The Emergency of Drug Resistant Pathogens

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ABSTRACT:
Antibiotics have dependably been viewed as one of the miracle revelations of the twentieth century. The phenomenal hereditary limits of organisms have profited from man's abuse of anti-toxins to misuse each wellspring of resistance qualities and each method for even quality transmission to build up numerous systems of resistance for every single anti-toxin brought into practice clinically, horticulturally, or something else. Hosts and microbes have coevolved over a huge number of years, amid which pathogenic microscopic organisms have adjusted their destructiveness instruments to adjust to host protection frameworks. In spite of the fact that the spread of pathogens has been impeded by the revelation and boundless utilization of antimicrobial operators, antimicrobial resistance has expanded all round. The development of safe microscopic organisms has quickened lately, for the most part as a consequence of expanded specific weight. Be that as it may, albeit antimicrobial resistance and bacterial destructiveness have created on various timescales, they share some regular attributes. The exchange between these components and the related organic expenses rely on upon four principle calculates: the bacterial species included, destructiveness and resistance instruments, the biological corner, and the host. The improvement of new procedures including new antimicrobials or non-antimicrobial mixes and of novel indicative strategies that emphasis on high-chance clones and fast tests to recognize harmfulness markers may resolve the expanding issue of the
relationship amongst destructiveness and resistance, which is turning out to be more advantageous for pathogenic microbes.

**Keywords:** Antibiotics, Antimicrobial compounds, Diagnostic methods, Pathogens, Resistance genes.

**INTRODUCTION:**

Microscopic organisms are available both inside and on the surface of the human body, particularly on the skin and the mucous layers. The majority of these microscopic organisms are harmless, numerous are advantageous, and some are even fundamental. Be that as it may, other microscopic organisms, which are ordered as pathogens, can colonize, attack, and harm the host and therefore cause ailment. Pathogenicity is a capacity of an operator to bring about infection, and the pathogenic microbes have a few components that empower them to improve their harmfulness (i.e., the level of pathogenicity). Most pathogens make utilization of a blend of two properties to bring about sickness: (i) poisonous quality, how much a substance causes mischief, and (ii) obtrusiveness, the capacity to infiltrate into the host and spread. The last adjust of an irresistible illness procedure will rely on upon the destructiveness or pathogenicity of the organism and in addition the host status in connection to hazard variables, for example, insusceptible status, age, eating routine, and anxiety, which decide the host helplessness to disease.

Hosts and microorganisms have coevolved over a huge number of years, amid which pathogenic microscopic organisms have changed their destructiveness to adjust to the host protection frameworks. This is valid for specialists utilized as a part of the treatment of bacterial, contagious, parasitic, and viral contaminations and for treatment of unending ailments, for example, growth and diabetes; it applies to sicknesses brought about or endured by any living life forms, including people, creatures, fish, plants, creepy crawlies, and so forth. An extensive variety of biochemical and physiological systems might be in charge of resistance. In the particular instance of antimicrobial specialists, the multifaceted nature of the procedures that add to rise and scattering of resistance can't be overemphasized, and the absence of fundamental learning on
these points is one of the essential reasons that there has been so minimal critical accomplishment in the successful counteractive action and control of resistance improvement. Most global, national, and nearby organizations remember this major issue. Numerous resolutions and suggestions have been propounded, and various reports have been composed, yet without much of any result: the advancement of anti-infection resistance is persistent [1].

The most striking cases and likely the most exorbitant regarding dreariness and mortality, concern microbes. The revelation of these irresistible specialists in the late nineteenth century fortified the quest for fitting protection and remedial regimens; be that as it may, fruitful treatment came just with the disclosure and presentation of anti-microbials a large portion of a century later. Anti-toxins have changed solution in numerous regards, and incalculable lives have been spared; their disclosure was a defining moment in mankind's history. Unfortunately, the utilization of these miracle drugs has been joined by the fast appearance of safe strains. Therapeutic intellectuals are presently cautioning of an arrival to the preantibiotic time; a late database records the presence of more than 20,000 potential resistance qualities (qualities) of about 400 distinct sorts, anticipated in the principle from accessible bacterial genome arrangements. Luckily, the number existing as practical resistance determinants in pathogens is much littler.

Numerous great audits depicting the hereditary qualities and natural chemistry of the birthplaces, advancement, and instruments of anti-toxin resistance have showed up throughout the most recent 60 years. The objective of this short article is not to condense such an abundance of data but rather to audit the circumstance as we see it now (most especially as for the roots and advancement of resistance qualities) and to give some individual perspectives on the eventual fate of antimicrobial treatment of irresistible ailments. Anti-infection revelation, methods of activity, and systems of resistance have been beneficial exploration subjects in the scholarly world and, up to this point, in the pharmaceutical business. As normal items, they give testing scholarly
activities and amazements concerning their synthetic nature, biosynthetic pathways, development, and biochemical method of activity [2].

