Chapter 129 (Ch. 121 9th Ed) – Bacteria

Episode Overview:

1. Describe the clinical features, diagnostic tests and management of Diphtheria.
2. What are the 3 phases of illness in pertussis?
3. Describe the management of a child:
    a. <1 year
    b. > 1 year.
4. Who needs post-exposure prophylaxis for pertussis and diphtheria? What is the regimen?
5. List 5 complications of pertussis.
6. What is the mechanism of action of the tetanus toxin? What are 4 types of tetanus?
7. List 5 differential diagnosis for Bell's Palsy
8. Describe 4 major components of management of tetanus
9. List 6 characteristics of high risk tetanus wounds
10. List 7 differential diagnosis for tetanus.
11. Describe wound management relating to tetanus prophylaxis
12. What is the mechanism of action of botulinum toxin? And describe the 5 types of botulism.
13. List 6 differential diagnosis for botulism toxicity
14. Describe treatment of botulism
15. Describe the clinical presentation and management of acute pneumococcemia. (Which antibiotics provide empiric treatment of s. pneumoniae?)
16. List 6 RFs for Meningococcemia and describe its clinical presentation
17. Describe the management of suspected meningococcemia
18. Which patients should receive prophylaxis for N. meningitidis? What is the prophylaxis?
19. What are the risk factors for toxic shock syndrome?
20. List criteria for toxic shock syndrome and describe management
21. Compare staph and strep toxic shock syndrome

Wisecracks:

1. What is on the differential diagnosis for respiratory diphtheria?
2. List 6 features of a high risk tetanus wound
3. List 8 causes of a non-blanching rash
4. What type of streptococcal infection occurs in pts with a recent splenectomy?
5. Which vaccines are used to prevent s. pneumoniae infections?
6. Which bacterial infections are patients with (functional) asplenia at risk for?
7. Which serotypes of N. meningitidis cause disease? Which one is not covered by the meningococcal vaccine?

Key Concepts:
• All patients appearing septic should be treated with broad-spectrum antibiotics as soon as possible, even before a definitive diagnosis is Made.

• A surgeon should be consulted as soon as possible for patients with sepsis and a débridable source of infection.

• Immunity to diphtheria, tetanus, and pertussis wanes significantly in adults.

Pertussis should be considered a cause of persistent cough in adults.

A tetanus vaccination history should always be obtained from patients with trauma or infection. When there is doubt about the history, the age-appropriate vaccine according to CDC guidelines is Administered.

• Neonates with suspected pertussis should be admitted to an intensive care setting.

• Botulism should be kept in the differential diagnosis for the infant with failure to thrive, constipation, or decreased muscle tone and for the injection drug user with neurologic symptoms.

• Patients with pneumococcemia, meningococcemia, and TSS can decompensate rapidly. Antimicrobial therapy should be initiated promptly, before identification of an organism.

[1] Describe the clinical features, diagnostic tests and management of Diphtheria.

Humans are the only known reservoir for ***Corynebacterium diphtheriae****. Spread is by person-to-person through* ***respiratory droplets or by direct contact with secretions, skin lesion exudates, or rarely fomites or food****. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage, or as asymptomatic carriers.*

Why is this disease called diphtheria? Because it comes from the Greek word for leather - describing the grey membrane seen in the pharynx. Thankfully, because of immunization, we're not seeing hundreds of thousands of cases of diphtheria each year, and instead it's a very rare occurrence!

Clinical features

- Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection.

- Cutaneous diphtheria can occur as a primary skin infection or as a secondary infection of a preexisting wound.
- Circulating exotoxin causes the systemic symptoms of diphtheria, most profoundly affecting the nervous system, heart, and kidneys.

Progression of symptoms/signs:

- **Generic URTI symptoms**
  - **Low grade fever and sore throat are the most frequent presenting complaints. Weakness, dysphagia, headache, voice changes, and loss of appetite**
- **⅓ develop cervical lymphadenopathy**
  - **The bull neck appearance is rare, and seen in very ill patients**
- **> 50% then develop the grey thick membrane in the location affected**
  - **diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane like appearance.**
- **Laryngeal diphtheria → respiratory tract edema with subsequent upper airway obstruction may develop.**
- **Patients with cutaneous diphtheria typically do not develop systemic toxicity. The skin characteristically has an ulcer with a grayish membrane.**

Diagnosis:

- **If you suspect it, you need to notify your lab, because they have to run special tests (or send it elsewhere)**
  - **The Elek test for toxin A** *is technically demanding and subject to misinterpretation by inexperienced users but is available at the CDC.*
  - **Polymerase chain reaction (PCR),** *which is more reliable but not as readily available, can be used to detect the toxin structural gene.*
- **A culture for** group A beta-hemolytic streptococcus doesn't rule out diphtheria - these infections can occur together
- Send sample immediately to lab for inoculation in **Tellurite selective culture medium**

Checklist for Assessing Patients with Suspected Diptheria (9th Edition Box 121.2)

