270-7.

Candida

Clinical pearls

- Candida species can cause a wide spectrum of disease ranging from local mucous membrane infections to dissemination with multisystem organ failure
- Considered normal flora in the gastrointestinal and genitourinary tracts
- Can cause disease when a change in host immunity or imbalance in the ecological niche in which the organisms exist is created
- Common organisms: Candida albicans (most common), *C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*. There has been an increase in non-albicans Candida species in the last 20 years. *C. auris* is a highly virulent, multidrug resistant species which emerged in 2016 as a cause of bloodstream, ear, and wound infections.
- Candida species are the 4th most common cause of bloodstream infections.
- More common candidal infections are included in this section. Vulvovaginal candidiasis is included in Gynecologic Infection and STI.
- Non-Candida yeasts (e.g., Cryptococcus and endemic mycoses) can cause infection in certain hosts. If there is concern for infection with other fungi, consider ID consultation for assistance with evaluation and management.

Candidemia and Invasive Candidiasis

- Risk factors for candidemia: ICU admission, immunocompromised state, central venous catheter use, TPN administration, broad-spectrum antibiotic use, breach of the GI tract mucosal barrier (such as intra-abdominal surgery) and Candida spp. colonization (especially at multiple sites).
- Chronic disseminated candidiasis (also known as hepatosplenic candidiasis) is a form in invasive candidiasis unique to patients with neutropenia

Diagnosis

- Blood cultures: standard blood culture broth easily grows Candida spp., no special fungal culture order needed. Yeast in the blood is **NEVER** considered a contaminant.
- Infectious disease consult teams are notified of all blood cultures growing yeast and will provide mandatory/automatic consultation.
- The microbiology laboratory will work up susceptibility to fluconazole. Susceptibility to other antifungal agents is not routinely performed.
- Invasive candidiasis is diagnosed by the presence of visceral involvement (i.e., skin, eye, kidney, liver, spleen) WITH or WITHOUT candidemia
- In patients with neutropenic fever not responding to empiric antibiotics, abdominal MRI may reveal lesions consistent with chronic disseminated candidiasis. Abdominal CT or ultrasound may detect these lesions but are less sensitive than MRI.
- Candidemic patients with or without ocular symptoms should have an ophthalmologic examination to exclude candidial endophthalmitis within one week of diagnosis, preferably once blood cultures have cleared, and neutrophil counts have recovered in neutropenic patients.
- Echocardiography to evaluate for endocarditis (TEE more sensitive than TTE) should be considered if the patient has persistent candidemia. (See endocarditis section)

Treatment

Empiric antifungals

- Micafungin 100 mg IV daily is recommended as initial therapy in most patients
- Clinically stable, no prior long-term azole therapy, no hematologic malignancy or BMT: fluconazole 800 mg IV/PO x1, then 400 mg IV/PO daily
- Patients who are intolerant to above therapies: liposomal formulation amphotericin B (LFAmB or Ambisome®) 3-5 mg/kg IV daily.
- Patients with candidemia and suspected endocardial or CNS involvement should NOT receive fluconazole as initial therapy and should receive micafungin or amphotericin B
- Discontinue empiric antifungals if cultures do not grow yeast and there is no clinical response observed after 4-5 days of therapy

DEFINITIVE ANTIFUNGALS

Species	Treatment	Alternative Treatment	Notes
C. albicans	Fluconazole OR Micafungin if clinically unstable	AmB-d/Ambisone® OR Voriconazole	-Follow UTH isolate susceptibility for fluconazole. -If on Echinocandin, transition from micafungin to fluconazole once clinically stable.
C. glabrata	Micafungin, Caspofungin, Anidulafungin Alternative: Lipid-based Amphotericin B,Voriconazole, Posazonazole	Fluconazole or Voriconazole if susceptible	Often non-susceptible to fluconazole- Follow UTH isolates susceptibility for fluconazole.
C. parapsilosis	Fluconazole	Micafungin OR AmB-d/Ambisome®	-Some isolates may be less susceptible to micafungin. -Consult ID for fluconazole intermediate strains
C. tropicalis	Fluconazole	Micafungin	-Consult ID for fluconazole intermediate strains.
C. krusei	Micafungin	Voriconazole if susceptible	-C. Krusei has intrinsic resistance to fluconazole
C. lusitaniae	Fluconazole	Micafungin	-C. lusitaniae is resistant to AmB/Ambisome® in approximately 20% of cases

