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Review Article

PREVENTION OF BACTERIAL RESISTANCE IN HEALTH CARE SETTINGS

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ABSTRACT
Antibiotic resistance is common in the society and in the hospital settings. It is a common occurrence to observe that in spite of highly potent anti-microbials the patients are not responding clinical and sometimes even deteriorates. Extended spectrum beta lactamases are on the rise and are responsible for the majority of this ever increasing resistance pattern specially in the health care settings. Antimicrobial resistance is here to stay. Hence it is extremely important to use judicious use of the available anti-microbials and proper precautions are undertaken for preventing the spread of this rising bacterial resistance. It may be naive to anticipate reaching a grand control over resistance. The hope perhaps lies in slowing down development of newer resistance while continuing to develop new agents at a rate sufficient to keep ahead of bacteria. In this clinical review we have tried to analyze the mechanisms of bacterial resistance and its clinical impact on the health care settings with emphasis over the preventive strategies.

Keywords: *Bacterial Resistance, Health Care Settings, ESBL, Beta Lactamases*

INTRODUCTION
At the dawn of the antibiotic era, resistant pathogens were rare. Antimicrobial use permitted resistant organisms to thrive within treated patients, but it is the movement of resistant microbes between individuals, communities, and nations that has led to a world where all are at risk of an untreatable infection. Thus any comprehensive strategy to address the threat of antimicrobial resistance must aim to decrease the transmission of resistant organisms – in homes, communities, healthcare settings, food chains, water supplies, and international trade routes. The key element is improved hygiene. For patients seeking medical care, healthcare providers have a particular responsibility to avoid patients acquiring infections as the result of medical decisions and interventions. Healthcare-associated infections are one of the primary causes of death and suffering in hospitalized patients throughout the world, so infection prevention is rightly considered to be a cornerstone of patient safety.

The introduction of antibiotics in the early 1940s has been recognized as a major milestone in the history of medicine. The synthesis of arsphenamine, in the fight against syphilis, by Paul Ehrlich marked the dawn of the antimicrobial era. The middle of the 20th century was the period when true antibiotics effective against bacteria were developed. Anti-tuberculous and antifungal agents then followed. Anti-virals were introduced to complete the arsenal against pathogens. Resistant strains of Staphylococcus aureus emerged shortly after the introduction of penicillin, and within 10 years, *59% of* S. aureus organisms were penicillin resistant. The remarkable ability of almost all species of bacteria, fungi, and viruses to adapt and prevail over hostile mechanisms used by antibiotics has presented clinicians with the prospect of a post antibiotic era (WHO, 1996).

Health Care-Associated Infections (HAI) and Bacterial Resistance
Health care-associated infections (HAI) are an important public health problem because they occur frequently, cause morbidity and mortality and represent a significant burden among patients, health-care workers and health systems. HAI occur worldwide and affect all countries, irrespective of their degree of development. The most common types of HAI include infections of surgical wounds, the blood stream, the urinary tract and the lower respiratory tract. In some settings, puerperal endometritis and gastrointestinal infections are also common. Infection rates are higher among patients with increased

