35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Kitchen Sink: Syndromes Not Covered Elsewhere

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Session plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

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Question 1

- A 51-year old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive athralgias, abdominal pain, diarrhea, weight loss, and low grade fevers.
- Work up thus far:

Negative blood cultures x 2
Negative Rheumatoid factor
Normal metabolic panels
Mild normocytic anemia

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Question 1

- Which of the following tests will most likely yield the diagnosis?

a) Anti-streptolysin O Antibody
b) Anti-nuclear Antibody
c) Stool ova and parasite
d) Duodenal biopsy

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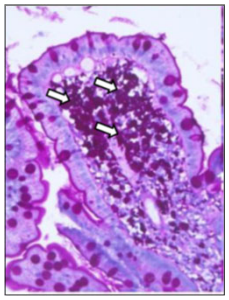
Whipple's disease

- Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle aged, Caucasian men
- Diagnosis often delayed due to indolent clinical presentation
- Most commonly diagnosed via duodenal biopsy, stained with PAS
- PCR increasingly used



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529–555. https://doi.org/10.1128/CMR.00033-16.

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Whipple's: clinical presentations

TABLE 1 Clinical manifestations of *Tropheryma whipplei* infection[a]

Classic Whipple's disease (% incidence)	Chronic localized infections[b]	Acute infections[b]
Weight loss (79–99)	Endocarditis	Gastroenteritis
Gastroenteritis (63–85)	Encephalitis	Pneumonia
Abdominal pain (23–60)		Bacteremia
Arthritis (20–83)		
Neurological symptoms (6–63)		

[a]See text for references.
[b]Values for relative incidence are unknown.

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555. https://doi.org/10.1128/CMR.00033-16.

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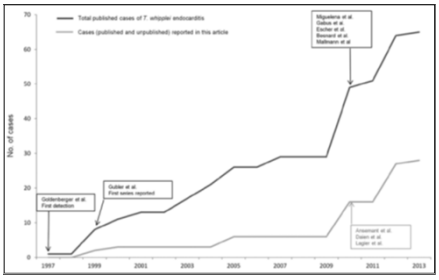
Whipple's endocarditis



- Increasingly recognized (PCR on heart valves)
- Analysis of > 1000 cardiac valves in Germany concluded that *T. whipplei* was the most common pathogen associated with *culture negative endocarditis*

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei endocarditis. Emerg Infect Dis. 2013;19(11):1721-1730. doi:10.3201/eid1911.121356
Geissdörfer W, Moos V, Moter A, et al. High frequency of Tropheryma whipplei in culture-negative endocarditis. *J Clin Microbiol*. 2012;50(2):216-222. doi:10.1128/JCM.05531-11

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Whipple's: treatment

No gold standard

Options:

- Ceftriaxone or meropenem plus prolonged co-trimoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555. https://doi.org/10.1128/CMR.00033-16
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- Cause: *Trophyrema Whipplei*
- Epidemiology: middle aged, Caucasian males
- Clinical presentation: classic – ***arthralgia, diarrhea, weight loss***
- Localized infection including ***endocarditis*** (increasingly recognized)
- Diagnosis with ***duodenal biopsy*** (***PAS*** stain; foamy macrophages) or ***PCR*** of infected tissue
- Prolonged treatment needed to prevent relapse

Whipple's disease

Take home points

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Question 2

- A 20 year-old female school teacher presents to her primary care doctor with fever and pain / swelling in multiple joints (knees, elbows and wrists). The pain seems to move from joint to joint.
- She is generally healthy, but reports being ill ~3 weeks prior with sore throat and headache which resolved without specific treatment. She has no skin rashes and no lymphadenopathy.
- She denies travel.
- She is sexually active with one male partner, using barrier protection (condoms)
- Labs are notable for elevated ESR and CRP and + ASO titer; pregnancy and HIV tests (4th generation Ag/Ab) are negative.

