How Pathogens Survive Drug Pressure?

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Abstract Antibiotic resistance can be a consequence of repeat-induced point (RIP) mutation and even by horizontal gene transfer in the pathogen genome for every chromosomal replication. On the account of a few vital antibiotic agents, point mutation of chromosomally encoded proteins is the essential instrument for resistance. Another procedure that may add to the development of resistance in the course of treatment is adaptive or induced change. Notwithstanding RIP mutation, resistance may likewise be interceded by enzymes that change the antibiotic and the target protein or lessen the intracellular concentration of the antibiotics. These systems of resistance are dispersed between microscopic organisms by horizontal gene transfer. Drug resistance grants bacterial development in the nearness of an antibiotic; in any case, it is by all account not the only variable adding to treatment failure. The resistance is also reflected in cases wherein the antibiotic fails to clear the infection regardless of the absence of resistant microbes. These microbes are tolerant, and clinical reports advocate that the level of tolerance to treatment failure and mortality in a few diseases can be as crucial as the nature of antibiotic resistance. Intelligent methodologies and awareness of potential harmful effects of drugs will expect to promise continuous worldwide access to efficient antibiotics.

1 Introduction

Antibiotic discovery was one of the momentous advances in the field of modern medicine. Antibiotics remain as a mainstay in therapeutic regimes. Antibiotics have saved numerous lives afflicted with bacterial infections and other life-threatening infections. The successful discovery of the first β-lactam, penicillin G, prompted the exploration and subsequent development of additional and effective antibiotics. This quest eventually led to the production of countless antimicrobial compounds,

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which are in widespread usage today. However, the major obstacle towards this end was the rapid emergence of drug resistance amongst various microorganisms, which thwarted the efficacy of therapeutic interventions. The first known resistance was seen in *Staphylococcus aureus* alongside penicillin (Keeney et al. 1979).This ultimately led to reduced usefulness of the drug and consequently limited therapeutic options. Till date, almost all known drugs have counterattack by their target microorganisms (Table 1). According to various reports, steady rise of resistance in *Plasmodium falciparum* against artemisinin-based combination therapy, spread of methicillin-resistant *Staphylococcus aureus* (MRSA) amongst hospital-acquired infections, resistance of *Neisseria gonorrhoeae* to cephalosporins and *Escherichia coli* to fluoroquinolones, etc. are emerging threats to the healthcare of modern society (Espadinha et al. 2013; Johnson et al. 2013; Ashley et al. 2014; Bharara et al. 2015; Pham et al. 2015). Resistance leads to life-threatening disease conditions and prolongs infection and prognosis. It aggravates mortality and cost of treatment, too. Drug resistance refers to the phenomenon when microorganisms such as bacteria, viruses, fungi and parasites alter ways such that the medications used to cure the infections are rendered ineffective. When the microorganisms become resistant to most antimicrobial compounds, they are often referred as "superbugs" (Khan and Khan 2016). This can give rise to major health crisis because such a deadly resistance may culminate into a fatal infection and lead to spread to others imposing huge treatment costs. Thus, it can have severe impact on healthcare and wreak havoc on individuals and society.

Microbes conquer antibiotic drug pressure by various biological processes (Fig. 1), which could be of two main types. First, it occurs when the microorganism has never encountered the drug against which it exhibits resistance. Second, as acquired resistance and it manifests itself following drug exposure. Antimicrobial drugs usually target a vital metabolic pathway or cell wall synthesis. To combat this threat, the microbe may either alter the target site of the drug (seen in fungi by altering cell wall composition rendering resistance to antifungal compounds) or might chemically modify it (e.g. aminoglycoside modification) (Shi et al. 2013), or plasmid-encoded degradative enzymes such as β-lactamases cleave the drug, thus hampering its action (Renneberg and Walder 1989). Genes of resistance are either plasmid-borne (Perlin and Lerner 1979) or present on mobile genetic elements (transposons) (Domingues et al. 2012) which may easily disseminate through conjugation, etc. This leads to spread of resistance in a population.

