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PANRESISTANT SUPERBUGS: ARE WE AT THE EDGE OF A 'MICROBIAL HOLOCAUST'

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Contemporary healthcare has progressed towards world health security through advancements in medication-based and surgical interventions, supported by the success of antimicrobial therapy. The emergence of panresistant infectious diseases is becoming a public health problem worldwide. Panresistance is attributable to a complex interplay of antimicrobial overuse in healthcare facilities due to lack of regulatory commitment in the backdrop of natural mutations in pathogens and rise in immunocompromised hosts. Developing countries are facing the brunt in epidemic proportions due to strained public health infrastructure and limited resource allocation to healthcare. Panresistance is a biological, behavioural, technical, economic, regulatory and educational problem of global concern and combating it will require concerted efforts to preserve the efficacy of the available antimicrobials. An intensified commitment needs to be taken up on a war footing to increase awareness in the society, increase laboratory capacity, facilitate antimicrobial research, foster emphasis on infection control and antimicrobial stewardship, and legislation on manufacturing, marketing and dispensing of antimicrobials.

KEY WORDS: **Panresistance; Antimicrobial Resistance; Totally Drug Resistant Tuberculosis; Infection Control; Antimicrobial Stewardship.**

Introduction

Infectious diseases of the antiquity such as plague, cholera, influenza, smallpox, measles and malaria, which have been responsible for claiming billions of lives, have either been eradicated, eliminated or controlled in various parts of the globe due to advanced antimicrobial therapeutics and vaccines. The discovery of penicillin in 1940s and consequent success at wound healing and survival of soldiers in World War II was a major breakthrough in the history of mankind. The subsequent discovery of a series of antimicrobials, some 22 of them credited to Selman Waksman, brought the menace of infectious diseases and ensuing sepsis under control. Antimicrobials conferred safety and reliability upon a wide variety of diagnostic and therapeutic procedures including advanced surgeries, organ transplantation and immunotherapy, being heavily dependent on antimicrobial support.

While the era of infectious diseases was being considered over, backed upon the success of antimicrobial therapy, there was re-emergence of infectious diseases due to rise in immunocompromised populace. The resurgence of infectious diseases consequent to Human Immunodeficiency Virus (HIV)-Acquired Immune Deficiency Syndrome (AIDS) pandemic resulted in 1.5 fold increase in infectious diseases mortality between 1980 and 1992. HIV-AIDS became the leading cause of mortality amongst infectious diseases in the following two decades [1]. Antimicrobial resistance, being unanticipated in its entirety, evolved manifolds to reach dangerous connotations towards panresistance. World Health Organization (WHO) theme for World Health Day 2011 was

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"Antimicrobial resistance: No action today, no cure tomorrow" [2]. Since then, despite progressive steps towards concept development, the magnitude of panresistance overshadows control efforts [3, 4]. Panresistance is a complete roadblock to years of progress made towards advanced healthcare. With infectious diseases being the second leading cause of mortality worldwide as per global health estimates, the day may not be far when it will be the leading cause of death due to emergence of panresistance emanating the realization of a 'Microbial Holocaust'.

Evolution of panresistance

The rise of panresistance is multifactorial. Microbial factors include natural evolution of microorganisms conferring increase in virulence, infectivity, pathogenicity and antimicrobial resistance. Opportunistic pathogens are crossing host barriers and are now being encountered as emerging pathogens [1, 5, 6, 7]. Established pathogens are evolving into panresistant potentially untreatable mutants such as glycopeptide resistant Gram negative bacteria, which are resistant to all available antimicrobials including tigecycline and colistin. In addition, totally drug resistant tuberculosis, multidrug resistant malaria and dual oseltamivir-adamantane resistant influenza viruses are emerging [8]. Tuberculosis has emerged as the leading cause of mortality amongst infectious diseases overtaking HIV-AIDS due to the development of resistance. Tuberculosis related deaths in 2014 were 1.5 million, surpassing 1.2 million HIV-AIDS related deaths.

Host factors include steep rise in immunocompromised populace owing to increased organ transplants, immunodeficiency disorders, neoplasms, old age as well as patients under intensive-care. Prescription trend factors include aggressive exposure of multiple antimicrobials to patients harbouring multiresistant microorganisms. Rising empiricism in antimicrobial therapy overshadows susceptibility guided therapy, facilitating development of resistance due to selection pressure [9, 10]. Panresistant microorganisms can spread resistance-conferring mobile genetic elements to susceptible microorganisms and commensal flora, contributing to the development of a reservoir of antimicrobial resistance in human body. Panresistant microorganisms can also colonize inanimate surfaces and create reservoirs from which they can get transmitted in healthcare facilities thereby rendering all patients and healthcare professionals at-risk. Human factors involved include a complex interplay of antimicrobial misuse in healthcare facilities due to lack of regulatory commitment in the backdrop of natural mutations which has contributed to the development of panresistance [1, 3]. Panresistance is increasingly being reported in Gram negative microbes [6, 11]. The South and South-East Asia region (SEAR) has one of the highest prevalence of tuberculosis with one death every few minutes [12]. All forms of resistant tuberculosis viz. Multi drug resistant tuberculosis (MDR TB), extremely drug resistant tuberculosis (XDR TB) and totally drug resistant tuberculosis (TDR TB) have been reported. The recent reports of TDR TB from Iran, India and Italy represent the tip of an iceberg as antitubercular susceptibility testing occurs in only 5% patients worldwide [12-15]. The DOTS (Directly Observed Treatment Short course) program for developing countries has been challenged by the emergence of XDR TB and TDR TB not only due to resistance but also due to limitations of antitubercular susceptibility testing, which is offered only at highly specialized centres. A seven year study on DOTS plus reported 61% cure, 19% deaths, 18% defaulters, 3% failed treatments and an average delay of 5 months in initiation of therapy [16]. Antimalarial resistance to artemisinin and quinine has been reported in SEAR and Africa [17, 18]. Antiviral resistance to almost all antivirals has been reported particularly in Hepatitis B, Herpes virus, Cytomegalovirus, Varicella zoster, Influenza and HIV [19–23].

Impact of panresistance

The emergence of panresistant infectious diseases is becoming a public health problem worldwide. Developing countries are facing the brunt in epidemic proportions due to strained public health infrastructure and limited resource allocation to healthcare. The rise of panresistance is discouraging the development of newer antimicrobials under private equity. Any new antimicrobial loses economic value in a few years due to emergence of resistance compared to medicines for lifestyle diseases which remain economically rewarding for many years [24, 25]. Inadvertent or intended release of panresistant bioweapons against humans, fauna and flora can wreak havoc leading to widespread disruption [26].

The future

Panresistance is a biological, behavioural, technical, economic, regulatory and educational problem of global concern and combating it will require concerted efforts to preserve the

efficacy of available antimicrobials. An intensified commitment needs to be taken up on a war footing.

Knowledge, Attitude and Practices of General Public

Examples from successful programs such as "Antibiotics are not Automatic" in France, "Get Smart" in the US and "Do Bugs Need Drugs?" in Canada need to be followed in developing countries [27]. Health educators, public health specialists, government officials and community leaders should be sensitized about the hazards of using antimicrobials. There should be active community participation in the cause of positive health. Citizens must foster sound belief and inculcate positive attitude and responsible behaviour in societal healthcare system. There is long standing need for increasing awareness about approach, operation, decision making and scope of healthcare amongst general population. Attitude and expectations need a paradigm shift from 'instant cure' and 'magic pill' to 'rational drug therapy' and 'evidence based healthcare'. Patients should not engage into unjustified requests or arguments or frequent change of doctor's advice. Self-medication, quack remedies, underdosing and uncompleted regimens should be stopped. Left over drugs from the last prescription should not be taken again for a similarly perceived symptom. The society should ensure availability of trained pharmacists through legislation to ensure adherence to prescription safety.

Hospital Infection Control

Nosocomial pathogens evolve under continuous selection pressure to become panresistant. Hospital Infection Control involves monitoring of hospital safety measures such as patient isolation, visitor control, contact precautions, barrier nursing, universal prophylaxis, hand hygiene, environmental surveillance and equipment sterilization in operation theatre, labour room, intensive care, oncology, burns, dialysis and transplant centres. Carriers are identified, quarantined and organisms are eradicated from hospital environment. Hand hygiene is considered to be the single most important step in controlling spread of panresistant pathogens. Compliance is limited due to overbearing pressures of patient volume, time, undue multitasking and paucity of washing infrastructure. Hand washing with soap followed by antiseptic handrub should be strongly encouraged as the standard of care for all healthcare practitioners and patients. A broad based policy and standards for infection control in healthcare facilities needs to be implemented. The Jaipur declaration on AMR-2011 for SEAR and the Chennai declaration for India are efforts to this end [25, 28].

Laboratory Surveillance

Laboratory based surveillance of infectious diseases, pathogens, susceptibility patterns, resistance phenotyping, outbreak investigation, hospital environmental surveillance and epidemiological typing is mandated to keep a track of panresistance development. A number of pathogens such as viruses, parasites, certain bacteria and fungi surpass identification under the constraints of resources available in routine labs [1, 5–7]. Antimicrobial susceptibility testing for tuberculosis, parasites, viruses and fungi are only available in reference labs which are far and few. Unavailability of testing facilities promotes empirical antimicrobial therapy to save the patient, thereby contributing to the development of panresistance. Enhancing laboratory capacity with automated phenotypic identification systems, molecular microbiology techniques and biostatistical softwares, precise organism identification to species level, antimicrobial susceptibility patterns, resistance phenotypes, typing and data analysis has been facilitated. The resistogram generated can be used to guide infection control strategies with other collaborating centres through a worldwide free web repository. The potential of the microbiology lab is largely underutilized in developing countries due to deficiencies in lab equipment and specialized staff.

Antimicrobial Stewardship

Antimicrobial stewardship including antimicrobial rotation and holiday, combination therapy and Standard Treatment Guidelines have proven to be beneficial [29, 30]. A dynamic antimicrobial policy should specify as to when escalation and de-escalation to reserve antimicrobials such as carbapenems, colistin, tigecycline, vancomycin, teicoplanin and daptomycin, needs to be undertaken. Spiralling empiricism, prophylactic antimicrobial usage and attitude to use the best antimicrobial should be discouraged and susceptibility guided therapy be promulgated [1, 5–7]. Regular availability of required antimicrobials, prescription audits, formulary restriction, pre-authorization and stop orders should be advocated to ensure policy implementation which in turn should be linked to grant of accreditation to hospitals. A multidisciplinary approach would include building of consensus across

clinicians and arbitration of disagreements. The WHO classification of antimicrobials into key, watch and reserve groups in Jun 2017 can form a guideline towards the successful implementation of antimicrobial authorization and prescription prudence [31].

Health Resource Allocation

The present situation demands an increase in resource allocation in the health sector to boost healthcare infrastructure, public awareness and accessibility. This would entail accommodative policy for establishment of specialized medical varsities, superspeciality hospitals, specialized laboratories, biocontainment facilities, promotion of antimicrobial research through grants, medical journals, medical societies, involvement of private sector through public private partnership and mass health campaigns. Comprehensive standards for surveillance and control should be established in association with international health regulations [32]. National surveillance systems similar to the National Nosocomial Infection Surveillance (NNIS) in the US and SENTRY Antimicrobial Surveillance Program can be instituted [32].

Antimicrobial Research

Research on the development of newer antimicrobials has multipronged implications. One, effective antimicrobials would foster prompt treatment of infections caused by resistant pathogens and prevent progression to disseminated infection and sepsis. Two, successful therapy will reduce transmission of resistant pathogens. Three, chemoprophylaxis can be directed for prevention of infections in susceptible host population. Four, behavioural research regarding non-adherence to prescribed drug schedules and self-medication are social issues in which there has been limited research. Research needs to be undertaken on these behavioural factors, so that targeted intervention can be planned for bringing about changes at the societal level.

Public Health Measures

Robust public health infrastructure and human resource with strengthened vector control programs, immunization coverage, screening programs, national health programs, rapid outbreak investigation, quarantine and control measures are required. Panresistant infectious diseases and resistant pathogens should be made notifiable. Effective public health will reduce reliance on antimicrobials and break chain of transmission of resistant microbes [25].

Legislation on Manufacturing, Marketing and Dispensing of Antimicrobials

Three important areas of intervention exist at manufacturing, marketing and dispensing of antimicrobials. Quality assurance in antimicrobial dosage and efficacy from manufacturers and ethical marketing can have profound downstream effects. While regulation regarding prohibition of sale of antimicrobials without proper prescriptions is in place, it is not being implemented. Regulatory mechanisms for ensuring good manufacturing practices, responsible marketing and dispensation by pharmacists need to be instituted and strengthened through industrial and marketing audit, and enhanced vigil on pharmacies. Antimicrobial and infection control advisory bodies need to be actively involved to integrate surveillance and legislation.

Role of WHO

WHO has issued a call for action to halt the spread of AMR by introducing a six-point policy package for all countries to combat AMR. This includes commitment to a comprehensive, financed national plan with accountability and civil society engagement; strengthening of surveillance and laboratory capacity; ensuring uninterrupted access to essential medicines of assured quality; regulation and promotion of rational use of medicines, including in animal husbandry, and ensuring proper patient care; reduction of antimicrobials usage in food-producing animals; enhancing infection prevention and control; and fosterage of innovations and research and development for new tools [2]. WHO has also laid down the procedure to establish national laboratory based surveillance including identification of pathogens and diseases of public health importance, creation of network of Antimicrobial Susceptibility Testing (AST) and standardization of involved methodologies. World bodies such as Association for Prudent Use of Antimicrobials (APUA) and World Alliance against Antibiotic Resistance (WAAR) are efforts to this end [33]. WHO has advocated a priority pathogens list in 2017 to highlight a list of bacteria for which newer antimicrobials are urgently required [34]. WHO has classified antimicrobials into key access, watch group and reserve group to optimize usage guidelines worldwide [35].

Conclusions

Panresistance is emerging in alarming proportions worldwide, thereby threatening the advances made towards public health

security of the world. There is a dire need to identify this threat, develop concerted multipronged strategy, develop infrastructure, foster expertise and take coordinated and urgent steps to tackle the serious public health challenge. It is time for action else we face the consequences of microbial genocide of mankind. Resolute conviction towards astute measures with a sustained momentum will hold a promise for safeguarding health of future generations.

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