**Skin Structure Infections**

Classification of skin infections

* Uncomplicated
* Superficial infections
  + Simple abscesses
  + Lesions from impetigo
  + Furuncles
  + Erysipelas
  + Cellulitis
* Complicated
  + Deep soft tissue cellulitis
  + Infected ulcers
  + Infected burns
  + Major abscesses
* Also may have significant underlying disease that complicated treatment

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001863/>

Impetigo

Itching blisters caused by staph & strep - A single or possibly many blisters filled with pus; easy to pop and -- when broken -- leave a reddish raw-looking base

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002445/>

Furuncles (boils)

A boil caused by staph may begin as a tender, pinkish-red, swollen, firm area in the skin. Over time, it will feel like a water-filled balloon or [cyst](http://www.ncbi.nlm.nih.gov/pubmedhealth/n/pmh_adam/A003240/).

Pain gets worse as it fills with pus and dead tissue, and improves as it drains. It may drain on its own. More often the patient or someone else opens the boil.

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001643/>

Erysipelas

Painful, very red, swollen, and warm skin underneath the sore (lesion) caused by strep

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001858/>

Cellulitis

Redness, warmth, and swelling of the skin caused by staph & strep

Hospital Skin Infections – Statistics

Cellulitis 28%

Surgical wound 20%

Diabetic foot ulcer 14%

Trauma wound 12%

Other 11%

Gangrene 9%

Decubitis ulcer 6%

Type of Skin/Skin Structure Infections: Focus of Lecture

* Cellulitis
* Soft Tissue Infections in Diabetic Patients
* Erysipelas
* Bite Wounds & Atypical Presentations
* Dermatophytic Fungal Infections

**CELLULITIS**

General

* Cellulitis: infection of the skin with some extension into the subcutaneous tissue
* Usually complication of a wound, skin break, ulcer or continuum of other skin infections

Epidemiology

* Incidence: top 20 most common diagnosis in hospitalized patients (probably higher)
* Appears to be more common in men
* Anatomical Features
  + Lower Extremities ~ 70%
  + Upper Extremities ~ 20%
  + Head and Neck ~ 7%

Predisposing Factors for Cellulitis

* Site of Entry (trauma, surgery, burns, ulcers, varicella, dermatophytes)
* Venous Insufficiency
* Leg Edema
* Overweight
* Diabetes
* Lymphedema

<http://www.jimbaun.com/vasc_chapter_chronic_venous_insufficiency.pdf>

Mechanism of venous insufficiency & leg edema causing cellulitis

It has been hypothesized that increased venous hydrostatic pressure is transmitted to the dermal microcirculation which leads to increased permeability of dermal capillaries. This increased permeability enables macromolecules, such as fibrinogen, to leak out into the pericapillary tissue where they obstruct normal capillary flow, reducing oxygen supply to the dermal tissues; the same mechanism that is responsible for hyperpigmentation, edema and clinical manifestations of CVI

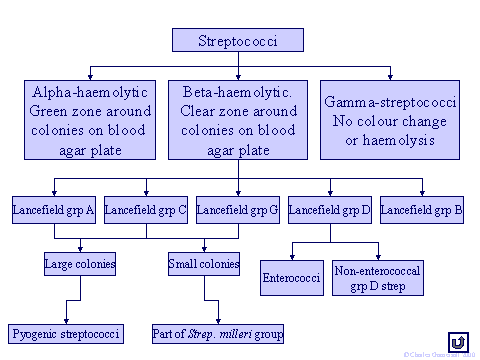
Microbiology of Cellulitis

* Beta hemolytic Streptococci
  + Group A: *Streptococccus pyogenes*
    - *“necrotizing fascitis’s flesh eating bacteria”*
  + *Most Common Cause of Cellulitis????*
    - Most virulent of the beta hemolytic streptococci
    - Exotoxins, Hemolysins and other virulent factors
      * Streptolysin O, Streptolysin S, Streptokinase, DNA-ase, Hyaluronidase, Erythrogenic toxin
  + Group B
  + Group G
  + Group C

<http://www.aic.cuhk.edu.hk/web8/streptococci.htm>

Classification of strep

Only beta-haemolytic strep Group A, B, C & G cause cellulitis not including Group D



