Can we stay positive, please?

Case studies of Gram-positive bacterial antimicrobial resistance

APHL ID Lab Con

Mimi Precit, PhD, D(ABMM), M(ASCP)

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Disclosures

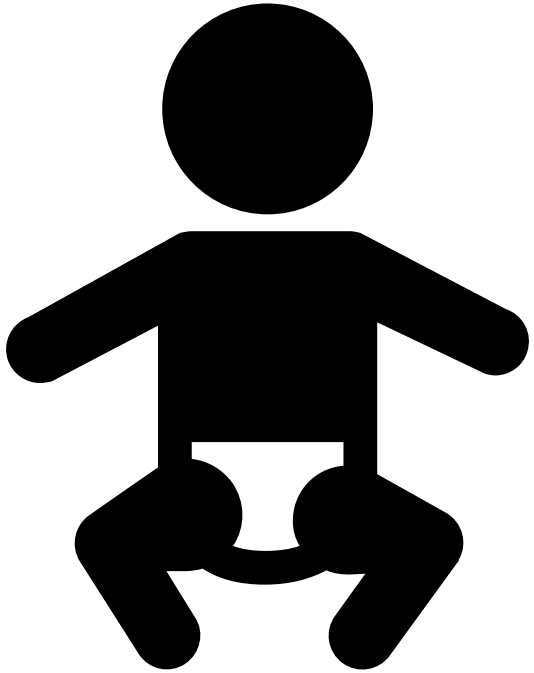
- None

Case 1: Positively Perplexed by PBPs

Clinical Presentation

Presentation:

- 3-week-old neonate
- Nasal congestion and cough
- Vomiting
- Reduced feeding



On exam:

- Alert
- Intercostal retractions
- Bilateral wheezing
- Clear nasal discharge
- Febrile at 38C

At birth:

- Uncomplicated vaginal birth

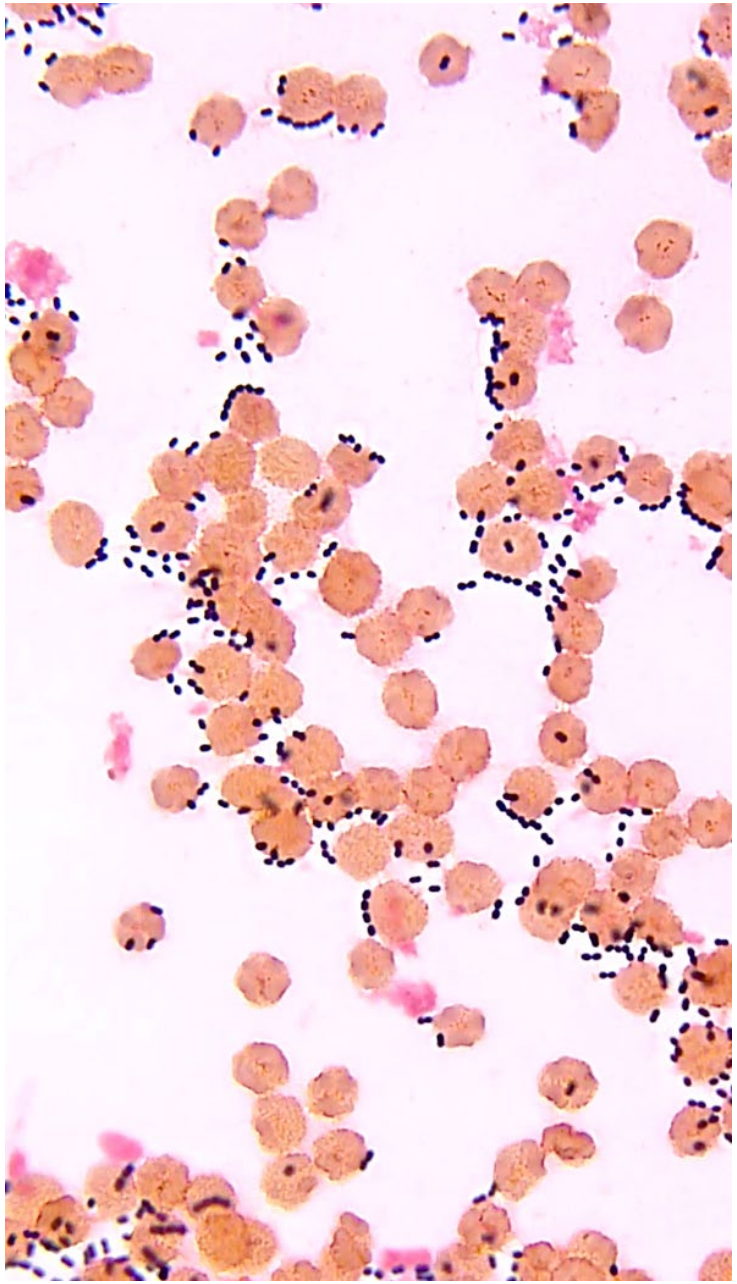
Microbiology studies ordered

- Molecular respiratory panel
  - No targets detected
- Cerebral spinal fluid (CSF) studies

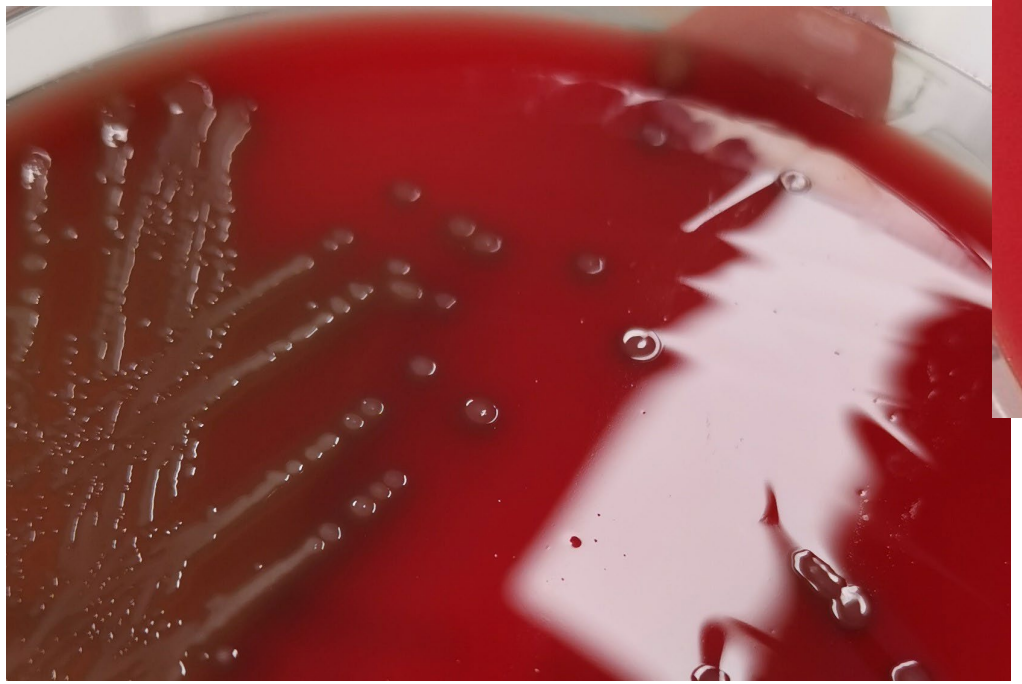
White blood cells	3 WBCs/mm^3	Normal
Glucose	45 mg/dl	Normal
Protein	58 mg/dl	Normal
Gram stain	No organisms seen	Unremarkable
Culture	No Growth	Unremarkable

- Blood cultures
  - Pediatric aerobic blood culture bottle flagged positive at 19 hours

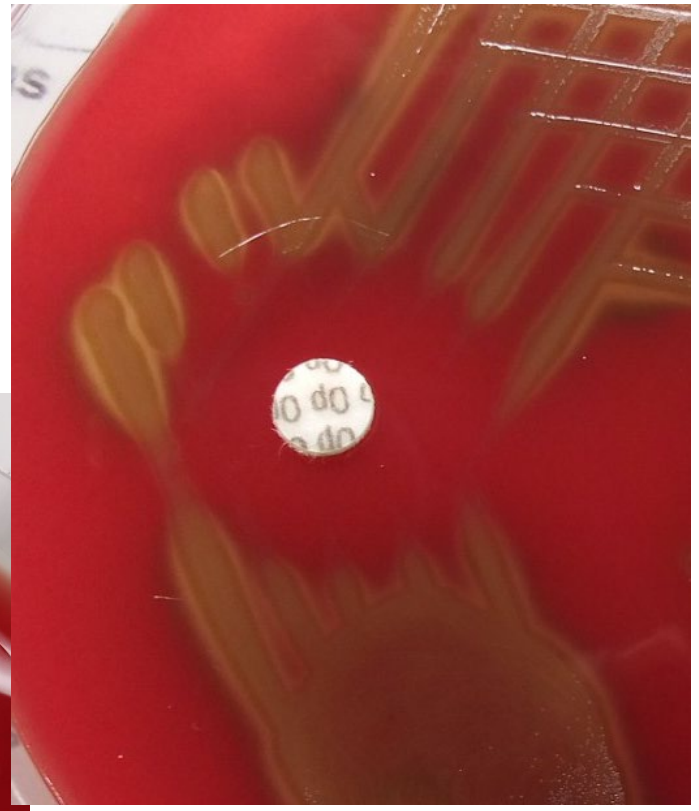
Blood culture results



Bottle Gram stain



Next day: subculture to blood agar grew the following organism



Based on the Gram-stain the tech also placed an optochin (P) disk, organism inhibition observed

Streptococcus pneumoniae

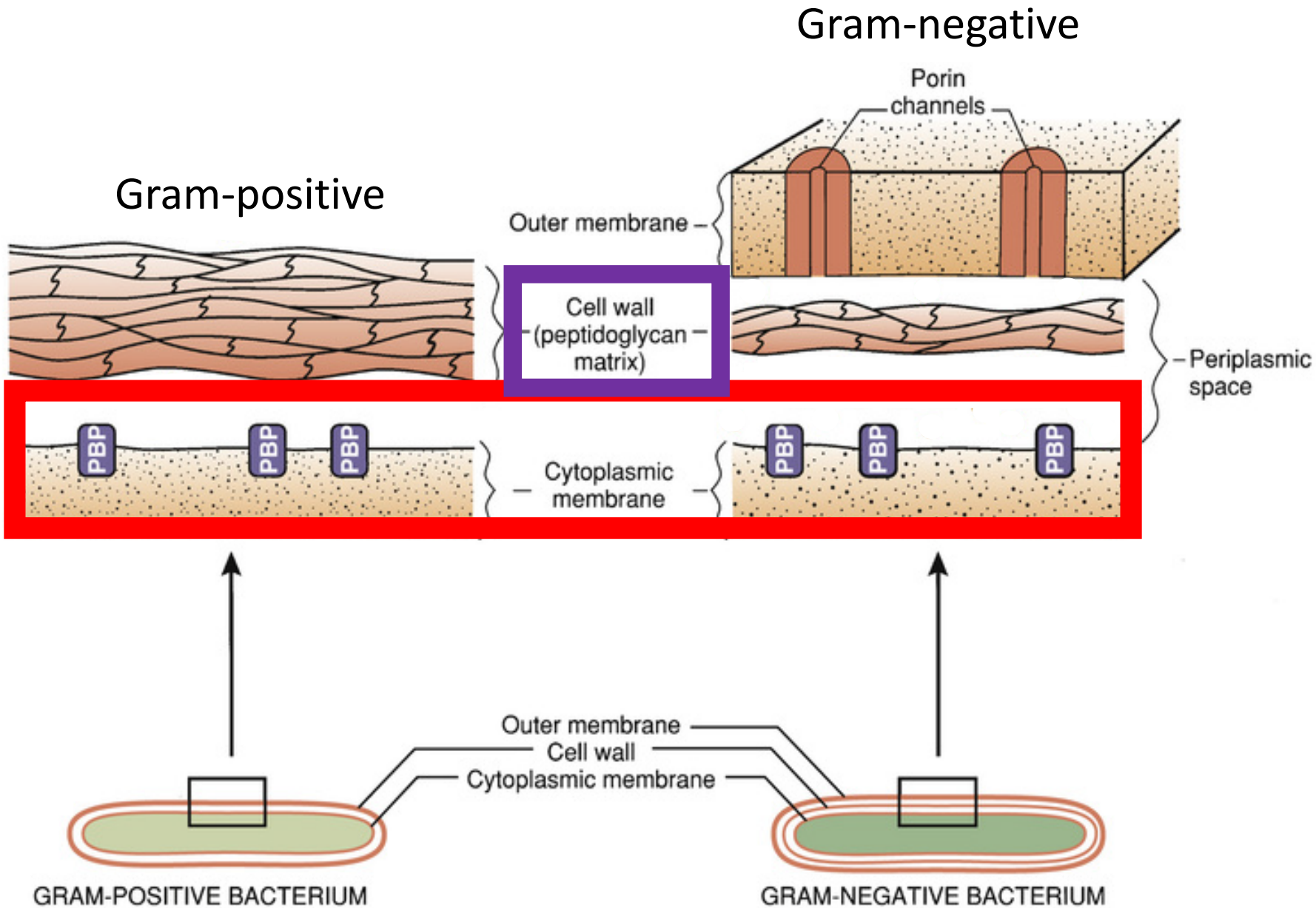
S. pneumoniae susceptibility results

Drug	Interpretation
Penicillin	Resistant
Ceftriaxone	Intermediate
Vancomycin	Susceptible
Levofloxacin	Susceptible

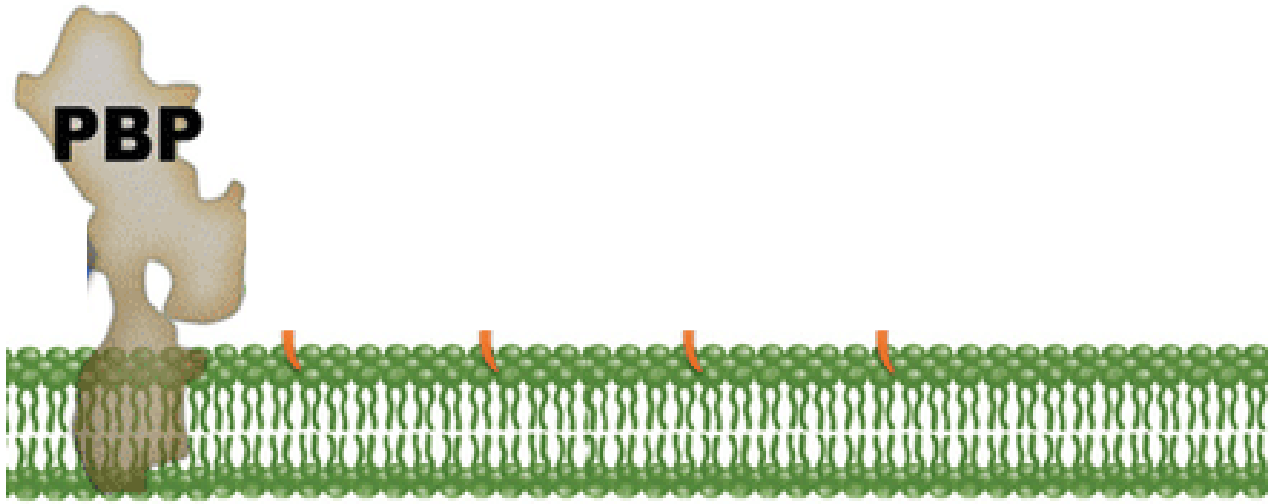
Patient was treated with vancomycin and recovered