Treatment Notes

- Patients should have blood cultures daily or every other day until candidemia is cleared

- Intravenous catheter removal is strongly recommended as this decreases duration of candidemia and improves mortality
- **Duration:** 14 days following documented clearance of blood cultures and clinical symptoms

Endophthalmitis

- Consult ophthalmology to evaluate for endophthalmitis in cases of persistent candidemia, especially with visual symptoms
- Primary therapy for chorioretinitis without vitritis:
  - Fluconazole 800 mg x1, then 400-800 mg IV/PO daily OR
  - Voriconazole 6 mg/kg IV BID x 2 doses then 4 mg/kg IV BD
- Primary therapy for chorioretinitis with vitritis
  - As above PLUS intravitreal amphotericin B deoxycholate 5-10 mcg/0.1 mL sterile water
- Azole resistant isolates: lipid Formulation of AmB (LFAmB) 5 mg/kg IV daily ± flucytosine 25 mg/kg PO q6h
- Avoid micafungin due to poor CNS and vitreal penetration
- Other treatment (e.g., vitrectomy) per Ophthalmology
- Duration: Minimum 4-6 weeks, determined by stabilization or resolution of lesions by repeated ophthalmological examination.

Endocarditis (native and prosthetic valve)

- Consultation with ID and Cardiac Surgery is strongly recommended. Fungal endocarditis can be difficult to treat and has high associated mortality.
- Primary therapy:
  - Surgical valve replacement. If the patient is not a candidate for surgery, then life-long suppression with fluconazole is likely required if the organism is susceptible.
  - Liposomal formulation amphotericin B (Ambisome®) 5 mg/kg IV daily ± flucytosine 25 mg/kg PO q6h OR
  - Micafungin 100-150 mg IV daily
- Treatment can be stepped down to fluconazole when candidemia cleared and patient clinically stable, if isolate is susceptible
- Treatment duration is for at least 6 weeks after valve replacement surgery, and longer in patients with perivalvular abscess and other complication.

Candiduria

- Candida is rarely a uropathogen, though frequently detected in urine. Colonization is common, even with pyuria on urinalysis.
- Urinary catheter removal will often resolve the candiduria
- Risk factors for true urinary tract infection with Candida spp.: immunocompromise, urinary obstruction, or abnormal GU tract.

Diagnosis

- See UTI section for UTI symptoms and interpretation of urinalysis and urine culture.

- Imaging of kidneys and collecting system may be indicated in those with risk factors (above) to exclude abscess, fungus ball, or urologic abnormality

Treatment

- Asymptomatic candiduria: Consider catheter change or removal
  - Consider treating as cystitis in patients at high risk for dissemination: neutropenic patients or those undergoing urologic manipulation, and prior to surgery to implant hardware (joints, cardiac valves, etc.)
  - Neutropenic patients should be treated as recommended above for candidemia
  - Patients undergoing urologic procedures: Fluconazole 400 mg IV/PO or AmB-d 0.3-0.6 mg/kg IV once daily for several days before & after the procedure
- Cystitis: remove urinary catheter if possible
  - Primary therapy: fluconazole 200mg IV/PO x 14 days
  - Fluconazole-resistant organism (suspected or confirmed): AmB-d 0.3-0.6mg/kg IV once daily x 1-7 days OR Flucytosine 25 mg/kg PO q6h x 7-10 days OR AmB-d bladder washes 50 mg/1L sterile water @ 40 ml/hr x 5 days
- Pyelonephritis: Remove urinary catheter if possible
  - *Candida spp.* pyelonephritis is usually secondary to hematogenous spread except for patients with renal transplant or abnormalities of the GU tract
  - Primary therapy: fluconazole 200-400 mg IV/PO x 14 days
  - Fluconazole-resistant organism (suspected or confirmed): AmB-d 0.5mg/kg IV once daily x 1-7 days +/- flucytosine 25 mg/kg po q6h OR Flucytosine 25 mg/kg PO q6h x 14 days
- Fungus ball or abscess
  - Therapy as above for pyelonephritis
  - Surgical intervention is strongly recommended
  - Irrigation through nephrostomy tubes with AmB-d 25-50mg in 200-500ml sterile water.

