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Review Article

Infectious Diseases Section

The Beta Lactam Antibiotics as an Empirical Therapy in a Developing Country: An Update on Their Current Status and Recommendations to Counter the Resistance against Them

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ABSTRACT

In a developing country like India, where the patients have to bear the cost of their healthcare, the microbiological culture and the sensitivity testing of each and every infection is not feasible. Moreover, there are lacunae in the data storage, management and the sharing of knowledge with respect to the microorganisms which are prevalent in the local geographical area and with respect to the antibiotics which are effective against them. Thus, an empirical therapy for treating infections is imperative in such a setting. The beta lactam antibiotics have been widely used for the empirical treatment of infections since the the discovery of penicillin. Many generations of beta lactams have been launched with, the claims of a higher sensitivity and less resistance, but their sensitivity has drastically decreased over time. Thus, the preference for beta lactams, especially the cephalosporins, as an empirical therapy, among the prescribers was justified initially, but the current sensitivity patterns do not support their empirical use in hospital and community acquired infections. There is a need for increasing the awareness and the attitudinal change among the prescribers, screening of the antibiotic prescriptions, the strict implementation of antibiotic policies in hospital settings, restricting the hospital supplies and avoiding the prescriptions of beta lactams, a regular census of the local sensitivity patterns to formulate and update the antibiotic policies, upgradation of the laboratory facilities for a better and faster detection of the isolates, proper collection, analyses and sharing of the data and the encouragement of the research and development of newer antibiotics with novel mechanisms of action.

Key Words: Beta lactams, Empirical use, Resistance, MRSA, ESBL, AmpC, MBL, HLAR

INTRODUCTION

When Alexander Fleming unearthed the mould that killed *Staphylococcal* colonies in his culture plate, he pioneered the antibiotic revolution by providing the source of the wonder drug, penicillin, the first beta lactam antibiotic. Ever since this landmark discovery and the remarkable success story of its use, when Howard Florey smuggled that mould out to America to help the Allied forces win the Second World War, the beta lactam ring has been one of the major weapons we have had against bacteria [1]. Numerous novel molecules have been discovered after penicillin and its derivatives (Amoxicillin and Methicillin). Many of them have a beta lactam ring as an integral part of their chemical structure, such as the cephalosporins, monobactams (Aztreonam), cephamycins and the carbapenems (Imipenem and Meropenem).

The international market of consumption of these beta lactam antibiotics amounts to annual sales of about US $15 billion and it makes up 65% of the total antibiotics market. The annual consumption of penicillin G acylase is estimated to be in the range of 10–30 million tons and this is increasing with time [2].

Over the years, the beta lactams like the cephalosporins have become first choice empirical use antibiotics in many infections that a physician encounters on a day to day basis. In India or in any other developing country, where the patients have to bear the cost of their healthcare, the microbiological culture and the sensitivity testing of each and every infection is still a distant dream. Though there are definite policies/standard treatment guidelines for the appropriate use of antimicrobials in specific national health programmes e. g. RNTCP (Revised National Tuberculosis Control Programme), NACP (National AIDS Control Programme) and NVBDCP (National Vector Borne Disease Control Programme), there are none for other diseases of public health importance like enteric fever, diarrhoea/dysentery, pneumonia, etc. Moreover, there are lacunae in the proper data storage, management and the sharing of the knowledge on antibiotic susceptibility testing for use by clinicians/public health experts/programme managers [3]. So, an empirical therapy for infections is a practical solution for the prescribers in such a setting. Whenever a physician encounters an infection, he/she has little locally applicable data to refer to and instead has to fall back on the recommendations which are based on the data of the western countries. In the worst case, he/she is influenced by the promotional literature of the medical representatives who are desperate to fulfill the monthly target sales of the drugs which are thrust upon them by their respective manufacturing companies [4]. Most of the hospitals in India do not have a standardized antibiotic policy or a constant infection surveillance program, wherein the microbiologist's advice on the physician's prescribing decision is fully utilized [3].

