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Crisis of Antibiotic Resistance -A Definite Ban on Healthcare

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Abstract: *Anti-microbial resistance patterns can vary regionally and even among different hospitals within the same community. Infections are the most common reasons for patients to seek medical advice and for antibiotics to be prescribed. Inappropriate or indiscriminate use of antibiotics can increase the cost of care by increasing drug cost, increasing toxicity, increasing resistance, and increasing laboratory costs. Prophylactic antibiotic use in some hospitals remains a problem. Antibiotics are prescribed unnecessarily and empirically for complaints where no antibiotic is required or where culture and sensitivity results could be safely awaited. The key action by the clinician should be the provision of a specimen for accurate identification of the offending pathogen by means of culture and sensitivity method. The pharmacist can present information at the point of care regarding antibiotic susceptibility and individual patient factors to improve antibiotic prescribing. The pharmacist can play a significant role in recommending the prescriber about the necessary changes to be made in the patient regimen, dose, and duration of antibiotic therapy.*

Keywords: *Antibiotic resistance,sensitivity pattern,rational prescribing*.

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Antibiotic resistance among bacteria is becoming more and more serious problem throughout the world. Resistance to antibiotics was declared a major global threat to public health by the World Health Organization (WHO).It is said that evolution of bacteria towards resistance to antimicrobial drugs, including multidrug resistance, is unavoidable because it represents a particular aspect of the general evolution of bacteria that is un-stoppable. Antibiotic resistance emerges commonly when patients are treated with empiric antimicrobial drugs. To overcome these difficulties and to improve the outcome of serious infections in our institutions, monitoring of resistance patterns in the hospital is needed. A number of studies have been carried out in the west to monitor antimicrobial resistance at national level. The academic and educational value of these studies is particularly useful for microbiologists and infectious disease clinicians. The data collected from these studies are useful in improving antimicrobial use in those communities. In our setting, establishment of surveillance programs to monitor the true extent of resistance at the local, regional and national levels is urgently needed. This will help in monitoring emerging trends in resistance at the local level to support clinical decision making, infection – control interventions, and antimicrobial – resistance containment strategies.

India has emerged as the world's largest consumer of antibiotics with a 62% increase in popping habits over the last decade. India's antibiotic use went up from 8 billion units in 2001 to 12.9 billion units in 2010.The study "Global Trends in Antibiotic Consumption, 2000-2010," by scientists from Princeton University has found that worldwide antibiotic use has risen a staggering 36% over those 10 years, with five countries — Brazil, Russia, India, China and South Africa (BRICS) — responsible for more than three-quarters of that surge.

As the world braces for its worst ever threat in the last century - global antibiotic resistance due to unnecessary and unregulated popping of antibiotics, an average Indian has been found to be popping over 11 antibiotic pills a year. That's five days of antibiotics for every person in the country which is much lesser than the Chinese or Brazilians. An average Chinese popped 7 antibiotic pills a year."This is both good news and bad news. It means that more Indians are able to access antibiotics, which are particularly important for those who previously died of easily treatable infections. However, the massive increase in use, both appropriate and inappropriate, is leading to increases in drug resistance. Antibiotic use is the single most important reason for resistance. Also use of last resort drugs like carbapenems has gone up significantly in India, and it is difficult to justify why such powerful antibiotics are being use so much more frequently".Continuing surveillance for the antibiotic resistance of respiratory pathogens is a recognized public health need, particularly in those countries with high resistance rates, since initial antimicrobial treatment for patients with bacterial community .

Methicillin resistant Staphylococcus aureus (MRSA) is a very versatile and dangerous organism causing infections ranging from mild skin and soft tissue to life threatening infections. MRSA can be defined as the strains of *S. aureus* that are resistant to the isoxazoyl penicillins such as methicillin,oxacillin and

flucloxacillin. The infections caused by methicillin-resistant Staphylococcus aureus increase the length of hospital stay, and are also responsible for rising health care expenses, morbidity and mortality[4].

In Indian hospitals based on antibiotic sensitivity test, Glycopeptides are widely used for the prophylaxis and treatment of various gram-positive infections. Vancomycin (IV administration) once considered the gold standard for the treatment of multidrug resistant (MDR) *S. aureus*, and is being used to treat other infections, such as pseudomembranous colitis due to *Clostridium difficile* and coagulase-negative staphylococci (CoNS) infections in hospitalized patients[5].

Linezolid, a member of the new oxazolidinone class of antibiotics, is highly active in vitro against MRSA and has excellent oral bioavailability and does not require monitoring of levels (Therapeutic drug monitoring not required as for vancomycin). Cumulative data indicates that linezolid and vancomycin have similar efficacy against MRSA infections. A study carried out in USA in year 2005 indicated that intravenous or oral linezolid was well tolerated and is superior to vancomycin in treating patients with MRSA. Linezolid, in contrast to other anti-MRSA agents, is 100% bioavailable after oral administration. In conclusion, empirical intravenous-to-oral linezolid therapy was safe, well tolerated, and as effective as vancomycin in the treatment of nosocomial infections due to MRSA[7].