* Staphylococcus aureus
  + Increased concerns of community acquired MRSA (Methicillin-resistant Staphylococcus aureus)
* Haemophilus influenza: facial cellulitis in children: Decreased incidence due to pediatric vaccination
* Gram negative Enterobacteriacae (E. coli, Klebsiella species, Proteus species)
  + Diabetic infections, necrotizing infections, bites

<http://www.cdc.gov/mrsa/definition/index.html>

Definition of MRSA

<http://en.wikipedia.org/wiki/Haemophilus_influenzae>

Gram-negative rod bacteria

Most strains of H. influenzae are opportunistic pathogens; that is, they usually live in their host without causing disease, but cause problems only when other factors (such as a viral infection, reduced immune function or chronically inflamed tissues, e.g. from allergies) create an opportunity

* Aerobes: puncture wounds
  + Pseudomonas, Aeromonas hydrophilia, Vibrio vulnificus, Mycobacterium marinum: cellulitis after exposure to water
* Anaerobes: puncture and bite wounds
  + Oral anaerobes
  + Bacteroides
  + Clostridium: gangrene
* Pasteurella multocida: cat and dog bites
* Eikenella corrodens: human bites

Diagnosis

* Clinical Presentation
  + Local findings
    - Macular erythema that is largely confluent
    - Generalized swelling of the area
    - Warmth to the touch of the involved skin
    - Tenderness
    - Tender regional lymphadenopathy
    - Abscess formation also may be present
    - **The absence of erythema, warmth, swelling and local tenderness argue strongly against the diagnosis of cellulitis**
  + **Systemic toxicity: fever, chills, myalgias, leukocytosis**

Cultures???

* Cellulitis primarily clinical
* Cultures of blood, skin aspirates and skin biopsies not routinely done
* Culturing reserved for those who:
  + Demonstrate systemic toxicity
  + Unresponsive to initial therapy
  + Unusual exposures (water, animals, human bites)
  + Recurrent infections

Hospitalization?

* Presence of tissue necrosis
* Sepsis
* SEVERE Pain
* Altered Mental Status
* Immunocompromised state
* Organ Failure

Treatment

* Empiric in nature
* Based on Clinical Presentation, Site of Infection, Exposure History
* Treatment directed against acute infection and whether to hospitalize or not
  + **High fever, rigors, chills, change in mental status = hospitalization**

Non-Drug Therapy

* Surgical incision and drainage
* Debridement of necrotic tissue
* Appropriate Wound Care
* Resuscitation to improve perfusion
* “Critters”

Empiric Parental Therapy

* Directed against Beta Hemolytic Streptococci primarily but should also cover Staphylococcus aureus:
  + Cefazolin 1 g IV q8h (1st generation Cephalosporins)
  + Nafcillin 2g IV q4h (beta lactam – penicillin- narrow spec – beta-lactamase resistant)
  + **If in a high risk area for Community Acquired MRSA Consider Vancomycin as Empiric Therapy**
    - Obtain a good medical history

Generally well tolerated; most likely effects are diarrhea, rash; nafcillin with a higher incidence of drug-induced neutropenia

<http://en.wikipedia.org/wiki/Nafcillin>

Nafcillin

Beta Lactam Allergy

* **Assure** accurate allergy history
* Clindamycin: most common used at 600 mg IV q8h
* Vancomycin ~ **15 mg/kg/dose**; frequency dependent on renal function

<http://www.the-hospitalist.org/details/article/262691/What_is_the_best_empiric_therapy_for_community-acquired_cellulitis.html>

Clindamycin vs Vancomycin for MRSA (methicillin-resistant staph)

For outpatients, trimethoprim/sulfamethox-azole (possibly in combination with a beta-lactam antibiotic), clindamycin, and linezolid can be used to treat community-acquired cellulitis.