In *S. pneumoniae*, primary mechanism(s) of beta-lactam resistance mediated by penicillin binding proteins (PBPs) NOT beta-lactamases

The ABC's of the PBPs



The ABC’s of the PBPs



- Classified into Class A, B, or C based on architecture and corresponding enzyme activity/domains
- Key enzymatic process: amino acid cross-linking through transpeptidase activity in final steps of peptidoglycan synthesis

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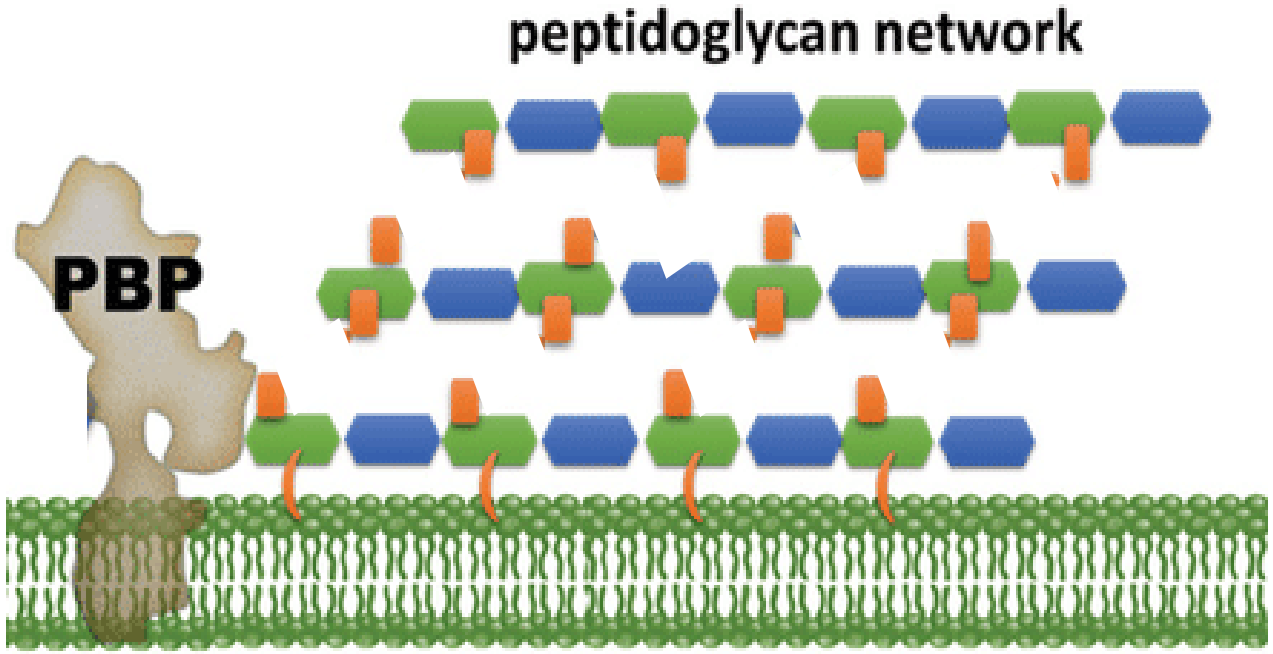

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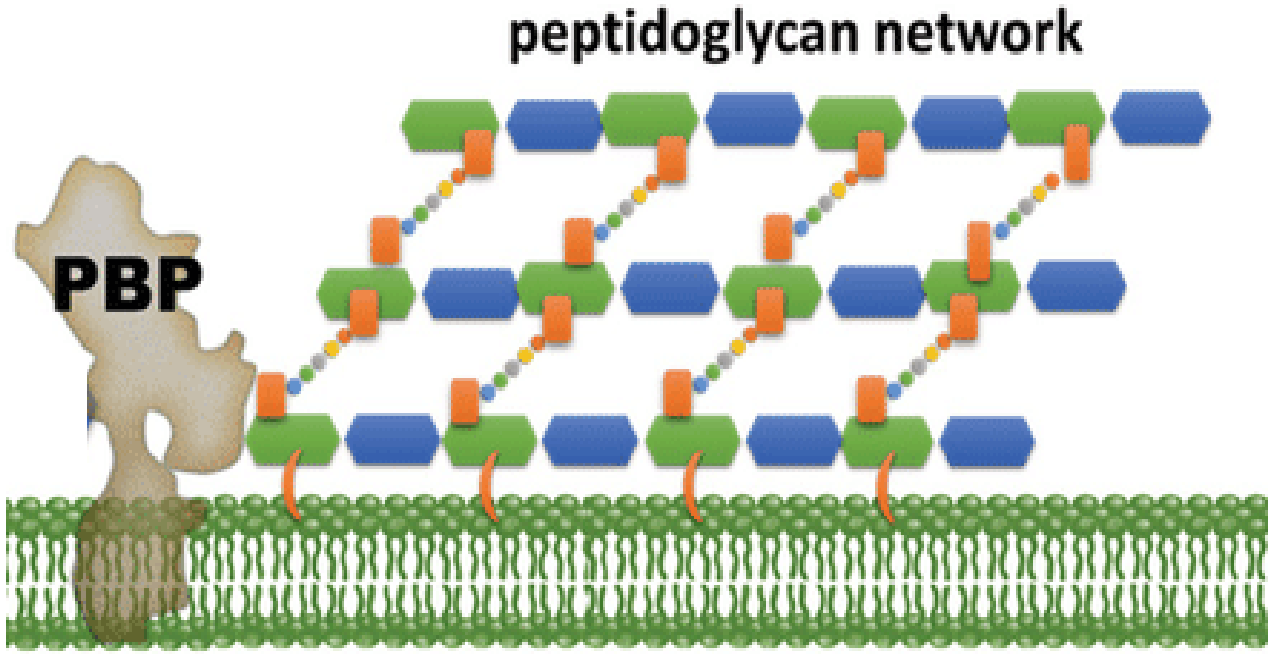

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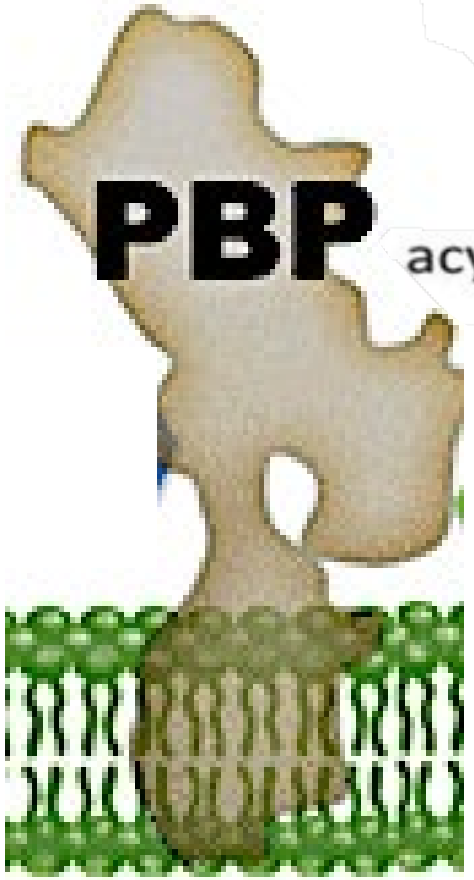
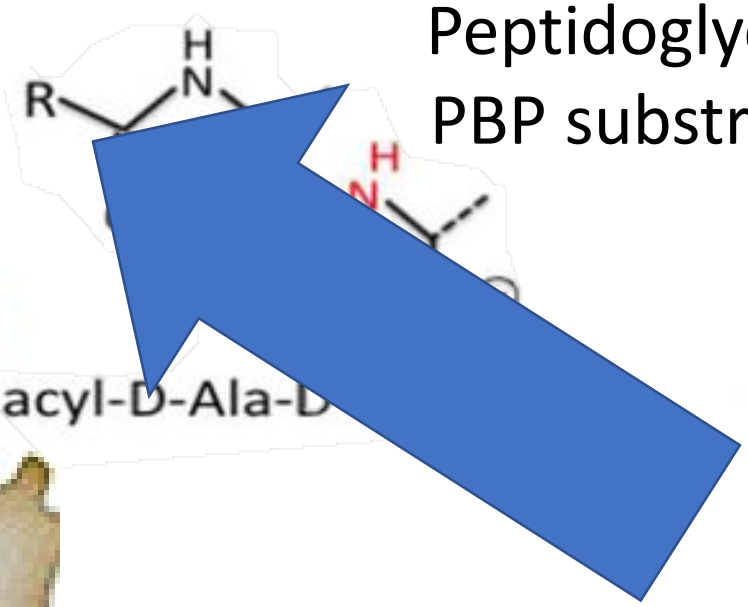
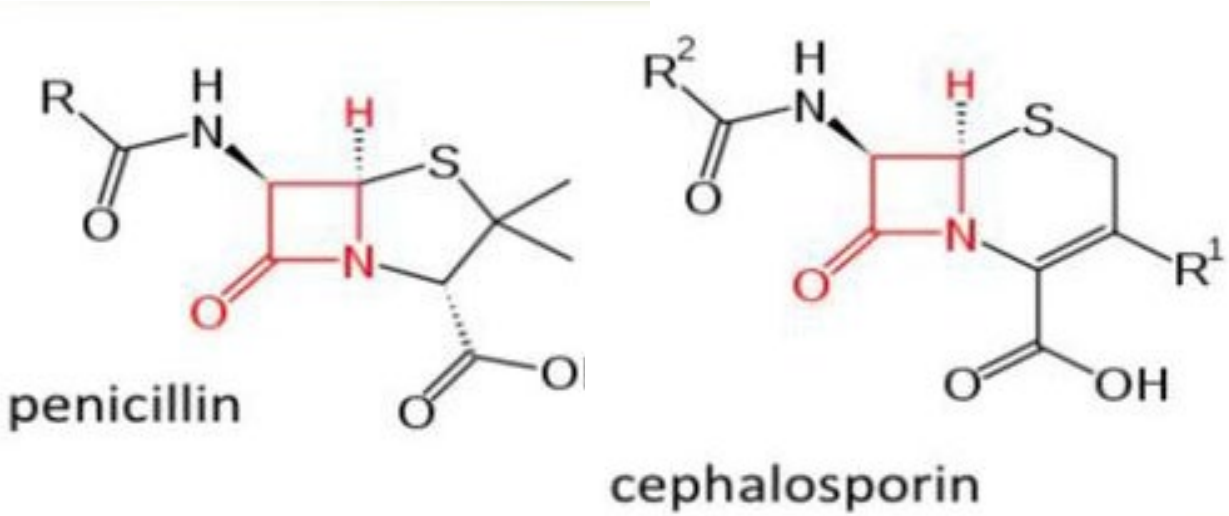
PBP transpeptidase substrate and the beta-lactams



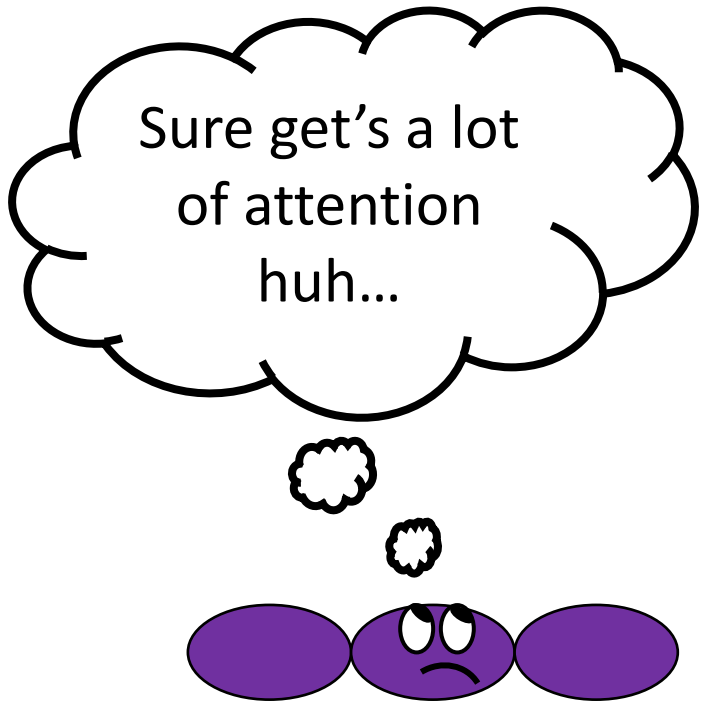
Peptidoglycan
PBP substrate





Bind in place of the normal substrate arresting cell wall synthesis resulting in cell death

Make way for the famous (acquired) PBPs



S. pneumoniae

PBP2c (*mecC*)

MRSA

PBP2a (*mecA*)

Methicillin resistant *Staphylococcus aureus* (MRSA)

How many penicillin binding proteins have been described in *S. pneumoniae*?

A) 5

B) 12

C) 6

D) 23

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Class	PBPs	Enzyme activity	Requirement for SPN
A	PBP1a PBP1b PBP2a	Bi-functional: transglycosylase and transpeptidase	Non-essential
B	PBP2x PBP2b	Mono-functional: transpeptidase	Individually essential
C	PBP3	D,D-carboxypeptidase activity	Non-essential

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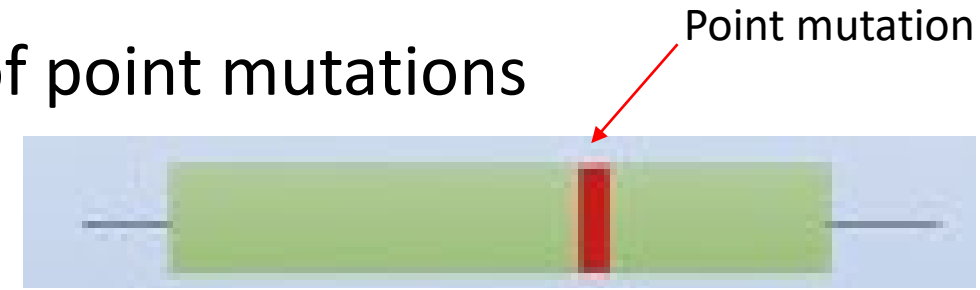
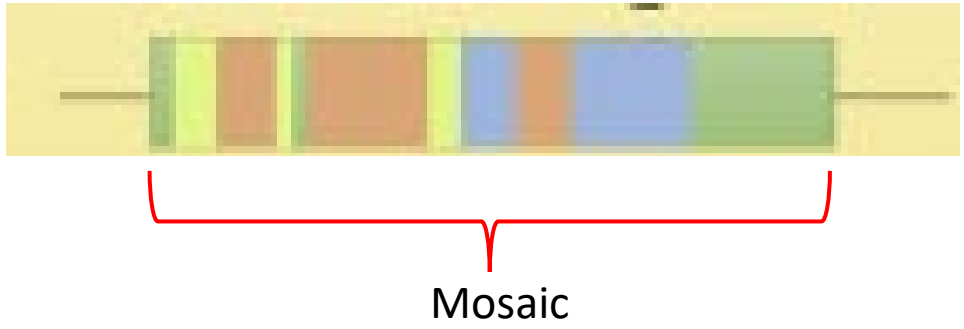
Main PBPs responsible for conferring beta-lactam resistance in *S. pneumoniae*

Primary mechanisms of beta-lactam resistance in *S. pneumoniae* are gene modifications affecting the PBP transpeptidase domain

