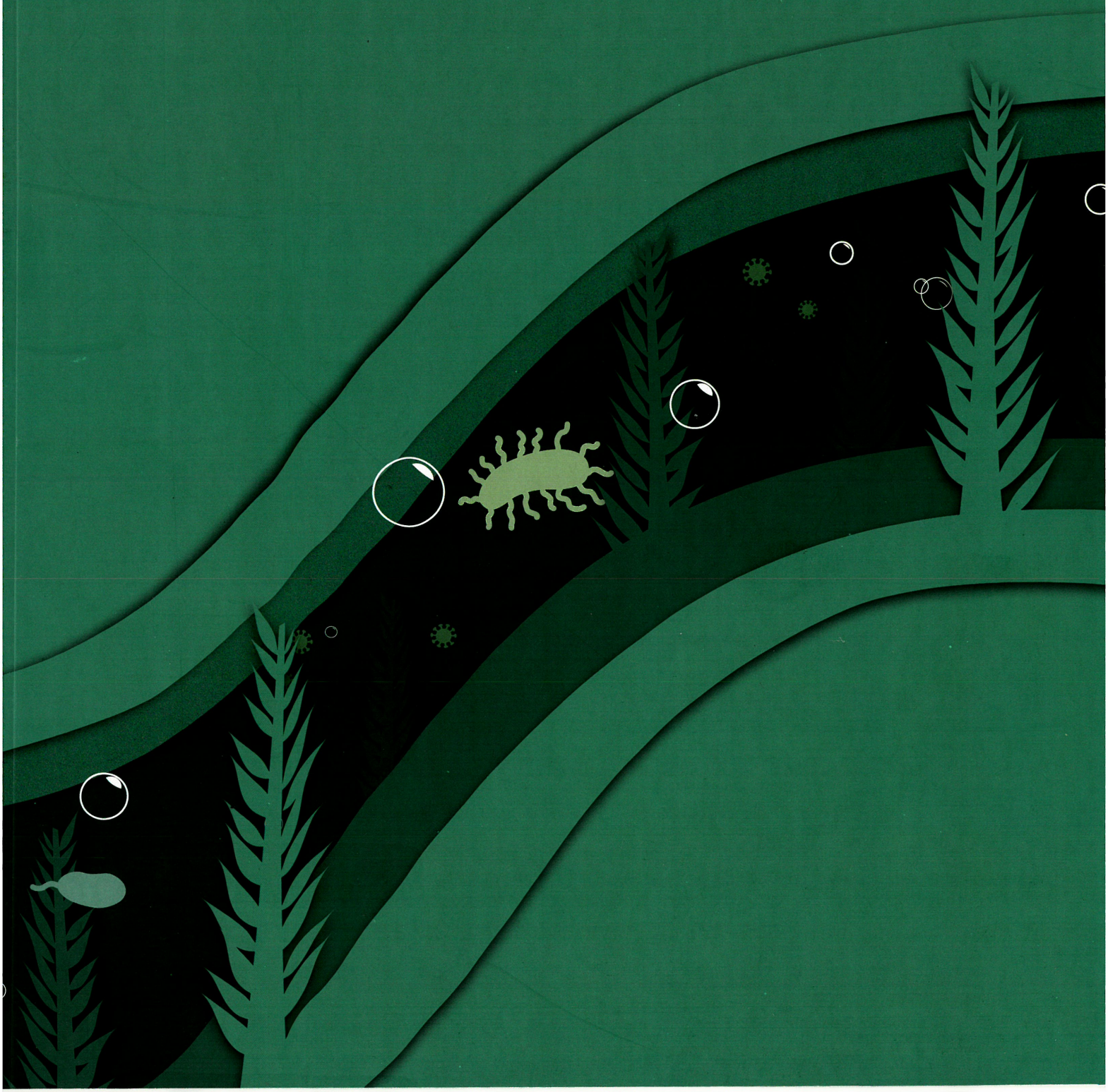
# INFECTIOUS DISEASES

Marrow SS Medicine



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## Fungal Infections



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# ANTIMICROBIAL STEWARDSHIP

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## Introduction

00:01:25

### Antimicrobial stewardship (AMS) :

- Co-ordinated interventions designed to improve & measure the appropriate use of antimicrobial agents by promoting the selection of optimal drug regimen including dosing, duration of therapy & route of administration.
- AMS means appropriate microbial selection.
- Not always means de-escalation/restriction.