Intraabdominal Candidiasis

- Consider empiric antifungal therapy in patients at risk: recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis
- Primary treatment is drainage or debridement
- Treat with antifungals as recommended above for invasive candidiasis
- Discontinue therapy after source control and clinical response

Mucocutaneous candidiasis

Oropharyngeal Candidiasis (thrush)

- Diagnosis is clinical, with presence of adherent white plaques on buccal or pharyngeal mucosa, which bleed when scraped with tongue depressor
- Primary treatment: clotrimazole 10 mg troches PO 5 times a day OR nystatin suspension 500,000 units/5 mL PO q6h OR fluconazole 100-200 mg PO daily, for 7-14 days

Esophageal Candidiasis

- Diagnosis and workup: A diagnostic trial of antifungal therapy is appropriate in most patients with mild symptoms of esophagitis (odynophagia, dysphagia in immunocompromised patient).
- Empiric treatment for presumed esophageal candidiasis: fluconazole 200-400 mg PO daily x 14-21 days
- Consider alternative diagnosis such as CMV esophagitis, HSV esophagitis, eosinophilic esophagitis, GERD, etc. if symptoms do not improve with fluconazole. Consult GI for endoscopy with biopsy. Culture specimens if lesions suggestive of Candida spp and fluconazole treatment has failed,
- Fluconazole refractory disease or unable to tolerate fluconazole: micafungin 100 - 150 mg IV daily x 14-21 days

Resources

- IDSA Clinical Practice Guideline for the Management of Candidiasis update. Pappas PG, et al... Clin Infect Dis. 2016 Feb 15;62(4):e1-50

Blastomycosis

Clinical pearls

- Systemic pyogranulomatous disease caused by inhalation of spores (conidia) from the fungus *Blastomyces dermatitidis*
- *B. dermatitidis* is a dimorphic fungus-yeast at body temperature and mold at ambient temperature
- Incubation period: 45 days (range from 21 to 106 days)
- Endemic in parts of North America and a few cases seen at UTH, Lusaka
- > 50% asymptomatic or minimally symptomatic
- Pulmonary disease
  - Localized to the lungs in 70-80% of all cases
  - Acute pneumonia: high fever, productive cough, pleuritic chest pain
  - Acute respiratory distress syndrome (ARDS)
  - Chronic pneumonia: indistinguishable from TB, other fungal infections, lung cancer, other granulomatous disease
- Disseminated disease (20-30% of all cases)
  - Cutaneous (40-80%): verrucous ulcer with irregular borders. Differential diagnosis: pyoderma gangrenosum, squamous cell carcinoma, keratoacanthoma
  - Skeletal (25%): chronic osteomyelitis with discharging sinus
  - Prostate, genitourinary (10-20%): prostatitis, epididymo-orchitis
  - Meningitis and brain (5-10%): intra-cranial or epidural abscess
  - Virtually any organ or tissue can be involved
- Risk factors
  - Exposure to infected soil in endemic areas
  - Excavation or digging in endemic areas
  - Immunocompromised states: HIV/AIDS, corticosteroids, cancer chemotherapy, organ transplant

Diagnosis

- Culture and cytopathology of tissue are gold standard but may take too long to be clinically useful
- Wet preparation for direction identification under microscopy provides the quickest diagnosis
- PCR

- Antigen detection
- Serology is not useful due to high degree of cross reactivity with other endemic mycoses
- Imaging – pursue as needed based on clinical presentation
    - CXR: non-specific finding
    - CT scan not usually necessary

Treatment

- Mild to moderate pulmonary disease
    - Itraconazole 600mg po daily for 3 days then 200-400mg po daily for 6 to 12 months
- Mild to moderate disseminated disease
    - Itraconazole 200-400mg daily for 6 months or 12 months for bone disease
- Moderately severe to severe disease
    - Amphotericin B 0.7-1mg/kg to a total dose of 1.5-2g or liposomal Amphotericin B 3-5mg/kg/day
    - Switch to itraconazole 200mg three times a day for 3days then two times a day for 6 months on clinical improvement on amphotericin B
- Central nervous system (CNS) disease and pregnant women
    - Same as severe disease. Liposomal amphotericin B at 5mg/kg/day iv for 4-6 weeks is preferred due to high CSF penetration
- Pregnancy
    - Azoles are contra-indicated
    - Amphotericin B 0.7-1mg/kg to a total dose of 1.5-2g or liposomal Amphotericin B 3-5mg/kg/day

Resources

- IDSA Clinical practice guidelines for the management of blastomycosis: 2008 update. Chapman SW, et al…. Clin Infect Dis. 2008 Jun 15;46(12):1801-12.

