Antimicrobial resistance: Bangladesh experience

Md. Abul Faiz* and Ariful Basher**

Abstract

Infectious diseases are major health problems in Bangladesh requiring frequent use of antimicrobials. Diagnosis and treatment of most of the bacterial diseases are empirical. Microbial sensitivity patterns of common infections like respiratory tract infection, urinary tract infection, enteric fever, wound infection are not routinely available for decision making in drug selection. Many infectious diseases do not respond to conventional antimicrobial agents. Standard treatment guidelines of different microbes are not sufficient for the purpose, moreover the community awareness programme is imperfect. There is no routine antimicrobial surveillance or quality assurance in place. Multidrug resistant (MDR) TB in primary infection is ~3%, and MDR enteric fever is an emerging threat in Bangladesh. Due to drug resistant falciparum malaria, artemisinin-based combination therapy is used; visceral leishmaniasis is treated with oral miltefosine although sodium stibugluconate is still sensitive but found to be at times toxic and difficult to deliver. Available evidence does not support the optimal diagnosis and treatment of bacterial infections in Bangladesh.

Antibiotics are available as non-prescription drugs in medicine shops and irrational use is not uncommon. Adherence to treatment protocol and compliance with treatment course of antimicrobials need to be emphasized at different levels.

Measures for prevention and containment of antimicrobial resistance are necessary in Bangladesh. It should be taken as a national priority and the establishment of a national alliance or regulation governing the use of antimicrobials should be considered.

Introduction

Antimicrobial resistance is a worldwide problem. The selection and spread of resistant organisms in developing countries that can often be traced to complex socioeconomic and behavioural antecedents contribute to the escalating problem of antibiotic resistance. Factors such as unregulated dispensing and manufacture of antimicrobials, truncated antimicrobial therapy, inadequate access to effective drugs and sometimes drugs of questionable quality and overall poverty are likely to be contributing to antimicrobial resistance.1

Antimicrobials are the most commonly prescribed group of drugs in general practice and in hospitals. Despite the improved trend of health care in Bangladesh, infectious diseases remain priority public health problem, where widespread use of different antimicrobials against bacterial, fungal, viral and parasitic infections is required. Most antimicrobials are prescribed, with the decision to apply based on best-guess empiric therapy. A majority of the prescribers in Bangladesh diagnose infection by clinical assessment and suspect a microbial aetiology.2 The important factors associated with resistant bacteria are poor hospital hygiene, overcrowding, lack of

*Professor of Medicine, (Post Retirement Leave), Sir Salimullah Medical College, Mitford, Dhaka-1100, Bangladesh.
**Medical Officer, KHFP Center, B. Baria, Bangladesh.
resources for infection control and lack of personnel trained in controlling infection in hospital.

**Methodology**

This article is based on a review of related literature, newspaper articles and online searches using PubMed, Google and Banglajol. Combinations of key words related to each of the subject areas were used. Websites of relevant institutions, government and nongovernmental organizations were also searched. The literature thus obtained was categorized and reviewed carefully.

**Drug resistance pattern of common infectious diseases**

Systematic drug sensitivity reports against microorganisms from countries like Bangladesh are sparse. Many studies and interventions have focused on surveillance in hospitals and on the education of physicians. So far very limited data are available on the use of antibiotics. Indeed, Bangladesh is facing dual problems. On the one hand it failed to eradicate age-old infectious diseases due to indiscriminate and irrational use of antimicrobials. On the other hand also it is facing ICU-related drug-resistant microorganisms like those in developed countries.

Antibiotics are most frequently prescribed for acute respiratory tract infections, acute watery diarrhoea, acute trauma and gastrointestinal symptoms. The most frequently prescribed antibiotics are ceftriaxone (30.19%) followed by cefixime (18.87%), and amoxicillin (16.98%). It was observed that cephalosporins accounted for more than 55% of the total antibiotics used, where the highest uses were by ceftriaxone, cefixime, and cefuroxime. This probably explains why ceftriaxone and cefixime have abnormally high resistance.