Correct Approach For Resistance Detection [1]

Two acceptable primary test methods are

(a) MIC (Minimum Inhibitory Concentration) method plus vancomycin screen plate and

(b) Disk diffusion. Based on this, possible VISA (Vancomycin Intermediate Staphylococcus Aureus) and VRSA (Vancomycin Resistant Staphylococcus Aureus) strains are identified.

The clinical microbiology laboratories must ensure using detection methods with good sensitivity and specificity. Failure with Vancomycin occurs due to its slow bactericidal activity and it increasing MICs. Alternative therapies should be considered where vancomycin MIC is >1 g/mL to avoid treatment failure. Early recognition of isolates resistant to the newer antibiotic agents is of paramount importance, and will allow appropriate treatment of affected patients.

Common Mechanisms of Resistance in Methicillin-Resistant Staphylococccusaureus[5]

1)Resistance to β-lactam antibiotics in methicillin-resistant *Staphylococcus aureus* is caused by the production of a β-lactamase enzyme (penicillinase) and a low-affinity penicillin-binding protein (PBP)

2) High-level resistance to glycopeptides is caused by the replacementof the last amino acid of peptidoglycan precursors (D-alanine [D-Ala] to D-lactate [D-Lac]).

3) Low-level resistance to glycopeptides is associated with increased synthesis of peptidoglycan, "trapping"the antibiotic in outer layers and preventing its interaction with precursors exiting the cytoplasm through the cell membrane.

4) Mechanisms of resistance involve mutations or modifications in either the DNA or ribosomal RNA(rRNA). D-Glu denotes D-glutamate, L-LysL-lysine, and UDP-GluNAc uridine diphosphate*N*-acetylglucosamine.

High vancomycin MIC for MRSA which are susceptible to vancomycin may indicate the drug resistance to many antibiotics. Until recently, carbapenems, such as imipenem, were almost uniformly active against resistant gram-negative organisms, but some strains have not developed very effective ways to deal with the carbapenems, including the production of β-lactamases (designated carbapenemases) that demolish the carbapenems; changes in outer-membrane porins that block the entry of these antibiotics; and active pumping of the antibiotic out of the cell using complex "efflux pumps." The resurrected polymixins (e.g., colistinwith or without rifampin) are often the only available alternativefor some pan-resistant gram-negatives, particularly acinetobacteral though toxicity (mainly renal) is still a problem, and reports of resistance are emerging. It is more difficult than ever toeradicate infections caused by antibiotic-resistant "superbugs," and the problem is exacerbated by a dry pipeline for new antimicrobials with bactericidal activity against gram-negative bacteria and enterococci [6].

Strategies to Reduce Antibiotic Resistance [3]

1)Appropriate antibiotic prescribing

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is the premier global surveillance system on antimicrobial resistance of microbes. Data from SMART studies show that the level of antimicrobial resistance differs by geographic region and is highest in Asia-Pacific countries, like in the case of patients with appendicitis. Latest results from the SMART study also showed that the ESBL-positive rates in *E. coli* isolated from intra-abdominal infections (IAIs) in the Asia-Pacific region almost doubled between 2002 and 2010 to 40.8%. Carbapenems(imipenem and ertapenem), is particularly a threat to the successful treatment of

enterobacterial infections, in addition to being a cause for lack of drugs for antibiotic-resistant Gram-negative pathogens.

In community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and healthcare-acquired pneumonia (HCAP), an adequate understanding of each type of infection can provide physicians with more informed choices of antibiotics and thus, help in preventing the development of resistance. As in cases of IAIs and nosocomial pneumonia, adherence to guidelines for appropriate prescribing of effective antibiotics (e.g., carbapenems) can minimize the selection of new resistance.

2)Antimicrobial Stewardship Programs

Many institutions conduct Antimicrobial Stewardship Programs (ASPs) to optimize antimicrobial therapy, reduce treatment-related cost, improve clinical outcomes and safety, and reduce or stabilize antimicrobial resistance. Typically, ASPs are executed by multidisciplinary antimicrobial utilization teams comprising physicians, pharmacists, microbiologists, epidemiologists and infectious disease specialists, with adequate experience in their respective fields. Many studies demonstrated that ASPs have the potential to restrict the emergence and spread of resistance.

ASPs are based primarily on education, coupled with the "front-end" interventions (e.g., restricting the availability of selected antimicrobial agents) or the "back-end" interventions (e.g., reviewing broad-spectrum empirical therapy and then streamlining or discontinuing therapy on the basis of antimicrobial susceptibility testing (AST) results and clinical response). In the "front-end" interventions, the following aspects can be included: (i) the development of situation-specific treatment guideline; (ii) education of prescribers; (iii) AST; (iv) accurate organism-identification; (v) understanding pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs which helps selecting optimal dose and duration of antibiotics; (vi) minimizing the effect of antibiotics on the microbiota and host immune homeostasis; and (vii) formulary restriction and preauthorization.