In this background, we are presenting this article to review the current status of the empirical use of the beta lactam antibiotics, keeping in view the micro-organisms which we encounter and their resistance patterns all over the world in general, with a focus

on the situation in India, in particular. We are also presenting a few possible solutions to counter the problem of antimicrobial resistance in general and beta lactam resistance in particular.

INDICATIONS FOR THE EMPIRICAL USE OF THE BETA LACTAM ANTIBIOTICS

The indications for using the beta lactam antibiotics vary from small boils, carbuncles, respiratory and urinary tract infections, ear or eye infections and gonorrhoea to life threatening conditions like ventilator associated pneumonia, meningitis, septicaemia and gangrene to a prophylactic use in bacterial endocarditis, agranulocytosis or in other immunocompromised situations and the prophylaxis of surgical site infections which are secondary to proper aseptic and antiseptic measures [5].

In this context, there are certain prevailing notions among the prescribers with respect to the effectiveness of the beta lactam antibiotics, that need our attention:

1. The beta lactam antibiotics are effective against most of the bacteria which we encounter in any kind of infection.
2. The combination of the beta lactams with beta lactamase inhibitors, is effective against the more resistant kind of organisms.
3. The higher the version, the greater is the sensitivity of the antibiotic against organisms, e.g., among the cephalosporins, the 3rd generation > the 2nd generation > the 1st generation.

We will address the merit of these beliefs on the basis of the current beta lactam sensitivity patterns globally and in India.

INDICATIONS FOR THE BETA LACTAMS AND THE RESISTANCE PATTERNS OF THE COMMONLY ENCOUNTERED ORGANISMS IN THE CLINICAL PRACTICE

Let us first discuss about the bacteria which we commonly encounter as the common causes of infections and their resistance patterns, for a better understanding of the problem. The preliminary background information about the mechanisms of resistance is given in [Table/Fig-1].

The Beta Lactamase Producers and the Beta Lactams

Staphylococcus aureus, *Hemophilus influenzae* and *E coli* produce beta lactamases which can hydrolyze the penicillins but not all the cephalosporins. Other beta lactamases which are produced by *Pseudomonas, Enterobacter, Neisseria gonorrhoeae* and *Moraxella catarrhalis* have the ability to hydrolyze both the penicillins and the cephalosporins [6].

MRSA and the Beta Lactams

Shortly after the introduction of penicillin, resistant strains of *S. aureus* were isolated. This led to the development of methicillin, for treating the resistant strains. However, Methicillin-Resistant

Entity	Definition	Found In	Choice Antibiotic (Reserve Drug)
Beta lactamases	Hydrolytic enzymes secreted by bacteria which cleave the beta lactam ring, the structural skeleton of any beta lactam antibiotic.	Most bacteria e.g., *Staphylococcus aureus*, *Hemophilus influenzae* and *E coli*	*Methicillin* (Resist the enzymatic action of Beta lactamases) Beta Lactam – beta lactamase inhibitor combination (beta lactamase inhibitor destroys the hydrolytic enzyme beta lactamase produced by the bacteria)
MRSA (Methicillin-resistant *Staphylococcus aureus*)	Due to conformational change in the receptor for antibiotic binding, the Penicillin binding protein 2a (PBP2a), no beta lactam antibiotic can bind to the receptor, rendering Methicilin resistant. Presently seen in all beta lactam antibiotics.	*Staphylococcus aureus*	Vancomycin, Linezolid or other antibiotic without a beta lactam ring
HLAR (High level aminoglycoside resistance)	Natural drug of choice for enterococcus infection is aminoglycoside with penicillin which acts synergistically on cell wall and ribosome of the bacteria. In HLAR, due to resistance to aminoglycoside antibiotics, synergism is lost rendering penicillin resistant.	*Enterococcus* (Inherently Cephalosporin resistant)	Vancomycin, Linezolid
VRE Vancomycin resistant *Enterococcus*	Due to conformational change in the cell wall receptor, vancomycin becomes resistant.	*Enterococcus*	?
ESBL (Extended spectrum beta lactamases)	Enzymes produced by a variety of Gram negative bacteria which confer an increased resistance to commonly used antibiotics. They hydrolyse cephalosporins and monobactams, but not cephamycins or carbapenems.	Most Gram negative bacteria like *E.coli, Klebseilla, Proteus*	Beta lactam – beta lactamase inhibitor combination/Carbapenem, Cephamycins
AmpC beta-lactamases:	A type of beta lactamase, whose over-expression confers resistance to broad-spectrum cephalosporins, monobactams, including cephamycins and Beta lactam–beta lactamase inhibitor combination.	Most Gram negative bacteria like *E.coli, Klebseilla, Proteus*	Carbapenem
Carbapenemases MBL, KPC Metallo-beta lactamases (MBL), Klebsiella producing carbapenemases (KPC)	Enzymes produced by bacteria, which destroy all beta lactam antibiotics, including Carbepenem group.	*Acinetobacter, Pseudomonas* and now also in Most Gram negative bacteria like *E.coli, Klebseilla, Proteus*	Polymixin B and E (Colistin), Tigecycline, Fosfomycin

