UPPER RESPIRATORY TRACT INFECTIONS

Introduction

I. Variety of organisms colonize oropharynx & upper respiratory tract
   A. Many commensals colonize upper respiratory tract
   B. Respiratory tract is continuum from sinuses to alveoli

![Diagram of the respiratory tract](image)

Fig. 15.2 The respiratory tract as a continuum. (*Asymptomatic nasopharyngeal colonization is common.*)
II. Distinction between primary and opportunistic respiratory tract pathogens

A. Many pathogens gains entry via upper respiratory tract and become systemic
B. “Professional invaders” uniquely adapted to upper respiratory tract
C. Secondary pathogens cause infection following initial insult by primary pathogen

<table>
<thead>
<tr>
<th>NORMAL RESPIRATORY TRACT FLORA</th>
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<tbody>
<tr>
<td><strong>RESIDENCY STATE (INCIDENCE RATE)</strong></td>
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</table>
| Common (>50%) | Oral streptococci  
Branhamella  
Corynebacteria  
Anaerobic cocci  
Candida albicans  
Haemophilus influenzae  
Streptococcus mutans |
| Occasional (<10%) | Streptococcus pyogenes  
Streptococcus pneumoniae  
Neisseria meningitidis |
| Uncommon (<1%) | Corynebacterium diphtheriae  
Klebsiella pneumoniae  
Pseudomonas aeruginosa  
E. coli |
| Latent tissue residents (common, with the exception of Mtb) | Mycobacterium tuberculosis  
Pneumocystis carinii  
Cytomegalovirus  
Herpesvirus  
Epstein-Barr virus |
<table>
<thead>
<tr>
<th>TYPE</th>
<th>MECHANISM</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional invaders that infect healthy respiratory tract</td>
<td>Adhesion to mucosal surface</td>
<td>Influenza virus</td>
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<td></td>
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<td>Rhinovirus</td>
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<td><em>Streptococcus pyogenes</em></td>
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<td><em>Streptococcus pneumoniae</em></td>
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<td></td>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
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<td></td>
<td><em>Chlamydia pneumoniae</em></td>
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<tr>
<td></td>
<td>Interfere with cilia</td>
<td><em>Bordetella pertussis</em></td>
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<td><em>S. pneumoniae</em></td>
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<td><em>M. pneumoniae</em></td>
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<td></td>
<td>Resist alveolar macrophages</td>
<td><em>Legionella pneumophila</em></td>
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<td></td>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
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<td></td>
<td>Damage local tissues</td>
<td><em>S. pneumoniae</em></td>
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<td></td>
<td></td>
<td><em>Corynebacterium diphtheriae</em></td>
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<tr>
<td>Secondary invaders that infect when host defenses are impaired</td>
<td>Primary viral infection</td>
<td><em>Staphylococcus aureus</em></td>
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<td><em>S. pneumoniae</em></td>
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<td>Impaired local defenses (e.g. Cystic fibrosis)</td>
<td><em>Pseudomonas aeruginosa</em></td>
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<td>Chronic bronchitis due to tumor</td>
<td><em>Haemophilus influenzae</em></td>
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<td><em>S. pneumoniae</em></td>
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<td>Depressed immunity (e.g. AIDS)</td>
<td><em>Pneumocystis carinii</em></td>
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<td><em>M. tuberculosis</em></td>
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<td>Decreased resistance (e.g. age, alcoholism)</td>
<td><em>S. aureus</em></td>
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<td><em>S. pneumoniae</em></td>
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<td><em>H. influenzae</em></td>
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BACTERIAL INFECTIONS OF THE ORAL CAVITY

Oral Anaerobes

(Bacteroides, Prevotella, Porphyromonas, Fusobacterium, Peptostreptococcus)

I. Virulence factors relevant to Oral Infections
A. Oral bacteria produce lymphocyte activators that induce host inflammatory response
B. Release of PMN contents & complement activation exacerbates tissue damage