- Acquisition of point mutations



- PBP gene recombination following interspecies horizontal gene transfer with other viridans group streptococci



"I get by with a little help from my friends"

Beta-lactam resistant *S. pneumoniae* is a WHO priority pathogen

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

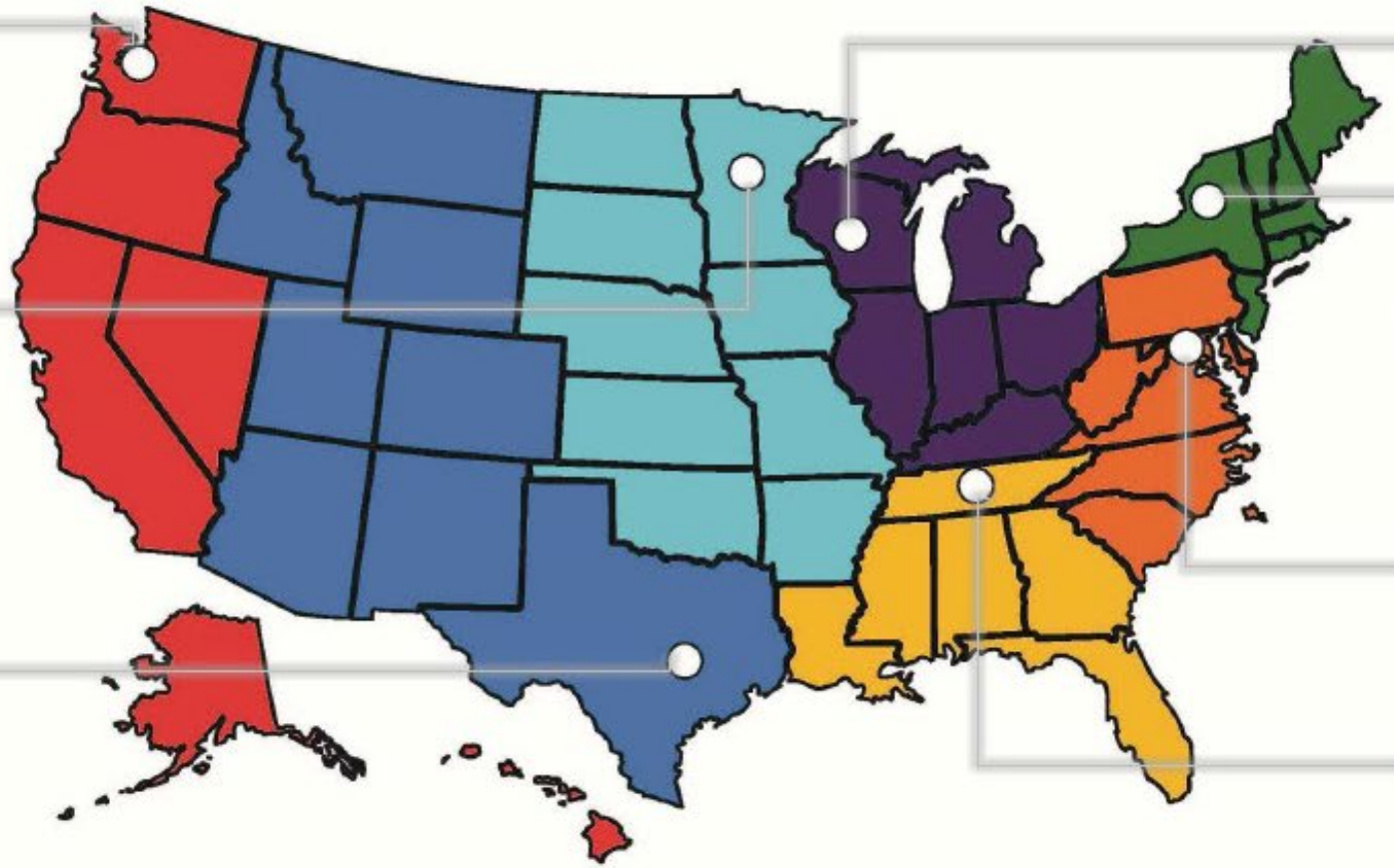
Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

- *S. pneumoniae* is a vaccine preventable, offers protection against severe infection
  - Our patient was too young to be vaccinated (6 weeks minimum age)
  - Different vaccine formulations
  - Pediatric and adult schedules

https://www.cdc.gov/vaccines/vpd/pneumo/index.html

Antimicrobial Resistance Laboratory Network



WEST
Washington State Public Health Laboratories
✓ Core Testing
+ *Candida*
+ *N. gonorrhoeae*

CENTRAL
Minnesota Department of Health PHL
✓ Core Testing
+ *Candida*
+ *C. difficile*
+ Reflex Culture Pilot
+ *S. pneumoniae*

MOUNTAIN
Texas DSHS Laboratory
✓ Core Testing
+ *N. gonorrhoeae*

MIDWEST
Wisconsin State Laboratory of Hygiene
✓ Core Testing
+ Reflex Culture Pilot
+ *S. pneumoniae*

NORTHEAST
Wadsworth Center Bacteriology Laboratory
✓ Core Testing
+ *Candida*

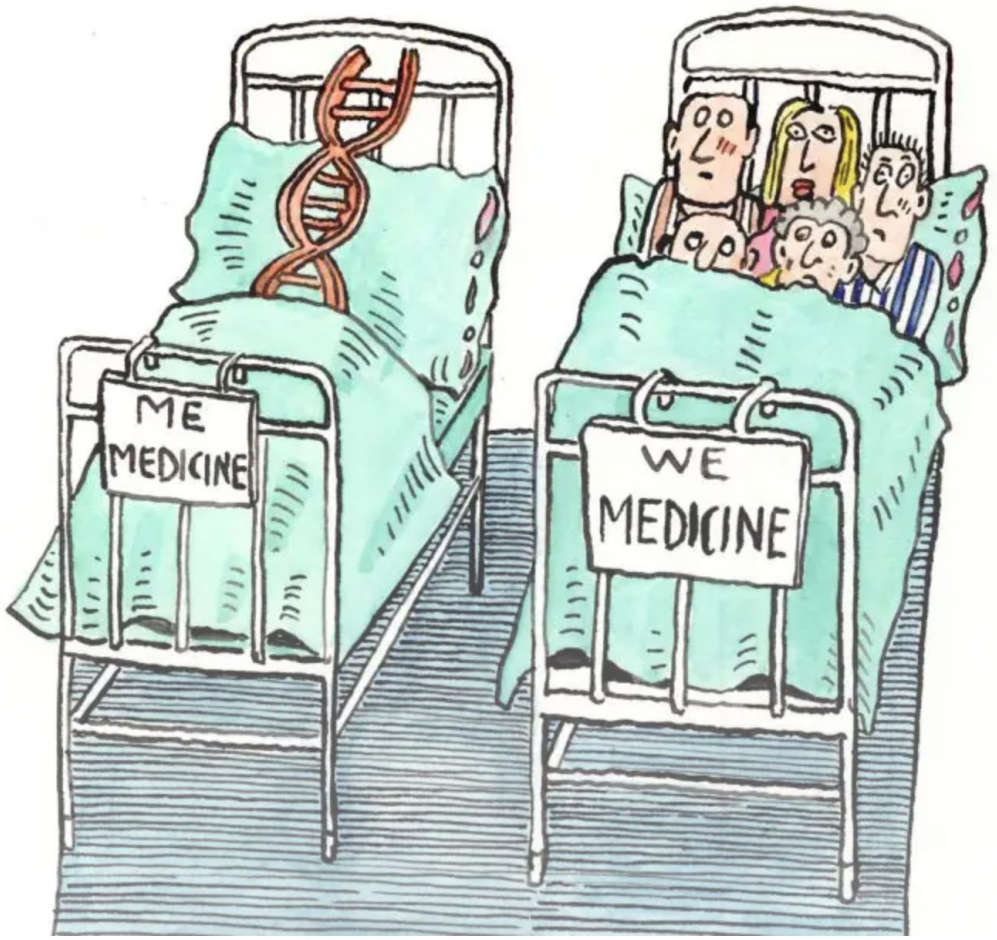
MID-ATLANTIC
Maryland Public Health Laboratory
✓ Core Testing
+ *N. gonorrhoeae*

SOUTHEAST
Tennessee State Public Health Laboratory
✓ Core Testing
+ *Candida*
+ *N. gonorrhoeae*
+ Reflex Culture Pilot

ARLABnetwork

ARLN *S. pneumoniae* initiative

- Request penicillin resistant isolates from sterile sites
- Associate serotypes with antibiotic resistance
- Detect and understand vaccine escape strains
- Inform treatment guidelines and vaccine formulations



Summary of Case 1

- Beta-lactam resistant *S. pneumoniae* is an important pathogen that can cause invasive disease, most often in pediatric and elderly patients
  - Vaccination is recommended

S. pneumoniae

- The primary mechanism(s) of beta-lactam resistance in *S. pneumoniae* is mediated by PBP transpeptidase domain modifications

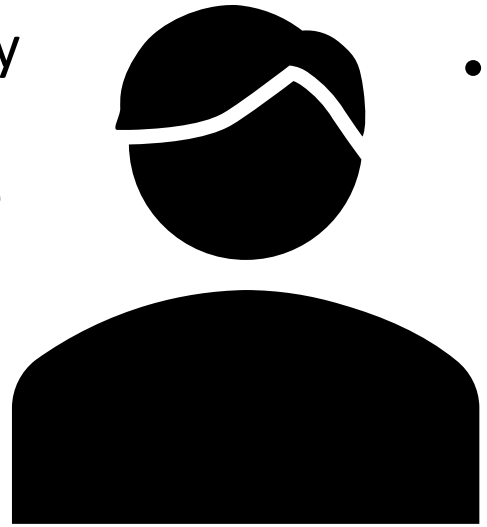
- The WHO, CDC, and APHL recognized drug resistant *S. pneumoniae* as a public health threat

Case 2: All aboard the roundworm bus!

Clinical Presentation

Presentation:

- 69 y/o male
- Currently hospitalized due to complications with recent splenectomy
- Day 45 of hospitalization showed signs of altered mental status and headache



On exam:

- Febrile, at 39.4C
- Nuchal rigidity
- Photophobia
- Agitated and disoriented

Past Medical History:

- Diabetes (on insulin)
- Autoimmune hemolytic anemia (on long term steroid therapy, 6 years)
- Recently diagnosed with *Strongyloides stercoralis* hyper infection

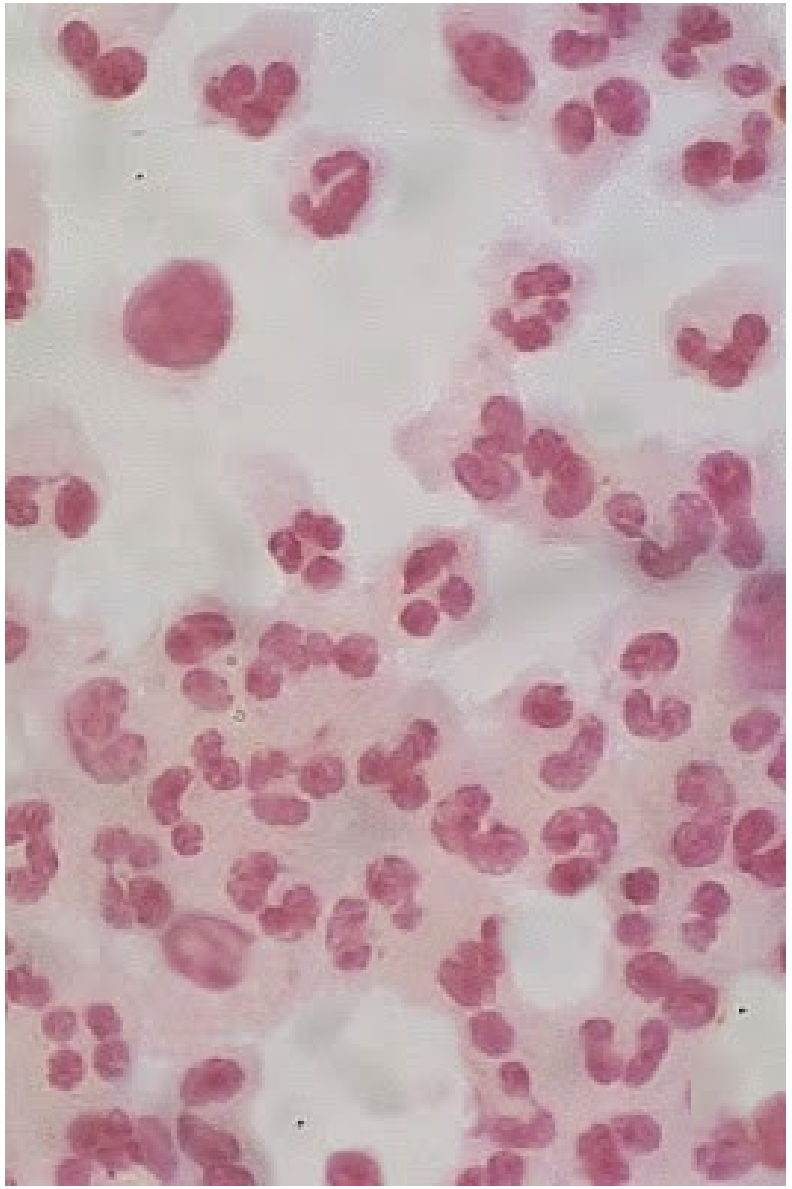
Microbiology studies ordered

- Blood cultures
  - 4 sets: No Growth

- CSF studies

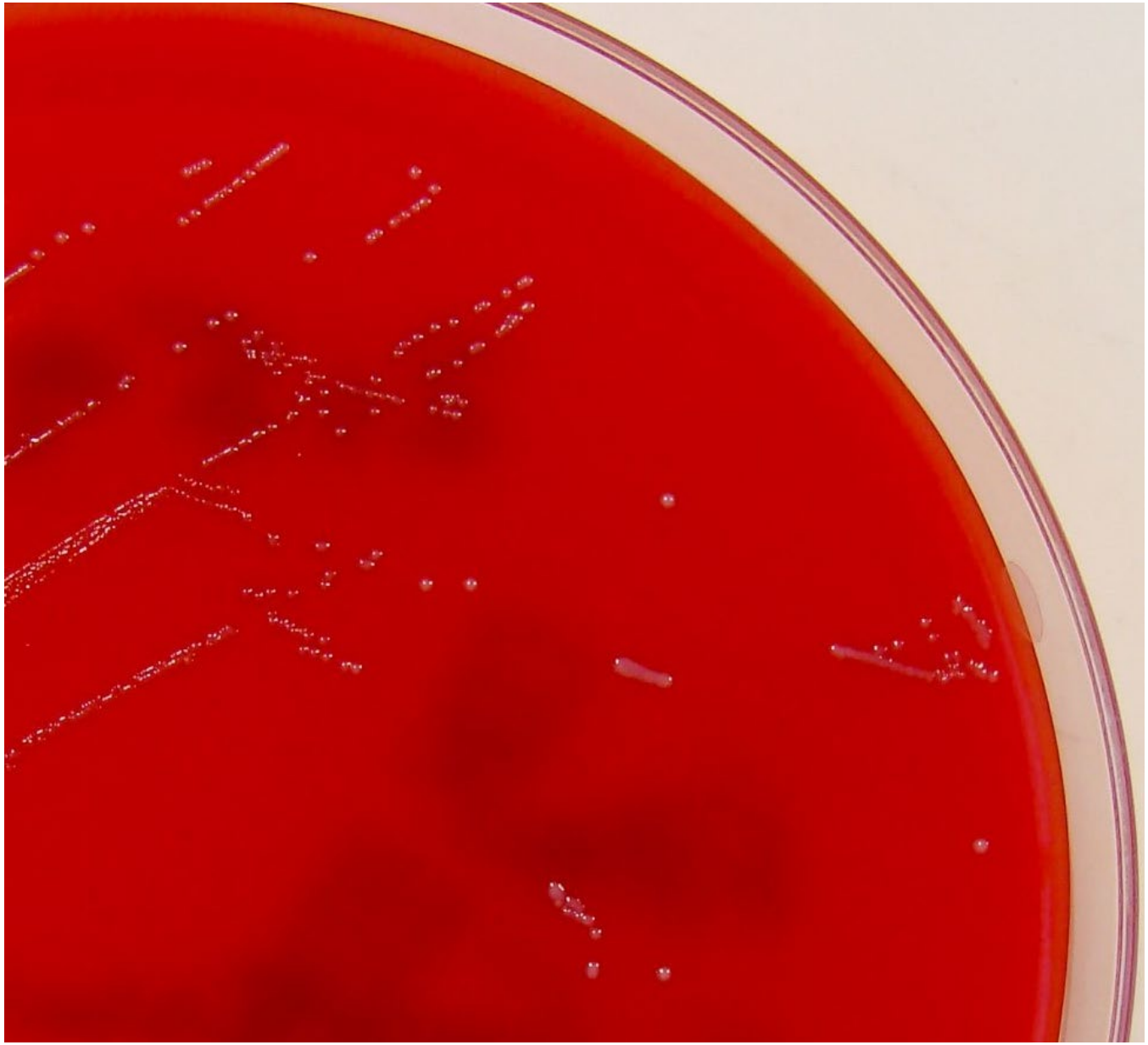
White blood cells	289 WBCs/mm^3 ↑
Glucose	18 mg/dl ↓
Protein	195 mg/dl ↑
Gram stain	No organisms seen, 4+ WBCs

