Gram Negative Bacteria in clinical medicine

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Objectives

Define the molecular structure of Gram-negative organisms
Highlight differences between Gram-negatives and Gram-positives
Discuss the most important clinically-relevant Gram-negative bacteria
Review treatments for Gram-negatives
Illustrate clinical scenarios involving Gram-negative infection

(Won’t discuss much about laboratory classification, eg oxidase test, lactose fermentation, etc. If you run a lab, you will need to know this!)
You can approach thinking about causes of infections in two different ways.

One way is by organ system, e.g. pneumonia:

*Streptococcus pneumoniae, Klebsiella pneumoniae, Chlamydophila pneumoniae, Mycoplasma, Moraxella, E. coli, Staph aureus*, etc.

Advantage is that you can memorize various causes in a way that makes sense and not have to review every single organism in your head when you think about an infection, as there are dozens.

*But...could you miss an organism this way?*
You can approach thinking about causes of infections in two different ways

The second way is by organism, via categories, e.g.:

“Gut Gram-negatives, including *E. Coli*, *Klebsiella*, *Salmonella*, *Shigella*, *Enterobacter*, *Citrobacter*, *Serratia*”

Advantage here is that you can review in your head the major infectious organisms and *not miss an important microbe*

The point is you need to use *both* ways of thinking about infections in order to make sure your differential is complete

Only a computer can list all the manifestations of disease by organism, or all the infectious causes of a focal infection

But a human brain can do pretty well if you switch back and forth
The “ID Differential”

Non-infectious causes

Opportunistic (i.e. HIV)

"Routine"

Unusual organisms (e.g. Mycoplasma, prions)

Gram Positives

Gram Negatives

Anaerobes

Viruses

Fungi

Parasites & Protozoa

Other bacteria:
--Intracellular
--Acid Fast/Modified
--Spirochetes
What is a Gram stain?

Named after Dr. Gram (1884 paper)

Some bacteria take up crystal violet dye; some don’t

Some take up a counter-stain (safranin), but some don’t

That is, not all bacteria can be seen by Gram stain (e.g. Mycobacteria)
Structural differences

The differences in the cell wall lead to differing pathogenesis, as well as different targets for antimicrobial (and other) therapy.
Gram-negative rod

Gram-positive rod
Gram Negatives

Gram Negative Cocci
- Neisseria meningitidis
- Neisseria gonorrhoeae
- Moraxella

Gram Negative Bacilli
- Enterobacter*
- Vibrios (cholera)
- Campylobacter
- Salmonella*
- Shigella*
- Yersinia*
- Pseudomonas
- Stenotrophomonas
- Burkholderia
- Acinetobacter
- Haemophilus

*denotes members of Enterobacteriaceae family
Enterobacteriaceae: GI/GU organisms

*Citrobacter*
*Enterobacter*
*Eschericia* (eg *E. coli*)
*Klebsiella*
*Morganella*
*Proteus*
*Providencia*
*Salmonella*
*Shigella*
*Yersinia*

Cholecystitis/cholangitis
Diverticulitis
Abdominal perforation
Appendicitis (perforation)
Gut translocation
Diarrhea
UTIs, esp *E. coli*, *Morganella*, *Proteus*, *Providencia*
Bacteremia
Gram-negatives are exceptionally good at developing drug resistance.

“Transformation”

“Transduction”

“Conjugation”

- Efflux pumps
- Decreased uptake
- Inactivating enzymes
- Target overproduced
- Modified target
- Antibiotic
Options for treatment of Gram Negatives

PCNs (often not effective)
PCNs with beta-lactamases (Augmentin, ie amox-clav)
Piperacillin (ureidopenicillins)
3rd/4th gen cephalosporins (ceftriaxone, ceftazidime)
Carbapenems (meropenem)

Fluoroquinolones (ciprofloxacin)
Aminoglycosides (gentamicin)
Tetracyclines
Chloramphenicol
Sulfonamides (Septrin)
A 58 year-old man presents with acute cough, fever, and chills. The cough produces a thick, red sputum. Gram stain is shown.

Which is the most likely organism?

