

# Multidrug Resistance in Bacteria: A Serious Patient Safety Challenge for India

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## ABSTRACT

Patient safety is an important issue affecting the delivery of health care in developed, transitional and developing countries. With the advancements in patient care, hitherto unknown issues relating to patient safety are emerging. An important problem endangering patient safety is infections acquired in the health care facilities. Health care associated infections (HCAIs) are no longer a local or regional problem. With the dissemination of multi-drug resistant bacteria across the globe, the problem of HCAIs has become even grimmer. The emergence of pan-resistant bacterial strains, compounded by lack of availability of new antimicrobials foretells a grave future for management of infections acquired in hospitals. Therefore, it is important to frame local policies and measures and take affirmative actions for prevention of HCAIs and reduce the burden of multi drug resistance.

**Key words:** Beta-lactamases, multidrug resistance, methicillin resistant staphylococcus aureus, patient safety, vancomycin resistant enterococcus

## INTRODUCTION

Patient safety is an important issue affecting the delivery of healthcare in developed, transitional, and developing countries. With the advancements in patient care, hitherto unknown issues relating to patient safety are emerging. Improvement in patient safety will in the long-term improve the quality of healthcare.<sup>[1,2]</sup> During the past few years, patient safety is being increasingly recognized as an issue of global importance, which is mobilizing increasing attention and actions for improvement.<sup>[3,4]</sup> The main reasons for these developments are the increasing public awareness; increasing role of media in disseminating healthcare related information; and the increasing focus on accountability of healthcare facilities (HCFs). Therefore, the 55<sup>th</sup> World Health Assembly in 2002 adopted a resolution urging nations

to focus attention on patient safety and strengthen safety and monitoring systems.<sup>[1,2,5]</sup>

An important problem endangering patient safety is infections acquired in the HCFs. Healthcare associated infections (HCAIs) are no longer a local or regional problem. The implications of HCAIs are enormous in terms of mortality, morbidity, disability, psychosocial effects on society, and the cost of healthcare. With the dissemination of multidrug resistant (MDR) bacteria across the globe, the problem of HCAIs has become even grimmer. Therefore, it is important to frame local policies and measures and take affirmative actions for prevention of HCAIs and reduce the burden of MDR.

That HCAIs are a global patient safety issue is exemplified by the monumental decision taken by the World Alliance for Patient Safety to choose HCAIs as the topic of the first global patient safety challenge.<sup>[6-8]</sup> Leading experts in various fields of Infection Prevention and Patient Safety have joined hands with a common motto of “Clean Care is Safer Care” (CCiSC). The activities promoted by this Alliance have stimulated country-level activities to enhance patient safety throughout the world.<sup>[6-8]</sup>

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As developments during the subsequent years have shown, this decision has catalyzed a chain of interventions in most of the countries, which had previously been without any vision or direction on infection control. A positive outcome of these measures is the reported improvements in hand hygiene in many hospitals across the globe.

## MULTI-DRUG-RESISTANCE IN BACTERIA

The emergence of pan-resistant bacterial strains, compounded by lack of availability of new antimicrobials foretells a grave future for management of infections acquired in hospitals. This may necessitate a “back to basics” approach of infection control, since simple maneuvers like hand hygiene have been found to reduce cross-transmission of resistant microbes. The major resistant pathogens in HCFs today are methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant Enterococcus (VRE), and extended spectrum  $\beta$ -lactamase (ESBL) producing *Klebsiella pneumoniae* and *Escherichia coli* or pan-drug resistant Gram negative bacteria like *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.<sup>[9-11]</sup> *Stenotrophomonas maltophilia* and *Burkholderia cepaciae* are also gaining increasing importance due to their intrinsic resistance to antimicrobials.<sup>[9]</sup> Currently, as high as 60% of hospital acquired infections (HAIs) may involve antibiotic resistant bacteria.<sup>[9,12-14]</sup> They are associated with a higher infection-related costs, longer duration of hospital stay, and higher mortality. The estimated annual costs related to antibiotic resistance range from 100 million \$ to 30 billion \$ in US hospitals alone.<sup>[12]</sup> The alarming scenario of pan-resistant microbial infections is amongst the most critical problems faced by physicians today and a major global public health concern.