Consistent with bacterial meningitis

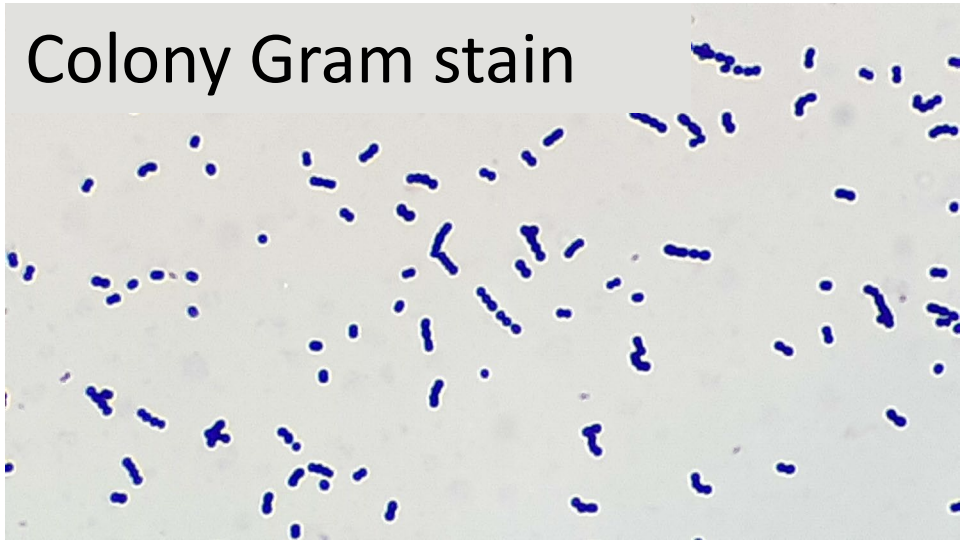


Patient placed empirically on ampicillin, ceftazidime, and vancomycin

CSF culture results



After 48 hours this organism was seen on blood agar

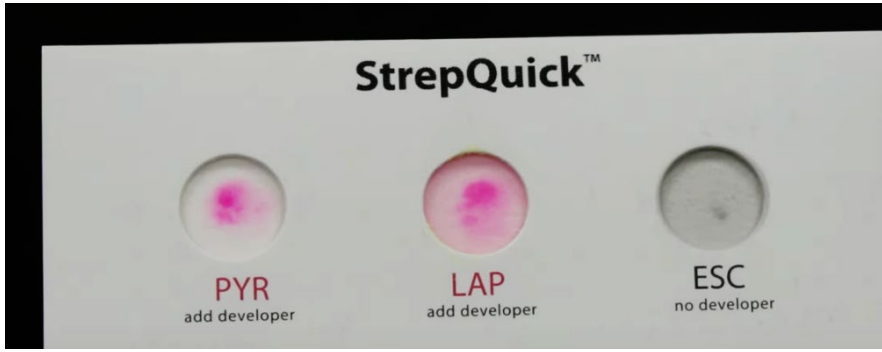


Catalase negative

PYR+

LAP+

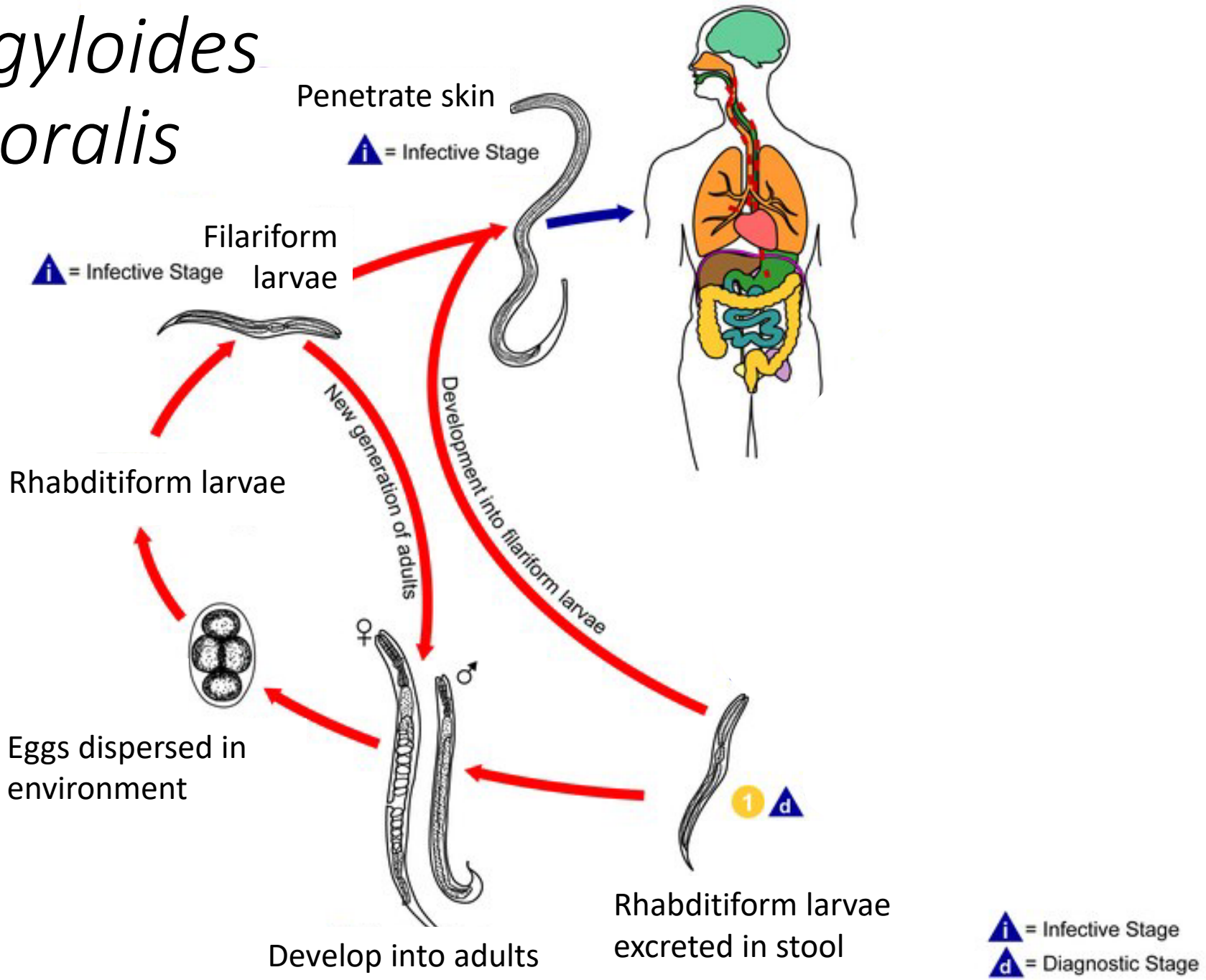
Esculin+



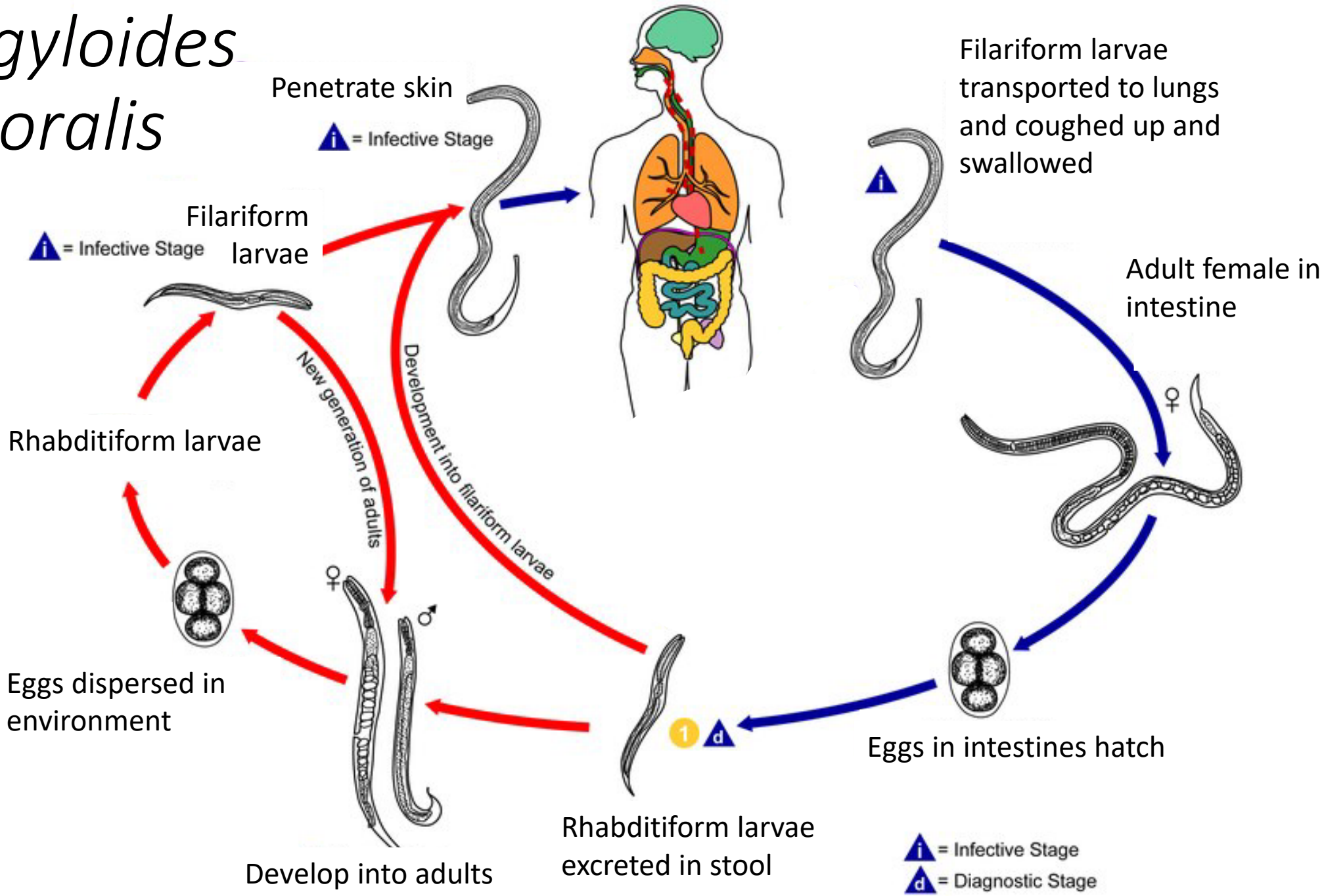
Enterococcus

E. faecium

Stongyloides stercoralis



Stongyloides stercoralis



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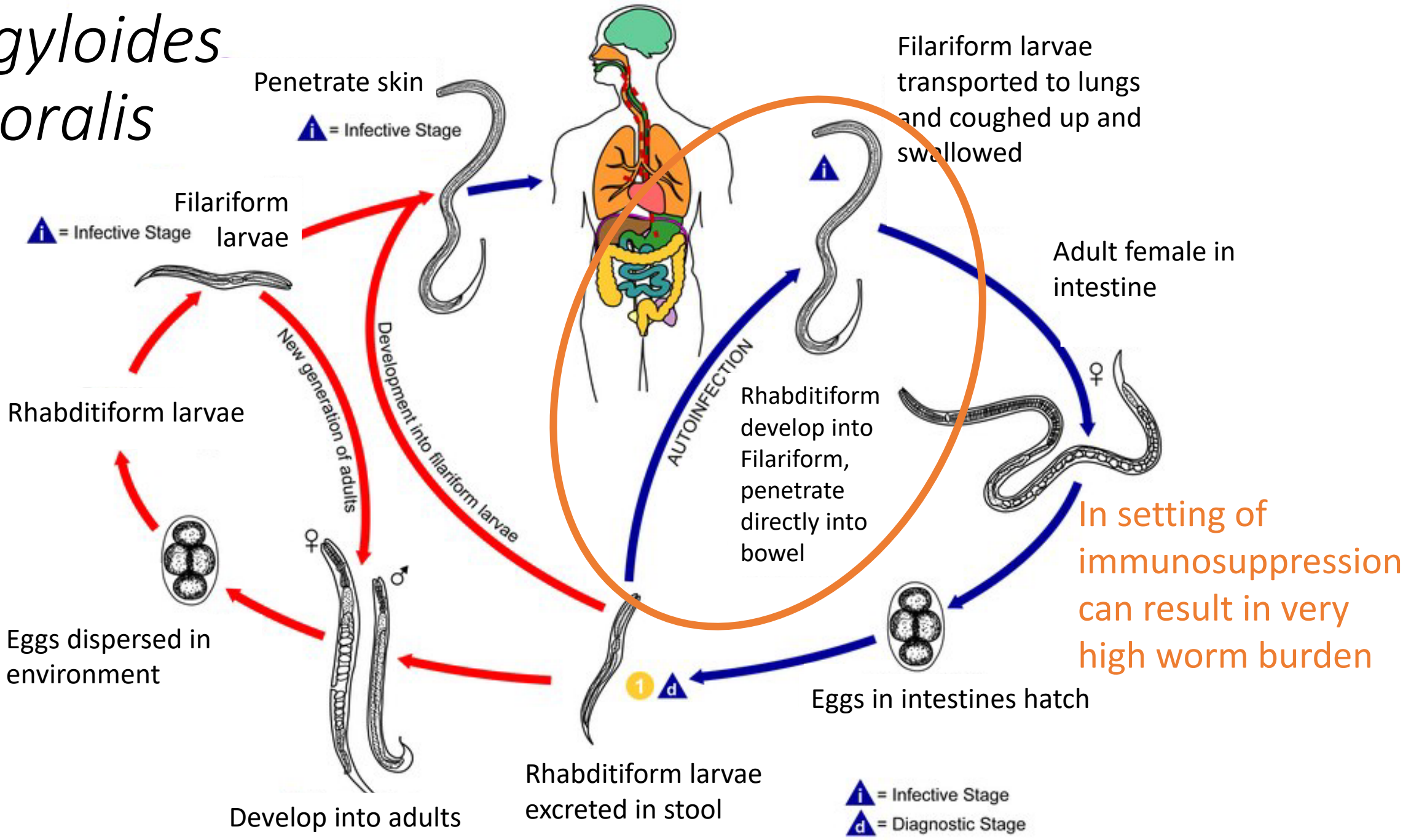
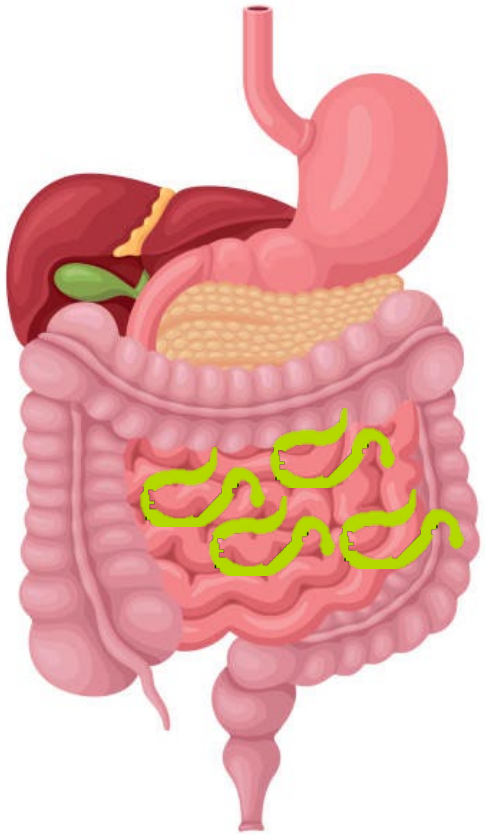
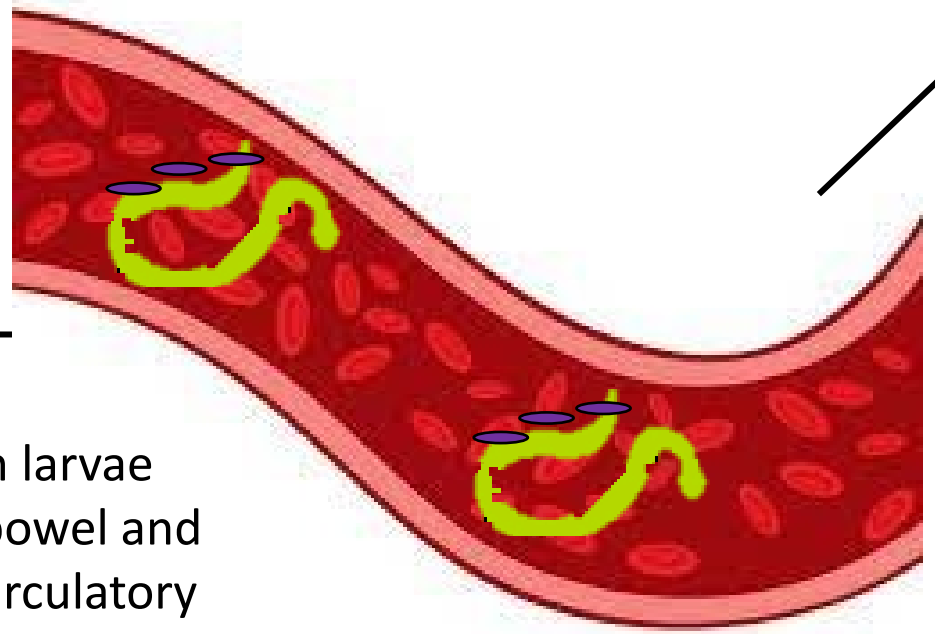


In setting of immunosuppression can result in very high worm burden

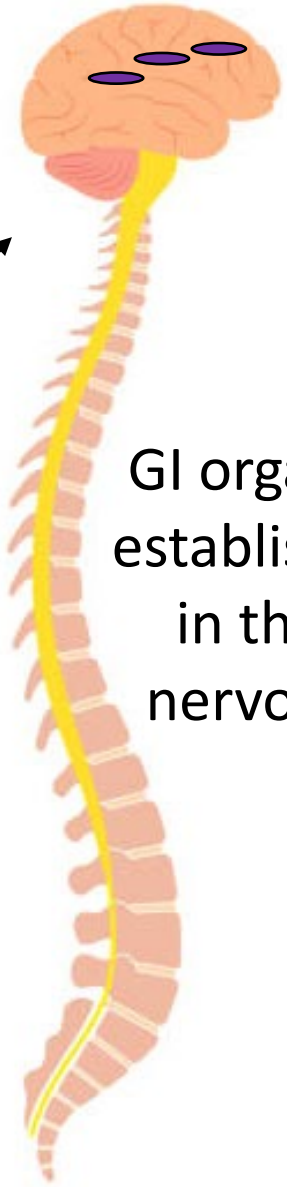
Consequences of *S. stercoralis* hyperinfection



Filariform larvae penetrate bowel and enter the circulatory system



With them they bring commensal gastrointestinal (GI) bacteria, enteric Gram-negative rods, enterococci



GI organisms can establish infection in the central nervous system

E. faecium isolate susceptibility results

Drug	Interpretation
Ampicillin	Resistant
Vancomycin	Resistant
Linezolid	Susceptible
Quinupristin/Dalfopristin	Susceptible
Chloramphenicol	Susceptible

Recall: Patient on ampicillin, vancomycin, and ceftazidime (NO effective therarpy)

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Patient treated with Linezolid for 28 days and recovered

Mechanisms of intrinsic and acquired resistance in enterococci are a complex alphabet soup…

Intrinsic resistance in enterococci

Organism \ Antimicrobial Agent	Cephalosporins	Vancomycin	Teicoplanin	Aminoglycosides	Clindamycin	Quinupristin-dalfopristin	Trimethoprim	Trimethoprim-sulfamethoxazole	Fusidic Acid
E. faecalis	R[a]			R[a]	R[a]	R	R	R[a]	R
E. faecium	R[a]			R[a]	R[a]		R	R[a]	R
