MEDICINE - ID
NEET-SS

CONTENT

ANTIMICROBIAL STEWARDSHIP

Definitions 00:01:25

AMS/Antimicrobial stewardship : Co-ordinated interventions designed to improve & measure the appropriate use of antimicrbial agents by promoting the selection of optimal drug regimen including dosing, duration of therapy & route of administration.

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 (e.g. C. difficile diarrhea, Pseudomonas etc).
- Increased cost of care.
- Improper utilization of resources.

AMS - appropriate microbial selection. Not always means de-escalation/restriction.

5 Ds of AMS :

Diagnosis.

Drug

Dose

Duration (shortest).

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De-escalation (review culture reports & change antibiotics to a lower spectrum if permitted)

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 program intervention 00:14:37

1. Persuasive :
   - Education.
   - Feedback.
2. Restrictive :
   - Preauthorization.
   - Automatic stop orders.
   - Selective susceptibility reporting - E.g. a patient is -

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infected & the organism is susceptible to low and high doses of an antibiotic both, The lab report can selectively mention the lower dose antibiotics only & the physician may be forced to use the drugs from them.

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.
5. Ward rounds.
6. Antibiograms (snapshot view of susceptibility profile & data from clinical samples needs to be combined).
7. Tracking drug allergies & adverse events.

9 common areas for improvement :

- Overprescribing - e.g antibiotics for URI/ diarrhea.
- Overly use of broad spectrum antibiotics - e.g for

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community acquired pneumonia/CAP, Piptaz gets started.

- Unnecessary combination treatment - Piptaz/carbapenem + metronidazole.
- Wrong choice - e.g daptomycin for pneumonia (inactivated on alveolar surface).
- Wrong dose - e.g meropenem 1gm TDS for meningitis.
- Wrong route - e.g IV vanvomycin for C.difficile infection.
- Wrong dosing interval - e.g Beta-lactams given OD.
- Wrong duration - for CAP, post discharge oral antibiotics given for 3 days for IV course in hospital.
- Delayed administration - e.g we are not able to inject antibiotics within 1 hour in a septic shock patient.

Case scenario 1:

During your weekly ward rounds as an AMS physician, you find that 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.

Comments: CHeck if TDM is available.
If yes, u can check therapeutic levels.
If sub therapeutic levels present - Switch to IV & give loading

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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 :
You are reviewing the charts of 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. Today is day 4 of reatment and on reviewing you discover a culture report that was updated 24 hours ago which shows Klebsiella pneumoniae sensitive to Meropenem/Imipenem/Pip-Taz/Cef Sul

Comment : (Right approach) De-escalation.

Case scenario 4 :
On the same day, you find another patient with VAP due to Pseudomonas aeruginosa. On this occasion also, patient was empirically started on Polymyxin B. However, after timely review of culture reports, treatment was de-escalated to Pip-Taz. However, the 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 grew S.aureus sensitive to vancomycin,

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teicoplanin, linezolid, cefoxitin (MSSA).
Primary team insists on continuing the initial treatment.

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

case scenario 6 :
70yr old male presents to emmergency 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 :
you are reviewing 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. A tissue culture was sent & as per culture reports patient was started on Levofloxacin 750mg OD. during hospital stay, he developed HAP & sepsis with renal dysfunction.
Patient had a cardiiac arrest & died.

Comments : Review charts daily as dose modification for levofloxacin wasn't done. It has cardiac toxicity (torsades de pontes) & the patient might have had cardiac arrest.

OPD scenarios :

- Ofloxacin-ornidazole combination for viral gastro-

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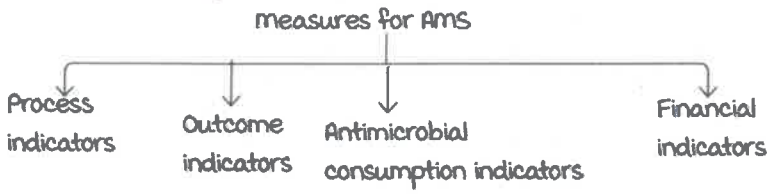
enteritis.

- Amoxicillin/ Azithromycin for URI.
- Nitrofurantoin along with urinary alkalizer for cystitis. Fluoroquinolones/ co-trimoxazole should be used instead with alkalizers.