II. Etiology / Pathogenesis
A. Chronic marginal gingivitis (between teeth and gums)
   1. Inflammatory infiltrate: PMNs & lymphocytes in connective tissue attached to tooth
   2. Gingivitis can occur in 2 weeks without proper tooth care
B. Periodontitis (teeth and supporting tissue)
   1. Progressive gingivitis results in periodontitis
   2. Resorption of bone around neck of tooth, loss of periodontal ligament and the tooth
   3. Agents of gingivitis not known; anaerobes responsible for chronic marginal periodontitis
   4. Oral anaerobes live in dental plaque next to gingival tissues
C. General features of anaerobic infections
   1. Average of $10^{11}$ microbes/g in gingival crevices, predominantly anaerobes
   2. Autoinfections caused by normal flora, usually mixed (polymicrobial)
   3. Anaerobes typically form localized abscesses
   4. Bacteria do not invade in gingivitis; remain part of plaque outside host defenses
   5. Bacterial invasion may occur with periodontitis
D. Acute necrotizing ulcerative gingivitis (trench mouth)
   1. Prevotella, Fusobacterium associated with ulceration of gingiva
   2. Invasion of oral epithelium and pharynx; can lead to bone resorption and tooth loss

III. Clinical identification of organism
A. Diagnosis of periodontal disease by symptoms
B. Mixed anaerobic infection not differentiated
   1. Generally, no specific designation of Gram reaction or morphology
   2. Abscess can be sampled
      a. Culture must be maintained under anaerobic conditions
      b. Predominantly Gram neg. rods, some Gram pos. (Peptostreptococcus) & PMNs
Actinomyces israelii

I. Etiology / Pathogenesis
   A. Actinomyces israelii is normal flora anaerobe of humans
      1. Colonizes mucosal surfaces, from oropharynx to lower intestine
      2. Endogenous infection only upon penetration of epithelial barrier (low O₂ tension)
   B. Actinomycosis in cervicofacial area follows mouth trauma, e.g. tooth extraction
      1. Slowly progressing disease
      2. Inflammatory sinuses filled with pus and bacteria from initial site of infection
      3. Sinus extension or aspiration may lead to thoracic actinomycosis

FIGURE 34-1 Pathogenesis and disease sites of three major forms of actinomycosis.
II. Clinical identification of organism

A. Isolation, staining and culturing of pus
   1. *Actinomyces* are Gram-positive filamentous rods resembling fungi
   2. “Sulfur granules” seen in pus, diagnostic for *Actinomyces* infection
      a. Yellow granules resembling sulfur
      b. Composed of intertwined *Actinomyces* elements with tissue exudates
   3. Infection is polymicrobial ⇒ sinuses also contain Gram-negative rods

B. Culture conditions
   1. Slow (4-10 day) growth under anaerobic or microaerophilic conditions
   2. Contaminating bacteria may overwhelm slow-growing *Actinomyces*
Viridans *Streptococci*

I. Virulence factors relevant to Oral Infections
   Glucans (complex polysaccharides) that permit attachment to teeth

II. Etiology / Pathogenesis
   A. Normal flora of oral and nasopharyngeal cavity; *S. mutans* associated with dental caries
   B. Subacute bacterial endocarditis
      1. Tooth extraction $\rightarrow$ transient bacteremia
      2. May lead to colonization of damaged heart valves

III. Clinical identification of organism
   A. Gram positive cocci, catalase negative
   B. Not Lancefield grouped
   C. Many different species, all classified as viridans Streptococci

**UPPER RESPIRATORY TRACT INFECTIONS**
**FUNGAL INFECTIONS OF THE ORAL CAVITY**

*Candida albicans*

I. Virulence factors relevant to Oral Infections
   A. Adhesion through mannoprotein binding to fibronectin receptors
   B. Invasion
      1. Invasive hyphae bind to fibronectin, collagen, laminin $\rightarrow$ transverse mucosal barriers
      2. Proteases and elastases may have role in the invasion process
II. Etiology / Pathogenesis
A. Stomatitis (inflammation of oral cavity)
   1. Oral thrush
      a. Occurs on tongue or palate
      b. Multiple white cheesy plaques loosely adherent to mucosal surface
   2. Inflammatory patches may appear on esophagus
B. Factors predisposing to candidiasis
   1. Antimicrobial therapy that depresses competing bacterial flora
   2. Compromised immune system: leukopenia, corticosteroids, AIDS
   3. Disruption of mucosa: indwelling devices or cancer chemotherapy
   4. Diabetes ⇒ ↑ glucose concentrations & ↑ surface receptors

III. Clinical identification of organism
A. Specimen collection: Scrapings from infected mucosa
B. KOH or Gram stains reveal budding round or oval yeast cells with hyphae
C. Germ tube formation can be used to speciate C. albicans
UPPER RESPIRATORY TRACT INFECTIONS
BACTERIA CAUSING EAR & SINUS INFECTIONS

