# Infectious diseases

| | 4/5th Semester Classes on Infectious Diseases, 8-9AM, Tuesdays (LT-1) |
|---|---|
| | **Topics** |
| 1 | Approach to Infectious Diseases and their prevention |
| 2 | Antibiotic stewardship practices |
| 3 | Community-Acquired Infections |
| 4 | Health Care–Associated Infections |
| 5 | Gram-Positive Bacteria (part-1) |
| 6 | Gram-Positive Bacteria (part-2) |
| 7 | Gram-Negative Bacteria (part-1) |
| 8 | Gram-Negative Bacteria (part-2) |
| 9 | Spirochetal Diseases |
| 10 | Diseases Caused by Atypical/Miscellaneous Bacterial Infections |
| 11 | **Revision-cum-exam on bacteria (Must to know type)** |
| 12 | Infections Due to DNA Viruses |
| 13 | Infections Due to RNA Viruses (part 1) |
| 14 | Infections Due to RNA Viruses (part 2) |
| 15 | HIV/AIDS – part 1 |
| 16 | HIV/AIDS – part 2 |
| 17 | Fungal Infections |
| 18 | Parasitic Infections (part 1) |
| 19 | Parasitic Infections (part 2) |

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## Streptococcal Infections

## Pneumococcal Infections

## Staphylococcal Infections

## Enterococcal Infections

# Streptococcal Infections

- Streptococcus, from the Greek streptos, meaning "**twisted**," and kokkos, meaning "berry"
- Normal flora **colonizing** the human respiratory, gastrointestinal, and genitourinary tracts
- Facultative anaerobes, although some are strict anaerobes, are Fastidious and **grow best in 5% CO2**
- **Respiratory droplets** are the usual mechanism of spread, although other routes, including food-borne outbreaks been described

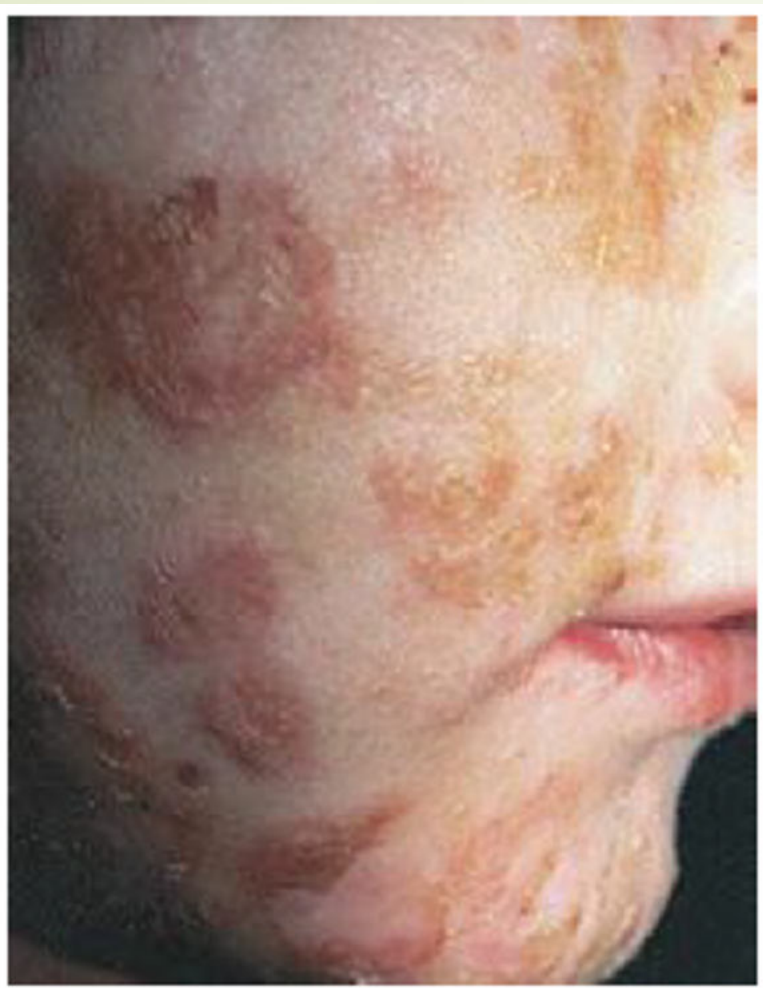
| Lancefield Group | Representative Species | Hemolytic Pattern | Typical Infections |
|---|---|---|---|
| A | *S. pyogenes* | β | Pharyngitis, impetigo, cellulitis, scarlet fever |
| B | *S. agalactiae* | β | Neonatal sepsis and meningitis, puerperal infection, urinary tract infection, diabetic ulcer infection, endocarditis |
| C, G | *S. dysgalactiae* subsp. *equisimilis* | β | Cellulitis, bacteremia, endocarditis |
| D | Enterococci[a]: *E. faecalis, E. faecium* | Usually nonhemolytic | Urinary tract infection, nosocomial bacteremia, endocarditis |
| | Nonenterococci: *S. gallolyticus* (formerly *S. bovis*) | Usually nonhemolytic | Bacteremia, endocarditis |
| Variable or nongroupable | Viridans streptococci: *S. sanguis, S. mitis* | α | Endocarditis, dental abscess, brain abscess |
| | *Intermedius* or *milleri* group: *S. intermedius, S. anginosus, S. constellatus* | Variable | Brain abscess, visceral abscess |
| | Anaerobic streptococci[b]: *Peptostreptococcus magnus* | Usually nonhemolytic | Sinusitis, pneumonia, empyema, brain abscess, liver abscess |

