**Latest Antibiotic Resistance Scenario and Current Antibiotic Policies**

**Manzoor Ahmed Thokar, MBBS; MD**

**Introduction**

Researchers have strived hard from time to time on antibiotic weaponry for mankind to tackle life threatening emerging and re-emerging infectious pathogens and our duty as researchers and prescribing practitioners is to keep these antibiotics away from developing resistance in order to keep them effective for future generations. Our duty is to make ways for rationalizing and optimizing choice, dose and duration of the antibiotics in therapeutic, empirical and prophylactic treatment modalities.

![Beta-lactam antibiotic weaponry](image1)

**Fig 1. Beta-lactam antibiotic weaponry**

![Mechanisms of action of antimicrobials](image2)

**Fig 2. Mechanisms of action of antimicrobials**

The threat posed by fast spreading antibiotic resistant pathogens is looming large on various antibiotic classes in general and some like beta-lactams, 3rd generation cephalosporins and carbapenems in particular. First we encountered antibiotic drug resistance (ADR) and had to counter it with resistance inhibitors. Microbes cleverly evaded this challenge also and more strikingly extended the resistance to other antimicrobials by various mechanisms and threw us into multidrug resistant scenario (MDR). Again in turn we had to resort to combination therapy for relief and bacteria as usual being ahead of us gave us Extensive drug resistance (XDR).

Presently, we are already working in multidrug-resistant, polymicrobial and co-infection scenario. Our duty henceforth is to rationalize and optimize antibiotic choice, dose and duration in therapeutic, empirical and prophylactic treatment modalities. Man first lived in prebiotic era which was followed by antibiotic era but we faltered in prescribing these antibiotics judiciously as some of our doctors wanted quick fame and patients instant relief and it was this time that seeds of antibiotic catastrophe were sown. Most of practitioners and experts presently prescribe antibiotics on educated guess i.e. empirically and prophylactically and not following culture/sensitivity (c/s) reports.

Resistance originally confined to some extent to gram positive cocci like staphylococcus aureus started disseminating to other microbes of gram negative nature like E. coli, Klebsiella etc and from more conducive hospital environments to the community. Resistance dissemination did not end with other bacteria only but was extended to other antibiotic classes like aminoglycosides as gentamicin and amikacin and to fluoroquinolones as ciprofloxacin and ofloxacin. In addition vancomycin resistant enterococci (VRE) are presently causing havoc all over the world and there is danger that vancomycin resistant MRSA (VRSA) may be a future challenge as some MRSA in some parts of the world are already established as VISA/GISA strains (vancomycin intermediate sensitive and glycopeptide intermediate sensitive staph. aureus).
Under these circumstances we need to update ourselves on changing pharmacodynamics (how a drug acts on the body) and pharmacokinetics (how the body acts on a drug) in different dimensions and situations. Misuse of antibiotics destroyed our normal bacterial flora and out of antibiotic selection pressure, resistant mutants took control of our body and pushed us to resistant bacterial overgrowth syndromes. Most of the situations now demand prescription of probiotics instead of antibiotics or antibiotics along with probiotics so as to restore our normal flora meaning that we are already in probiotic plus antibiotic era. If we falter once again in prescribing antibiotics, chances are that we may land in complete probiotic era as we will have no choice but to do something like normal flora transplant which will later on push us back to previous era within no time. We should desist from working in isolation as situation demands us to contribute together under one roof as all medical/surgical/dental/veterinary/practitioners and pharmaceutical specialists prescribe antibiotics. We all need to know the mechanisms of bacterial resistance onslaught and accordingly concentrate on their control measures.

To accomplish all this we better undertake and then apply need based research tools in our day to day practice and on top of it, make awareness about it through conferences/seminars/symposia and involve electronic/print and mass media so that we reach to the common man with important messages of avoiding self medication. All of us prescribe some percentage of antibiotics and thus contribute equally to resistance if we are not using them judiciously. Antibiotic drug resistance in dentistry and veterinary sciences also affects humans through resistance in dental pathogens and zoonotic diseases respectively as some of veterinary practitioners use too many antibiotics unnecessarily for healthier offspring yield and better milk production.

Culture and sensitivity interpretation redefined:
Scientific innovations get modified from time to time and so get interpretations. What is logic today may not be applicable tomorrow. We have to change as per demands and keep abreast with latest developments and incorporate need based surveillance and research tools in our systems. Then only can we keep pace with changing times. Our main antibiotic weaponry i.e. beta lactams as the penicillin group, 3rd generation cephalosporins as ceftazidime, cefeperazone, cefotaxime etc and carbapenems as impipenem are at a stage of so to say extinction. To start with we encountered penicillinase/beta-lactamase enzyme inactivation onslaught by microbes against beta-lactams and making them ineffective by hydrolysing their beta lactam ring, secondly these beta-lactamases became extended spectrum and made our penicillinase resistant penicillins as methicillin, oxacillin, cloxacillin etc also defunct.

