Antibiotic policy: Why and for whom?

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Abstract: There is no place for the indiscriminate use of antibiotics. If we continue with the practice, the fact that we have antibiotics may not matter in due course of time. The basis of an antibiotic policy rests in generating microbiological data and prescription auditing at any one geographical place. The concept of a class of antibiotics that is time-and concentration dependent, with an understanding of their pharmacokinetics and pharmocodynamics are important factors for successful antibiotic therapy. It is important to recognize that antibiotics have a high (ampicillin, ciprofloxacin, imipenem, ceftazidime, tetracycline, etc.) or low (piperacillin, quinolones other than ciprofloxacin, third-generation cephalosporins other than ceftazidime, meropenem, etc.) resistance potential. Various issues involved in formulating an antibiotic policy are discussed.

Introduction

Appropriate antibiotic use is one of the main goals of the medical community.[1] Overuse of antimicrobial agents has been described worldwide in both community[2,3] and hospital[4,5] settings. In addition to the effect on patients,[6] antibiotic misuse can provoke the emergence of bacterial resistance[4] and increase healthcare costs.[7] It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken.

It has been observed that the infectious diseases physician plays a crucial role in controlling antibiotic use in the hospital,[8] as does a multidisciplinary team approach with the active involvement of a clinical microbiologist and a pharmacist.[7,9] Bantar *et al.*[10] published an alarming rate of bacterial resistance in a surveillance study involving 27 Argentinian healthcare centres and noted a high rate of nosocomial infection, surgical prophylaxis errors leading to unnecessary cost increases in the hospital,[11] and confirmation of misuse of antibiotics in the same hospital.[5] These findings provide compelling evidence of the need for more rational use of antimicrobial agents. To our knowledge, a systematic strategy for the control of antibiotic use in India has not been undertaken or published.

Inappropriate and empirical antibiotic therapy is widespread and associated with increased mortality in critically ill patients. The initial selection of antibiotic must account for a variety of host, microbiological and pharmacological factors. Institution-specific data, such as susceptibility patterns and local antibiotic use, must be considered. Tailoring antimicrobial therapy according to the culture and sensitivity results will help reduce cost, decrease the incidence of superinfection, and minimize the emergence of resistance.

A few years back, I wrote an article for the souvenir of the Annual Conference of the Hospital Infection Society of India held in New Delhi titled 'Have we reached the dead end?' and I summed up by saying 'If we are not discrete and act now, after another 20 years, it may not matter if we have antibiotics.' But now, I revise this deadline further to only 10 years. We, the human species have to remember that whatever we may do, bacteria shall remain ahead of us by the sheer number of years of their existence on earth, which far outnumber ours. Bacteria are genetically better evolved than us.

'Antibiotic policy: for whom and why'. The answer to both these questions is similar the medical fraternity, at large, feels safe at present with the usage of antibiotics at the slightest pretext.

The concept of antibiotic policy is not new and a great deal of effort goes into this exercise wherever it is undertaken. It is its implementation in letter and spirit that requires serious thinking. When we say that a dead end has been reached, it signifies that we are at the end of a road from where we have nowhere to go. This further means that while treating a case of overwhelming infection, it is unlikely that the patient can be salvaged. With the current anti-infective therapies, multidrug resistant (MDR) organisms have come to stay unless we change our practices. The matter is rendered more complicated due to the presence of extended spectrum β-lactamase (ESBL) producing organisms as a result of the unbridled use of cephalosporins, particularly ceftazidime, a strong inducer of ESBL organism.[12] Though this is the scenario the world over, in India we are more vulnerable due to the overwhelmingly indiscrete use and over-the-counter availability of antibiotics.

Rational antibiotic usage

We have to start from somewhere to begin an era of rational antibiotic usage, which includes the type of antibiotic chosen, its dosage and duration of therapy. The concept of pharmacokinetics and pharmacodynamics (PK/PD) while treating a patient of sepsis with an antibiotic, in the background of the knowledge of the minimum inhibitory concentration (MIC) of the organism in question is, unfortunately, yet to evolve in this part of the world. All this is not attempted in the

