Neisseria

General Characteristics of Neisseria spp.

- **Aerobic**
- **Gram-negative** cocci often arranged in pairs (**diplococci**) with **adjacent sides flattened** (like coffe beans)
- **Oxidase positive**
- Most **catalase positive**
- Nonmotile
- Acid from oxidation of carbohydrates, not from fermentation

Important Human Pathogens

Neisseria gonorrhoeae

Neisseria meningitidis

Other species normally colonize mucosal surfaces of oropharynx and nasopharynx and occasionally anogenital mucosal membranes

Neisseria Associated Diseases

Organism	Diseases
N. gonorrhoeae	Urethritis, cervicitis, salpingitis, pelvic inflammatory disease, proctitis, bacteremia, arthritis, conjunctivitis, pharyngitis
(ophthalmia neonatorum)	
N. meningitidis	Meningitis, meningoencephalitis, bacteremia, pneumonia, arthritis, urethritis
Other *Neisseria* species	Opportunistic infections

Differential Characteristics of Commonly Isolated Neisseria spp.

Characteristic	*N. gonorrhoeae*	*N. meningitidis*	*N. lactamica*	*N. sicca*	*N. mucosa*	*N. flavescens*
Growth on:						
CHOC, BA (22°C)	0	0	V	+	+	+
MTM, ML (35°C)	+	+	+	0	0	0
Nutrient agar (35°C)	0	V	+	+	+	+
Acid from:						
Glucose	+	+	+	+	+	0
Maltose	0	+	+	+	+	0
Lactose	0	0	+	0	0	0
Sucrose	0	0	0	+	+	0
Fructose	0	0	0	+	+	0
Nitrate reduction	0	0	0	0	+	0

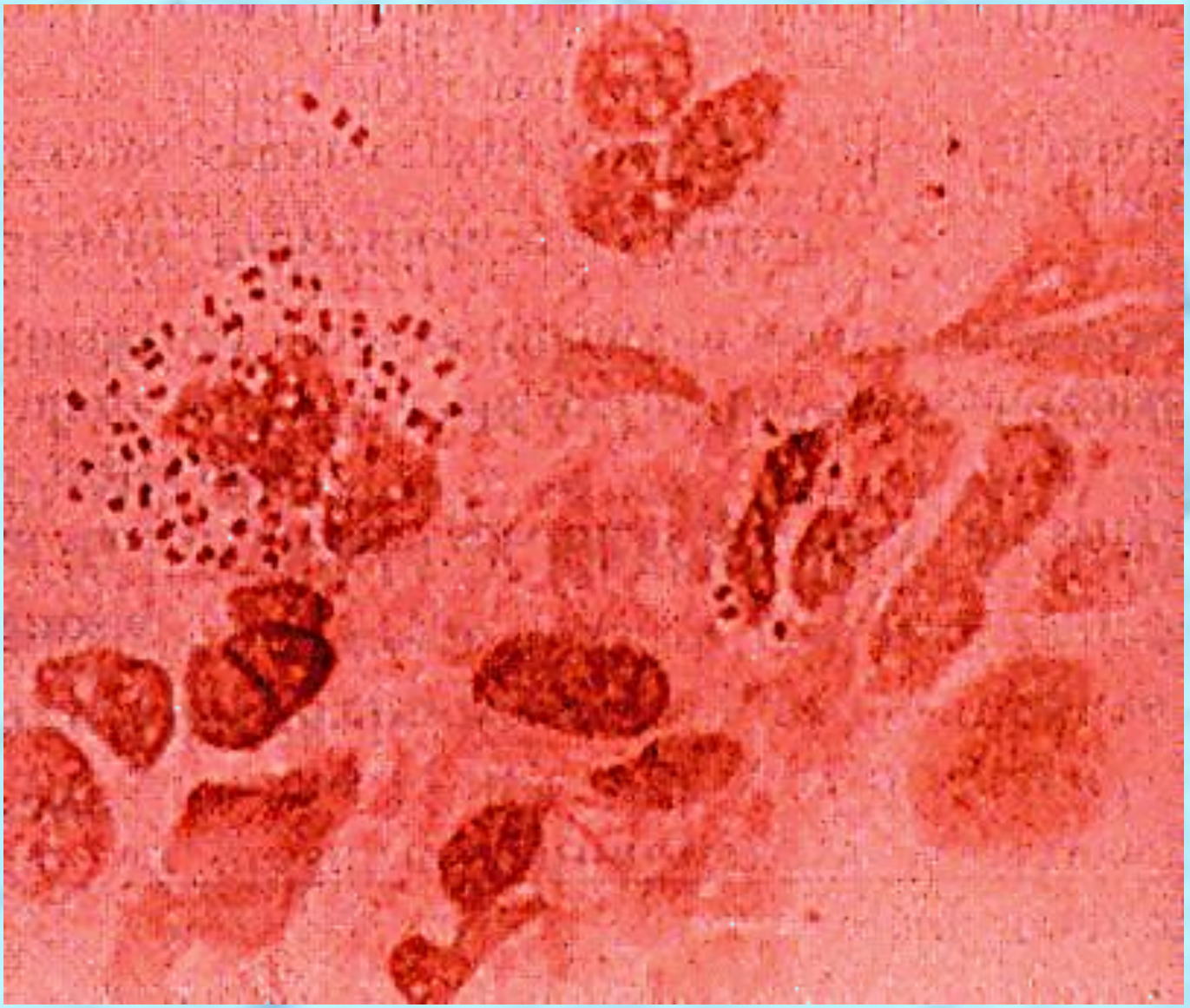
Neisseria gonorrhoeae

(gonococcus)

General Overview of Neisseria gonorrhoeae

- **Readily transmitted by sexual contact**
- **Gram-negative diplococci flattened along the adjoining side**
- **Fastidious**, **capnophilic** and **susceptible to cool temperatures, drying and fatty acids**
  - Requires complex media pre-warmed to 35-37C
  - Soluble starch added to neutralize fatty acid toxicity
  - Grow best in moist atmosphere supplemented with CO_2
- Produce **acid from glucose**, but not from other sugars