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Question 2

- Which of the following is the best explanation for her symptoms?

a. Acute HIV infection
b. Mononucleosis due to Epstein Barr Virus
c. Acute rheumatic fever
d. Lemierre's syndrome

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REVISED JONES CRITERIA

For patients with evidence of prior GAS infection*,
Acute Rheumatic fever =
2 MAJOR
OR
1 MAJOR plus 2 MINOR

Major	Minor
Arthritis (usually migratory polyarthritis)	Arthralgia
Carditis (clinical or subclinical)	Fever
Chorea	Elevated ESR or CRP
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

*e.g. rapid strep test; culture; anti-streptolysin-O titer (ASO)

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a

Question 3

- A 34 year old male with a history of injection drug use presents to the emergency room with a 2 day history of progressive muscle weakness and blurry vision. He also notices some difficulty swallowing.
- On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

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Question 3

- Which of the following treatment(s) are recommended?

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

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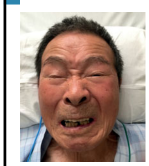
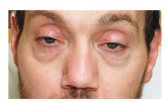
Explanation



Tetanus: sardonic smile

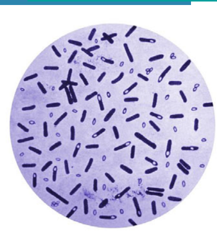


Botulism: ptosis

- Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)
- Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)
- Tetanus antitoxin – for tetanus (rigid paralysis)
- Botulinum antitoxin – for botulism

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltex
https://www.nejm.org/doi/pdf/10.1056%2FNEJMicm1003352

Botulism



https://phil.cdc.gov/details.aspx?pid=2107

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Symptoms due to TOXINS which prevent release of acetylcholine in neuromuscular junction
- Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)
- DX: culture or detection of toxin

**other neurotoxin producing species of Clostridium: C. butyricum, or C. baratii*

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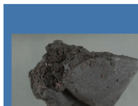
Botulism

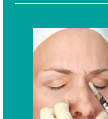
Foodborne

Infant



Wound (black-tar heroin)

Iatrogenic



Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR Morb Mortal Wkly Rep 2019
https://www.cdc.gov/botulism/
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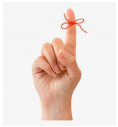
Botulism treatment

Supportive care	Antitoxin
• Ventilatory support for respiratory compromise • Wound debridement	• Botulinum anti-toxin (adults) Or • Botulinum immune globulin (infants)

https://www.cdc.gov/botulism/
Principles and Practice of Infectious Diseases, 9th ed.

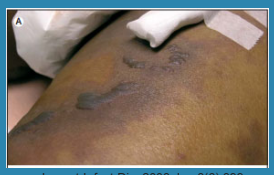


- Cause: *Clostridium botulinum* toxin impedes acetylcholine release from neuromuscular junction
- Epidemiology: food (home canned veggies / fruits / fish); infant (honey); wound (black-tar heroin); iatrogenic (rare)
- Clinical presentation: *descending flaccid paralysis*, starting with *cranial nerves* (ptosis, blurred vision, slurred speech)
- Diagnosis: clinical; confirmed by culture or ID of toxin
- Treatment: *antitoxin* plus supportive care; wound debridement

Botulism

Take home points

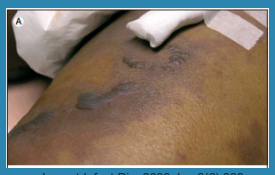
Question 4



Lancet Infect Dis. 2008 Jun;8(6):399.

- A 44 year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic. Skin exam is as pictured.

Question 4

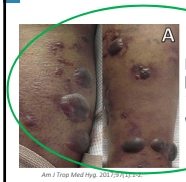


Lancet Infect Dis. 2008 Jun;8(6):399.

- The patient's clinical syndrome was most likely caused by which of the following exposures?

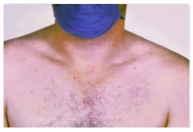
A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

Explanation



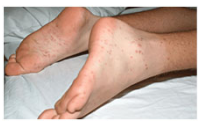
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2017;97(1):1-2.



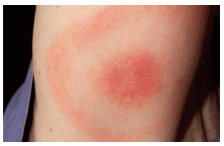
Rose spots from *Salmonella typhi*

https://www.cdc.gov/vaccines/vpd/typhoid/public/photos.html



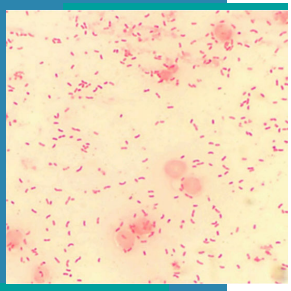
Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/lyme/signs_symptoms/rashes.html



Vibrio vulnificus

- Gram-negative, curved bacillus
- Halophilic (salt loving) – *brackish water*
- Cause: *consumption of raw seafood (oysters) or contamination of open wound*
- At risk: *liver disease* (cirrhosis); iron overload; renal disease; immunosuppression
- High mortality

Beatty NL, Marquez J, Al Mukaiel M. Skin Manifestations of Primary *Vibrio vulnificus* Septicemia. *Am J Trop Med Hyg.* 2017;97(1):1-2.