susceptibility because of their age (the very young and the elderly), severity of the underlying disease, use of invasive devices and procedures, or conditions that impair the immune system (such as chemotherapy and transplants).Outbreaks of HAI may have severe consequences in hospitals and transmission from former patients, visitors and staff may also lead to outbreaks in the community. The emergence of infections such as severe acute respiratory syndrome (SARS), viral haemorrhagic fevers, avian influenza, and the threat of pandemic influenza highlight the need for efficient infection-control practices in health-care settings. Among many lessons learnt from the SARS epidemics is the fact that health-care facilities can act as amplifiers of the outbreaks, increasing the number of cases occurring. "Drug selection pressure" is the single most important factor in the evolution of drug resistance in bacteria. The reasons for drug pressure are multi factorial and involve both human and animal use. Although drug resistance is primarily a medical problem, the factors that influence the spread of resistance are ecological, epidemiological, cultural, social, and economic. Patients, physicians, veterinarians, and healthcare facilities and retailers from large pharmacies to local drug sellers have little motivation (economic or otherwise) to acknowledge the consequences of their use of antibiotics on others, especially on future generations. Every time an antibiotic is used whether appropriately or not, the probability of the development and spread of antibiotic resistant bacteria is increased (Barrett *et al.,* 1968; WHO, 2001). Antibiotic effectiveness is a globally shared resource and a shared responsibility. That responsibility is to maintain antibiotic effectiveness as long as possible while allowing the maximum possible health benefits to accrue to the world's population. Adequate preparation and an ongoing institutional culture of safe health-care practices to prevent and control the dissemination of pathogens are relevant in the control of many outbreaks of communicable disease that may affect the community. The emergence and spread of antimicrobial resistance among many microorganisms, such as multidrug-resistant/extensively drug-resistant strains of Mycobacterium tuberculosis and Gram-negative bacilli, has rendered many formerly easily treatable infections more difficult to manage. While resistance to antimicrobial agents is a problem in the community as well as in health-care facilities, it is particularly important in hospitals, where the highly susceptible population may act as a permanent reservoir of resistance or source of amplification of the transmission of resistant bacteria, in the absence of effective infection-control programmes. A considerable proportion of the burden of disease attributable to HAI is preventable and many interventions that have been proven to be effective are of low cost. Infection prevention and control (IPC) activities and programmes have been successful in controlling HAI in various settings in a sustainable way and with a favourable cost–benefit ratio (WHO, 2008). Many of these programmes developed as a result of an outbreak or crisis and included a response characterized by strong political support and leadership (local and/or national) (CDC, 2015).

ICARE (Intensive Care Antimicrobial Resistance Epidemiology) was a two-phase project designed to assess the extent of antimicrobial resistance in a subset of hospitals participating in the National Nosocomial Infection Surveillance (NNIS) program. Specifically, this project focused on resistance observed in ICUs as compared with the community. Phase I of the project demonstrated that resistance was significantly higher among hospitalized patients than outpatients. ICU patients demonstrated the highest rates of resistance. Phase II of the project then proved that ICU patients demonstrated higher rates of resistance than non-ICU patients (NNIS Report, 2000; Couper *et al.,* 1997).

Beta-lactamases are enzymes capable of hydrolyzing the beta-lactam ring of penicillins, cephalosporins, and other related antibiotics, thereby making them ineffective. Cephalosporins were continuously modified to the extent that extended-spectrum members of this class (such as ceftazidime, ceftriaxone, and cefotaxime), possessing better stability against beta-lactamases, became available. Enteric Gram-negative bacilli with transferable resistance to the extended-spectrum cephalosporins were first reported in Europe in the mid-1980s. These strains were reported in the United States shortly thereafter. The term extended-spectrum beta-lactamases refers to plasmid-mediated beta-lactamases that hydrolyze penicillins, cephalosporins, and aztreonam, but are inhibited by the beta-lactamase inhibitors, such as sulbactam, clavulanate, and tazobactam. Genes encoding the ESBLs are carried on plasmids, which are circular and supercoiled segments of DNA, physically separate from the bacterial chromosome, and replicate

independently of the chromosome. Because these genes are carried on transposable elements, they can be disseminated widely among Gram-negative bacilli. Genes targeted by mutations include TEM-3 to -28, and SHV-2 to -6, TEM and SHV being the representive beta-lactamases (Fridkin *et al.,* 1999). Studies have demonstrated that the ESBLs arose as a result of selective pressure created by the use of extended-spectrum cephalosporins. Many ESBL-producing organisms do not appear to be resistant to the newer cephalosporins and aztreonam upon "routine" susceptibility testing. Therefore, laboratories must have methods to specifically look for ESBLs. Prevalence of ESBLs varies from country to country. In a study of clinical isolates in the United States, between 1.3 and 8.6% of Escherichia coli and Klebsiella pneumoniae isolates were resistant or intermediately susceptible to ceftazidime. When a subgroup of these isolates was examined closely, half were found to be ESBL producers (Gibot *et al.,* 2004). Patients especially at risk of acquiring ESBL infections include those with prolonged hospital stays, surgery, previous antibiotic exposure, admission to an ICU, and admission to a long-term care facility. Ceftazidime use, in particular, has been implicated as an important factor in HAIs caused by ESBL producers (Paramythiotou *et al.,* 2004).