The evolution of antimicrobial resistant bacteria stems from a multitude of factors, the most important being the widespread and inappropriate use of antimicrobials and their extensive use as growth enhancers in animal feeds. These pathogens easily cross geographic barriers, highlighting the close ecological niche which humans share with them.<sup>[15-18]</sup> Another factor is the growing emphasis on outpatient medical management, which has increased the severity of illness of those who are admitted to the hospitals. Patients with advanced malignancies, organ transplantation, multiorgan failure, or HIV infection are severely immunocompromised and constitute a larger portion of hospital patients now than in the past. These patients are often colonized or infected with unusual and resistant opportunistic organisms. They are also more likely to be treated with procedures (e.g., bone marrow transplantation)

and devices (e.g., urinary and central venous catheters) that increase the risk of acquisition of infections.<sup>[19]</sup>

Apart from the therapeutic challenge posed by multiresistant pathogens in hospitals, they are now gradually infiltrating into the community, as the patient is discharged from the facility and carries resistant pathogen with him. On the other hand, increased treatment of patients in the community can lead to de novo generation of resistance in the community that is introduced to the hospital by patients on admission. Readmission of patients colonized with resistant organisms represents a hidden reservoir that also needs monitoring and control.<sup>[19]</sup> It is likely, given the trend toward greater outpatient care, that prevention and control of antimicrobial resistance will be as important in the outpatient arena as in the inpatient setting.

## PREVENTION OF SPREAD OF INFECTIONS DUE TO MDR PATHOGENS

The rapid spread of resistant pathogens across boundaries only certifies the fact that the emergence of resistance in one organism in any part of the world, even in animal population may have long-term implications for human health globally. Thus, tackling the menace of antimicrobial resistance is a community responsibility, within and outside the hospital.<sup>[19]</sup> The patient related factors for development of HCAs caused by MDR pathogens like age, underlying illnesses, severity of illness, type of surgeries, etc., are difficult to modify. Thus, basic infection control protocols of hand hygiene, barrier precautions, screening, cohort nursing, environmental cleaning, and judicious antibiotic use are the most effective measures to control the dissemination of multiresistant pathogens in HCFs.

The measures to control the spread of antimicrobial resistance in HCFs are:

- Administrative support
- Standard precautions and contact precautions
- Institution of Stringent Hand Hygiene programs at local, regional, and national levels
- Continuous training of staff at peripheral health centers (PHCs) on basic methods of antimicrobial susceptibility; provision of adequate laboratory reagents, media, and chemicals and equipment to these centers for accurate performance of tests
- Continuous training of healthcare workers in remote areas and PHCs to restrict usage of antimicrobials.
- Education of staff of all cadres on hospital infection control practices in all HCFs

- Cohorting of patients in hospitals
- Good clinical practices
- Implementation of preventive bundles for device-associated infections
- Accurate and prompt diagnosis of infectious etiologies
- Judicious use of antimicrobials and formulary restriction
- Regulations to prevent over-the-counter sale of antimicrobials
- Use of pharmacodynamics/pharmacokinetic data for deciding antimicrobial treatment regimens
- De-escalation of antimicrobial treatment for infections like ventilator-associated pneumonia (VAP), urinary tract infection (UTI), etc.
- High dose, short course treatment regimens
- Implementation of strict perioperative antimicrobial prophylactic guidelines
- Formulation and implementation of prophylactic antimicrobial prescription policies by every institution.
- Establishment of pharmacies (at least in larger Indian Hospitals)
- Involvement of clinical microbiology laboratory and prompt communication within an healthcare center
- Proper sterilization and disinfection practices
- Stringent environmental cleaning
- Establishment of few state-of-the-art laboratories in our country for characterization of molecular means for detection of resistance and epidemiological tracing; networking of laboratories
- Continuous research and development for alternative antimicrobials, preventive methods of infections, and environment/ecofriendly techniques.

In essence, antimicrobials cannot cover for faulty practices and improper cleaning and decontamination.