Histoplasmosis

Clinical pearls

- A fungal infection caused by *Histoplasma capsulatum*, a dimorphic, soil-dwelling saprophyte which exists as a mould in the environment and as a yeast in tissues (at 37℃)
- Infection is often caused by inhalation of conidia or mycelial fragments
- It is usually asymptomatic but occasionally result in severe illness
- Manifestations range from a self-limited flulike syndrome to pneumonia, mediastinal fibrosis or chronic cavitary disease and disseminated histoplasmosis (more frequent immunocompromised and infants)
- **Primary infection** presents as acute and subacute pulmonary histoplasmosis; often asymptomatic or flulike (fever, cough, headache, chest pain)
- Pulmonary disease should be considered in patients in an appropriate clinical setting with pneumonia with mediastinal and hilar lymphadenopathy, mediastinal or hilar masses, pulmonary nodule, cavitary lung disease, pericarditis with mediastinal lymphadenopathy
- **Chronic pulmonary histoplasmosis**: cavitary upper lung lesions
- **Disseminated histoplasmosis** in immunocompromised patients is a rare opportunistic infection that mimics sepsis syndrome and may progress to multiple organ failure
- Extra-pulmonary manifestations: pericarditis, rheumatologic and ocular involvement
- H. capsulatum is found worldwide particularly in North and Central America

- **Risk factors** include excavation near bird nests, demolition or remodelling old building, exposure to decayed wood or dead trees, and immunosuppression
- **Monitoring & follow-up**: chest imaging and antigen testing, if not improving or suspected CNS involvement call ID

Diagnosis

- Histopathology using fungal stains
- Sputum cultures (for acute and chronic pulmonary histoplasmosis)
- Blood cultures (for disseminated disease)
- Serology for Histoplasma specific antibodies
- Serum and urine antigen detection (higher rates when combined, false positives from cross reactivity from *Coccidiodes spp* and *Blastomyces*)
- Imaging - pursue as needed based on clinical presentation
    - Chest x-ray- miliary, cavities, nodules, diffuse infiltrates
    - CT head-cerebral histoplasmosis
- Other lab findings: mild anaemia, elevated LDH, elevated ALP

Treatment

- Consider PTB, sarcoidosis and malignancy as differentials
- Always exclude histoplasmosis before treating for sarcoidosis, as immunosuppressive therapy can be disastrous
- Acute pulmonary histoplasmosis
    - Asymptomatic: no treatment
    - Mild symptoms: monitor for worsening. If symptoms persist > 4 weeks or overwhelming pulmonary involvement, initiate medical therapy
    - Mild to moderate disease: Itraconazole 200 mg BD for 3 days then 200mg once daily for 6-12 weeks
    - Moderately severe to severe disease: amphotericin B for 1-2 weeks then change to itraconazole 200mg once daily for 1 year. Methylprednisolone for 1-2 weeks in those in respiratory distress
- Chronic pulmonary histoplasmosis
    - Fatal if not treated
    - Itraconazole 200 mg BD for 3 days then 200mg once daily for 1 year
- Progressive disseminated histoplasmosis
    - Initiate medical therapy to all
    - Amphotericin B for 1-2 weeks then change to itraconazole 200mg once daily for 1 year
- Broncholithiasis
    - **Surgery. Antifungal therapy has no role**
- Ocular histoplasmosis
    - Treat with steroids
- Mediastinal histoplasmosis
    - Only treat symptomatic patients
    - Itraconazole for 6-12 weeks
- Amphotericin B doses: Liposomal Amphotericin B 3mg/kg/day iv, Amphotericin B lipid complex 5mg/kg/day iv, Amphotericin B deoxycolate 0.7-1 mg/kg/day
- Adjunct Therapy: Surgical for cavitary disease refractory to antifungal therapy
- Prevention or prophylaxis if indicated

Resources

- IDSA Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update. Wheat LJ, et al... Clin Infect Dis. 2007 Oct 1;45(7):807-25

Parasitic Infections

Parasitic Infections

Echinococcosis

Cystic echinococcosis is the larval cystic stage of the dog tapeworm, *Echinococcus granulosus*. It is also known as Hydatid Disease. It causes disease in the intermediate host, generally herbivorous animals and people who get infected accidentally.