### AMS programme :

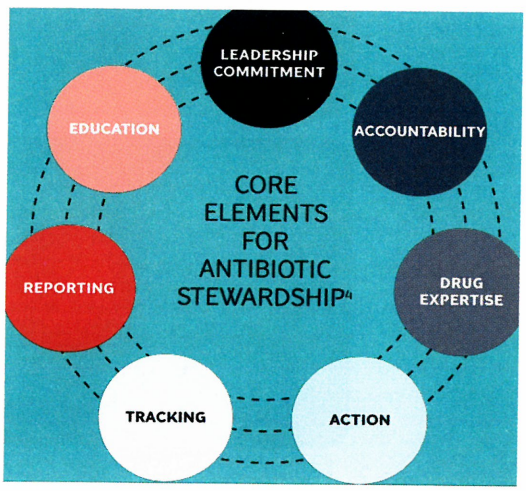
Organisational/system-wide health care strategy to promote appropriate use of antimicrobials through the implementation of evidence based interventions.

### Ultimate goals :

- Promote optimal antibiotic usage.
- Improve clinical outcomes.
- Decreased antimicrobial resistance.
- Improve resource utilization.

### Consequences of irrational antibiotic usage :

- Antibiotic resistance.
- Adverse events related to antibiotic usage (Side effects).
- Hospital acquired infections (Eg : C. difficile diarrhea, pseudomonas etc).
- Increased cost of care.
- Improper utilization of resources.




### 5 Ds of AMS :

- Diagnosis.
- Drug.
- Dose.
- Duration (Shortest).
- De-escalation (Review culture reports & change antibiotics to a lower spectrum if permitted).

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**Core elements :**

- Leadership commitment : Dedication of necessary manpower, money, IT support for the cause.
- Accountability : Senior physicians & hospital administrators can be appointed to manage the programme.
- Drug expertise : Clinical pharmacists guide regarding the dosage, dose adjustment etc.
- Action : Prospective audits, intervention tracking etc used in the programme.
- Tracking : measurement of actions is required.
- Reporting : AMS team should have regular communication with the treating team.
- Education : Ams can also be driven by educating the nursing staff along with doctors.

## Stewardship programme intervention 00:14:37

**AWARE classification of drugs :**

### ACCESS GROUP

This group includes antibiotics and antibiotic classes that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. Access antibiotics should be widely available, affordable and quality-assured to improve access and promote appropriate use.

Selected Access group antibiotics (shown here) are included on the WHO EML as essential first-choice or second-choice empirical treatment options for specific infectious syndromes.

- **Amikacin**
- **Amoxicillin**
- **Amoxicillin + clavulanic acid**
- **Ampicillin**
- **Benzathine benzylpenicillin**
- **Benzylpenicillin**
- **Cefalexin**
- **Cefazolin**
- **Chloramphenicol**
- **Clindamycin**
- **Cloxacillin**
- **Doxycycline**
- **Gentamicin**
- **Metronidazole**
- **Nitrofurantoin**
- **Phenoxymethyl-penicillin**
- **Procaine benzylpenicillin**
- **Spectinomycin**
- **Sulfamethoxazole + trimethoprim**

### WATCH GROUP

This group includes antibiotics and antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials (CIA) for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Watch group antibiotics should be prioritized as key targets of national and local stewardship programmes and monitoring.

Selected Watch group antibiotics (shown here) are included on the WHO EML as essential first-choice or second-choice empirical treatment options for a limited number of specific infectious syndromes.

- **Azithromycin**
- **Cefixime**
- **Cefotaxime**
- **Ceftazidime**
- **Ceftriaxone**
- **Cefuroxime**
- **Ciprofloxacin**
- **Clarithromycin**
- **Meropenem**
- **Piperacillin + tazobactam**
- **Vancomycin**

### RESERVE GROUP

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi drug-resistant organisms, and treated as "last-resort" options. Their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. They could be protected and prioritized as key targets of national and international stewardship programmes, involving monitoring and utilization reporting, to preserve their effectiveness.

Selected Reserve group antibiotics (shown here) are included on the WHO EML when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem-resistant Enterobacteriaceae.