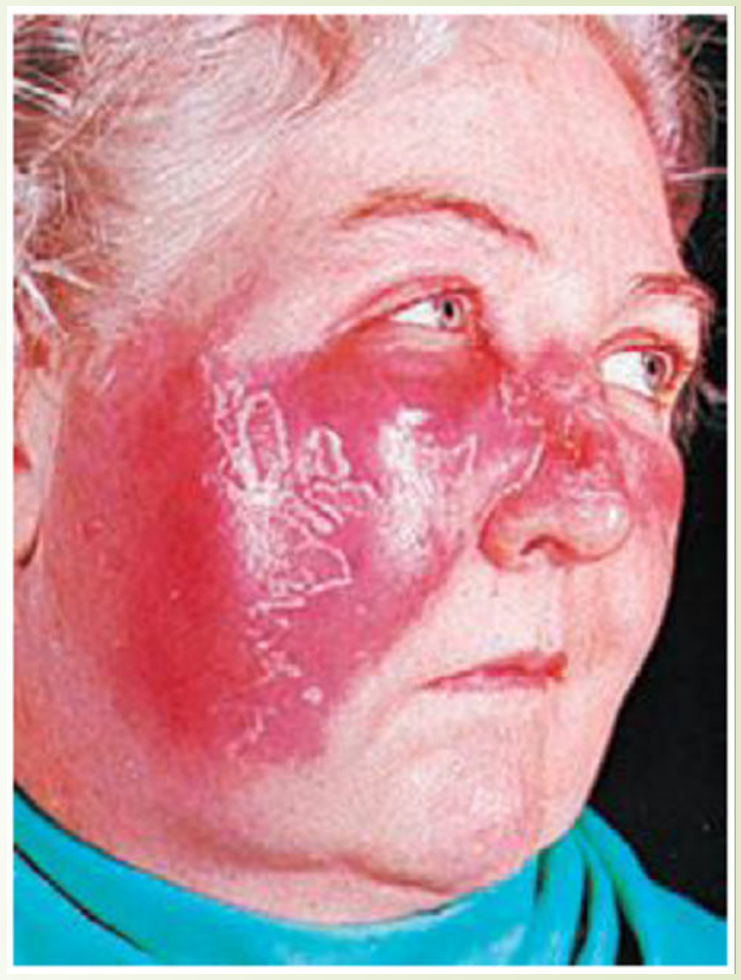
# GROUP A STREPTOCOCCI (GAS)

- Elaborates a number of cell-surface components (**M protein, Polysaccharide** capsule) and extracellular products (streptolysins S and O, streptokinase, DNAses, SpyCEP, several pyrogenic exotoxins)
- Differential diagnosis of streptococcal pharyngitis includes many, however, Symptoms and signs suggestive of viral infection to be ruled out (**conjunctivitis, coryza, cough, hoarseness, or discrete ulcerative lesions** of the buccal or pharyngeal mucosa)
- The throat culture remains the diagnostic **gold standard (**properly collected, by vigorous rubbing of a sterile swab over both tonsillar pillars)
- A rapid diagnostic kit for latex agglutination or enzyme immunoassay of swab specimens is a useful adjunct with **>95% specific**ity
- Treatment is given **primarily to prevent** suppurative complications and ARF AND requires **10 days** of penicillin treatment