Our further new approaches with other resistance inhibitor combinations i.e. antibiotics with clavulanic acid sulbactam, tazobactam etc for augmentation along with antibiotics as more effective bactericidal combinations are also encountering resistance at an alarming pace up to the tune of 20-70% at various tertiary care centers around the world.
Outbreak causing pathogens like *E. coli*, *Klebsiella*, *Pseudomonas* and MRSA.

Other mechanisms i.e. mutation, efflux pump, conjugation, transduction, and transformation, all get a boost when antibiotics are not used judiciously and serves as a launching pad for micro-organisms to evade the antibiotic onslaught. These resistance mechanisms remind us of microbial intelligence, being ahead of us, at all crucial junctures. MRSA (Methicillin resistant *staph. aureus*), ESBLs (extended spectrum beta-lactamases) and MBLs (Metallo- beta-lactamases) are one of such bacterial enzyme onslaught resistance mechanisms, where we have to act fast and apply our mind in prescribing antibiotics.

In these circumstances c/s reports are with a discrepancy as beta-lactam group of antibiotics in MRSA, 3rd generation group of cephalosporins, in ESBL producing gram negative bacteria and carbapenems i.e. imipenem in MBL producing *pseudomonas aeruginosa* are not to be prescribed even if they are sensitive in vitro as they are resistant in vivo because of increased tolerance threshold of bacteria. We have to be cautious as many times single disease entities in different forms need to be tackled differently. For example, in Pneumonias which can be community acquired, hospital acquired, ventilator associated or as aspiration pneumonias, antibiotic prescription protocol differs from one situation to another.

Hospital acquired ventilator associated pneumonias need prompt treatment with vancomycin and Ceftriaxone for one week in early onset entity or Vancomycin and Cefepime with added quinolones or aminoglycoside therapy for one week in late onset entity whereas community acquired pneumonias should be treated with Ceftriaxone and doxycycline for one week and in severe cases with addition of levofloxacin for 5 days.

Serious cases needing admission have to be treated with Ceftriaxone along with Azithromycin or Vancomycin.

FDA approved drugs for MRSA also differ in different circumstances. In nosocomial pneumonias with MRSA, linezolid and vancomycin are the drugs of choice and daptomycin or vancomycin are the regimes preferred in MRSA bacteremia and endocarditis, Daptomycin and tagecyclins are needed sometimes as last resort choices in complicated cases. In simple MSSA nosocomial bacteremia vancomycin suffices and with the addition of cefazolin for 2 weeks and for 4-6 weeks it suffices for complicated cases.

Sometimes an antibiotic may be effective in one genus and at the same time ineffective against other genus e.g. quinaprestin use in VRE is effective in fecium species and not in faecalis species of enterococci. Carbapenems being poor substrates for bacterial degradation onslaught are drugs of choice for ESBL producers but MBL producing pseudomonas species have inactivated them also.

Currently we have system-, organ- and procedure-directed separate antibiotic policies for nosocomial wound infections, urinary tract infections, respiratory tract infections, bacteremias, septicemias, endocarditis and other disease entities.

Ertapenem never acts on nosocomial pseudomonas and acinetobacter sp. but is still being given irrationally in many cases.

Cilastatin should be ideally given in combination with vancomycin which inhibits renal enzyme degradation problems of cilastatin. Mutans and beta hemolytic group of streptococci, *staph. aureus*, bacteroids, candida, lactobacilli, actinomyces, fusobacterium, eubacterium, oral mycoplasma, violonella, propionibacterium, treponema, denticoles and bifibobacterium constitute the main bulk of dental pathogens in dental caries, plaque formation, gingivitis, root canal infections and periodontitis with modes of infection mostly being trauma and dental extraction.
Streptococci-50%, Staphylococci-25%, Enterococci-6%, GNB-5% and rest of bacteria-14% constitute percentage wise commonly encountered pathogens in dental practice.