- **Ceftazidime + avibactam**
- **Colistin**
- **Fosfomycin (intravenous)**
- **Linezolid**
- **Meropenem + vaborbactam**
- **Plazomicin**
- **Polymyxin B**

AWARE classification of drugs

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Access group :
Freely available drugs and do not require pre-authorisation for its use.
Available for all.

Watch group :
Given to critically ill patients mostly.
Require close watch on the usage.

Reserve group :
High end and reserved for culture proven indications.
Used on pre-authorisation.

**Types :**

1. Persuasive :
   - Education.
   - Feedback.

2. Restrictive :
   - Preauthorization.
   - Automatic stop orders.
   - Selective susceptibility reporting.

3. Structural :
   - Round the clock lab support.
   - RDTs ( for dengue, malaria etc.)
   - Availability of therapeutic drug dosage monitoring (Vancomycin, voriconazole, posiconazole etc).
   - Problems : Poor patient outcome & antibiotic resistance.

4. Local guidelines:
   Using antibiograms : Snapshot view of susceptibility profile & data from clinical samples needs to be combined.

5. Ward rounds.
6. Tracking drug allergies & adverse events.

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### Common areas for improvement :

- Overprescribing : Eg → Antibiotics for URI/ diarrhea.
- Overly use of broad spectrum antibiotics : Eg → For community acquired pneumonia/CAP, Piptaz gets started.
- Unnecessary combination treatment : Piptaz/carbapenem + metronidazole.
- Wrong choice : Eg → Daptomycin for pneumonia (Inactivated on alveolar surface).
- Wrong dose : Eg → meropenem Igm TDS for meningitis.
- Wrong route : Eg → IV vanvomycin for C.difficile infection.
- Wrong dosing interval : Eg → Beta-lactams given OD.
- Wrong duration : For CAP, post discharge oral antibiotics given for 3 days for IV course in hospital..
- Delayed administration : Eg → We are not able to inject antibiotics within 1 hour in a septic shock patient.

## Case scenarios 00:26:26

### Case scenario 1 :

2 catheterized patients are being treated with antibiotics.
Only one of them had symptoms suggestive of catheter associated UTI (Fever with no other localization).
Both the patients are being treated with Tab Nitrofurantoin (SR) 100mg BD based on the culture sensitivity report.

Comments :

- Asymtomatic patients need not be treated.
- In presence of fever with UTI, we suspect complicated UTI/ascending tract infection where nitrofurantoin isn't the correct treatment choice as it doesn't reach the therapeutic concentration.
- Quinolone /co-trimoxazole would be a better choice.

### Case scenario 2 :

During your weekly ward rounds as an AMS physician, you find that a case of probable IPA is on day 6 of voriconazole (tablet, 200mg BD). He is on O2 by facemask (6-8lit/min) and has poor oral intake. On reviewing charts you find that no loading dose was given.

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Comments :

- Check if TDM is available If yes, you can check therapeutic levels.
- If sub therapeutic levels present : Switch to IV & give loading dose (6mg/kg 2 doses followed by maintenance dose of 4mg/kg 2 daily BD).

Desirable voriconazole therapeutic drug level : 1-6.

**Case scenario 3 :**

Patient in the ICU who has developed VAP.

Given the high incidence of Carbapenem Resistant Enterobacteria/CRE in the ICU, he was started on polymyxin B (with a loading dose) when he was clinically suspected to have VAP.

Day 4 of treatment : On reviewing, you discover a culture report that was updated 24 hours ago which shows Klebsiella pneumoniae sensitive to Meropenem/Imipenem/Pip-Taz/Cef/Sulbactam.

Comment :

De-escalation is the right approach.

**Case scenario 4 :**

Another patient with VAP due to Pseudomonas aeruginosa.

Patient was empirically started on polymyxin B.

After timely review of culture reports, treatment was de-escalated to Pip-Taz.

Patient has failed to show significant clinical response despite 5 days of therapy.

Pseudomonas susceptibility profile : Pip-Taz, Cef-Sul, Meropenem, Imipenem.

Comments :

Pseudomonas are inducible Amp C producers (Resistant to third generation cephalosporins). Susceptibility can get converted to resistance while on treatment.

**Clinical scenario 5 :**

A 14yr old boy presented to the emergency with right upper limb cellulitis, secondary to trauma.

He is also running with high grade fever.

He was empirically started on Ceftriaxone and vancomycin in the emergency.

Blood was sent for culture sensitivity before starting the antibiotics.