## GROUP A STREPTOCOCCAL INFECTIONS

| Infection | Treatment[a] |
|---|---|
| Pharyngitis | Benzathine penicillin G (1.2 mU IM) *or* penicillin V (250 mg PO tid or 500 mg PO bid) × 10 days<br>(Children <27 kg: Benzathine penicillin G [600,000 units IM] *or* penicillin V [250 mg PO bid or tid] × 10 days) |
| Impetigo | Same as pharyngitis |
| Erysipelas/cellulitis | Severe: Penicillin G (1–2 mU IV q4h)<br>Mild to moderate: Procaine penicillin (1.2 mU IM bid) |
| Necrotizing fasciitis/ myositis | Surgical debridement *plus* penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) |
| Pneumonia/empyema | Penicillin G (2–4 mU IV q4h) *plus* drainage of empyema |
| Streptococcal toxic shock syndrome | Penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) *plus* IV immunoglobulin[b] (2 g/kg as a single dose) |





## PROPOSED CASE DEFINITION FOR THE STREPTOCOCCAL TOXIC SHOCK SYNDROME[a]

I. Isolation of group A streptococci (*Streptococcus pyogenes*)
   - A. From a normally sterile site
   - B. From a nonsterile site

II. Clinical signs of severity
   - A. Hypotension *and*
   - B. ≥2 of the following signs
     1. Renal impairment
     2. Coagulopathy
     3. Liver function impairment
     4. Adult respiratory distress syndrome
     5. A generalized erythematous macular rash that may desquamate
     6. Soft tissue necrosis, including necrotizing fasciitis or myositis; *or* gangrene

# Complications

1. Suppurative complications result from the spread of infection from the pharyngeal mucosa to deeper tissues **by direct extension or by the hematogenous or lymphatic route** and may include cervical lymphadenitis, peritonsillar or retropharyngeal abscess, sinusitis, otitis media, meningitis, bacteremia, endocarditis, and pneumonia
2. Local complications, such as peritonsillar or parapharyngeal abscess formation,
3. Nonsuppurative complications include ARF and PSGN
   - ARF is not a sequela to streptococcal skin infections, although **PSGN may follow either** skin or throat infection. The reason for this difference is not known.
   - One hypothesis is that the immune response necessary for development of ARF occurs only after infection of the pharyngeal mucosa.
   - In addition, the strains of GAS that cause pharyngitis are generally of different M protein types than those associated with skin infections.

- **up to 20%** of individuals in certain populations may have asymptomatic pharyngeal colonization
- When a carrier is transmitting infection to others, attempts to eradicate carriage are warranted, but no specific treatment/guidelines

# Pneumococcal Infections

- Belongs to the **a-hemolytic group**, but growth is inhibited in the presence of optochin (ethylhydrocupreine hydrochloride), and bile soluble
- Rapid and dramatic **changes** in the epidemiology of during the past decade after routine childhood vaccine (PCV)
- Not all pneumococcal serotypes are equally likely to cause disease; serotype distribution **varies by** age, disease syndrome, and geography
- Intermittent inhabitants of the healthy human **nasopharynx** and are transmitted by respiratory **droplets**
- Spread either via the bloodstream to distant sites or locally to mucosal surfaces
- In children, nasopharyngeal **ecology varies** by geographic region, socioeconomic status, climate, degree of crowding, and particularly intensity of exposure to other children

| Clinical Risk Group | Examples |
|---|---|
| Asplenia or splenic dysfunction | Sickle cell disease, celiac disease |
| Chronic respiratory disease | Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g., cerebral palsy), severe asthma |
| Chronic heart disease | Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure |
| Chronic kidney disease | Nephrotic syndrome, chronic renal failure, renal transplantation |
| Chronic liver disease | Cirrhosis, biliary atresia, chronic hepatitis |
| Diabetes mellitus | Diabetes mellitus requiring insulin or oral hypoglycemic drugs |
| Immunocompromise/ immunosuppression | HIV infection, common variable immunodeficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic glucocorticoid treatment for >1 month at a dose equivalent to ≥20 mg/d (children, ≥1 mg/kg per day) |
| Cochlear implants | … |
| Cerebrospinal fluid leaks | … |
| Miscellaneous | Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters |

# Invasive pneumococcal disease (IPD)

- Pathophysiology of severe pneumococcal pneumonia among adults reflects a rapidly progressive cascade of events that **often unfolds irrespective** of antibiotic administration
- Rates of pneumococcal disease **vary by** season, by sex, and by risk group
- Local cytokine production after a viral infection is thought to **upregulate adhesion factors**
- Delayed ontogeny of **capsule-specific IgG** in young children is associated with susceptibility to infection
- There is **no pathognomonic presentation** of pneumococcal disease
- The suspicion should be in differential diagnosis of
  - pneumonia,
  - otitis media,
  - fever of unknown origin, and
  - meningitis

# Clinical syndromes

- Classified as noninvasive (e.g., otitis media and nonbacteremic pneumonia) or invasive (e.g., bacteremic pneumonia)
- The presentation of pneumococcal pneumonia **does not reliably distinguish** it from pneumonia of other etiologies
- The differential diagnosis includes
  - Cardiac conditions such as myocardial infarction and heart failure with atypical pulmonary edema;
  - Pulmonary conditions such as atelectasis; and pneumonia caused by viral pathogens, mycoplasmas, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Legionella*, or (in immunocompromised hosts) *Pneumocystis*
  - Cholecystitis, appendicitis, perforated peptic ulcer disease, and subphrenic abscesses

# Pneumonia

- The **gold standard** for etiologic diagnosis of pneumococcal pneumonia is pathologic examination of lung tissue
- Gram's staining and culture of sputum
- Chest radiography helps in diagnosis, but an infiltrate can be absent either early in the course of the illness or **with dehydration**; upon rehydration, an infiltrate usually appears
- The appearance **varies;** lobar or segmental or patchy consolidation
- **Parapneumonic effusions are more common** than empyema
- Pleural fluid with frank pus, bacteria, or a pH of ≤7.1 indicates empyema
- Blood cultures are positive in a minority **(<30%)**
- Urinary **pneumococcal antigen** assays**; important** among whom nasopharyngeal colonization is relatively low

# Meningitis

- Pneumococcal meningitis typically presents **as a pyogenic condition** that is clinically indistinguishable from meningitis of other bacterial etiologies
- Definitive diagnosis of pneumococcal meningitis rests on CSF examination
  - (1) evidence of turbidity (visual inspection);
  - (2) elevated protein level, elevated white blood cell count, and reduced glucose concentration (quantitative measurement); and
  - (3) specific identification of the etiologic agent (culture, Gram's staining, antigen testing, or polymerase chain reaction [PCR])
- Blood culture or detection of antigen in urine is considered highly specific
- Mortality rate for pneumococcal meningitis is ~20%

# Other Invasive Syndromes

- Primary bacteremia without other sites of infection (bacteremia without a source; occult bacteremia),
- Osteomyelitis
- Septic arthritis
- Endocarditis
- Pericarditis
- Peritonitis

- The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR

# Noninvasive Syndromes

- Otitis media is the **most common** pneumococcal syndrome and most often affects young children
- Sinusitis presents with facial pain, congestion, fever, and— in many **cases—persistent nighttime cough**

# Treatment

- **Meningitis: V**ancomycin (adults, 30–60 mg/kg per day) and cefotaxime or ceftriaxone (adults, 4 g/d in 1 dose or 2 divided doses)
- If hypersensitive to β-lactam agents, **rifampin** (adults, 600 mg/d) can be substituted
- A repeat lumbar puncture should be considered **after 48 h**
  - if the organism is not susceptible to penicillin and information on cephalosporin sensitivity is not yet available,
  - if the patient's clinical condition does not improve or deteriorates, or
  - if dexamethasone has been administered and may be compromising clinical evaluation.
- When antibiotic sensitivity data become available, treatment should be modified accordingly
- Glucocorticoids significantly **reduce** rates of mortality, severe hearing loss, and neurologic sequelae in adults and should be administered to those with community-acquired bacterial meningitis