- Suspect Case
  - Pharyngitis, nasopharyngitis, tonsillitis, laryngitis, tracheitis (or any combination of these), absent or low grade fever)
  - Grayish adherent pseudomembrane present
  - Membrane bleeds, if manipulated or dislodged
- Probable Case (suspect case above, plus any one of the following)
  - Stridor
  - Bull-neck (cervical edema)
  - Toxic circulatory collapse
  - Acute renal insufficiency
  - Submucosal or subcutaneous petechiae

    - Myocarditis
    - Death
    - Recent return (<2 weeks) from travel to area with endemic diphtheria
    - Recent contact (<2 weeks) with confirmed diphtheria case or contact
    - Recent contact (<2 weeks) with visitor from area endemic with diphtheria
    - Recent contact with dairy or farm animals or domestic pets
    - Immunization status
- Laboratory Confirmed Case
    - Positive culture *and*
    - Positive Elek test *or*
    - Positive PCR for Tox gene (positive for subunit A and B)

Management

- Patients with clinical evidence of diphtheria should be **placed in respiratory isolation** and treated presumptively for C. diphtheriae.
    - Need cardiac monitoring
    - Contact the CDC
- **The goals of therapy are:**
    - **To protect the airway,**
        - **Consider early intubation for laryngeal involvement**
    - **Limit the effects of already produced toxin**
        - **Equine serum DAT should be administered promptly after the**
        - **clinical diagnosis of respiratory diphtheria is deemed probable**
        - **and before laboratory confirmation.**
    - **Stop future toxin production by terminating bacterial growth.**
        - **Antibiotics prevent growth and spread of the organism but are no substitute for antitoxin.**
            - **Erythromycin 40 mg/kg/day (**
            - **maximum of 2 g) intravenously or orally in divided doses is the preferred treatment.**
            - **Penicillin G is an alternative**
            - Active immunization

Complications:

- **Airway obstruction (due to membrane formation), congestive heart failure, cardiac conduction disturbances, MYOCARDITIS, muscle paralysis.**
- **The mortality rate for patients with left bundle branch block and atrioventricular block is 60% to 90%.**

[2] What are the 3 phases of illness in pertussis?

Respiratory illness transmitted by aerosolized droplets. It can occur at any age but is predominantly a pediatric and adolescent illness. Pertussis means "violent cough." It is also called whooping cough because the severe episodes of coughing are followed by forceful inspiration, which creates a characteristic whooping sound.

Pertussis has three clinical stages: the catarrhal phase, the paroxysmal phase, and the convalescent phase.

1. **The catarrhal or prodromal phase (1-2 weeks)**
    a. **begins after an incubation period of approximately 7 to 10 days Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections.**
    b. **Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection. A dry cough usually begins at the end of the catarrhal phase.**
2. **The paroxysmal phase begins as fever subsides.**
    a. **Cough increases and lasts 1 to 6 weeks,** but it may persist for up to 10 weeks. Paroxysms of staccato coughing occur and average of 15 times per day and are followed by a single, sudden, forceful inhalation that produces the characteristic "whoop."
    b. **Only one-third of adults with pertussis develop this whoop, and it is rare in young infants = may present with apneic episodes and no other symptoms.**
    c. **Paroxysms may be spontaneous, occur more frequently at night, or be** precipitated by noise or cold. During the paroxysm, the patient may exhibit cyanosis, diaphoresis, tongue protrusion, salivation, and lacrimation. Post-tussive vomiting, syncope, and apnea may occur. Infants may be exhausted after a typical paroxysm. Between episodes of coughing, patients do not appear acutely ill.
3. **In the convalescent phase a residual cough may last several weeks to months.**
    a. **Paroxysms of coughing may be triggered by unrelated respiratory infection or by exposure to a respiratory irritant. This recurrence of coughing does not represent recurrence of pertussis infection.**

*******Pertussis should be considered in patients with cough lasting longer than 2 weeks with either paroxysms, whoops, or post-tussive emesis, regardless of previous vaccination status. Up to 27% of adults in the United States with a prolonged cough have serologic evidence of pertussis.********

[3] Describe the management of a child.

Get the swab to the lab:

- *Nasopharyngeal aspirate or swab (synthetic, non-cotton) should be obtained for culture and PCR, if both are available; sputum and throat swabs are inadequate because ciliated respiratory epithelial cells are required.*
- *Colonies of B. pertussis take 3 to 7 days to appear. Pertussis cultures are 30% to 50% sensitive, and this drops to less than 3% 3 weeks after the onset of cough.*

- <1 year
    - Admit! Droplet isolation

        - Neonates → NICU to monitor for apnea and cardiac arrhythmias
    - Supportive care
        - Fluids, lytes, hydration
        - Suctioning
        - Oxygen
        - May need parenteral nutrition
    - Antibiotics
        - Antibiotic treatment does not significantly reduce the severity or duration of illness at any phase. The goal of antibiotic therapy is to decrease infectivity and carriage.
        - Azithromycin 10 mg/kg/day for 5 days is recommended in infants younger than 1 year old because of an association between oral erythromycin and hypertrophic pyloric stenosis.
- 1 year
    - Admit vs. discharge with follow-up
    - Supportive care
    - Antibiotics
        - The CDC recommends erythromycin estolate ester 40 to 50 mg/kg/day (maximum of 2 g/ day) in four divided doses for 14 days.
    - Standard cough suppressants and antihistamines are ineffective.

