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Understanding Evolution of Resistant Strains in Recent Decades and Approach Towards Antibiotic Therapy

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ABSTRACT

Developing resistance to antibiotics is a natural process, and a rising threat to human society. These emergent strains have worsened the burden on existing regimen of antibiotic therapy. Resistance, classified under multidrug resistance (MDR), extensively drug-resistance (XDR) and pandrug-resistance (PDR), is widely seen in hospital setup. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), *Escherichia coli* and Klebsiella (Resistant to third-generation cephalosporins), carbapenem-resistant Enterobacteriaceae (CRE) are currently spread infectious agents which call for careful and proper antibiotic management. Antibiotic control programs, better hygiene, antibiogram-based empirical therapy with improved antimicrobial activity are needed to limit bacterial resistance.

Keywords: Antibiotics resistance, mechanisms, biofilm resistance, multidrug resistance, extensively drug-resistance, pandrug-resistance

Discovery of antibiotic was a milestone in the history of medical science, which revolutionized clinical world. The antibiotics are wonder drugs which have immense role in health sector by reducing morbidity as well as mortality. They are the main weapons against infectious diseases which is a serious issue on a global level, and save countless lives. The antibiotic era started in the 1940s, which changed the profile of infectious diseases and human demography. With due course of time, there evolved a large variety of pathogens and discovery of new antibiotics became necessary. However, as antibiotics served as magical bullets, equally infectious agents challenged by rapid appearance of resistance through unbelievable molecular mechanisms emerged. Over a period of 65 years, newer antibiotics were introduced in the market, which was followed by emergence of resistant strains. Due to increased concern of change in resistance, this is an attempt to point out how far our chemotherapy with antibiotics has reached, emerging resistant strains, mechanisms, multidrug resistance (MDR), extensively drug-resistance (XDR) and pandrug-resistance (PDR) and how intense use of reserve antibiotics will affect in future.

EVOLUTIONARY CHANGE OF ORGANISMS AFTER ANTIBIOTIC DISCOVERY

The extensive use and misuse of antibiotics are the major factors driving the high numbers of resistant pathogenic bacteria worldwide, which is a rising threat to the society. The introduction of new antibiotics to counter those pathogens has frequently been closely followed by the emergence of resistant strains. These emergent strains have worsened the burden on existing regimen of antibiotic therapy in both clinical and economical aspects. Some of the examples are *Staphylococcus aureus* isolates resistant to β-lactams due to β-lactamase as well as extensive spectrum β-lactamase and many of these are also resistant to β-lactamase-resistant penicillins. Methicillin-resistant *S. aureus* (MRSA) isolates are one of the most challenging resistant pathogens now-a-days. Evolutionary pattern of resistant strains of *S. aureus* is given in Figure 1. They are usually associated with hospitals and require implementation of appropriate control measures, which usually reduces prevalence

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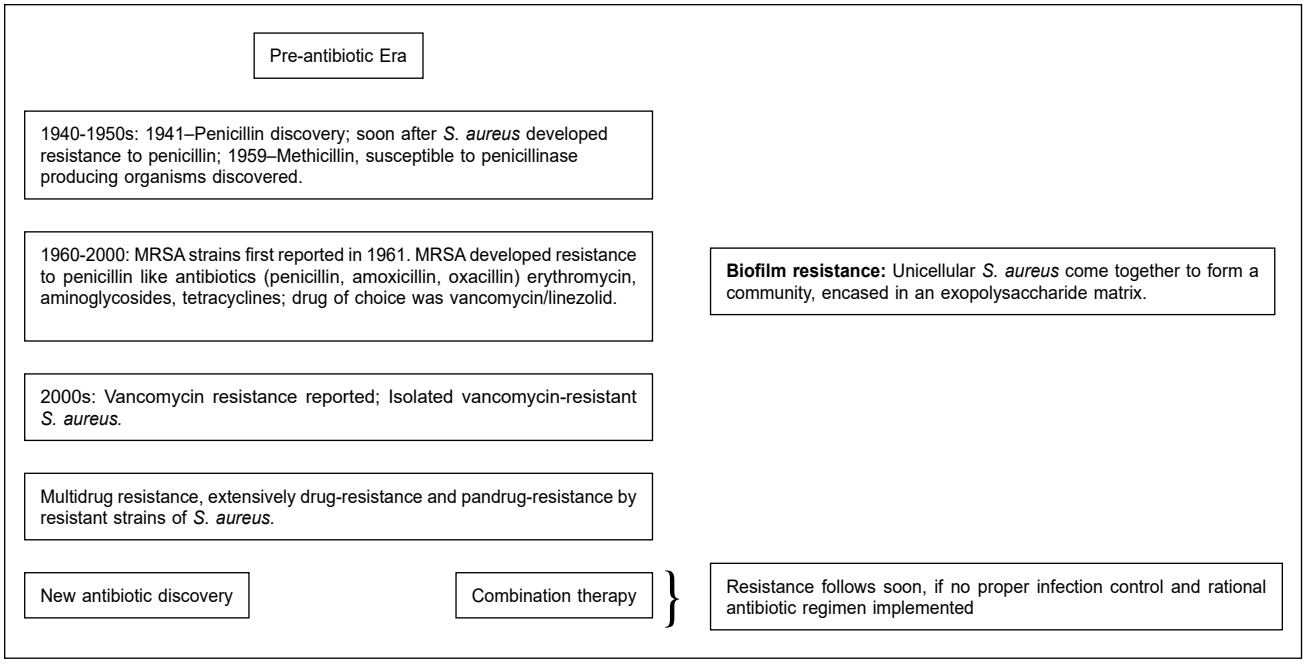