2 Aminoglycoside Resistance

Aminoglycosides represent important class of drugs. Chemically these contain an amino sugar attached to the aminocyclitol. These antibiotics are so essential attributable to their expansive range of movement against range of microscopic organisms. Amikacin, gentamicin, kanamycin, streptomycin and tobramycin are some examples and most effective in treatment of gram-negative and gram-positive

Table 1 Outline of resistance mechanism(s) of various classes of antibiotics

Antibiotic class	Target	Mechanism(s) of resistance	Example(s)	Reference (s)
Aminoglycosides	Translation	Phosphorylation, acetylation, nucleotidylation, efflux, altered target	Gentamicin, streptomycin, spectinomycin	Bryan and Kwan (1983), Busse et al. (1992), Mahbub et al. (2005)
β-Lactams	Peptidoglycan synthesis	Hydrolysis, efflux, altered target	Penicillins (ampicillins), cephalosporins (cephamycins), penems (meropenems)	Spratt and Cromie (1988), Philippon et al. (1989), Pournaras et al. (2005)
Cationic peptides	Cell membrane	Efflux, altered target	Colistin	Cai et al. (2012)
Glycopeptides	Peptidoglycan synthesis	Reprogramming peptidoglycan synthesis	Vancomycin, teicoplanin	Arthur and Courvalin (1993)
Lincosamides	Translation	Nucleotidylation, efflux, altered target	Clindamycin	Leclercq and Courvalin (1991), Leclercq (2002)
Lipopeptides	Cell membrane	Altered target	Daptomycin	Tenover (2006), Boucher and Sakoulas (2007)
Macrolides	Translation	Hydrolysis, efflux, altered target, glycosylation, phosphorylation	Erythromycin, azithromycin	Ross et al. (1990), Leclercq and Courvalin (1991), Leclercq (2002)
Oxazolidinones	Translation	Efflux, altered target	Linezolid	Prystowsky et al. (2001), Meka and Gold (2004)
Phenicols	Translation	Acetylation, efflux, altered target	Chloramphenicol	Schwarz et al. (2004), Mingoia et al. (2007)

(continued)

Table 1 (continued)

Antibiotic class	Target	Mechanism(s) of resistance	Example(s)	Reference (s)
Pyrimidines	C1 metabolism	Efflux, altered target	Trimethoprim	Huovinen (2001), Holmes et al. (2016)
Quinolones	DNA replication	Acetylation, efflux, altered target	Ciprofloxacin	Ferrero et al. (1995), Webber and Piddock (2001), Jacoby (2005)
Rifamycins	Transcription	ADP-ribosylation, efflux, altered target	Rifampin	Palomino and Martin (2014)
Streptogramins	Translation	C-O lyase (type B streptogramins), acetylation (type A streptogramins)	Synercid	Jensen et al. (2000)
Sulphonamides	C1 metabolism	Efflux, altered target	Sulphamethoxazole	Huovinen (2001), Sanchez and Martinez (2015)
Tetracyclines	Translation	Monooxygenation, efflux, altered target	Minocycline, tigecycline	Fluit et al. (2005), Linkevicius et al. (2015)

bacterial infection. The drug elicits its effect by binding to the bacterial ribosome irreversibly and hindering protein synthesis though drug interactions (Chen and Murchie 2014; Dunkle et al. 2014; Song et al. 2014). Drug-modifying enzymes make the drug inactive by introducing chemical changes. Several aminoglycoside-modifying enzymes are known (Fluit and Schmitz 1999; Schmitz et al. 1999). Resistance to aminoglycoside drugs can be mediated through enzymatic chemical modifications like phosphorylations, adenylations and acetylations. Phosphorylations are catalysed by ATP-dependent O-phosphorylation (APH), nucleotidyltransferases catalysed O-adenylation (ANT) and acetyltransferases mediate N-acetylation which requires acetyl-coA-cofactor (AAC) (Marengo et al. 1974; Araoz et al. 2000; Chesneau et al. 2007). These transformations make the drug incapable of binding to the ribosome, and hence translation process remains uninhibited. In addition to enzymatic aminoglycoside-modifying enzymes, efflux pumps and ribosomal RNA mutations also contribute to reduced drug susceptibility (Kriengkauykiat et al. 2005; Corcoran et al. 2006; Takaya et al. 2013).