[4] Who needs post-exposure prophylaxis for pertussis and diphtheria? What is the regimen?

Pertussis:

- **Exposed people / vulnerable people = get a macrolide**
- ***For those at high risk for developing severe pertussis:***
    - ***Including household contacts of a pertussis case,***
    - ***Infants and women in their third trimester of pregnancy (risk of transmitting the infection to the unborn)***
    - ***Persons with preexisting health conditions that may be exacerbated by a pertussis infection***
    - ***Contacts who themselves have close contact with any of the above listed people.***
        - ***E.g. NICU staff, childcare workers, maternity workers***
- ***Vaccination:***

Pertussis immunity wanes 5 to 10 years after immunization and 15 years after natural infection, causing an increasing incidence of the disease in people older than 15 years old.

- ***Those > 65 yrs who spend a lot of time around kids <12 mo - should get the Tdap booster.***

Diphtheria:

- **CARRIERS**
    - *Carriers of C. diphtheriae should receive oral penicillin G or erythromycin for 7 days or intramuscular (IM) benzathine penicillin (600,000 units for those*

weighing less than 30 kg and 1,200,000 units for those weighing more than 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy, cultures should be obtained; if positive, erythromycin therapy should be given for 10 additional days.

- ***EXPOSED CONTACTS* = four groups of people.**
  - ***Immunized in the last 5 yrs = observe:*** *Individuals who have been in close contact with infected patients should have cultures taken and be kept under surveillance for 7 days.*
  - ***Immunized > 5 yrs = immunize:*** *Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and acellular pertussis (DTaP) or diphtheria-tetanus (DT or Td) as appropriate for age.*
  - ***Close unimmunized contacts or those whose immunization status is unknown = abx, immz, cultures*** *should receive the same antimicrobial therapy as carriers (previously described), have culture specimens taken before and after therapy [?DAT], and have active immunization initiated.*
  - ***Close contacts who cannot be kept under surveillance*** *should receive benzathine penicillin intramuscularly to ensure compliance and a Td booster (appropriate for age and immunization history). DAT is not recommended for this group because of the risk of horse serum allergy.*
- **IMMUNITY BOOSTING**
  - *A universal primary immunization program with regular boosters every 10 years is the most effective method for controlling diphtheria. Emergency clinicians should routinely administer age-appropriate tetanus and diphtheria toxoids as part of wound management.*

[5] List 5 complications of pertussis.

Bacterial or viral pneumonia superinfection complicating pertussis is a leading cause of death, especially in infants and young children.

Pertussis Complications (9th Edition Box 121.3)

- Periorbital eema
- Subconjunctival hemorrhage
- Petechiae
- Epistaxsis
- Hemoptysis
- Subcutaneous emphysema
- Pneumothorax
- Pneumomediastinum
- Diaphragmatic rupture
- Umbilical and inguinal hernias
- Rectal Prolapse

[6] What is the mechanism of action of the tetanus toxin? What are 4 types of tetanus?

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Respiratory muscle involvement leads to hypoventilation, hypoxia, and death.

Mechanism of action - C. tetani produces the neurotoxin tetanospasmin at the site of tissue injury. Tetanospasmin binds the motor nerve ending and moves by retrograde axonal transport and trans-synaptic spread to the CNS.

It binds preferentially to inhibitory (GABAergic and glycinergic) neurons and ***blocks the presynaptic release*** *of these neurotransmitters.* ***Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.***

******no brake pedal = muscles, cardiovascular system go haywire*****

Tetanospasmin may also affect preganglionic sympathetic neurons and parasympathetic centers, resulting in autonomic nervous system dysfunction. The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure and heart rate. The binding of tetanospasmin at the synapse is ***irreversible;*** *recovery occurs only when a new axonal terminal is produced.* Incubation period - from 1 day to 1 month!

Exerts effects on:

- CNS
  - Systemic muscle spasms - irreversible
- Autonomic nervous system
  - Fluctuations in HR, BP, rhythm

Types:

- Generalized
  - Most common form - trismus or "lockjaw," caused by masseter muscle spasm, and is present in 50% to 75% of patients.
  - Sardonic smile (risus sardonicus) appears.
  - Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling.
  - Progression to: Opisthotonos, whole body spasms, long bone #s, dislocations, vertebral subluxations
  - Spasms of laryngeal and respiratory muscles can cause ventilatory failure and death.
  - Autonomic dysfunction is the major cause of death in patients who survive the acute phase and is manifested by tachycardia, hypertension, hyperpyrexia, cardiac dysrhythmias, and diaphoresis.
  - Survive or die by 4 weeks.
- Localized
  - Can be mild or severe, and may progress to generalized tetanus