[Table/Fig-1]: Shows the mechanisms of resistance to beta lactams

Staphlococcus Aureus (MRSA) was quickly noted, wherein the beta lactam antibiotics were totally ineffective [7]. Even ceftobiprole, a new fifth generation cephalosporin with a different mechanism, is starting to show signs of resistance [8,9].

The US based Centers for Disease Control and Prevention (CDC) reports that MRSA currently causes 1% of all *Staphylococcus* infections and more than 50% of the healthcare associated *Staphylococcus* infections in the US. MRSA causes 78% of the skin and soft tissue infections in the community and about 64% of the hospital-acquired and 14% of the community-associated invasive infections [10]. In India also, the incidence of MRSA is increasing, with prevalence rates which vary from 23.6 % to as high as 59.3% [11-13]. In fact, vancomycin, which was regarded as the drug of choice for the MRSA infections, is showing early signs of emerging resistance, leading to a complete loss of options in an infected patient.

High Level Aminoglycoside Resistance (HLAR), Vancomycin Resistant Enterococci (VRE) and the Beta Lactams

The *Enterococcus* spp, *E. faecalis* and *E. faecium* are the normal inhabitants of the intestinal tract, the female genital tract and the oral cavity. *E. faecalis* is the most common species which is isolated from human intestine samples (80-90%), whereas *E. faecium* is found among 5-10% of the isolates worldwide. The enterococci are common nosocomial pathogens, which account for 10% of the hospital – acquired infections in the US. They are responsible for about 16% of the nosocomial urinary tract infections. Most of the strains remain susceptible to the penicillins and vancomycin, but the strains which are resistant to the β-lactams, the aminoglycosides and, increasingly, vancomycin, have been described [14]. All the cephalosporins which are currently in use are resistant to the enterococci [15]. Indian studies have reported a prevalence of HLAR, which ranges from 7.8% to as high as 56% [16-19]. It is interesting to note that the prevalence of resistant organisms has kept on increasing over the years, as has been proved in the chronological sequence of these studies. The prevalence of the Vancomycin Resistant Enterococci (VRE) worldwide is 0 to 20 %, with the prevalence in the US being 22.1% [20]. In India, the prevalence rates which have been detected, varied from 1.4-8% in a few studies [21-24], but one study from Mumbai reported a prevalence of 23% [25].