The aggregate union of such regular items in the lab is troublesome, since these little atoms are frequently to a great degree complex in usefulness and chirality. Investigations of methods of activity have given biochemical data on ligands and focuses all through anti-toxin history, and the utilization of anti-infection agents as "phenotypic mutants" has been a significant methodology in cell physiology thinks about. The field of concoction science/hereditary qualities developed from investigations of those collaborations. We have a pitiful comprehension of how anti-infection agents work, and in just a couple examples can the cozy cooperations of the little atom and its macromolecular receptor be deciphered as far as characterized phenotypes. All the more shockingly, there is a lack of learning of the regular natural elements of anti-infection agents, and the transformative and environmental parts of their synthetic and organic responses remain themes of significant premium and quality.

To start, the meaning of "anti-toxin," as initially proposed by Selman Waksman, the pioneer of streptomycin and a pioneer in screening of soils for the nearness of biologicals, has been truly overinterpreted; it is basically a portrayal of an utilization, a research facility impact, or an action of a concoction compound. It doesn't characterize a class of compound or its regular capacity, just its application. At the danger of assault from idealist partners, the nonexclusive term "anti-infection" is utilized here to signify any class of natural atom that restrains or murders microorganisms by particular connections with bacterial focuses, with no thought of the wellspring of the specific compound or class. In this way, simply engineered therapeutics are considered anti-microbials; all things considered, they collaborate with receptors and incite particular cell reactions and biochemical instruments of cross-resistance in pathogens.

The fluoroquinolones (FQs), sulfonamides, and trimethoprim are great cases. As in any field of organic study, anti-microbial history is packed with misguided judgments, misinterpretations, mistaken
expectations, and different slip-ups that have once in a while prompted reality. This record tries to concentrate on reality. The revelation of anti-microbials is properly viewed as a standout amongst the most critical wellbeing related occasions of advanced times, and not just for its effect on the treatment of irresistible infections. Examines with these mixes have frequently demonstrated sudden nonantibiotic impacts that show an assortment of other natural exercises; the outcome has been countless restorative utilizations of "anti-infection agents" as antiviral, antitumor, or anticancer specialists. Sometimes, the option applications have surpassed those of anti-infection action in significance, for example, in the treatment of cardiovascular illness or use as immuno-suppressive specialists [3].

Shockingly, the monster requirement for these profitable medications has had a critical ecological drawback. In the 60 years since their presentation, a great many metric huge amounts of anti-toxins have been created and utilized for a wide assortment of purposes. Changes underway have given progressively less costly exacerbates that support nonprescription and off-name employments. The expense of the most established and most oftentimes utilized anti-infection agents is (likely) fundamentally in the bundling. The planet is soaked with these dangerous operators, which has obviously contributed altogether to the choice of safe strains. The improvement of eras of anti-toxin safe organisms and their circulation in microbial populaces all through the biosphere are the consequences of numerous years of unremitting determination weight from human utilizations of anti-toxins, by means of underuse, abuse, and abuse. This is not a characteristic procedure, but rather a man-made circumstance superimposed on nature; there is maybe no better case of the Darwinian thoughts of determination and survival.

In solid people, sharp pathogens are not ready to create contamination since they do not have the essential instruments of lethality and obtrusiveness that empower essential pathogens to conquer the host insusceptible framework. Be that as it may, in a few people, for example, invulnerable traded off patients, pioneering pathogens can deliver disease, which can be anticipated mostly
by the utilization of antimicrobial treatments. Certain multiresistant crafty species, for example, Pseudomonas aeruginosa and Acinetobacter baumannii, can colonize corners where numerous different species can't survive (situations with high anti-toxin weight) and can even uproot the commensal verdure. This is one case of how antimicrobial resistance can expand the destructiveness or wellness of specific species in a few situations, regularly helping these species to colonize new specialties. Subsequently, although anti-toxin resistance is not in itself a destructiveness variable, in specific circumstances it is a key component being developed of disease, and it might be viewed as a harmfulness like element in particular biological corners which anti-microbial safe microscopic organisms can colonize [4]. This is particularly valid in the healing facility environment (escalated care units, smoker units, and so on.), in which if a sharp pathogen is medication safe, it can bring about illness all the more promptly. In situations where specific anti-infection weight wins, some sharp pathogens can colonize new natural specialties on account of their pliancy and capacity to adjust through the securing or improvement of components of resistance and diligence.

The use of antibiotics has changed the natural evolution of bacteria by reducing susceptible pathogenic populations and increasing resistant populations. Resistance is often associated with a fitness cost because the genetic burden required for resistance may be deleterious in antibiotic-free environments. In this case, restriction of the use of antibiotics has been proposed, with the aim of eradicating resistant bacteria. However, the genetic background of resistant pathogens allows them to persist in the presence of minimal concentrations of antibiotics or even in the absence of these, as discussed throughout this review. Hypermutation, compensatory mutations, and cross coselection are a few of the many mechanisms that favor the persistence of resistant pathogens and even, in some cases, selection of the most virulent and most resistant pathogens.
ANTIMICROBIAL RESISTANCE AND VIRULENCE

All through this area we will allude much of the time in which we have endeavored to clear up and outline the illustrations given in the content of connections amongst destructiveness and resistance determinants in the most normally considered or clinically pertinent pathogens. To rearrange the various studies reported in the writing, we have grouped the case as indicated by groups of anti-infection agents for which the resistance components have been inspected [5].