A study suggested that Pseudomonas aeruginosa responsible for wound, urine, ear, throat and other infections were more than 50% resistant to commonly-used antibiotics in Bangladesh, including ciprofloxacin, gentamicin, ceftriaxone, cefixime and azithromycin. Azithromycin was 100% ineffective in wound and urine infections, while ceftriaxone and cefixime was 100% ineffective in tracheal infections. Another study also reports that *Escherichia coli* was resistant in 40% of cases to commonly used antibiotics ceftriaxone, levofloxacin, ciprofloxacin, amoxicillin and ampicillin and 95% resistant to azithromycin. *Klebsiella pneumoniae* also showed similar patterns. It was observed that 43.2% and 39.5% of isolated *E. coli* and *K. pneumoniae* respectively had ESBL phenotypes. This rate is higher than in countries of the Western Pacific Region, North America or Europe and some South American nations.

Cholera germs have acquired resistance to a number of antimicrobials including tetracycline. Over the year, shigellosis have shown great propensity to develop resistance to antibiotics. In 1996, reports from Matlab and Dhaka showed that more than 95% *Shigella dysenteriae* isolated were resistant to ampicillin, cotrimoxazole and nalidixic acid and 14%-40% were resistant to methicillin. In 1973, *S. flexneri* isolates were universally susceptible to ampicillin; however, by 1979 susceptibility decreased to 79% in urban Bangladesh. Similarly, the susceptibility of *S. flexneri* to tetracycline dropped from 79% in 1973 to 15% in 1979. In a recent study, at least 25% of *S. flexneri* were resistant to three commonly used antibiotics such as ampicillin, co-trimoxazole and nalidixic acid.

Ciprofloxacin has been extensively used in Bangladesh for the treatment of suspected gonorrhoea as it is relatively cheap and effective, and only a single oral dose is required. But as a consequence of the long-time, versatile and large-scale use of this group of antimicrobial agents in areas where over-the-counter availability of drugs without...
prescription is common, a substantial increase in resistant strains occurred. Data from one study seem to reflect the consequence of the long standing usage of ciprofloxacin for the treatment of suspected gonorrhea using syndromic management at sexually transmitted infections (STI) clinics in Bangladesh. The most striking finding of the study is the emergence of isolates resistant to three or more antimicrobial agents. More than half of the isolates are resistant to three drugs, including ciprofloxacin. Of the multidrug-resistant isolates, more than half were both PPNG (penicillinase-producing Neisseria gonorrhoeae) and TRNG (tetracycline resistant Neisseria gonorrhoeae).14

“Wonder drugs” for treating typhoid have now become a challenge to the physicians. A study conducted in an urban hospital of Bangladesh noted that 75% of Salmonella typhi were resistant to nalidixic acid vis-à-vis ciprofloxacin.15 In another study conducted in one referral centre in 2005 a total of 57% of S. Typhi strains isolated were MDR (multidrug-resistant) and NAR (nalidaxic acid resistant).16

A study report from Dhaka Shishu Hospital revealed that the principal organisms for neonatal sepsis are Klebsiella, Acinetobacter, E coli, coagulase negative staphylococci and Staphylococcus aureus. Maximum sensitive drugs are imipenem, ciprofloxacin, gentamycin and cotrimoxazole.17 Imipenem is costly and ciprofloxacin has inadequate safety data. Bacterial isolates are becoming resistant to a different generation of cephalosporin.17

Infections caused by opportunistic organisms are difficult to control due to multidrug resistance, which limits therapeutic options in critically ill and debilitated patients, especially from the intensive care units (ICU), where prevalence of the organism is the most noted. Acinetobacter baumannii is now recognized to be the species commonly found.18

The prevalence of MDR-TB was 3% among new and 15.4% in previously treated patients in Bangladesh.4 In a published report, 42 isolates of sputum samples from different areas of Bangladesh were studied in a supranational reference laboratory (SRL) in Antwerp, Belgium. Among 42 strains, 35 (83%) were found resistant to both isoniazid and rifampicin (MDR). Among these MDR strains, 40% were found resistant to any one of the second-line drugs (kanamycin, ofloxacin, ethionamide, and para- amino salicylic acid). However, none of the strains were found to be extensively drug resistant (XDR).19 Another study found drug resistance of Mycobacterium tuberculosis to at least one drug in 53.68 % cases which is highly alarming. The highest resistance (40%) was found against isoniazid, which is the most popular drug, followed by rifampicin (32.63 %). Resistance to streptomycin was found in 13.68 % cases, to ethambutol in 11.58 % and to pyrazinamide in 10.53% cases.20 Experts identified inappropriate and irregular treatment beyond programmatic control, lack of diagnostic facility and treatment of existing MDR cases as the contributing factors to the rising number of MDR and XDR-TB patients.21

