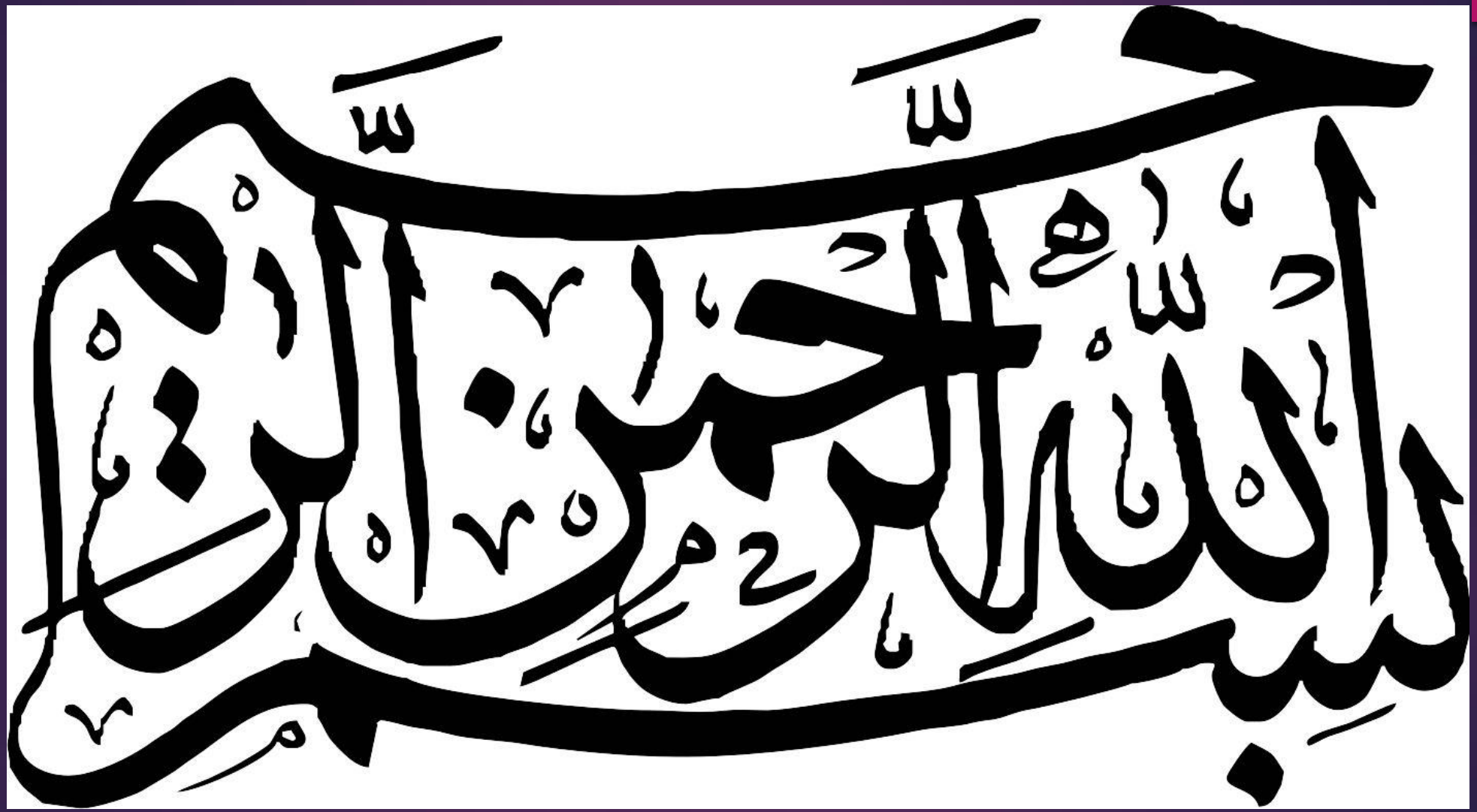
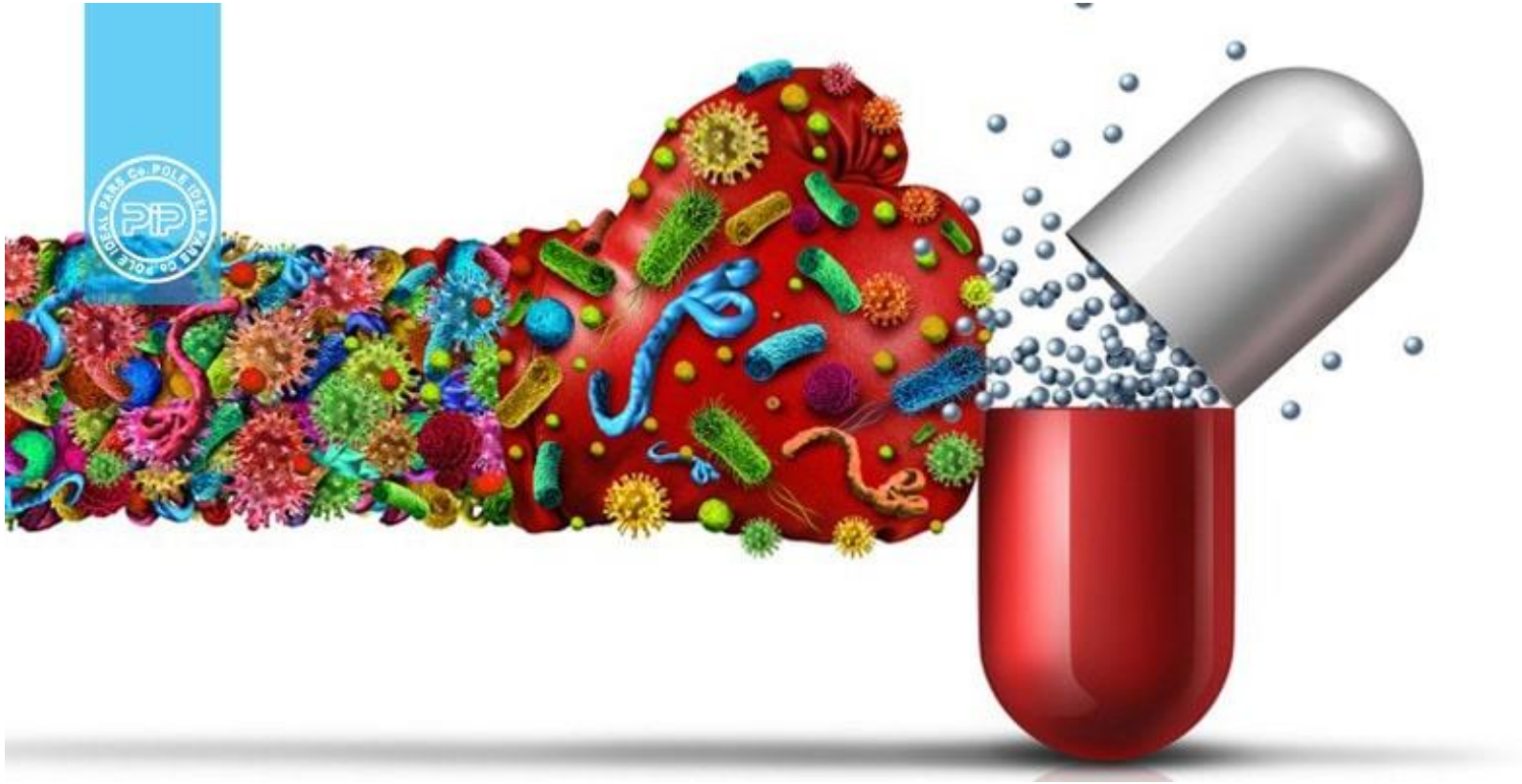

بسم الله الرحمن الرحيم

مقاومت آنتی بیوتیکی

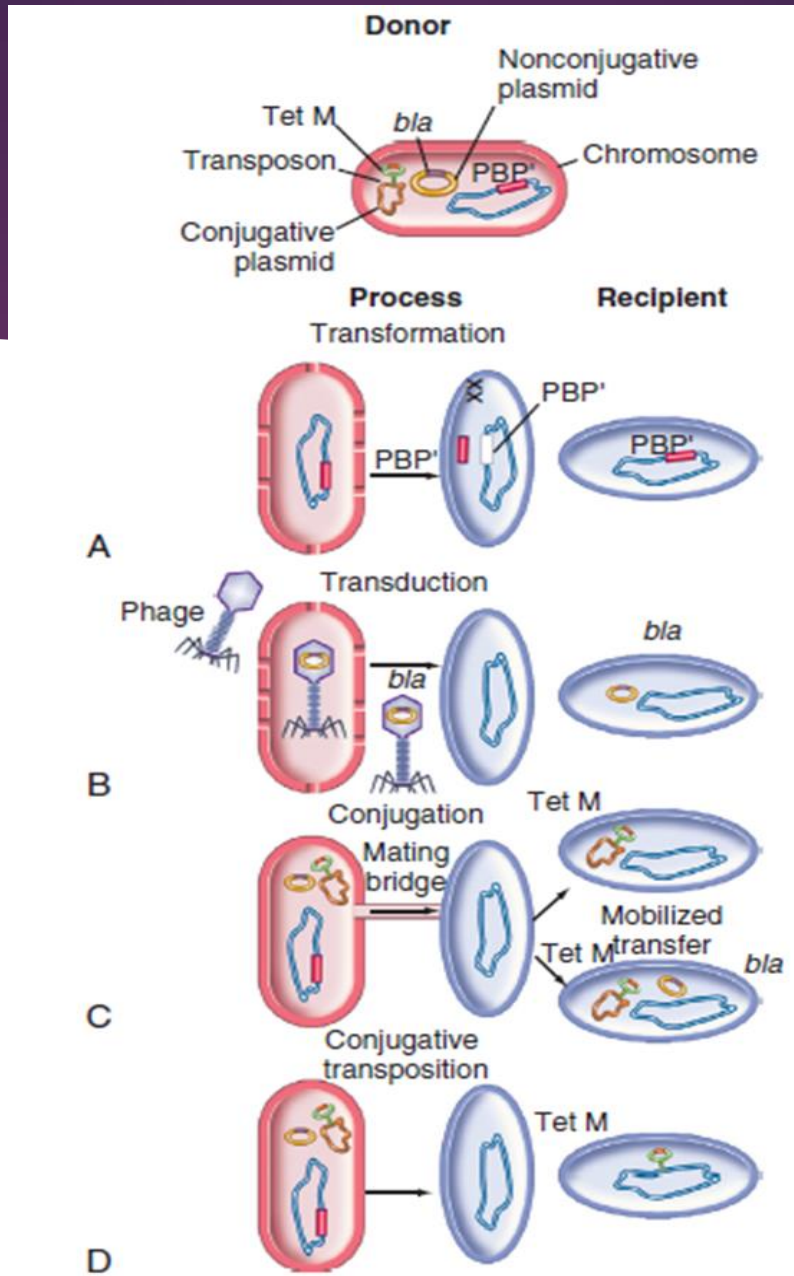
تعریف آنتی بیوتیک

- آنتی بیوتیکها داروهایی هستند که عفونت هایی را که به وسیله باکتریها و انگل های خاصی ایجاد میشوند را از بین می برند
- آنتی بیوتیک ها به روشهای مختلفی عمل می کنند
- Bacteriocid
- Bacteroistatic
- آنتی بیوتیک های وسیع الطیف
- آنتی بیوتیک های با طیف محدود



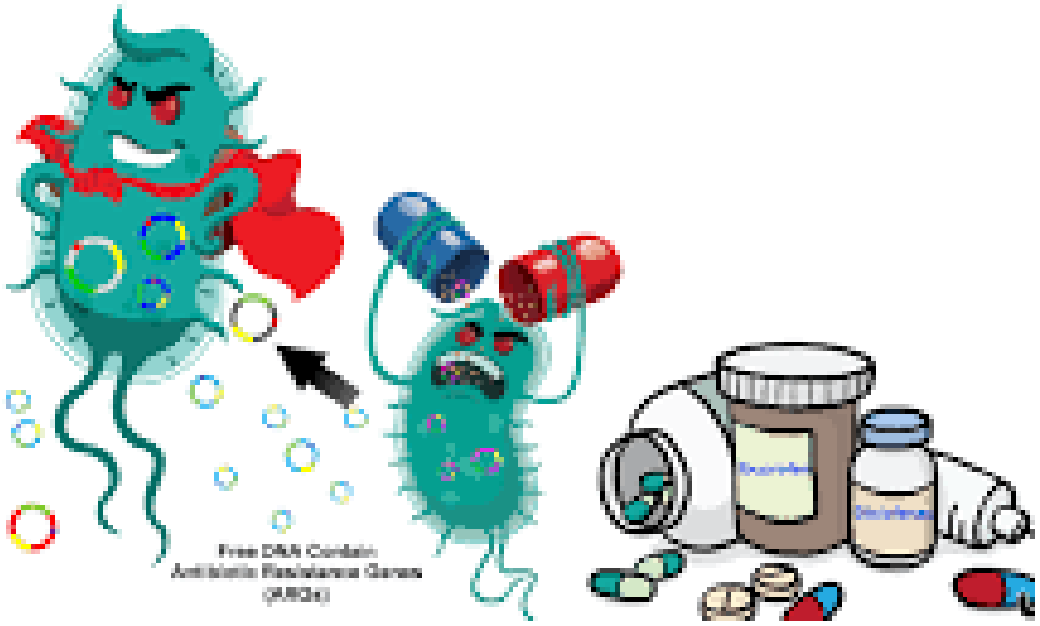
مقاومت آنتی بیوتیکی

- منظور از مقاومت میکروبی چیست
- در مقاومت میکروبی میکروبها در می یابند که چگونه اثر داروها برای کشتن و یا ضرر زدن به آنها را متوقف کنند اما چگونه
- علل بروز مقاومت میکروبی کدامند
- ژن مقاومت به آنتی بیوتیک می تواند از راههای مختلفی از باکتری مقاوم به باکتری حساس به آنتی بیوتیک منتقل شود


Donor
Nonconjugative plasmid
Tet M
bla
Transposon
PBP'
Chromosome
Conjugative plasmid
Process
Recipient
Transformation
PBP'
PBP'
PBP'
A
Transduction
Phage
bla
bla
B
Conjugation
Tet M
Mating bridge
Mobilized transfer
Tet M
bla
C
Conjugative transposition
Tet M
D

پیامد های مقاومت میکروبی

- مشکل جدی در درمان عفونت های کوچک وساده
- گسترش مقاومت چند وجهی میکروبهای مقاوم
- مشکل بودن درمان ویا غیر ممکن بودن درمان میکروبهای مقاوم به چند آنتی بیوتیک
- بستری طولانی تر در بیمارستان وپرداخت هزینه بیشتر
- گسترش باکتری های مقاوم با سرعت فراوان در بین اعضای خانواده وهمکاران وغیره


Free DNA Contain
Antibiotic Resistance Genes
(ARGs)

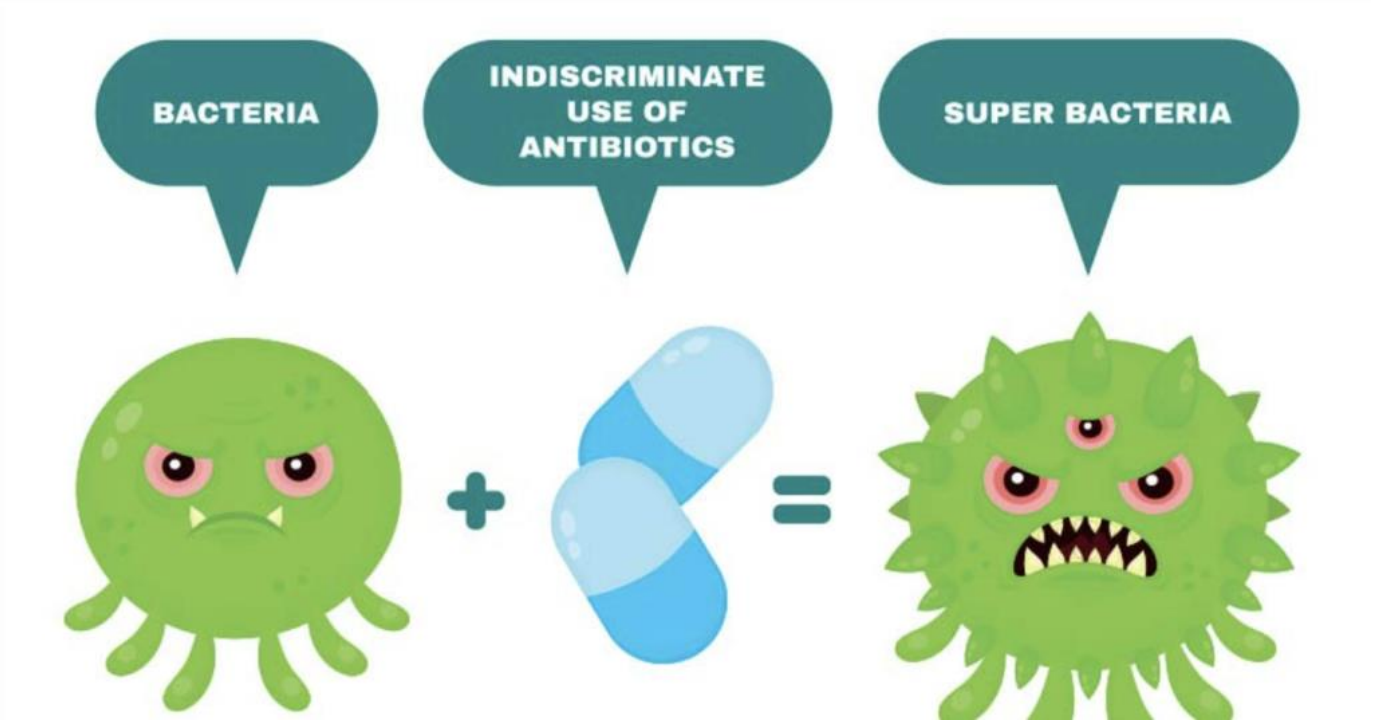
چه عواملی در ایجاد مقاومت میکروبی موثر است