Table 1: Mechanisms of antimicrobial resistance and virulence

<table>
<thead>
<tr>
<th>Antimicrobial group</th>
<th>Mechanism of resistance</th>
<th>Implication in virulence</th>
<th>Pathogen(s)</th>
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<tbody>
<tr>
<td>β–Lactams</td>
<td>PBP modifications</td>
<td>Regulation of Agr quorum-sensing system; biofilm formation; attenuated virulence in mouse model; infection persistence</td>
<td>S. aureus</td>
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<tr>
<td>β–Lactams</td>
<td>Penicillin–binding protein 2 (mecA)</td>
<td>Expression of phenol-soluble modulins</td>
<td>S. aureus</td>
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<td>Efflux pumps</td>
<td>SCCmec</td>
<td>Regulation of Agr quorum-sensing system; biofilm formation; attenuated virulence in mouse model; infection persistence</td>
<td>S. aureus</td>
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<tr>
<td>A. baumannii</td>
<td>AdeABC</td>
<td>Colonization, infection, and persistence of microorganism in host</td>
<td>A. baumannii</td>
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<tr>
<td>Enterobacteriaceae</td>
<td>AcrAB-TolC</td>
<td>Colonization, infection, and persistence of microorganism in host</td>
<td>Enterobacteriaceae</td>
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<tr>
<td>P. aeruginosa</td>
<td>Mex system</td>
<td>Colonization, persistence, and expression of virulence genes; MexAB is involved in quorum-sensing/quorum-quenching system; MexCD is associated with regulation of type III secretion system; MexEF regulation implicated in GacA/RsmA/RsmB (RsmZ) signal</td>
<td>P. aeruginosa</td>
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<tr>
<td>Class</td>
<td>Mechanism</td>
<td>Fitness Cost</td>
<td>Bacteria</td>
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<tr>
<td>Aminoglycosides</td>
<td>Efflux pumps (as for β-lactams above)</td>
<td>E. coli</td>
<td>E. coli, B. subtilis, S. aureus</td>
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<td></td>
<td>Ribosomal methylases/RmtC</td>
<td>No fitness cost</td>
<td>E. coli</td>
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<td></td>
<td>Ribosomal mutations/RpsL</td>
<td>Fitness cost</td>
<td>E. coli, Salmonella spp., M. tuberculosis</td>
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<td>Fluoroquinolones</td>
<td>Target modifications (topoisomerases and DNA gyrase)</td>
<td>No fitness cost; presence of the type III secretion system genes</td>
<td>P. aeruginosa</td>
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<td></td>
<td>Antibiotic modification tetX gene</td>
<td>No fitness cost in B. fragilis; probable fitness cost in aerobic Gram-negative bacteria</td>
<td>B. fragilis</td>
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<td>Macrolides</td>
<td>Efflux pumps</td>
<td>Decreased twitching motility</td>
<td>P. aeruginosa</td>
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<td>MuxABC-Omp</td>
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<td></td>
<td>BpEAB-OprB</td>
<td>Excretion of acyl homoserine lactone quorum-sensing molecules (biofilms, siderophores, and phospholipase C)</td>
<td>B. pseudomallei</td>
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<td>Glycopeptides</td>
<td>Cell wall modifications</td>
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<td>GISA</td>
<td>Fitness cost</td>
<td>S. aureus</td>
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<td>Attenuated virulence in nonmammalian model system G. mellonella</td>
<td>S. aureus</td>
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<td>Oxazolidones (linezolid)</td>
<td>rRNA mutations</td>
<td>Fitness cost</td>
<td>Coagulase-negative staphylococci, S. aureus, S. pneumoniae</td>
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<td>rRNA methylation</td>
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<td>Colistin, polymyxin B</td>
<td>Lipopolysaccharide modifications</td>
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<td>PmrA-PmrB</td>
<td>Global regulation, including virulence and resistance</td>
<td>S. enterica</td>
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<td>Overproduction of</td>
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**Transduction System**

- SecDF
- Expression of virulence genes
- E. coli, B. subtilis, S. aureus
OMVs carrying virulence factors such as toxins

| Overproduction of bacterial capsule | Increased virulence, evasion of phagocytosis, and complement resistance | K. pneumoniae, S. pneumoniae, P. aeruginosa |

*a*Implication in resistance not clearly demonstrated.

*b*Implication in virulence not clearly demonstrated.

