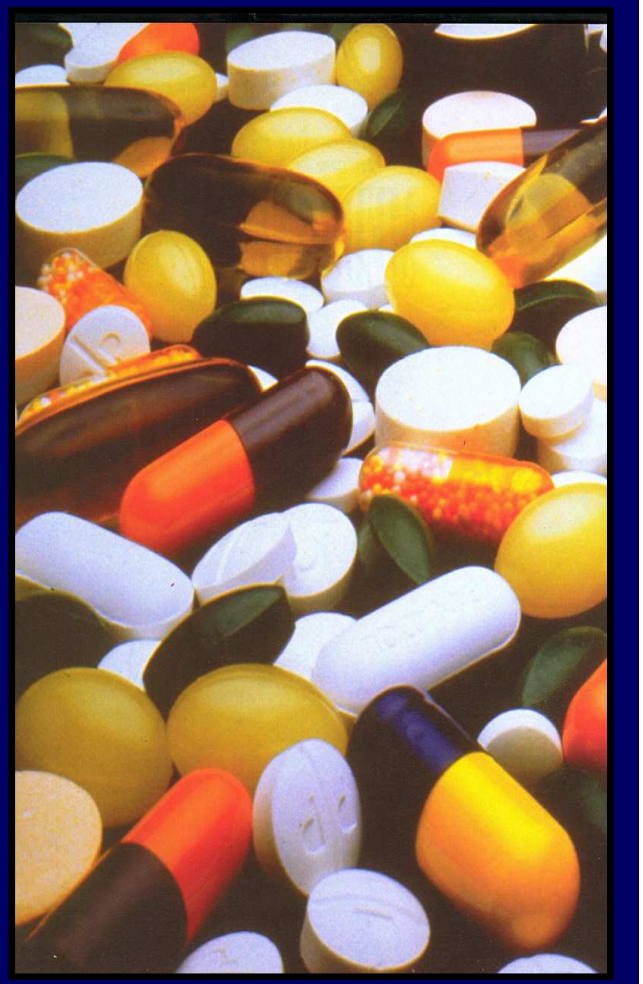
# GENETIC BASIS OF THE RESISTANCE TO ANTIBIOTICS



# INTRODUCTION

-ANTIBIOTICS: LOW-MOLECULAR-WEIGH COMPOUNDS THAT KILL OR INHIBIT THE GROWTH OF BACTERIA

-TYPES: -BACTERICIDAL(KILL BACTERIA)
-BACTERIOSTATIC (ONLY INHIBIT GROWTH)

-CRITERIA TO BE USEFUL:
- -SHOULD HAVE A BROAD SPECTRUM OF ACTIVITY
- -MINIMUM TOXICITY
- -ABLE TO REACH THE PART OF THE HUMAN BODY WHERE THE INFECTION IS OCCURING
- -LEVEL OF BACTERIAL SUSCEPTIBILITY

# SITE OF ACTION

-INHIBITORS OF BACTERIAL CELL WALL SYNTHESIS:

- β-LACTAM AGENTS: PENICILLINS, CEPHALOSPORINS, MONOBACTAMS, CARBAPENEMS
- GLYCOPEPTIDES
- OTHERS: FOSFOMYCIN, BACITRACIN, CYCLOSERINE, ISONIAZID

-INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS:

- TETRACYCLINES
- CHLORAMPHENICOL
- AMONIGLYCOSIDES
- MACROLIDES
- LINCOSAMIDES
- OTHERS: FUSIDIC ACID, LINEZOLID, STREPTOGRAMINS, MUPIROCIN

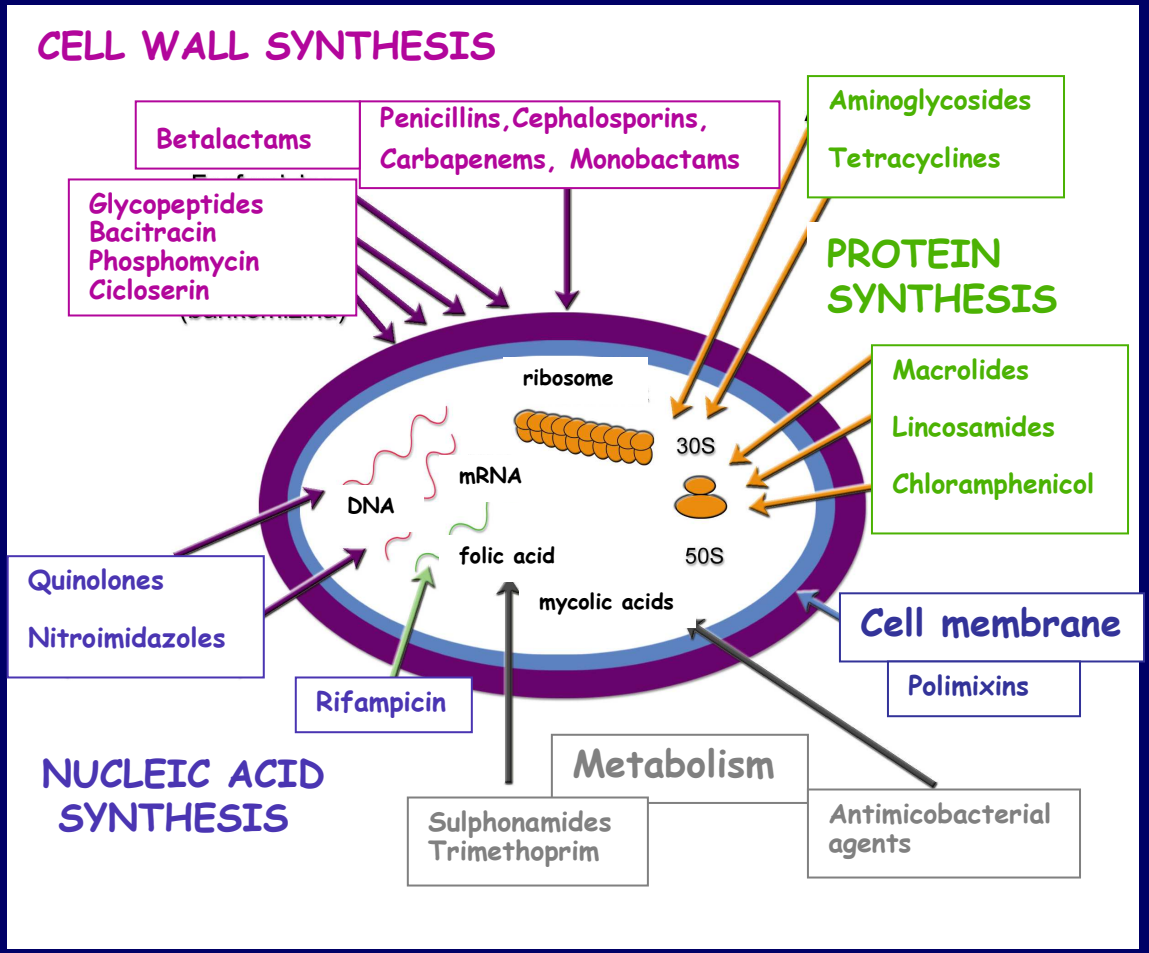
-INHIBITORS OF NUCLEIC ACID SYNTHESIS:

- SULPHONAMIDES & DIAMINOPYRIMIDINES
- QUINOLONES
- NITROIMIDAZOLES
- OTHERS: NITROFURANS, NOVOBIOCIN, RIFAMYCIN

-MISCELLANEOUS AGENTS:

- POLYMIXINS, DAPTOMYCIN, ANTIMICOBACTERIAL AGENTS

# TARGETS


CELL WALL SYNTHESIS
Betalactams
Penicillins,Cephalosporins,
Carbapenems, Monobactams
Glycopeptides
Bacitracin
Phosphomycin
Cicloserin
Aminoglycosides
Tetracyclines
PROTEIN SYNTHESIS
Macrolides
Lincosamides
Chloramphenicol
ribosome
30S
mRNA
DNA
folic acid
50S
mycolic acids
Quinolones
Nitroimidazoles
Rifampicin
Cell membrane
Polimixins
NUCLEIC ACID SYNTHESIS
Metabolism
Sulphonamides
Trimethoprim
Antimicobacterial agents

# RESISTANCE MECHANISMS

-GRAM-NEGATIVE OUTER MEMBRANE: LIMITS ANTIBIOTIC ACCESS TO THE CYTOPLASMIC MEMBRANE

-ENZYMATIC INACTIVATION OF THE ANTIBIOTIC:

- -BETALACTAMASES
- -AMINOGLYCOSIDE-MODIFYING ENZYMES
- -TETRACYCLINASES

-ACTIVE EFFLUX OF THE ANTIBIOTIC

-MODIFICATION OF THE ANTIBIOTIC TARGET:

- - PENICILLIN-BINDING-PROTEINS
- - RESISTANCE TO GLYCOPEPTIDES, TETRACYCLINES, MACROLIDES, LINCOSAMIDES, QUINOLONES, RIFAMPICIN, TRIMETHOPRIM AND SULFONAMIDES

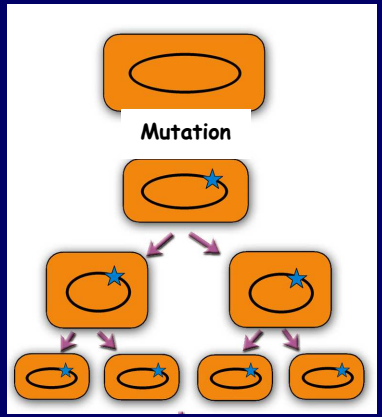
-REGULATION OF RESISTANCE GENES

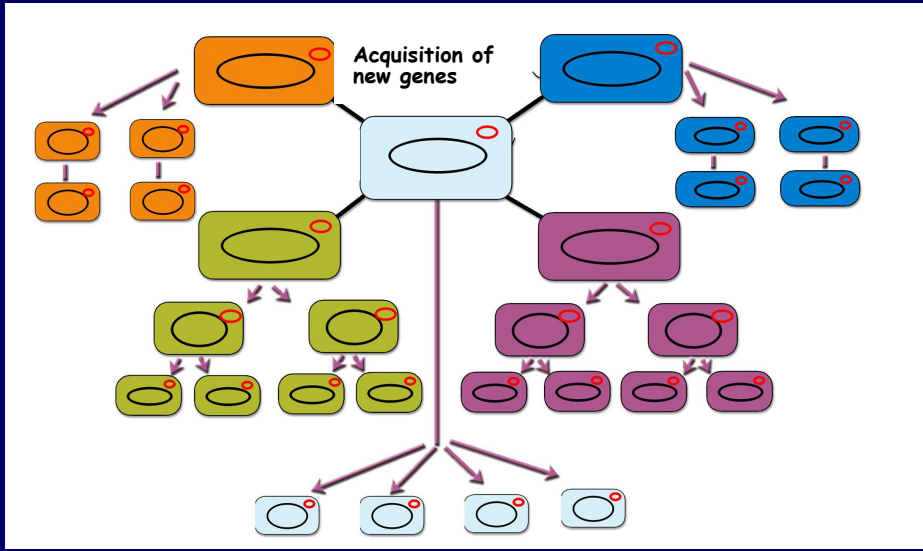
# GENETIC SUPPORT OF THE RESISTANCE

-RESISTANCE CAN BE ACQUIRED BY:

- MUTATION

-ACQUISITION OF NEW GENES:
- -BACTERIOPHAGE TRANSDUCTION
- -TRANSFORMATION
- -CONJUGATION:
  - -PLASMIDS
  - -CONJUGATIVE TRANSPOSONS (chromosomal elements)



# ANTIMICROBIAL RESISTANCE

1. A GLOBAL PROBLEM THAT NEEDS URGENT ACTION:

- INCREASING NUMBER OF NOSOCOMIAL INFECTIONS

- RESPIRATORY INFECTIONS, DIARRHOEAL DISEASES, MEASLES, AIDS, MALARIA AND TUBERCULOSIS:

  - ACCOUNT FOR MORE THAN OF 85% OF THE MORTALITY FROM INFECTION WORLDWIDE

  - RESISTANCE TO FIRST-LINE DRUGS IN THE PATHOGENS CAUSING THESE DISEASES RANGES FROM ZERO TO ALMOST 100%

<u>GLOBALIZATION</u>:

MASSIVE INCREASES IN TRADE AND HUMAN MOBILITY

↓

RAPID SPREAD OF INFECTIOUS DISEASES

# ANTIMICROBIAL RESISTANCE

2. COST OF RESISTANCE:
- HAS AN IMPACT ON THE COST OF HEALTH CARE WORLDWIDE
- ASSOCIATED WITH:
  INCREASED HUMAN SUFFERING,
  LOST PRODUCTIVITY and
  OFTEN DEATH