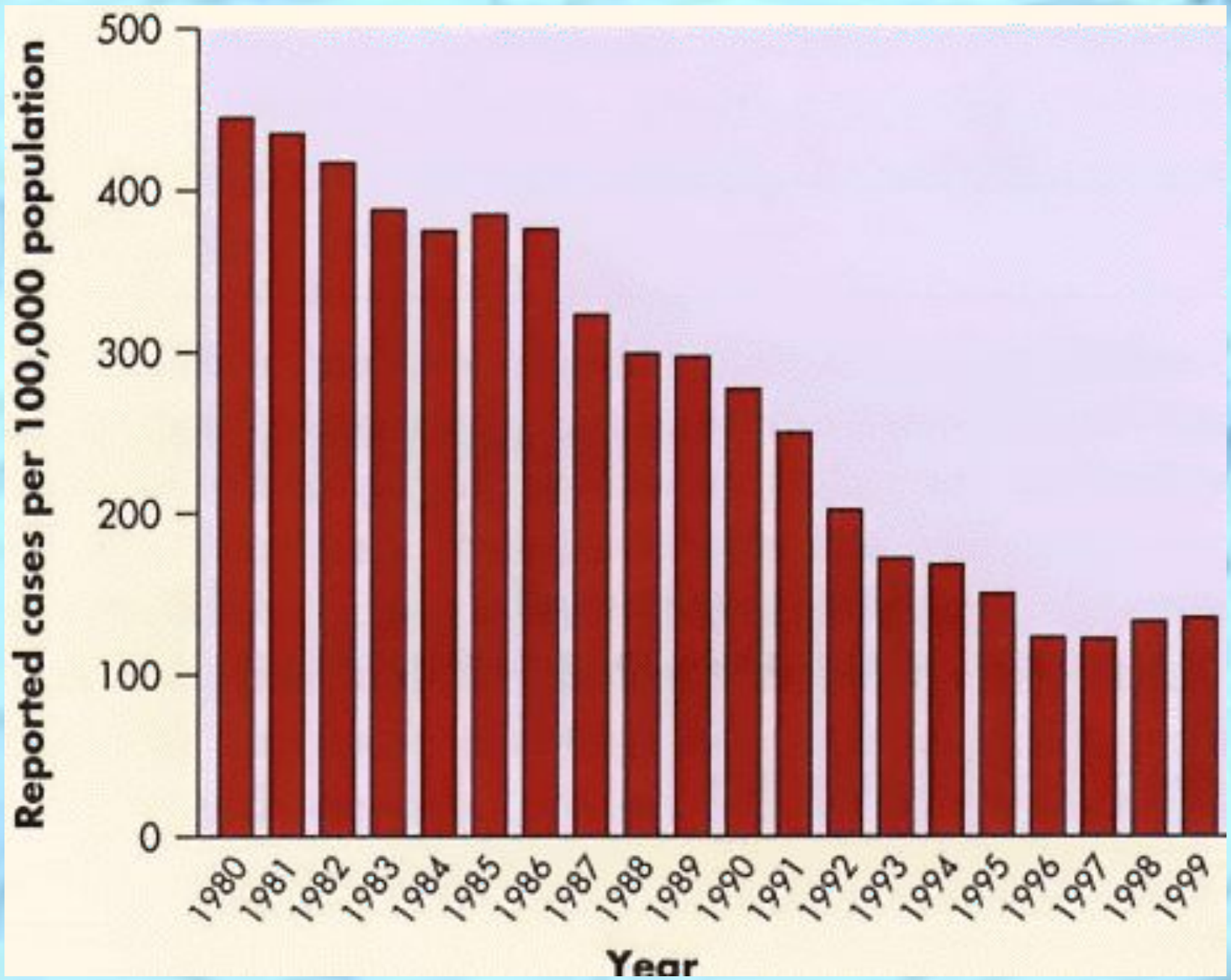
Neisseria gonorrhoeae in Urethral Exudates



Epidemiology of Gonorrhea

- Seriously **underreported** sexually-transmitted disease
  - ✔ 350,000 reported cases in USA in 1998
  - ✔ Down from 700,00 cases in 1990
- Found **only in humans** with strikingly different epidemiological presentations for females and males
- Asymptomatic carriage is major reservoir
- Transmission primarily by sexual contact
- Lack of protective immunity and therefore **reinfection**, partly due to **antigenic diversity** of strains
- Higher risk of disseminated disease in patients with late complement deficiencies

Incidence of Gonorrhea in USA



Differences Between Men & Women with Gonorrhea

IN MEN:

- **Urethritis**; Epididymitis
- Most infections among men are acute and symptomatic with **purulent discharge & dysuria** (painful urination) after 2-5 day incubation period
- Male host **seeks treatment** early preventing serious sequelae, but not soon enough to prevent transmission to other sex partners
- The two bacterial agents primarily responsible for **urethritis** among men are *N. gonorrhoeae* and *Chlamydia trachomatis*

Differences Between Men & Women with Gonorrhea (cont.)

IN WOMEN:

- **Cervicitis**; Vaginitis; **Pelvic Inflammatory Disease (PID); Disseminated Gonococcal Infection (DGI)**
- Women often **asymptomatic** or have atypical indications (subtle, unrecognized S/S); Often untreated until PID complications develop
- **Pelvic Inflammatory Disease (PID)**
  - May also be asymptomatic, but difficult diagnosis accounts for many false negatives
  - Can cause scarring of fallopian tubes leading to infertility or ectopic pregnancy

Differences Between Men & Women with Gonorrhea (cont.)

IN WOMEN (cont.) :

- **Disseminated Gonococcal Infection (DGI):**
  - Result of gonococcal bacteremia
  - Often skin lesions
  - Petechiae (small, purplish, hemorrhagic spots)
  - Pustules on extremities
  - Arthralgias (pain in joints)
  - Tenosynovitis (inflammation of tendon sheath)
  - Septic arthritis
  - Occasional complications: Hepatitis; Rarely endocarditis or meningitis

Gonorrhea

Females	Males
50% risk of infection after single exposure	20% risk of infection after single exposure
Asymptomatic infections frequently not diagnosed	Most initially symptomatic (95% acute)
Major reservoir is asymptomatic carriage in females	Major reservoir is asymptomatic carriage in females
Genital infection primary site is cervix (cervicitis), but vagina, urethra, rectum can be colonized	Genital infection generally restricted to urethra (urethritis) with purulent discharge and dysuria
Ascending infections in 10-20% including salpingitis, tubo-ovarian abscesses, pelvic inflammatory disease (PID) , chronic infections can lead to sterility	Rare complications may include epididymitis, prostatitis, and periurethral abscesses
Disseminated infections more common, including septicemia, infection of skin and joints (1-3%)	Disseminated infections are very rare
Can infect infant at delivery (conjunctivitis, opthalmia neonatorum)	More common in homosexual/bisexual men than in heterosexual populatiuon

Pathogenesis of Neisseria gonorrhoeae

- Fimbriated cells attach to intact mucus membrane epithelium
- **Capacity to invade intact mucus membranes or skin with abrasions**
  - Adherence to mucosal epithelium
  - Penetration into and multiplication before passing through mucosal epithelial cells
  - Establish infection in the sub-epithelial layer
- **Most common sites of inoculation:**
  - **Cervix (cervicitis)** or vagina in the female
  - **Urethra (urethritis)** or penis in the male

Gonococcal Virulence Factors

- **Antiphagocytic** capsule-like negative surface charge
- **Only fimbriated (piliated) cells** (formerly known as colony types T1 & T2) **are virulent**
- **Outer membrane proteins** (formerly Proteins I, II, & III)
  - **Por (porin protein)** prevents phagolysosome fusion following phagocytosis and thereby promotes intracellular survival
  - **Opa (opacity protein)** mediates firm attachment to epithelial cells and subsequent invasion into cells
  - **Rmp (reduction-modifiable protein)** protects other surface antigens from bactericidal antibodies (Por protein, LOS)
- **Acquisition of iron** mediated through Tbp 1 and Tbp 2 (**transferrin-binding proteins**), Lbp (**lactoferrin binding protein**) & Hbp (**hemoglobin-binding protein)**

Gonococcal Virulence Factors (cont.)