Streptococcus pneumoniae

I. Virulence factors relevant to Ear & Sinus Infections
   A. Polysaccharide capsule (84 capsular serotypes)
      1. Primary virulence factor of S. pneumoniae
      2. Interferes with classical and alternate complement pathways
      3. Anti-capsule antibodies confer immunity
   B. Cell wall teichoic acid and peptidoglycan contribute to inflammatory response

II. Etiology / Pathogenesis
   A. High nasopharynx carriage rate (10-30%) predisposes for upper respiratory tract infections
   B. Acute Otitis Media (middle ear infection)
      1. S. pneumoniae single most common cause after 3 months of life (35-40%)
      2. Viral infection or allergies are predisposing factors
      3. Eustachian tube inflammation→ bacterial enter middle ear from nasopharynx
      4. Shortness & pliancy of infants’ eustachian tubes contributes to susceptibility
   C. Sinus infection
      1. S. pneumoniae is major cause of acute and chronic sinusitis in all age groups
      2. Predisposing factors: viral infection, allergy, or anatomical blockage

III. Clinical identification of organism
   A. Diagnosis generally based on clinical examination
      1. Tympanic membrane swells due to pus formation with otitis media
      2. Symptoms and radiography used for diagnosis of sinusitis
   B. Needle aspiration
      1. Pus behind tympanic membrane can be collected in difficult cases of otitis media
      2. Sinus wall puncture or catheterization for sinusitis
      3. Stain of aspirate shows Gram-positive lancet-shaped diplococci
   C. Biochemical assays
      1. S. pneumoniae (a.k.a. pneumococcus) not part of Lancefield grouping
      2. Serotyping; Optochin (P disk) susceptibility

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<thead>
<tr>
<th>BIOCHEMICAL REACTIONS OF STREPTOCOCCI &amp; ENTEROCOCCI</th>
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<tbody>
<tr>
<td>Bacitracin susceptible</td>
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<tr>
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<tr>
<td>Group A Streptococci</td>
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<tr>
<td>Group B Streptococci</td>
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<td>S. pneumoniae</td>
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<tr>
<td>Viridans Streptococci</td>
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<td>Enterococci</td>
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M. Jackson
URT
August 29, 2001
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**Haemophilus influenzae**

I. Virulence factors relevant to Ear & Sinus Infections

A. Polysaccharide capsule most important virulence factor of *H. influenzae*
   1. Capsule is antiphagocytic and subject to antigenic variation
   2. Capsule of polyribitol phosphate (PRP) ⇒ 6 different serotypes, a-f
   3. *H. influenzae* serotype b (Hib) most virulent

B. IgA protease may facilitate colonization of nasopharynx

C. Non-pilus adhesins that direct tissue tropism to mucosal surfaces

**FIGURE 30-4** Macrophage or polymorphonuclear leukocyte phagocytosing *H. influenzae* coated with antibodies specific for the capsule and somatic antigen.
II. Etiology / Pathogenesis

A. *H. influenzae* 2nd most common cause of otitis media and major cause of sinusitis
   1. Common cause of otitis media in children less than 5 years old
   2. Viral infection is predisposing, displacement of *H. influenzae* (flora) into sterile sites

B. High carriage rate (50-80%) of *H. influenzae* in upper respiratory tract
   1. Normal flora strains usually lack capsule
   2. Most otitis media isolates non-typable and may not be influenced by Hib vaccine

C. Otitis media or sinusitis caused by Hib may lead to meningitis

III. Clinical identification of organism

A. Diagnosis based on clinical examination; needle aspirate in refractory cases

B. *H. influenzae* is small, Gram-negative coccobacillus

C. *H. influenzae* require Hematin (X factor) and/or NAD (V factor) for growth

D. Capsule serotyping

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<thead>
<tr>
<th>SPECIAL CASE BACTERIAL EAR &amp; SINUS INFECTIONS</th>
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<tbody>
<tr>
<td><strong>Bacterium</strong></td>
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<tr>
<td><em>Moraxella catarrhalis</em></td>
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UPPER RESPIRATORY TRACT:
BACTERIAL INFECTIONS OF THE PHARYNX

*Streptococcus pyogenes*

I. Virulence factors relevant to Infections of the Pharynx

A. Extracellular factors that facilitate immune evasion
   1. M protein is anti-phagocytic and anti-opsonic
      a. Exposed amino terminus antigenically variable ⇒ >80 serotypes
      b. Re-infection with different M type possible due to antigenic variation
      c. Cross-reactive antibodies ⇒ to acute glomerulonephritis & rheumatic heart disease
   2. Protein G binds the Fc portion of antibodies, covers bacteria with antibodies
   3. Hyaluronic acid capsule is antiphagocytic