E. gallinarum/E. casseliflavus	R[a]	R		R[a]	R[a]	R	R	R[a]	R

Abbreviation: R, resistant.

a. **Warning:** For *Enterococcus* spp., cephalosporins, aminoglycosides (except for high-level resistance testing), clindamycin, and trimethoprim-sulfamethoxazole may appear active *in vitro* but are not effective clinically and should not be reported as susceptible.

NOTE: These gram-positive bacteria are also intrinsically resistant to aztreonam, polymyxin B/colistin, and nalidixic acid.

Enterococci are naturally multi-drug resistant organisms, care must be taken in selecting treatment

Cell wall related mechanisms of resistance in enterococci

Site of resistance	Strategy	Antibiotic	Primary gene or gene product	Notes
Cell wall	PBP (enzyme) modification	Beta-lactams	*pbp5*	Low-affinity PBPs allow peptidoglycan synthesis in the presence of β-lactams
	Drug inactivation	Beta-lactams	*blaZ*	β-Lactamase. Low-level constitutive production may be missed on routine laboratory screening
	Alternate pathway	Beta-lactams/ glycopeptides	LDT_{fm}	L,D-Transpeptidation only observed *in vitro*
	Cell signaling	Cephalosporins	*croRS* *ireK*	Mutations in these pathways sensitize enterococci to cephalosporins
	Altered target	Glycopeptides	*van* operons	• *vanA/B* – Acquired genes • Intrinsic low-level resistance in *E. gallinarium* and *E. casseliflavus vanC*

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Ampicillin resistance

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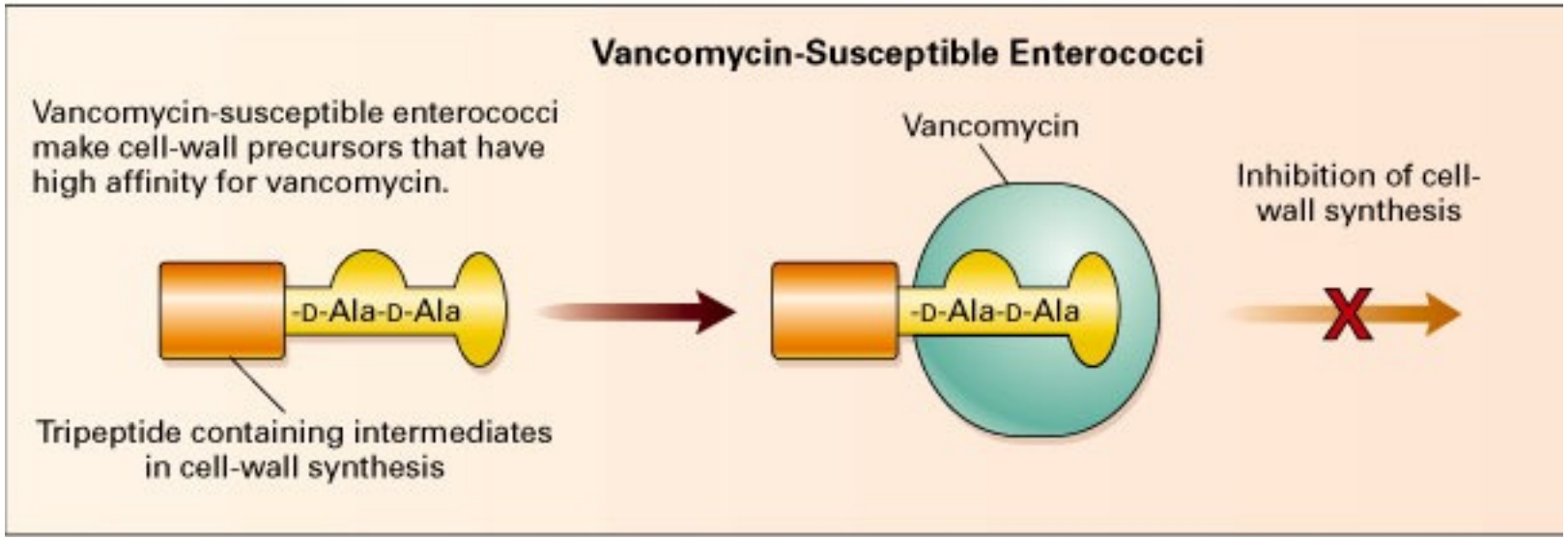
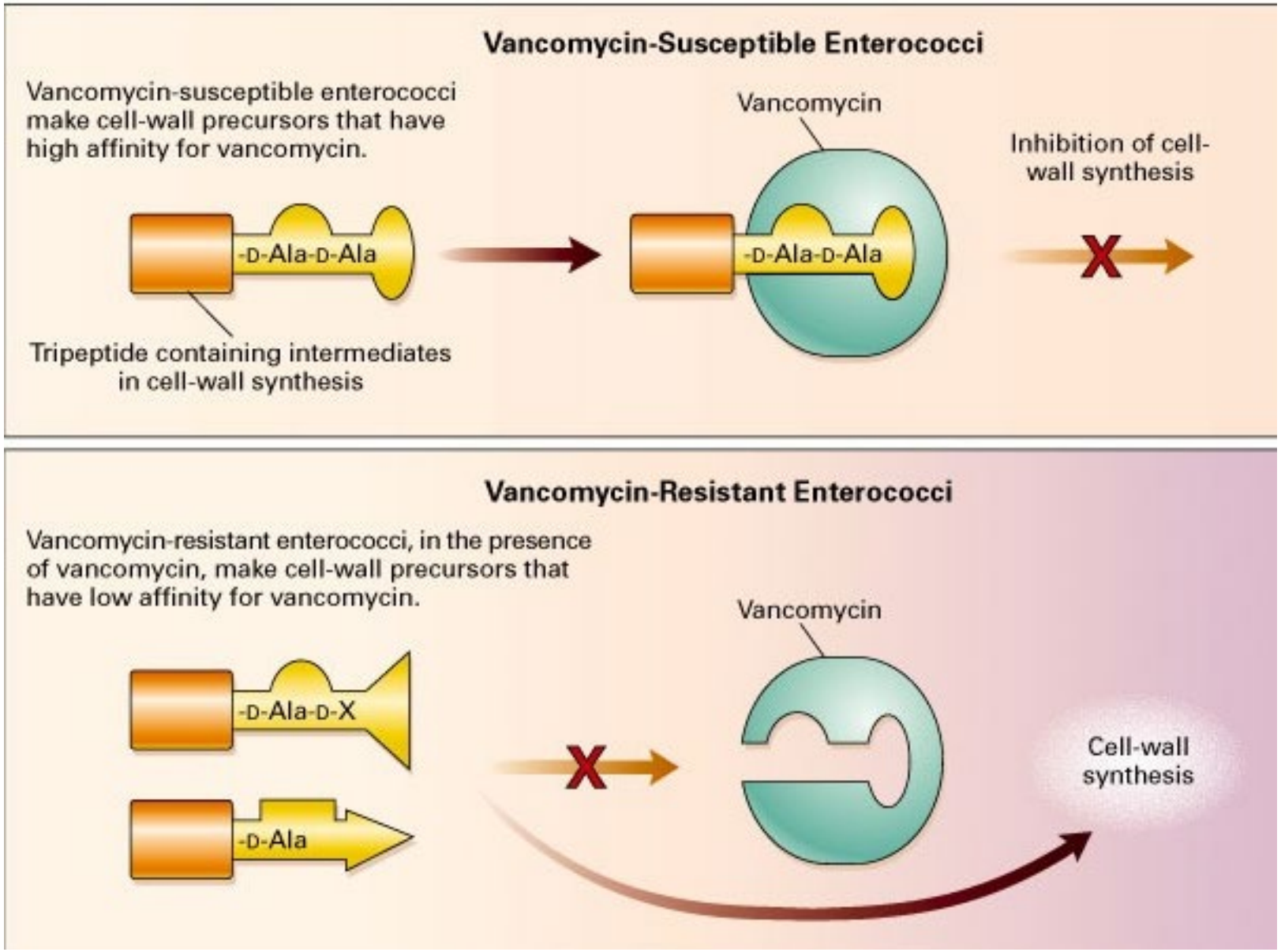
Vancomycin resistance

VanA/B mediated Vancomycin resistance in enterococci



VanA/B mediated Vancomycin resistance in enterococci



VanA or B activity confers modifications to from D-Ala-D-Ala → D-Ala-D-Lac in the peptidoglycan cell wall.

Vancomycin no longer binds.

