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Public Health Open Access
ISSN: 2578-5001

AMR: An Emerging Threat

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Mini Review
Volume 8 Issue 1
Received Date: December 18, 2023
Published Date: January 10, 2024
DOI: 10.23880/phoa-16000263

Abstract

Antimicrobial resistance (AMR) has become a global threat now, posing insurmountable challenge to clinicians and nursing personnel alike. Resistance of *Mycobacterium tuberculosis*, *Staphylococcus aureus* to hitherto effective antibiotics has been around for many decades now. Relatively recently, more microbial pathogens have started rendering antibiotics ineffective. They include *Mycobacterium leprae* against rifampicin, dapsone and ofloxacin, *Enterococcus* SPP. against vancomycin. Even resistant fungal species are not unheard of. One such example is *Candida auris* which does not respond to multiple antifungal agents. Healthcare givers need to take AMR very seriously now, both in the community and in hospital setting.

Keywords: AMR; Problem; Resistant; Emerging

Abbreviations: MRSA: Methicillin Resistant *Staphylococcus aureus*; CA-MRSA: Community-Associated MRSA; HA-MRSA: Hospital-Acquired MRSA; VRE: Vancomycin Resistant *Enterococcus*; ESBL: Extended Spectrum Beta Lactamase; NDM: New Delhi Metallo-Beta Lactamase; HDU: High Dependency Unit; ICU: Intensive Care Unit; HLAR: High Level Aminoglycoside Resistance.

Introduction

Antimicrobials are drugs used to kill or stall multiplication of microbes. Antibiotic resistance occurs when bacteria or other microorganisms. Antibiotic resistance occurs when bacteria, viruses, or other microorganisms evolve to withstand the effects of antibiotics. When antibiotics are used inappropriately or excessively, the sensitive bacteria are killed, but the resistant ones survive and multiply, leading to the spread of antibiotic-resistant infections. Overuse of antibiotics in human medicine as well as animal husbandry, compounded by factors like long time to develop new antimicrobial classes, has made AMR a problem of gigantic proportion on a global scale. Lack of awareness, premature discontinuation of antibiotic therapy and the common practice of self-medication, owing to an urge for instant relief, on part of general population has added fuel to fire. This was predicted way back in 1945 by Alexander Fleming, the discoverer of antibiotics, who prophesied that men will soon run out of options as far as antibiotics are concerned, simply because of imprudent usage of antibiotics. The objective of this review is to provide a brief introduction to the ongoing AMR crisis.

Methicillin Resistant *Staphylococcus aureus* (MRSA): MRSA can be of 2 types, Community-Associated MRSA (CA-MRSA) and Hospital-Acquired MRSA (HA-MRSA). MRSA occurs due to substitution of Penicillin Binding Protein-2 (PBP2) with PBP 2a which has lesser affinity to bind with Beta lactam antibiotics. MRSA isolates are also resistant to

Fluoroquinolones and Aminoglycosides. MRSA are mostly reported from cases of skin and respiratory infections in the hospital.

Vancomycin Resistant *Enterococcus* (VRE): Vancomycin is ineffective in many strains of *Enterococcus fecium* now and also in many isolates of *E. fecalis*. VRE is particularly common in the nosocomial setting for causing urinary tract and bloodstream infections.

Extended Spectrum Beta Lactamase (ESBL): Extended spectrum beta lactamases are also an emerging threat in Gram negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa*.

New Delhi metallo-beta lactamase (NDM): Discovered in Denmark in 2008, the NDM has become a cause of great concern. It is resistant to all Cephalosporins. NDM-1 enzyme can break down a wide range of β-lactam antibiotics, including carbapenems, which are the antibiotics of last resort for treating infections caused by bacterial strains resistant to other, less potent antimicrobials [1]. *Enterobacteriaceae* isolates which harbour NDM-1 have now been found in many areas of India and Pakistan and also in the United Kingdom MDR and XDR in TB:- TB cases resistant to both Isoniazid and Rifampicin are defined as multi drug resistant tuberculosis (MDR-TB). TB variants resistant to Rifampicin alone is called Rifampicin Resistant Tuberculosis (RR-TB) and put in the same treatment group as MDR-TB. The first MDR-TB case was found in 1956 in Great Britain. This has emerged as a worrisome strain in emerging countries including India and South Africa, two hotspots of TB infection. Globally, the estimated proportion of new TB cases with MDR/RR-TB was 3.9% (95% CI: 2.8–5.0%) in 2015 and 3.6% (95% CI: 2.7–4.4%) in 2021. An even more dangerous clinical entity, is Extensively Resistant Tuberculosis (XDR TB). XDR TB is actually a rare type of MDR TB that is resistant to Isoniazid and Rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (like amikacin, kanamycin, or capreomycin) [2]. XDR TB emerged [3] in 2005 in KwaZulu-Natal province of South Africa, and has spread to India and worldwide now. Global prevalence of XDR-TB is now considered to be 2.5% among all TB patients [4] and 9% among MDR-TB cases [4]. CBNAAT and other PCR based methods can detect MDR and XDR effectively. Other assays like proportion-based method in Löwenstein-Jensen (LJ) and Microscopic Observation Drug Susceptibility (MODS) assay may also be helpful.