3. RISK MANAGEMENT AND NATIONAL SECURITY

4. ANTIMICROBIAL RESISTANCE IS FREQUENTLY IRREVERSIBLE

5. A DWINDLING SUPPLY OF NEW ANTIMICROBIALS

# ANTIMICROBIAL RESISTANCE

1. IT IS A NATURAL BIOLOGICAL PHENOMENON

-MAY BE A CHARACTERISTIC ASSOCIATED WITH THE ENTIRE SPECIES OR EMERGE IN STRAINS THROUGH MUTATION OR GENE TRANSFER

2. ALL ANTIMICROBIAL AGENTS HAVE THE POTENTIAL TO SELECT DRUG-RESISTANCE SUB-POPULATIONS OF MICROORGANISMS

3. THE TOTAL CONSUMPTION OF ANTIMICROBIALS IN THE CRITICAL FACTOR IN SELECTING RESISTANCE

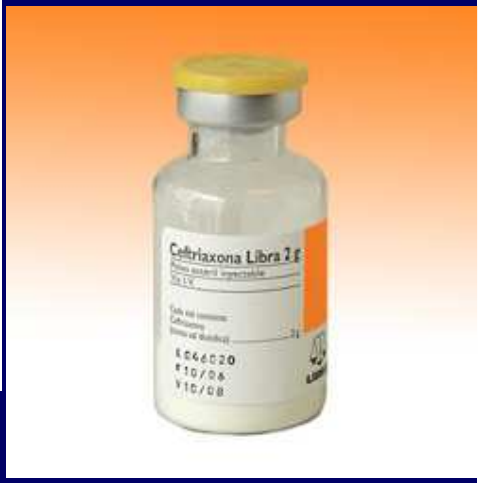
- UNDERUSE: INADEQUATE DOSING, POOR ADHERENCE AND SUBSTANDARD ANTIMICROBIALS
- OVERUSE

# APPROPIATE ANTIMICROBIAL USE AND EMERGING RESISTANCE: ISSUES AND INTERVENTIONS

1. PATIENTS AND THE GENERAL COMMUNITY
2. PRESCRIBERS AND DISPENSERS
3. HOSPITALS
4. USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS
5. NATIONAL GOVERNMENTS AND HEALTH SYSTEMS
6. DRUG AND VACCINE DEVELOPMENT
7. PHARMACEUTICAL PROMOTION
8. INTERNATIONAL ASPECTS OF CONTAINING ANTIMICROBIAL RESISTANCE

# Return to the preantibiotic era?

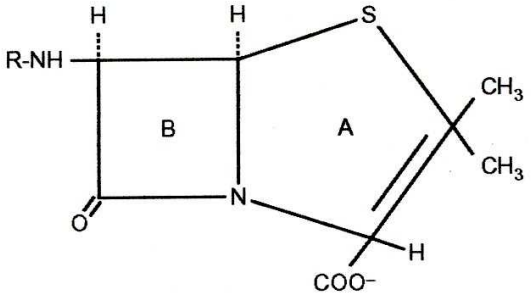
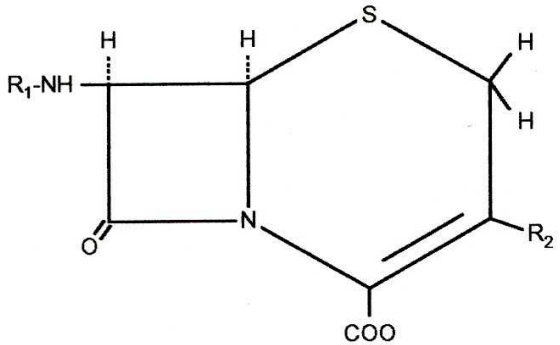
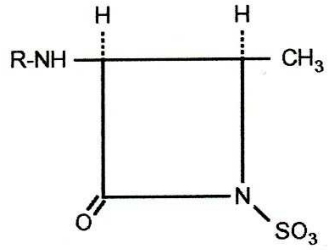
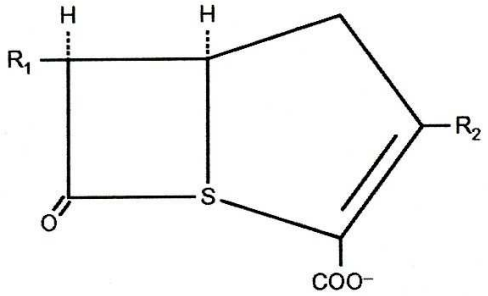
# RESISTANCE TO β- LACTAM ANTIBIOTICS IN GRAM-NEGATIVE BATERIA

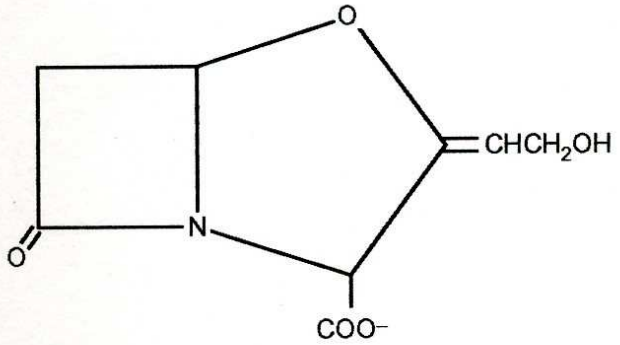
# β-LACTAM ANTIBIOTICS

1. PENICILLINS, CEPHALOSPORINS AND OTHER COMPOUNDS THAT FEATURE A β-LACTAM RING IN THEIR STRUCTURE
2. ALL BIND TO PROTEINS SITUATED AT THE CELL WALL-CELL MEMBRANE INTERFACE (PBP)
3. THESE PBPS ARE INVOLVED IN CELL WALL CONSTRUCTION, INCLUDING THE CROSS-LINKING OF THE PEPTIDOGLYCAN STRANDS

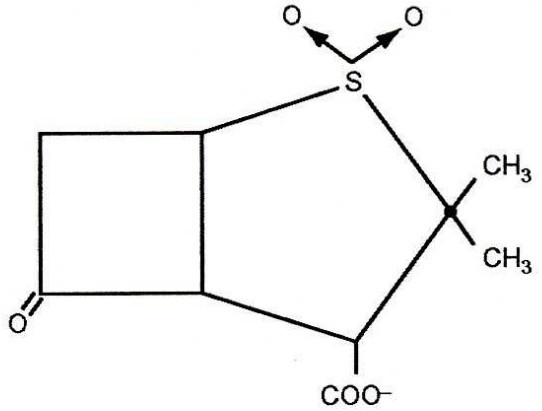
1. ARE THE LARGEST GROUP OF ANTIBACTERIAL AGENTS
2. THE MOST USED IN CLINICAL MEDICINE
3. BACTERICIDAL ACTIVITY
4. LOW TOXICITY
5. MEMBERS OF THE GROUP HAVE WIDELY DIFFERENT PROPERTIES

| NÚCLEO DEL ANTIBIÓTICO BETALACTÁMICO | | GRUPO ANTIBIÓTICO |
|---|---|---|
|  | 6-α-penicilánico | PENICILLINS |
|  | 7-α-cefalosporánico | CEPHALOSPORINS |
|  | Monobactámicos | MONOBACTAMS |
|  | Carbapenámico | CARBAPENEMS |