Plasmid-borne, acquired resistance mechanism

MORE mechanisms of resistance in enterococci

Drug(s)	Genes described
Daptomycin	LiaFSR, YycFG Cls, GdpD
Aminoglycosides	AAC(6')-Ii, APH(3')-IIIa, *aadA*/ANT(3'), AAC(6')-Ie/APH (2')-Ia, *efmM*
Quinupristin/ Dalfopristin	*vatD* and *vatE, vgbA* and *vgbB* *lsa, msrC, eatA*
Linezolid	genes coding for 23S rRNA: G2576T, G2505A, U2500A, G2447U, C2534U, G2603U
Tetracyclines	*tetM, tetO, tetS, tetK, tetL*
Quinolones	*gyrA, parC, norA, qnr*
Rifampicin	*rpoB*
Trimethoprim/ Sulfamethoxazole	Intrinsic – use exogenous folate

Which of the following newer-ish drugs have CLSI recognized enterococci breakpoints

A) Dalbavancin

B) Eravacycline

C) Delafloxacin

D) Omadacycline

Which of the following newer-ish drugs have CLSI recognized enterococci breakpoints

A) Dalbavancin

B) Eravacycline (FDA and EUCAST)

C) Delafloxacin (FDA)

D) Omadacycline (FDA)

New-ish drugs with activity against enterococci

	Enterococcus Breakpoints		
Drug	CLSI	FDA	EUCAST
Telavancin	MIC[a,b]	CLSI	-
Oritavancin	MIC[a,b]	CLSI	-
Dalbavancin	MIC[a,b]	CLSI	-
Tedizolid	MIC[a,e]	CLSI	-
Delafloxacin	-	MIC[e,f] DD[e,f]	-
Omadacycline	-	MIC[e,f] DD[e,f]	-
Eravacycline	-	MIC[a,c]	MIC[c] DD[c,d]

[a]Only a susceptible breakpoint is published

[b]Breakpoint applies to vancomycin-susceptible *Enterococcus faecalis* isolates only

[c]Breakpoint applies to *Enterococcus faecalis* and *Enterococcus faecium* only

[d]Breakpoints differ between *Enterococcus faecalis* versus *Enterococcus faecium*

[e]Breakpoint applies to *Enterococcus faecalis* isolates only

[f]Breakpoint applies to acute skin/skin structure infections only

Vancomycin resistant *E. faecium* WHO Priority Pathogen

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

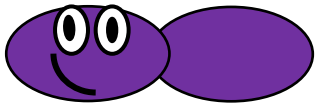
Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

Summary of Case 2

- Multidrug resistant enterococci can present a treatment challenge
- The mechanisms of intrinsic and acquired resistance in enterococci are numerous and complex
- There are more novel, less commonly used antimicrobials with activity against the enterococci but there are limitations in their use
- The WHO recognizes vancomycin resistant *E. faecium* as a high priority public health threat



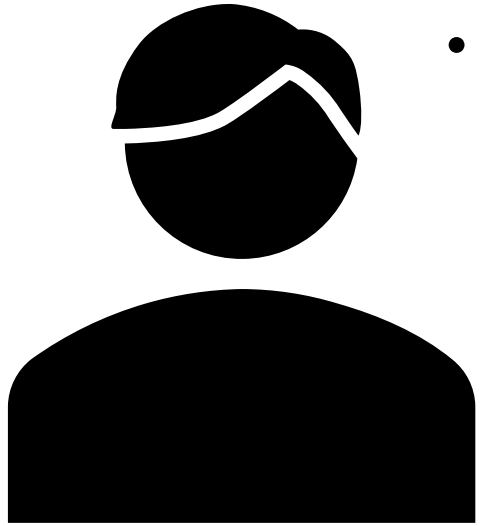
Enterococcus

Case 3: Well aren’t you looking DAP-R

Clinical Presentation

Presentation:

- 78 y/o male hemodialysis patient
- Drainage, erythema, swelling at permanent hemodialysis catheter site
- Fever



On exam:

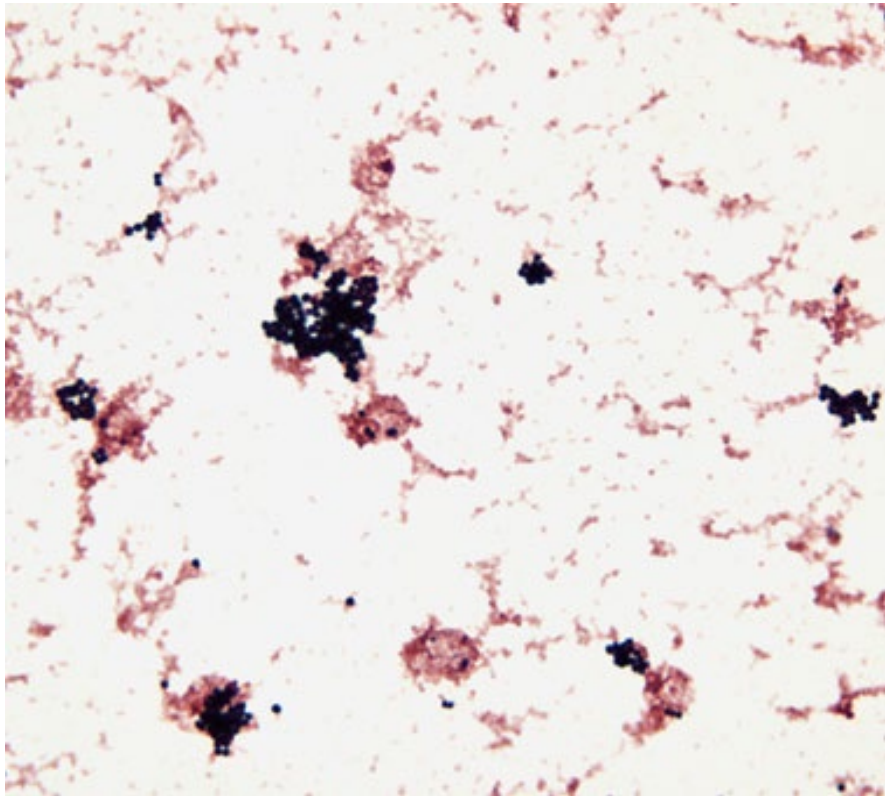
- Febrile, at 39C
- Tachycardic
- Hypertensive

Past Medical History:

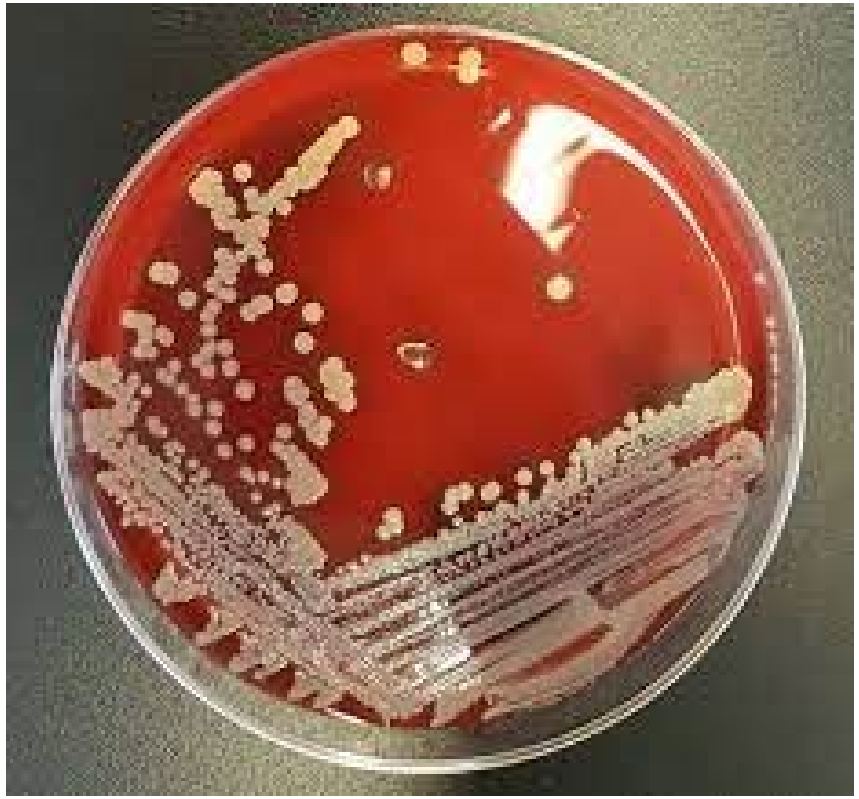
- Diabetes (on insulin)
- Renal failure on dialysis
- Chronic coronary artery disease

Microbiology studies ordered

- Peripheral blood cultures
  - 2 of 2 sets flagged positive within 24 hours of incubation



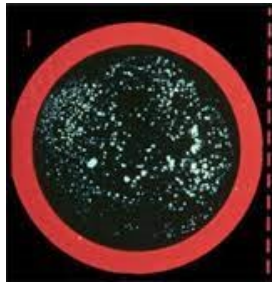
Bottle Gram stain



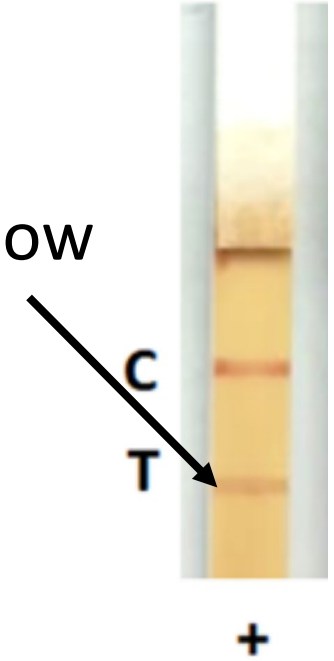
Next day: subculture to blood agar grew the following organism

Catalase +

Staphaurex +



PBP2a + lateral flow



Methicillin Resistant *Staphylococcus aureus*

Susceptibility Profile

Drug	Interpretation
Oxacillin	Resistant
Vancomycin	Susceptible (MIC 2 ug/mL)
Daptomycin	Susceptible (MIC 0.5 ug/mL)

Susceptible, but elevated vancomycin MICs (e.g., 2 µg/ml) in some older studies demonstrated association with worse clinical outcomes

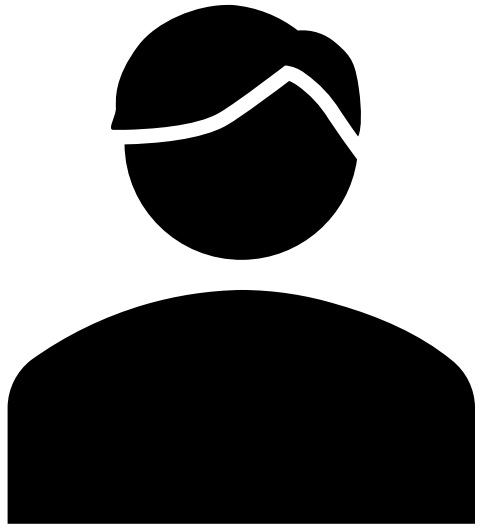
Patient had catheter replaced, was treated with long course of Daptomycin, improved and was discharged

Tenover et al. CID. 2007
Musta et al. JCM. 2009
Soriano et al. CID 2008
Takesue et al. J Infect Chemother. 2010

And we’re back… round 2 clinical presentation

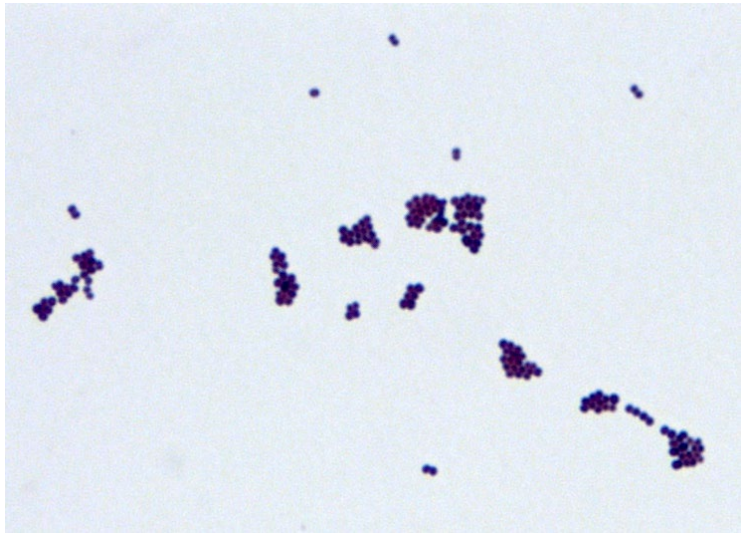
<u>Presentation:</u>

- ~1 month later returned to ED
- Respiratory distress
- Purulent drainage and swelling at catheter site
- Fever

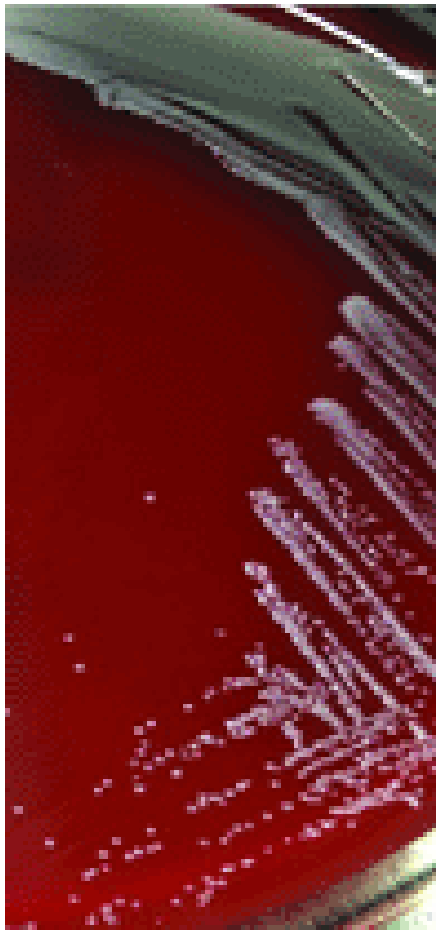


Microbiology studies ordered

- Peripheral blood cultures
  - 3 of 3 sets flagged positive



Bottle Gram stain



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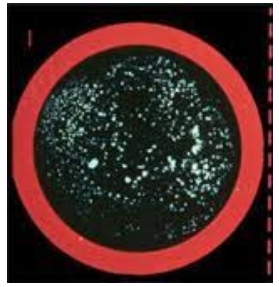
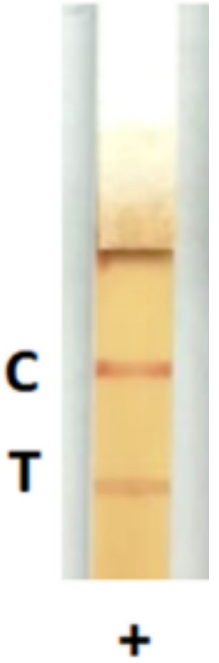
Staphaurex +



PBP2a + lateral flow



Methicillin Resistant *Staphylococcus aureus*

New susceptibility profile after daptomycin therapy

Drug	Old Result	New Interpretation
Oxacillin	Resistant	Resistant
Vancomycin (VANC)	Susceptible (MIC 2 ug/mL)	Intermediate (MIC 4 ug/mL)
Daptomycin (DAP)	Susceptible (MIC 0.5 ug/mL)	Non-susceptible (MIC 8 ug/mL)
Tetracycline	N/A	Susceptible
Linezolid	N/A	Susceptible
Trimethoprim-sulfamethoxazole	N/A	Susceptible

Li et al. Frontier Micro. 2017

New susceptibility profile after daptomycin therapy

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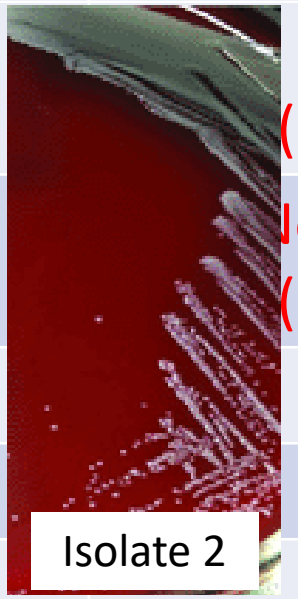
Tetracycline		Susceptible
Linezolid		Susceptible
Trimethoprim-sulfamethoxazole	N/A	Susceptible



Likely the same MRSA, difference in colony morphology explained by fitness cost observed in multi-drug resistant isolates.