Clinical pearls

Risk factors

The normal lifestyle involves a dog sheep cycle where the tapeworm is passed in the faeces of an infected dog and may subsequently be ingested by grazing sheep. Hence Hydatid disease is endemic in countries where dogs are fed on the viscera of home slaughtered sheep or other livestock.

Common pathogens:

- Four species of Echinococcus (*E. granulosus, E. multilocularis, E. vogeli, E. oligarthrus*) are known but only the two (*E. granulosus, E. multilocularis*) cause disease in humans.
- *E. granulosus* usually causes cystic hydatid disease whilst E. multilocularis causes alveolar disease
- *E.mulilocularis* produces daughter cysts by external, not internal budding 98% in the Liver, other sites are rare. It invades progressively like malignant tumor. May take up to 15-30 years to become symptomatic. Metastatic in 10%.
- Others such as *E. Vogeli* and *E. oligarthrus* cause Polycystic disease but are very rare, (around 100 cases reported). Associated with rodents and wild felines/canines. Predominantly affect the liver.

Typical Symptoms

- Clinical symptoms are highly variable and depend on the organ that is involved, the size of the cysts and their sites within the affected organs; symptoms caused by mass effect and anaphylaxis from spillage.
- Liver:
  - Cysts often asymptomatic for years. Can become secondarily infected. Can leak – hypersensitivity to anaphylaxis.
  - Biliary obstruction
  - Cholangitis
  - Lung: dyspnea, chest pain, cough, haemoptysis, cough, anaphylaxis
- CNS: seizures
- Eye: proptosis
- Bone: knee pain, bone compression.

Diagnosis

- Imaging
  - plain chest xray film, U/S, CT, MRI
  - Ultrasonography is 90% to 95% sensitive for *E.granulosus*. Based on ultrasonographic images, echinococcal cysts have been categorized by WHO to help in guiding the correct treatment. This categorization is as follows:

WHO stage	**Description**	**Stage**
CE1	Unilocular unechoic cystic lesion with double line sign	Active
CE2	Multiseptated, "rosette-like" "honeycomb" cyst	Active

CE3a	Cyst with detached membranes (water-lily sign)	Transitional
CE3b	Cyst with daughter cysts in solid matrix	Transitional
CE4	Cyst with heterogenous hypoechoic/hyperechoic contents; no daughter cysts	Inactive
CE5	Solid plus calcified wall	Inactive

- Serology
  - ELISA is the most specific and sensitive one
  - Few limitations to serological testing involve nonviable and calcified cysts. Also, liver cysts tend to be more seropositive than lung cysts, and serology is more specific for *E. multilocularis* than for *E. granulosus.*
- Percutaneous aspiration or biopsy is preferred when other modes have proven to be inconclusive (potential anaphylaxis and secondary spread of infection, aspiration, if required).

Treatment

- There are four modalities of treatment for echinococcal disease. These include **surgery, percutaneous management**, **drug therapy**, and **observation**.
- The WHO classification helps to choose the modality of choice for the treatment of echinococcal cysts as follows:

WHO stage	**Size**	**Preferred treatment**	**Alternate treatment**
CE1	<5 cm	Albendazole alone	PAIR (Puncture, Aspirate, Injection, Re-aspiration)
	>5 cm	Albendazole + PAIR	PAIR
CE2	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE3a	<5 cm	Albendazole alone	PAIR
	>5 cm	Albendazole + PAIR	PAIR
CE3b	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE4	Any	Observation	-
CE5	Any	Observation	-

- **For *E. multilocularis* preferred treatment is radical surgery plus albendazole.**

Surgery

- Aspiration: “PAIR”
- Scolicide (silver nitrate, alcohol)

Drug treatment

- Albendazole (15 mg/kg/day divided into two doses or 400 mg twice daily with food in an adult) or mebendazole is given continuously for 1 to 3 months or even 6 months depending on clinical factors.
- It should be known that medical therapy is futile in cases of cysts larger than 5 cm or having daughter cysts.
- In adjunctive therapy to surgery and percutaneous management, albendazole or mebendazole is given 4 to 30 days preoperatively and should be given for 1 month in case of albendazole and 3 months in case of mebendazole after surgery.
- Adjunctive therapy reduces recurrence by inactivating the protoscolices and renders the cyst wall soft, thus facilitating its removal.