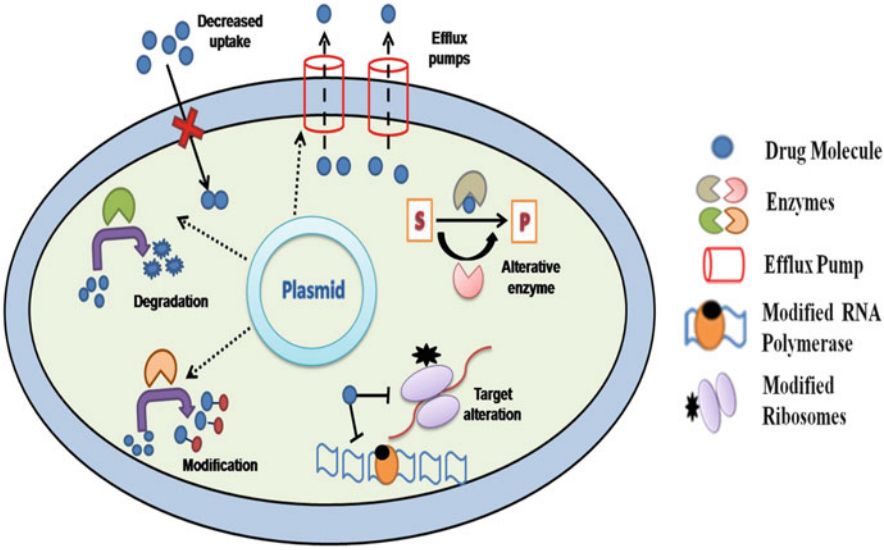

Fig. 1 Diverse biological processes used by microbes against drug pressure

3 Resistance to β-Lactam

The very first β-lactamase was identified from *Escherichia coli* long before penicillin came in clinical use. Kirby (Kirby and Burnell 1954) extracted "penicillin inactivators" from *Staphylococcus aureus*. The surge in the usage of β-lactam antibiotics has put a kind of selection pressure on bacteria, which ultimately resulted in the survival of drug-resistant bacteria that have the capacity to express multiple β-lactamases. Until date, several β-lactamases have been acknowledged. These enzymes have the potential to degrade the antibiotic by hydrolysing the β-lactam ring of antimicrobial drugs like cephalosporins, penicillin, etc. (Kasik and Peacham 1968). Through this mechanism of degradation of β-lactamases, antibiotics lead to lowering down of the efficacy of these molecules, ultimately leading to the survival of the bacterial species in the presence of the drug pressure. Different β-lactamases exhibit different specificities towards the substrate and differ in host range (Hanaki et al. 2007). Various types of β-lactamases are usually secreted by gram-negative bacteria which can degrade some cephalosporins like cephalothin. In few bacterial species, these enzymes are encoded by chromosomes, for example, cephalosporinases of *Pseudomonas*. In other bacteria such as *Enterobacteriaceae*, these enzymes result due to the presence of plasmid that encodes them. As found by Dhara and Tripathi (2014), plasmid-encoded enzymes also degrade a number of penicillins, and this effect can be overcome by the presence of β-lactamase inhibitors like clavulanic acid (Song et al. 2010). β-Lactam antibiotics elicit their response by targeting and inhibiting the action of key enzymes involved in the synthesis of bacterial cell wall. The basic mechanisms linked to resistance of this

class of antibiotics are bacterial synthesis of β-lactamase enzymes that has the potential to degrade antibiotic β-lactam (Song et al. 2010). This form of resistance mechanism is the most important and prevalent mode especially in gram-negative bacteria. Alteration in penicillin-binding protein (PBP) active site may be another means of attaining drug resistance that results in lower drug binding affinity (e.g. low-affinity PBP2x of *Streptococcus pneumoniae*) (Moisan et al. 2010). This mechanism has been reported in *Neisseria* spp. and *Streptococcus* spp. (Zapun et al. 2008). By the rigorous recombination and transformation mechanisms, these two bacterial species have developed low-affinity PBPs that are highly resistant to antibiotics. Overexpression of mecA gene that translates into penicillin-binding proteins 2a which in turn confer methicillin resistance to *Staphylococcus* spp. and moreover mecA overexpression desensitise bacteria against high concentrations of cephalosporins and penicillins by allowing them to synthesise new cell wall even under drug pressure (Laible et al. 1989). This antibiotic-resistant bacterial strain poses a great clinical challenge to today's medicinal world (Neu 1984).