When patients require hospitalization for the optimal treatment of cellulitis, it is important to select a parenteral antibiotic that provides coverage for MRSA. Vancomycin, daptomycin, linezolid, and tigecycline are the most commonly used agents

<http://cid.oxfordjournals.org/content/early/2011/01/04/cid.ciq146.full>

Outpatient Clindamycin PO

Inpatient: Vancomycin IV or Clindamycin IV

<http://www.rxkinetics.com/vanco.html>

Vancomycin nephrotoxicity appears to be concentration-related, with an increased risk at trough concentrations greater than 30mcg/ml

MRSA cellulitis

* Considered in patients
  + Multiple medical contacts with health care system
  + > 15 % community acquired MRSA: Philadelphia ~ > 50%
  + IVDU (intravenous drug users)
  + Long-term care facility patient
  + Previous antibiotic use within one month
* If vancomycin used inappropriately can lead to superinfection Community acquired MRSA on the rise
  + NEJM 2005;1436-1444 showed 1647 of Community Acquired MRSA with 77% of these being skin infections
  + NEJM 2006; 355:666-674 MRSA was the most common identifiable cause of skin infections in EDs in 11 US cities (including Philadelphia)
* **Therapy with beta-lactam antibiotics can no longer be relied on as sole empiric therapy for severely ill outpatients whose infections may be Staphylococcal in origin.**

Agents with Activity Against MRSA Hospital-acquired MRSA?

* Vancomycin
* Quinupristin/Dalfopristin
* Daptomycin
* Tigecycline
* Linezolid
* Ceftaroline
* Telavancin

**VANCOMYCIN**

* Vancomycin: 15 mg/kg/dose with frequency dependent on renal function
* Vancomycin nephrotoxicity appears to be concentration-related, with an increased risk at trough concentrations greater than 30mcg/ml

**LINEZOLID (Zyvox)**

* Linezolid 600 mg IV q12h or po
  + Bacteriostatic agent
  + Brand name Zyvox
  + MOA: block protein synthesis at ribosomal level
  + Side effects
    - Thrombocytopenia, myelosuppression (including anemia, leukopenia, pancytopenia, and Thrombocytopenia)
    - GI (N,V,D)
    - MAO-I so properties potential drug and food interactions
      * See FDA labeling changes with SSRIs (selective serotonin reuptake inhibitors)
    - No renal or hepatic dose adjustments

<http://www.fda.gov/drugs/drugsafety/ucm265305.htm>

Linezolid is used to treat vancomycin-resistant *Enterococcus faecium* (VRE) infections.

Linezolid is used to treat infections such as nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

linezolid has monoamine oxidase inhibitor (MAOI) properties - Linezolid (Zyvox) can interact with serotonergic psychiatric medications and cause serious CNS toxicity

**DAPTOMYCIN**

* Bactericidal
* Active against important gram-positive organisms
* IV only
  + 4 mg/kg (actual body weight) q24h
  + CrCl < 30 ml/min (including dialysis)
    - 4 mg/kg q48 hour
  + Main adverse effect: skeletal myopathy

**TIGECYCLINE**

* Glycylcycline (deriative of minocycline)
* Bacteriostatic agent
* Approved for cSSSTi (complicated skin and skin structure infections)
* Gram negative, gram positive, anaerobic and atypical pathogens (? Pseudomonas or Proteus)
* Dose
  + 100 mg IV load followed by 50 mg IV q12h
  + No renal dose adjustment
* 25% of N&V
* Other adverse effects similar to tetracyclines

<http://www.merckmanuals.com/professional/infectious_diseases/bacteria_and_antibacterial_drugs/tigecycline.html>

It is not effective against Pseudomonas aeruginosa, Providencia sp, Morganella morganii, or Proteus sp.

**CEFTAROLINE (Teflaro)**

* “Fifth generation cephalosporin”
* Like other beta lactams ceftaroline binds to PBPs (penicillin-binding protein) inhibiting cell wall synthesis
* Unlike other beta-lactams, ceftaroline has high affinity *in vitro*  for PBP2a, a unique PBP encoded by the *mecA* gene in MRSA.
* Dosing: 600 mg IV q12h
  + Renal dosing required
    - 31-50 ml/min: 400 mg IV q12h
    - 15-30 ml/min: 300 mg IV q12h
    - < 15 ml/min: 200 mg IV q12h
  + Side effects/adverse effects similar to other cephalosporins
* Efficacy
* Comparison of ceftaroline vs. (vancomycin+aztreonam) ….. similar cure rates
* 1300 patients with complicated skin infections
* Excluded: diabetic foot ulcers, decubitus ulcers, burn related infections, or known or suspected Pseudomonal infections
* Clinical cure rates were 91.6% vs. 92.7% between two groups
* Clinical cure rates for MRSA isolated (n = 330)
  + 93.4% vs. 94.3%

<http://depts.washington.edu/hivaids/derm/case6/discussion.html>

Mechanism of mecA gene in MRSA

<http://en.wikipedia.org/wiki/Pressure_ulcer>

Decubitus ulcers – pressure ulcers or bedsores

Other Therapies Community-acquired MRSA?