The Extended Spectrum Beta Lactamase (ESBL) Producers and the Beta Lactams

The extended spectrum beta lactamases (ESBLs) confer an increased resistance to the commonly used antibiotics [26]. The combinations of Beta-lactam with the beta-lactamase inhibitors (e.g, amoxycillin-clavulanic acid) are not optimal for the treatment of serious infections which are produced by the ESBL-producing organisms. Although a significant activity is seen against the ESBLs *in vitro*, the clinical effectiveness of such combinations against serious infections which are caused by the ESBL-producing organisms is controversial. The hyper-producing strains or the infections with a high organism burden (intra-abdominal collections and sepsis) may produce enough beta-lactamase to overcome the effect of the inhibitor. Again, the beta-lactams need to traverse the outer membrane proteins to reach the penicillin-binding proteins. The organisms such as *K. pneumoniae* may become deficient in these crucial outer membrane proteins [27], which can lead to beta lactam resistance.

The prevalence of the bacteria which produce ESBLs varies worldwide, with reports from North America, South America, Europe, Africa, and Asia. The data from the Tigecycline Evaluation and Surveillance Trial (TEST) global surveillance database shows that the rate of the ESBL production was the highest among the *K. pneumoniae* isolates which were collected in Latin America, followed by those of the Asia/Pacific rim, Europe, and North America (44.0%, 22.4%, 13.3%, and 7.5%, respectively) [26]. Previous studies which have documented the prevalence of ESBL in India, puts the rate at 24.8-63.8% among the *E.coli* isolates [28-36], at 10.1-76.2% among the *Klebsiella pneumoniae* [28-36, 37-39] and at 14.4-70.5% among *Proteus mirabilis* [28,29,38]. In these studies, the cephalosporins were found to be ineffective in a large number of gram negative isolates.

The carbapenems, the antibiotics of choice against severe infections which are caused by the ESBL producers, are displaying resistance in some strains of *Klebsiella* and *E. coli* species, in the form of carbapenemases (*Klebsiella* producing carbapenemases (KPC) and New Delhi metallo-β-lactamases (NDM) and there is an increasing concern regarding the overdependence on the carbapenem therapy [26].

The AmpC Beta Lactamases and the Beta Lactams

The AmpC beta-lactamases are encoded on the chromosomes of many *Enterobacteriaceae* and a few other organisms, and they mediate resistance to cephalothin, cefazolin, cefoxitin, most of the penicillins, and to the beta-lactamase inhibitor-beta lactam combinations [40]. So, the beta lactams are likely to be ineffective whenever the AmpC beta lactamases are present in the bacteria.

The organisms that produced the plasmid-mediated Amp C β-lactamases were first reported in the 1980s [40]. But, their presence and problem statement remained unnoticed till the first decade of this century, when an increase in the cephamycin-resistant isolates was noticed during 2002 and 2003. In the early screening studies which were done on the possible mechanisms of this resistance, the production of the AmpC beta lactamases was detected and their prevalence in the *Enterobacteriaceae* was found to be 1.7-7.6% in Canada [41], 1.91-7.54% in China [42], 3.1-3.6% in Korea [43-45] and 1.2% in the US [41]. The carbapenems can usually be used to treat the infections which are caused by the AmpC-producing bacteria, but a carbapenem resistance can arise in some organisms due to the mutations which occur in them [46].

Indian studies have detected prevalence rates of the AmpC beta lactamases of 3.3-24.1% among the *E.coli* isolates [47-52], 2.2-37.5% among *Klebsiella pneumonia* [47-52,34] and 37.77% among *Proteus mirabilis* [53].

The Metallo-Beta Lactamases (MBL), the Klebsiella Producing Carbapenemases (KPC) and the Beta Lactams

These enzymes are responsible for conferring resistance to the carbapenems, to the beta lactam class with the broadest spectrum of antibacterial activity, as well as to the other beta lactams [54].

The carbepenemase production was naturally found in many bacteria, but over the years, it has become a much known entity among the common nosocomial organisms like *Pseudomonas* and *Acinetobacter,* as chromosomal carbapenem-hydrolyzing beta lactamases. Several recent reviews have summarized the properties of the carbapenemases [55-57].