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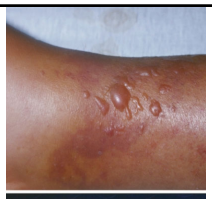
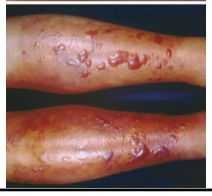
Clinical presentation and treatment





- Abrupt onset
- Fever, hypotension
- Rapidly progressive skin lesions: erythema → ***hemorrhagic bullae*** → necrosis
- Bacteremia common
- Treatment:
  - Fluoroquinolone plus 3rd generation cephaloporin
  - Debridement

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- Epidemiology: consumption of raw seafood; contamination of wound (organism lives in warm, brackish water)
- At risk: liver disease, iron overload (also renal; immune suppression)
- Clinical presentation: rapidly progressive skin lesions with *hemorrhagic bullae; fever, hypotension, sepsis*
- Diagnosis: clinical; blood cultures usually positive
- Treatment: fluoroquinolone plus 3rd generation cephalosporin; debridement

Vibrio vulnificus

Take home points

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Question 5

- A 23-year-old otherwise healthy college student presents to the university clinic with a non-productive, intermittent cough for 3 weeks. She describes spells during which she coughs repeatedly for several minutes. On two occasions she vomited after coughing.
- She reports episodes of sweating but has had no fever or other constitutional symptoms.
- She has tried several cough medicines, but nothing seems to help. She knows several other students who have been "coughing for weeks," and says the showers in her dorm are "covered with mold."

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Question 5

- She is afebrile and has a completely normal exam.
- Her CBC is normal; chest x-ray is normal.
- Specific nasopharyngeal culture for *Bordetella pertussis* is negative.

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Question 5

- Which one of the following is the most likely cause of her illness?

A. Bordetella pertussis
B. Chlamydophila pneumoniae
C. Respiratory syncytial virus
D. Mycoplasma pneumoniae

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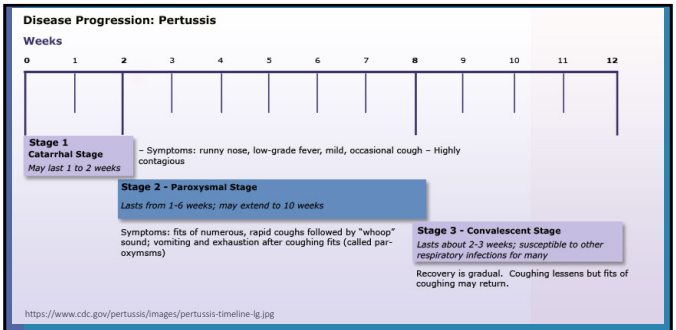

Pertussis: clinical stages

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Pertussis diagnosis – no perfect test

Clinical case criteria (in absence of alternate dx):

- cough illness lasting ≥2 weeks, with at least one of the following:
  - Paroxysms of coughing; **OR**
  - Inspiratory whoop; **OR**
  - Post-tussive vomiting; **OR**
  - Apnea (with or without cyanosis)

Test	*Sensitivity (%)*	*Specificity (%)*	*Advantages*	*Disadvantages*
Culture	15	100	Specific; confirms diagnosis; most useful in first two weeks	Fastidious growth requirements; delayed results; inaccurate in late stages of disease
Polymerase chain reaction	45	85	Confirms diagnosis; rapid results; most accurate in early stages of disease	Sensitivity declines in late stages of disease
Serology	65	89	Accurate in late stages of disease	Cannot confirm acute infection (can be positive because of past infection or immunization); testing method not standardized

https://www.cdc.gov/media/conditions/pertussis/case-definition/2020/
Am Fam Physician. 2013 Oct 15;88(8):507-514.

