Intrinsic antibiotic resistance

Fariba Dinarvand

Head of Microbiology Department - Reference Laboratory of the Social Security Organization

CAUSES OF ANTIBIOTIC RESISTANCE

HANDLE ANTIBIOTICS WITH CARE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

Over-prescribing of antibiotics

Patients not finishing their treatment

Over-use of antibiotics in livestock and fish farming

Poor infection control in hospitals and clinics

Lack of hygiene and poor sanitation

Lack of new antibiotics being developed

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www.who.int/drugresistance

#AntibioticResistance

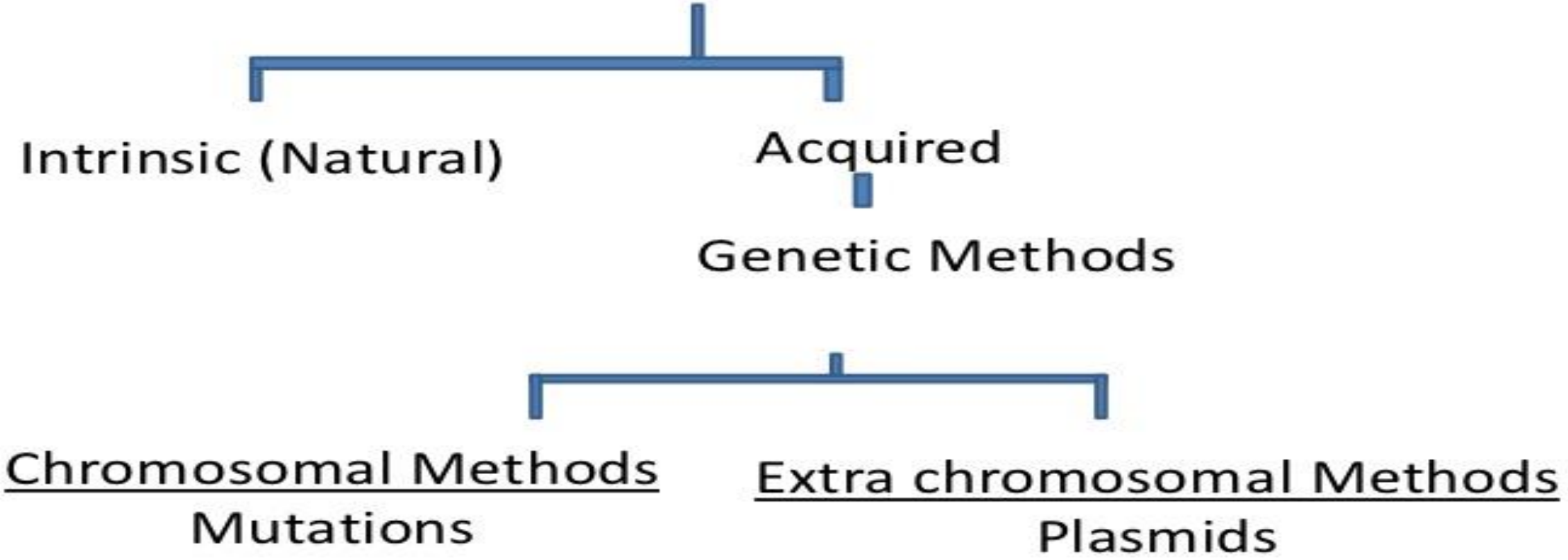
World Health Organization

Some microorganisms may ‘born’ resistant,

some ‘achieve’ resistance by mutation or some

have resistance ‘thrust upon them’ by plasmids

Mechanism Antibiotic Resistance



Natural & acquired resistance

Natural resistance

- Chromosomic genetic support
- Affect almost all species strains
- Existed before antibiotic use (*Enterobacter sp.* - amoxicillin)

Acquired resistance (mutation)

- Chromosomic, plasmidic or transposon genetic support
- Affects a fraction of strains
- Increased with antibiotic use
  (extended spectrum beta-lactamase producing *E. coli)*

Intrinsic resistance - they're born with it

Another example of intrinsic resistance occurs with vancomycin. This drug interferes with cell wall assembly, but it is only active against Gram-positive cells because vancomycin can't cross the outer membrane of Gram-negative bacteria. (Clearly, it pays to be Gram-negative.)