The spread of the carbapenemases to the *Enterobacteriaceae* family is a major concern for the future [58]. Although the prevalence of the carbapenem resistant *Enterobacteriaceae* varies from region to region, a review of the data from the US based National Healthcare Safety Network found that in 2009-2010, about 13% of the *Klebsiella* species which were reported from the Central Line-Associated Bloodstream Infections (CLABSIs) and the Catheter-Associated Urinary Tract Infections (CAUTIs) were carbapenem-nonsusceptible. About 2% of *Escherichia coli* which were reported from the CLABSIs and the CAUTIs were carbapenem-nonsusceptible [59].

Among the *Enterobacteriaceae*, KPC was first detected in 1996 in North Carolina, and it has now spread all over the USA. Outside the USA, KPC had been reported in several European countries by the early part of 2000 [60-63]. The genes which code for KPC can be transmitted between bacteria via the mobile genetic elements, which potentially facilitate the transmission of these organisms, thus spreading the resistance to the beta lactams.

The MBL production generally follows the pattern of an increasing prevalence that is country specific. MBL-producing organisms have been identified in the US, but they appear to be less common than the KPC-producing organisms. *Enterobacteriaceae* which produce the NDM-1 metallo beta lactamases were first reported from Pakistan and India, but they can now be found worldwide. A recent study detected the presence of the novel NDM-1 in the nosocomial isolates of *Enterobacteriaceae* from Chennai, Mumbai, Varanasi, New Delhi, Bangalore, Pune, Kolkata, Hyderabad, Port Blair and Haryana, and from many locations in Pakistan; some isolates from Chennai and Haryana were obtained from community-acquired urinary tract infections, thus suggesting that this problem was not restricted to hospitals [64-66, 67].

Indian studies have documented prevalence rates of between 10–54.54% for MBL among the isolates of *Pseudomonas* and *Acinetobacter* [68-72] and of 1-11% among the *Enterobacteriaceae* [73-76]. The above observations have been summarized in [Table/Fig-2 and 3].

THE FACTS AND MYTHS ABOUT THE EMIPIRICAL USE OF THE BETA LACTAMS

In the light of the current resistance patterns of the commonly encountered organisms in the clinical practice, the beta lactam antibiotics are not effective against most of the bacteria. A study which was conducted in a western population two decades ago, revealed that the cephalosporins were in-effective against all the bacteria which were commonly isolated in a hospital microbiology laboratory [77]. The Beta lactam-Beta-lactamase inhibitor combination as well as the higher versions of the cephalosporins are ineffective against the MRSA, AmpC and the MBL organisms.

Hence, the previously mentioned notions that are generally held by the prescribers are myths and they have no rationale to support them. So, the current pattern of use of the beta lactams as an empirical therapy for most of the common indications in a developing country like India, does not seem to be justified.

One pertinent point against our argument may be that the predominating causative organisms of the common infectious diseases and their resistance patterns are true only for the hospital acquired infections, but not for the outpatients who suffer from community acquired infections. If we go by the mere prevalence of these resistance mechanisms in a community versus hospital setting, this might turn out to be true. But, if we consider the increasing incidence of these organisms in the community, which, at one time, were considered to be hospital acquired only, we can come to the conclusion that all these bacteria are very much increasing in the community acquired settings also. This has led to the terminologies like community acquired MRSA (CA MRSA), CA ESBL, etc. In a recent study, there has been a demonstration of the presence of MBL positive *Pseudomonas* in tank water and pond water in various parts of India [78]. So, we can conclude that these beta lactam resistant bacteria have already reached the community.

There are other points to ponder upon, before we choose a beta lactam antibiotic, such as the danger which is posed by adverse drug reactions. Among the beta lactam drugs, the rampant use of the third generation cephalosporins causes *Clostridium difficile* induced pseudomembranous enterocolitis. There have been documented instances of how a strict antibiotic policy can decrease the rate of the *Cl. difficile* associated diarrhoea [79, 80]. Besides that, there are reports on cephalosporin-induced hypoprothrombinaemia, which is uncommon but serious, which causes coagulation abnormalities and bleeding [81]. Similar severe adverse effects have been seen with the other widely used beta lactams, e.g, the carbepenem group is associated with a potential risk of seizures and renal impairment.