Blood culture : S. aureus sensitive to vancomycin, teicoplanin, linezolid, cefoxitin (MSSA).

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Comments :
In cases of MSSA : Vancomycin & veicoplanin therapy is inferior to lower generation cephalosporins.

**Case scenario 6 :**
70yr old male presents to emergency with complaints of cough & shortness of breath along with fever for 3 days.
He was recently admitted for a similar complaint around 2 months back & required ICU care with IV drugs.
He has been started on ceftriaxone & azithromycin.

Comments :
Higher end antibiotics should be started. Review is required.

**Case scenario 7 :**
A case of hospital acquired meningitis (Post EVD).
The drain fluid has grown pseudomonas aeruginosa sensitive to meropenem & imipenem.
Treating team has started meropenem 1g IV TDS but with no significant improvement.

Comments :
Dose of meropenem for meningitis : 2g IV TDS.

**Case scenario 8 :**
65yr old T2DM presented with diabetic foot.
As per tissue culture reports, patient was started on levofloxacin 750mg OD.
During hospital stay, he developed HAP & sepsis with renal dysfunction.
Patient had a cardiac arrest & died.

Comments :
Review charts daily as dose modification for levofloxacin wasn't done.
S/E of levofloxacin : Cardiac toxicity (Torsades de pontes).

**OPD scenarios commonly used :**
- Ofloxacin-ornidazole combination for viral gastro-enteritis.
- Amoxicillin/Azithromycin for URI.
- Nitrofurantoin along with urinary alkalizer for cystitis.
  Fluoroquinolones/ co-trimoxazole should be used instead with alkalizers.

## Indicators for AMS programmes

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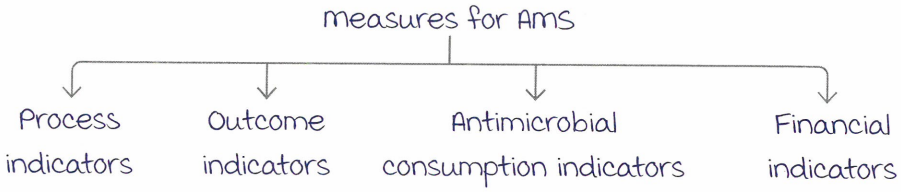


Outcome measures/indicators for AMS programmes :
Used in AMS activities to capture quantitative change in patient/economic outcomes, antibiotic use etc.

Process indicators :
It aims to capture information about the key processes that contribute to achieving the desired outcomes.

Examples :

- Percentage of cases where therapy is appropriate.
- Frequency at which de-escalation occurs.
- Timely cessation of antibiotics given for surgical prophylaxis.
- Antibiotics not prescribed to treat asymptomatic bacteria.
- Appropriate cultures obtained before starting antibiotics.
- Adherence to hospital-specific guidelines.
- Acceptance of ASP recommendations.
- Frequency of performance of antibiotic time-outs/ reviews.
- Timely administration of appropriate antibiotics.

Outcome indicators :

- Length of stay.
- Cure of infection.
- Risk adjusted mortality.
- Hospital readmissions for select infections.
- Hospital onset C. difficile infections.
- Rates of HAIs.
- Adverse drug reactions(number/percentage/rate).

Antimicrobial consumption indicators :

i. Days of therapy (DOTs) :
One DOT represents the administration of a single agent on a given day regardless of number of doses administered/dosage strength.

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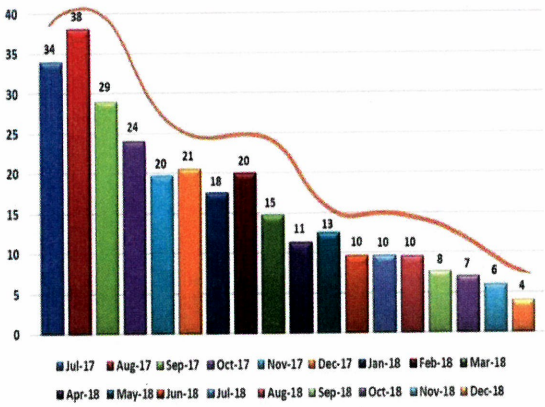
Eg :

| Antibiotic | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | DOT |
|---|---|---|---|---|---|---|
| Ceftriaxone | x (2 doses) | x (2 doses) | x (1 dose) | | | 3 |
| Cefixime | | | x (1 dose) | x (2 doses) | x (2 doses) | 3 |
| Total | | | | | | 6 |