# FOR INVASIVE INFECTIONS (EXCLUDING MENINGITIS)

- For Noncritical illness, **ceftriaxone**, 50–75 mg/d (doses 12–24 h apart)
- For critically illness, including those who have myocarditis or multilobular pneumonia with hypoxia or hypotension, **vancomycin** may be added if the isolate may possibly be resistant to β-lactam drugs, with its use reviewed once susceptibility data become available
- For outpatient management, amoxicillin (1 g every 8 h) may be given
- The optimal duration of treatment for pneumococcal pneumonia is uncertain, but its continuation for **at least 5 days** once the patient becomes afebrile appears to be a prudent approach
- Amoxicillin (80–90 mg/kg per day) is recommended for acute otitis media or sinusitis

# Prevention

1. Vaccination against *S. Pneumoniae* and influenza viruses,
2. Reduction of comorbidities that increase the risk of pneumococcal disease,
3. Prevention of antibiotic overuse

- **PPSV23** for all persons ≥65 years of age and for those 2–64 years of age who have underlying medical conditions that put them at increased risk for pneumococcal disease or, if infected, disease of increased severity
- It **does not** induce an anamnestic response, and antibody concentrations wane over time; thus revaccination is particularly important
- **PCV13** followed by a dose of PPSV23 is now recommended for all immunocompromised children and adults

# Staphylococcal Infections

- *S. aureus* is a **pluripotent** pathogen (both a commensal and an opportunistic), causing disease through both toxin- and non-toxin-mediated (**pyogenic**) mechanisms
- **Leading** cause of health care–associated infections
- Approximately **30%** of healthy persons are colonized with *S. aureus*, with a smaller percentage (~10%) persistently colonized
- The **rate of colonization** is elevated among insulin-dependent diabetics, HIV-infected patients, patients undergoing hemodialysis, injection drug users, and individuals with skin damage
- More infections also with neutropenic patients, those with chronic granulomatous disease, and those with Job's or Chediak-Higashi syndrome
- The **anterior nares and oropharynx** are frequent sites of human colonization, although the skin (especially when damaged), vagina, axilla, and perineum may also be colonized
- Transmission of *S. aureus* most frequently results from **direct personal contact**, rarely in aerosols
- In recent outbreaks for CA-MRSA, **Risk factors** common to these outbreaks include poor hygienic conditions, close contact, contaminated material, and damaged skin

# Pathogenesis

1. Contamination and colonization of host tissue surfaces,
2. Breach of cutaneous or mucosal barriers,
3. Establishment of a localized infection,
4. Invasion
5. Evasion of the host response; an **antiphagocytic polysaccharide microcapsule and intracellular survival** including host response
6. Metastatic spread

- It produces **three types of toxin**:
  - cytotoxins,
  - pyrogenic toxin superantigens, and
  - Exfoliative toxins.
- Antitoxin antibodies **are protective** against illness in TSS, staphylococcal food poisoning, and staphylococcal scalded-skin syndrome (SSSS), however, Illness ~~develops after toxin synthesis and absorption and the subsequent~~ **~~toxin-initiated host~~ response**

**Skin and Soft Tissue Infections**

- Folliculitis
- Abscess, furuncle, carbuncle
- Cellulitis
- Impetigo
- Mastitis
- Surgical wound infections

**Musculoskeletal Infections**

- Septic arthritis
- Osteomyelitis (hematogenous or contiguous spread)
- Pyomyositis
- Psoas abscess

**Respiratory Tract Infections**

- Ventilator-associated or nosocomial pneumonia
- Septic pulmonary emboli
- Postviral pneumonia (e.g., influenza)
- Empyema

**Bacteremia and its Complications**

- Sepsis, septic shock
- Metastatic foci of infection (kidney, joints, bone, lung)
- Infective endocarditis