Amoxicillin, cloxacinil, amoxyclyl, metronidazole, other penicillins, cephalosporins, aminoglycosides, erythromycin tetracycline and lincomsides are commonly used antibiotics to treat these infections and unfortunately most of them are with high resistance potential. High use of these antibiotics and long acting penicillins, used for prophylaxis of infective endocarditis and rheumatic fever prior to dental extraction is not justified considering the fact that only 50 persons/million/year get infective endocarditis as per British surveys. Antibiotics in dentistry have to be prescribed carefully in view the overall bacterial challenge, concentration of drug in saliva, host factors and the predominant pathogen involved. Facilities have also to be incorporated for beta-lactamase, ESBL and Mbl detection in dental microbiology labs. Violinella, provotella, porphirimonas gingivalis and oral streptococci are proved beta-lactamase producers. Metronidazolode should not be used in actinomycetes and eikinella infections because of their intrinsic resistance nature to this drug. Fusobacterium and violinella are showing increased resistance to clindamycin so should be used cautiously. Concentration of antibiotics in saliva varies even for members of same class of antibiotics e.g. azithromycin is a more effective macrolide in dental infections than erythromycin because of its higher concentration in saliva. Bacteroids, Borelia, anerobic cocci, candida and other miscellaneous etiological agents should be kept in mind in patients with immunocompromised status.

Contributory factors like mushrooming of fake and spurious antibiotic drug manufacturing companies, irrationul use of antibiotics, faulty disinfection and hand hygiene practices, faulty hospital waste management practices, antibiotic classes not being used on rotation basis, unawareness (latest developments on antibiotic resistance has to be disseminated through conferences/workshops/symposia), visitors rush to patients, carrier states of hospital personnel and food handlers, not prescribing antibiotics as per C/S reports and lack of facilities to diagnose new developments, faulty disinfection of endoscopes, bronchoscopes, incubators, surgical instruments etc., self medication, nonadherence to antibiotic prescription auditing, not making antibiotic policies on regular basis as per surveillances, noninclusion of clinical trial reports in antibiotic policies, not keeping away high resistance potential antibiotics, not minimizing hospital stay of critically ill patients, noninvolvement of veterinarians/dentists in such programs, laboratory contamination/colonization being reported as pathogens and lack of vaccination facilities against life threatening diseases like Hepatitis B add to the proliferation of antibiotic resistance.

Conclusions

In today’s polymicrobial, multidrug resistant and combination therapy scenario, as witnessed globally, not only efficient detection, early reporting and rationale in treatment are important but aggressive infection control practices are necessary and for this. The need of the hour is to incorporate cost effective MRSA/ESBL/Mbl screening and confirmatory tests at different hospitals so as to avoid treatment failures. Reporting of MRSA, ESBL and Mbl production from microbiology laboratories has to be interpreted scientifically as in vitro sensitivity to beta-lactams in MRSA, 3rd generation cephalosporins in ESBL producing bacteria and carbapenems in Mbl producing Pseudomonas organisms amounts to in vivo resistance. These MRSA/ESBL/Mbl producing resistant strains which emerge out of irrational use of antimicrobials are difficult to treat and thus pose a big challenge for the future especially in tertiary care hospital setups. Microbiologists’ advice in such setups will be of immense help while interpreting these sensitivity reports and will definitely help in curbing the proliferation of these multi drug resistant pathogens.

Contributory factors responsible for proliferation of these infections in hospitals and their dissemination to community need immediate attention and awareness through conferences/symposia and workshops as these resistant microbial strains which emerge out of irrational use of antimicrobials are difficult to treat and pose a big challenge for the future.

In the author’s one such national level study in India on molecular epidemiology and dissemination aspects of MRSA published in 2006 in Annals of Cl. Microbiology and Antimicrobials (1) on carrier strains of MRSA, using PCR (polymerase chain reaction) and PFGE (pulse field gel electrophoresis) for isolation of plasmids and molecular typing of strains respectively along with antibiotic sensitivity as per NCCLS guidelines showed colonized infected inpatients and colonized hospital workers as reservoirs of MRSA infections and carriers at risk of getting endogenous infections and then transmitting these infections to community. Resistance markers got transferred from clinical to carrier staph. aureus and amikacin resistance was also transferred from staph. aureus to E. coli and it is evident that we have to take extra care in surveying colonized hospital workers, visitors and admitted patients so as to control spread of antibiotic drug resistance.

References:

2. Thokar MA. ESBL- burgeoning problem and its control measures. Journal of Medical Sciences. March 2008;vol 2 no1

Conflict of Interest: None

Author Information: Manzoor Ahmed Thokar is Professor Medical Microbiology, Faculty of Medicine, Al-Arab Medical University, Benghazi, Libya. Email: manzoor_thakur@rediffmail.com

Manzoor Thakur 1, 2, 3, 4

2. Thokar MA. ESBL- burgeoning problem and its control measures. Journal of Medical Sciences. March 2008;vol 2 no1

Conflict of Interest: None

Author Information: Manzoor Ahmed Thokar is Professor Medical Microbiology, Faculty of Medicine, Al-Arab Medical University, Benghazi, Libya. Email: manzoor_thakur@rediffmail.com