Enterococci are normal inhabitants of the gut flora and usually cause infections only when the immunity of the host is low (Moellering, 1992). Almost all nosocomial enterococcal infections are caused by either Enterococcus faecium *or* Enterococcus faecalis, and most arise in the urinary tract or the intra-abdominal cavity. However, enterococci in general have been prevalent in critically ill patient populations. The most common clinical impact of VREs is intestinal colonization, which does not result in symptoms, may last for long periods, and serves as a reservoir for transmission of VREs to other patients. Certain VRE-colonized patients are at risk of infection, including hematology and oncology patients, patients in ICUs, and recipients of solid (especially abdominal) organ transplants. Patients susceptible to VRE infections include those who have received multiple courses of antibiotics and those with prolonged hospitalizations. A well-established association exists between colonization or infection with VRE and administration of vancomycin (oral or parenteral), third-generation cephalosporins, and antianaerobic drugs such as metronidazole, clindamycin, or imipenem (Linden, *et al.,* 2003).

The emergence of VRE in US hospitals is clearly shown by the longitudinal surveillance data on antibiotic susceptibilities in nosocomial pathogens collected by the NNIS system of the CDC (CDC, 1999). Almost all enterococcal blood isolates were susceptible to vancomycin in 1989, but the proportion of resistant strains increased to 12.8% and 25.9% in 1995 and 2000, respectively (Niedermann, 2003). Across the United States, VRE seemed to spread from the Northeast to the Midwest, and subsequently to the West Coast. More and more patients became colonized with VRE, and by 1995 situations of endemicity were described (Woodford, 1998). Colonization was most frequent in critically ill and immune compromised patients, treated in wards where antibiotic use was highest, and cross-transmission was identified as an important route of bacterial spread, suggesting serious lapses in infection-control practices (Morris *et al.,* 1995). Currently, VRE are the second commonest cause of hospital-acquired urinary tract and wound infections, and the third most common cause of hospital-acquired bloodstream infections (Gold and Moellering, 1996).

Methicillin was the first semisynthetic penicillinase-resistant penicillin and was introduced in 1961. MRSA was first identified in the United States in 1968.15 At present, approximately 20 to 25% of S aureus isolates obtained from patients hospitalized in the United States are resistant to methicillin, but the proportion of resistant isolates varies greatly from institution to institution and from country to country. For the first time in 1999, NNIS data indicated that more than 50% of ICU S aureus isolates were methicillin resistant (CDC, 1999). The nares, rectum, and wounds are the most common sites of MRSA colonization for patients in both acute and long-term care facilities. Risk factors for nosocomial MRSA in the acute setting include prolonged hospital stay, exposure to broad-spectrum antibiotics, long duration of antimicrobial therapy, stay in ICU or burn unit, presence of a surgical wound, and proximity to another patient with MRSA (Hancock, 1998). Traditionally thought to be a major problem in patients with some health-care exposure, more recently, there have been increasing numbers of patients with community-acquired MRSA (Said-Salim *et al.,* 2003).