Moreover, we must be aware of the resistant flora which we are generating due to the rampant use of the higher generation antibiotics; many a time, we fail to differentiate a colonization from

Gram Positive Bacteria	Resistance Pattern	Meaning	Beta Lactam Drug	Beta Lactam/Beta Lactamase Inhibitor Combination	Prevalence of Resistance Pattern
Staphylococcus	Beta-lactamase producer	Enzyme produced destroys the beta lactam ring	Mostly resistant	Sensitive	Widespread.
	MRSA*	No Beta lactam antibiotic can bind to act on cell wall of bacteria	All resistant	Resistant	23.6-59.3% [11-13]
Enterococcus Treatment of choice is Aminoglycoside antibiotic with Beta lactam, not a beta lactam alone. All cephalosporins are ineffective	HLAR†	As Beta lactam is effective only in conjunction with Aminoglycoside, Beta lactams alone will not be effective in HLAR	All resistant	All resistant	7.8 - 56 % [16-19]
	VRE‡		All resistant	No role	1.4-8%, 23% [21-25]

[Table/Fig-2]: Shows the current resistance patterns of gram positive bacteria in India and its implications for beta lactam drug therapy
*MRSA = Methicillin resistant *Staphylococcus aureus*
†HLAR = High level aminoglycoside resistance
‡VRE = Vancomycin resistant enterococci , ††, ‡‡

Gram Negative Bacteria	Resistance Pattern	Antibiotics Ineffective	Role of Beta Lactam Drugs	Role of Beta Lactam/Beta Lactamase Inhibitor Combination	Prevalence of Resistance Pattern
Enterobacteriaceae + Non fermenters - *E coli, Klebsiella, Citrobacter, Enterobacter, Pseudomonas, Acinetobacter*	ESBL[§]	1st, 2nd and 3rd generation cephalosporins	1st, 2nd and 3rd generation cephalosporin resistant. Only 4th generation cephalosporin as per sensitivity pattern is sensitive. (But now % sensitivity of 4th generation cephalosporins is also poor)	Might be effective, but now % sensitivity is coming down.	23.8-63.8% for *E.coli* 10.1-76.2% for *Klebsiella pneumoniae* [28-36, 37-39] 14.4-70.5% for *Proteus mirabilis* [28,29,38].
	AmpC	1st, 2nd, 3rd and 4th generation cephalosporins + combination drugs	Resistant	Resistant	3.3-24.1% in *E.coli* isolates, [47-52] 2.2-37.5% in *Klebsiella pneumoniae,* [47-52,34] 37.77% among *Proteus mirabilis* [53].
	Carbepenamase ([‖]MBL/[**]KPC)	All beta lactams, including penems	Resistant	Resistant	10-54.54% for MBL from *Pseudomonas* and *Acinetobacter* [67-71] 1-11% for *Enterobacteriaceae*. [72-75])

[Table/Fig-3]: Shows the current resistance patterns of gram negative bacteria in India and its implications for beta lactam drug therapy
[§]ESBL = Extended spectrum beta lactamases
[‖]MBL = Metallo beta lactamases
[**]KPC = *Klebsiella pneumoniae* carbapenemases

an infection and we needlessly prescribe these antibiotics which were initially meant to be used as reserve drugs to be used sparingly. The organisms that are not inhibited by the cephalosporins, for example, consequently overgrow, with varying potential, to cause infections and the association between the cephalosporin usage and the emergence of multiple drug-resistant organisms has been proved [82].