B. Factors that facilitate colonization
   1. Protein F for binding to nasopharyngeal epithelium (pharyngitis); regulated by \( O_2 \) levels
   2. M protein for binding to epidermis (impetigo)

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*Figure 16-1. Antigenic structure of *S. pyogenes*, and adhesion to an epithelial cell. The location of peptidoglycan and Lancefield carbohydrate antigen in the cell wall is shown in the diagram. M protein and lipoteichoic acid are associated with the cell surface and the pilus. Lipoteichoic acid and protein F mediate binding to fibronectin on the host surface.*
C. Exotoxins

1. SLO & SLS
   a. Cause $O_2$-labile (SLO) or $O_2$ stable (SLS) $\beta$-hemolysis on blood agar plates
   b. Form large pores in cell membranes $\Rightarrow$ lysis of leukocytes

2. Streptococcal Pyrogenic Exotoxins (Spe A-C)
   a. Erythrogenic or Scarlet Fever Toxins
   b. SpeA produced only by minority of lysogenized Group A Streptococcus
   c. Superantigens with sequence homology to staphylococcal exotoxins
   d. Induce cytokine release
      i. Fever & rash (scarlet fever)
      ii. T-cell stimulation and B cell suppression
      iii. Enhanced sensitivity to endotoxic shock
   e. Responsible for toxic shock like syndrome in S. pyogenes bacteremia

![Diagram of extracellular substances and cell surface structure of S. pyogenes](image-url)

**FIGURE 13-2** Cell surface structure of S. pyogenes and extracellular substances.
II. Etiology / Pathogenesis

A. Pharyngitis
1. Viruses predominate; most frequent bacterial cause is group A *S. pyogenes*
2. Common in 5-15 yr. age group; spread person-person by droplet
3. Prompt antimicrobial therapy required
   a. Prevents poststreptococcal sequelae
   b. Circumvents natural development of type-specific immunity

B. Scarlet Fever can occur simultaneously with pharyngitis
1. Caused by pyrogenic exotoxins (Spe)
2. Scarlet rash spreads from mouth & face to trunk & extremities; strawberry tongue
3. Occurrence and severity reduced in comparison to early 1900s

C. Poststreptococcal Sequelae: Acute Rheumatic Fever
1. Formerly on decline, rheumatic heart disease has reappeared in some parts of the world
2. Begins ~3 wk. after pharyngitis
3. Syndrome
   a. Symptoms: fever, subcutaneous nodules, chorea (neurologic), migratory polyarthritis
   b. Cardiac: carditis, cardiac enlargement, murmurs, heart failure
   c. Aschoff body seen with rheumatic carditis
      i. Lesion of lymphocytes and macrophages aggregated around fibrinoid deposits
      ii. Caused by cell-mediated response
   d. Subacute bacterial endocarditis
      i. Acute rheumatic fever may damage heart valves ⇒ formation of vegetations
      ii. Provides site for colonization during transient bacteremia by viridans streptococci

4. Heart damage caused by anti-streptococcal antibodies that cross-react with cardiac tissue
   a. Anti-streptococcal antibodies are to cell wall, cell membrane, and M protein
   b. Epitopes shared with cardiac sarcolemma membranes, smooth muscle cells, valves
   c. Recurrent attacks with new M types leads to progressive heart damage
   d. SLO, Spe, streptokinase may contribute directly to cardiac damage

\[ \text{Figure 28-1} \quad \text{Hypotheses about the pathogenesis of RF (A) and acute glomerulonephritis (B).} \]
D. Poststreptococcal Sequelae: Acute Glomerulonephritis

1. Follows respiratory (rare) or skin infection with group A streptococcus
2. Syndrome
   a. 10 day latent period following infection
   b. Edema, hypertension, proliferative lesion of glomeruli
3. Associated with a few M types (nephritogenic strains)
4. Antibody cross-reactivity and inflammatory response
   a. Anti-M protein antibodies react with glomerular proteins
   b. Deposition of antigen-antibody and complement complexes in glomeruli contribute