Poor source control of catheter site.

Li et al. Frontier Micro. 2017

New susceptibility profile after daptomycin therapy

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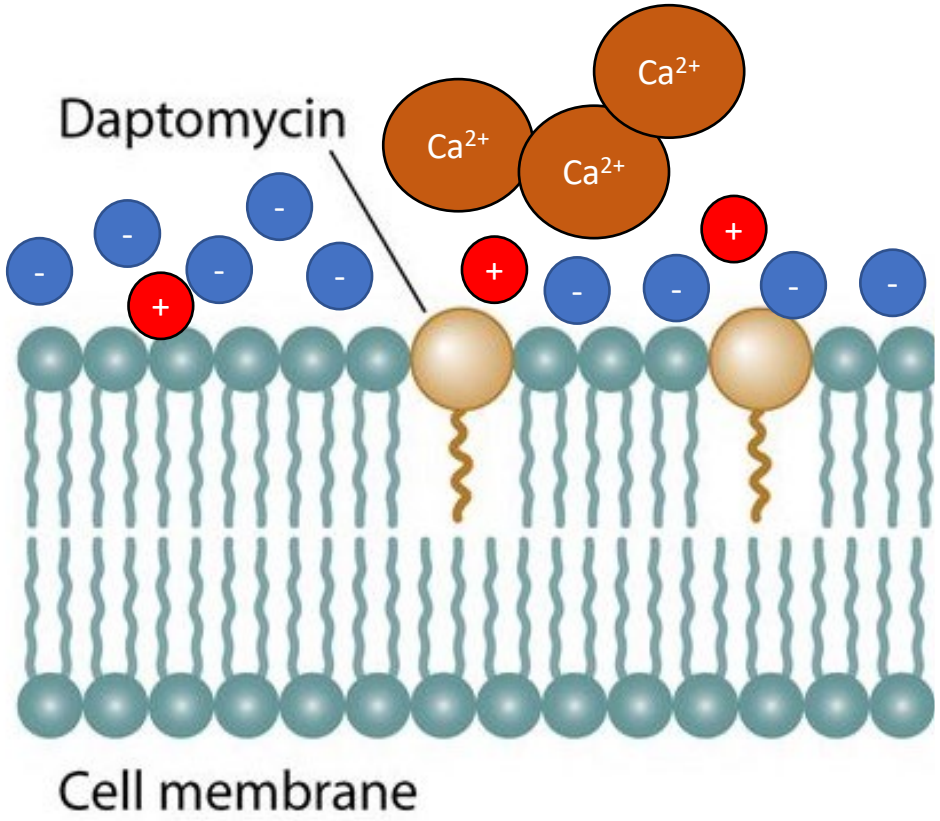
Trimethoprim-sulfamethoxazole	N/A	Susceptible

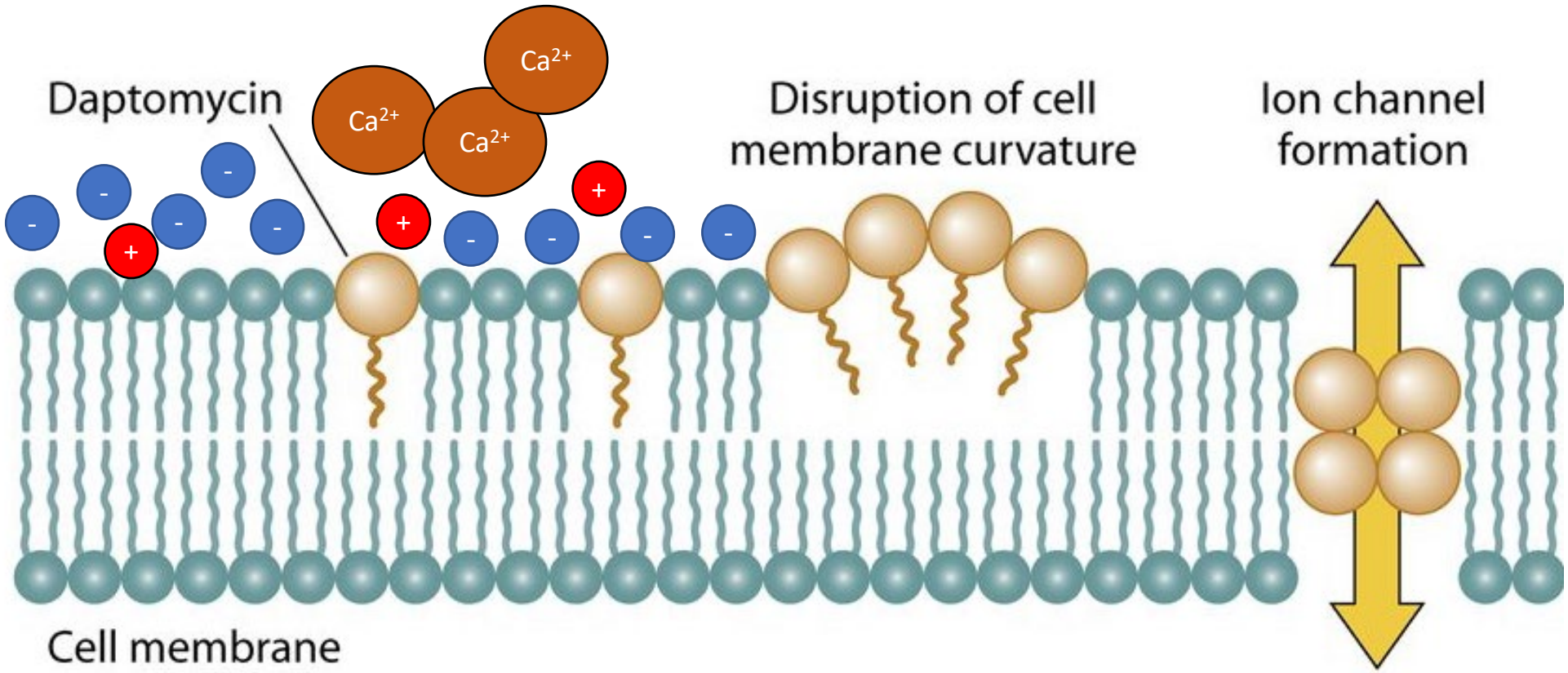
Reduced susceptibility to both vancomycin and daptomycin following therapy….

Daptomycin mechanism of action



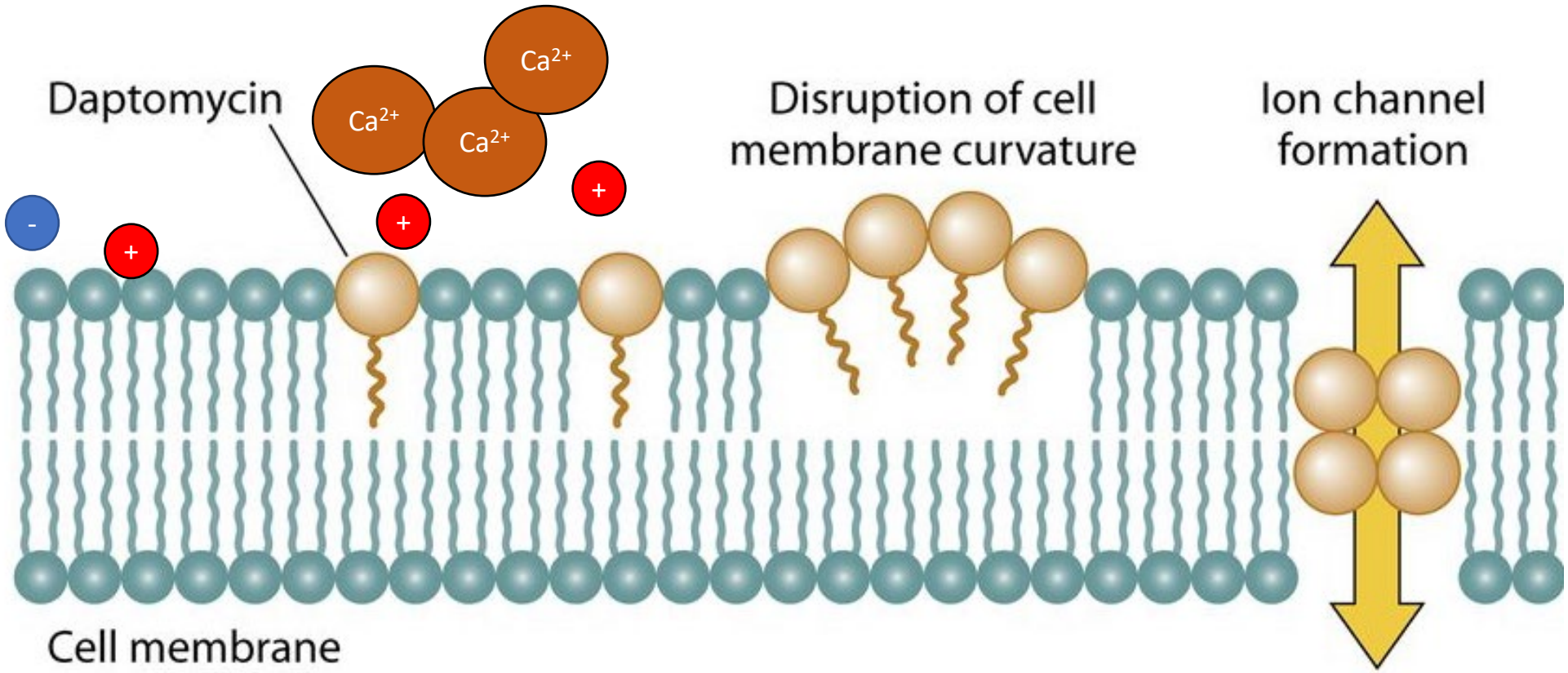
Humphries. CMR. 2013

Daptomycin mechanism of action



Humphries. CMR. 2013

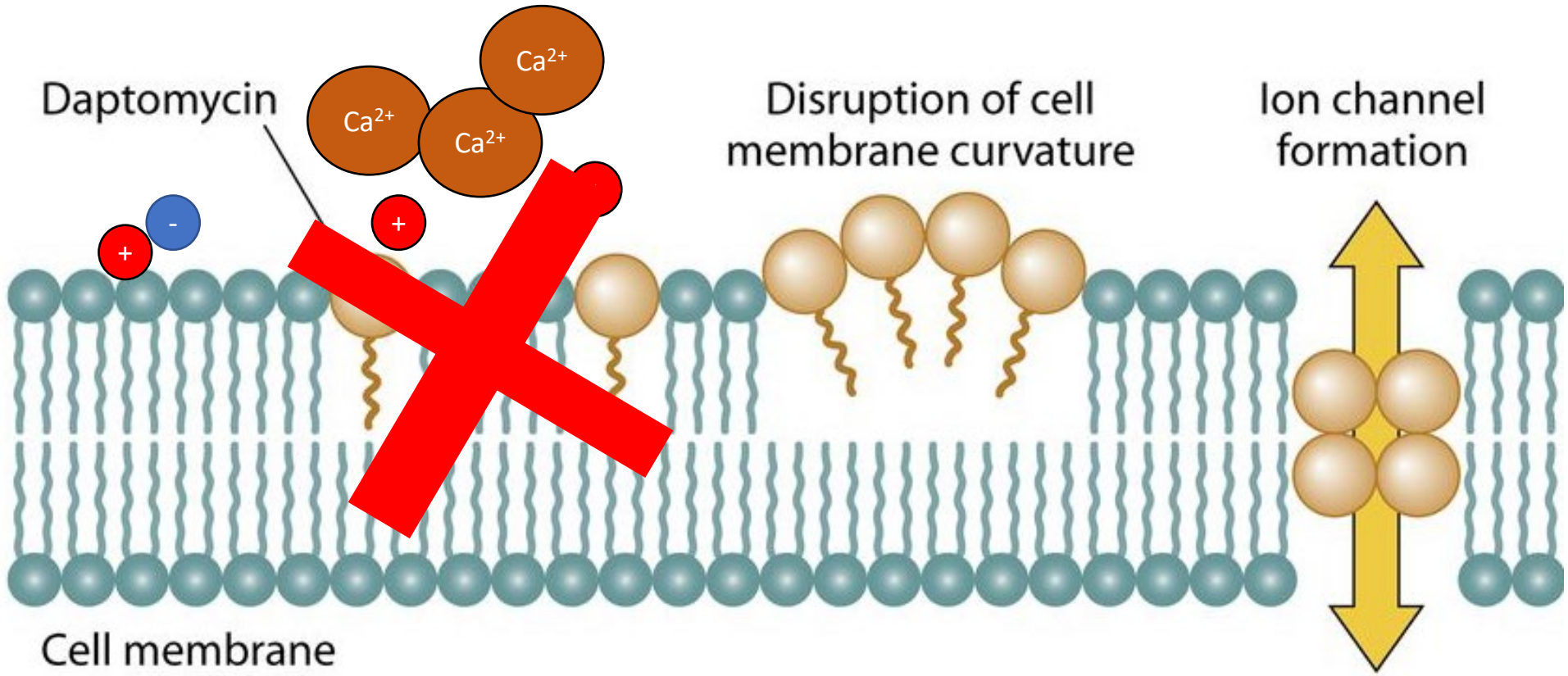
Mechanism of resistance



- Following exposure to DAP the cell membrane presumably loses the anionic surface, resulting in net positive charge +