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Treatment and post exposure prophylaxis

- TREAT with macrolide (e.g. azithromycin) if within 3 weeks of onset
- Treat within 6 weeks of onset for infants or pregnant women

- POST EXPOSURE PROPHYLAXIS (PEP) given to household members and contacts at risk of severe infection (within 3 weeks of exposure)

https://www.cdc.gov/pertussis/

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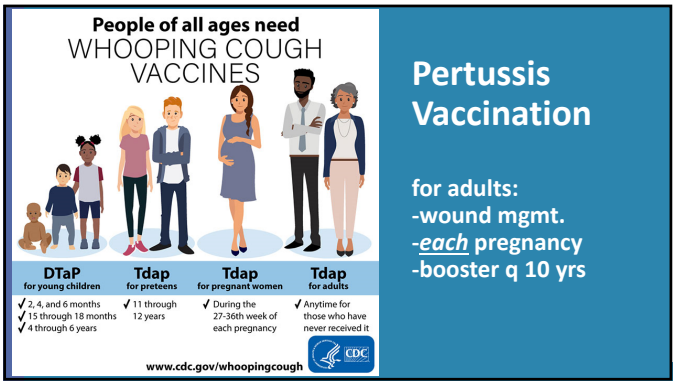
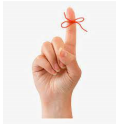


Pertussis Vaccination

for adults:
-wound mgmt.
-*each* pregnancy
-booster q 10 yrs



- Epidemiology: in past infants / kids; now young adults (waning immunity?)
- *Severe disease: infants, pregnant women*, lung disease
- Clinical presentation: *cough* lasting 2+ weeks plus *paroxysmal cough*, *inspiratory whoop*, *post-tussive vomiting or apnea*
  Stages:
  - *catarrhal*: URI
  - *paroxysmal*: coughing fits / whoop
  - *convalescent*: gradual lessening of cough
- Diagnosis: clinical; culture (insensitive), PCR, serology (late)
- Treat with *macrolide within 3 wks* of onset
- *PEP* for household contacts / at risk of severe dz *within 3 wks* of exposure

Bordatella pertussis

Take home points

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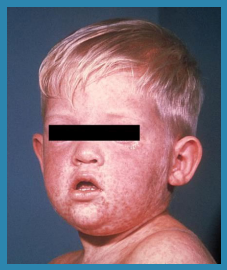
Question 6



- A 25-month old child is brought to the emergency room for *fever, rash and fussiness*. The rash *started on the face and spread to trunk* and extremities within 1-2 days.
- 10 days ago, the family returned to the United States following a 1-month trip to Tanzania (where the parents conduct research as university professors).
- The child's 4-year old sibling is also ill, with cough and watery eyes, but does not have a rash.
- The parents do not believe in vaccination for their children due to fear of adverse effects (autism).

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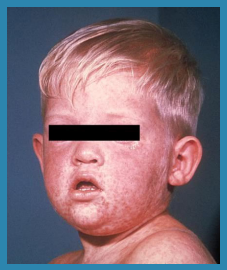
Question 6



- Which of the following could have prevented the development of the patient's illness?

A. Varicella zoster virus vaccination
B. Measles, mumps, rubella vaccination
C. Mefloquine prophylaxis
D. Influenza vaccination

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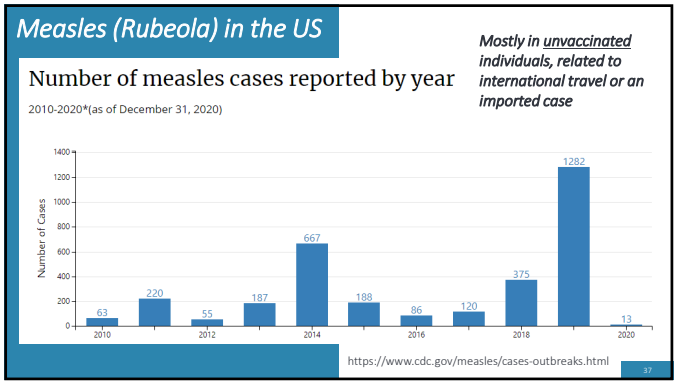