Observation:

- This is for uncomplicated stage 4 and 5 cysts.
  Note: For alveolar Echinococcus, surgery is the main treatment of choice with two years of adjunctive drug therapy.

Adjunctive Therapy: Surgery or PAIR?

- PAIR plus albendazole or mebendazole against 952 matched historical controls
- Surgery plus albendazole or mebendazole

Follow up

- By ultrasonography and serology is done for 3 to 5 years.

Prevention and control

- Meat inspection and infected offal disposal
- Health education (parasite lifecycle, hygiene, dog contact, dog management)
- Prevent dogs' access to livestock offal and treat them with a purgative or anthelmintic.
- Vaccinate cattle (& dogs)

Resources:

- Echinococcosis. McManus DP, Zhang W, Li J, Bartley PB. Lancet. 2003 Oct 18;362(9392):1295-304.
- Prevention and control of cystic echinococcosis .Craig PS et al.. Lancet Infect Dis 2007; 7:385–394.
- Cystic echinococcosis in sub-Saharan Africa .Wahlers K et al.. Lancet Infect Dis 2012;12: 871–80
- CDC Echinococcosis 2019 Guideline available at : https://www.cdc.gov/dpdx/echinococcosis/index.html

Filariasis

- Anthroponosis caused by round worm Wuchereria bancrofti.
- Vector transmitted: Mosquitoes (Culex, Mansonia, Aedes and Anopheles) transmit the microfiliaria (MF) which have the Wolbachia bacteria. The MF migrates through the tissues. Culex mosquitoes breed in stagnant water anywhere including urban areas.
- The vector usually has a nocturnal feeding pattern.

Clinical pearls

- Tropical pulmonary eosinophilia (paroxysmal nocturnal cough, wheezing, low grade fever, fatigue, eosinophilia, IgE raised, bronchovascular marking on CXR)
- Produces acute inflammation, chronic scarring and lymphatic obstruction
- Elephantiasis - lymphatic obstruction by the adult worms. Lymphagenitis and lymphadenopathy may follow.
- Chyluria may also occur when there is erosion of ureters

Diagnosis

- Night blood films (22:00 hours to 02:00 hours. May need up to 1 ml of blood to diagnosis if routine smear is negative (concentration using centrifuging can be done)
- Ultrasound.
- Serology IgGC3 ELISA; 99% sensitivity, excellent NPV but lower to determine active disease as antigen may persist for many months post treatment.
- FBC- eosinophilia

Treatment

- Preferred:
  - Diethycarbamazine (DEC) 6mg/kg PO x single dose (yields 90% + MF reduction at one year follow up).
  - Pre-treat with doxycycline 100mg PO BID x 4 weeks then DEC
- Alternative:
  - Albendazole 400mg/kg PO QD x 3days (kills adults not MF therefore gradual decrease in MF)
  - Ivermectin 150micrograms/kg PO x 1 dose (kills MF not adults, thus repeat doses will be necessary).

Trypanosomiasis

Human African Trypanosomiasis (HAT)

- HAT is endemic to sub-Saharan Africa
- Caused by flagellated protozoa Trypanosoma brucei species which include two subspecies *T. brucei rhodesiense* and *T. brucei gambiense* which cause **East African Trypanosomiasis** and **West African Trypanosomiasis** respectively
- Mostly commonly transmitted to humans through bite by an infected Tse Tse fly (Glossina species) and rarely through blood transfusion, congenital, organ transplantation.

East African Trypanosomiasis (EAT)

- Acute HAT is caused by *T. b. rhodesiense*
- Most commonly seen in Zambia in foci such as Rufunsa, Nyimba, Mpika, Mambwe, South Luangwa, Lower Zambezi, Kafue National Park.
- Transmitted by infected tse tse fly Glossina morsitans
  Can present as:
  Stage 1 (Early, Haemolyphatic)-with indurated chancre at bite site, headache, malaise, myalgia, arthralgia, lymphadenopathy (axillary, inguinal), pyrexia, tachycardia, organomegaly
  Stage 2(Late, CNS involvement) – develops within weeks to months from exposure.
  headache, daytime somnolence, behavioural changes, mood depression, seizures in children, neck stiffness, irritability, hemiparesis, ataxia.