Assessing the impact :



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

Process measures/indicators for AMS programmes :
It aims to cature information about the key processes that contribute to achieving the desired outcomes.

Process indicators :

- 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 00:40:29

Length of stay.
Cure of infection.
Risk adjusted mortality.

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Hospital readmissions for select infections.
Hospital onset C.difficile infections.
Rates of HAIs.
Adverse drug reactions(number/percentage/rate).

Antimicrobial consumption indicators :

Days of therapy/DOTs - one DOT represents the administration of a single agent on a given day regardless of number of doses admininstered/ dosage strength.

Defined daily dose/ DDD - Assumed avg maintainence dose/ day for a medicine used for its main indication in adults as establlished by WHO collaboratin Centre for drug sttatistics & methodology.

e.g 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.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.

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.

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.

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DOT :

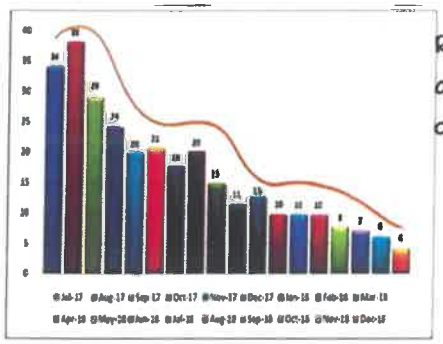
It allows patient population comparison.

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.

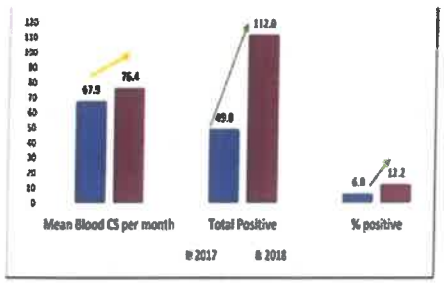
DOT for patients that recieve a dosing interval > 24 hrs doesn't reflect patient exposure (only reflects antibiotic administration).

Overestimation with 1 time doses (e.g surgical prophylaxis).



Reported redundant anaerobic coverage during 18 months.

Mean blood CS per month & blood culture positivity rates.



Summary : AMS is the need of the hour.
It is a team effort.
Better patient care > personal ego.
Labour, cost & resource intensive activity.
Short term & long term results.

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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.

Definition

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 :

Multiple drug resistant (MDR) :

Non-susceptible to ≥1 agent in >3 antimicrobial categories.

Extreme drug resistant (XDR) :

Non-susceptible to ≥1 agent in all but ≤2 categories.

Pan drug resistant (PDR) :

Non-susceptible to all antimicrobial agents.

If so employ experimental therapy like fast therapy (not currently used).

Source of resistance :

1. 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 structual make of the organism.

Intrinsic resistance examples :

- Pseudomonas aeruginosa :

Amoxicillin

Cefoxitin

Tigecycline

Minocycline

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Ertapenem.

- Acinetobacter baumannii :

Penicillin
Cephalosporins
Chloramphenicol
Fosfomycin
Aztreonam :
A popular combination of polymyxin sparing regimen (Ceftazidime + Avibactam + Aztreonam) is used nowadays. But this combination will not work for Acinetobacter because as Aztreonam does not work against acinetobacte .
Ertapenem
Trimethoprim.
Ceftran maybe sensitive to Acinetobacter.

Organism	Intrinsic resistance
Bacteroides (anaerobes)	aminoglycosides, many β-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, 1st and 2nd generation cephalosporins, chloramphenicol, tetracycline
Stenotrophomonas maltophilia	aminoglycosides, β-lactams, carbapenems, quinolones
Acinetobacter spp.	ampicillin, glycopeptides

In Enterococcal infection, combination of aminoglycoside + cephalosporins is effective.

a. Acquired resistance :
Due to :
Mutation of genes :
Like point mutation, deletions, insertions.
Acquisition of foreign resistance genes :
In the form bacteriophages/plasmids/ naked DNA.

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.

A single mechanism is seldom responsible for Antimicrobial.