For determining the optimal dosing regimen with minimal induction of resistance, the two useful points of reference are minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC). Emergence of resistance occurs within in the frame of a selective compartment, termed as the mutant selection window (MSW): the lower boundary corresponds to the MIC of the susceptible cells, whereas the upper boundary, the MPC, restricts the growth of the entire population including the resistant mutants. In recent years, novel approaches for the rapid detection recent years, novel approaches for the rapid detection of resistance in bacterial pathogens are developed. Included among these are the PCR-based techniques, mass spectrometry, microarrays, microfluidics, flow cytometry, isothermal microcalorimetry (IMC), cell lysis-based approaches and whole-genome sequencing, whose ability to detect resistance in various bacterial species has been demonstrated.

Although the therapy can be continued indefinitely, at the discretion of the treating clinician, for 48–72 h after initial antimicrobial prescription, post-prescription review by multidisciplinary antimicrobial utilization teams is required to either modify or discontinue treatment, depending on the clinical responses and guidelines; also, appropriate feedback can be provided to prescribers in order to modify or discontinue therapy.

3. Education

Much of the success of ASPs depends on educating the clinicians, especially on making their everyday treatment decisions. To optimize antimicrobial prescribing, the prescribers should have appropriate knowledge of general medicine, microbial virulence, immunological and factors, PK and PD properties of drugs, and basic knowledge of epidemiology. On the other hand, they have a responsibility to future patients and to public health in sustaining the efficiency of antibiotics and minimizing antibiotic resistance. The Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infection (ARHAI) was established to educate both healthcare professionals and the public. The public education subgroup took on the public-facing antimicrobial campaigns. These public campaigns can induce in outpatients the habit of more prudent use of antibiotics, especially in high-prescribing countries. The professionals must give the public clear information about the duration of symptoms, self-care, benefits and limitations of antibiotics, and antibiotic resistance.

4. Hygiene and Disinfection

Although the main source of MDR pathogens is thought to be the endogenous flora of patients, healthcare workers are also considered an important source. The Centers of Disease Control and Prevention (CDC) offered guidelines for preventing nosocomial transmission of MDR bacteria in hospitals. Transmission of healthcare-associated pathogens through the hands of healthcare workers is particularly the most common cause for spreading.

Many studies have demonstrated that the gloves or gowns of healthcare workers can be colonized with MDR pathogens, such as MRSA or VRE. And, environmental cleaning in hospitals is also associated with a reduction in the transmission of healthcare-associated pathogens, including MRSA, VRE(Vancomycin resistant enterococci), and *C. difficile*, and *Acinetobacter* species.

5. The Development of Novel Antibiotics

A limited number of antibiotics targeting Gram-negative bacteria, such as polymyxin/colistin with high MWs, can penetrate the outer membrane of Gram-negative bacteria using active transport . However, some novel classes of agents against MDR Gram-positive pathogens, such as MRSA, are currently in diverse stages of development and are undergoing clinical trials. Unlike conventional antimicrobial drugs, new strategies are also presented for the treatment of microbial diseases, such as host defense peptides, bacteriophages, vaccines, immunoglobulins, and probiotics[3]. Then MRSA began developing resistance to glycopeptides, first evolving, through largely undefined mutations, low-level resistance to vancomycin, which was associated with a thickening of the pathogen's cell walls[3].

Such isolates were designated VISA, for vancomycin (or glycopeptide) intermediately resistant*S. aureus*. VISA is difficult for clinical laboratories to detect, but its presence is associated with the therapeutic failure of glycopeptides. Though multidrug resistant *Pseudomonas aeruginosa* and acinetobacter are the best known therapeutic challenges among the gram-negative bacteria. Until recently, carbapenems, such as imipenem, were almost uniformly active against resistant gram-negative organisms, but some strains have now developed very effective ways to deal with the carbapenems, including the production of β-lactamases (designated carbapenemases) that demolish the carbapenems; changes in outer-membrane porins that block the entry of these antibiotics; and active pumping of the antibiotic out of the cell using complex "efflux pumps."

The carbapenems be classified into three groups:

Group 1 includes broad-spectrum carbapenems, with limitedactivity against non-fermentative Gram-negative bacilli, that areparticularly suitable for community-acquired infections (e.g. ertapenem);

Group 2 includes broad-spectrum carbapenems, with activity against non-fermentative Gram-negative bacilli, that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem);

Group 3 includes carbapenems with clinical activity against MRS

The higher groups in the proposed classification scheme reflect an increasing antimicrobial spectrum against resistant organisms (i.e. non-fermentative Gram-negative bacilli and MRS) [5].

I. Conclusion

As with the introduction of any new antimicrobial,antimicrobial susceptibility patterns should be monitored overtime. Based on the recommended pattern of use, the risk of resistance development should be low and should not preclude the use of this agent in the appropriate clinical setting. Several compounds have been developed or resurrected to treat grampositive infections. However, the available agents have important limitations: none have been shown to work better than vancomycin against MRSA; quinupristin–dalfopristin and linezolid, daptomycin has sometimes failed against MRSA and enterococci, and resistance to it has emerged[6].

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