Figure 1. Evolutionary pattern of resistant *S. aureus* strains.

to sporadic levels. Antibiotic resistance often results in failures of empirical therapy. These conditions call for the need for the revolutionary change by either discovery of new antibiotics or combination antibiotic therapy in future. But it is not a rational solution to the problem because resistance follows with these approaches. In short, antibiotic resistance is the major challenge associated with chemotherapy against infectious diseases. Resistant pathogens developed are more virulent, so as a first step, knowledge of etiological agents of infections, antibiotic resistance mechanisms, pattern of developing resistance and sensitivities to available drugs is of immense value for the rational empirical therapy of antibiotics and to slow down the process of antibiotic resistance.

RESISTANT STRAINS IN RECENT DECADES

The susceptible populations of bacteria may become resistant to antimicrobial agents through mutation and selection, or by acquiring from other bacteria, the genetic information that encodes resistance. The infectious agents may get intrinsically resistant to more than one class of antimicrobial agent, or may acquire resistance by *de novo* mutation or via the acquisition of resistance genes from other organisms. These spontaneous mutations may cause resistance by: a) altering the target protein to which the antibacterial agent binds by modifying or eliminating the binding site; b) up regulating the production of enzymes that inactivate the antimicrobial agent; c) down-regulating or altering an outer membrane protein channel that the drug requires for cell entry; or d) up regulating pumps that expel the drug from the cell (Table 1).

However, acquisition of new genetic material by antimicrobial-susceptible bacteria from resistant strains may occur by means of conjugation, transformation or transduction, with transposons often facilitating the incorporation of the resistance genes into the host's genome or plasmids. Some of the important or recently developed resistant strains in our community and its mechanisms are discussed below.

E. coli and Klebsiella: Resistance to Third-generation Cephalosporins

Escherichia coli is a common cause of urinary tract infections (UTI) and bacteremia in humans. It has been observed that there is a generalized decrease in bacterial susceptibility of common oral antibiotics to community-acquired UTI, which is frequently resistant to aminopenicillins, such as amoxicillin or ampicillin and narrow-spectrum cephalosporins. Resistance is typically mediated by the acquisition of plasmid-encoded β-lactamases. But the third-generation cephalosporins are broad-spectrum drugs with intrinsic activity against Gram-negative species. Resistance to third-generation cephalosporins and monobactams (aztreonam) occurs through the acquisition of extensive spectrum beta-lactamases (ESBLs). ESBL are strong bacterial enzymes that raise the burden of resistance to even highly