Mechanisms of Resistance

Antibacterial use disrupts the microbial ecology of the patient, unit, or population. Entire species may be selected. The increasing role of enterococci as opportunist pathogens in the past 20 years partly reflects increasing use of fluoroquinolones and cephalosporins, to which these organisms are inherently resistant (Rice, 2000). As DNA is replicated, uncorrected base substitutions occur randomly, at a frequency of 9–10 per gene. In addition, copying errors may lead to the partial or complete deletion of individual genes. As a result, the targets of antibacterials may be altered, drug inactivation or efflux systems may be up‐ or down regulated, and uptake pathways (porins and active transporters) may be lost or activated. Resistance genes or their repressors also can be activated or inactivated by the migration of insertion sequences. The *mecA* gene (the gene responsible for methicillin resistance) is part of a mobile genetic element found in all MRSA strains. Katayama *et al.*, (2000) demonstrated that *mecA* is part of a genomic island designated staphylococcal cassette chromosome *mec* (SCC*mec*). To date, four different SCC*mec* elements varying in size from 21 to 67 kilobases have been characterized.20 *mecA* is responsible for the synthesis of penicillin-binding protein 2a, which substitutes for other penicillin-binding proteins. Penicillin-binding protein 2a has very low affinity for beta-lactam antibiotics and this mechanism enables MRSA to survive even high concentrations of beta-lactams and cephalosporins.

Beta‐lactamases are enzymes capable of hydrolyzing the beta‐lactam ring of penicillins, cephalosporins, and other related antibiotics, thereby making them ineffective. Cephalosporins were continuously modified to the extent that extended spectrum members of this class (such as ceftazidime, ceftriaxone, and cefotaxime), possessing better stability against beta‐lactamases, became available. Enteric Gram‐negative bacilli with transferable resistance to the extended‐spectrum cephalosporins were first reported in Europe in the mid‐1980s (Hancock, 1998). These strains were reported in the United States shortly thereafter. The term extended‐spectrum beta‐lactamases refers to plasmid‐mediated beta‐lactamases that hydrolyze penicillins, cephalosporins, and aztreonam, but are inhibited by the beta‐lactamase inhibitors, such as sulbactam, clavulanate, and tazobactam. Genes encoding the ESBLs are carried on plasmids, which are circular and supercoiled segments of DNA, physically separate from the bacterial chromosome, and replicate independently of the chromosome. Because these genes are carried on transposable elements, they can be disseminated widely among Gram‐negative bacilli (Pitout *et al.*, 1997).

Three basic mechanisms of resistance are of importance in P. aeruginosa (Morris *et al.*, 1995): (1) intrinsic resistance, (2) acquired resistance, and (3) genetic resistance. Intrinsic resistance is associated with a reduction in the permeability of the outer membrane to antibiotic classes, such as beta-lactams. Another mechanism of intrinsic resistance in Pseudomonas involves the discovery of an efflux system mediating decreased susceptibility to quinolones, beta-lactams, tetracycline, and chloramphenicol. Acquired resistance implies the resistance develops without any change in the genotype of the bacteria. A major disparity occurs between *in vitro* minimum inhibitory concentrations and *in vivo* efficacy. In spite of achieving "adequate" antibiotic concentrations, cure is not achieved. This type of resistance is associated with the exposure of a microbe to a set of inducing conditions such as antibiotic exposure, media composition, growth phase and growth rate of the organism, and other environmental factors. Such resistance will revert to full susceptibility when the inducing conditions (such as antibiotics) are removed. Genetic resistance involves the stable acquisition of new genetic information through mutation or a plasmid-dependent mechanism.

For instance, the main mechanism of genetic resistance to beta-lactams in Pseudomonas is by the mutational derepression of beta-lactamase. Plasmid-encoded beta-lactamases, such as PSE-1, PSE-2, PSE-3, and PSE-4 represent less important mechanisms of beta-lactam resistance in Pseudomonas. For imipenem and meropenem, the major mechanism of resistance is the loss of a specific porin, OprD. Aminoglycoside resistance in Pseudomonas involves the acquisition of certain plasmids that encode for enzymes that acetylate, adenylate, or phosphorylate the antibiotic molecule. This causes reduced uptake and reduced ribosomal interaction between the microbe and antimicrobial. Quinolone resistance in

Pseudomonas is mediated either by target site mutations in DNA gyrase or by efflux mutations (Hiramatsu *et al.*, 2001).