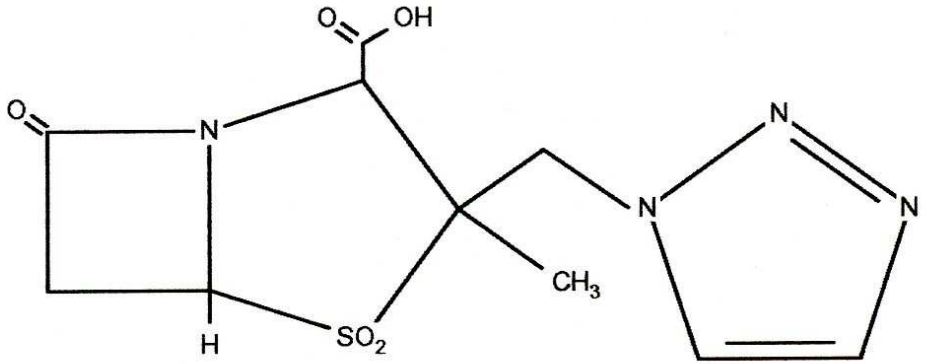
# β-LACTAMASE INHIBITORS




**Ácido clavulánico**



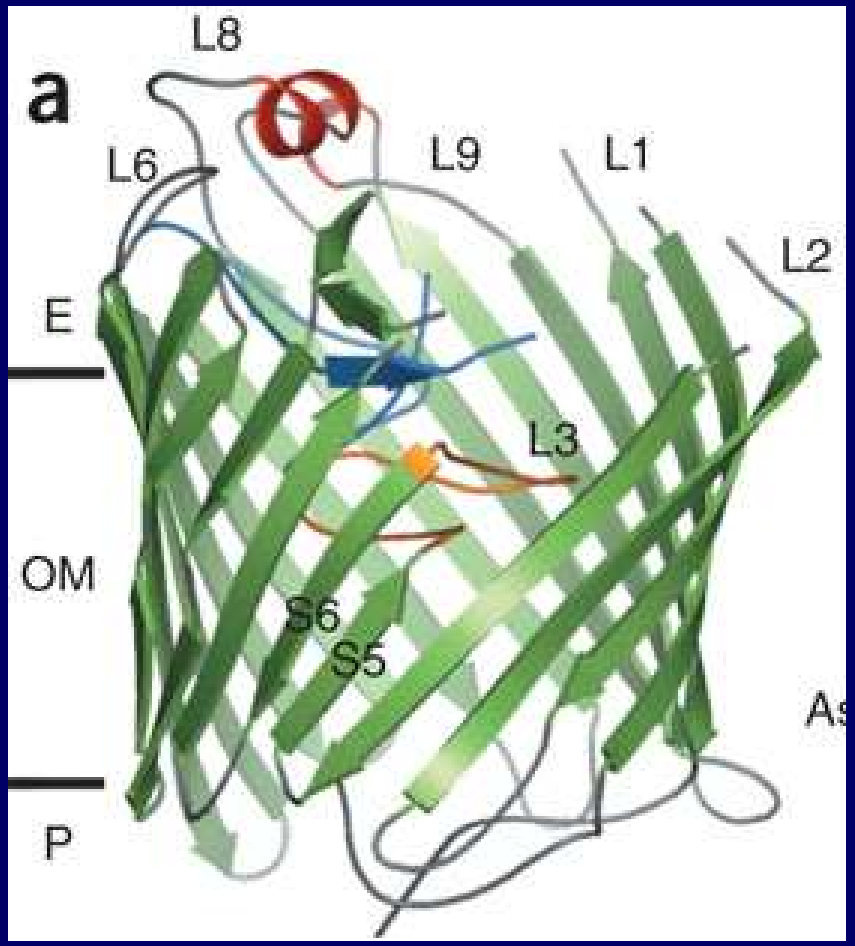

**Sulbactam**

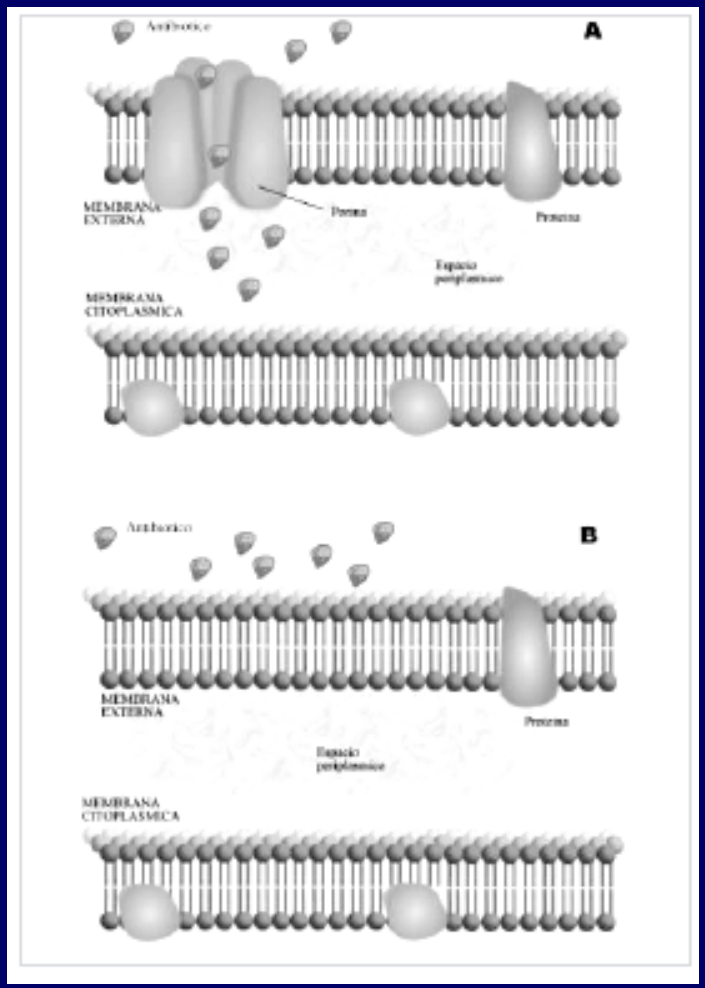



**Tazobactam**

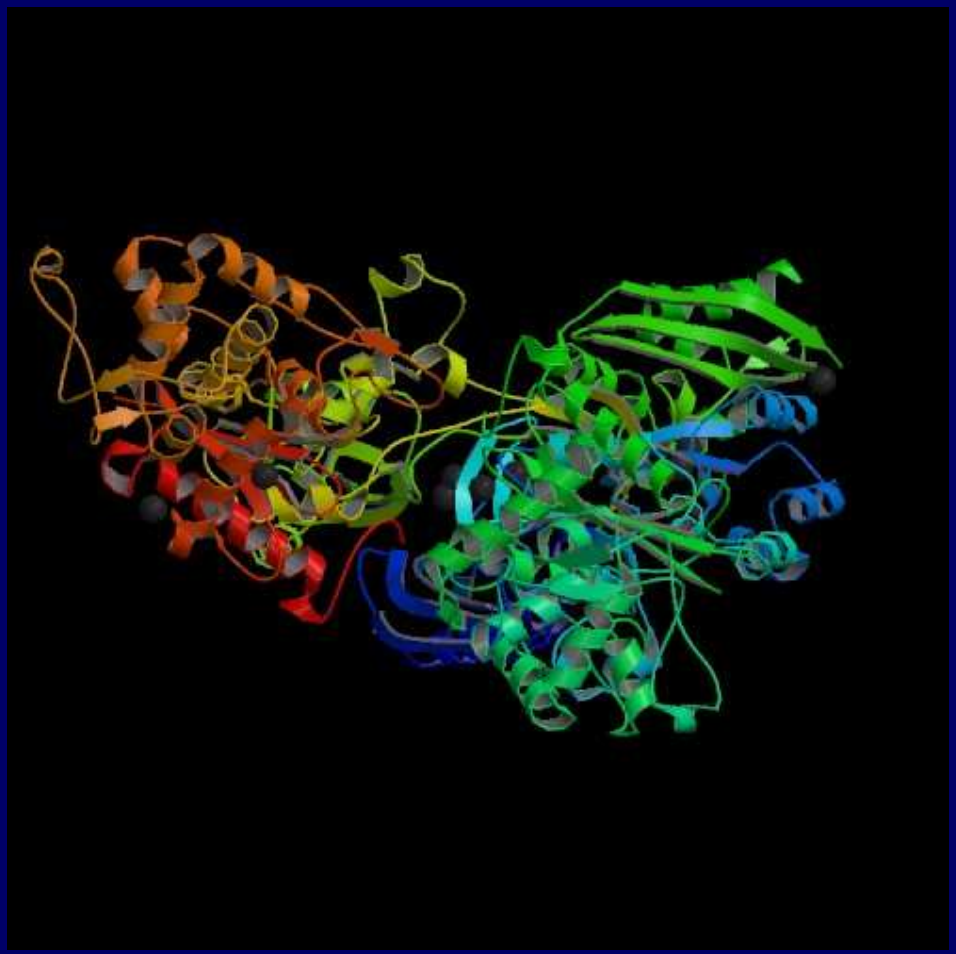