- **Llipooligosaccharide** (LOS) (Lipid A plus core polysaccharide but **no O-somatic antigen polysaccharide side chain**) has endotoxin activity
- IgA_1 protease
- Acquisition in last two decades of two types of **antibiotic resistance**:
  - Plasmid-encoded **beta-lactamase** production
  - Chromosomally-mediated **changes in cellular permeability** inhibit entry of penicillins, tetracycline, erythromycin, aminoglycosides

Laboratory Characterization

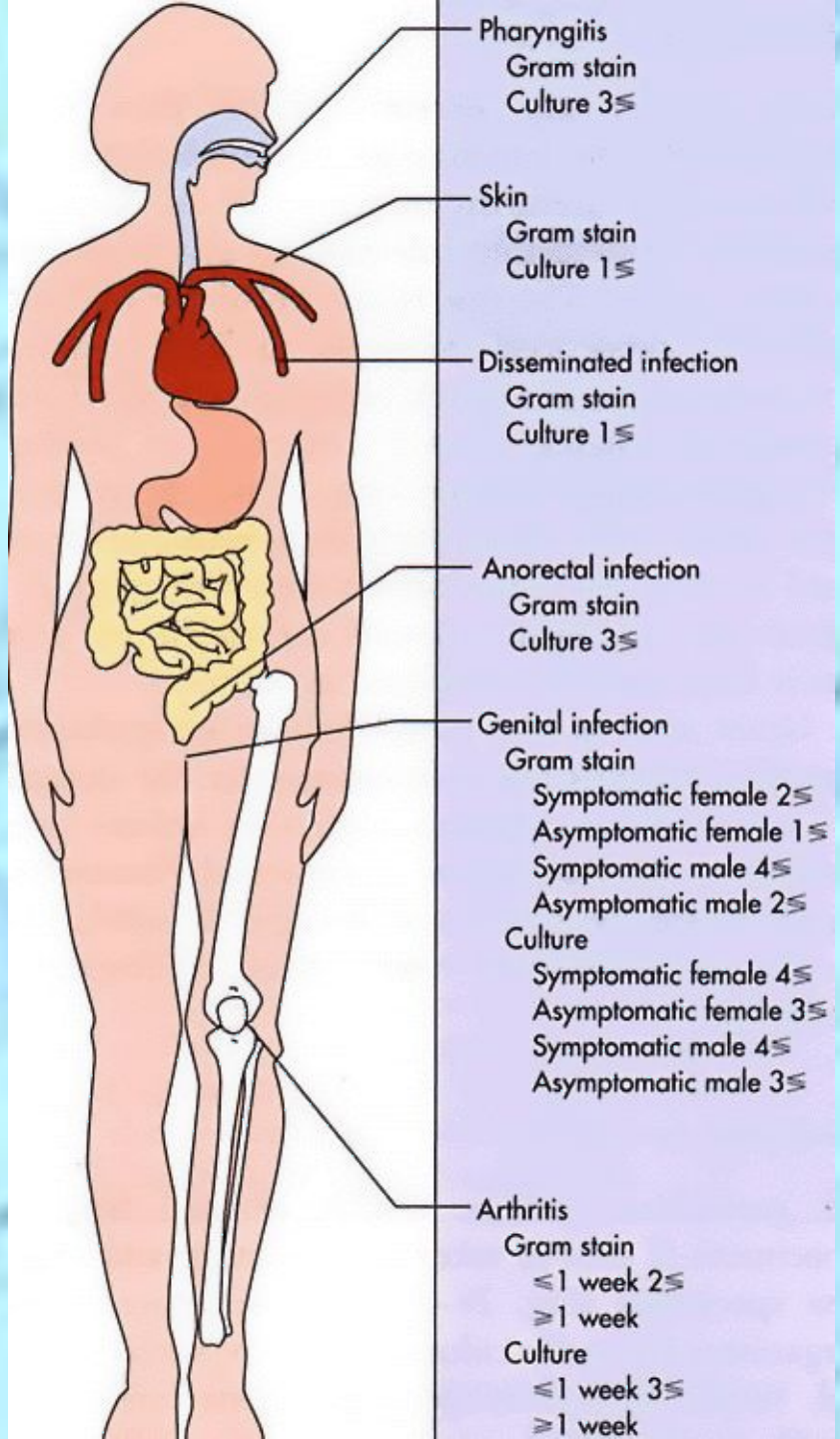
- Small, gram-negative diplococci in presence of polymorphonuclear leukocytes (PMN's) seen microscopically in **purulent urethral discharge**
- **Susceptible to drying and cooling**, so **immediate culture** of specimen onto **pre-warmed selective** (e.g., modified Thayer-Martin, Martin-Lewis agars) **and non-selective media** (chocolate blood agar) with **moist atmosphere containing 5% carbon dioxide**
- **Some strains inhibited** by vancomycin (in many selective agars) and toxic substances like fatty acids and trace metals in protein hydrolysates and agar found in nonselective media
- Five morphologically **distinct colony types** (formerly T1 through T5) that can undergo phase transition are no longer considered to be a useful distinction

Prevention & Treatment

- Penicillin no longer drug of choice due to:
  - Continuing rise in the MIC
  - Plasmid-encoded beta-lactamase production
  - Chromosomally-mediated resistance
- Uncomplicated infxn: ceftriaxone, cefixime or fluoroquinolone
- Combined with doxycycline or azithromycin for dual infections with *Chlamydia*
- **Chemoprophylaxis of newborns against opthalmia neonatorum** with 1% silver nitrate, 1% tetracycline, or 0.5% erythromycin eye ointments
- Treatment of newborns with opthalmia neonatorum with ceftriaxone
- Measures to limit epidemic include **education, aggressive detection, and follow-up screening** of sexual partners, use of **condoms** or **spermicides** with nonoxynol 9

Analytic Performance of Different Laboratory Detection Methods for Nesseria gonorrhoeae

NOTE: Importance of **Sensitivity vs. Specificity** for any Diagnostic Test



See Handout on Sensitivity & Specificity of Diagnostic Tests

(Next two slides)

Analytic Performance of a Diagnostic Test

	ACTUAL POSITIVE	ACTUAL NEGATIVE	TOTALS
TEST POSITIVE	**80** True Positives	**25** **False Positives**	**105** Test Positives
TEST NEGATIVE	**20** **False Negatives**	**75** True Negatives	**95** Test Negatives
TOTALS	**100** Actual Positives	**100** Actual Negatives	**200**

Analytic Performance of a Diagnostic Test (cont.)