- عوامل اجتماعی اقتصادی بهداشتی موثر بر مصرف آنتی بیوتیک ها توسط مردم
- باورهای غلط خانواده دوستان ویا جامعه
- خود درمانی
- درمان ناقص ونادرست
- مصرف غیر ضروری مثلا در سرماخوردگی
- مصرف کمتر از حد مطلوب آنتی بیوتیک
- تجویز غیر ضروری آنتی بیوتیک ها توسط پزشکان
- پوشیده شدن علائم بیماری به علت مصرف خود سرانه دارو
- ندادن اطلاعات کافی به پزشک در مورد سابقه بیماری وداروهای دریافتی

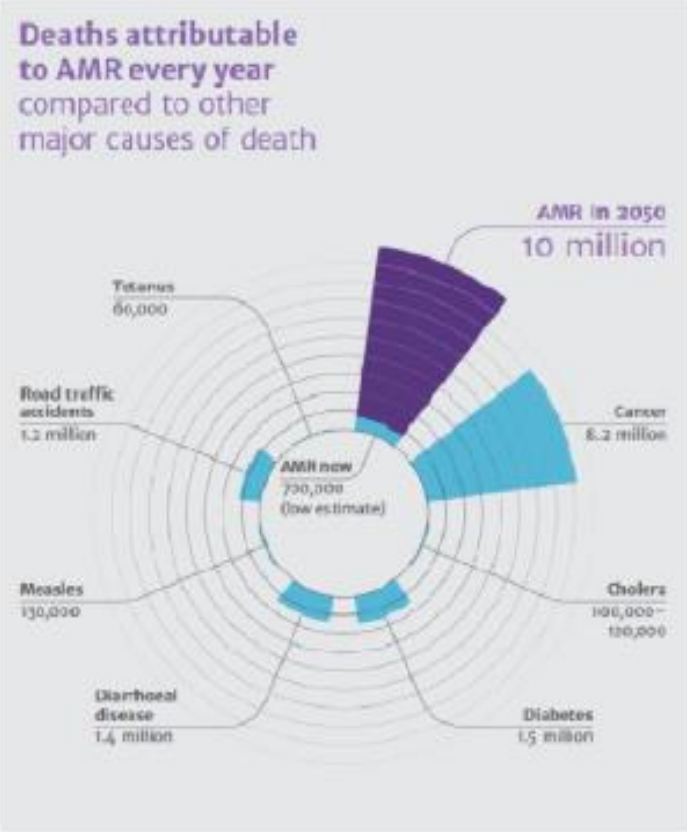
- Antibiotic resistance is rising to dangerously high levels in all parts of the world. New resistance mechanism are emerging and spreading globally threatening our ability to treat common infectious diseases.
- Where antibiotics can be bought for human or animal use without a prescription the emergence and spread resistance is made worse . Similarly in countries without standard treatment guidelines antibiotics are often over-prescribed by health workers and veterinarians and over-used by the public .

- Without urgent action we are heading for a post – antibiotic era in which common infectious and minor injuries can once again kill.
- **Overuse-misuse and inappropriate use**

- Antimicrobial resistance [AMR] is still a growing and global health problem
- Prevention and control of AMR can be achieved by:
- Prudent use of existing of antimicrobial agents.
- Good hygiene practices [infection control]
- Novel antimicrobial agents active on resistant bacteria .
- Need to ascertain the perceived gap between
- Infectious due to resistant bacteria
- Development of novel aimed at treating such infections


BACTERIA
INDISCRIMINATE USE OF ANTIBIOTICS
SUPER BACTERIA

Why are antibiotics and antimicrobial resistance important?



- Use of antibiotics has an impact not just for the patient using them but the global community as well

The tragedy of the commons

Individual benefit:

Immediate effectiveness of antibiotics against disease

Common externalities:

Other patients: antibiotic-resistant infections

Society: reduced antibiotic effectiveness and higher healthcare costs

Mechanisms of resistance of Gram-positive bacteria

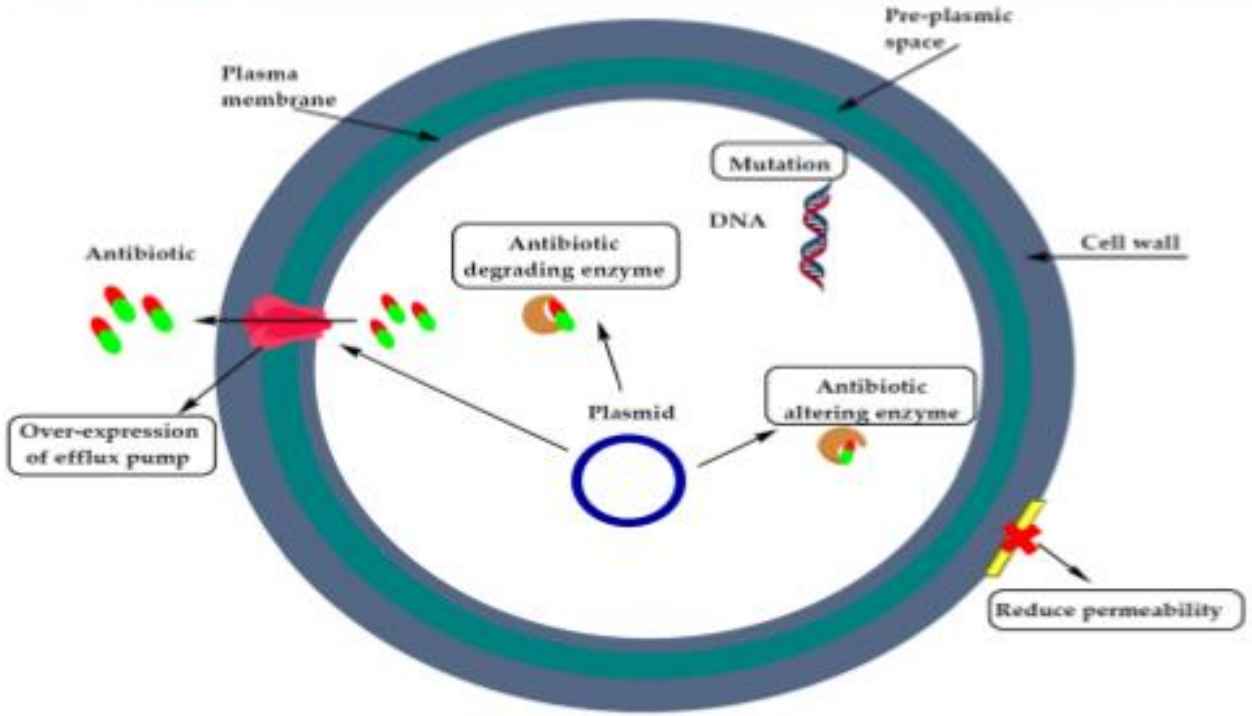


Figure 2. Mechanisms of resistance of Gram-positive bacteria.

Selected resistant bacteria of public health importance

- Based on the most frequent bacteria responsible for bloodstream infections
- Certain resistances were used as indicators for multidrug resistance
- 3 most frequent gram positive resistant bacteria:
- *Methicillin – resistant staphylococcus aureus [MRSA]*
- *Vancomycin –resistant enterococcus faecium[VRE]*
- *Penicillin –resistant streptococcus pneumonia[PRSP]*


ANTIBIOTIC
ANTIBIOTIC

Recent developments

- During the last decade 11 antibiotics with main activity against gram-positive microorganism have received international regulatory approved ,ie,.ceftobiprole;ceftroline;telavancin;oritavancin;dalbavancin;tedizolid;besifloxacin;delafloxacin;ozenoxacin; omadacycline;and lefamulin
- Specifically emerging options for gram-positive cocci we reviewed include ceftaroline ;ceftobiprole;tedizolid;dalbavancin and fosfomycin

Common MDR microorganisms of clinical relevance, main resistance mechanisms, and current/emerging antimicrobial options.

	Mechanism(s) of Resistance	Current Options	Emerging Options
GRAM-POSITIVE COCCI			
Methicillin-resistant staphylococci (MRSA, MRCoNS)	PBP2a expression	Daptomycin, Linezolid	Ceftaroline, Ceftobiprole, Tedizolid, Dalbavancin, Fosfomycin
Vancomycin intermediate *Staphylococcus aureus* (VISA)	Chromosomal mutations	Daptomycin, Linezolid	Tedizolid, Dalbavancin
Vancomycin resistant *Staphylococcus aureus* (VRSA)	*vanA* gene expression	Daptomycin, Linezolid	Tedizolid, Dalbavancin
Ampicillin-resistant enterococci (ARE)	PBP mutation/overexpression	Vancomycin, Linezolid, Daptomycin	Dalbavancin, Ceftobiprole
Vancomycin-resistant enterococci (VRE)	*vanA*, *vanB* gene expression	Linezolid, Daptomycin	Tedizolid, Dalbavancin
Penicillin-resistant *Streptococcus pneumoniae* (PRSP)	PBP mutation	Ceftriaxone	Ceftaroline, Ceftobiprole, Tedizolid

Multi-drug-resistant organisms

- When discussing 'multi-drug-resistant' organisms (MDRO), we currently refer to a standardized and well-accepted classification dividing clinically relevant bacteria into multi-drug resistant **(MDR)**, extensively drug resistant **(XDR)**, and pan-drug resistant **(PDR)** .

- **In this classification, MDR is defined as nonsusceptibility (or intermediate resistance) to at least one molecule in three or more categories of antibiotics.**

S. aureus

- The most successful resistant Gram-positive coccus has been S. aureus.
- S. aureus is often resistant to penicillin, due to the production of lactamases, and methicillin, due to the mutation of transpeptidase binding site of PBP2 **(giving rise to PBP2a).**
- It can become nonsusceptible to vancomycin as vancomycin intermediate strains (**VISA**), due to multiple mutations leading to a thickened, poorly crosslinked cell wall, or
- **true vancomycin resistant strains (VRSA): vanA- or vanB.**

Enterococci

- In enterococci, resistance mostly affects three drug classes:
  - **penicillin/ampicillin,**
  - **high-level gentamicin**
  - **vancomycin.**
- PBP
- B- Lactamase

- **Vancomycin-resistance, more common in E. feacium strains. (due to the vanA or vanB)**

- Whilst intrinsic resistance to gentamicin derives from decreased cell wall permeability or low-level expression of aminoglycoside-modifying enzymes, high-level resistance to gentamycin is common and results from high-level expression of aminoglycoside-modifying enzymes .
- **These MDR/XDR enterococci often retain susceptibility to linezolid.**

Antibiotic resistance in enterococci

- **E. faecium—Vancomycin-Resistant:**
- Vancomycin-resistance gene clusters (such as, van A, B, D, and M) are responsible for the **low binding affinity of vancomycin.** Van A gene cluster is the most common type.