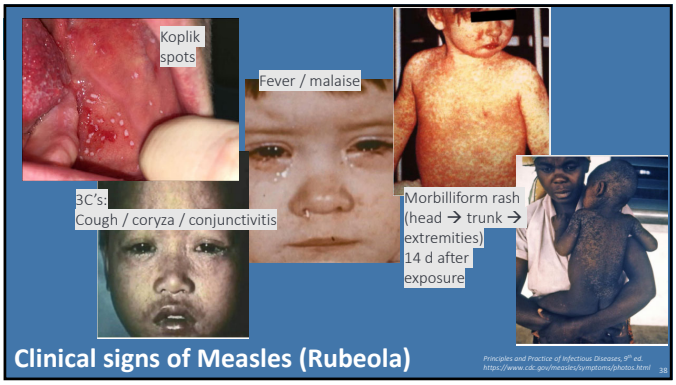

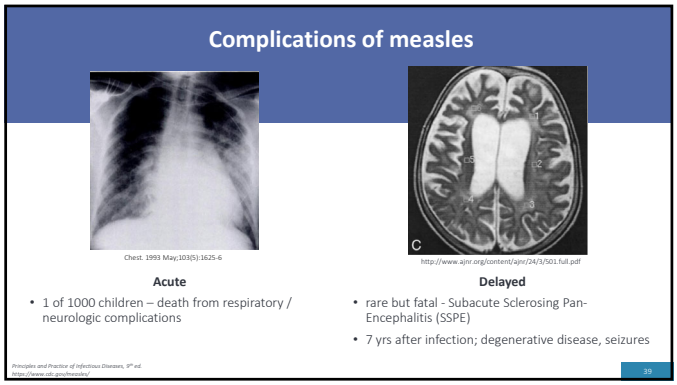

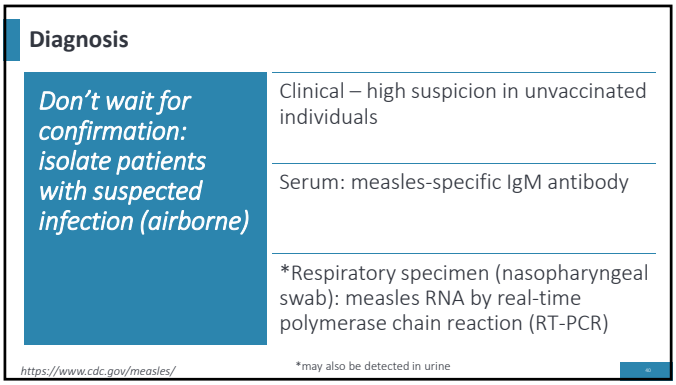

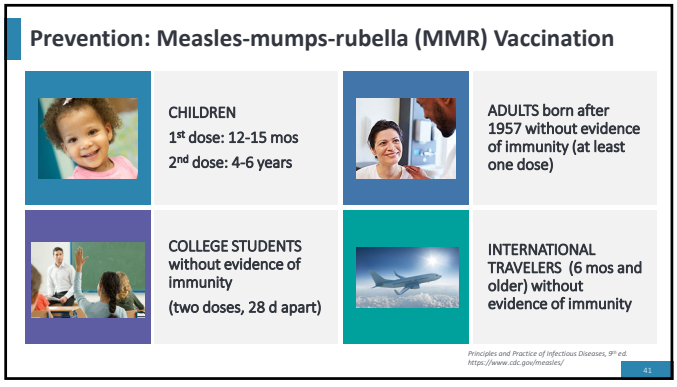

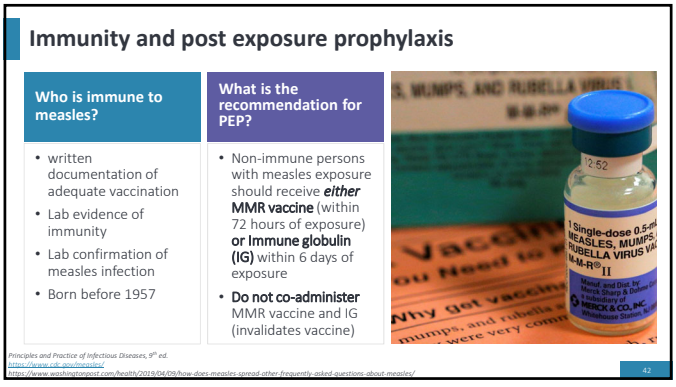

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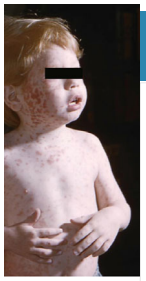
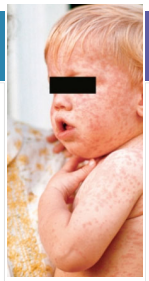
"German measles" (Rubella) vs. Measles (Rubeola)