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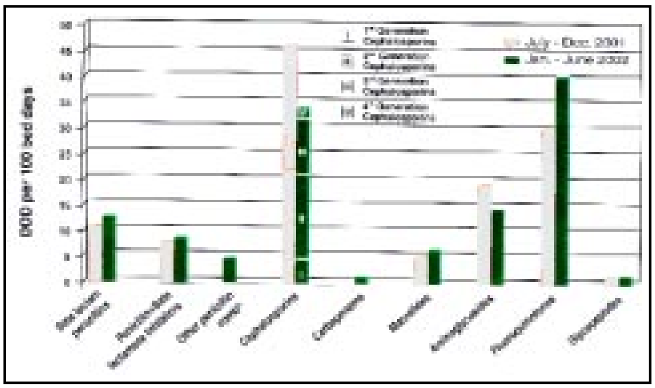
name of increasing the burden of the cost of therapy! The cost-benefit ratio loses its significance when faced with the outcome of irrational treatment with expensive antibiotic usage. Moreover, the concept of a concentration-dependent and-independent class of antibiotics has not emerged and a scientific way of treating infections guided by various scientific parameters remains to be developed.

Prescription Auditing

In light of this, the onus falls on the medical fraternity to evolve an empirical antibiotic policy for every clinical setting and at a given place, based on the existing knowledge of antibiogrammes and antibiotics, their bioavailability and pharmacokinetics. To formulate an antibiotic policy in any hospital or geographical area it is necessary to know the prevailing antibiogramme of that area besides knowledge of the most commonly isolated pathogens both in the outpatient and inpatient departments. It is necessary that such data be generated and antibiotic preferences studied using prescription auditing as a tool (Fig. 1) for the same period of the respective pharmacy that dispenses antibiotics in that area or institution.



I, II, III, IV : first-second-third-fourth generation cephalosporins respectively; July-December 2001; January-June 2002; DDD: daily defined dose

At Sir Ganga Ram Hospital, we are lucky to have the infrastructure whereby this kind of study is being undertaken on a six-monthly basis since 1995. It was interesting to see the prescription auditing figures getting reflected in our antibiogrammes. Keeping this in mind, an antibiotic policy was framed at our hospital. It is necessary to have the following specialties come together with a consensus opinion, i.e. the Department of Internal Medicine and its allied specialties, Department of Clinical Microbiology, and Department of Surgery and its allied specialties. Every institution has a peculiar situation or a set of problems to tackle. Similarly, the intensive care expectations of an institution also vary from one place to another.

Antibiotic class and resistance

Various parameters are central to this theme such as the class of antibiotics being used in their order of preference. Though there is a feeling that class resistance or shift of resistance is limited to a few classes of antibiotics, the key concept of antibiotic resistance is that it is agent specific and not related to an antibiotic class or duration of use. If antibiotic resistance has to emerge in a particular agent, it occurs very early in the course of therapy rather than later.[12] Amikacin, which has been in use for over a decade, is an example, and the level of resistance is still low. Antibiotics with a high resistance potential should be restricted for use; for example, ampicillin, carbenicillin, gentamicin, tetracycline, ciprofloxacin, imipenem and ceftazidime. Antibiotics with little or no resistance potential should not be restricted; for example, piperacillin, piperacillin + tazobactum, amikacin, doxycycline, quinolones (other than ciprofloxacin), third-generation cephalosporins (except ceftazidime), cefipime and meropenem.[12]

To formulate antibiotic policy at any place, besides the need for the availability of local data, it is also important to understand the genesis of antibiotic resistance. Antibiotic resistance with some organisms has become a worldwide problem such as methicillin-resistant *Staphylococcu s aureus* (MRSA), pencillinase producing Neisseria gonorrhoeae (PNG), aminoglycoside, ceftazidime and ciprofloxacin resistant *Pseudomonas*. Resistance among pathogens such as *Moraxella, Streptococcus pneumoniae and Haemophilus influenzae* has also started causing concern in the medical world. The emergence of MDR *Enterobacter* and *Escherichia coli* is worrying. Resistance in anaerobes is by and large not clinically significant. A distinction has to be made between increase in prevalence versus emergence of resistant organisms, which is seen with enterococci. Vancomycin-resistant enterococci (VRE) are not an example of increasing antibiotic resistance but a change in the selective pressure of the faecal flora favouring VRE as a colonizer. However, in the Indian scenario we are lucky to have almost no vancomycin resistance in Gram-positive organisms vancomycin-resistant Staphylococcus aureus [VRSA/E] epidermidis even though VRE have started to emerge.