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**Figure 8.2.**
III. Clinical identification of organism
   A. Throat swab of tonsils and pharynx → culture on blood agar for β-hemolysis
      1. Gram positive cocci in chains
      2. Clear zone around colony; SLO (CO₂ incubation) and SLS responsible for β-hemolysis
   B. Rapid agglutination tests to identify Lancefield Group A
   C. Throat culture contaminants: S. pneumoniae, S. aureus, N. meningitidis, H. influenzae
   D. Biochemical tests
      1. Catalase test negative (differentiation from Staphylococcus)
      2. Bacitracin sensitivity assay on agar plate
   E. High titers of anti-SLO antibodies (ASO) seen in patients with rheumatic fever

*Corynebacterium diphtheriae*

I. Virulence factors relevant to Infections of the Pharynx
   A. Diphtheria toxin (DT) sole virulence factor of Diphtheria
      1. Best and earliest studied bacterial cytotoxin
      2. Basis for concept of “virulence factor”
   B. Structure and function of DT
      1. AB toxin with enzymatic (A) and binding (B) subunits
      2. Synthesized as single polypeptide chain nicked between A and B subunits
      3. Receptor binding and entry
         a. B subunit binds epidermal growth factor precursor in mammalian cell membranes
         b. Holotoxin uptake by receptor mediated endocytosis
         c. Reduction in endocytotic vesicle releases A subunit
      4. A subunit enzymatic mechanism of action
         a. A subunit ADP-ribosylates elongation factor 2 (ADPR-EF2) of any eucaryotic cell
         b. Reaction: NAD + EF2 ⇔ ADPR-EF2 + nicotinamide + H⁺
         c. EF2 for translocation of ribosome along mRNA; ADPR-EF2 ⇒ translation ceases
         d. DT A subunit has same mechanism as Pseudomonas exotoxin A
Figure 17-1. Action of diphtheria toxin. The toxin-binding (B) portion attaches to the cell membrane, and the complete molecule enters the cell. In the cell, the A subunit dissociates and catalyzes a reaction that ADP-ribosylates and thus inactivates elongation factor 2 (EF-2). This factor is essential for ribosomal reactions at the acceptor and donor sites, which transfer triplet code from messenger RNA (mRNA) to amino acid sequences via transfer RNA (tRNA). Inactivation of EF-2 stops building of the polypeptide chain.
C. Genetics of DT synthesis

1. tox gene carried by bacteriophages β and θ
2. DT synthesis negatively regulated by iron

Figure 9.1.
Lysogeny of phage that causes C. diphtheriae to produce toxin.
D. Toxin chimeras directed against tumor cell and HIV-infected cells developed using DTA.

II. Etiology / Pathogenesis
A. *C. diphtheriae* colonizes human pharynx and causes diphtheria
   1. Very rare in the US
      a. ~10 cases/yr. - transients, migrant workers, those refusing immunization
      b. Endemic in some developing countries
   2. Paradigm of bacterial toxinoisis with no invasion
      a. DT solely responsible for all pathogenesis
      b. Only lysogenized strains produce DT
         i. Asymptomatic carriers of toxinogenic strains may transmit disease
         ii. In vivo lysogenization possible to convert strain to toxin-production

B. Pathogenesis
   1. *C. diphtheriae* spread by droplet, contact with cutaneous infection or fomites
   2. Manifestation of diphtheria due to DT-mediated cytotoxicity at site
      a. Pseudomembrane from oropharynx down to trachea, can cause suffocation
      b. Systemic manifestations include DT attack of heart and central nervous system
III. Clinical identification of organism
   A. Diagnosis principally based on clinical symptoms

   B. Isolation from throat swab difficult - normal resident of many individuals
      1. Gram positive, club-shaped rods, cells remain attached after division⇒ “Chinese letters”
      2. Culture of organism with demonstration of toxin production

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<tr>
<th>Bacterium</th>
<th>Classification</th>
<th>Syndrome</th>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Gram negative diplococcus</td>
<td>Oral-genital contact</td>
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CASE STUDY
FOR
UPPER RESPIRATORY TRACT INFECTIONS

An 18-month-old girl developed a runny nose, watery eyes, and a cough. As her symptoms of rhinitis abated, the girl became irritable and developed a slight fever (38°C). She also complained of a sore throat and an earache. Her pediatrician observed a bulging tympanic membrane and prescribed a 7-day course of antibiotics.

Questions:
What are the most likely etiologic agents causing the ear infection?
Name a key virulence factor that the common etiologic agents possess.
What predisposing feature of this case contributed to the otitis media?