Multi-drug resistance of Plasmodium falciparum parasites developed in Asia earlier than in other malarious areas around the world. As early as 1957, chloroquine (CQ) resistance appeared, whilst sulfadoxine—pyrimethamine (SP) resistance first emerged in 1967, both at the Thai-Cambodia border. Since then, it has been described in all Asian countries. In Bangladesh, the restrictions, together with clear case definitions and treatment guidelines for malaria, have not been able to block the spread of resistance to the country’s malaria treatment and the current situation of antimalarial drug resistance. Drug resistance to chloroquine and sulphadoxine-pyrimethamine is reported from areas of Chittagong Hill Tract Districts.22 Antimalarial drug efficacy trials documented that chloroquine had been found to be resistant for treatment of Plasmodium falciparum malaria
to the extent ranging from 40% to 70% in the highly endemic malaria areas.\textsuperscript{23,24}

The Ministry of Health therefore revised the guidelines for malaria treatment with the introduction of artemisinin-based combination therapy (ACT) for the treatment of uncomplicated \textit{falciparum} malaria.

The adequacy of methods used to conduct studies on treatment of visceral leishmaniasis and reports on them varied. Unresponsiveness to antimony has developed steadily in the past to such an extent that antimony is now being replaced, despite attempts to stop its progression by increasing the dose and duration of therapy. The classic second-line treatments are unsuited — pentamidine is toxic and its efficacy has also declined, and amphotericin B deoxycholate is effective but requires hospitalization for long periods and toxicity is common. Liposomal amphotericin B is very effective and safe but currently unaffordable because of its high price.\textsuperscript{25} Miltefosine — the first oral drug for visceral leishmaniasis — is now registered but its efficacy is controversial. At present, a combination drug trial is going on in Bangladesh to find out the optimal management and to prevent resistance. Meanwhile, the WHO Expert Committee has published a report on the control of leishmaniasis emphasizing the advantages of combination treatment including cost, toxic effects and reducing the probability of selection of drug-resistant parasites.\textsuperscript{26} In several phase 3 studies in India, three separate combinations showed 98%-99% cure rates.

There are a wide range of prescribers in the private and public sectors. The private health sector is rapidly expanding and is not well supervised and regulation of antibiotics is virtually non-existent. There is no central organization entrusted to oversee the use and investigations related to antibiotic use. Many patients use out-of-pocket expenditure for treatment and investigations even in public sector facilities. There is no national antimicrobial policy and few institutes have antimicrobial guidelines which are also not in practice.\textsuperscript{27} There is no uniformity among the prescribers in commonly prevalent infections although national guidelines are prepared for certain important prevalent infections, for example malaria, kala-azar and tuberculosis. Completion of the course of the prescribed antibiotic is not supervised and is likely to be poor in compliance for various reasons. All these factors facilitate antimicrobial resistance.

**Societal issues outside the medical sphere**

Many developing countries including Bangladesh allow the dispensation of antibiotics without a prescription; this can lead to self-medication and dispensation of drugs by untrained people. In one survey from the Rajbari district, 100 000 doses of antibiotics had been dispensed without a prescription in one month.\textsuperscript{28} In another study, 92% medications dispensed by pharmacies were without a prescription.\textsuperscript{29} Poverty-stricken patients may forgo the cost of a physician consultation and self-medicate. They demand antibiotic treatment even when not indicated.

Antimicrobials are available over the counter and any antimicrobials can be prescribed by any health care provider. Most of the drugs are prescribed or sold in Bangladesh by non-qualified or relatively less qualified health workers.\textsuperscript{30} In the national disease control programmes antibiotics are allowed to be given by health workers in certain cases like ARI. Antibiotics are also prescribed unnecessarily for example in viral fevers, and clean post-operative cases.\textsuperscript{31} Due to the unresponsiveness of the health system with respect to basic amenities, inappropriate client–provider interaction and staff attitudes, patients especially the poor prefer to seek health care from informal providers. These informal providers are deeply embedded in the local community and culture, easily accessible and provide inexpensive services to the villagers with occasional deferred payments and payment in kind instead of cash.
The providers include traditional practitioners and unqualified allopathic practitioners having varying duration of training in diagnosing and treating common ailments mostly from unregulated private institutions of dubious quality. These categories of providers, of greatest importance to the poor and disadvantaged population in rural areas, have largely been ignored by the public sector/government till now, as well as by NGOs.