### SCENARIO OF MULTI-DRUG RESISTANCE IN INDIA

In India, ESBL producing strains of *Enterobacteriaceae* have emerged as a challenge in hospitalized as well as community-based patients. A study conducted at New Delhi in 2002 found 68% of Gram negative bacteria to be ESBL producers, in which 80% of *Klebsiella* were ESBL producers.<sup>[20]</sup> ESBLs have been reported from community isolates from north India as well. Studies from Coimbatore and Nagpur have shown the prevalence of ESBL to be 40-50% in urinary isolates.<sup>[21,22]</sup> A study from Karnataka showed the frequency of ESBLs in neonatal septicemic cases to be 22.7%.<sup>[23]</sup> A similar study from Lucknow showed high levels of ESBL production (63.6-86.6%).<sup>[24]</sup>

Metallo-beta-lactamase production is a significant problem especially in hospital isolates of *P. aeruginosa* and *Acinetobacter* sp. In a study conducted at New Delhi in 2005, of the 2,626 strains of Gram negative bacteria, carbapenem resistance was seen in 22%.<sup>[25]</sup>

The Indian Antimicrobial Resistance Study Group has recently published their findings on broad-spectrum  $\beta$ -lactam resistance and ESBL phenotypes in *Enterobacteriaceae* including *Salmonella* sp. The isolates were part of the MYSTIC Program and consisted of nonduplicate samples from ten different Indian sites in six cities (New Delhi, Mumbai, Indore, Lucknow, Bangalore, and Vellore). From initial phenotypic screening, 92% *E. coli* and 96% *Klebsiella* sp. were confirmed as being ESBL producers.<sup>[26]</sup> The latest report from National Institute of Communicable Diseases (NICD), New Delhi, India, shows a rise in resistance to cefepime.<sup>[27]</sup>

In recent studies conducted on Gram positive and Gram negative bacteria from obstetric cases in different parts of our country, a high level of resistance was noted to beta-lactams, fluoroquinolones, and cotrimoxazole. This finding is significant in view of the fact that most of the pathogens would be community acquired.<sup>[28,29]</sup> The Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group, India, in a study conducted at 15 tertiary care centers on 26,310 isolates of *S. aureus* found the prevalence of MRSA to be 41%. A high rate of resistance to ciprofloxacin, gentamycin, cotrimoxazole, erythromycin, and clindamycin was also seen in MRSA.<sup>[30]</sup> In comparison, the rates of VRE are slightly lower.<sup>[31]</sup>

### PATIENT SAFETY

Patient safety is the absence of preventable harm to a patient during the process of healthcare. The discipline of patient safety deals with the coordinated efforts to prevent harm, caused by the process of healthcare itself, from occurring to patients.<sup>[7]</sup>

### GLOBAL SAFETY CHALLENGES

The World Alliance for Patient Safety identifies specific areas for action which address significant risk to patient safety, relevant to all countries. Thus, the World Alliance selects a new and important global patient safety issue and establishes a program to tackle this.<sup>[5,8,32]</sup> It devices modules and guidelines to stimulate country-level actions on this issue. These programs are called the Global Patient Safety

Challenge (GPSC). The topic of the challenge is selected every 2 years, based on a significant risk to patients in every World Health Organization (WHO) member state. The WHO has been entrusted with the task of framing global norms and standards and supporting country efforts in developing patient safety policies and practices.

In view of the increasing burden of HCAs in developed, transitional, and developing countries; the topic for the first global patient safety challenge has been very appropriately chosen as HCAs. This challenge focuses on creating awareness and reducing the burden of HCAs as a vital element of patient safety. The theme of this challenge, promulgated for 2005-2006 was "Clean Care is Safer Care" (CCiSC). A key objective of the program was to launch a feasible and practical approach to improve hand hygiene in healthcare globally.<sup>[1,2,5,33]</sup>

With the slogan of CCiSC, the first global challenge aims at implementing several actions to reduce HCAI worldwide, irrespective of the level of development of a country or its healthcare systems and the availability of resources. The four major objectives of the first challenge were: Awareness raising about the problem and impact of HCAI on patient safety; building commitment from countries, that is, motivating Country Pledges to tackle HCAs as a priority; to draft recommendations based on scientific evidence to promote hand hygiene in health set-ups; and to field test the implementations of the new WHO Guidelines on Hand Hygiene in Health Care.<sup>[1,2,5,32,33]</sup>

The ultimate objective of all these actions is to enable acceptance of hand hygiene as a basic healthcare activity or a fundamental procedure during delivery of healthcare which will reduce the risk of infection. Thus, the first challenge envisages the institutionalization of hand hygiene in each member country, with the help of the WHO guidelines.