**Infective Endocarditis**

- Injection drug use–associated
- Native-valve
- Prosthetic-valve
- Nosocomial

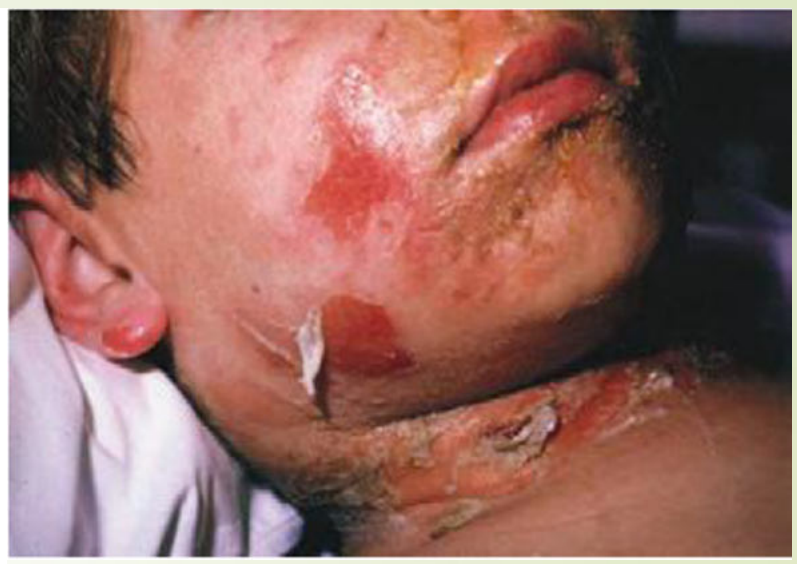
**Device-Related Infections** (e.g., intravascular catheters, prosthetic joints)

**Toxin-Mediated Illnesses**

- Toxic shock syndrome
- Food poisoning
- Staphylococcal scalded-skin syndrome

**Invasive Infections Associated with Community-Acquired Methicillin-Resistant *S. aureus***

- Necrotizing fasciitis
- Waterhouse-Friderichsen syndrome
- Necrotizing pneumonia
- Purpura fulminans



# Diagnosis

- **Gram's stain and microscopic examination** of abscess contents or of infected tissue
- Routine culture of infected material and blood cultures (*S. aureus* is rarely a blood culture contaminant)
- Uniformly positive blood cultures suggest an **endovascular infection** such as endocarditis
- Polymerase chain reaction (PCR)–based assays have also been applied to the rapid diagnosis

# Treatment

- **Surgical incision and drainage** of all suppurative collections, and **device removal** constitute the most important therapeutic intervention
- Prolonged (4–6 weeks) antibiotics

| Sensitivity/Resistance of Isolate | Drug of Choice | Alternative(s) |
|---|---|---|
| **Parenteral Therapy for Serious Infections** | | |
| Sensitive to penicillin | Penicillin G (4 mU q4h) | Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (1 g q12h[b]) |
| Sensitive to methicillin | Nafcillin or oxacillin (2 g q4h) | Cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8–12h[b]) |
| Resistant to methicillin | Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg IV q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q12h) |
| Resistant to methicillin with intermediate or complete resistance to vancomycin[e] | Daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | Same as for methicillin-resistant strains; check antibiotic susceptibilities<br>*or*<br>Ceftaroline (600 mg IV q12h)<br>Newer agents include tedizolid (200 mg administered once daily either IV or orally) or dalbavancin (two IV doses: 1000 mg followed in 1 week by 500 mg). Both drugs are approved only for the treatment of skin and soft tissue infections. |
| Not yet known (i.e., empirical therapy) | Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections | — |
| **Oral Therapy for Skin and Soft Tissue Infections** | | |
| Sensitive to methicillin | Dicloxacillin (500 mg qid), cephalexin (500 mg qid) | Minocycline or doxycycline (100 mg q12h[b]), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg/kg tid), linezolid (600 mg PO q12h), tedizolid (200 mg PO q24h) |
| Resistant to methicillin | Clindamycin (300–450 mg/kg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h[b]), linezolid (600 mg bid) or tedizolid (200 mg once daily) | Same options as "Drug of Choice"[e] |

# Prevention and other staphs

1. Primary prevention of *S. aureus* infections in the hospital setting involves **hand washing** and careful attention to appropriate **isolation** procedures
2. Decolonization strategies, using both universal and targeted approaches with topical agents
3. "Bundling" for nosocomial infections
4. Immunization strategies failed