German Measles (Rubella)

- Caused by RNA virus of *Togaviridae* family
- Often **mild** / asymptomatic
- Viral prodrome → maculopapular rash which spreads from head to extremities, +/- **arthritis**
- Transmitted in utero (**congenital** rubella): deafness, cataracts, glaucoma, heart disease, cognitive defects



Measles (Rubeola)

- Caused by RNA virus of Paromyxovirus family
- **Severe** disease with complications including death
- Viral prodrome → **cough / coryza / conjunctivitis, fever, Koplik spots** → maculopapular rash which spreads from head to extremities

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- Cause: Rubeola (RNA virus of Paramyxovirus family)
- Epidemiology: worldwide distribution; *in US, seen in unvaccinated persons due to travel or exposure to imported case*
- Clinical presentation: three C's (*cough, coryza, conjunctivitis*), Koplik spots, morbilliform rash spreading from head → trunk → extremities (14 d after exposure)
- Diagnosis: clinical; serum IgM; PCR on respiratory swab (or urine)
- Treatment: supportive care, Vit A for severe cases in children
- Post-exposure ppx: vaccination (within 72 h) or IG (within 6 days)

Measles (Rubeola)

Take home points

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Question 6

- A 19 year old male, previously healthy, complained of abdominal pain and nausea after eating leftovers from a restaurant.
- Within several hours, his symptom progressed to include weakness, headache and neck stiffness.
- Five hours later, he had developed purplish skin discolorations and a friend brought him to the emergency room for evaluation.

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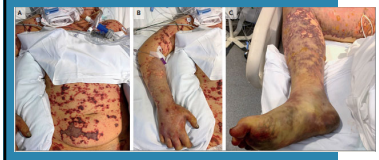
Question 6



- Upon arrival to the hospital, he was noted to be febrile (40.4 degrees Celsius), tachycardic (HR 166), and tachypneic (RR 28), with BP 120/53, and with rapidly progressive reticular, purpuric rash.
- Within 24 hours, gram stain of blood cultures showed gram-negative diplococci.

N Engl J Med. 2021 Mar 11;384(10):953-963.

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Question 6

- Which of the following is the most likely diagnosis?

A. Meningococcemia
B. Disseminated *Streptococcus pneumonia*
C. Disseminated gonorrhea
D. Secondary syphilis

N Engl J Med. 2021 Mar 11;384(10):953-963.

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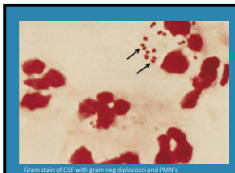
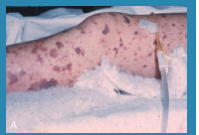


Gram stain of CSF with gram neg diplococci and PMN's
https://www.cdc.gov/meningitis/lab-manual/chp106-culture-id.html



Principles and Practice of Infectious Diseases, 9th ed

Invasive meningococcal disease (*N. meningitidis*)

- Main manifestations:
  - *meningococcemia*
  - *acute meningitis*
- **Petechial or purpuric rash** in 40-80% of meningococcemia cases
- Fulminant disease **can progress to death within hours**
- Treat with 3rd generation cephalosporin (**ceftriaxone or cefotaxime**) and supportive care

Principles and Practice of Infectious Diseases, 9th ed.
https://www.cdc.gov/meningococcal/clinical-info.html

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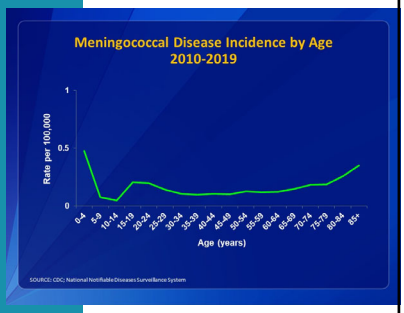
35 – Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

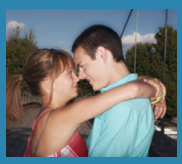
Epidemiology

In the US, infants, young adults, and adults >80 years of age have the highest rates of meningococcal disease



https://www.cdc.gov/meningococcal/surveillance/index.html

Transmission and risk factors



https://www.cdc.gov/meningococcal/about/causes-transmission.html

Transmission: person to person (respiratory droplets, oral secretions) from asymptomatic carriage or invasive disease