* Community Acquired MRSA
  + Doxycycline; minocycline
  + **Bactrim (2 DS po q12h; dose adjust in renal impairment) …..** trimethoprim and sulfamethoxazole
  + Clindamycin 600 mg IV q8h or 300-450 mg po TID
* Quinolones???

Oral Therapy for Cellulitis(primarily when MRSA NOT suspected)

* Cephalexin: 500 mg po q6h
* Dicloxacillin: 500 mg po q6h
* Cefuroxime axetil: 500 mg po q12h
* Beta lactam allergy
  + Erythromycin 500 mg po q6h
  + Clindamycin 300 mg po q6h
  + Levofloxacin 750 mg po daily

Duration of Therapy

* Duration of therapy is typically 10-14 days
* If still exhibiting erythema; extend therapy
* Switch to PO therapy when possible
  + Patients that are non-toxic
  + Able to tolerate PO
  + Can keep limbs elevated
  + Monitoring as outpatient for resolution

Therapy for Cellulitis: Atypical cases

* Water exposure
  + Folliculitis from “loofa sponges” & hot-tubbing
  + Cuts in water
  + Aquaria
* Fresh water/Hot-tubbing: dictates coverage for Aeromonas and possible Pseudomonas:
  + Ciprofloxacin 400 mg IV q12h
  + Levofloxacin 750 mg IV daily
  + Other anti-Pseudomonal agents
* Salt water =? Vibrio vulnificus: tetracyclines
* Bites
  + Cat and Dog: Pasteurella multocida
    - Augmentin 500 mg po q8h
  + Human: Oral anaerobes, viridans streptococci, Eikenella corrodens
    - Augmentin 500 mg po q8h
* Very odd cases:

Salt Water Aquaria: Mycobacterium marinum

Rose gardeners: Sporothrix schenkii (dimorphic mold)

**Diabetic Foot Infections**

* Polymicrobial in nature
* Occurs in 25% of patients
* 5-15% may end up with amputation of limb
* Risk of foot problems
  + Neuropathies
  + Peripheral vascular disease
  + Poor nail care
* Mild: treat like routine cellulitis +/- metronidazole or clindamycin
* **Moderate to Severe** (i.e. non-healing plantar ulcers)
  + Very broad spectrum (gram positive cocci, gram negative rods, anaerobes)
    - Ampicillin/sulbactam (first line)
    - Imipenem
    - Meropenem
    - Piperacillin/tazobactam
  + ? Vancomycin addition if MRSA is to be considered

**Erysipelas**

* Characteristic form of cellulitis which affects the superficial epidermis
* Risk factors
  + Skin ulcers
  + eczema
  + Local trauma
  + lymphedema
* Primary cause: beta hemolytic streptococci
* Features
  + Raised border sharply demarcated from normal skin (other cellulitis forms are more “flat”)
  + Skin is also:
    - Painful
    - Edematous
    - Intensely reddened
    - Indurated: peau d’orange or ORANGE PEEL
    - Generally no localized purulence
    - Face is common site but can occur anywhere
* Treatment
  + Penicillin: PenVK 500 mg po QID or IV for those who require hospitalization
  + Allergic: Erythromycin 500 mg IV or PO QID
  + Other options: Clindamycin, Levofloxacin, Vancomycin, and of course Cephalosporins
  + Duration of therapy 10-14 days or until all signs of erythema involved

**Superficial and Cutaneous Mycoses**

* Onychomycosis: Tinea Unguium
  + Nail infections
* Tinea Pedis
  + Athletic foot’s
  + (Review therapeutics from your OTC class notes)