Table 1. Common Resistance Mechanisms and Examples

Common resistance mechanisms	Example	Antibiotics
a) Altering the target protein to which the antibacterial agent binds	Change in penicillin-binding protein 2b in pneumococci, which results in penicillin resistance	Penicillin G, ampicillin, amoxicillin, ticarcillin, piperacillin, methicillin
b) Up regulating the production of enzymes that inactivate the antimicrobial agent	Erythromycin ribosomal methylase in staphylococci	Penicillins, monobactams, carbapenems and cephalosporins, aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.)
c) Down-regulating or altering an outer membrane protein channel that the drug requires for cell entry	OmpF in *E. coli*	β-lactams, carbapenems, fluoroquinolones, chloramphenicol have specific porins
d) Up regulating pumps that expel the drug from the cell	Efflux of fluoroquinolones in *S. aureus*	Aminoglycosides, ampicillin, ciprofloxacin, chloramphenicol, clindamycin, cephalosporin, erythromycin, fluoroquinolones, macrolides, nalidixic acid, novobiocin, norfloxacin, streptogramin B, tetracycline, tigecycline, trimethoprim, vancomycin

effective antibiotics. The problem of resistance due to ESBL, even though more reported on Klebsiella, now-a-days has a similar pattern for *E. coli*. Different studies showed that ESBL-producers are also resistant to fluoroquinolone, trimethoprim-sulfamethoxazole and aminoglycoside. However, resistance to cephamycins and other β-lactams may arise as a result of changes in the porins in the outer membrane.

Methicillin-resistant *S. aureus*

Methicillin, the first of the semi-synthetic penicillinase-resistant penicillins, was introduced to target strains of penicillinase-producing *S. aureus*. However, resistance to methicillin was reported very quickly after its introduction in 1960s and detection of MRSA has been associated with more severe clinical presentation of community-acquired pneumonia and it is a leading pathogen in skin infection. It was the beginning of global outbreaks of community-associated MRSA infection. MRSA is a common cause of infection among hospitalized patients. Consequently, treatment of these infections has become more difficult and is a healthcare burden. The studies show that MRSA bacteremia is linked with significantly higher mortality rate compared to methicillin-susceptible *S. aureus* (MSSA) bacteremia. Resistance occurs following the chromosomal acquisition of novel DNA, resulting in the production of a new penicillin-binding protein (PBP2a), with a low-binding affinity for methicillin. PBP2a substitutes for all other penicillin-binding proteins, and because of its low affinity for all β-lactam antibiotics, it confers resistance to all β-lactam agents, including cephalosporins. Vancomycin is currently the gold standard for the treatment of MRSA bacteremia, but over the last decade, there has been increasing concern about the development of MRSA strains with reduced susceptibility to vancomycin.

Vancomycin-resistant *S. aureus*

Another major concern after the emergence of MRSA is the vancomycin-resistant strains (VRSA), that is, evolution of strains resistant to vancomycin, which is the typical treatment for MRSA infection. However, the therapeutic failure of vancomycin therapy is explained by the reduced susceptibility of glycopeptides rather than using the term resistance in clinical world and is associated with minimum inhibitory concentration (MIC). *S. aureus* strains with reduced susceptibility to glycopeptides can be divided into three categories - vancomycin-resistant strains (VRSA; MIC, ≥16 μg/mL); vancomycin-intermediate strains (VISA; MIC, ≥4 μg/mL) and heterogeneous vancomycin-intermediate strains (hVISA; MIC <4 μg/mL). Reduced susceptibility versus resistance of vancomycin is controversial, as the term resistance is reserved for those with MIC ≥16 μg/mL. However, the prevalence of hVISA among MRSA is rising.

The exact mechanism of vancomycin resistance remains unclear, but it probably involves thickening of the organism's cell wall due to the accumulation of cell wall fragments capable of binding vancomycin extracellularly, thereby preventing them from reaching their bacterial target. High-level vancomycin resistance occurs because of expression of vanA, which is

associated with alteration of the vancomycin-binding site in the cell wall. Expression of vanA and other genes made the affinity of vancomycin 1,000 times lower than for the native peptidoglycan precursor and resulted in high resistant density.

E. coli, *S. aureus*, *Streptococcus pyogenes*: Biofilm Resistance

Bacterial biofilm is an emerging mechanism of resistance, as it succeeded in explaining the reason of chronic infectious diseases that ends in treatment failure. Biofilms are communities of microorganisms attached to a surface. Bacterial biofilms are formed when unicellular organisms come together to form a community that is attached to a solid surface and encased in an exopolysaccharide matrix. Example-biofilm development in both commensal and pathogenic *E. coli* - the polysaccharide matrix contributes to the development of phenotypic resistance of pathogenic *E. coli* biofilms and leads to persistent infections. Biofilm bacteria show much greater resistance to antibiotics than their free-living counterparts. Its mechanisms is entirely different from familiar mechanisms of resistance such as familiar plasmids, transposons and mutations. This emerging mechanism has grabbed the attention of clinical world and calls the need for potential antibiotic therapies.