Five types of vancomycin resistance have been described in enterococci (Van A, Van B, Van C, Van D, and Van E). Van A through E represents the clusters of genes that are translated into enzymes that make cell wall precursors to which vancomycin binds with lower affinity. This is accomplished by the synthesis of cell wall precursors ending in D-alanyl-D-lactate or D-alanyl-D-serine, to which vancomycin binds with significantly reduced affinity. In contrast, vancomycin-susceptible enterococci synthesize cell wall precursors ending in D-alanyl-D-alanine and these bind vancomycin with high affinity (Murray, 2000).

Prevention and Control

Surveillance

Antibiotic resistance and antibiotic use: Two complementary types of surveillance are recommended: Surveillance for antibiotic resistance and surveillance for antibiotic use. This supports a recommendation made in the national policy document. By itself, surveillance

of any type will not change the antibiotic use or the spread of resistant organisms, but knowing resistance levels and tracking them over time is a powerful tool to support real changes. Once the link between resistance and antibiotic use is accepted, tracking antibiotic use can be used as a surrogate for changes in resistance patterns. To some extent, these patterns can produce evidence for whether interventions are working, and can help identify problem areas, as is the case for antibiotic resistance surveillance (Ibrahim, *et al.*, 2000). Surveillance results/data can also be fed into standard treatment guidelines and essential drug lists.

Distributing Standard Treatment Guidelines

Standard treatment guidelines have been developed at various levels, from the hospital (e.g., for diarrhea and pneumonia) to national level programs (e.g., for tuberculosis and HIV/AIDS) (Sinha, 2011). These guidelines should be tailored to local situations and specific to levels of care. However, employees at all levels in the healthcare system often have little knowledge of the content of these STGs. One means of distributing STGs is through drug bug "pocket cards:" These cards would provide summaries of locally recommended treatments for common conditions, and prescribers would be encouraged to carry and refer to these.

Infection Control Interventions

Hospitals create their own ecology in the bacterial human interface. The use of antibiotics is much more intense in hospitals than in the community, and highly resistant bacteria may be found and spread there. In response, infection control interventions have been developed to contain bacterial infections in hospitals, including increased hand washing, isolation rooms, reminders to limit catheter use, and use of gloves and gowns. The Ministry of Health and Family Welfare task force recommends that all hospitals create an infection control plan, committee, and team. It further recommends that clinical microbiologists conduct audits, such as by spot‐checking prescribing sheets in wards (Singh *et al.*, 2000).

Continuing education of doctors, nurses, dentists, pharmacists, and veterinarians is a perpetually attractive opportunity for instructing these professionals about antibiotic use and resistance. In India, continuing education is beginning to be required for certain professionals. A new Medical Council of India rule that doctors must attend 30 h of continuing medical education every 5 years to maintain their licenses will help encourage such courses (Srivastava *et al.*, 2011). Workshops on antibiotics could be offered as part of this, and similarly for other professions. Furthermore, the establishment of clinical microbiology and infectious diseases post graduate courses should be encouraged.

In a review by Kollef *et al.*, (2001) focusing on antibiotic resistance in the ICU, the antimicrobial strategies deemed effective at limiting the emergence of resistance included the establishment of protocols and guidelines to avoid unnecessary use of antibiotics, hospital formulary restrictions, use of narrower-spectrum antibiotics, use of quantitative bacterial cultures in instances such as ventilator-associated pneumonia (VAP), combination antibiotic therapy, routine input by infectious disease specialists, antibiotic cycling, area-specific modification of antibiotic use, and prudent use of newer antimicrobial agents. However, the authors advocate use of selective digestive decontamination only in