# MECHANISMS OF RESISTANCE

## 1. PERMEABILITY MODIFICATIONS: PORINS

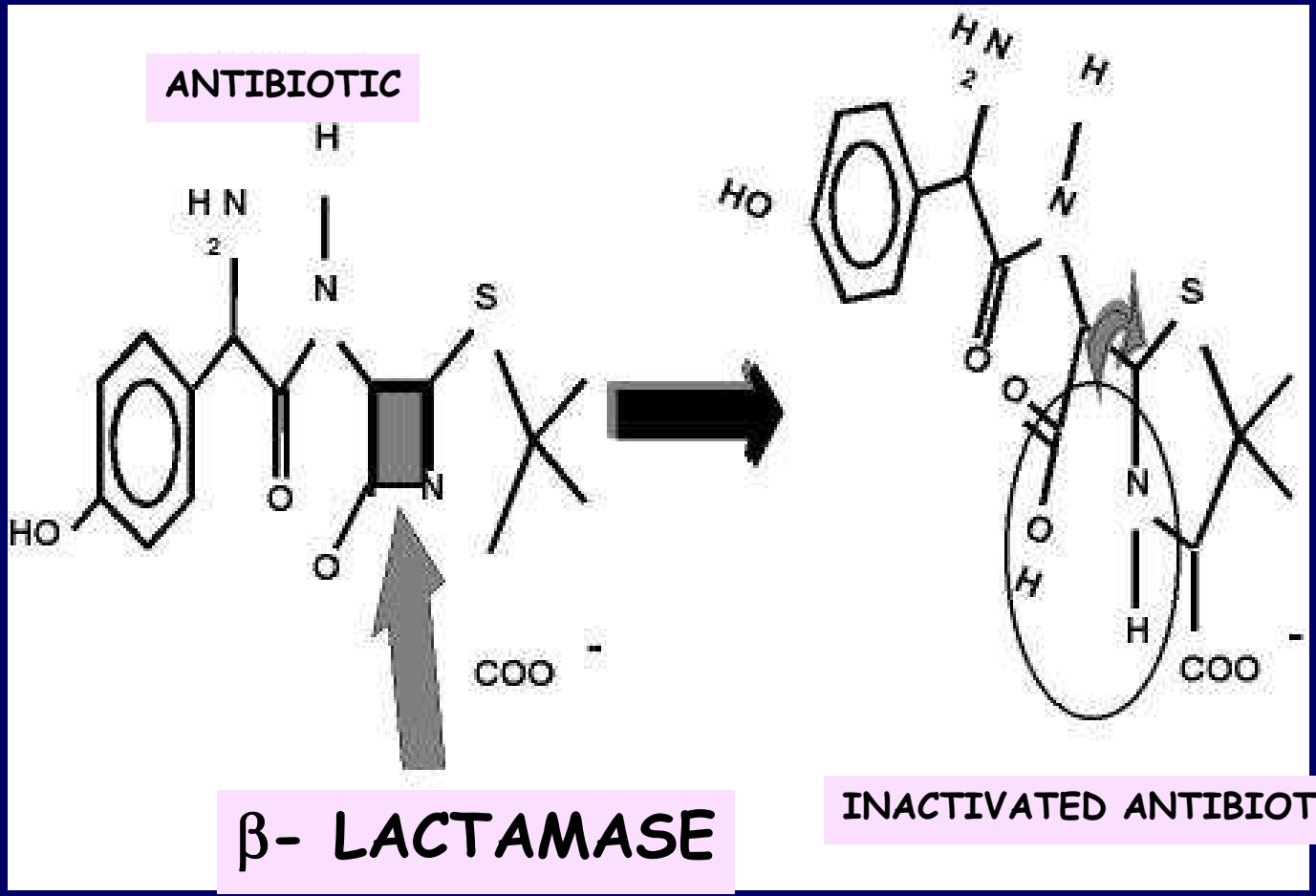


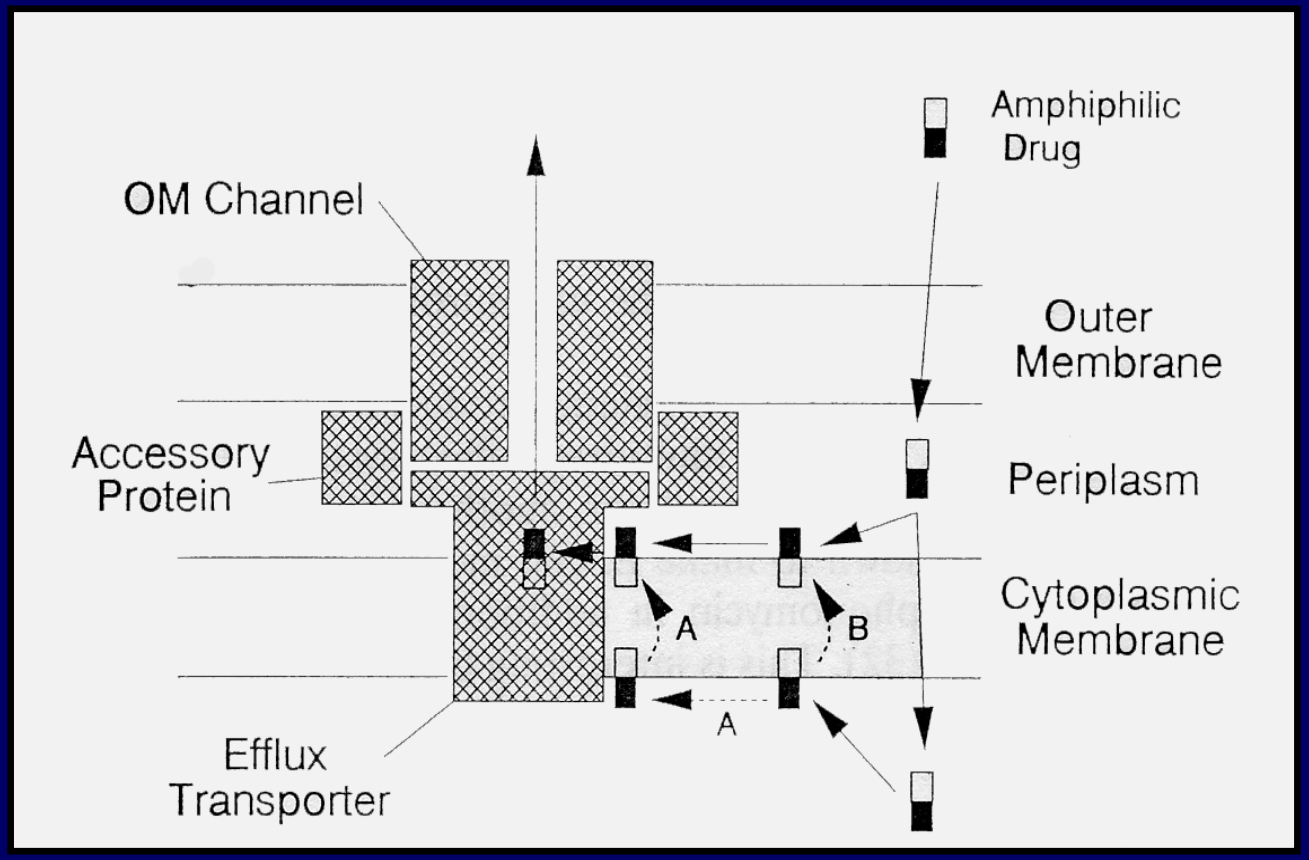
# 2. CHANGES IN PBPs



# 3. HYDROLYSING ENZYMES: β-LACTAMASES

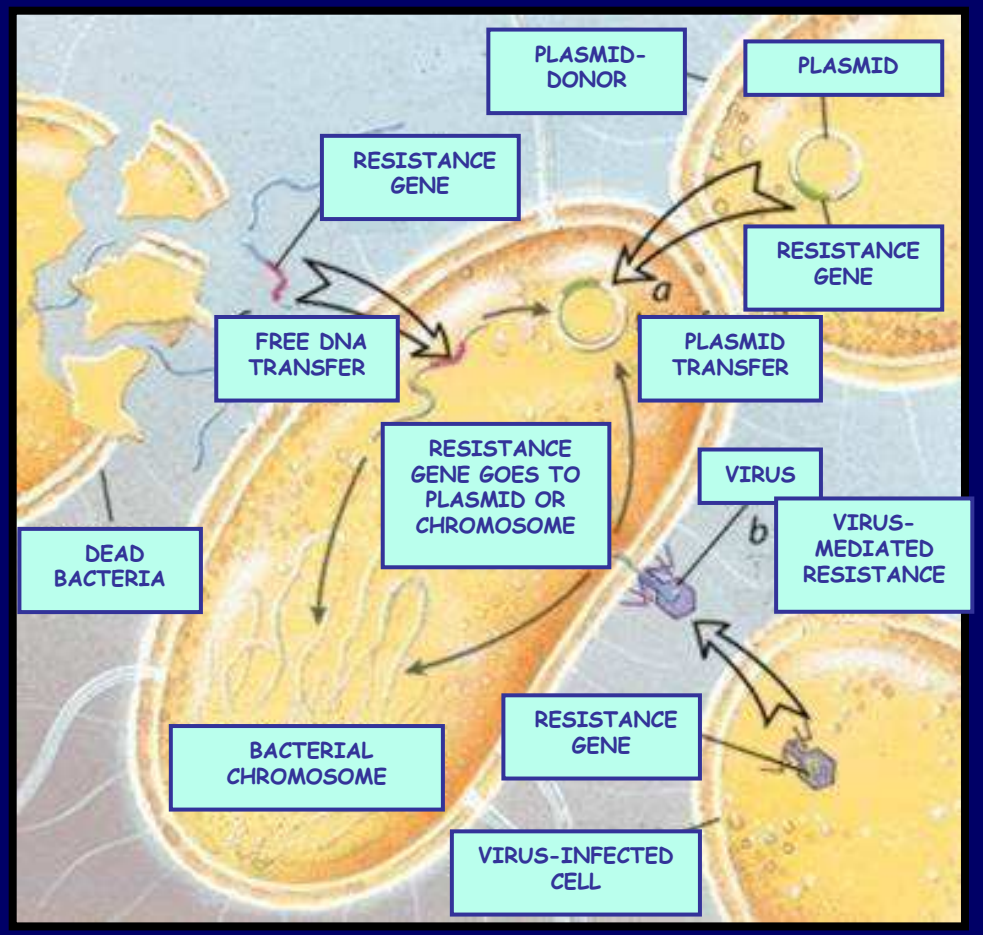


# 4. EFFLUX PUMPS

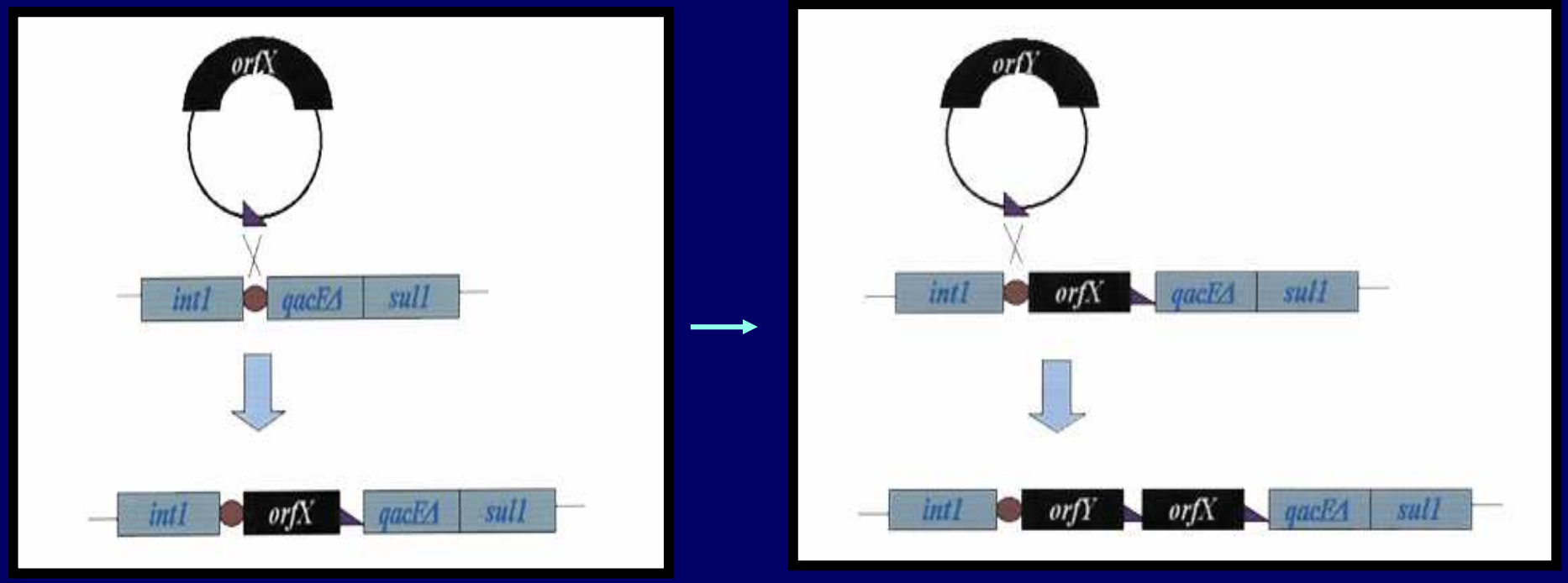