- Usually have muscle spasms close to the injury
- Cephalic
  - A rare variant of localized tetanus, results in cranial nerve palsies and muscle spasms.
  - Usually involves CN VII
  - May have trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII ipsilateral to the site of local infection.
  - May progress to generalized tetanus
- Neonatal
  - Aka generalized tetanus of the newborn
  - *Occurs almost exclusively in developing countries where **maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords**. Symptoms begin during the first week of life and include irritability and poor feeding.*
  - *Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support. Even with limited resources, mortality can be reduced to less than 50% with basic medication and experienced medical personnel.*

[7] List 5 DDx for Bell's Palsy

Common entities:

- CVA
- Trigeminal neuralgia
- Herpes zoster oticus (Ramsay Hunt syndrome)
- CNS tumour - acoustic neuroma; cerebellopontine angle lesions (meningioma); facial nerve schwanoma, parotid gland tumour, sarcoma
- Parotitis
- Malignant otitis externa

Uncommon entities

- Cephalic tetanus
- Tick paralysis
- Botulism
- CN palsies
  - Due to cerebral aneurysms
- Amyloidosis GBS
- HIV
- Neurosyphillis

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus also includes Bell's palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

[8] Describe 4 major components of management of tetanus

There are no laboratory tests to confirm or to exclude the diagnosis of tetanus.

Physical Examination - *The spatula test involves touching of the oropharynx with a tongue blade. With a negative test result, the patient gags and expels the tongue blade. With a positive test result, the patient has reflex masseter muscle spasm and bites the spatula. This test is 94% sensitive and 100% specific for tetanus.*

Management

- Aggressive supportive care,
  a. Control muscle spasms
     i. Avoid unnecessary stimulation / loud noises = these can trigger severe spasms
     ii. Treat spasms with benzodiazepines
     iii. Diazepam - widely used
     iv. GABA agonists and indirectly antagonize many of the effects of tetanospasmin. They have no effect on the inhibition of glycine release by tetanospasmin.
  b. Adjunctive options:
     i. Dantrolene
     ii. Propofol infusion
     iii. Magnesium
  c. Intubation and ICU care:
     i. Should receive neuromuscular blockade and mechanical ventilation. Succinylcholine can be used in the initial phase of the disease, but there is a risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease. Long-acting nondepolarizing agents are preferred.
     ii. Progress to IV NDMR (pancuronium)
     iii. Consider for early Tracheostomy
     iv. Autonomic instability requires monitoring and aggressive treatment. Sympathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists, such as labetalol and propranolol. Esmolol is ideal.
     v. Consider morphine and magnesium infusions. Try to avoid catecholamines.
  d. Elimination of unbound tetanospasmin
     i. Passive immunization with human tetanus immune globulin (HTIG) as soon as possible in all patients with suspected tetanus.
     ii. HTIG neutralizes circulating toxin, as well as toxin at the site of production, and reduces mortality; <u>it does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms</u>.
     iii. HTIG should be administered at a site separate from the Td. A dose of 500 units is as effective as higher doses. Adult and pediatric doses are the same.

e. Active immunization
    i. active immunization with Td**[see notes below]
    ii. ***ensure injection is in a SEPARATE SITE FROM THE htig***
f. prevention of further toxin production.
    i. Metronidazole
    ii. Doxycycline, macrolides an alternative
    iii. Toxin production is eliminated by treatment of the C. tetani infection. Wound débridement and antibiotic administration can cause a transient release of tetanospasmin, so these measures should be delayed until after the HTIG is administered. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for C. tetani.

****Tetanus toxoid is an inactivated form of tetanospasmin. Vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high-risk patients such as elders, injection drug users, and patients with human immunodeficiencyvirus (HIV) infection and other causes of immunocompromise, immunity wanes more quickly and response to the vaccine is slower. Adults with an uncertain history of a complete primary immunization series should receive a primary series of three tetanus toxoid doses, followed by booster doses every 10 years.*

[9] List 6 characteristics of high risk tetanus wounds

Highest risk groups in north America:

- The elderly
- IVDU
- HIV / immunocompromised

Neonates in the developing world

High risk tetanus wound:

1. >6 hours old,
2. >1 cm deep,
3. Contaminated,
4. Stellate
5. Denervated
6. Ischemic
7. Infected

Deep penetrating wound in someone who has inadequate primary immunization and/or waning immunity

- Wounds contaminated with soil and dust; feces from animals and humans.
- Tetanus prone wounds have damaged or devitalized tissue, foreign bodies, or other bacteria.

[10] List 7 Differential Diagnoses for tetanus.