high-risk patients in an outbreak situation in conjunction with infection-control practices. In the same review, the authors advocate the following nonantimicrobial strategies for the prevention of resistance: reducing the duration of mechanical ventilation; minimizing use of central venous catheters with strict hygiene precautions during insertion; vaccination against Haemophilus influenzae, Streptococcus pneumoniae, and influenza virus (to name just a few); hand washing; reducing nursing and house-staff workloads in the ICU; and use of gloves and gowns. Even though transmission of microorganisms occurs mainly from the hands of health-care workers, and hand washing remains the most important preventive measure, a large observational study demonstrated the following: nurses were more likely to wash hands than physicians; hand washing was more likely to occur during weekends; pediatric care units had the highest rate of hand washing compliance; ICUs had the poorest rates of compliance; the higher the workload, the lower was the compliance; and the overall compliance rate was about 50% (Rice, 2000).

The CDC (2015), in a campaign to prevent antimicrobial resistance in health-care settings, has elucidated the following 12 steps: Vaccinate, get the catheters out, target the pathogen, access the experts, practice antimicrobial control, use local data, treat infection, not contamination, know when to say no to vancomycin, stop antimicrobial treatment, isolate the pathogen, and break the chain of contagion. In one study (Arroliga *et al.*, 2003) the usefulness of penicillin skin testing in patients with a history of "penicillin allergy" was studied. It was observed that, only 1% of the patients had a positive skin test, 89% had negative results, and 10% had a nondiagnostic test. About 81% of the patients received a penicillin compound without significant side effect. Thus it can be believed that penicillin skin testing represents a safe and effective strategy to potentially reduce the use of broad-spectrum antibiotics.

Two other studies merit mention here. Singh *et al.*, (2000) randomly assigned patients with VAP to receive either standard therapy with multiple antibiotics or monotherapy for 3 days, based on a clinical pulmonary infection score. None of the patients randomized to the monotherapy group showed progressive infection, and this group had a significantly lower incidence of infections caused by resistant organisms. Gibot and colleagues (2004) addressed the challenge of difficulty in diagnosing VAP with the use of soluble triggering receptor expressed on myeloid (TREM-1) cells in bronchoalveolar fluid. TREM-1 is a member of the immunoglobulin superfamily that is specifically up-regulated in the presence of microbial products. In the future, this test may help clinicians differentiate patients with or without VAP, thus obviating the need for unnecessary antibiotic therapy.

Surveillance for HAI

Infection prevention and control (IPC) activities should respond to actual needs. In order to fulfill the objectives of IPC programmes, surveillance systems for HAI and for assessment of compliance with IPC practices should be in place. These will also contribute to the assessment of the impact of IPC interventions (WHO, 2011). Surveillance activities are time-consuming and need to be balanced with the time needed for prevention and control activities. More advanced surveillance systems also require good quality microbiological laboratory procedures and data for the identification of etiological agents and patterns of resistance to antimicrobials. Surveillance should have clear objectives (CDC, 2015). At the very least, surveillance should provide information for: i) Describing the status of infections associated with health care (i.e. incidence and/or prevalence, type, etiology, severity, attributable burden of disease); ii) Identification of high-risk populations, procedures and exposures; iii) Early detection of outbreaks; and iv) Assessment of the impact of interventions. There are several models of surveillance for HAI in different settings, mostly in acute care facilities (i.e. hospitals) and in long-term hospitalized care. All should include: i) The objectives of surveillance; ii) A standardized set of case definitions; iii) A method for detecting infections (numerators); iv) A method for detecting the exposed population (denominators); v) The process for the analysis of data and reports, including numerator and denominator data and calculation of rates; and vi) Some models should include a method for evaluating the quality of the data.

CONCLUSION

Antimicrobial resistance is here to stay. In a telling commentary by Livermore (2005) the author reports that it may be naive to anticipate reaching a grand control over resistance. The hope perhaps lies in

slowing down the development of newer resistance while continuing to develop new agents at a rate sufficient to keep ahead of bacteria. Preventing the further propagation by adhering to the strict control guidelines is the key component in preventing the spread of the bacterial resistance in the health care settings.

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