Diagnosis

- **DEFINITIVE DIAGNOSIS -** Blood smear (thin or thick)- to be examined within 15-20 minutes
    - Chancre aspirate
    - Lymph node aspirate
    - Haematocrit centrifugation technique for buffy coat
    - SRA LAMP (send sample to VET lab)
    - CSF microscopy (WBC> 5cells/ml, high protein, +/- trypanosomes)
    - **(ALWAYS PERFORM LUMBAR PUNCTURE TO HELP STAGE DISEASE)**
    - **Send samples immediately to the Lab for examination**
- **LABS-**FBC (neutropenia, thrombocytopenia)
    - LFTs (hypoalbuminemia), Urea, Creatinine, Electrolyte, ESR
- **IMAGING**
    - CT/MRI brain if suspecting late-stage disease

Treatment

- Consult ID team
- Stage 1(Early) disease-Suramin 100-200mg iv test dose then 1 g (20mg/kg) on days 1,3,7,14 and 21
- Alternative regimen-Pentamidine 4mg/kg/day IM or IV for 7 days
- Stage 2(Late, CNS) disease
    - Melarsoprol 2.2 mg/kg/day iv for 10 days
    - Prednisolone1mg/kg for 5 days then taper (may prevent/attenuate encephalopathy)
    - Pretreatment with suramin is often used to clear the haemolymphatic system of trypanosomes before administration of melarsoprol.
    - **Alternative regimen-** Melarsoprol 2-3.6 mg/kg/day IV (progressively increase to maximum) for 3 days; repeat the course at 3.6 mg/kg/day after 7 days and for 3rd time 7 days after 2nd course.

Monitoring

- Creatinine
- Encephalopathy

West African Trypanosomiasis

- Caused by *T. b. gambiense*
- Transmitted by infected tse tse fly Glossina palpalis
- **Stage 1** and **Stage 2** presentation similar to East African trypanosomiasis, stage 1 present with posterior cervical lymphadenopathy ("Winterbottom's sign")
- CNS disease develops more slowly

Diagnosis

- As with East African trypanosomiasis serology-card agglutination test for trypanosomiasis (CATT)

Treatment

- Stage 1 (Early) disease- Pentamidine 4mg/kg/day IM for 10 days

- Alternative regimen- Suramin 100-200mg IV test dose then 1 g(20mg/kg) IV on days 1,3,7,14 and 21
- Stage 2 (Late, CNS) disease- Nifurmox-Eflornithine Combination (NEC) therapy (Eflornithine 400 mg/kg/day IV in 4 divided doses for 7 days, Nifurtimox 15mg/kg/day PO in 3 divided doses for 10 days)
- Alternative regimen-Eflornithine 400 mg/kg/day IV in 4 divided doses for 14 days
- Combination therapy may be more effective than monotherapy for late-stage West African Trypanosomiasis (melarsoprol-nifurtimox)
- Relapse- Melarsoprol 2.2 mg/kg/day IV for 10 days

Resources

- IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Chow AW, et al.. Clin Infect Dis. 2012 Apr;54(8):e72-e112

Schistosomiasis

Clinical pearls

- Caused by trematodes (flukes) called *Schistosoma spp*. Each species has different primary site of infection.
    - *S. haematobium* - urogynecological and CNS transverse myelitis
    - *S. mansoni* - gastrointestinal and pulmonary
    - *S. intercalatum* (uncommon variant of *S. mansoni*) - gastrointestinal
    - *S. japonicum* (Not prevalent in Zambia but travel history from Asia is needed)
    - *S. mekongi* (uncommon variant of *S. japonicum*)- gastrointestinal

- Risk factors for transmission: residence in fishing camps and exposure to fresh waters
- Humans are the definitive hosts and snails are intermediate hosts
- In Zambia, highest prevalence is in Western and Central provinces. Lake Malawi is a well-known source of schistosomiasis.
- Praziquantel is regularly given in some provinces to school-children as mass drug administration. Genitourinary schistosomiasis has been shown to increase HIV transmission risk by 3-fold.
- Presentation varies by chronicity of infection:
    - Swimmer's itch: occurs as early as 15 minutes after water exposure. This is due to cutaneous penetration of cercarial forms.
    - Acute Katayama fever / acute toxaemic schistosomiasis: occurs 4-6 weeks after exposure, and is an immunological reaction to antigen in newly laid eggs. Symptoms include fever, cough, wheezing. It occurs more commonly in people not native to the endemic area.
- Bacteraemia from enteric or urologic pathogens can occur from migration of flukes. Check blood culture.
- Clinically may mimic malaria, typhoid, or other systemic tropical infections. Eosinophilia suggests schistosomiasis.
    - Chronic infection with end organ damage:
        - GU:
            - Hematuria
            - Bladder cancer (Squamous Cell Carcinoma)
            - Cervical fibrosis