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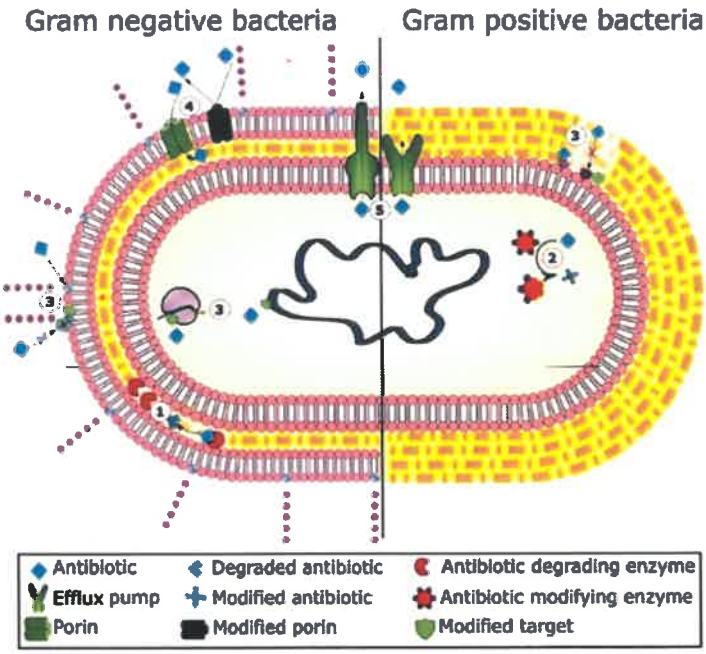
Resistance (AMR) in a bacteria.
The outcome is based on a multiple complex processes and it may not be always possible to interpret resistance mechanism by microbiology/culture report.

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).

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It works by acetylation /adenylation / phosphorylation.

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.

	β-LACTAM	AMINO-GLYCOSIDE	CHLORAM-PHENICOL	MACROLIDE	SULFONAMIDE	TETRACYCLINE	TRIMETHOPRIM	QUINOLONE	GLYCOPEPTIDE	LINCOSAMIDE/ STREPTOGRAMIN	RIFAMPIN
Enzymatic inactivation	+++	+++	+++	+ (gram-negatives)	-	-	-	+	-	-	-
Decreased permeability	+ (gram-negatives)	+ (gram-negatives)	+ (gram-negatives)	++ (gram-negatives)	-	+ (gram-negatives)	+ (gram-negatives)	+ (gram-negatives)	++ (gram-negatives)	+ (gram-negatives)	-
Efflux	+	-	+	++	-	+++	-	+	-	-	-
Alteration of target site	++	++		+++	-	+ (Acinetobacter spp.)	++	+++	+++	+++	+++
Protection of target site		-	-	-	-	++	-	-	-	-	-
Overproduction of target	-	-	-	-	++	-	++	-	+	+	-
Bypass of inhibited process	-	-	-	-	-	-	+	-	-	-	-
Loss of activator	-	-	-	-	-	-	-	-	++	-	-

+++ Most common mechanism, ++ common, + less common

Major mechanisms of resistance to Beta Lactam antibiotics :

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

Beta Lactamases (BL):

Splits the amide bond of the β-lactam ring

Types of BL :

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

Ambler classification of BL

00:18:58

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, doxacillin, 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 metallogenzyme carbapenemase; *OXA*, oxacilin; *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, *IFM*, lemonera, *VIM*, 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.
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 (Chromosomal)	Organisms
S	Serratia
P	Pseudomonas Proteus Providencia
A	Acinetobacter
C	Citrobacter freundii
E	Enterobacter spp

Mnemonic : 'space'

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.

Extended spectrum AmpC :
New enzyme class.
Resistance to carbapenems.

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more difficult to treat.

Once this extended spectrum AmpC becomes more important clinically leads to carbapenem.