- Less virulent than *S. aureus*, **CoNS** are among the most common causes of prosthetic-device infections
- *Staphylococcus epidermidis* is found on the skin as well as in the oropharynx and vagina
- *Staphylococcus saprophyticus* is a common pathogen in UTIs
- *Staphylococcus lugdunensis* and *Staphylococcus schleiferi*, produce more serious infections (native valve endocarditis and osteomyelitis)
- **Only 10–25%** of blood cultures positive for CoNS reflect true bacteremia

# Enterococcal Infections

- Normal inhabitants of the large bowel of human adults, two species, *E. faecalis* and *Enterococcus faecium*
- **Originally classified** as streptococci but Only after DNA hybridization studies and later 16S rRNA sequencing enterococci grouped as a genus distinct
- They hydrolyze esculin in the presence of 40% bile salts and grow at high salt concentrations (e.g., 6.5%) and **at high temperatures** (46°C)
- Main reason for Increased gastrointestinal colonization by enterococci is the administration of **antimicrobial agents**, In particular, that are excreted in the bile and have broad-spectrum activity
- **Second most common** organisms (after staphylococci) isolated from hospital associated infections in the United States
- The most important factors associated with VRE colonization and persistence in the gut include
  1. Prolonged hospitalization;
  2. Long courses of antibiotic therapy;
  3. Hospitalization in long-term-care facilities, surgical units, and/or intensive care units;
  4. Organ transplantation;
  5. Renal failure (particularly in patients undergoing hemodialysis) and/or diabetes;
  6. High acute physiology and chronic health evaluation (APACHE) scores;
  7. Physical proximity to patients infected or colonized with VRE or these patients' rooms

# CLINICAL SYNDROMES

- Urinary tract infection and prostatitis
- Bacteremia and endocarditis
- Meningitis
- Intraabdominal, pelvic, and soft tissue infections
- Neonatal infections, including sepsis (mostly late-onset), bacteremia, meningitis, pneumonia, and UTI

# Treatment

- Intrinsically resistant and/or tolerant to several antimicrobial agents
- *Tolerance* defined as lack of killing by drug concentrations **32 times higher** than the minimal inhibitory concentration [MIC])
- Combination therapy with a cell wall–active agent and an aminoglycoside has been the standard of care
- The treatment of *E. faecalis* **differs substantially from** that of *E. faecium*, mainly because of differences in resistance profiles

## SUGGESTED REGIMENS FOR THE MANAGEMENT OF INFECTIONS CAUSED BY *ENTEROCOCCUS FAECALIS*

| Clinical Syndrome | Suggested Therapeutic Options[a] |
|---|---|
| Endovascular infections (including endocarditis) | • Ampicillin[b] (12 g/d IV in divided doses q4h or by continuous infusion) *or* penicillin (18–30 million units/d IV in divided doses q4h or by continuous infusion) ***plus*** an aminoglycoside[c]<br>• Ampicillin[b] (12 g/d IV in divided doses q4h) *plus* ceftriaxone (2 g IV q12h)<br>• Vancomycin[d] (15 mg/kg IV per dose) *plus* an aminoglycoside[c]<br>• High-dose daptomycin[e] ± another active agent[f]<br>• Ampicillin[b] *plus* imipenem |
| Nonendovascular bacteremia[g] | • Ampicillin (12 g/d IV in divided doses q4h) *or* penicillin (18 million units/d IV in divided doses q4h) ± an aminoglycoside[c] or ceftriaxone<br>• Vancomycin[d] (15 mg/kg IV per dose)<br>• High-dose daptomycin[e] ± another active agent[f]<br>• Linezolid (600 mg IV/PO q12h) |
| Meningitis | • Ampicillin (20–24 g/d IV in divided doses q4h) *or* penicillin (24 million units/d IV in divided doses q4h) ***plus*** an aminoglycoside[c,h] or ceftriaxone<br>• Vancomycin (500–750 mg IV q6h)[d] ***plus*** an aminoglycoside[c] *or* rifampin<br>• Linezolid<br>• High-dose daptomycin[e] (*plus* intrathecal daptomycin) ± another active agent[f] |
| Urinary tract infections (uncomplicated) | • Fosfomycin (3 g PO, one dose)[i]<br>• Ampicillin (500 mg IV or PO q6h)<br>• Nitrofurantoin (100 mg PO q6h) |

# Thank you