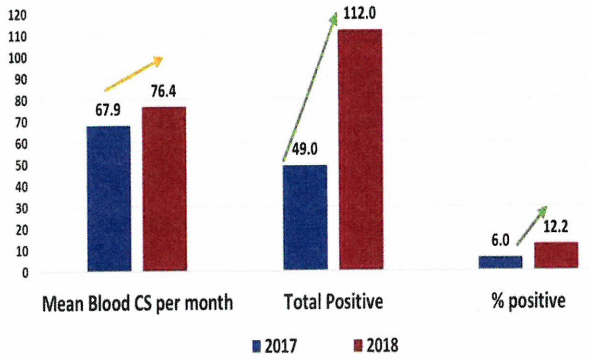
Length of therapy/LOT : 5 days.

Features :

- It allows patient population comparison.
- Can help in identifying antibiotics for stewardship (Pre/post design).
- Favors those who use broad spectrum mono therapy over those who use narrow spectrum combination therapy.
- DOT for patients that receive a dosing interval >24 hrs doesn't reflect patient exposure (Only reflects antibiotic administration).
- Overestimation with 1 time doses (Eg : surgical prophylaxis).




Reported redundant anaerobic coverage during 18 months




mean blood C/S per month & blood culture positivity rates.

ii. Defined daily dose (DDD) :
Assumed average maintenance dose per day for a medicine used for its main indication in adults as established by WHO collaboration Centre for drug statistics & methodology.

Example :
For meropenem, ATC/DDD on WHO site is 3g.
'X' hospital used 12000 g of meropenem = 4000 DDD = 300,000 patient days.
4000\300000 x 1000 = 13.33DDD.
Similar values for different wards/hospitals can be calculated.

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Relevance :

- Allows fair comparison.
- No patient level data is needed.

Disadvantages :

- Not based on prescribed doses.
- Not useful in pediatric & neonatal ward/hospital.
- Underestimated in renally impaired, overestimates in indications that require higher doses.

iii. Standardized antimicrobial administration ratio (SAAR) :
It is a ratio comparing observed/reported, antimicrobial use to the antimicrobial use predicted by a referent, or baseline, population.

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# ANTIMICROBIAL RESISTANCE

In some patience even on starting the right drug in the right concentration, the outcome might be poor because the pharmacokinetics and pharmacodynamics in the patient of the draft changes.

## Introduction 00:02:36

**WHO definition :**

Microorganisms that are not inhibited by achievable systemic concentration of the antimicrobial agent.

The micro organism maybe sensitive to a drug at a higher concentration but that may not be achievable in the blood leading to resistance to the antibiotic.

**Classification of drug resistance :**

i. Multiple drug resistant (MDR) : Non-susceptible to ≥1 agent in >3 antimicrobial categories.
ii. Extreme drug resistant (XDR) : Non-susceptible to ≥1 agent in all but ≤2 categories.
iii. Pan drug resistant (PDR) : Non-susceptible to all antimicrobial agents.
If so employ experimental therapy like fast therapy (Not currently used).

**Source of resistance :**

i. Natural/intrinsic resistance :
By virtue of its composition.

Example :

- Gram-negative organism are not killed by vancomycin.
- Gram-positive are resistant to colistin.
Both are due to structural make of the organism.
- Pseudomonas aeruginosa :
  - Amoxicillin.
  - Cefoxitin.
  - Tigecycline.
  - Minocycline.
  - Ertapenem.

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- Acinetobacter baumannii :
  - Penicillin.
  - Cephalosporins.
  - Chloramphenicol.
  - Fosfomycin.
  - Aztreonam.
  - Ertapenem.
  - Trimethoprim.
  - Ceftran maybe sensitive to acinetobacter.