It has been suggested that this matrix prevents the access of antibiotics to the bacterial cells embedded in the community. However, *Staphylococcus epidermidis* biofilms formed allowed for the diffusion of rifampicin and vancomycin. These results suggest that inhibition of diffusion cannot always explain resistance to antimicrobial compounds and other mechanisms must be in place to promote biofilm cell survival. Some organisms in biofilms have been shown to express biofilm-specific antimicrobial resistance genes that are not required for biofilm formation. The 38% of the *E. coli* genome is affected by biofilm formation (ompR gene, csgD gene involved in bacterial adhesion). However, the exopolysaccharide matrix does act as an initial barrier that can delay penetration of the antimicrobial agent. Phenotypic and genotypic characteristics associated with biofilm formation of *E. coli*, *S. aureus*, *Streptococcus pyogenes* have been widely studied. Pharyngitis treatment failure has been seen in patients with isolates of *S. pyogenes* having a biofilm-positive phenotype and increased minimum biofilm eradication concentration (MBEC) for all contemporary antibiotics that are used to treat acute pharyngitis cases. *S. epidermidis* infections on indwelling medical devices point towards biofilm formation. *S. aureus* infections, such as osteomyelitis, specifically cases of juvenile osteomyelitis, periodontitis and peri-implantitis, wound infection, endocarditis, are types of biofilm infection. Device-mediated infections are also common and such devices need to be replaced more frequently than those infected with *S. epidermidis*. Biofilm infections must be either prevented from forming or be surgically removed once formed in order to resolve the infection, together with potential antimicrobial therapy.

Carbapenem-resistant Enterobacteriaceae

The difficult situation has not ended with the emergence of broad-spectrum third-generation cephalosporins, carbapenems (example: *E. coli*-resistant to imipenem). These entered the clinical world with extreme potency and broad-spectrum of activity, but are also showing resistance now-a-days. This may have serious public health consequences, resulting in the elimination of many effective antimicrobial drug treatments against the most common human bacterial pathogens. Many studies support the use of carbapenem as an empirical antibiotic for patients with community-onset bacteremia and those with high risk of resistance. Increased consumption of carbapenems after rise of third-generation cephalosporin-resistant *E. coli* and *Klebsiella pneumoniae* may be the reason for emergence of carbapenem-resistant strains of organisms. Resistance density of carbapenem-resistant *K. pneumonia*e is also increasing along with third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*.

Carbapenemases are powerful enzymes that inactivate carbapenems. Bacterial acquisition of carbapenemases has a role in the emergence of carbapenem-resistant Enterobacteriaceae (CRE). It also led to resistance to all cephalosporins, aztreonam and β-lactamase inhibitors including clavulanic acid and tazobactam. CRE isolates are increasingly reported as multidrug-resistant, extensively drug-resistant or pandrug-resistant. In a short time, isolates of *E. coli*, Klebsiella, Enterobacter, Serratia, and Salmonella species have reported carbapenem resistance and it globally changed the epidemiology of resistance. Combination regimen or monotherapy of agents such as polymyxins (such as colistin), aminoglycosides, tigecycline and fosfomycin are the available therapeutic options.

Multidrug Resistance, Extensively drug-resistance and Pandrug-resistance

Multidrug resistance, extensively drug-resistance and pandrug-resistance have been defined differently in medical literatures. The standardized international

terminology was created by group of international experts that came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) defines these terms as follows: MDR is defined as nonsusceptibility to at least one agent in three or more antimicrobial categories; XDR is defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (bacterial isolates remain susceptible to only one or two categories). PDR is defined as nonsusceptibility to all agents in all antimicrobial categories (no agents tested as susceptible for that organism). The pictorial representation of relation between MDR, XDR and PDR is shown in Figure 2.