- **"Other things causing lock-jaw or trismus" - usual oral infections**
- **"Other things causing cramping, body spasms" - (note that rabies does not cause trismus)**
- **The only true mimicker: *Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus.***

Differential Diagnosis of Tetanus (9th Edition Box 121.5)

- Acute abdomen
- Black widow spider bite
- Dental abscess/infection
- Dislocated mandible
- Dystonic reaction
- Encephalitis
- Head trauma
- Hyperventilation syndrome
- Hypocalcemia
- Meningitis
- Peritonsillar abscess
- Progressive fluctuating muscle rigidity (stiff man syndrome)
- Psychogenic
- Rabies
- Sepsis
- Status Epilepticus
- Strychnine poisoning
- Subarachnoid Hemorrhage
- TMJ syndrome

[11] Describe wound management relating to tetanus prophylaxis

- Wound irrigation, and ER debridement
- Discuss with plastics/ortho re: operative debridement for any deep wounds/abscesses
- Consider local injection of TIG around wound (but no clear evidence to support this)
- Antibiotics (metronidazole) to prevent further tetanospasmin production
- Passive immunization

Tetanus vaccination should be updated for all patients who present for wound management. **Patients with unknown or uncertain immunization status should be considered to have no previous tetanus immunization**. Those younger than 7 years old should receive diphtheria-tetanus or DTaP. Patients 7 years old or older should receive Tdap.

HTIG prophylaxis (250 units IM) is recommended for unimmunized and underimmunized patients with high risk wounds (>6 hours old, >1 cm deep, contaminated, stellate, denervated, ischemic, infected). When tetanus toxoid and HTIG are given concurrently, separate injection sites should be used. The only contraindication to tetanus and diphtheria toxoids is a history oyf a neurologic or severe hypersensitivity reaction to a previous dose. The most common side effects of tetanus vaccine are minor: local swelling, pain, erythema, pruritus, fever, nausea, vomiting, malaise, and nonspecific rash. Local reactions do not preclude future use of toxoid.

No evidence exists that tetanus and diphtheria toxoids are teratogenic.
HTIG is not contraindicated in pregnancy.

[12] What is the mechanism of action of botulinum toxin? And describe the 5 types of botulism.

Botulism is a rare life-threatening paralytic illness caused by neurotoxins produced by Clostridium botulinum. {the opposite presentation to tetanus}

[*In 1820, Kerner first noted an association between sausage ingestion and a paralytic illness. The term botulism comes from the Latin botulus, meaning "sausage,"]*

Mechanism of action

- **This is a toxin mediated disease**
- **Works on the NMJ causing flaccid paralysis**
- The botulinum neurotoxin is similar in structure and function to the tetanospasmin toxin produced by C. tetani, but the clinical effects differ dramatically. Tetanospasmin targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas **botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, causing flaccid paralysis.**
- The toxin binds to the presynaptic nerve membrane, becomes internalized, and **inhibits the release of acetylcholine predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction.**

Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and descending flaccid paralysis. Once affected with type A toxin, the **nerve is permanently damaged, and recovery requires axonal regeneration** and the formation of new synapses, which may take several months.

The disease occurs in one of five forms:

- **Food-borne botulism,**
    - *Typical food-borne botulism results from the ingestion of preformed heat-labile toxin rather than from the ingestion of spores or live bacteria.*
    - *One taste can expose a person to enough toxin to cause clinical illness. Digestive enzymes do not destroy preformed toxin.*
    - *Home-canning, mass produced foods, restaurants*
- **Infant botulism (the most common form of the illness now)**
    - *Caused by the ingestion of spores with in vivo production of toxin. Honey and to a lesser extent corn syrup have been implicated as sources of C. botulinum spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases.*
- **Wound botulism,**
    - In IVDU who use black tar heroin

- **Unclassified botulism,**
    - *The Clostridium bacterium produces its toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnormal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin.*
- **Inadvertent botulism / iatrogenic botulism**
    - **Inadvertent generalized weakness as well as unintentional focal weakness may be seen in patients receiving botox injection**
- **Biologic weapon of mass destruction**
    - Aerosolized form
    - Widely produced in Iraq

C. botulinum is an anaerobic, gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. It produces a potent exotoxin that is responsible for the disease. Each strain of C. botulinum produces a specific toxin type—A through G. Only types A, B, E, and F produce disease inhumans.* ***Botulinum toxins are the most potent known biologic compounds**. Doses as small as 0.09 to 0.15 µg IV or 0.7 to 0.9 µg inhaled can cause death in a 70-kg human.35 Heating at 185°F (85°C) for 5 minutes destroys any* ***botulism toxin****, and* ***heating of toxin-contaminated food just before ingestion prevents foodborne botulism.*** *Spores are highly heat resistant and can survive at a temperature of 212°F (100°C) for several hours.*

[13] List 6 differential diagnosis for botulism toxicity

Clinical presentation:

- Early symptoms: weakness, malaise, lightheadedness, nausea, vomiting, and constipation.
- *Cranial nerves first to be affected:*
    - *Diplopia, blurred vision, dysphonia, dysphagia, dysarthria, and vertigo. Next, a symmetrical descending muscle weakness occurs, involving the upper and lower extremities and the muscles of respiration.*
- *Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are affected more than those of the lower extremity, and proximal muscles are weaker than distal muscles.*

Infant botulism presents differently:

- *Constipation followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. On physical examination, patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless secondary infection is present.*

Hallmark signs: gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suspicion. The diagnosis is confirmed by detection of botulinum toxin in the patient's blood;

botulinum toxin or C. botulinum in the gastric contents, stool, or wound of the patient; or toxin or organisms in the suspected food source.