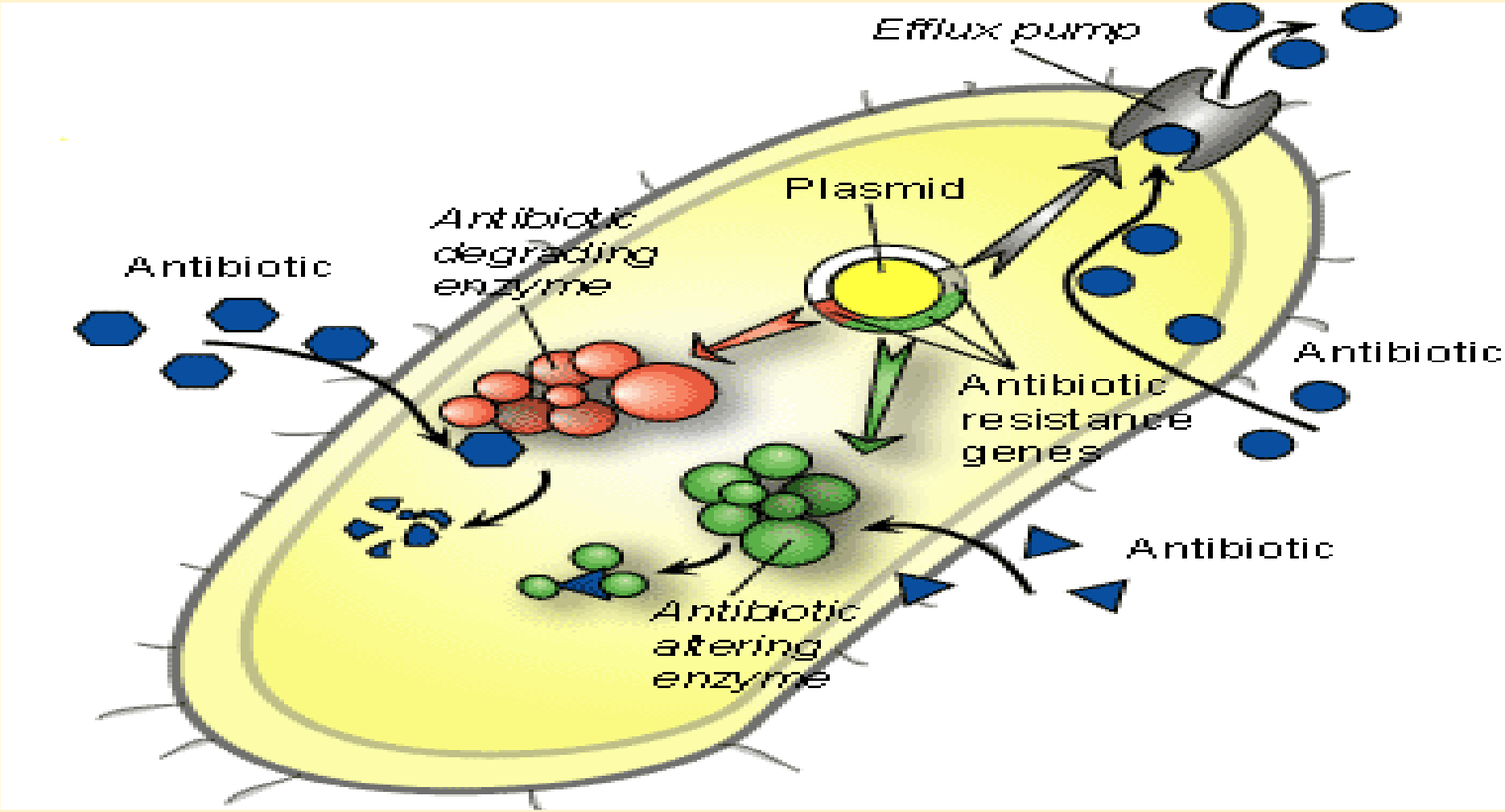
Gram-positive bacteria, on the other hand, are bound by a cytoplasmic membrane surrounded by a layer of peptidoglycan. This layer of peptidoglycan actually allows rather larger molecules to pass through, as does the cytoplasmic membrane. These factors make the Gram-positive bacteria intrinsically susceptible to antibiotics.

For example, daptomycin readily kills Gram-positive bacteria, but it doesn't kill Gram-negative bacteria. This is because anionic phospholipids in the cytoplasmic membrane help daptomycin enter the cell - Gram-positive bacteria have a lot of these, Gram-negatives don't.

Knowledge of the inherent resistance of bacteria can be useful in at least 5 ways:

1) They provide a way to evaluate the accuracy of testing methods
2) They aid in the recognition of common phenotypes
3) They can assist with verification of cumulative antimicrobial susceptibility test data.
4) It prevents of false statistics report in the microbial resistance of hospitals.
5) Choosing the correct disk cause saves the responsing time and the costs of lab.

How Bacteria Survive Antibiotic Treatment

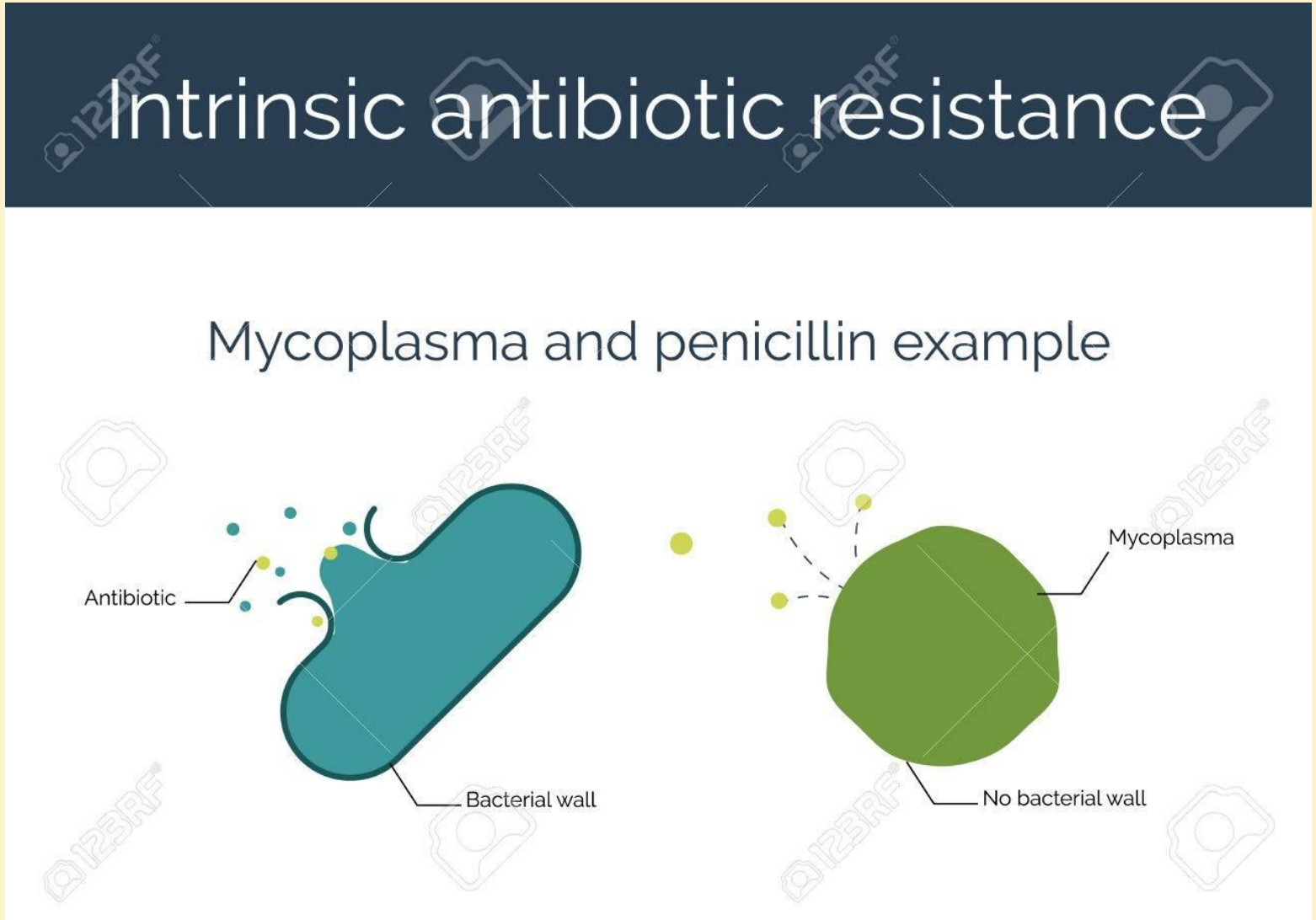


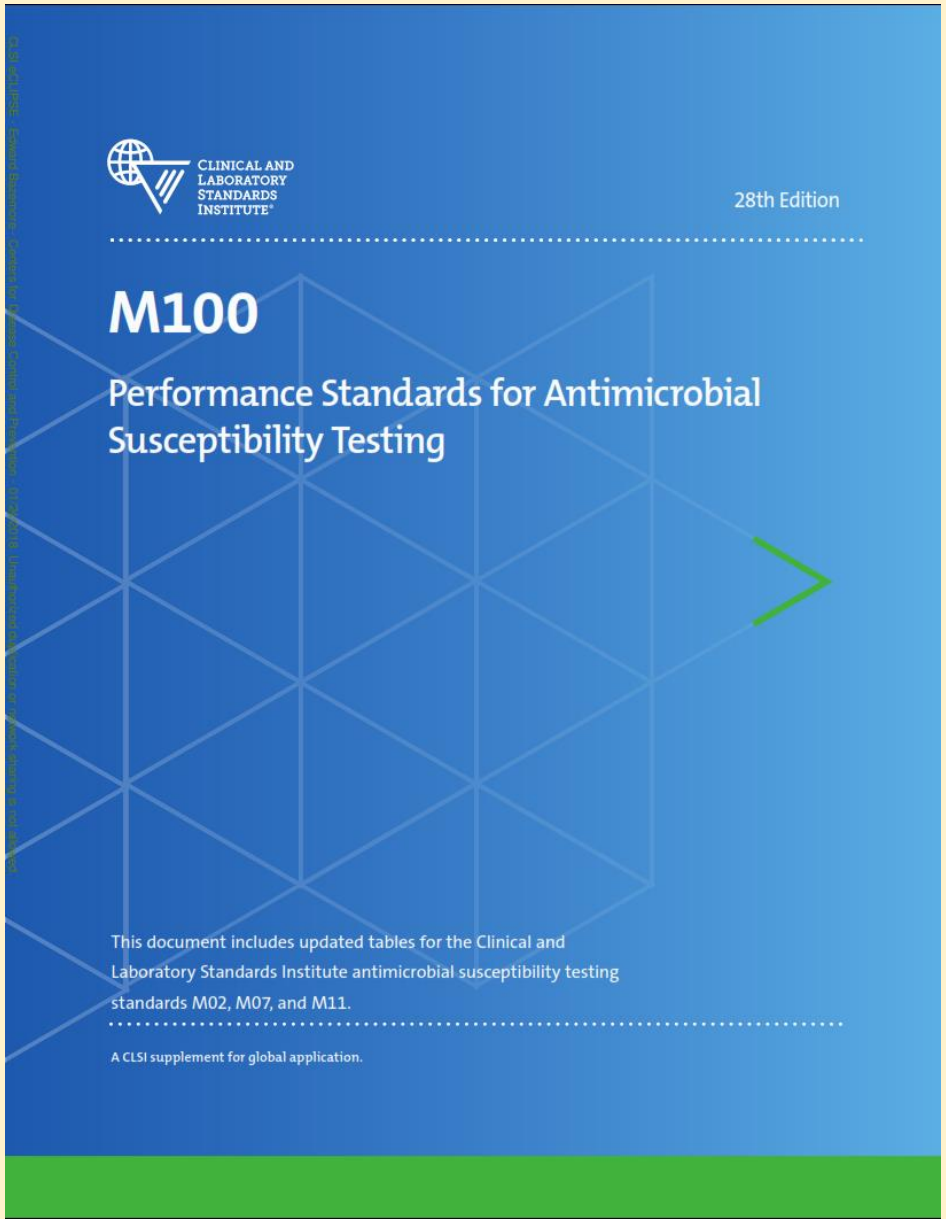
Intrinsic Resistance

It occurs naturally.

1. **Lack target :**
   - No cell wall; innately resistant to penicillin
2. **Innate efflux pumps:**
   - Drug blocked from entering cell or ↑ export of drug (does not achieve adequate internal concentration). Eg. *E. coli*, *P. aeruginosa*
3. **Drug inactivation:**
   - Cephalosporinase in *Klebsiella*

Intrinsic resistance - they're born with it




CLINICAL AND LABORATORY STANDARDS INSTITUTE®
28th Edition
M100
Performance Standards for Antimicrobial Susceptibility Testing
This document includes updated tables for the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M02, M07, and M11.
A CLSI supplement for global application.