**Resistance to β-Lactams and Impact on Virulence**

β-Lactam antibiotics are a large class of antibiotics that have a β-lactam ring in their molecular structure. They are the most widely used antibiotics and include penicillin derivatives, cephalosporins, monobactams, carbapenems, and β-lactamase inhibitors. Resistance to β-lactams involves several mechanisms, which are different in Gram-positive and Gram-negative bacteria. In Gram-positive microbes, mutations and/or reduction of or expression alterations in penicillin-binding proteins (PBPs) are the most important mechanisms, followed by β-lactamase production. Conversely, in Gram-negative microorganisms, the most prevalent mechanism of β-lactam resistance is the production of β-lactamases, followed by permeability alterations, extrusion by efflux pumps, and to a lesser extent PBP alterations.

Before further discussion of this topic, it is important to point out that interpretation of the data and any conclusions drawn may differ greatly depending on the specific microorganism under study, even within a family, e.g., *Enterobacteriaceae*. Therefore, caution must be exercised when discussing this topic, and conclusions should be assumed to be organism specific [6].

**PBP modifications.**

The PBPs involved in resistance and virulence are PBP2 (encoded by *mecA*) (in *Staphylococcus aureus*), PBP2b-PBPX (in *Streptococcus pneumoniae*), and PBP7-8 (in *A. baumannii*). Previously reported data suggest that expression of homogeneous methicillin resistance in *S. aureus* influences the biofilm phenotype and attenuates virulence (it reduced protease
production and significantly reduced virulence in a mouse model of device-related infection). Clinical isolates of *S. aureus* can express biofilm phenotypes promoted by the major cell wall autolysin and the fibronectin (Fn)-binding proteins or the polysaccharide intercellular adhesin (PIA) and the polymeric *N*-acetylglucosamine (PNAG), which are synthesized and exported by proteins encoded by the *ica*ABC gene cluster. Biofilm production in methicillin-susceptible *S. aureus* (MSSA) strains is associated with PIA/PNAG, whereas methicillin-resistant isolates express an Atl/FnBP-mediated biofilm phenotype (which produces a proteinaceous biofilm), which suggests a relationship between biofilm production and susceptibility to β-lactam antibiotics.

This leads to reduced expression of the toxin and lowered virulence in a murine model of sepsis. This interesting finding may explain why some strains of hospital-acquired MRSA show a reduced ability to spread in the community. It may also explain the recent increase in the incidence of community-associated MRSA (CA-MRSA) strains, which typically express less penicillin-binding protein 2a (encoded by *mecA*) and thus maintain full virulence for success in the community setting. This is a typical example of how the acquisition of resistance to a specific antibiotic (oxacillin) is related to a decrease in virulence. However, Queck et al. described the presence of a *psm* gene (*psm-mec*), associated with staphylococcal methicillin resistance, which encodes a mobile genetic element (MGE), SCCmec. Phenol-soluble modulins (PSMs), which are staphylococcal cytolytic toxins, play a crucial role in immune evasion. Although all known PSMs are core genome encoded, Queck et al. described this gene inside the SCCmec clusters of types II and III in a series of staphylococcal strains, including strains of *S. aureus, S. epidermidis, S. saprophyticus, S. pseudointermedius*, and *S. sciuri* [7]. This very interesting study revealed a previously unknown role for methicillin resistance clusters in staphylococcal pathogenesis and showed that both antibiotic resistance and virulence determinants may be combined in staphylococcal MGEs (the exception to the above-mentioned rule).
*S. pneumoniae* was previously considered to be universally susceptible to penicillin. However, reports of isolates with decreased susceptibility to penicillin have increased worldwide in recent years. In one study, Rieux et al. analyzed the relationship between acquisition of β-lactam resistance and loss of virulence in *S. pneumoniae*. The authors transformed a virulent and penicillin-susceptible strain with *pbpX* and *pbp2b* from a penicillin-resistant strain to assess the relationship between acquired resistance and virulence. After transformation, the virulence of these receptor strains was significantly reduced. Penicillin resistance in *S. pneumoniae* caused by PBP modifications may occur via different mechanisms, such as acquisition of an additional low-affinity PBP, overexpression of an endogenous low-affinity PBP, alteration of endogenous PBPs by point mutations or homologous recombination, or a combination of these. Several studies have assessed whether resistance to this first-line antibiotic may affect the virulence of pneumococci. For instance, Azoulay-Dupuis et al. examined the relationship between virulence and penicillin susceptibility in an experimental murine model of peritoneal infection and capsular type, using 122 clinical strains of *S. pneumoniae* belonging to 24 different serotypes. All 32 virulent strains were penicillin susceptible, while all 41 strains with reduced susceptibility to penicillin were avirulent, independently of the serotype. In a later study, Fernandez et al. used a rabbit model of meningitis to test the inflammatory activity induced by three different strains of pneumococci, belonging to serotypes 3, 6B, and 23F (the prevalent serotypes in Western Europe), with different susceptibilities to β-lactams. The authors’ conclusions supported the idea that penicillin-resistant pneumococcus isolates are avirulent in immunocompetent mice, regardless of the isolation site. Overall, the data suggest that acquisition of penicillin resistance in pneumococci is associated with loss of virulence in different models of infection [8].