Differential Diagnosis:
Adult botulism

- **Autoimmune disease**
  - GBS - miller fisher syndrome
  - Myesthenia
  - Lambert-eaton syndrome
- **Vascular disease**
  - **Brainstem CVA**
- **Infectious**
  - **Poliomyelitis**
  - **Diphtheria**
- **Medication overdose**
  - Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium with alterations in mental status.
  - Organophosphate insecticides cause hyperthermia and altered mental status.
  - Dystonic reactions are self-limited and respond to diphenhydramine or benztropine.
  - Neuromuscular blockade from the administration of aminoglycosides is distinguished by medication history.
  - Heavy metal poisoning produces changes in mental status.
  - Magnesium toxicity may mimic botulism, but the history and serum magnesium levels distinguish these entities.
  - In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.
- **Toxin mediated disease**
  - **Tick paralysis**

Infant botulism:

- **Broad DDx:**
  - ***Sepsis, viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.***
  - ***Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential diagnosis consideration,*** *as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.*

[14] Describe treatment of botulism

1. **Supportive ICU care**

   a. *A decrease in vital capacity to less than 30% of predicted or less than 12 mL/kg is an appropriate criterion for intubation. Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter.*

2. **Antitoxin**
   a. *Equine antitoxin contains antibodies to toxin types A, B, and E. It should be administered as soon as possible after appropriate laboratory specimens have been obtained.* ***It neutralizes circulating toxin but has no effect on bound toxin (remember this is irreversible and requires axonal regeneration)***
   b. *After skin testing for hypersensitivity,* ***one 10-mL vial should be given IV. The serum half-life is 5 to 8 days****.*
      i. *For these reasons, and contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.*
   c. ***Infant botulism is treated with human botulism immune globulin (BabyBIG)****, which is pooled plasma from immunized adults with high titers of antibodies to toxins A and B.*
3. **Consideration for antibiotics:**
   a. **Not widely recommended for:**
      i. **Infant, wound, or food botulism**
   b. **May be considered AFTER antitoxin has been administered:**
      i. **debridement and antibiotic administration**

Otherwise, the use of antibiotics should be limited to treatment of secondary infections that may develop.

[15] Describe the clinical presentation and management of acute pneumococcemia.

Pneumococcemia is defined as the presence of S. pneumoniae in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome.

Clinical presentation

- **Ranges from mild illness to fulminant disease, progressing to death within several hours.**
- **Febrile illness (occult bacteremia) → watch for hyper or HYPOthermia**
  - **Fever, chills, cough, shortness of breath, headache, and rash.**
  - **Rigors** *(The shaking chills that occur with pneumococcemia are believed to be caused by a toxin)*
- **Progression to SIRS**

****Fever (temperature >101.3°F [38.5°C]) occurs in 90% of younger patients but in less than 60% of those older than 65 years old.****

A focal primary source of infection is more common in adults than in children. Clinicians should evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out Invasive Pneumococcal Dz.

Management

- Resuscitate and stabilize
- Eradicate infection
- Early antibiotics:
    - *Ceftriaxone (1 to 2 g IV every 12 to 24 hours; 50 to 100 mg/kg/day in children) or cefepime (1 to 2 g IV every 12 hours; 50 mg/kg every 8 hours in children).*
    - *When meningitis is present, the higher doses should be given.*
    - *In areas where ceftriaxone resistance has emerged, vancomycin should be given (1 g IV every 12 hours; 40 mg/kg/ day divided every 6 to 8 hours in children) should be considered.*
- Other options (depending on local resistance)
    - Penicillin G
    - Meropenem
    - Chloramphenicol
- Source control
- Manage other comorbidities

[16] List 6 risk factors for meningococcemia and describe its clinical presentation

Risk factors:

- Winter season
- Crowded living conditions (military recruits, college dormitories)
- close contact with an infected patient,
- complement deficiency
- properdin deficiency
    - Rare X-linked disease in which properdin, an important complement factor, is deficient
- Asplenia
- chronic alcohol abuse,
- active and passive smoking,
- Corticosteroid use
- recent respiratory illness.

Clinical presentation- *All of the major pathophysiologic events of meningococcal sepsis are caused by the host's inflammatory response to the organism causing functional and histologic damage to the microvasculature, resulting in increased vascular permeability,*

pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.

Range in presentation:

- *Mild febrile illness to fulminant disease progressing to death within hours.*
- *Most patients have **fever on presentation.** Other complaints:*
    - *include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea.*
    - ***Anywhere from 27% to 77% of patients will present with the classic hemorrhagic skin lesions**.*
    - ***These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure. The following categories detail the five patterns of presentation:***

1. ***Occult bacteremia***
    a. *+ve blood culture in a patient worked up for a febrile illness*
    b. *N. meningitidis accounts for less than 1% of occult bacteremia cases, but these patients are much more likely to develop meningitis (up to 58%) than are those with S. pneumoniae. Despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.*
    c. *Some can clear the infection spontaneously*
2. ***Meningococcal meningitis***
    a. ***headache, photophobia, vomiting, fever, and signs of meningeal inflammation.** This classic triad of fever, neck stiffness, and altered mental status is present in less than 30% of patients.*
    b. ***Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures.** Onset of symptoms is less abrupt (usually during 24 hours) and prognosis is better for patients with meningococcal meningitis than for patients with meningococcemia without clinical signs of meningitis.*
3. ***Meningococcal septicemia***
    a. ***lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28% to 77% of patients, but a macular or maculopapular rash may occur and be mistaken for a variety of viral exanthems.***
    b. *Purpura fulminans → DIC*
    c. *Shock results from both intravascular volume loss and congestive heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.*
4. ***Fever and non-blanching rash***
    a. *"Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a non blanching rash and no other specific*

findings. If they are untreated, meningitis or fulminant septicemia and shock can develop.