Leprosy

Drug resistance has also come up in Leprosy. Earlier it occurred due to Dapsone monotherapy, but now is has been reported even after MDT [5]. Rifampicin (*rpoB* gene mutation) and Ofloxacin resistances are common (*gyrA* gene mutation).

Candida auris: *Candida auris* is a drug resistant and highly persistent yeast pathogen, discovered from the external ear of a person in 2009 in Japan [6]. Based on the CDC guidelines, about 90%, 30%, and 2% - 10% of *C. auris* isolates are resistant to three major antifungal drug groups viz. fluconazole (FLU), amphotericin B (AMB), and echinocandins, respectively. Taken together, about 90% of *C. auris* strains are resistant to at least 1 drug, 30% - 41% to 2 drugs and about 4% to all 3 aforesaid antifungals [7]. It is highly prevalent in hospital settings like High Dependency Unit (HDU) and Intensive Care Unit (ICU). Patients may be colonized asymptomatically by *C. auris* on their skin, or in oropharynx, nostrils, rectum and other body sites. However, unlike most other *Candida* species, that colonize the gastrointestinal tract, *C. auris* predominately tends to colonize the skin [8]. *C. auris* grows appreciably at 40–42°C and is also able to survive in the environment and under alkaline conditions, although it does not tolerate anaerobiosis. The transformation of *C. auris* from an environmental fungus to a human pathogen is possibly due to the overuse of antifungals or due to the thermal adaptation owing to climate change.

Hence AMR is really a very serious public health problem now and hence it needs to be understood and mitigated. Also important is to know the mechanisms leading to AMR.

Mechanisms of AMR

- Mutations in drug target: This is commonly seen in cases of aminoglycoside and macrolide resistance in bacteria.
- Altered drug binding sites: MRSA is a good example of alteration of target site. Here the PBP or penicillin binding protein is altered to PBP-2a which does not effectively bind beta-lactam antibiotics.
- Drug modifying enzymes: Aminoglycoside modifying enzymes confer resistance to these antibiotics in Enterococci and other bacteria. In fact, aminoglycoside modifying enzymes are responsible high level aminoglycoside resistance (HLAR) in *Enterococcus* spp. This phenomenon renders the synergistic activity of bet-lactams and aminoglycosides on Enterococci ineffective [9]. Such modifying enzymes include acetyltransferases, phosphotransferases, and nucleotidyltransferases which can alter the effects of other aminoglycosides. Recently, a new antibiotic has been discovered, namely Plazomicin, which is not affected by aminoglycoside-modifying enzymes [10].
- Efflux pumps:- *Tet* efflux pumps mediate Tetracycline resistance in *Staphylococcus aureus*. Efflux pumps may also be important for Plazomicin resistance in Enterococci. These efflux pumps belong to the major

facilitator superfamily of transporters, and are able to effectively decrease intracellular tetracycline concentration via exchange of a tetracycline molecule against a proton [11]. Also, tetracycline efflux genes are associated with mobile genetic elements, like plasmids or transposons, which helps in their wide dissemination across species or genus boundaries.

- Thickened cell wall impeding penetration of drug into target site:- This is seen in VISA or Vancomycin indeterminate *Staphylococcus aureus*. A thick cell wall impairs the entry f Vancomycin into target site. Also, increased cell wall turnover can be responsible.
- Intrinsic drug resistance:- Gram negative bacteria are always resistant to Vancomycin. *Enterococus casseliflavus* is always inherently resistant to Vancomycin. This resistance can be mediated by the *vanC* gene. The vanC resistance determinants are found on the chromosome in *Enterococcus casseliflavus* and *Enterococcus gallinarum* and are intrinsic characteristics of these species. VanC-harboring enterococci exhibit low-level resistance to vancomycin and are generally susceptible to teicoplanin [12]. Among yeasts, Candida krusei in intrinsically resistant to Fluconazole. The Table 1 below shows illustrative tabulation of infection, resistance to drugs and the mechanisms.