Sensitivity = Measure of True Positive Rate (TPR)

$$= \frac{\text{No. of True Pos.}}{\text{No. of Actual Pos.}} = \frac{\text{No. of True Pos.}}{\text{No. of (True Pos. + False Neg.)}} = \frac{80}{80+20} = 80\% \text{ Sensitivity}$$

In conditional probability terms, the probability of a positive test given an actual positive sample/patient.

Specificity = Measure of True Negative Rate (TNR)

$$= \frac{\text{No. of True Neg.}}{\text{No. of Actual Neg.}} = \frac{\text{No. of True Neg.}}{\text{No. of (True Neg. + False Pos.)}} = \frac{75}{75+25} = 75\% \text{ Specificity}$$

In conditional probability terms, the probability of a negative test given an actual negative sample/patient.

Neisseria meningitidis

(meningococcus)

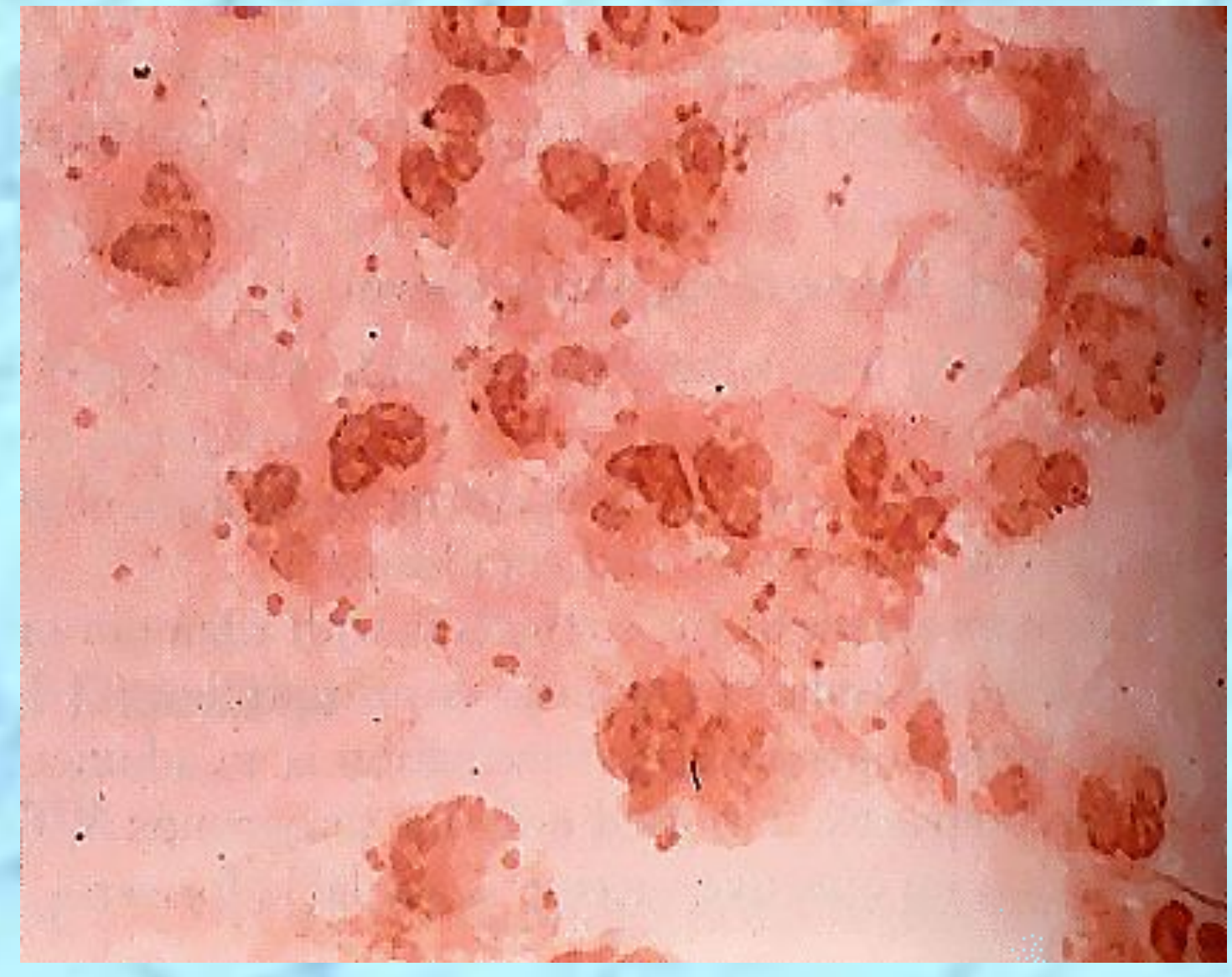
General Overview of Neisseria meningitidis

- Encapsulated small, gram-negative diplococci
- Second most common cause (behind *S. pneumoniae)* of **community-acquired meningitis** in previously healthy adults; swift progression from good health to life-threatening disease
- **Pathogenicity:**
  - Pili-mediated, **receptor-specific colonization of nonciliated cells of nasopharynx**
  - **Antiphagocytic** polysaccharide **capsule** allows systemic spread in absence of specific immunity
  - Toxic effects mediated by **hyperproduction of lipooligosaccharide**
- Serogroups A, B, C, Y, W135 account for about 90% of all infections

Diseases Associated with Neisseria meningitidis

- **Following dissemination of virulent organisms from the nasopharynx:**
  - ✔ **Meningitis**
  - ✔ Septicemia (**meningococcemia**) with or without meningitis
  - ✔ **Meningoencephalitis**
  - ✔ Pneumonia
  - ✔ Arthritis
  - ✔ Urethritis