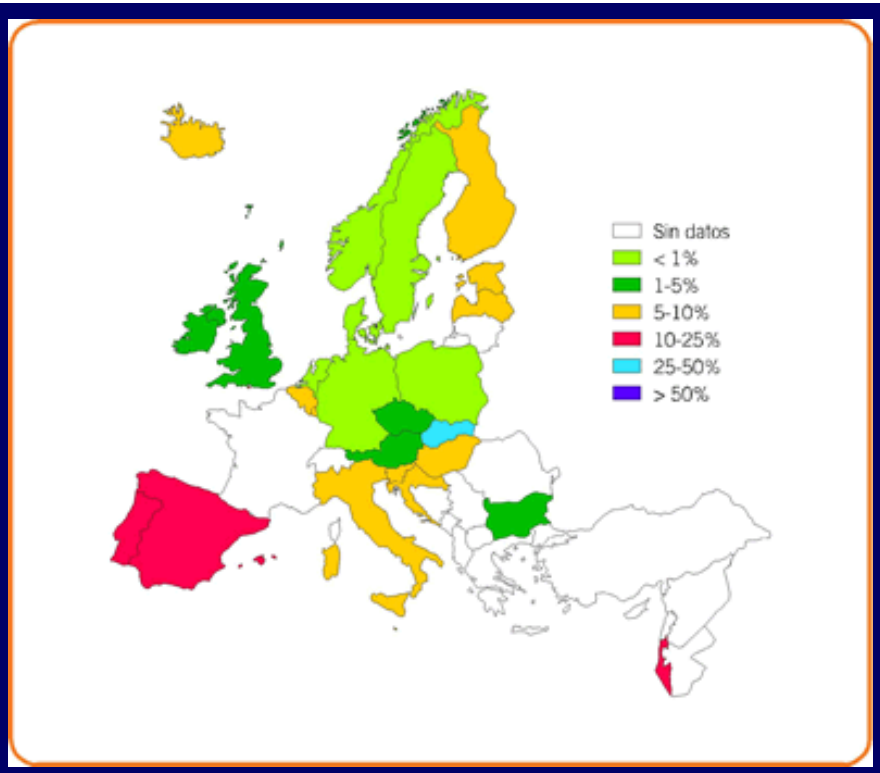
# GENETIC CONTROL OF THE RESISTANCE

1. CHROMOSOME
2. PLASMID
3. TRANSPOSON
4. INTEGRON

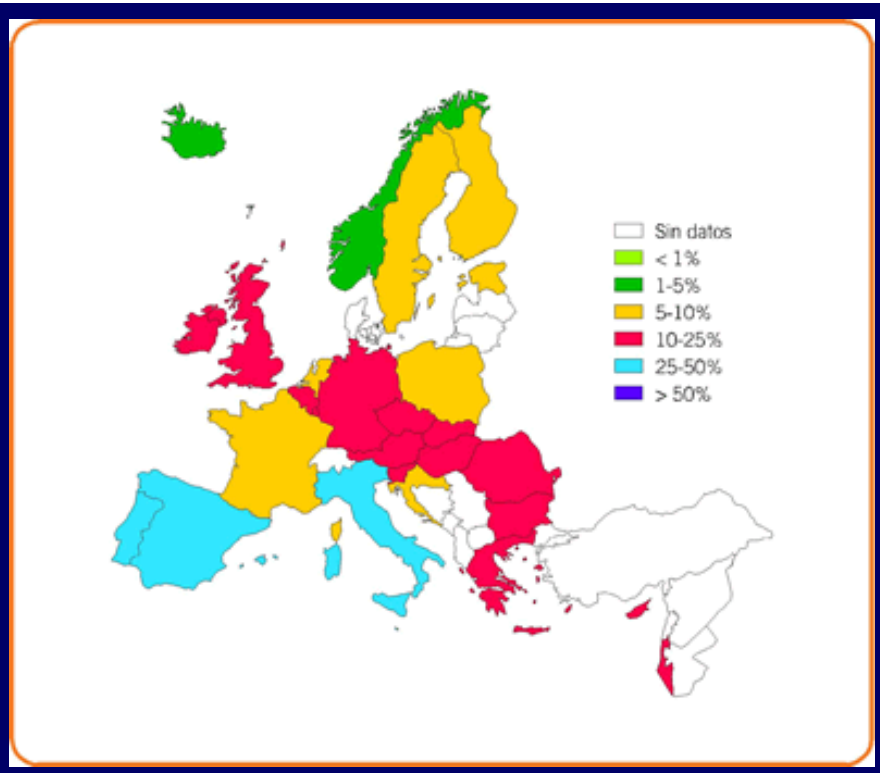


# INTEGRATION OF GENE CASSETTES INTO INTEGRONS






Resistance to β-lactams




β- lactamases

PREVALENCE IN OUR ENVIRONMENT

*Salmonella enteritidis*: 20-40% Amoxicillin, 1-5% Amoxi/clavulanate

*Shigella sonnei* 15-20% Ampicillin

*E. coli*: 40% Amoxicillin and Piperacillin

*Klebsiella pneumoniae* 10-30% Cephalosporins (3erd & 4th generation), Aztreonam and inhibitors