Humphries. CMR. 2013

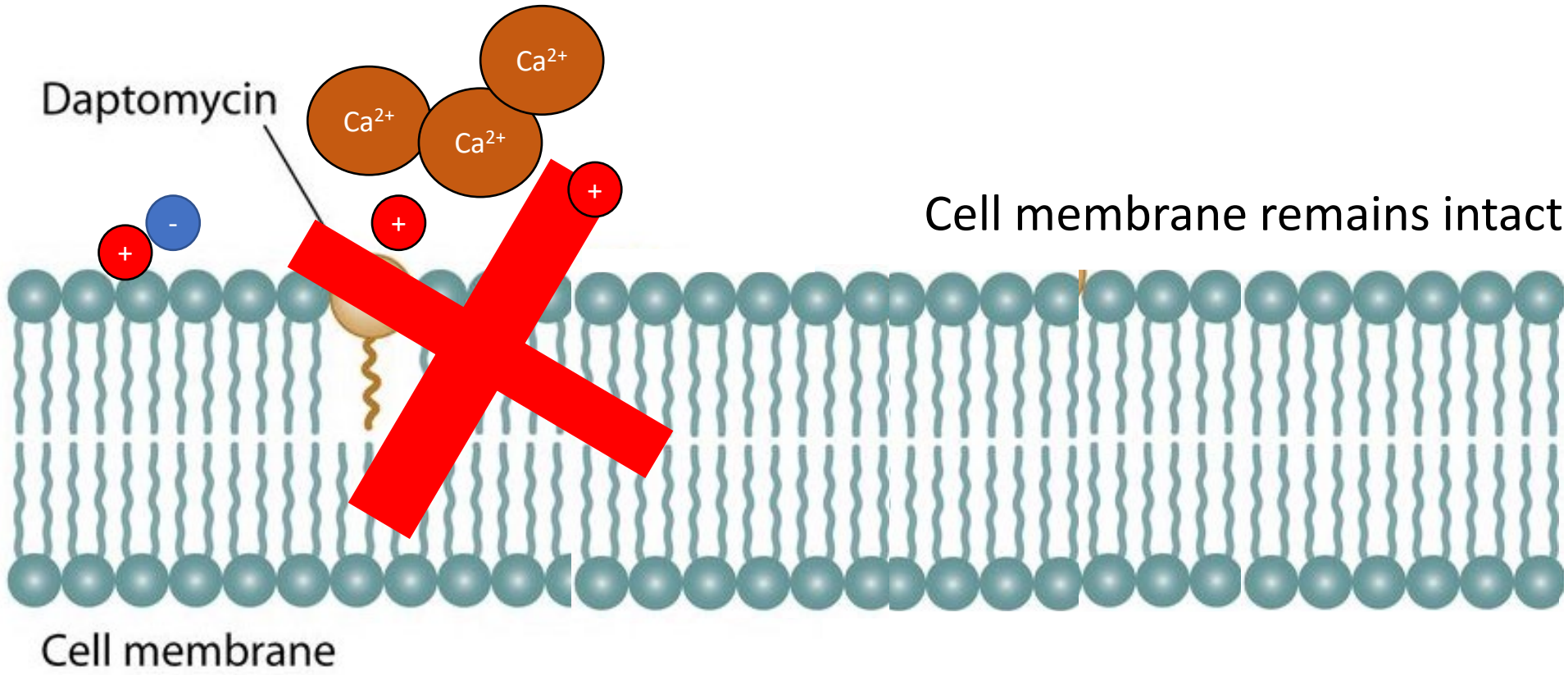
Proposed primary mechanism of resistance



- Following exposure to DAP the cell membrane presumably loses the anionic surface, resulting in net positive charge +
- DAP+CA^{2+} no longer binds the same way, effectively repelled

Humphries. CMR. 2013

Proposed primary mechanism of resistance



- Following exposure to DAP the cell membrane presumably loses the anionic surface, resulting in net positive charge

- DAP+CA^{2+} no longer binds the same way, effectively repelled

Humphries. CMR. 2013

Which of the following has been described to play a role in daptomycin resistance in MRSA?

A) *erm*

B) *blaZ+mecC*

C) *mprF*

D) *rpoB*

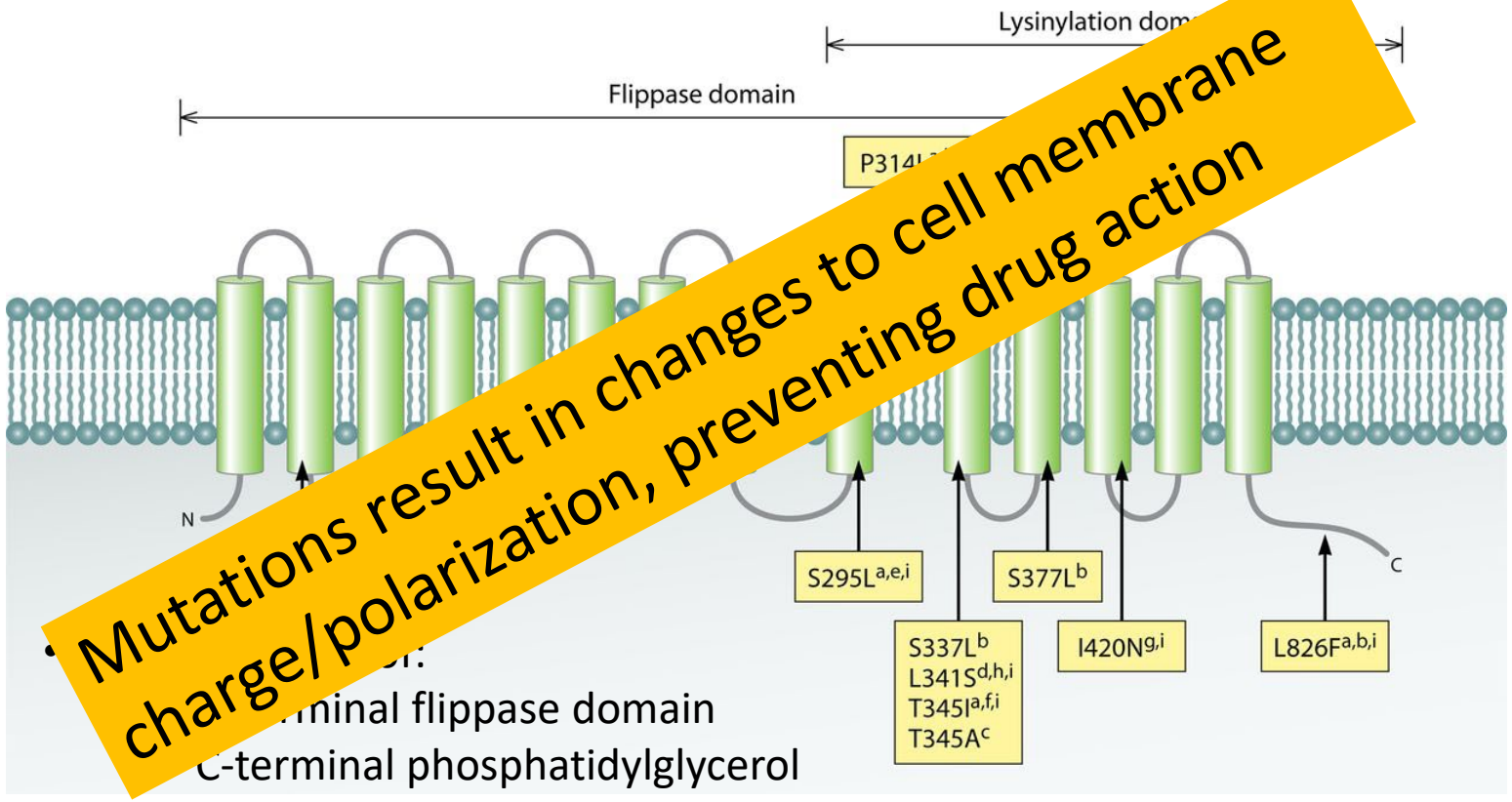
Which of the following has been described to play a role in daptomycin resistance in MRSA?

A) *erm* (macrolide)

B) *blaZ+mecC* (beta-lactams)

C) *mprF*

D) *rpoB* (rifampin)



- [illegible]
  - [illegible]minal flippase domain
  - C-terminal phosphatidylglycerol lysylination domain
  - Mutations have been identified in both domains

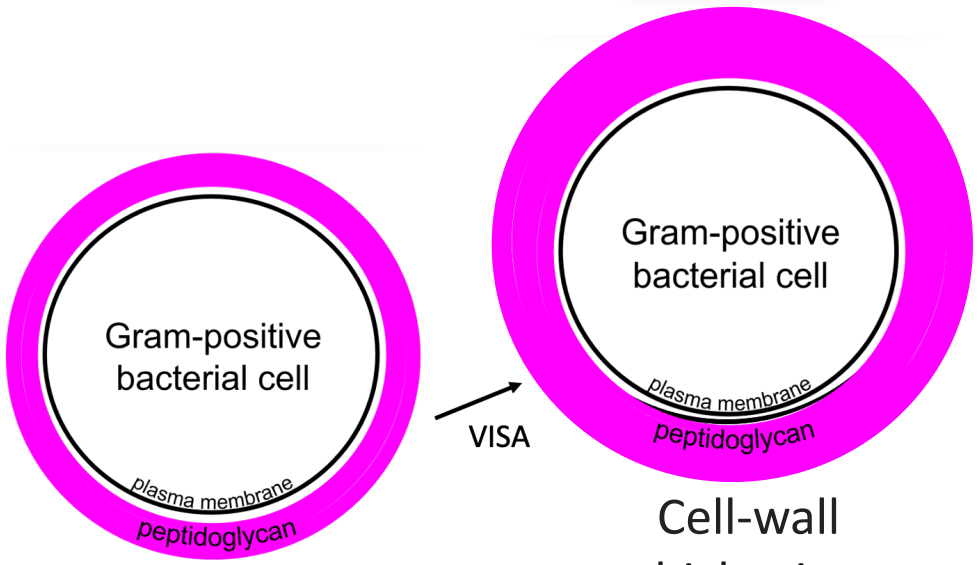
Humphries. CMR. 2013

What about that elevated VANC?

What about that elevated VANC?

Vancomycin intermediate *S. aureus*
VISA

Several genes described
walK, *clpP*, *graSR*, *vraSR*, *msrR*, *rpoB*,

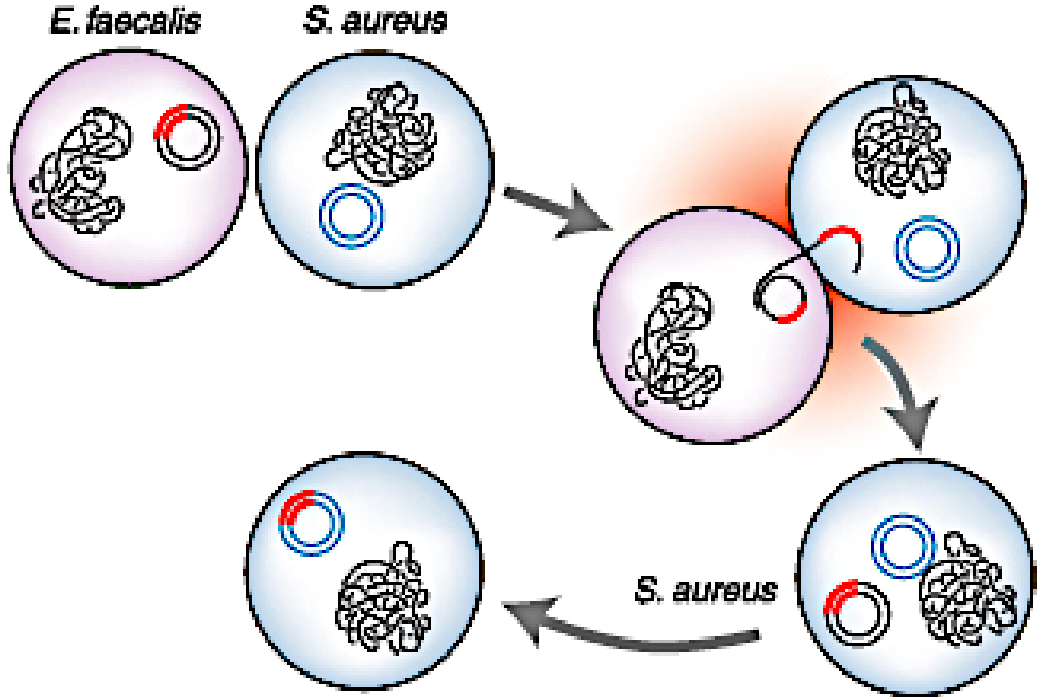


Cell-wall thickening

Daptomycin non-susceptible isolates have been shown to have increased cell wall thickening

Vancomycin resistant *S. aureus*
VRSA

Mediated by the *vanA* cluster from *Enterococcus*



Ferber. Science. 2003, Camargo et al. 2008, Mishra et al., 2009, Bertsche et al. 2011. AAC

MRSA with elevated MICs to VANC is a WHO priority pathogen

- Daptomycin resistance and/or vancomycin resistance are uncommon clinical findings

- If encountered
  - Confirm ID
  - Confirm pure isolate was tested
  - Retest
  - Send out for confirmation

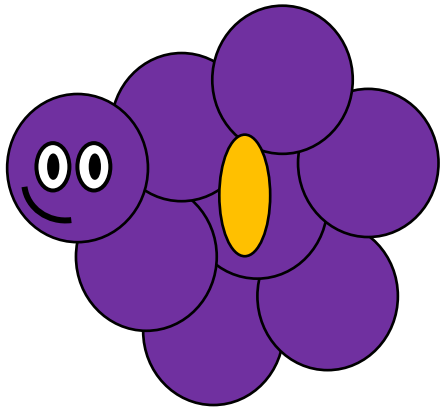
Markwart et al. Front Microbiol. 2021 PMID: 34135877

Shariati et al Sci Rep. 2020 PMID: 32728110

Summary of Case 3

- MRSA with reduced susceptibility to vancomycin and/or daptomycin are rare but important pathogens

- Daptomycin resistance is typically seen following treatment with the drug in conjunction with an uncontrolled source
  - Catheter associated



MRSA

- The WHO recognizes vancomycin intermediate and resistant MRSA as a high priority public health threat

Thank you for your attention!

mimi.precit@providence.org

EXTRA Slides

Case	General	History	Examination	Vitals	Laboratory Results	Antibiotics	Culture	Susceptibility	Outcome
1	CA: 20 G: M R: W GA: 40 ROM: 2 h Apgar*: 8/9 BW: 4.15 kg Del: Vaginal	Maternal: Fever 37.7°C; iv Ampicillin 40 min before delivery. Infant: Nasal congestion and cough for 1 wk; retractions and tachypnea, vomiting with cough anorexia for 1 day. Exposure to pneumonia and upper respiratory infection	Alert, intercostal retractions, bilateral wheezing, clear nasal discharge	T = 37.1°C P = 156/min	CBC: WBC = 3, S = 27%, L = 6%, M = 9%, O = 3% CSF: WBC = 3, M = 100%, G = 45 mg/dl, P = 48 mg/dl CXR = Normal (RSV ELISA)	iv ampicillin/Cefotax for 2 days iv Cefotax for 8 days	Blood: + CSF: − Urine: −	Pen-resistant Cefotax = intermediate	Survived No sequelae

https://journals.lww.com/pidj/Fulltext/1999/11000/Neonatal_Streptococcus_pneumoniae_infection__case.16.aspx

https://journals.lww.com/pidj/Abstract/1995/05001/Emergence_of_resistant_Streptococcus_pneumoniae__a.4.aspx

https://pubmed.ncbi.nlm.nih.gov/1617076/

Clinical resistance to penicillin in Streptococcus pneumoniae was first reported by researchers in Boston in 1965; subsequently, this phenomenon was reported from Australia (1967) and South Africa (1977). Since these early reports, penicillin resistance has been encountered with increasing frequency in strains of S. pneumoniae from around the world. In South Africa strains resistant to penicillin and chloramphenicol as well as multiresistant strains have been isolated. Similar patterns of resistance have been reported from Spain. Preliminary evidence points to a high prevalence of resistant pneumococci in Hungary, other countries of Eastern Europe, and some countries in other areas of Europe, notably France. In the United States most reports of resistant pneumococci come from Alaska and the South, but resistance is increasing in other states and in Canada. Pneumococcal resistance has also been described in Zambia, Japan, Malaysia, Pakistan, Bangladesh, Chile, and Brazil; information from other African, Asian, and South American countries is not available. The rising prevalence of penicillin-resistant pneumococci worldwide mandates selective susceptibility testing and epidemiological investigations during outbreaks.

https://www.cdc.gov/mmwr/preview/mmwrhtml/00040449.htm

- https://pubmed.ncbi.nlm.nih.gov/8994784/