Data from studies of Gram-negative bacilli are very scarce, and the impact of PBP alterations on virulence is unclear. With the aim of simplifying the interpretation of the data, this review will focus only on *A. baumannii*. Russo
et al. have demonstrated that PBP7-8 contributes to both the in vitro and in vivo survival of A. baumannii. These authors screened a random transposon mutant library and identified a mutant, AB307.27, which contained a transposon insertion in pbgG, encoding the putative low-molecular mass PBP7-8. This mutant showed lower survival in a rat soft tissue infection model and in a rat pneumonia model than the isogenic wild-type strain. Although no clear data have been obtained with regard to the putative role of PBP alterations in β-lactam resistance of A. baumannii (they are an important resistance mechanism in other species, such as P. aeruginosa), it has been suggested that such alterations (at least in PBP7-8) may lead to a decrease in the virulence of A. baumannii.

MECHANISMS AND ORIGINS OF ANTIBIOTIC RESISTANCE

The molecular mechanisms of resistance to antibiotics have been studied extensively and have involved investigations of the genetics and biochemistry of many different facets of bacterial cell function. In fact, the study of antibiotic action and resistance has contributed significantly to our knowledge of cell structure and function. Resistance processes are widely distributed in the microbial kingdom and have been well described for a variety of commensals and pathogens; most can be disseminated by one or more distinct gene transfer mechanisms. A few of the resistance types that illustrate the difficulties in maintaining effective antibiotic activity in the face of the genetic and biochemical flexibility of bacteria deserve special mention [9].

Genetic Jugglery

The genes for β-lactamase enzymes are probably the most international in distribution; random mutations of the genes encoding the enzymes have given rise to modified catalysts with increasingly extended spectra of resistance. The archetypical plasmid-encoded β-lactamase, TEM, has spawned a huge tribe of related enzyme families, providing ample proof of this adaptability. The β-lactamase genes are ancient and have been found in remote and desolate environments, which implies that novel β-lactamases with
altered substrate ranges occur in the environment.

As another example, a new extended-spectrum β-lactamase (CTX-M) clinically significant level. The CTX-M genes and subsequent variants (upwards of 100 different amino acid substitutions have been identified so far) are highly successful at transmission and are a global phenomenon and threat. Such epidemics of r genes with efficient HGT and rapid mutational radiation are next to impossible to control. Macrolide antibiotics, such as erythromycin and its successors, were introduced to contend with the problem of methicillin resistance and are widely used for the treatment of Gram-positive infections. Not surprisingly, strains resistant due to a number of different mechanisms are now widely disseminated. The macrolides and related antibiotics act by binding at different sites in the peptide exit tunnel of the 50S ribosome subunit. Resistance can occur by modification of the RNA or protein components of the tunnel. A specific rRNA modification that engenders resistance to all antibiotics acting at this site on the ribosome was described recently, and this modification is spreading.

**Intrinsic Resistance**

Intrinsic resistance refers to the existence of genes in bacterial genomes that could generate a resistance phenotype, i.e., proto- or quasi-resistance. Different genera, species, strains, etc., exhibit ranges of antibiotic response phenotypes. Since the beginning of this millennium, the availability of genomewide mutagenesis techniques and rapid bacterial genome sequencing has revealed many potential/intrinsic gene functions in bacteria that may lead to resistance phenotypes in clinical situations. For example, a common genetic route to enhanced antibiotic resistance is gene amplification, notably for resistance to the sulfonamides and trimethoprim. These studies provide good clues as to what may happen in the future [10]. Phenotypic analyses of partial or “complete” gene knockout libraries by saturation mutagenesis of bacterial genomes permit the identification of specific mutants eliciting hypersensitivity responses to antibiotics. It is assumed that overexpression of the
corresponding wild-type gene would generate a resistance phenotype. Such prognostic studies have been carried out with a number of organisms and have led to the prediction of novel resistance classes. This type of analysis was first done with a partial mutant library of *Acinetobacter baylyi*. A more comprehensive survey of the Keio *E. coli* mutant gene library identified a total of 140 distinct isolates that were hypersensitive to a range of different antibiotic classes; related studies have been done with *Pseudomonas aeruginosa*. Many of the putative “susceptibility” genes identified, such as genes that are genetically recessive, might not lead to a resistance phenotype. Nonetheless, such approaches identify potential resistance genes and provide information on the systems biology of resistance. RNA microarray analyses of the effects of antibiotics have provided similar predictive information. Simply put, increasing the number of copies of the target genes for an antibiotic can lead to reduction in the intracellular concentration of the inhibitor as a result of titration.