*P. aeruginosa*: 15-35% Piperacillin, Ceftazidime, Cefepime, Aztreonam, Carbapenems

*A. baumannii*: >50% multidrug-resistance

# *P. aeruginosa*, *Acinetobacter* & *Enterobacteriaceae*: RESISTANCE TO CARBAPENEMS

# GENERAL CONSIDERATIONS

1. RESISTANCE IS FREQUENT AMONG *P.aeruginosa* AND *A. baumannii* ISOLATES

2. CARBAPENEMS ARE THE LAST THERAPEUTIC OPTION IN INFECTIONS CAUSED BY RESISTANT ISOLATES

3. LEVEL OF RESISTANCE IS INCREASING WORLDWIDE (SENTRY, WHONET, VIRA…) WITH LOCAL VARIATIONS

4. RESISTANCE MECHANISMS:
   - INHERENT (NATURAL) & ACQUIRED RESISTANCE
   - HYDROLYSIS, DECREASED PERMEABILITY, EFFLUX PUMPS, TARGET MODIFICATIONS

5. RESISTANCE IS CAUSED BY COMBINATION OF SEVERAL MECHANISMS BEING THE MOST IMPORTANT ONES:

β-LACTAMASE (AmpC & CARBAPENEMASE) PRODUCTION

+

PORIN LOST

# CARBAPENEMASES

1. AmpC: CEFALOSPORINASES

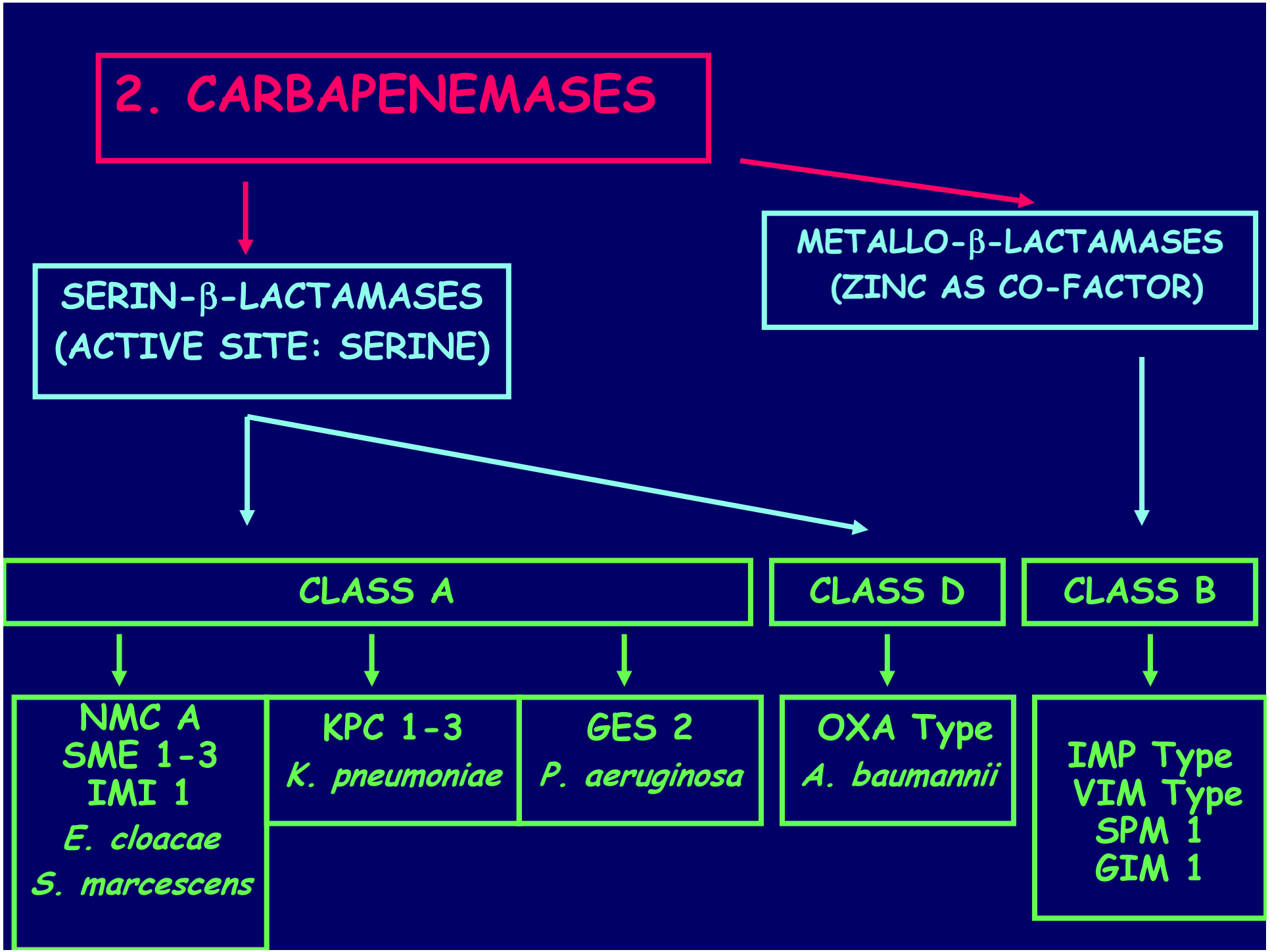
-CONFER RESISTANCE TO:

CEPHALOSPORINS (3erd GENERATION)
AZTREONAM
CEFAMICINS
BETALACTAMASE INHIBITORS

- LOW CARBAPENEM AFFINITY

- CHROMOSOMAL AmpC GENE (REGULATED): *E. cloacae, Citrobacter freundii, Serratia marcescens, P. aeruginosa and A. baumannii*

-PLASMIDIC AmpC GENE (CONSTITUTIVE PRODUCTION): *K. pneumoniae, Salmonella spp.*


2. CARBAPENEMASES
SERIN-β-LACTAMASES
(ACTIVE SITE: SERINE)
METALLO-β-LACTAMASES
(ZINC AS CO-FACTOR)
CLASS A
CLASS D
CLASS B
NMC A
SME 1-3
IMI 1
E. cloacae
S. marcescens
KPC 1-3
K. pneumoniae
GES 2
P. aeruginosa
OXA Type
A. baumannii
IMP Type
VIM Type
SPM 1
GIM 1