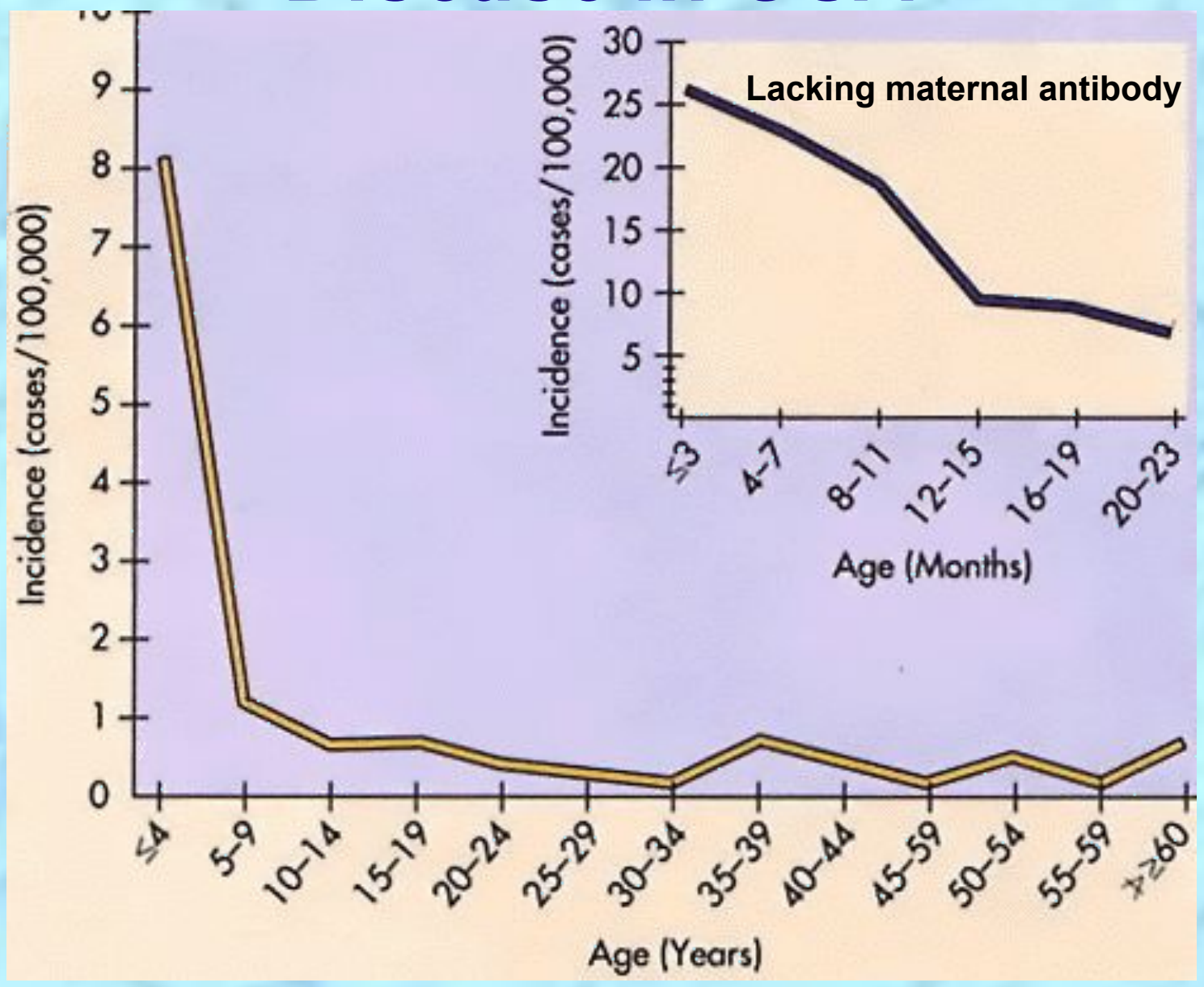
Neisseria meningitidis in Cerebrospinal Fluid



Epidemiology of Meningococcal Disease

- **Humans only natural hosts**
- **Person-to-person transmission** by aerosolization of respiratory tract secretions in crowded conditions
- **Close contact** with infectious person (e.g., family members, day care centers, military barracks, prisons, and other institutional settings)
- Highest incidence in **children younger than 5 years** and particularly those **younger than 1 year** of age as passive maternal antibody declines and as infants immune system matures
- Commonly **colonize nasopharynx** of healthy individuals; highest oral and nasopharyngeal carriage rates in school-age children, young adults and lower socioeconomic groups