**Onychomycosis -** Tinea Unguium

* Fungal infection of the fingernails and toenails
* Most prevalent in older adults
* Younger patients…off shoot from athlete’s foot
* May lead to secondary superinfections
* Quality of life problems
* 90% of onychomycosis is caused by dermatophytes (mold)
  + Trichophyton species
* Other fungal causes
  + Candida species (yeast)
  + Non-dermatophytic molds
    - Scopulariopsis
    - Aspergillus
* Nail physiology
  + Nails develop from cells in the basal layer of the epidermis
  + Nail surface: densely compacted heavily keratinized, dead skin cells….virtually impossible to penetrate
  + Nails replacement
    - Fingernails: 6-9 month
    - Toenails: 12-18 month
* Infection begins as a primary fungal invasion of the health nail plate and hyponychium (skin under the distal end of the nail)
* Nail plate appearance
  + Thickened
  + Distorted
  + Opaque, white or yellow
  + Crumbly

**Treatment**:

* Surgical/mechanical: removal of the nail
* Nonprescription: basically not efficacious….never cure
* Prescription Therapies
  + Oral
    - Griseofulvin
    - Ketoconazole
    - Itraconazole
    - Terbinafine
  + Topical: ciclopirox 8%

**Griseofulvin**

* Fungistatic agent vs. fungicidal
* Treatment up to 12 months
* Unpopular treatment
* Side Effects
  + Photosensitivity
  + Cross-reactivity to penicillin
  + CNS
  + GI
  + Rare: hepatotoxicity, hematologic

<http://www.merckmanuals.com/vet/pharmacology/antifungal_agents/griseofulvin.html>

Griseofulvin is fungistatic rather than fungicidal, except in young active cells.

**Ketoconazole**

* Fungistatic agent
* Unpopular due to side effects and many drug interactions
  + Hepatotoxicity
  + Adrenal-corticol insufficiency
  + Gynecomastia/ decreased libido
  + GI
  + CNS
* Gastric acidity needed for maximal absorption
* Many Drug interactions

**Itraconazole**

* Fungistatic: block ergosterol synthesis
* Regimens shorter than former agents: Dose 200 mg once daily x 12 weeks
* Pulse dosing: 200 mg BID x 1 week then 3 weeks off and repeat for 3-4 “pulses”
* Also need acidity for absorption
* Warnings: regarding cardiotoxicity and prolonged QTc interval: contraindicated for onychomycosis with patient with underlying cardiac risk factors
* Other side effects:
  + Liver dysfunction: monitor LFTs
  + GI
  + Allergy
  + Many drug interactions: memorize

<http://www.genemedrx.com/PGP_Introduction.php>

Itraconazole is a P-glycoprotein inhibitor and increases the concentration of some drugs

Since P-gps block absorption in the gut, they should be considered part of the "first-pass effect". In fact, they can "set up" or act as "gatekeepers" for later P450 cytochrome actions.

<http://dermnetnz.org/treatments/itraconazole.html>

Drug interactions of itraconazole

As itraconazole needs acid for its absorption, antacids, H2 antagonists (cimetidine, famotidine, ranitidine) and omeprazole should not be taken for 2 hours after itraconazole

These drugs should not be taken by those on itraconazole:

* HMG Co-A reductase inhibitors (atorvastatin, lovastatin, simvastatin); fluvastatin, rosuvastatin and pravastatin are acceptable alternatives. Toxicity results in muscle pain and weakness, which may be serious.
* Midazolam, triazolam
* The [antihistamines](http://dermnetnz.org/treatments/antihistamines.html) astemizole (Hismanal®) and terfenadine (Teldane®)

The dose of these drugs should be reduced due to high concentration or side effects

* Warfarin
* Digoxin
* Methyl prednisolone
* [Cyclosporin](http://dermnetnz.org/treatments/cyclosporin.html)e
* [Tacrolimus](http://dermnetnz.org/treatments/tacrolimus.html)
* Vinca alkaloids
* Quinidine
* Calcium channel blockers
* Antidiabetic sulphonylurea medication (tolbutamide, glibenclamide, gliclazide, glipizide)

The following drugs decrease the concentration of itraconazole:

* [Rifampicin](http://dermnetnz.org/treatments/rifampicin.html)
* Isoniazid
* Phenytoin
* Carbamazepine

Itraconazole is **not** thought to interact with the oral contraceptive pill.