HOST factors: asplenia; terminal complement deficiencies (native or acquired, such as use of complement inhibitors: eculizumab or ravulizumab)

ENVIRONMENTAL factors: crowded conditions (dorms, military barracks; Hajj and Umrah pilgrimages); daycare / preschool facilities; microbiologists

ANTIBIOTIC	CONSIDERATIONS
Rifampin	Drug interactions
Ceftriaxone	Recommended in pregnancy
Ciprofloxacin	Not generally recommended for persons < 18 yrs
Azithromycin	Limited data

Chemoprophylaxis for:

- Household members
- Childcare center contacts
- Anyone directly exposed to an infected person's oral secretions (kissing; mouth to mouth resuscitation; intubation) within 7 d before symptom onset
- HCW with exposure to respiratory secretions of infected patient

https://www.cdc.gov/vaccines/pubs/pink-book/mening.html

BOX 1. Meningococcal vaccination recommendations — Advisory Committee on Immunization Practices, United States, 2020

ACIP recommends MenACWY vaccination for the following groups:

- Routine vaccination for adolescents aged 11 or 12 years, with a booster dose at age 16 years.
- Routine vaccination of persons aged ≥2 months at increased risk for meningococcal disease (dosing schedule varies by age and indication, and interval for booster dose varies by age at time of previous vaccination):
  - Persons with certain medical conditions including anatomic or functional asplenia, complement component deficiencies (e.g., C3, C5-C9, properdin, factor H, or factor D), complement inhibitor (e.g., eculizumab [Soliris] or ravulizumab [Ultomiris]) use, or human immunodeficiency virus infection.
  - Microbiologists with routine exposure to *Neisseria meningitidis* isolates.
  - Persons at increased risk during an outbreak (e.g., in community or organizational settings, and among men who have sex with men [MSM]).
  - Persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
  - Unvaccinated or undervaccinated first-year college students living in residence halls.
  - Military recruits.
- Booster doses for previously vaccinated persons who become or remain at increased risk.

ACIP recommends MenB vaccination for the following groups:

- Routine vaccination of persons aged ≥10 years at increased risk for meningococcal disease (dosing schedule varies by vaccine brand; boosters should be administered at 1 year after primary series completion, then every 2–3 years thereafter):
  - Persons with certain medical conditions, such as anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use.
  - Microbiologists with routine exposure to *N. meningitidis* isolates.
  - Persons at increased risk during an outbreak (e.g., in community or organizational settings, and among MSM).
- Vaccination of adolescents and young adults aged 16–23 years with a 2-dose MenB series on the basis of shared clinical decision-making. The preferred age for MenB vaccination is 16–18 years. Booster doses are not recommended unless the person becomes at increased risk for meningococcal disease.
- Booster doses for previously vaccinated persons who become or remain at increased risk.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; MenACWY = quadrivalent (serogroups A, C, W, Y) meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine.

Immunization

- Recommendations revised in 2020

Summary:

- MenACWY for all adolescents plus persons at increased risk due to host or environmental factors
- MenB for those at increased risk due to host or environmental factors; shared decision making for others

https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6909a1-H.pdf

- Epidemiology:
  - Host (*asplenia*; *complement deficiencies*; *complement inhibitors* – eculizumab or ravulizumab)
  - Environmental (crowded conditions – dorms, barracks, day care)
  - Person to person transmission from oral / respiratory droplets
- Clinical presentation: *acute meningitis* or *meningococcemia*; rapidly progressive, *petechial / purpural rash*
- Treatment: ceftriaxone or cefotaxime; immunize for prevention and during outbreaks
- Chemoprophylaxis for close contacts within 7 d of exposure: *rifampin*, *ceftriaxone* (pregnancy), or *ciprofloxacin* (adults)

Invasive meningococcal disease (*Neisseria meningitidis*)

Take home points

Kitchen Sink summary

Whipple's:

- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- or PCR of tissue (heart valve for endocarditis)

Acute Rheumatic fever:

- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for10 years or to age 40 if carditis + residual valvular disease

35 – Kitchen Sink: Syndromes Not Covered Elsewhere

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