Age Distribution of Meningococcal Disease in USA

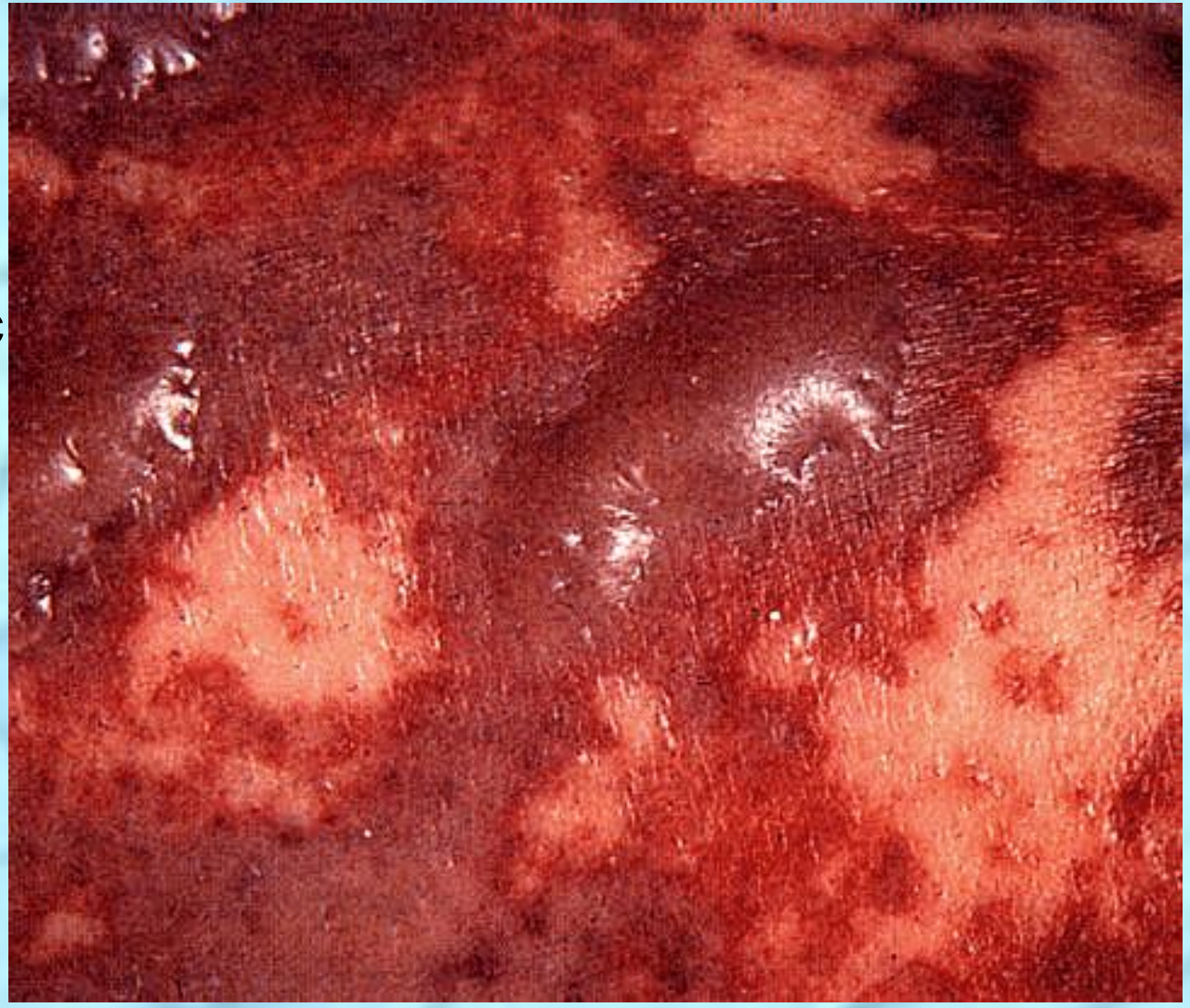


Pathogenesis of Meningococcal Disease

- Specific receptors (GD1 ganglioside) for bacterial fimbriae on **nonciliated** columnar epithelial cells in **nasopharynx** of host
- Organisms are **internalized into phagocytic vacuoles**, **avoid intracellular killing** in absence of humoral immunity and complement system (patients with late complement deficiencies are particularly at risk)
- **Replicate intracellularly** and **migrate to subepithelial space** where excess membrane fragments are released
- **Hyperproduction of endotoxin (lipid A of LOS**) and **blebbing into surrounding environment** (e.g., subepithelial spaces, bloodstream) mediates most clinical manifestations including diffuse vascular damage (e.g., endothelial damage, vasculitis (inflammation of vessel walls), thrombosis (clotting), disseminated intravascular coagulation (DIC)

Skin Lesions of Meningococcemia

NOTE: Petechiae have coalesced into hemorrhagic bullae.



Immunogenicity of Neisseria meningitidis

- Following colonization of the nasopharynx, **protective humoral immunity develops** against the same or closely related organisms of the same serogroup, but not against other serogroups
- **Bactericidal activity** of the **complement** system is required for clearance of the organisms
- **Cross-reactive protective immunity** acquired with colonization by closely related antigenic strains and with normal flora of other genera (e.g., *E. coli* K1); progressive disease can occur in absence of serogroup-specific immunity

Laboratory Characterization of Neisseria meningitidis

- Large numbers (e.g., >10^7cells/ml) of encapsulated, small, gram-negative diplococci (flattened along adjoining side) and polymorphonuclear leukocytes (PMN's) can be seen microscopically in **cerebrospinal fluid (CSF)**
- Transparent, non-pigmented nonhemolytic colonies on **chocolate blood agar** with **enhanced growth in moist atmosphere with 5% CO_2**
- Oxidase-positive
- Acid production from glucose and maltose but not from other sugars

Prevention and Treatment of Meningococcal Disease

- **Penicillin is drug of choice** for treatment in adjunct with supportive therapy for meningeal symptoms
  - **Increasing MIC** mediated by genetic alteration of target penicillin binding proteins is being monitored)
  - Chloramphenicol or cephalosporins as alternatives
- **Chemoprophylaxis of close contacts** with rifampin or sulfadiazine (if susceptible)
- **Polyvalent vaccine** containing serogroups A, C, Y, and W135 is effective in people older than 2 years of age for **immunoprophylaxis** as an **adjunct to chemoprophylaxis**
  - Serogroup B is only weakly immunogenic and protection must be acquired naturally from exposure to cross-reacting antigens

REVIEW

of

Neisseria

General Characteristics of Neisseria spp.

- **Aerobic**
- **Gram-negative** cocci often arranged in pairs (**diplococci**) with **adjacent sides flattened** (like coffe beans)
- **Oxidase positive**
- Most **catalase positive**
- Nonmotile
- Acid from oxidation of carbohydrates, not from fermentation

Neisseria Associated Diseases

Organism	Diseases
N. gonorrhoeae	Urethritis, cervicitis, salpingitis, pelvic inflammatory disease, proctitis, bacteremia, arthritis, conjunctivitis, pharyngitis
(ophthalmia neonatorum)	
N. meningitidis	Meningitis, meningoencephalitis, bacteremia, pneumonia, arthritis, urethritis
Other *Neisseria* species	Opportunistic infections

REVIEW

Review of Neisseria gonorrhoeae

General Overview of Neisseria gonorrhoeae

- **Readily transmitted by sexual contact**
- **Gram-negative diplococci flattened along the adjoining side**
- **Fastidious**, **capnophilic** and **susceptible to cool temperatures, drying and fatty acids**
  - Requires complex media pre-warmed to 35-37C
  - Soluble starch added to neutralize fatty acid toxicity
  - Grow best in moist atmosphere supplemented with CO_2
- Produce **acid from glucose**, but not from other sugars

REVIEW

Summary of Neisseria gonorrhoeae

REVIEW

Physiology and Structure

Gram-negative diplococci with fastidious growth requirements.

Growth best at 35°C to 37°C in a humid atmosphere supplemented with CO_2.

Oxidase- and catalase-positive; acid produced from glucose oxidatively.

Outer surface with multiple antigens: pili protein; Por proteins; Opa proteins; Rmp protein; protein receptors for transferrin, lactoferrin, and hemoglobin; lipooligosaccharide; immunoglobulin protease; β-lactamase.

Virulence

Refer to Table 28–2.

Epidemiology

Humans are the only natural hosts.

Asymptomatic carriage is the major reservoir.

Transmission primarily by sexual contact.

More than 350,000 cases reported in United States in 1998 (underestimates true incidence of disease).

Disease most common in blacks, people aged 15 to 24 years, residents of southeastern states, people who have multiple sexual encounters.

Higher risk of disseminated disease in patients with deficiencies in late components of complement.

Summary of *Neisseria gonorrhoeae* (cont.)

Diseases

Refer to Table 28–1.

Diagnosis

Gram stain of urethral specimens is accurate for symptomatic males only.

Culture is sensitive and specific but has been replaced with molecular probe techniques in many laboratories.

Treatment, Prevention, and Control

Ceftriaxone, cefixime, ciprofloxacin, or ofloxacin can be administered in uncomplicated cases.

In vitro susceptibility should be determined in cases unresponsive to therapy, because antibiotic resistance is increasing.

Penicillin should be avoided, because resistance is common.

Doxycycline or azithromycin should be added for infections complicated by *Chlamydia*.