        - Endometriosis and Salpingitis
        - Ureteric obstruction (colitis)
    - GU/biliary:
    - Colonic polyps, granulomas due to retained eggs
    - Periportal fibrosis, portal hypertension and lung sequalae of pulmonary hypertension
    - Cardiac:
        - Myocarditis
    - Neuro: common symptoms include
        - Delirium
        - Seizures
        - Loss of consciousness
        - Myeloradiculopathy (uncommon)

- Chronic infection increases the risk of transmission by continued shedding

Diagnosis

- Parasitological; direct visualization of ova from sedimented urine, faecal concentrate, or in biopsy (rectal snips, liver, bladder); biopsy is 45% sensitive.
    - In lighter/asymptomatic infections, eggs are usually not present in stool or urine, and serology is needed.
- Chronic: biopsy (bladder, rectal, hepatic) preferred
- Acute: urine or stool sample preferred
- Serological; antibody to soluble egg antigen ELISA 92-96% SENSITIVE but takes 6 weeks to seroconvert (not readily available).

Treatment

- Testing has poor sensitivity so patients can be treated on basis of clinical symptoms.
- Drug of choice: Praziquantel 40 mg/kg 1 or 2 doses the same day. This is active only against the adult worm; one single dose stops egg excretion in 70-100% of the adult worm, leading to 95% reduction in egg load. Patient should receive Praziquantel at time of presentation, and again in 6 weeks to kill any remaining eggs that have grown into adult worms.
- Fever is self-limiting but patients must still receive treatment to prevent chronic infection.
- **Katayama fever:**
- Steroids are primary therapy to control immune reaction to egg antigens prednisolone 40 mg PO qday for 3-5 days. (Praziquantel should not be given alone but can be given with steroids.)
- Asymptomatic infection:
    - Praziquantel 40 mg/day PO qday if exposure within last 3 months, and retreat after 6 weeks.
- Symptomatic infections:
    - Praziquantel 40 mg/day PO daily for all species except for *S. japonicium* & *S. mekongi* (60mg/kg – split into 2 doses).
- Neuroschistosomiasis:
    - Praziquantel 40 mg/day PO daily for 3 days PLUS prednisone 1 mg/kg/day for 6 months.
- Treatment often focuses on management of complications of chronic infection. If eggs are no longer present, anti-parasitics are not needed.

Resources:

- Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. Swai B, et al... BMC Infect Dis. 2006 Aug 23;6:134
- Association between genital schistosomiasis and HIV in rural Zimbabwean women. Kjetland EF, et al.AIDS. 2006 Feb 28;20(4):593-600.

Leprosy

Clinical pearls

- Caused by *Mycobacterium leprae*, slow growing, obligate intracellular pathogen
- Chronic, progressive skin and neurological disorder with high morbidity
- Transmission most likely from nasal discharge of leprosy patients but skin shedding may play a role
- Cardinal signs: localized skin lesions, nerve trunk thickening, AFB demonstrated in lesion

Diagnosis

- History, examination, and smears of slit skin
- AFB from skin smears from 6-8 sites.
- Nerve damage with reduced sensation with monofilament testing

Treatment

- Multibacillary (Skin-smear positive; usually borderline, borderline lepromatous or lepromatous on Ridley-Jopling Classification)
    - Dapsone 100 mg daily + rifampicin 600 mg once monthly + clofazimine 50 mg daily (after a once monthly 300 mg loading dose)
    - Duration: 12 months
- Paucibacillary (Skin smear negative; usually tuberculoid, borderline tuberculoid or indeterminate on Ridley-Jopling Classification)
    - Rifampicin 600 mg once monthly + dapsone 100 mg daily + clofazimine 50 mg daily (with once monthly 300 mg loading dose)
    - Duration: 6 months
- Prophylaxis
    - Single dose rifampicin (600 mg for adults) may be beneficial for household contacts

Resources

- WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy available at: https://apps.who.int/iris/handle/10665/274127