Bush-Jacoby/Functional classification of BL:

GROUP	ENZYME TYPE	INHIBITION BY CLAVULANATE	MOLECULAR CLASS	NO. OF ENZYMES	EXAMPLES*
1	Cephalosporinase	No	C	57	*Enterobacter cloacae* P99 (C), MIR-1 (P)
2a	Penicillinase	Yes	A	20	*Bacillus cereus* I, *Staphylococcus aureus* (B)
2b	Broad spectrum	Yes	A	16	SHV-1 (B), TEM-1 (P)
2be	Extended-spectrum	Yes	A	81	*Klebsiella oxytoca* K1 (C), TEM-3 (P), SHV-2 (P)
2br[a]	Inhibitor-resistant	Diminished	A	13	TEM-30 (IRT-7) (P)
2c	Carbenicillinase	Yes	A	15	AER-1 (C), PSE-1 (P), CARB-3 (P)
2d	Cloxacillinase	Yes	D or A	21	*Streptomyces cacaoi* (C), OXA-1 (P)
2e	Cephalosporinase	Yes	A	19	*Proteus vulgaris* (C), FEC-1 (P)
2f[a]	Carbapenemase	Yes	A	3	IMI-1 (C), NMC-A (C), KPC (P), Sme-1 (C)
3	Carbapenemase	No	B	15	*Stenotrophomonas maltophilia* L1 (C), NDM-1 (P), IMP-1 (P)
4	Penicillinase	No		7	*Burkholderia cepacia* (C), SAR-2 (P)

*B, Both; C, chromosomal; P, plasmid.
[a]New groups, derived from Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for β-lactamases and its correlation with molecular structure. *Antimicrob Agents Chemother* 1995; 39:1211–1233.
AER, Aeromonas; CARB, carbenicillin; FEC, isolated from feces; IMI, imipenem hydrolyzing; IMP, imipenem; IRT, inhibitor-resistant TEM; KPC, K. pneumoniae carbapenemase; MIR, Miriam Hospital; NDM, New Delhi metallo-β-lactamase; NMC-A, not metallocenzyme carbapenemase-A; OXA, oxacillin; PSE, Pseudomonas-specific enzyme; SAR, southern Africa-related enzyme; SHV, sulfhydryl variable; TEM, Temoniera

Carbapenemases 00:32:33

Carbapenemases :

Class A – Klebsiella pneumoniae carbapenemase (KPC) :

Inhibited by newer BLIs (avibactam/relebactam / vaborbactam)

Class D – OXA :

OXA-48 is inhibited by avibactam

Does not act against non OXA-48.

Non OXA-48 Carbapenemase (OXA-23, OXA-51) more important in Acinetobacter.

Class B OR metallo-beta-lactamase :

New Delhi metallo-beta lactamase (NDM) -1 in Enterobacteriaceae. Carba

Others : IMP, VIM, SIM, GIM, SPM.

Inhibited by EDTA, Aztreonam.

methods for detecting carbapenemases :

Disc potentiation test, Double disc synergy test, modified Hodge's test, Carba NP, eCIM, mCIM.

Carba R :

Like gene expert, Clostridium difficile toxin detection cartridge, nucleic acid amplification tests.

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Indicate type of beta lactam.

Eg :

Clinically isolated organism is a carbapenem resistant with resistance due to :

- KPC -> Ceftazidime + Avibactam.
- KPC + NDM -> Ceftazidime + Avibactam + Aztreonam.
  Because NDM neutralised by Aztreonam.
- KPC + Oxa 48 -> Ceftazidime + Avibactam.
- Oxa 23 :

Ceftazidime + Avibactam + Aztreonam not effective.

Polymyxin best therapy will be helpful.

Examples of other mechanisms :

OprD Porin loss :

Imipenem resistance in Enterobacter aerogenes, Klebsiella pneumoniae and Pseudomonas aeruginosa.

may retain meropenem sensitivity.

Efflux pumps :

mexAB-Oprm against meropenem in Pseudomonas.

AcrAB multidrug efflux pump in E. coli for penicillin.

Altered PBP2 (Pen A gene) :

Penicillin and cephalosporin resistance in N.gonorrhoeae.

Q. What determines the resistance to any beta-lactam antibiotic in addition to presence of the enzymes?

1. Rate of production of enzyme
2. Rate of hydrolysis
3. Rate of diffusion into periplasm
4. Affinity for the antibiotic
5. All

Interpret the resistance mechanism in an isolate (GNB) based on the sensitivity profiles :

Antibiotic	Sensitivity 1	Sensitivity 2	Sensitivity 3
Ceftriaxone	R	R	S
Ceftazidime	S	R	S
Ciprofloxacin	R	R	S
Amikacin	R	S	S

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