- **vancomycin resistance in Enterococcus (VRE) :**
  MIC of ≥ 32 μg/ml
- **intermediate resistance as: 8–16**
- **susceptible as ≤ 4**

S. pneumoniae

- MDR streptococci are also emerging, although not to the extent of other pathogenic Gram-positive cocci.
- The most common mechanisms of resistance include PBP affecting penicillin, ampicillin, and amoxicillin .
  - Ribosomal methylases, such as ermB
  - efflux pump (e.g., mef)
  - gyrase/topoisomerase IV

Vancomycin

- **Glycopeptide antibiotic**

Mechanism of Action: inhibits the cell wall synthesis of Gram-positive bacteria

Vancomycin Resistance in S. aureus

CLSI

- S. aureus complete vancomycin resistance: (VRSA):MIC of ≥16 µg/mL
- Intermediate resistance(VISA) : 4–8 µg/mL
- susceptible as ≤2 µg/mL

EUCAST

- MIC of vancomycin susceptible S. aureus:

  ≤ 2 µg/mL

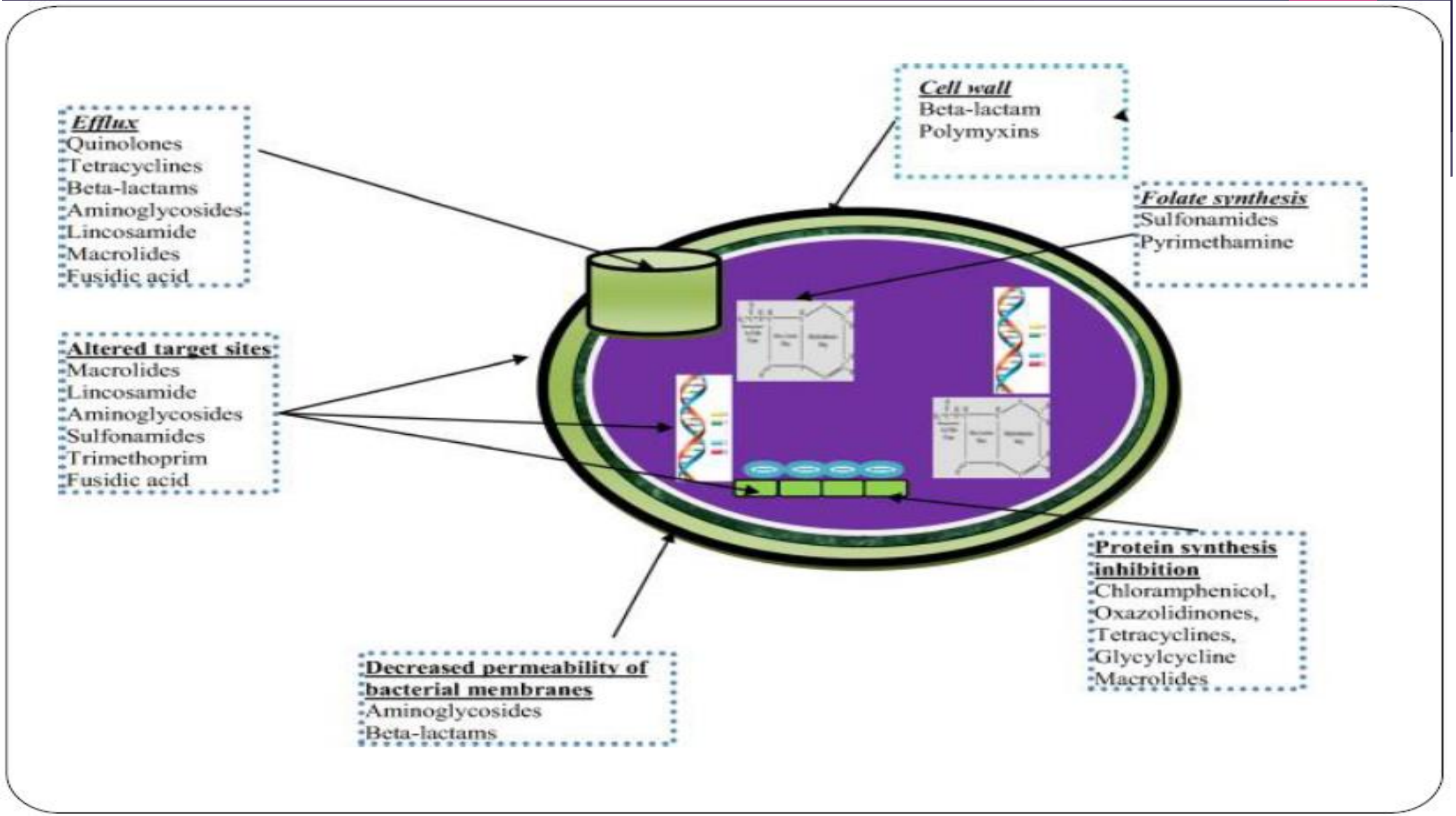
- vancomycin-resistant S. aureus to be >2 µg/mL

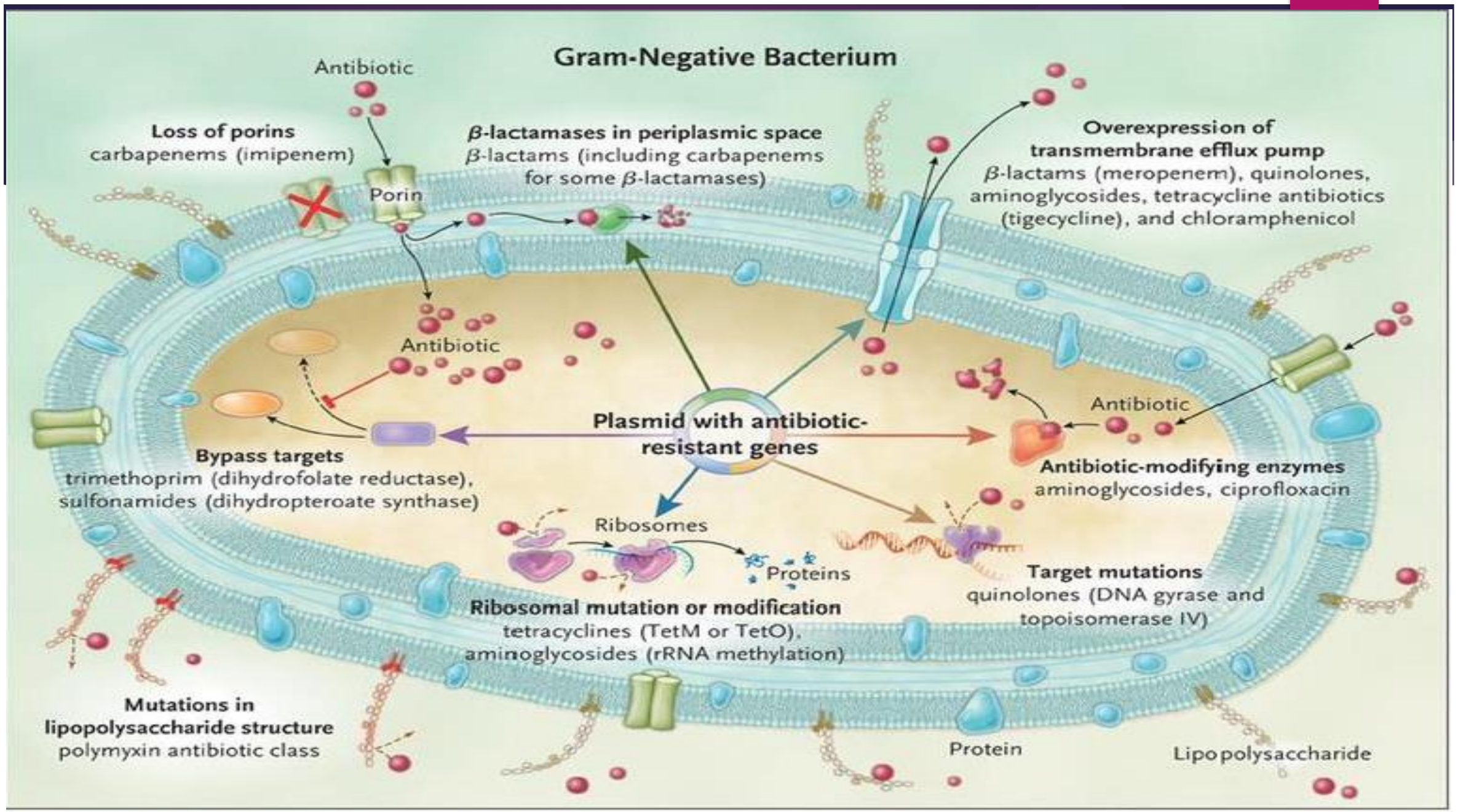
Vancomycin

- **loading dose of 25 to 30 mg/kg**
- In adults with normal renal function, the maintenance dose is 15 to 20 mg/kg every 12 hours.
- (obtaining trough levels ≤15 µg/mL).
- For serious infections caused by MRSA, such as **endocarditis, bacteremia, osteomyelitis, meningitis, HAP, and severe ABSSSI, recommends trough vancomycin between 15 and 20 µg/mL.**
- **Trough vancomycin serum level should be obtained before the fourth dose.**

Mechanisms of antibacterial resistance

- Efflux
- Altered target sites
- Decreased permeability of bacterial membranes
- Protein synthesis inhibition
- Fulate synthesis
- Cell wall


Efflux
Quinolones
Tetracyclines
Beta-lactams
Aminoglycosides
Lincosamide
Macrolides
Fusidic acid
Cell wall
Beta-lactam
Polymyxins
Folate synthesis
Sulfonamides
Pyrimethamine
Altered target sites
Macrolides
Lincosamide
Aminoglycosides
Sulfonamides
Trimethoprim
Fusidic acid
Protein synthesis inhibition
Chloramphenicol,
Oxazolidinones,
Tetracyclines,
Glycylcycline
Macrolides
Decreased permeability of bacterial membranes
Aminoglycosides
Beta-lactams


Gram-Negative Bacterium
Antibiotic
Loss of porins
carbapenems (imipenem)
Porin
β-lactamases in periplasmic space
β-lactams (including carbapenems
for some β-lactamases)
Overexpression of
transmembrane efflux pump
β-lactams (meropenem), quinolones,
aminoglycosides, tetracycline antibiotics
(tigecycline), and chloramphenicol
Antibiotic
Plasmid with antibiotic-
resistant genes
Antibiotic
Bypass targets
trimethoprim (dihydrofolate reductase),
sulfonamides (dihydropteroate synthase)
Antibiotic-modifying enzymes
aminoglycosides, ciprofloxacin
Ribosomes
Proteins
Target mutations
quinolones (DNA gyrase and
topoisomerase IV)
Ribosomal mutation or modification
tetracyclines (TetM or TetO),
aminoglycosides (rRNA methylation)
Mutations in
lipopolysaccharide structure
polymyxin antibiotic class
Protein
Lipopolysaccharide

Mechanisms of resistance of gram-negative bacteria

1-the most common mechanism of resistance is production of b-lactamses

2-down –regulation of porins

3-efflux pumps most common in p.aeruginosa

Combination therapy

1. Empiric

- HAP/VAP/septic shock
- Pts at risk for MDR
- High risk of p.aeruginosa

2.Targeted

- P.aeruginosa;only in empiric initial choice
- A.baumanii
- K.pneumoniae[KPC]

- The use of B-lactams should be maximized with the administration of high dosages and prolonged infusion strategies maximizing the time above the MIC [t>MIC]
- A loading dose followed by maintenance doses with extended or continuous infusion is recommended

Ambler Classification of β-Lactamases

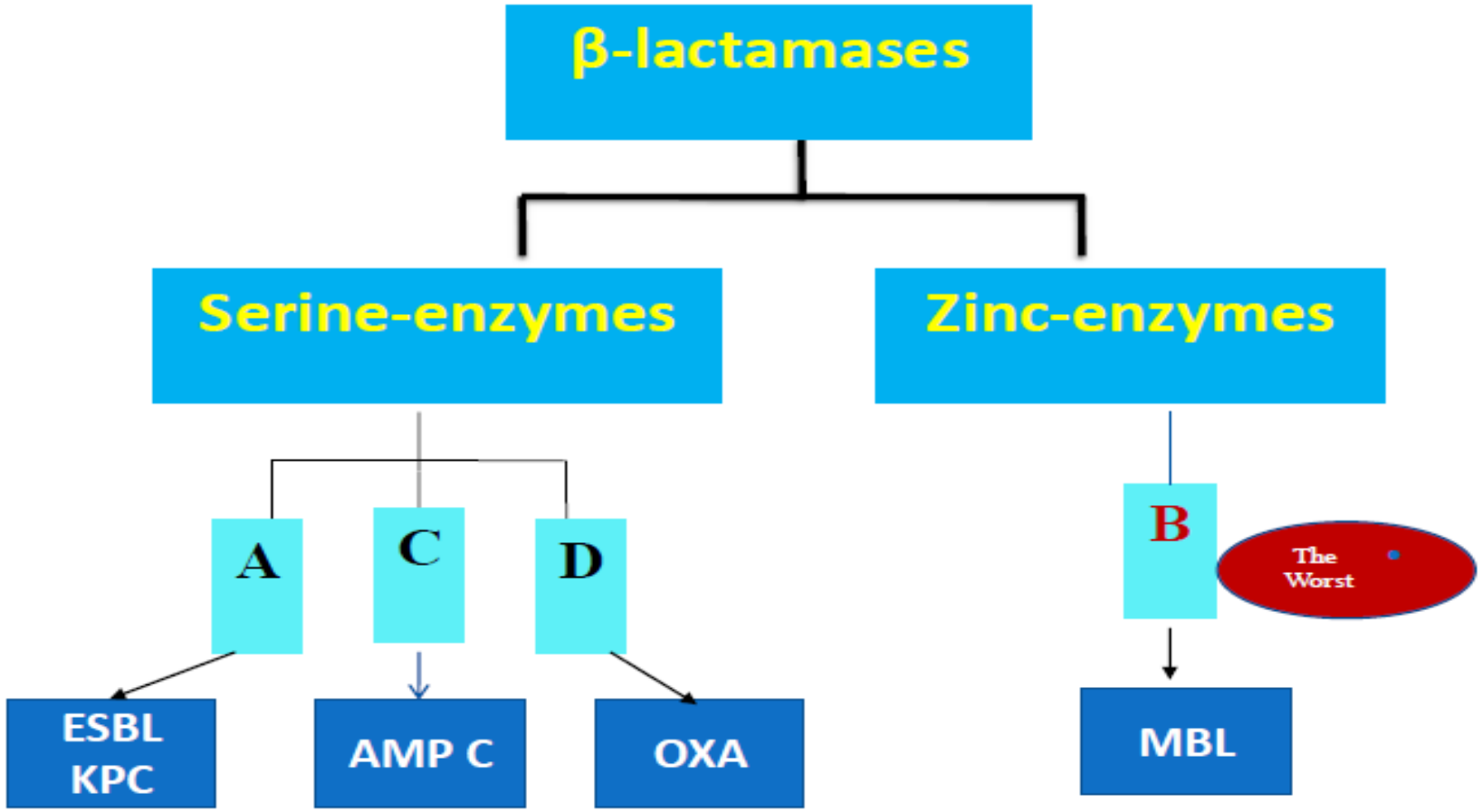


TABLE 20.1 Classification of β-Lactamases

AMBLER MOLECULAR CLASS	MAJOR SUBTYPES[a]	PREFERRED SUBSTRATES	INHIBITOR[b]	MAIN GENETIC LOCALIZATION	REPRESENTATIVE ENZYME(S)
A	Gram-positive β-lactamase 2a	Penicillins	Clavulanic acid	Chromosome or plasmid	PC1
	Gram-negative β-lactamase 2b	Penicillins, early cephalosporins	Clavulanic acid	Plasmid or chromosomal	TEM-1, SHV-1
	Extended-spectrum β-lactamase 2be	Penicillins, extended-spectrum cephalosporins, aztreonam	Clavulanic acid	Plasmid	TEM-24, SHV-12, CTX-M-15
	Inhibitor-resistant TEM β-lactamase 2br	Penicillins	Clavulanic acid[c]	Plasmid	TEM-30, SHV-10
	Carbenicillin-hydrolyzing β-lactamase 2c	Carbenicillin	Clavulanic acid[c]	Plasmid	PSE-1, CARB-3
	Cephalosporin-hydrolyzing β-lactamase 2e	Extended-spectrum cephalosporins	Clavulanic acid	Chromosome	CepA
	Carbapenem-hydrolyzing β-lactamase 2f	Carbapenems	Avibactam[d]	Chromosome or plasmid	KPC-2, SME-1
B	Metallo-β-lactamase 3a	All β-lactams except monobactam	EDTA, divalent cation chelators	Chromosome or plasmid	IMP-1, VIM-2, NDM-1
C	AmpC-type β-lactamase 1	Cephalosporins	Cloxacillin, avibactam	Chromosome or plasmid	AmpC, CMY-2
D	Oxacillin-hydrolyzing β-lactamase 2d	Oxacillin	Clavulanic acid[c]	Chromosome or plasmid	OXA-1, OXA-10
	Extended-spectrum β-lactamase 2de	Extended-spectrum cephalosporins	Clavulanic acid[c]	Plasmid	OXA-11, OXA-15
	Carbapenem-hydrolyzing β-lactamase 2df	Carbapenems	None[e]	Plasmid	OXA-23, OXA-40, OXA-48

[a]The updated Bush-Jacoby group[3] is indicated

Conclusions

- *Knowledge of mechanisms of action and resistance pattern allows physicians to increasingly drive antimicrobial treatment towards a precision medicine approach.*
- *Strict adherence to antimicrobial stewardship practices will allow us to preserve the emerging antimicrobials for our future.*

Thank you for your attention