Emerging and spreading of MDR (emerged strains are referred as 'super bugs') is a natural phenomenon, followed by the inappropriate use of antimicrobial drugs, inadequate sanitary conditions, inappropriate food-handling and poor infection prevention and control practices. XDR ('extreme drug resistance', 'extensive drug resistance') was the term created initially to describe drug-resistant *Mycobacterium tuberculosis.* Eventually, the condition changed and the resistance profile of non-Mycobacterium that compromised most standard antimicrobial regimens was also described by same term. Pandrug-resistant (pan-'all') means 'resistant to all antimicrobial agents'. The management of pandrug-resistant Gram-negative bacterial infections is very difficult. Only few drugs, including colistin, in combination with β-lactam antibiotics, polymyxins, an old class of antibiotics, are recommended. Now the time has been reached where there are only limited therapeutic options. Even though many antibiotics are in our hand, it's time to focus on careful handling of antibiotics.

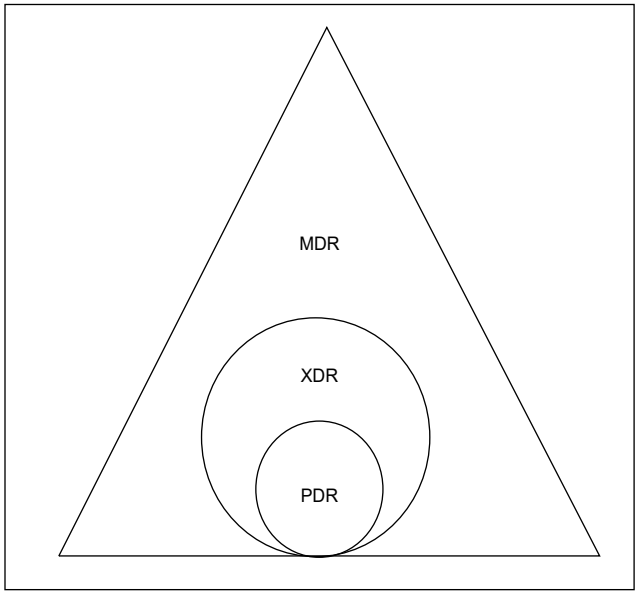

Figure 2. Relation between MDR, XDR and PDR.

MANAGEMENT OF ANTIBIOTIC RESISTANCE

Most of the antibiotic drug resistance is nosocomial or of hospital origin. In India, 1 in 4 patients admitted into hospital acquire nosocomial infection. So, for adequate management of critically ill patients and patients undergoing various operative procedures and other medical interventions, hospital antibiotic policies need to be revisited. In the management of infectious diseases, initially more care should be given in the selection of antibiotics based on hospital antibiogram in empirical therapy. More rational selection of antibiotics based on the most likely pathogens for a given infection and the susceptibility profiles of these pathogens that are specific to each institution will reduce density of resistance in and around institution. Antibiogram considerably helps in proper empirical selection of antibiotics. Each practitioner should have updated knowledge about evolutionary stage of resistant isolates in the hospital, while prescribing each antibiotic. Proper infection control should be employed in hospitals. In short, antibiotic control programs, better hygiene, antibiogram-based empirical therapy and synthesis of agents with improved antimicrobial activity are needed to limit bacterial resistance. In a developing country like India, there is an urgent need to develop and strengthen antimicrobial policy and standard treatment guidelines at the national, community and hospital level.

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Antibodies Against Coronavirus Detectable up to 7 Months After COVID-19 Onset: Study

Antibodies against the novel coronavirus show a rapid rise within the first 3 weeks after symptoms, and are detectable for up to 7 months after contracting the disease, suggests a new study that evaluated 300 patients infected with COVID-19 and 198 post-COVID-19 volunteers.

The research, published in the *European Journal of Immunology*, revealed that the participants had antibodies with confirmed neutralization activity for up to 6 months after the infection with the virus. Nearly 90% of the subjects were reported to have detectable antibodies up to 7 months post contracting the viral disease. Age was not a confounding factor in levels of antibodies produced, though disease severity is, reported the research… (*ET Healthworld – PTI*)

The Americas Facing Risk of Polio Outbreak Due to Disruptions Caused by Pandemic

Health experts are worried about an outbreak of the polio virus in the Americas during the COVID-19 pandemic caused by a delay in vaccinations and surveillance.

Experts at the Pan American Health Organization (PAHO) stated that countries in the region should maintain polio vaccinations and surveillance during the pandemic in order to prevent an outbreak. PAHO Director Carissa Etienne stated that if vaccination coverage rates fall and become too low, there will be a risk for polio circulation in the communities. During the ongoing pandemic, there is a need to work extra hard to not lose what has been gained, said Cuauhtemoc Ruiz Matus, head of PAHO's Immunization Program… (*CNN*)

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