Other examples :

| Organism | Intrinsic resistance |
|---|---|
| Bacteroides (Anaerobes) | Aminoglycosides, many Beta-lactams, quinolones |
| All gram positives | Aztreonam |
| Enterococci | Aminoglycosides, cephalosporins, lincosamides |
| Listeria monocytogenes | Cephalosporins |
| All gram negatives | Glycopeptides, lipopeptides |
| Escherichia coli | macrolides |
| Klebsiella spp. | Ampicillin |
| Serratia marcescens | macrolides |
| Pseudomonas aeruginosa | Sulfonamides, ampicillin, Ist and 2nd generation cephalosporins, chloramphenicol, tetracycline |
| Stenotrophomonas maltophilia | Aminoglycosides, Beta-lactams, carbapenems, quinolones |
| Acinetobacter spp. | Ampicillin, glycopeptides |

Enterococcal infection : combination of aminoglycoside + Cephalosporins is effective.

ii. Acquired resistance :

- Due to mutation of genes : Like point mutation, deletions, insertions.
- Due to acquisition of foreign resistance genes : In the form bacteriophages/ plasmids/naked DNA.

iii. Fitness cost or maintenance cost :

- For the organism it has a fitness cost or maintenance cost.
- Certain organism that was resistant earlier turns sensitive later because : Under pressure the organism gains a component making it resistant → Over time the organism loses that component → making it sensitive.
- Example : Chloramphenicol, colistin.

iv. A single mechanism is seldom responsible for antimicrobial resistance (AMR) in a bacteria.

- The outcome is based on a multiple complex processes.
- It may not be always possible to interpret resistance mechanism by microbiology/culture report.

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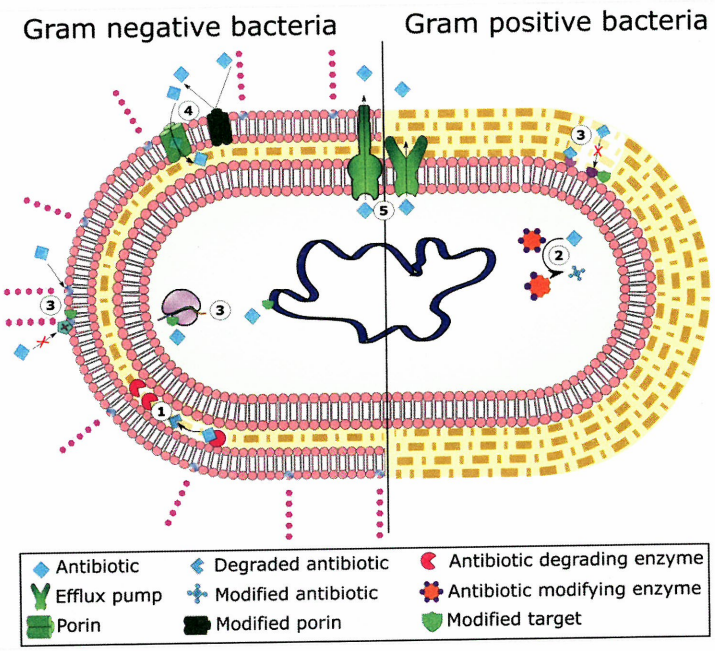
## mechanisms of AMR :




Alteration in structure of cell membrane (Binding site) :

Example :

- Colistin (Positively charged) attracted towards the negatively charged polysaccharide → Change in composition of cell membrane → will not bind.
- In Neisseria gonorrhea there is alteration in the structure of penicillin binding protein .
- In aminoglycosides there could be drug modifying enzymes as well as alteration in the structure of its binding site.

Degradation of antibiotics :

The most important.

2 types of enzymes :

- Degrading enzymes :
  Like Beta lactamases.
  Antibiotic degrading enzyme → Come in contact with the antibiotics → Leave the antibiotic useless.

- Modifying enzymes :
  Like aminoglycosides modifying enzymes (AGE).
  It works by acetylation/adenylation/phosphorylation.

Note :

In case of glycopeptide antibiotics : Over production of the targets.

It increases the thickness of the cell wall or altered cell wall components → Failure of drug therapy.

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Major mechanisms of resistance to beta lactam antibiotics :

- Enzymatic degradation.
- Efflux pumps.
- Decreased permeability.
- Altered binding site.

## Beta lactamases (BL)

00:17:58

Splits the amide bond of the β-lactam ring.

### Types of BL :

- Penicillinase (Eg : TEM-1).
- Cephalosporinase (TEM-2, SHV-1).
- ESBL (Eg : CTX-M, PER-1, VEB-1, TEM/SHV derived /OXA).
- AmpC.
- Carbapenemases (Eg : KPC, MBLs, OXA).