Lowering down the expression of outer membrane proteins (OMPs) is yet another vital mechanism of resistance. OMPs facilitate the drug to traverse through them and interact with PBPs present on the inner side of the plasma membrane in gram-negative bacteria. For example, resistance against carbapenems in some *Enterobacteriaceae* (*Klebsiella pneumoniae* and *Enterobacter* spp.) has been developed due to downregulation of these OMPs (Doumith et al. 2009); lowering down the expression of OprD gene is also linked with resistance towards imipenem and decrease in efficacy of meropenem in non-fermenter *Pseudomonas aeruginosa* (Moghoofei et al. 2015; Rodriguez-Beltran et al. 2015). Resistance against meropenem and imipenem has been reported due to downregulation of the CarO outer membrane protein (OMP) in multidrug-resistant clinical isolates of *Acinetobacter baumannii* (Fernandez-Cuenca et al. 2011). Various point mutations or insertion sequences in the genes coding for these porins proteins can produce altered OMPs that have loss in function or retarded function and permeability. Activation of efflux pumps provides intrinsic or acquired resistance phenotype. These efflux pumps are main determinants of multidrug resistance in various gram-negative pathogens, above all in *Acinetobacter* spp. and *Pseudomonas aeruginosa* (Morita et al. 2012). In *P. aeruginosa*, upregulation of the MexA-MexB-OprD framework and organism's low outer membrane permeability have been reported in several reports (Tamber et al. 2006), which have been attributed to formidable drug resistance such as decreased susceptibility against antibiotics like tetracycline (tet), penicillins, cephalosporins, chloramphenicol and quinolones. Moreover, upregulation of efflux pumps (e.g. AdeABC which is resistance-nodulation-division (RND) family sort efflux pump ordinarily found in *A. baumannii*) has been reported to confer carbapenem resistance by synthesising catalytically poor form of β-lactamase (del Mar et al. 2005).

3.1 Penicillin Resistance

The most potent mechanism of evading the action of penicillin by pneumococci is elicited through alteration in the penicillin-binding proteins (PBPs). These proteins are absolutely essential for the cell wall synthesis and serve to enforce the efficacy of β-lactam antibiotics by binding to them; therefore these alterations substantially decrease the affinity of PBPS to the drug and related classes of drugs, hence effectively hampering drug action and effect (Dowson et al. 1990). "Mosaics" comprising of mixed regions of native and acquired foreign DNA segments are responsible for encoding these altered PBPs. More often than not, the DNA from foreign source belongs to the more resistant strains like viridians streptococci. There are evidences about the transfer of such mixed and hybrid genetic elements between pneumococci and gram-positive bacteria like *Streptococcus oralis* (Sibold et al. 1994).

4 Quinolone Resistance

Nalidixic acid was the first discovered quinolone. Many derivatives have been made available since then, fluoroquinolones being the most important ones (Emmerson and Jones 2003). These compounds possess a fluorine substitution at sixth position on the quinolone moiety, making it highly efficient against gram-positive to gram-negative bacteria and anaerobes. Quinolone drug action is brought about by inhibiting an important class of enzymes called as bacterial topoisomerases (DNA gyrase and topoisomerase IV) (Chen et al. 1996). These enzymes play an important role in bacterial DNA replication and are central to the maintenance of bacterial replication fork by modifying the topology of double-stranded DNA. Enzyme structure comprises of two subunits, namely, A and B that are heterotetrameric in nature making it highly efficient against gram-positive to gram-negative bacteria and anaerobes (Chen et al. 1996; Higgins et al. 2003).