### **HAND HYGIENE AS THE FOUNDATION OF CLEAN CARE IS SAFER CARE**

Since hand hygiene has been proven to reduce infections in HCFs, a major action within the global challenge is to promote its implementation in healthcare segments globally as well as at country level. In order to provide healthcare workers, hospital administrators, and health authorities with the best scientific evidence and recommendations to improve practices and reduce HCAs; the WHO had developed new guidelines on Hand Hygiene in Health Care (advance draft). Thus, one of the major actions to improve patient safety within CCiSC

is to advance hand hygiene as the basic foundation of infection prevention.<sup>[8,33-36]</sup>

Towards this end, an international awareness raising campaign has been initiated, focusing primarily on hand hygiene. Such campaigns would promote political and administrative support and action. The following actions have been strategized to implement universal hand hygiene: System change; availability of alcohol-based hand rubs at point of care; access to soap and clean running water; training and education; monitoring and evaluation; reminders in the work place; and institutional safety climate, including patient partnership activity.

### **TACKLING ANTIMICROBIAL RESISTANCE: THE THIRD GLOBAL PATIENT SAFETY CHALLENGE**

In 2008, the World Alliance for Patient Safety announced its 3<sup>rd</sup> Global Patient Safety Challenge: Tackling Antimicrobial Resistance. The work builds upon previous works of the WHO, particularly the Global Strategy for Containment of Antimicrobial Resistance published in 2001. The new project, under the leadership of David Heymann and Didier Pittet, is facilitating an international coalition to address the threat to patient safety posed by antimicrobial resistance. At a first international consultation in July 2008, at WHO headquarters in Geneva, it was agreed that the 3<sup>rd</sup> Patient Safety Challenge will concentrate on five key action areas:<sup>[37]</sup>

- Animal husbandry, aquaculture, and agriculture; including the examination of the regulation of antimicrobial use in food production processes.
- Infection control including the promotion of simple and effective interventions to reduce transmission of resistant microbes in both hospital and community settings.
- Rational drug use and regulation including access, quality, and misuse of antimicrobial agents.
- Research and development of efficient and affordable diagnostic methods to support rapid, targeted treatment, and new antimicrobial agents including vaccines and alternative therapies.
- Surveillance including developing laboratory capacity and the development of a long-term strategy to collect and report high quality data in a systematic fashion.

The work is being undertaken in two stages. During the initial 'foundation' period in 2008 and 2009, five expert working groups met to formulate a WHO Global Work Plan for Antimicrobial Resistance. In 2010, WHO launched the 'challenge' component, encouraging all member states to sign up to an intervention, or a focused bundle of interventions, to reduce the threat of resistance.



On 8 March, 2012, WHO launched a new book “The evolving threat of antimicrobial resistance-Options for action”. It examines the experiences with interventions which address the growing threat of antimicrobial resistance, describes the lessons learnt along the way and highlights the gaps still remaining. It draws attention to areas where knowledge is lacking and where urgent action is still needed.

It is hoped that formulation and implementation of these challenges will truly catalyze actions towards reduction of HCAs and antimicrobial resistance, thereby benefitting the patients and the healthcare community at large.

### Where does India stand with respect to patient safety?

India was the first SEARO country to pledge support to the CCiSC campaign. This was done on 14<sup>th</sup> June, 2006. As part of the 1-day meeting, a technical session on infection prevention was held with participation from various experts.<sup>[38]</sup>

### Road ahead

It is now time that implementable policies and affirmative actions are taken to prevent the dissemination of MDR pathogens in Indian hospitals; stop the rampant misuse of antimicrobials; and ultimately, provide an environment of patient safety in all types of HCFs of our country.

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