5. ***Chronic meningococcemia - rare < 2%***
    a. *fever, rash, and arthritis in conjunction with a positive blood culture for N. meningitidis.*

[17] Describe the management of suspected meningococcemia

Lab proven:

- If occult bacteremia → management plan determined by patient's signs and symptoms. If asymptomatic consider VERY close observation; perhaps repeat cultures
    - If any symptoms consider empiric treatment with oral agents and followup.

In suspected cases:

- ***Respiratory isolation!***
- ***Fulminant meningococcemia: airway management, IV fluid resuscitation, and vasopressors***
    - *Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities.*
    - *Fresh frozen plasma should be considered for patients with bleeding complications.*
- ***The role of steroids for the treatment of meningococcemia without meningitis remains controversial.***
    - *We believe that patients with persistent shock despite vigorous fluid resuscitation and vasopressor therapy should receive glucocorticoid therapy and adrenal function testing.*
    - **The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children but not for neonates.**
    - **Corticosteroid administration before antibiotic administration decreases long-term neurologic sequelae in adults and children.** There is also a mild decrease in mortality. Although these benefits are not seen in patients with meningococcal meningitis, the organism is typically not identified when steroids are initiated. Dexamethasone (0.4 to 0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. **The first dose should be given before the first dose of antibiotics if possible.**
- **Ceftriaxone** (100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and **cefotaxime** (100 mg/kg/day IV in divided doses every 6 hours, up to a maximum of 12 g) are appropriate initial antibiotics as well. **The cephalosporins are safe and have rapid onset of action and excellent coverage for S. pneumoniae and H. influenzae.**

[18] Which patients should receive prophylaxis for N. meningitidis? What is the prophylaxis?

- ***Close patient contacts*** *(household, nursery schools, daycare centers, military recruits, college dormitories, teammates) should receive antibiotic prophylaxis.*
- ***Intimate contacts***
- ***health care workers with intimate exposure*** *(eg, mouth-to-mouth resuscitation, intubation, or suctioning) should receive :*

Options:

- **Rifampin PO x 4 doses**
  - *10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for neonates is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining.*
- **Ceftriaxone IM (pregnancy; patients who will not take rifampin)**
  - *IM ceftriaxone (125 mg for children younger than 15 years old and 250 mg for those older than 12 years old) is effective and is an alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured.*
- **Ciprofloxacin 500 mg PO x 1 dose (for adults)**

[19] What are the risk factors for toxic shock syndrome?

TSS is a ***toxin-mediated systemic inflammatory response syndrome*** *that was first described in 1978 in a series of seven children 8 to 17 years old who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock.* **S. aureus was the culprit: this organism is NOT invasive and produces the TSS-toxin 1.**

Nowadays there are Strep TSS* and Staph. TSS cases.** ***Streptococcal TSS is caused by invasive infection with toxigenic strains of group A streptococcus.*** ***The effects of various exotoxins produced by S. aureus and group A streptococcus cause the shock and multiorgan dysfunction associated with TSS. S. aureus produces TSST-1.*

**Group A streptococcus produces streptococcal pyrogenic exotoxins A and B. These exotoxins are absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and to release cytokines, tumor necrosis factor alpha (TNF-α), and interleukins at a rate and magnitude many fold greater than with the normal antigen presentation, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease.*

Anything that puts you at risk for developing Staph. Aureus infections!

- Orifices packed with foreign bodies, concurrent infections, comorbidities

- *Non-menstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza associated).*

Risk Factors for Toxic Shock Syndrome (9th Edition Box 121.8)

- Use of superabsorbent tampons
- Postoperative wound infections
- Post partum period
- Nasal packing
- Cancer
- Common bacterial infections
- Ethanol abuse
- Infection with Influenza A virus
- Infection with varicella virus
- Diabetes mellitus
- HIV
- Chronic cardiac disease
- Chronic pulmonary disease
- NSAID use

[20] List criteria for toxic shock syndrome and describe management

these case definitions are not "foolproof or specific"

Probable TSS:

- Labs/cultures -ve and ⅘ of the clinical criteria

Confirmed TSS:

- Labs/cultures -ve and 5/5 of the clinical criteria present

Clinical criteria:

- High fever
- Diffuse Rash
- Desquamation
- Hypotension
- >3 systems involved.