In vitro susceptibility testing and its pitfalls

While we are familiar with natural and acquired resistance it is equally important to understand the methodology of susceptibility. Moreover, we know that *in vitro* susceptibility testing does not necessarily reflect *in vivo* efficacy, because of the variability of both host and pathogen, culture media used, conditions of incubation, method of identifying the organism and its sensitivity. There is no universal agreement on how to conduct a susceptibility test; for example, in anaerobes, undue emphasis on *in vitro* susceptibility can be misleading at times. Similarly, it is necessary to know the synergy test results of beta-lactams and aminoglycoside groups of antibiotics for the treatment of enterococci or group D streptococci isolated from samples other than the urine. Non-synergistic Kirby-Bauer (disc diffusion) antibiotic sensitivity results can be misleading for these organisms. Thus, knowledge of the variabilities can help clinicians to use the data to their advantage in a given clinical setting.

Gross resistance to a group of antibiotics requires the use of another class of antibiotics to eliminate the resistant organism. However, with some organisms, gross resistance to one antibiotic within the class does not necessarily mean that others in the same class are also resistant. For example, ciprofloxacin resistant *Strept pneumoniae* are sensitive to levofloxacin and strains of gentamicin-resistant *P. aeruginosa* are sensitive to amikacin. It should be noted that third-generation cephalosporin-induced ESBL organisms are resistant to all third-generation cephalosporins. In such cases, treatment should be commenced with an effective agent from a different antibiotic class; for example, carbapenems. When ESBL organisms are prevalent in any clinical or institutional setting, it is worthwhile considering the use of antibiotics combined with β-lactamase inhibitors; for example, piperacillin + tazobactum, cephalosporins with β-lactamase inhibitors (cefoperazone, sulbactum), or ticarcillin clavulanic acid empirically as the first-line antibiotic in severe infections. 'Susceptibility drift' is a term that has also been used. It refers to a temporary decrease in susceptibility to one antibiotic caused by another in the same group; for example, the use of ceftazidime may result in decreased susceptibility to cefpirome in *P. aeruginosa* infection. It is suggested that replacement of ceftazidime with cefpirome may restore sensitivity in *P. aeruginosa* to cefpirome after some months. This implies that the simultaneous use of ceftazidime and cefpirome by a particular medical centre should be discouraged. Nor should a step-up therapy from ceftazidime to cefpirome be considered in the same patient in case of treatment failure. Resistance of *P. aeruginosa* to imipenem implies that it is also meropenem resistant.

Predictor of antimicrobial efficacy

A good predictor of antimicrobial efficacy has emerged from the concept of the area under curve (AUC)/MIC ratio. However, it has not been found to be superior to traditional kill ratios, i.e. antibiotic serum levels to MIC ratios. However, AUC/MIC ratios also cannot predict the development or emergence of resistance. The best means of controlling antibiotic resistance is to recognize the resistance potential of a particular antibiotic class. The control of resistance in the community is dependent on the selective use of antibiotics by physicians, particularly oral antibiotics. A physician, out of habit or compulsion, prescribing an antibiotic for outpatients, that too in an inadequate dose for an imprecise duration, can have far-reaching consequences in terms of resistance. For example, oral ampicillin or ciprofloxacin prescribed for a short period of time results in the selection of resistant mutants in the gut. This resistant organism can re-infect the same patient even after cessation of therapy, or others within the family or community, and this should be a matter for concern.

Antibiotic resistance in hospitals

We are usually faced with one of the two forms of antibiotic resistance in hospital settings.

(i) Generalized resistance to multiple antibiotics primarily due to non-selective formulary usage of high-resistance potential antibiotics, e.g. ciprofloxacin, ceftazidime, ampicillin.

(ii) Outbreaks of infection due to highly resistant organisms in selected areas of the hospital, e.g. CCU, ICU, Urology Department, etc. Barrier nursing (handwashing) is an effective measures controlling such outbreaks in hospital settings.

In a non-outbreak situation, hospital formularies can play a major role. The magnitude of antibiotic resistance as a result of the unbridled dispensing of antibiotics by formularies in Delhi has resulted in a scenario such as that seen in Table 1. It is interesting to see the prescription auditing get reflected in the development of resistance (Fig. 1). I believe the situation in the rest of the country is not very different. The use of antibiotics at the slightest pretext gives a false sense of security while an infectious disease might still be raging within the victim.