RECOMMENDATIONS FOR THE EMPIRICAL USE OF ANTIBIOTICS IN GENERAL AND FOR THE BETA LACTAMS IN PARTICULAR

Raising an Awareness among the Prescribers

It is necessary to convince the clinicians that the antibiotic therapy should be more tailored to meet the specific patient needs, according to the infections which they are suffering from. This is because even the experienced practitioners may not realize that prescribing antibiotics affects not only their patient, but also their environment and all the people who are exposed to that environment.

Clinico-microbiologic/pharmacologic cum pharmacy/hospital therapeutic committee meetings should be regularly organized in hospitals, for increasing the prescribers' awareness on the local sensitivity patterns, to guide the rational use of antibiotics, especially their empirical use.

Screening of the Antibiotic Prescriptions

Some researchers have suggested that the clinical freedom of prescribing, which is the privilege of the medical practitioners, should be curtailed in case of the antimicrobials. Such prescriptions should be reviewed by microbiologists/infectious disease specialists before their administration to the patients [83].

Regulatory Enforcement

It has been proposed by the Directorate General Health Services of the Government of India that the sale of antibiotics Over the Counter (OTC) without proper prescriptions, should be stopped. It should be brought under a new law which governs the sale of antibiotics in India, Schedule H1 [3].

Imparting an Attitudinal Change among the Undergraduates

It is important to inculcate a culture of rational prescribing, especially when it comes to antibiotics, among the budding prescribers. The education of the rational prescribing of antibiotics for students should include the incorporation of exercises, small projects and the practical application of the principles of the rational antibiotic therapy in the medical/dental undergraduate curriculum.

The Rational Antibiotic Therapy and Differentiating between a Colonization and an Infection

The strict implementation of a proper antibiotic policy which is based on the microbial growth in our backyard is the need of the hour. In the cases where a colonization is seen, a communication between the microbiologist and the clinician is necessary for correlating the growth with the clinical presentation and other parameters of the infection, such as, the CRP and the ESR. Once a bacterium is exposed to an antibiotic, it prepares itself to fight against that antibiotic by natural selection and this becomes the very basis of the genesis of drug resistance. Thus, a prophylactic antibiotic use which is caused due to the misinterpretation of a colonized growth as an infection, should be checked in time. Along with the adherence to a proper antibiotic policy, this can decrease the menace of drug resistance.

An antimicrobial stewardship is of paramount importance. The selection pressure must be avoided by a judicial and a prudent use of antibiotics. An antibiotic policy which restricts the use of the broad spectrum agents (especially the third-generation cephalosporins) has been well recognized as the key [26].

The reserve drugs such as vancomycin or those which are used against the resistance to the carbapenems, like polymyxin B and E (colistin), tigecycline and fosfomycin [84] should never be used indiscriminately.

Stopping the Empirical Use of the Cephalosporins

In diseases like enteric fever, the cephalosporins should only be used as reserve drugs, in the fluoroquinolone resistant cases, but they continue to be clinically prescribed as the first choice drugs. Such a presumptuous use should be discouraged and a limited use of the cephalosporins with evidence based indications only, should be followed.

The hospital pharmacies should stock only limited supplies of the beta lactams, especially the cephalosporins, to be dispensed only on the advice of microbiologists or infectious disease physicians.

The Greater Empirical Use of an Antibiotic without a Beta Lactam Ring

The use of the non-beta lactam antibiotics as an empirical choice, should be increased in resource poor settings, as there are more chances of it being sensitive. Many researchers have made the same recommendation about the cephalosporins, in that they should not be used for a routine prophylaxis [85].

The Regular Census of the Local Pattern of the Micro-organisms

The regular census of the local microbial sensitivity pattern, with its sensitivity percentage, should guide the formulation and the updating of the hospital antibiotic policy.

Upgrading the Laboratory Services and Facilities

The availability of rapid diagnostic kits for detecting microbial organisms, is needed to decrease the lag time between the collection of the sample from the patient and the reporting. The prescribers need not feel unduly worried about waiting for the lab reports, while the patient is without an antibiotic cover.