Lab criteria:

a. Body cultures -ve (except bloods may show staph. aureus)
b. Rise in titre to RMSF, rubeola, leptospirosis

Management:

- Resuscitation!
  - Often large volumes needed for to combat distributive shock
  - 10-15 L/day!
- Airway management and oxygenation
- Source control / culture:

- *The source of bacteria, such as tampons, nasal packs, and other foreign bodies, should be removed. Prompt surgical consultation should be obtained to debride wounds.*
- Empiric antibiotics:
  - *We recommend clindamycin as a first-line agent.*
- Clindamycin has four benefits, it is:
  - *A potent suppressor of bacterial toxin synthesis;*
  - *It also facilitates phagocytosis of streptococci by inhibiting M protein synthesis,*
  - *Decreases monocyte synthesis of cytokines*
  - *Has a longer postantibiotic effect than the β-lactams.*
  - *The dose is 600 to 900 mg IV every 8 hours. (The pediatric dose is 20-40 mg/kg/day divided every 6 to 8 hours.)*
- Consider IVIG
- For patients with pulmonary edema, or requiring intubation
- Generally no steroids:
  - Unless refractory hypotension and adrenal insufficient
- Consider early hemodialysis to remove pre-formed toxins

[21] Compare staph and strep toxic shock syndrome

TSS should be considered in patients who present with fever, rash, hypotension, and evidence of end-organ damage, such as respiratory failure or altered mental status.

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

Comparison of Staphylococcal and Streptococcal Toxic Shock Syndrom (9th Edition 121.7)

Feature	**Staphylococcal**	**Streptococcal**
Age	15-35	20-50
Sex	Women>Men	Either
Severe Pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal Failure	Common	Common
Bacteremia	Low	60%
Tissue Necrosis	Rare	Common
Predisposing Factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality Rate	<3%	30-70%

Wisecracks

[1] What is on the differential diagnosis for respiratory diphtheria?

Differential Diagnosis of Respiratory Diphtheria (9th Edition Box 121.1)

- Strep pharyngitis
- Viral pharyngitis (EBC, adenovirus, HSV)
- Tonsillitis
- Vincent's Angina
- Acute epiglottitis
- Mononucleosis
- Laryngitis
- Bronchitis
- Tracheitis
- Candida thrush
- Rhinitis

[2] List 6 features of a high risk tetanus wound

Wounds contaminated with:

- Dirt
- Feces
- Soil
- Saliva

Types of wounds:

- OLD > 6 hrs
- DEEP > 1 cm
- Puncture
- Avulsions
- Missiles
- Crush
- BURNS

[3] List 8 causes of a non-blanching rash

Infectious:

- N. meningococcemia
- S. pneumococcemia
- Viral exanthems
- Rocky Mountain spotted fever
- Typhus
- Typhoid fever
- Endocarditis
- Toxic shock syndrome (TSS)
- Acute rheumatic fever
- Dengue fever

Non-infectious

- Drug reactions

- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Vasculitis syndromes (polyarteritis nodosa and Henoch-Schönlein purpura)

[4] What type of streptococcal infection occurs in patients with a recent splenectomy?

Streptococcus pneumoniae - can cause a septic syndrome, or localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.

The big one we worry about: <u>Adults and children with functional or anatomic asplenia may have fulminant pneumococcemia, called overwhelming postsplenectomy infection (OPSI), characterized by septic shock, adrenal hemorrhage, and DIC.</u>

[5] Which vaccines are used to prevent S. pneumoniae infections?

- Common vaccines:
    - Prevnar 13 in Canada
    - PCV 7
    - PCV 13 in USA
    - PPSV23 in USA

See tables 121.4-6 for people that should be vaccinated. But a few general categories:

- Adults / children with chronic heart/lung/liver disease, diabetes, alcoholism, smoking, cochlear implants, CSF leaks
- Acquired asplenia
- Immunocompromised
- Steroid use

In patients with pneumococcal infections, antibodies specific to the capsule serotype develop within several days of onset of infection. This response occurs approximately 30 days after a patient receives the pneumococcal vaccine. Patients who demonstrate substantial host resistance are able to develop active immunity, and some children can spontaneously clear culture-proven pneumococcemia.

****Approximately 50% of IPD in children with comorbidities is caused by serotypes not included in either the 13-valent or 23-valent vaccine.****

Other preventive measures for pneumococcemia include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.

[6] Which bacterial infections are patients with (functional) asplenia at risk for?

The large population with functional asplenia are those with sickle cell disease/other hemoglobinopathies. They are at risk for:

- **Strep. Pneumoniae**
- **Neisseria meningitidis**

[7] Which serotypes of N. meningitidis cause disease? Which one is not covered by the meningococcal vaccine?

Humans are the only reservoir for N. meningitidis.

- Of the more than 13 serogroups, groups A, B, C, Y, and W-135 cause most of the infections.
- More than half of the cases in infants are caused by **serogroup B, for which there is no effective vaccine**. Serogroups C, Y, and W-135 cause 75% of meningococcal disease in patients older than 11 years old.
- Although grouping is important for tracking of the disease, all groups are capable of causing the same spectrum of clinical disease.