### Ambler classification of BL :

| CLASS | ACTIVE SITE | ENZYME TYPE | SUBSTRATES | EXAMPLE |
|---|---|---|---|---|
| A | Serine | Penicillinases: | | |
| | | Broad-spectrum | Benzylpenicillin, aminopenicillins, carboxypenicillins, ureidopenicillins, narrow-spectrum cephalosporins | PC1 in *Staphylococcus aureus* TEM-1, SHV-1 in *Escherichia coli, Klebsiella pneumoniae,* other gram-negative bacteria |
| | | Extended-spectrum (β-lactamase) | Substrates of broad-spectrum plus oxymino-β-lactams (cefotaxime, ceftazidime, ceftriaxone) and aztreonam | In Enterobacteriaceae: TEM-derived, SHV-derived, CTX-M–derived; PER-1, VEB-1, VEB-2, GES-1, GES-2, IBC-2 in *Pseudomonas aeruginosa* |
| | | Carbapenemases | Substrates of extended-spectrum plus cephamycins and carbapenems | KPC-1, KPC-2, KPC-3 in *K. pneumoniae;* NMC/IMI, SME family |
| B | Metallo-β-lactamases ($Zn^{2+}$) | Carbapenemases | Substrates of extended-spectrum plus cephamycins and carbapenems | NDM-1 in Enterobacteriaceae, IMP, VIM, GIM, SPM, SIM lineages in *P. aeruginosa, Acinetobacter* spp. |
| C | Serine | Cephalosporinases | Substrates of extended-spectrum plus cephamycins | AmpC-type enzymes in Enterobacteriaceae, *Acinetobacter* spp. |
| D | Serine | Oxacillinases: | | |
| | | Broad-spectrum | Aminopenicillins, ureidopenicillin, cloxacillin, methicillin, oxacillin, and some narrow-spectrum cephalosporins | OXA-family in *P. aeruginosa* |
| | | Extended-spectrum | Substrates of broad-spectrum plus oxymino-β-lactams and monobactams | OXA-derived in *P. aeruginosa* |
| | | Carbapenemases | Substrates of extended-spectrum plus cephamycins and carbapenems | OXA-derived in *Acinetobacter* spp. |

*AmpC,* Ampicillin C; *CTX-M,* cefotaxime-M; *GES,* Guyana extended-spectrum β-lactamase; *GIM,* German imipenemase; *IBC,* integron-born cephalosporinase; *IMI,* imipenem hydrolyzing; *IMP,* imipenem; *KPC, K. pneumoniae* carbapenemase; *NDM,* New Delhi metallo-β-lactamase; *NMC,* not metalloenzyme carbapenemase; *OXA,* oxacillin; *PC1,* penicillin 1; PER, *Pseudomonas* extended resistance; *SHV,* sulfhydryl variable; *SIM,* Seoul imipenemase; *SME, Serratia marcescens* extended-spectrum β-lactamase; *SPM,* Sao Paulo metallo-β-lactamase; *TEM,* Temoneira; *VEB,* Vietnam extended-spectrum β-lactamase; *VIM,* Verona integron-encoded metallo-β-lactamase.

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Based on structure/aminoacids constituents of enzymes.
EDTA & aztreonam : Effective against metallo BL but better to prefer combination therapy.

| | Extended spectrum (ESBL) | AmpC |
|---|---|---|
| Inhibition by BLI (Older) | S | R |
| Cefoxitin/Cefotetan | S | R |
| Ceftriaxone (3rd gen CS) | R | R |
| Cefepime | S/R | S |

Cefoxitin rather than clinical use, it is more significant in indicating ESBL.

Note :

- Older BLI : Clavulanic acid , sulbactam, tazobactam.
  Newer BLI :
  - Avibactam, relebactam.
  - These work against AmpC.
- Combination of Ceftazidime + Avibactam + Aztreonam effective against many organisms :
  - Avibactam : ESBL, AmpC, KPC, OXA48 type of carbopenam.
  - Aztreonam : Covers NDM.

**Inducible AmpC :**

- Chromosomally mediated resistance (Not plasma acquired).
- Isolated organisms maybe initially sensitive but on starting this Patient fails to respond.
- Due to presence of beta lactam antibiotics → Induction of AmpC production → Organisms will become resistant.
- Hence only option will become carbapenem.

| Inducible AmpC (chromosomal) | Organisms |
|---|---|
| S | Serratia |
| P | Pseudomonas<br>Proteus<br>Providencia |
| A | Acinetobacter |
| C | Citrobacter freundii |
| E | Enterobacter spp |