Proper Data Collection, Analyses and Sharing

Though a need was felt for a long time, no organized system of collection, storage, classification and analyses of the data on the prevalence and the sensitivity patterns was available, for formulating new effective standard treatment guidelines for the infectious diseases, except for tuberculosis, AIDS and vector-borne diseases. In this context, the National Policy for Containment of Antimicrobial Resistance, India, which was initiated by the Director General of Health Services, Government of India, in 2011, is a welcome gesture. But as it is in the early stages of implementation, which concentrates only on the resistance pattern in a few hospitals in Delhi, India, its scope, at least initially, would be limited. Moreover, the task at hand is very cumbersome and the competent workforce is less; so it would take years to build up the national database.

The WHO has also come forward with a new software for solving this problem, by introducing the free WHONET [86], but it is yet to achieve popularity, as it needs dedicated persons in the resource poor laboratories. Moreover, it is not compatible with the software which is being used by the advanced laboratories.

At the level of the hospitals at least, proper data collection, storage, classification and analyses should be done and these should be shared with all the stakeholders – the practising physicians, administrative heads, policy makers and the government departments which are connected with health in their particular geographical locations.

The Thrust for the Research and Development of Newer Antibiotics

The greatest worry is that although many new antibiotics are being launched every year, not a single one of them is a novel molecule or one with a unique new mechanism of action. This is a major cause for concern [87]. Each newly introduced antibiotic is only a "Me-too" drug [4] – a higher version of an antibiotic that has already existed (e.g., the 4th and 5th generation cephalosporins). So, the bacteria already know how they work and how to nullify their effect.

In June 2010, the Infectious Diseases Society of America gave a testimony before the House Committee on Energy and Commerce Subcommittee on Health, on the urgent necessity of research and development into newer therapies [26]. In this context, it may be pertinent to mention the potential of novel approaches, such as, the use of bacteriocins and bacteriophages to counter the problem of the antimicrobial resistance in general [88,89].

CONCLUSION

Since the beginning of the antibiotic era, there have been reports on the novel beta lactams, which are sensitive to all kinds of enzymatic destructions, but the wave fizzled out before it could make a significant impact clinically (like methicillin). New generations of the beta lactams have come (and gone) with the claims of a higher sensitivity and less resistance. Thus, we have seen the emergence of five generations of the cephalosporins, but after their initial (launching) success, the sensitivity of each and every one of them effectively came down to a miserable low percentage. The initial preference of the beta lactams, especially the cephalosporins, as an empirical therapy, among the prescribers could be justified, considering the relatively broad spectrum activity and the fewer adverse effects. However, the current sensitivity patterns do not support the empirical use of the beta lactams, especially the cephalosporins, in the hospital and community acquired infections. Moreover, the adverse effects like pseudomembranous enterocolitis are common and serious. There is a need for increasing the prescribers' awareness, imparting an attitudinal change among the budding medical and dental undergraduates towards the prescribing of antibiotics in general, and the beta lactams in particular, screening of the antibiotic prescriptions by infectious disease specialists/microbiologists, the strict implementation of antibiotic policies in hospital settings, restricting the hospital supplies of the beta lactams, especially the cephalosporins, towards a non-empirical use only, avoiding the prescriptions of drugs with a beta lactam ring, regular census of the local sensitivity patterns to formulate and update the antibiotic policies, upgrading the laboratory facilities for a better and a faster detection of the isolates, proper collection, analyses and sharing of the data and encouraging the research and development of newer antibiotics with novel mechanisms of action.

Based on the evidence of the recent sensitivity patterns globally, as well as in India, it certainly seems that the beta lactam antibiotics have outlived their use as an empirical therapy and there is little rationale for the prescribers to favour these drugs for this purpose, unless their local sensitivity patterns reveal otherwise. It remains to be seen whether the new approach which involves the antimicrobial, (but not necessarily antibiotic) property with the use of bacteriocins and bacteriophages, will be the way forward in the continual battle between the bugs and the drugs.

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