Two principal mechanisms can very well explain the resistance seen against quinolones. Firstly by modifying the target enzyme and second by limiting the permeability of the drug (Nikaido 1998; Hernandez et al. 2011). Quite plausibly, most changes are centred at the active domains of the enzyme, which drastically reduce drug binding. DNA gyrase activity is mostly inhibited in gram-negative bacteria, but in gram-positive either DNA gyrase or topoisomerase IV can be inhibited depending on the choice of fluoroquinolones used (Jacoby 2005). In majority of the cases, there is an amino acid substitution in quinolone-resistance-determining region, which introduces a bulky hydrophobic residue instead of a polar hydroxyl group (Mehla and Ramana 2016). Mutations in gyrA gene modify the enzyme-binding site or alter a charge that leads to conformational changes essential in maintaining drug enzyme interaction. Alterations in the outer membrane structure culminate into resistance as displayed by most gram-positive

bacteria (Ferrero et al. 1994). Consequently, there is reduced drug influx and uptake. More unexpectedly, resistance mechanism spread by transmission leading to fluoroquinolone inactivation has also surfaced. This mechanism has cropped up because of the ability of aminoglycoside N-acetyltransferases to modify a secondary amine on the fluoroquinolones thus leading to lowered activity. The latter mechanism confers a low-level tolerance favouring the selection of resistance mutants (Robicsek et al. 2006). *Mycobacterium smegmatis* and *Mycobacterium bovis* elicit a basal and low-level resistance to several fluoroquinolones (Montero et al. 2001). The chromosomal gene called MfpA expression is plasmid encoded, the plasmid being present in multiple copies within the bacterium. Conversely, MfpA gene disruptions enhance drug efficacy and making wild type *M. smegmatis* more prone to drug action. Hence, drug susceptibility is directly linked to MfpA expression level.

A very fascinating mechanism of resistance against fluoroquinolones has been investigated in *Mycobacterium tuberculosis*. Studies elucidating *M. tuberculosis* MfpA structure have unfolded a unique three-dimensional structure of MfpA that shows similarity to bacterial DNA double helix. It is speculated that MfpA could serve to sequester the entire drug and free the bacterial DNA from drug effect. Therefore, target mimicry seen in mycobacterium affords protection against fluoroquinolones (Hegde et al. 2005). In addition, point mutations in genes like cytochrome b, or dihydrofolate reductase, are known to cause atovaquone resistance or pyrimethamine resistance, respectively (Meneceur et al. 2008).

5 Tetracycline Resistance

The ease of availability, broad range of activity and cost-effectiveness make tetracyclines as the most favourite and widely used antibiotics. Since their discovery in the 1940s, they have been readily used for therapeutic interventions (Nguyen et al. 2014). The drug elicits its inhibitory effects by impeding bacterial translation through the prevention of aminoacyl-tRNA attachment to the ribosomes (Connell et al. 2013). These antibiotics successfully combat pathogenic challenges from a wide array of microorganisms including gram-positive and gram-negative microbes, atypical life forms, for example, protozoan, *Chlamydiae*, *Rickettsiae* and *Mycoplasma* parasites. Tetracyclines include agents like tetracycline, minocycline, oxytetracycline and doxycycline (Rasmussen et al. 1997). The phenomenon of resistance against this class of drugs can be due to drug efflux, protection of bacterial ribosomes or chemical modification of the drug. Export proteins can contribute to the resistance by mediating drug efflux (Piddock et al. 2000). These gatherings of proteins have a place with the real facilitator superfamily. Tetracycline (tet) efflux pumps encode these fare proteins and subsequently encourage drug efflux (Stavropoulos and Strathdee 2000; Tuckman et al. 2000). The expulsion of drug ultimately lowers the drug concentration, and the inhibitory effects on the ribosomes are diminished. Ribosome protection proteins that are

cytoplasmic in nature aid ribosomal protection. This mode of resistance is mostly prevalent in case of doxycycline and minocycline, whereas drug efflux is the major mechanism imparting resistance against most other classes of tetracyclines (Kobayashi et al. 2007). These efflux proteins share a marked homology with other class of efflux proteins that confer multidrug resistance to various other classes of antibiotics (Wang et al. 2004). Large plasmids, encoding for such efflux genes, are transmitted through conjugation and are believed to confer resistance to gram-negative bacteria (Roberts 1997). Another important means of resistance involves enzymatic inactivation of the drug. The role of tet (X) gene has been implicated in altering tetracycline function. The tet (X) gene encodes a 44 kDa product that is capable of modifying tetracycline chemically in the presence of oxygen and NADPH. This resistance gene is present on transposons and found in anaerobic *Bacteroides* species (Speer et al. 1991). More recently tetracycline destructases have been discovered. These are a novel class of inactivating enzymes belonging to flavoenzyme family and catalyse oxidation of the drug. Consequently, there is modification in the structure and function of the drug (Forsberg et al. 2015).

6 Peptide-Based Drug Resistance

The intrinsic and widespread resistance to most common and rampantly used antibiotics has led to the emergence of enterococci garnering the ability to survive in a hospital-borne environment (Canton et al. 1999). Their extensive survival and resilience to the most front-line drugs used in trauma care and hospital can be attributed to wide arrays of genomic changes such as mutations, acquisition of foreign genetic element harbouring resistance genes, plasmid transfer, transposons, etc. (Rossi et al. 2014; Hu et al. 2015a). The commonest resistance ensues against drugs of classes β-lactam and glycopeptides. Synergising antibiotics such as glycopeptides with an aminoglycoside can prove to be extremely fruitful in circumventing the deleterious emergence of hospital-borne antibiotic resistance (Hu et al. 2015b). A highly regulated clustered gene unit termed as operon is believed to mediate the acquisition of glycopeptide resistance in enterococci (James et al. 2012). This operon encodes an alternative pathway responsible for the production of a transformed cell wall component. Consequently, vancomycin binds to this modified precursor peptidoglycan more readily as the normal substrate remains unaffected and available for cell wall synthesis. Thus, the progression of the normal biosynthetic pathway remains unhindered (Fraise et al. 1997). Innate resistance to vancomycin can be attributed to two types of gene cluster designated as vanA and vanB gene clusters (Grissom-Arnold et al. 1997; Baptista et al. 1997). These confer resistance by modifying target from D-alanine-D-alanine to D-alanine-D-lactate (Marshall et al. 1997).

7 Resistance to Echinocandins and Azoles

Reduced susceptibility to echinocandins can be linked to genetic events such as mutations or instigation of an adaptive stress response (Astruey-Izquierdo et al. 2011). Mutations are mostly centred around regions known as "hot spots". These are much conserved gene clusters and are hubs of intrinsic point mutations. Mutation in FKS gene encoding, fungal FKS subunits of β(1,3)D-glucan synthase lead to cross resistance and decreased drug efficacy (Marti-Carrizosa et al. 2015; Dichtl et al. 2015). The drug-induced threat is bypassed by fungal cells through commencement of a stress response. This compensates for the drug-induced loss of a cell wall component by overproducing one or more other constituents.

The cell wall synthesis is highly regulated. In response to the drug, chitin levels are unregulated to balance the inhibition by echinocandins (Prasad et al. 2016). These elaborate metabolic changes are believed to be mediated via high-osmolarity glycerol, protein kinase C responses and Ca^{2+}-calcineurin signalling pathways. This helps in negating the fatal effects of echinocandins (Walker et al. 2010). A pivotal role is also played by genomic plasticity in aggravating resistance. This is achieved by loss of heterozygosity and is acquired by genetic rearrangements and amplifications majorly at genetic regions that are linked with resistance (Niimi et al. 2010). Frequent and rampant use of antifungal compounds, particularly fluconazole, has prompted the rise of resistance amongst different types of *Candida* species. These organisms display varied levels of susceptibility depending on the amount of selection pressure and the prevalence of infections (Mane et al. 2016). The activity of an important enzyme catalyst, i.e. lanosterol 14-α-sterol demethylase involved in cell wall biosynthesis, is inhibited by azoles (Warrilow et al. 2012). Additionally, accrual of a toxic by-product, namely, 14-α-methyl-3,6-diol, further contributes to the inhibitory effects of the antifungal agent (Warrilow et al. 2012). As a result, cell wall structure, with regard to ergosterol content, is altered leading to disruptions in membrane integrity and functioning.

Candida species are adept in manifesting resistance and can successfully evade prophylactic and therapeutic regimes. Three major mechanisms dictate this first mechanism involves upregulation and overexpression of efflux pumps. This leads to significantly lowered drug levels inside the cells (Niimi 2004). Efflux pumps of *Candida* spp. are CDR gene encoded belonging to ATP-binding superfamily or are products of MDR1 locus which encode major facilitator superfamily (MFS) proteins (Shao et al. 2016). Enhanced expression of CDR gene product culminating into expanded no. of efflux pumps presents imperviousness to all known azoles. Nevertheless, MDR-encoded efflux pumps bolster just fluconazole resistance. Examples of *Candida* spp. evoking azole resistance are as per the following: *Candida glabrata* (CgCDR1, CgCDR2) and *C. albicans* (CDR1, CDR2, MDR1) (Shao et al. 2016). One more resistance mechanism comprises the alteration or overproduction of the target molecule. A key player determining this mode of resistance is ERG11 gene that codes for the enzyme lanosterol 14-a-demethylase. Mutations pertaining to this gene lead to subtle modifications in the target enzyme

that change the binding affinity of the enzyme to the drug (Martel et al. 2010). Lowered susceptibility of ERG11p to fluconazole as seen in *C. krusei* is due to this kind of altered binding (Martel et al. 2010). Overproduction of ERG11p makes the antifungal agent ineffective at its normal dosage, which is due to the outnumbering of target molecules with reference to drug molecules. Consequently, drug is present in insufficient amounts as compared to its target to successfully exhibit the inhibitory effects (Wang et al. 2009). ERG3 gene mutations circumvent the accumulation of toxic metabolic products and lead to formation of proper and functional cell membrane. Devising an alternate/bypass biosynthetic pathway paves way for another mechanism of resistance in fungi (Wang et al. 2009; Lo et al. 2015).

8 Methicillin-Resistant *Staphylococcus aureus*

The presence of MRSA has been detected in both the community-acquired and hospital settings. These are found to express mecA gene, which confers them resistance against methicillin and other β-lactams (Neu 1984). However, mecA gene's genetic environment is found to be different for the hospital-acquired and community-acquired isolates. Nosocomial MRSA is an example of multidrug resistance (Panda et al. 2016). Imperviousness to methicillin and a few other β-lactams has been connected to the ability of mecA to encode low-affinity penicillin-binding protein PBP2a (Roychoudhury et al. 1994). PBP2a-encoding mecA gene is located on a genetically mobile element that is termed as staphylococcal chromosomal cassette (SCC-mec) (Hososaka et al. 2007). In particular, resistance towards fluoroquinolone is regarded as a hallmark for nosocomial MRSA. Expression of EMRSA-17 lead to development of resistance towards a wide range of antibiotics like methicillin, macrolides (erythromycin), fluoroquinolones (ciprofloxacin), tetracycline, fusidic acid, aminoglycosides (kanamycin, streptomycin, gentamicin and neomycin) and rifampicin (Aucken et al. 2002).

9 Prospective

Augmentation in a number of diabetic patients and burn patients increases the susceptibility to acquired infections and spread of resistance. The resistant strains may evolve naturally when microorganisms replicate themselves in an erroneous fashion or by the exchange of resistant traits between them. Our abuse of antibiotics in people incomprehensibly quickened the procedure of drug resistance; however drug administration in intensive care units of hospitals and treatment of immunocompromised patients further leads to expansion of multidrug resistance and prevalence of nosocomial infections. To contain antibiotic resistance, motivating forces for drug organisation, clinics, specialist and patients have to be devised to act in ways that may restrain the exhaustion of antimicrobial efficacy.

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