The Resistome

It has been known for some time that bacterial strains resistant to antibiotics can be isolated by plating environmental bacteria on antibiotic-containing media in the laboratory. This is not surprising for antibiotic-producing actinomycetes, since most possess genes encoding resistance to the compounds that they produce. In several cases, the resistance mechanisms have been identified and shown to be specific enzymatic modifications of the antibiotics. Streptomycetes have long been known to produce a variety of β-lactamases that may well be the source of some of the clinical forms of β-lactam resistance. As mentioned earlier, environmental *Kluyvera* species have been found to be the origins of the CTX-M genes. In other cases, resistance of producing organisms to their products has been identified as due to efflux systems. Multiple mechanisms of resistance, as found in the tetracycline producer *Streptomyces rimosus*, are frequent in producing bacteria. Based on biochemical and genetic similarities, such resistance mechanisms have presaged those found subsequently in antibiotic-resistant pathogens.
In a recent, all-inclusive approach to quantifying the $r$ genes/phenotype density in the environment, Wright and colleagues screened a collection of morphologically distinct spore-forming actinomycetes (including many known antibiotic-producing strains) for resistance to 21 different antibiotics. A significant number of strains were resistant to an average of 7 or 8 antibiotics; they were naturally multidrug resistant. The population of $r$ genes in nature is referred to as the environmental antibiotic resistome [11]. This is the best evidence available for the presence of a vast environmental pool of genes with the potential to be captured and expressed as resistance determinants for any overused inhibitor. Similar surveys of other antibiotic-producing bacteria, such as the Bacillaceae, pseudomonads, cyanobacteria, and the extensive family of Actinobacteria, a phylogenetic group known to produce many low-molecular-weight molecules, will be valuable in extending our understanding of the nature of $r$ genes existing in the wild.

Resistance Due to Anthropogenic Activities

The predominant role of human activities in the generation of environmental reservoirs of antibiotic resistance cannot be disputed. Since the 1940s, ever-increasing amounts of antibiotics designated for human applications have been manufactured, used clinically, released into the environment, and widely disseminated, thus providing constant selection and maintenance pressure for populations of resistant strains in all environments. Obtaining accurate figures on the quantities of antimicrobials produced by the pharmaceutical industry is difficult, but it can be estimated that many millions of metric tons of antibiotic compounds have been released into the biosphere over the last half-century. Some alternative uses of antimicrobial agents are as follows: (i) growth promotion/prophylactic use in animals; (ii) therapeutic/prophylactic use in humans; (iii) therapeutic/prophylactic use in aquaculture; (iv) therapeutic/prophylactic use in household pets; (v) pest control/cloning for plants and agriculture; (vi) use as biocides in toiletries and in hand care and household cleaning products; and (vii) culture sterility, cloning, and
selection in research and industry. It should be noted that therapeutic use in humans accounts for less than half of all applications of antibiotics produced commercially.

**Important resistant pathogens**

During the past decades, a shift in the MDR dilemma has been noted from gram-positive to gram-negative bacteria, especially due to the scarceness of new antimicrobial agents active against resistant gram-negative microorganisms. Among gram-positive organisms, the most important resistant microorganisms in the ICU are currently methicillin-(oxacillin-) resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci. In gram-negative bacteria, the resistance is mainly due to the rapid increase of extended-spectrum Beta-lactamases (ESBLs) in *Klebsiella pneumonia*, *Escherichia coli*, and *Proteus mirabilis*;
high level third-generation cephalosporin Beta-lactamase resistance among *Enterobacter* spp. and *Citrobacter* spp., and MDR in *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. Together with the rise of difficult-to-treat MDR infections, several other types of infections become more difficult to treat, whereof the anaerobic *Clostridium difficile* spp., and fungal infections will be described briefly.

**Methicillin-resistant Staphylococcus aureus (MRSA)**

Although methicillin-resistant *Staphylococcus aureus* (MRSA) is already dethroned as the most feared MDR microorganism by the emerging MDR gram-negatives, it remains difficult to eradicate. Being endemic in numerous hospitals worldwide, MRSA is still among the most important causes of hospital-associated bacterial infections. The driving force of resistance in MRSA is cross-contamination and admission of already colonised patients to the ICU. Due to resistance to several other (beta-lactam) antimicrobials, treatment of MRSA often relies on vancomycin. Yet, transmission of resistance plasmids from enterococci to *staphylococci* resulted in an increase of high-level, vancomycin-resistance among *S. aureus*. The National Nosocomial Infection Surveillance (NNIS) study reported a rise of MDR in *S. aureus* from 3% in the early 1980s to 53% at the beginning of the 21st century. The epidemiology of MRSA is extremely sensitive to changes in admission prevalence and failures in infection control, which are only partially influenced by reductions in antibiotic use. Previous stay in hospital or long-term care facilities, ICU stay, intravascular devices, prior or prolonged antibiotic therapy, chronic underlying conditions, surgical wounds, advanced age, and cross-contamination are the most important risk factors for MRSA colonization and infection [12].