For neonates, prophylaxis with 1% silver nitrate; ophthalmia neonatorum is treated with ceftriaxone.

Prevention consists of patient education, use of condoms or spermicides with nonoxynol 9 (only partially effective), and aggressive follow-up of sexual partners of infected patients.

Effective vaccines are not available.

Epidemiology of Gonorrhea

- Seriously **underreported** sexually-transmitted disease
  - ✔ 350,000 reported cases in 1998
- Found **only in humans** with strikingly different epidemiological presentations for females and males
- Asymptomatic carriage is major reservoir
- Transmission primarily by sexual contact
- Lack of protective immunity and therefore **reinfection**, partly due to **antigenic diversity** of strains
- Higher risk of disseminated disease in patients with late complement deficiencies

REVIEW

Females	Males
50% risk of exposure after single exposure	20% risk of exposure after single exposure
Asymptomatic infections frequently not diagnosed	Most initially symptomatic (95% acute)
Major reservoir is asymptomatic carriage in females	Major reservoir is asymptomatic carriage in females
Genital infection primary site is cervix (cervicitis), but vagina, urethra, rectum can be colonized	Genital infection generally restricted to urethra (urethritis) with purulent discharge and dysuria
Ascending infections in 10-20% including salpingitis, tubo-ovarian abscesses, pelvic inflammatory disease (PID) , chronic infections can lead to sterility	Rare complications may include epididymitis, prostatitis, and periurethral abscesses
Disseminated infections more common, including septicemia, infection of skin and joints (1-3%)	Disseminated infections are very rare **REVIEW**
Can infect infant at delivery (conjunctivitis, opthalmia neonatorum)	More common in homosexual/bisexual men than in heterosexual populatiuon

Pathogenesis of Neisseria gonorrhoeae

- Fimbriated cells attach to intact mucus membrane epithelium
- Capacity to invade intact mucus membranes or skin with abrasions
  - Adherence to mucosal epithelium
  - Penetration into and multiplication before passing through mucosal epithelial cells
  - Establish infection in the sub-epithelial layer
- **Most common sites of inoculation:**
  - **Cervix (cervicitis)** or vagina in the female
  - **Urethra (urethritis)** or penis in the male

REVIEW

Virulence Factors Associated with Neisseria gonorrhoeae

Virulence Factor	Biologic Effect
Pilin	Protein that mediates initial attachment to nonciliated human cells (e.g., epithelium of vagina, fallopian tube, and buccal cavity); interferes with neutrophil killing
Por protein (protein I)	Porin protein—promotes intracellular survival by preventing phagolysosome fusion in neutrophils
Opa protein (protein II)	Opacity protein—mediates firm attachment to eukaryotic cells
Rmp protein (protein III)	Reduction-modifiable protein—protects other surface antigens (Por protein, LOS) from bactericidal antibodies
Transferrin-binding proteins	Mediate acquisition of iron for bacterial metabolism
Lactoferrin-binding proteins	Mediate acquisition of iron for bacterial metabolism
Hemoglobin-binding proteins	Mediate acquisition of iron for bacterial metabolism
LOS	Lipooligosaccharide—has endotoxin activity
IgA_1 protease	Destroys immunoglobulin A_1 (role in virulence is unknown)
β-lactamase	Hydrolyzes β-lactam ring in penicillin

REVIEW

See Handout on Sensitivity & Specificity of Diagnostic Tests

(Next two slides)

Analytic Performance of a Diagnostic Test

	ACTUAL POSITIVE	ACTUAL NEGATIVE	TOTALS
TEST POSITIVE	**80** True Positives	**25** **False Positives**	**105** Test Positives
TEST NEGATIVE	**20** **False Negatives**	**75** True Negatives	**95** Test Negatives
TOTALS	**100** Actual Positives	**100** Actual Negatives	**200**

REVIEW

Analytic Performance of a Diagnostic Test (cont.)

Sensitivity = Measure of True Positive Rate (TPR)

$$= \frac{\text{No. of True Pos.}}{\text{No. of Actual Pos.}} = \frac{\text{No. of True Pos.}}{\text{No. of (True Pos. + False Neg.)}} = \frac{80}{80+20} = 80\%$$

Sensitivity

In conditional probability terms, the probability of a positive test given an actual positive sample/patient.

Specificity = Measure of True Negative Rate (TNR)

$$= \frac{\text{No. of True Neg.}}{\text{No. of Actual Neg.}} = \frac{\text{No. of True Neg.}}{\text{No. of (True Neg. + False Pos.)}} = \frac{75}{75+25} = 75\%$$

Specificity

In conditional probability terms, the probability of a negative test given an actual negative sample/patient.

REVIEW

Review of Neisseria meningitidis

General Overview of Neisseria meningitidis

- Encapsulated small, gram-negative diplococci
- Second most common cause (behind *S. pneumoniae)* of **community-acquired meningitis** in previously healthy adults; swift progression from good health to life-threatening disease
- **Pathogenicity:**
  - Pili-mediated, **receptor-specific colonization of nonciliated cells of nasopharynx**
  - **Antiphagocytic** polysaccharide **capsule** allows systemic spread in absence of specific immunity
  - Toxic effects mediated by **hyperproduction of lipooligosaccharide**
- Serogroups A, B, C, Y, W135 account for about 90% of all infections

REVIEW

Summary of Neisseria meningitidis

Physiology and Structure

Gram-negative diplococci with fastidious growth requirements.

Grows best at 35°C to 37°C in a humid atmosphere.

Oxidase- and catalase-positive; acid produced from glucose and maltose oxidatively.

Outer surface antigens include polysaccharide capsule, pili, and lipooligosaccharides (LOS)

Virulence

Capsule protects bacteria from antibody-mediated phagocytosis.

Specific receptors for meningococcal pili allow colonization of nasopharynx.

Bacteria can survive intracellular killing in the absence of humoral immunity.

Endotoxin mediates most clinical manifestations.

Epidemiology

Humans are the only natural hosts.

Person-to-person spread occurs via aerosolization of respiratory tract secretions.

Highest incidence of disease is in children younger than 5 years, institutionalized people, and patients with late complement deficiencies.

Meningitis and meningococcemia most commonly caused by serogroups B and C; pneumonia most commonly caused by serogroups Y and W135; serogroup A associated with disease in underdeveloped countries.

Disease occurs worldwide, most commonly in the dry, cold months of the year.

REVIEW

Summary of Neisseria meningitidis (cont.)

Diseases

Refer to Table 28–1.

Diagnosis

Gram stain of cerebrospinal fluid is sensitive and specific but is of limited value for blood specimens (too few organisms are generally present except in overwhelming sepsis).

Culture is definitive, but organism is fastidious and dies rapidly when exposed to cold or dry conditions.

Tests to detect meningococcal antigens insensitive and nonspecific.

Treatment, Prevention, and Control

Breast-feeding infants have passive immunity (first 6 months).

Treatment is with penicillin (drug of choice), chloramphenicol, ceftriaxone, and cefotaxime.

Chemoprophylaxis for contacts is with rifampin or sulfadiazine (if isolated organism is susceptible).

For immunoprophylaxis, vaccination is an adjunct to chemoprophylaxis; it is used only for serogroups A, C, Y, and W135; no effective vaccine is available for serogroup B.

Polysaccharide vaccines conjugated with protein carriers offer protection for infants younger than 2 years.

REVIEW

Diseases Associated with Neisseria meningitidis

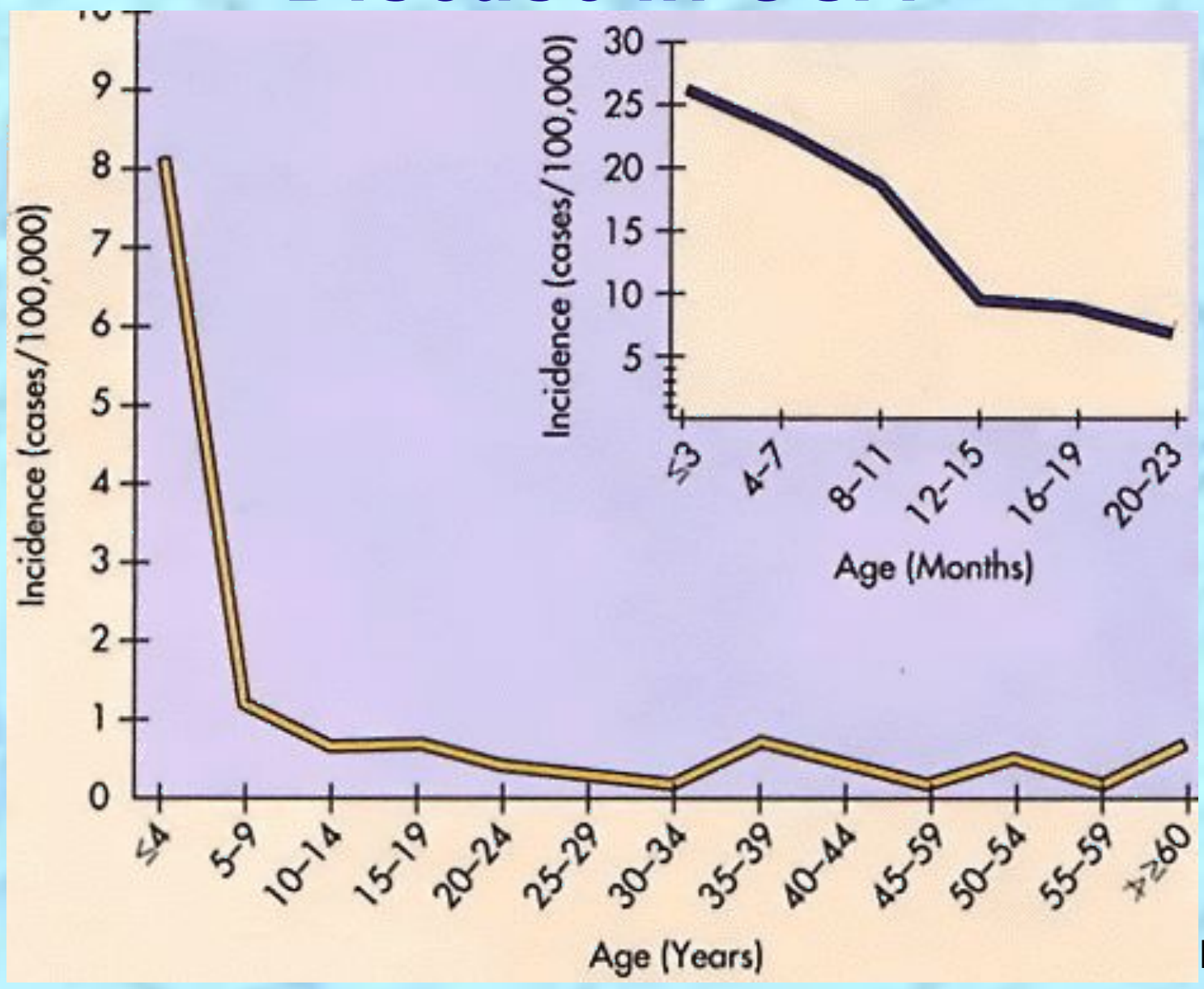
- **Following dissemination of virulent organisms from the nasopharynx:**
  - ✔ **Meningitis**
  - ✔ Septicemia (**meningococcemia**) with or without meningitis
  - ✔ **Meningoencephalitis**
  - ✔ Pneumonia
  - ✔ Arthritis
  - ✔ Urethritis

Epidemiology of Meningococcal Disease

- **Humans only natural hosts**
- **Person-to-person transmission** by aerosolization of respiratory tract secretions in crowded conditions
- **Close contact** with infectious person (e.g., family members, day care centers, military barracks, prisons, and other institutional settings)
- Highest incidence in **children younger than 5 years** and particularly those **younger than 1 year** of age as passive maternal antibody declines and as infants immune system matures
- Commonly **colonize nasopharynx** of healthy individuals; highest oral and nasopharyngeal carriage rates in school-age children, young adults and lower socioeconomic groups

REVIEW

Age Distribution of Meningococcal Disease in USA



REVIEW

Pathogenesis of Meningococcal Disease

- Specific receptors (GD1 ganglioside) for bacterial fimbriae on **nonciliated** columnar epithelial cells in **nasopharynx** of host
- Organisms are **internalized into phagocytic vacuoles**, **avoid intracellular killing** in absence of humoral immunity and complement system (patients with late complement deficiencies are particularly at risk)
- **Replicate intracellularly** and **migrate to subepithelial space** where excess membrane fragments are released
- **Hyperproduction of endotoxin (lipid A of LOS**) and **blebbing into surrounding environment** (e.g., subepithelial spaces, bloodstream) mediates most clinical manifestations including diffuse vascular damage (e.g., endothelial damage, vasculitis (inflammation of vessel walls), thrombosis (clotting), disseminated intravascular coagulation (DIC)

REVIEW

Immunogenicity of Neisseria meningitidis

- Following colonization of the nasopharynx, **protective humoral immunity develops** against the same or closely related organisms of the same serogroup, but not against other serogroups
- **Bactericidal activity** of the **complement** system is required for clearance of the organisms
- **Cross-reactive protective immunity** acquired with colonization by closely related antigenic strains and with normal flora of other genera (e.g., *E. coli* K1); progressive disease can occur in absence of serogroup-specific immunity

REVIEW