**Terbinafine**

* Allylamine antifungal: fungicidal and fungistatic
* Highly effective for onychomycosis
* Dose 250 mg daily for up to 12 weeks
* Side effects
  + GI including dysgeusia
  + Rare liver toxicity
* Drug interactions: less significant-see table

**Ciclopirox 8%: Penlac**

* Topical nail lacquer (8% solution)
* ONLY FDA approved topical preparation for onychomycosis
* Used for mild to moderate onychomycosis
* MOA: binds trivalent cations (Iron and Chromium) that are essential co-factors for fungal mitochondrial enzymes
* Lacquer delivery system
  + 8% ciclopirox as a free acid
  + Solvents in lacquer evaporate and the concentration of the ciclopirox increase by 35% providing a higher concentration gradient to penetrate the nail
  + Apply repeatedly for 7 days, then wash off with alcohol
  + Reapply: treatment up to 48 weeks’ removed as much as possible any damaged nail
  + Side effects: no systemic

**Nail Hygiene**

* Avoid injury and irritation by wearing protective footwear and gloves when appropriate
* Use sandals/slippers in health clubs, public showers, locker rooms, and hotel carpets
* Keep feet cool and dry; use a medicated powder if feet are prone to sweating
* Air shoes out daily; switch them often; Clean hosiery and socks thoroughly

Question

For the skin infection powerpoint, patients with MRSA cellulitis can

be treated with:

Vancomycin

Daptomycin

Tigecycline

Linezolid

Quinupristin/Dalfopristin (Synercid)

Not used often b/c myalgia

Ceftaroline (5th gen cef)

Telavancin

How do I know which one to choose?

Attached, I have a pdf of a simple algorithm for treating MRSA skin

infections. Can you help me find a more detailed procedure on how to

treat MRSA skin infections?

Answers with PPT

http://publichealth.lacounty.gov/acd/MRSA/MRSAguide.htm

Flow chart: Guidelines for evaluation & management of CAMRSA skin & soft tissue infections in outpatient settings (WA, 2007)

**Guidelines for Management of *S. aureus* Skin & Soft Tissue Infection, December, 2007\***

*Infectious Diseases Society of Washington, Public Health – Seattle & King County, Tacoma-Pierce County*

*Department of Health, and Washington State Department of Health*

Guidelines for Empiric Oral Antimicrobial Treatment of Outpatients with Suspected MRSA Skin and Soft Tissue Infections (SSTI)

* Trimethoprim-sulfamethoxazole (TMPSMX) DS
* Minocycline or doxycycline
* Clindamycin

Hospital setting – Selection of drugs based on results of culture & susceptibility testing

* Vancomycin
* Daptomycin
* Linezolid

Answers with Web links

<http://publichealth.lacounty.gov/acd/docs/CAMRSA_ProviderFactSheet.pdf>

If the patient is found to have an MRSA skin infection and antibiotics are indicated, use culture to select an antibiotic the organism is susceptible to. The predominant strain in this outbreak has been susceptible to TMP/SMX (Bactrim or Septra), clindamycin, gentamicin and rifampin.

<http://publichealth.lacounty.gov/acd/docs/MRSA-TPHJulAug05.pdf>

Physicians are encouraged to perform incision and drainage (I&D) on all appropriate lesions and send the product for culture

With an increasing prevalence of CAMRSA, physicians should consider empiric treatment of skin infections with antibiotics that have activity against CAMRSA such as TMP-SMX, clindamycin, or tetracyclines.

<http://publichealth.lacounty.gov/acd/MRSA/MRSAguide.htm>

General

<http://www.bop.gov/news/PDFs/mrsa.pdf>

Management of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections

Federal Bureau of Prisons Clinical Practice Guidelines

April 2012

<http://www.cdc.gov/mrsa/pdf/MRSA-Strategies-ExpMtgSummary-2006.pdf>

Strategies for Clinical Management of MRSA in the Community:

Summary of an Experts’ Meeting Convened by the Centers for

Disease Control and Prevention

March 2006