The widespread and inappropriate use of antibiotics has resulted in the development of a progressively antibiotic-resistant microbial ecosystem in Bangladesh. A study among children from a rural community showed that 50% children had enteric flora resistant to ampicillin, cotrimoxazole and streptomycin throughout the year.32

No information is available from resource-poor settings on the extent of environmental antibiotic usage and its relationship to the prevalence of antibiotic resistant bacteria in animals. Most surprising was the widespread use of animal antibiotics and the anecdotal reports of “resistant” animal infections.33

Overview of the prevailing drugs market

Unethical drug promotion and marketing of substandard and unnecessary drugs in Bangladesh is not uncommon. A medical practitioner can prescribe any drug used for the common cold to cancer. Moreover, polypharmacy is very common among the rural medical practitioners with antibiotics and vitamins prescribed widely.31 The prescription procedure of antibiotics in Bangladesh is less than ideal as prior identification of the pathogens and its sensitivity to the drug is rarely determined before the drug is prescribed.34 Currently, drug companies are the only organizations in Bangladesh to provide information to health personnel and it is often not appropriate information.33

The excessive and inappropriate use of antibiotics adds an unnecessary economic burden to healthcare system and coincides with an increase in drug-resistant organisms, which has resulted in the use of more expensive and toxic drugs. The quality and efficacy of locally manufactured antimicrobial drugs are also largely unregulated. Often multiple brands of the same agent are available, and potency equivalents of the active antibiotic may be a fraction of the appropriate dose. A recent assay involving 15 brands of ciprofloxacin showed that 47% of samples contained less than the specified amounts of the active ingredient.35 Counterfeit drugs like other counterfeit materials are likely to compete favorably in the markets of a developing country like Bangladesh.

Prescription patterns of antimicrobials

Some sporadic studies reported disturbing self-medication behaviors among the general population in Bangladesh.35 Children are mostly affected by inappropriate prescribing of antibiotics. In a study it was shown that 26% of purchased drugs were antibiotics for children aged 0-4 year(s) and 48% of antibiotics were purchased in quantities of less than a single day’s dose.36 Pneumonia and diarrhoea are the two most common infectious diseases among children in Bangladesh with annual deaths of about 230,000 children due to diarrhoea.37 But the percentages of appropriate antimicrobial treatment of pneumonia and diarrhoea were 57.1% and 67.8% respectively as shown in one study.38 Misuse of drugs in the treatment of acute diarrhoea among under-five children is highly prevalent and WHO-recommended treatments were seen in only 26.7% of cases and metronidazole was prescribed in all 38.6% cases.39

Multiple and inappropriate antimicrobial drugs is the most common treatment error in dysentery.39 About 50% to 80% of Bangladeshi patients infected with shigellae have a history
of taking at least one antibiotic in the 15 days before a hospital visit.40

Some examples of obsolete treatment used for a long time are: thiacetazone-based antitubercular regimen; use of ineffective chloroquine; S-P or short course quinine Q3F for treatment of falciparum malaria on clinical criteria; over-reliance on sodium antimony gluconate for treatment of kala-azar; over-the-counter purchase of unnecessary antibiotics for viral syndrome; and provision of incomplete course of antibiotic in public hospitals and private practice.

One study in a medical college hospital revealed that the total number of patients who received antimicrobials (69.0%) were prescribed antibiotics for suspected or proven infection and 31.0% and 42.1% of all antimicrobials prescribed were considered inappropriate for prophylaxis. Lack of hospital restrictions on antibiotic use and inappropriate usage for prophylaxis are the main reasons for inappropriate therapy.41

Conclusion

A good, representative database on the current status of antibiotic resistance among common and important pathogens is essential for the proper treatment of infectious diseases in the country. Energetic measures to slow down the emergence and spread of antimicrobial resistance should include programmes on surveillance, education and research on antimicrobial resistance, and regulation of use of antimicrobials in hospitals and in the community.

It is indeed urgently needed to determine antimicrobial practices in the low-income population, determine the duration of compliance to therapy, reasons for non-compliance, sources of medications and prevalence of use of antimicrobials so that we can better apply the regional recommendations for containment of antimicrobial resistance.

References and bibliography