A. *Streptococcus pneumoniae*
B. *Providencia stuartii*
C. *Mycobacterium avium*
D. *Klebsiella pneumoniae*
E. *Mycoplasma pneumoniae*
Answer: *Klebsiella pneumoniae*

- Gram negative encapsulated organism
- “Currant jelly” sputum: localized tissue necrosis & tissue inflammation
- contrast with pneumococcus “rust colored” sputum
- ? May be more common in Africa than in Europe or US
CAP is most often **pneumococcus**, followed by everything else with lots of Gram-negatives (African epidemiology/distribution may be different)

https://www.ncbi.nlm.nih.gov/books/NBK519004/

A 22 year-old woman presents with dysuria, foul-smelling urine, chills, and pelvic pain x 48 hours.

Treated for UTIs at least six times over past 1-2 years. Can’t remember which abx given, been to different clinics & pharmacies.

Temp 100.7 F, HR 110, BP 120/78. Exam notable for mild/moderate tenderness on CVA percussion.

UA: 1.030, >100 WBCs, Leuk Est pos, nitrite pos, microscopy shown
Which of the following organisms are likely causes of her presentation?

A. *Staphylococcus saprophyticus*
B. *E. coli*
C. *Moraxella catarrhalis*
D. *Enterococcus faecium*
E. *Pasturella multocida*
Which of the following statements are true?

A. She requires short-course (ie, 3-day) treatment for UTI.
B. She is at low risk for sepsis secondary to bacteremia.
C. A fluoroquinolone such as cipro is the best choice to treat her.
D. Septrin would be contraindicated since it does not treat Gram-negatives.
E. This is a person for whom a urine culture with antibiotic susceptibilities would be very helpful in establishing proper treatment.
Recurrent UTIs

- *E. coli* accounts for ~80% of UTIs in women, ~70% in men
- Much more common in women however
- This patient has *pyelonephritis*, no cystitis (CVA tenderness)
- Will require prolonged abx as consequence
- At high risk of having drug resistance, most likely to FQs or Septrin since they are the most commonly prescribed UTI abx
- May require hospitalization
- *Minimum* five days therapy required, possibly longer

A 16 year-old male presents with sore L arm.

Onset early this morning. Woke out of sleep with pain; has gotten worse since then, now severe.

Noted playing with a dog who bit him yesterday.

Exam: HR 126, T 102.2, BP 110/68

Tremulous, diaphoretic, hand & forearm exquisitely tender, minimally swollen; streaking erythema across wrist & forearm
What is the *next* step in the patient’s management?

A. Consult surgery immediately.
B. Obtain echocardiogram to evaluate endocarditis.
C. Order CT of L upper extremity to evaluate for fluid collection.
D. Provide pain relief, await abx pending CBC.
E. Start empiric abx and admit for observation.
The following antibiotics are likely to be effective except:

A. Penicillin VK
B. Ampicillin
C. Clindamycin
D. Ciprofloxacin
E. Doxycycline
Animal bites and Gram-negatives

- Commonly associated with cat & dog bites
- *Pasturella multocida* seen in both
- Cat tooth = natural syringe
- *Bartonella* infections
- *Capnocytophaga* in dogs; encapsulated organism, issues with dogs & pts without spleens or partial spleens (eg Sickle Cell pts)

Bites are forms of injections— they move faster than “typical” cellulitis

Pain out of proportion to exam signals a surgical emergency

Immediate abx

PCNs most effective with *Pasturella*; most β-lactams

Clindamycin and erythromycin not likely to be effective

Don’t forget about rabies!
An 18 yo male presents with abdominal pain, fever and constipation x 72 hours

- Dry cough, non-productive
- Brought in by family
- Exam: HR 120, BP 116/68, T 103F
- Diffuse abd tenderness, mild, no rebound
- Neck supple

You consider typhoid fever in your differential. Which of the following is true?

A. A fluoroquinolone such as ciprofloxacin may be adequate tx
B. Ceftriaxone is always ineffective
C. Typhoid is unlikely because there is not a pulse-pressure dissociation
D. Hepatitis is not a complication
E. Typhoid is unlikely if there is not a “rose spot” rash
Typhoid fever

*Salmonella typhi* & *S. paratyphi*

Fecal-oral spread infection

HIV pts at 20- to 100-fold higher risk (all *Salmonella* spp. incl non-typhoidal)

Extra-intestinal manifestations (CNS, hepato- & splenomegalgy, bone/joint)

Widal test: good not great, have index of suspicion

Treat empirically while awaiting BCx

FQ resistance *may* be a problem in Liberia? (Research project!)

Cipro, chloramphenicol, ampicillin or amoxicillin, TMP/SMX, ceftriaxone, azithro all good empiric choices