Available tables have intrinsic strengths in two groups (CLSI 2018) :

- **Optional aerobic :** ***Enterobacteriaceae B1 table ,NonEnterobacteriaceae B2 table,*** **Staphylococci B3 table,** ***Enterococcus*** **spp B4 table**

- **Anaerobic bacteria: Gram-Positive Bacilli B5 table , Gram-Negative Bacilli B6 table,**

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Enterobacter *aerogenes* ⟹ ***Klebsiella*** *aerogenes*

جدول روند تکاملی گزارش « مقاومت ذاتی » باکتری های مختلف در مستند CLSI

Bacteria ' Family	Tables	Report' year
Enterobacteriaceae	B1	2011
Enterobacteriaceae	B1	2012
Enterobacteriaceae	B1	2013
Enterobacteriaceae / Non Enterobacteriaceae /Staphylococci	B1+ B2 + B3	2014
Enterobacteriaceae / Non Enterobacteriaceae /Staphylococci / Enterococcus spp	B1+ B2 + B3 + B4	2015
Enterobacteriaceae / Non Enterobacteriaceae /Staphylococci /Enterococcus Spp/Anaerobic Gram Positive Bacilli / Anaerobic Gram Negative Bacill	B1+ B2 + B3 +B4+ B5 + B6	2016
Enterobacteriaceae / Non Enterobacteriaceae /Staphylococci /Enterococcus Spp/Anaerobic Gram Positive Bacilli / Anaerobic Gram	B1+ B2 + B3 +B4+	2017

B1. *Enterobacteriaceae*

Organism \ Antimicrobial Agent	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporin I: Cefazolin, Cephalothin	Cephamycins: Cefoxitin, Cefotetan	Cephalosporin II: Cefuroxime	Imipenem	Tetracyclines	Tigecycline	Nitrofurantoin	Polymyxin B Colistin	Aminoglycosides
Citrobacter freundii	R	R	R			R	R	R						
Citrobacter koseri	R			R	R									
Enterobacter aerogenes	R	R	R			R	R	R						
Enterobacter cloacae complex	R	R	R			R	R	R						
Escherichia coli	There is no intrinsic resistance to β-lactams in this organism.													
Escherichia hermannii	R				R									
Hafnia alvei	R	R	R			R	R							
Klebsiella pneumoniae	R				R									
Morganella morganii	R	R				R		R	*		R	R	R	
Proteus mirabilis	There is no intrinsic resistance to penicillins and cephalosporins in this organism.								*	R	R	R	R	
Proteus penneri	R					R		R	*	R	R	R	R	
Proteus vulgaris	R					R		R	*	R	R	R	R	
Providencia rettgeri	R	R				R			*	R	R	R	R	
Providencia stuartii	R	R				R			*	R	R	R	R	†
Salmonella and *Shigella* spp.	There is no intrinsic resistance to β-lactams in these organisms; refer to **WARNING** below for reporting.													
Serratia marcescens	R	R	R			R	R	R				R	R	
Yersinia enterocolitica	R	R			R	R								

Lists of Bacterial Pathogens Associated with Intrinsic Antibiotic Resistance

Generally, when people (either general public or a physician or laboratory personnel) listen/read the term "antibiotic resistance" they think that, a bacterium which was previously sensitive to a particular antibacterial agent has now developed resistance against it (either through acquisition of gene via horizontal gene transfer or by mutation) but in this universe there are innumerable species of bacteria which are innately resistant to a particular drugs.

According to CLSI 2018, "Intrinsic resistance is so common that susceptibility testing is unnecessary. For example, Citrobacter species are intrinsically resistant to ampicillin".

Intrinsic antibiotic resistance is a naturally occurring phenomenon which is independent of previous antibiotic exposure and is not caused by a horizontal gene transfer. Remember the famous example of intrinsic resistance, penicillin not working against Mycoplasma. Penicillin kills bacteria by interfering with their cell wall synthesis.