Table I – Percentage Antibimicrobial Resistance

Organisms	1995	1996	1997	1998	1999	2000	2001
Staphylococcus aureus:							
Penicillin	55	75	70	79	83	91	92
Oxacillin	24	33	30	29	39	46	43
Clindamycin	20	18	22	18	26	33	26
Ciprofloxacin	19	29	45	43	48	51	47
Gentamicin	21	23	15	37	41	38	42
E. coli:							
Gentamicin	38	62	59	62	65	57	63
Cefotaxime	37	44	55	60	63	64	67
Ofloxacin	40	58	69	77	73	53	62
Coamoxyclav	55	61	77	80	82	88	82
Pseudomonas aeruginosa:							
Ceftazidime	50	42	57	76	42	50	52
Ciprofloxacin	42	51	50	62	49	54	58
Amikacin	20	24	30	51	30	45	49

We were all aware that VRE would be a problem at some stage in India and our first case (VRE VanB phenotype) was isolated in July 2001. By September 2003, we had 15 such cases. Any institution, in which the prescribing rate of third-generation cephalosporins is high, has been found to be associated with a higher incidence of MRSA. Once the rate of MRSA is high, the likelihood of having to use glycopeptides is very high. This is a classical setting for VRE or VRSA/E to emerge.

The increasing prevalence of resistance to penicillin and other drugs among pneumococci (PRP) has considerably complicated the empirical treatment of community-acquired pneumonia. Penicillin resistance is a worldwide occurrence. We do not have the exact figures for PRP from India. From our centre approximately 33% PRP was documented in the year 2003. Resistance to other classes of antibiotics traditionally used as alternatives in the treatment of pneumococcal infections has also been reported. In some areas of the USA, Europe and East Asia, a prevalence of macrolide resistance as high as 35% or more has been reported recently.[13] Resistance to fluoroquinolones remains low but several treatment failures have been reported from different parts of the world. Resistance or increased MIC to quinolones in *Salmonella* infections has already been reported.[14] We have isolated 72 strains that are moderately sensitive to quinolones (ciprofloxacin) having an MIC of ≥4 µg (Vitek System, BioMerieux) and all these strains were nalidixic acid resistant (in print). Penicillin G remains the mainstay of therapy for the treatment of penicillin-susceptible pneumococcal pneumonia. Penicillin-resistant pneumococcal pneumonia (MIC <4 µg/ml) can be safely treated with high-dose beta-lactams. The newer fluoroquinolones are very active and effective in pneumococcal pneumonia.[13]

Formulation of an antibiotic policy

Several strategies for regulating antimicrobial prescribing practices have been proposed, such as formulary replacement or restriction,[15] introduction of order forms,[16] healthcare provider education, feedback activities[17] and required approval from an infectious diseases physician for drug prescription.[18] Although most of these interventions have been assessed separately, data from prospective studies evaluating the impact of these different strategies applied systematically over time in the same hospital setting remain scarce. In addition, the results of a coordinated approach by a multidisciplinary team composed of infectious disease physicians, clinical microbiologists and pharmacists have rarely been reported.[9]

We have shown a significant reduction in antibiotic use when the Hospital Infection Control Committee (HICC) performed feedback activities. This is not surprising, because we noted a number of unjustified prescriptions during the baseline phase. A further decrease in antibiotic consumption was reached during the subsequent intervention periods (framing of an antibiotic policy, education and active control phase with feedback activities). Linezolid remains a reserve drug in our hospital only for use in glycopeptide resistance or overwhelming MRSA infections.

Because of the alarming prevalence of bacterial resistance found during the baseline period, our education strategy should emphasize 3 major issues. An effort should be made to document the infection microbiologically before starting antimicrobial therapy and the use should be avoided of certain antibiotics known to be associated with the emergence of bacterial resistance.[12,18,19] A proactive approach by the HICC is the intervention of choice.

Recommendations

- Perform focused diagnostic tests and procedures according to the Fever Assessment Guidelines before instituting antibiotic therapy.
- Start haemodynamically unstable patients with a suspected infectious aetiology on broad-spectrum antibiotics preferably guided by the local antibiotic policy for empirical therapy.
- Convert direct empirical antimicrobial selection into definitive therapy as soon as possible and justify continuation of antibiotics in any given patient (antibiotic audits).
- Base the use of antibiotics on the culture and susceptibility results where ever available.
- Monitor the usage of antibiotics in any institution.

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