Infection	Resistance to drugs developing	Mechanisms of drug resistance
Skin and lung infections by *S. aureus*	MRSA is common	PBP-2 replaced by PBP-2a
Bone infections by *S. aureus*	SCV (small colony variants) *S. aureus* is common (along with MRSA)	PBP-2 replaced by PBP-2a
Urinary, bloodstream infections and wound infections caused by *Enterococcus* spp.	VRE is common	van a, van B, van C genes . These genes encode an alternate biosynthetic pathway for the production of cell wall precursors that bind vancomycin poorly
Skin infections, abscess, pneumonia, and infection of heart valves, bones, or bloodstream by S. aureus	VISA (Vancomycin indeterminate *Staphylococcus aureus*) is common	increase in cell wall turnover which leads to an increase of non-cross-linked d-alanyl-d-alanine side chains, which are capable of binding Vancomycin outside of cell wall, making less Vancomycin available for intracellular target molecules

Table 1: Tabulation of infection, resistance to drugs and the mechanisms.

How to Reduce the Burden of AMR in the Community

Some steps can be taken to recue AMR burden in community, like:-

I. Proper awareness needs to be generated about AMR in the community. Even today, many common people think that Paracetamol and Cetirizine are antibiotics.

II. Resistance to antibiotics is very common in the community. In our experience, Nitrofurantoin resistance in uropathogenic *Escherichia coli* is not low (27.27%). This means that commonly used empiric drugs can no longer be safely used for treating common ailments like urinary tract infections.

III. Data on antibiotic susceptibility patterns over time should be sought and antibiotics changed accordingly. Genetic methods should be used for surveillance of drug resistance, more commonly in *Mycobacterium tuberculosis* and *M. leprae*. Such methods include NAAT (Nucleic acid amplification tests)/PCR and Whole genome sequencing.

How to Reduce Burden of AMR in the Hospital

Some things have to be remembered and implemented for infection control in the hospital settings, like:-

A. Proper antibiotic stewardship has to be there, along with other things that should be emphasized, like proper biomedical waste disposal and vaccination to prevent infections.

B. Hand hygiene is also very important to prevent cross-transmission of resistant bugs(6 steps and 5 points of hand hygiene have to be kept in mind).

C. Operation theatres should be kept free of trespassers as far as possible to prevent nosocomial infections by multidrug-resistant bugs. Air and surface microbial flora of operation theatres should, hence always be assessed before commencement of any operational procedure.

D. Each hospital should have its own antibiotic registry and also do regular antibiotic audit. Also, periodical antibiotic ward rounds should be carried out to assess and ensure proper usage of antibiotics in the wards.

E. Cleaning and disinfection should be stressed upon. Hydrogen peroxide and Povidone Iodine are good at

reducing the burden of *C. auris* in hospitals by killing planktonic and biofilm cells of *C. auris* [13].

F. No cobweb should be allowed in hospitals to prevent accumulation of dirt and along with that, multidrug resistant microbes. For this reason only, hospital flooring should also be seamless wherever possible.

G. Each hospital/healthcare facility should have its own antibiotic policy which should be periodically revised. This policy should be created and maintained by ICC (Infection control committee) of the healthcare facility, comprising one clinician, one Microbiologist and one nursing staff, along with others. It is to be headed by the Medical Superintendent of the hospital or equivalent person.

Discussion

Resistant infections caused by these bacteria, also called superbugs, are difficult to treat [1]. As the world greys and more people spend longer years in their sunset years with diminished immunity, it'd be logical to expect some so far treatable infections to progress to prolonged and life-threating conditions. Thus, AMR should be treated as a potential pandemic waiting in the wings. A multifaceted approach would be necessary to tackle the grave situation. Some of the components include adopting a One Health approach which monitors antibiotic use in animal husbandry acknowledging the interconnected nature of human, animal, and environmental health and antibiotic stewardship programme to optimize antimicrobial chemotherapy in healthcare settings. Overuse of antibiotics in animal husbandry contributes t a major chunk of AMR in the country. It is also very important to monitor extant drug resistance in pathogenic bacteria alongside speeding up development of newer antimicrobials and vaccine. New drugs should be discovered, like Bedaquiline for XDR TB. Separate approaches may have to be developed in the community as well as the hospital to solve the issue of AMR [14-16].

Conclusion

AMR is an emerging problem in bacteria and fungi. In addition to clinical measures, it is essential that all drugs, which have been proven to cause resistance, must be purchased in pharmacies only with a prescription under severe monetary punishment for the sellers. As a public health measure, it is necessary to widely disseminate drug resistance mechanisms by the WHO in all countries. This is not a problem that can be easily solved.

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