Intrinsic Antibiotic Resistance in Gram Negative Bacteria

Bacterial pathogen that are Intrinsically resistance to Ampicillin

1. *Acinetobacter baumanni complex*
2. *Citrobacter freundii*
3. *Citrobacter koseri*
4. *Enterobacter aerogenes*
5. *Enterobacter cloacae complex*
6. *Klebsiella pneumoniae*
7. *Morganella morganii*
8. *Proteus vulgaris*
9. *Pseudomonas aeruginosa*
10. *Serratia marcescens*
11. *Yersinia enterocolitica*

Bacterial pathogens that are Intrinsically Resistant to

Amoxicillin - Clavulanate combination

1. *Citrobacter freundii*
2. *Enterobacter aerogenes*
3. *Enterobacter cloacae complex*
4. *Morganella morganii*
5. *Pseudomonas aeruginosa*
6. *Serratia marcescens*
7. *Yersinia enterocolitica*

Bacterial pathogens that are Intrinsically Resistant to

Ampicillin-sulbactam combination

1. *Citrobacter freundii*
2. *Citrobacter koseri*
3. *Enterobacter aerogenes*
4. *Enterobacter cloacae complex*
5. *Proteus vulgaris*
6. *Pseudomonas aeruginosa*
7. *Serratia marcescens*

Citrobacter koseri is intrinsically resistant to Piperacillin whereas *Proteus* spp is intrinsically resistant to Tetracycline/Tigecycline, Nitrofurantoin and Polymyxin B Colistin .

Acinetobacter baumanni complex is notorious pathogen which is resistant to most of the available antibiotics. It is intrinsically resistant to :

1. Ampicillin, Amoxicillin
2. Aztreonam
3. Ertapenem
4. Trimethoprim
5. Chloramphenicol

Similarly *Pseudomonas aeruginosa* is intrinsically resistant to :

1. Ampicillin, Amoxicillin
2. Ampicillin-sulbactam
3. Amoxicillin-Clavulanate
4. Cefotaxime
5. Ceftriaxone
6. Ertapenem
7. Tetracyclines/Tigecyclines
8. Trimethoprim
9. Trimethoprim-sulfamethoxazole
10. Chloramphenicol

Both *Acinetobacter* and *Pseudomonas* are also intrinsically resistant to penicillin (ie, benzylpenicillin), cephalosporin I (cephalothin,cefazolin), cephalosporin II (cefuroxime), cephamycins (cefoxitin, cefotetan), clindamycin, daptomycin, fusidic acid, glycopeptides(vancomycin, teicoplanin), linezolid, macrolides (erythromycin, azithromycin, clarithromycin), quinupristin-dalfopristin, and rifampin.

***Bacteroides spp*. which is one of the most frequently isolated anaerobic Gram negative bacilli is intrinsically resistant to :**

1. **Aminoglycosides**
2. **Penicillin**
3. **Ampicillin**

Anaerobic Gram positive bacilli, *Clostridium spp* is resistant to:

Aminoglycosides

Intrinsic Antibiotic Resistance in Gram Positive Bacteria

Among gram positive bacteria, *S. saprophyticus* is intrinscially resistance to Novobiocin which is the basis for Novobiocin sensitivity test done in urine isolate (if CONS is isolated).

Enterococcus faecalis/faecium are intrinsically resistant to:

- Cephalosporin*
- Aminoglycosides*
- Clindamycin*
- Trimethoprim
- Trimethoprim-sulfamethoxazole*
- Fusidic acid

****may appear active in vitro but are not effective clinically and should not be reported as susceptible.***

Both Enterococci and Staphylococci are also intrinsically resistant to aztreonam, polymyxin B/colistin, and nalidixic acid.

CLSI COMMENT

Each laboratory should decide which agents to test and report in consultation with institutional leaders representing infectious diseases practitioners, the pharmacy and therapeutics and infection control committees of the medical staff, and the antimicrobial stewardship team. If tested, the result for an antimicrobial agent/organism combination listed as having intrinsic resistance should be reported as resistant. Consideration may be given to adding comments regarding intrinsic resistance of agents not tested.

The intrinsic antibiotic resistome is a naturally occurring phenomenon that predates antibiotic chemotherapy and is present in all bacterial species. In addition to the intrinsic resistance mediated by the bacterial outer membrane and active efflux, studies have shown that a surprising number of additional genes and genetic loci also contribute to this phenotype.

conclusion

Actinobacter bacterial genes, the inherent resistance genes, seem to be the source of the acquired resistance. Hence, the recent desire to study the inherent resistance genes of bacteria is increasing, because the products of these genes may not only be attractive therapeutic targets for the development of new drugs that help the antibiotics to function, but may also Foresee future resistance to pathogenic bacteria.


YOU
CAN
MAKE A
DIFFERENCE
I WILL
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از توجه شما سپاسگزارم