**Vancomycin-resistant enterococci (VRE)**

Enterococci have a remarkable ability to adapt to environmental changes and acquire antimicrobial resistance, leading to multiple vancomycin-resistant phenotypes, but also resistance to ampicillin, aminoglycosides, and other beta-lactam antibiotics. As in MRSA, cross-contamination and admission of already
Colonized patients to the ICU are important causes for the spread of VRE. In addition, VRE genes can be transmitted to other species through plasmids. Enterococci also are among the most frequent causes of hospital-acquired infections and the rise of VRE during the past decades has been remarkable (from < 1-25% since the early 1980s). According to the EPIC II study, rates of vancomycin resistance among enterococcal isolates were approximately 33-40% in Western Europe, Eastern Europe, and Asia but approximately 50% in the Americas and Oceania. The rate of vancomycin resistance varies among enterococcal spp., and is highest in *E. faecium*, of which >80-85% also is resistant to ampicillin and penicillin and >50% to high-level gentamicin. VRE favors the highly compromised patient, with as most important independent risk factors for VRE colonization or infection, previous antibiotic exposure (vancomycin, cephalosporins, or agents with anaerobic activity), enteral feeding, cross-contamination, and prolonged hospital stay.

**Enterobacteriaceae**

In contrast to MRSA and VRE, for which a single antibiotic indicates the resistance phenotype of interest, MDR is usually more difficult to define in gram-negative bacilli, due to cross-transmission of resistance characteristics and the wide range of antimicrobials not active against (most) gram-negative microorganisms. Resistance of gram-negative bacteria is consequently emerging in the hospital setting, especially through the production of extended spectrum beta-lactamases (ESBLs), in particular by *E. coli* and *Klebsiella* spp. and *Proteus* spp. ESBLs are plasmid-mediated, and their potential for transfer makes effective control and treatment difficult, which has resulted in endemic and epidemic outbreaks. ESBLs were first recognized in the early 1980s among *K. pneumoniae* in Europe, and its prevalence has increased dramatically in the ICUs and in the community (e.g., extended care facilities), with now more than 500 different types of beta-lactamases identified from clinical isolates. A decreasing efficacy in gram-negatives of third-generation cephalosporins, carbapenems, and fluoroquinolones has been described. The development of quinolone resistance
needs only two mutations, e.g., expression of inducible cephalosporin-
resistance in Enterobacter spp. Especially the production of Klebsiella pneumonia carbapenemase (KPC) by Enterobacteriaceae becomes problematic, because KPC beta-
lactamases result in decreased susceptibility or resistance to virtually all beta-lactam antibiotics; and many strains of Enterobacteriaceae were already resistant to a wide range of non-
beta-lactam antibiotics.

Spread of multidrug resistance

The emergence of MDR often is dedicated to excessive use of broad-spectrum antimicrobial agents (more than 60% of all ICU patients receive antibiotics during their stay), but the epidemiology of MDR is much more complex and multifactorial in nature. During the past few decades, it appeared that some antibiotics have a higher risk of promoting antimicrobial resistance, e.g., third-generation cephalosporins, vancomycin, imipenem, and intravenous fluoroquinolones. Other antibiotics have been used for decades and still barely caused resistance (e.g., colistin). Bonten and Mascini recognized four main forces behind the emergence and further spread of MDR microorganisms: 1) induction of resistant strains; 2) selection of resistant strains; 3) introduction of resistant strains; and 4) dissemination of resistant strains. These alterable/relative forces should be especially considered as incentives to tackle the spread of antimicrobial resistance, especially because all microorganisms have their own mechanism and flexibility to become resistant depending on their ideal environment to tackle antimicrobial efficacy.

Induction of resistant stains

Resistance of susceptible bacteria can occur during antimicrobial treatment, e.g., by mutations. Quinolone and cephalosporin resistance in Enterobacter spp. may arise through this mechanism, but it is very unlikely that it causes methicillin or vancomycin resistance in S. aureus or enterococci in a single patient.

Selection of resistant strains

Antimicrobial therapy may select and favor overgrowth of preexisting resistant flora. Therefore, it is important to maintain the nonpathogenic (anaerobic) flora, e.g., in the gastrointestinal tract, to prevent
overgrowth of gram-negative MDR microorganisms.

**Introduction of resistant strains**

The growing community reservoir of MDR microorganisms also results in a rise of MDR microorganisms in the ICU, especially for species, such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. Healthcare workers often are carriers but also can be vectors (cross-transmission). In addition, an increasing number of patients is already colonized with resistant bacteria on admission in the ICU. When colonization pressure with resistant strains is above a certain level, the risk of cross-transmission becomes extremely high and very difficult to overcome (inoculum effect). Thus, in countries with a high endemic level of resistance (e.g., MRSA), there is a real risk of antibiotic "spiral".

**COMPENSATORY MUTATIONS**

In the recent past it was assumed that the development of antibiotic resistance was inexorably linked to virulence and to fitness costs and that in the absence of antimicrobials in the environment, the susceptible strain would be more competitive than the resistant strain (which may display, e.g., lower growth rates, invasiveness, and transmission capacity). However, antimicrobial treatment could hypothetically reduce the fitness of the susceptible strain, thus creating more favorable circumstances for resistant mutants with a higher fitness in this environment and leading to the development of resistant populations. Many studies in recent years have highlighted the importance of the ability of resistant mutants to adapt and recover their fitness and virulence by secondary-site mutations or compensatory mutations. Molecular studies with different bacteria (both laboratory and clinical strains) show that the recognition of additional compensatory mutations is key to understanding the evolution of microorganisms in recent decades, during which antimicrobial agents have been extensively used.

In a hypothetical first situation, A, without treatment, resistant mutants can appear only via unlikely mutations, which also have a fitness cost and therefore will not prevail; resistance will not emerge. Oceans or seas are examples of such environments in which antibiotics are present at low levels. Similarly, in hypothetical situation B, if
the treatment covers only a small percentage of the population or antimicrobials are present at low levels, resistant mutants are unlikely to appear, but they may appear, because of the low number of individuals subjected to antibiotic pressure. In this scenario, resistant mutants could acquire a level of fitness similar to that of the parental strain. This could include bacteria that colonize or infect anatomical niches with low levels of distribution of the antibiotic in a treated host (e.g., gut microbiota in treatment for otitis). In a third situation, C, in which treatment levels are higher, resistant mutants with a low degree of fitness would probably emerge; these could lead to the emergence of resistant mutants with restored fitness due to compensatory mutations, although this is unlikely due to the low number of resistant mutants.

A real example of this is the nosocomial environment, in which antibiotics are present and there is a high risk of selection of resistant clones. In the last case, D, in which the population would be massively subjected to the drug, emergence of resistant mutants from the original generations or from the following generations would be likely; these mutants would have restored fitness and would therefore be able to prevail over time, for instance, in treatment of infection of an animal or human host with antimicrobial therapy.

Figure 2: Theoretical model of the emergence and persistence of antimicrobial resistance in different ecological niches.
RESISTANCE TO ANTIVIRULENCE COMPONENTS

To date, the only known study of the mechanism of resistance to antivirulence components is that by Maeda et al. concerning resistance to furanone C-30. Furanones interact with the transcriptional regulator descending signal LASR acyl homoserine lactone and therefore attenuate the virulence in a pulmonary infection model of *P. aeruginosa* in mice. The authors worked with mutants of the *mexR* and *nalC* genes, which are negative regulators of the MexAB-OprM efflux pump, and observed expulsion of compound C-30 by the MexAB-OprM efflux pump in the mutants. Furthermore, the results were confirmed in the Liverpool epidemic strain (overexpression of MexAB-OprM, *nalC* and *mexR* mutants), which is known to increase morbidity in patients with cystic fibrosis. On the other hand, a *mexA* mutant with reduced MexAB-OprM efflux pump activity was previously found to be less virulent in a pathogenesis model (*P. aeromonas* and *C. elegans*). Moreover, Maeda et al. reported that the *mexR* mutant (with enhanced MexAB-OprM efflux pump activity) is as virulent as the wild-type strain and is much more virulent in the presence of the QS inhibitor (C-30) than the wild-type strain.
Figure 3: The *mexR* and *nalC* mutations decrease C-30 inhibition of *P. aeruginosa* QS phenotypes. (a) Swarming motility. The *rhlR* mutant (*rhlR* encodes the two transcriptional regulators of the acyl homoserine lactone system of *P. aeruginosa*) was used as a negative control. MeOH was used as a negative control for C-30. (b) Production of pyocyanin (phenazine toxic metabolites).

**CONCLUSIONS**

The significance and estimation of anti-infection agents can't be overestimated; we are absolutely reliant on them for the treatment of irresistible maladies, and they ought to never be viewed as insignificant wares. Notwithstanding their utilization in the treatment of irresistible infections, antimicrobials are basic to the achievement of cutting edge surgical methods, including organ and prosthetic transplants. Despite every great aim to control anti-microbial utilization (however constrained activity), there is little uncertainty that the circumstance
Regarding anti-microbial resistance is bleak. Resistance components are pandemic and make a colossal clinical and monetary weight on human services frameworks around the world. There are no straightforward answers for the issue. Conclusive activities that require huge responsibility and implementation are never famous, regardless of the possibility that lives can be spared. Luckily, not every single bacterial pathogen are safe constantly, and numerous react to exact treatment with antimicrobial operators managed in the group.

Achievement is maybe because of fortunes instead of to decision making ability. Given the numerous imponderables, as well as can be expected expect is that all doctors and medicinal services focuses give their patients surroundings that are sans resistance by taking stricter measures in disease control and anti-microbial use. This must be went down by endeavors to forestall dumping of anti-toxins into the earth through sewer frameworks; complete pulverization of anti-toxins before transfer ought to be regular practice.

REFERENCE:


