Antimicrobial Therapy for Shigellosis: Issues on Antimicrobial Resistance

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INTRODUCTION

Shigellosis is an infectious disease of global importance, and also an important cause of traveler's diarrhea (1). Although improved public health measures have greatly reduced its incidence in the developed countries where the disease is now sporadic, it continues to be a major cause of childhood morbidity, deaths and growth-faltering in the developing world where epidemic form of the disease is associated with increased morbidity and deaths (1-5).

S. dysenteriae, S. flexneri, S. boydii and S. sonnei are the four species of Shigella which together have over 45 serotypes. S. dysenteriae type 1, the epidemic serotype in the developing countries, causes the most severe form of the disease as well as more complications, and is also the most efficient in acquiring antimicrobial resistance (1, 6, 7). S. flexneri, endemic in many developing countries, causes a disease of intermediate severity, and S. sonnei, prevalent in the developed countries, generally causes a milder, non-dysenteric form of illness, however, is also efficient in acquiring antimicrobial resistance (1, 8, 9).

Clinical management of shigellosis

Three important aspects in the clinical management of shigellosis are: (i) prevention and management of dehydration, (ii) continued feeding, and (iii) institution of an effective antimicrobial agent.

The amount of body fluid loss in shigellosis is much less than in watery diarrhea (10), and thus clinical dehydration is also uncommon. However, dehydration is a recognized risk factor for death from shigellosis (3) which can be prevented by administering home-based fluids, and can be efficiently treated using oral rehydration salt (ORS) solution.

For a number of reasons, the nutritional consequences of shigellosis is
much greater than the other, specific-etiologic diarrhea. First, shigellosis causes an intense inflammatory response in the large intestine (11-13) associated with severe anorexia and decreased food intake which may persist for weeks (14). Second, there is incomplete absorption of nutrients (15). Third, the acute phase response in shigellosis is associated with decreased protein synthesis (16). Fourth, there is extensive loss of endogenous protein through ulcerated gut (17, 18). Last is the metabolic cost of infection which is heightened in presence of fever- a feature present in the majority of patients with shigellosis (1). Acting together, these factors contribute to deterioration in the nutritional status, and may cause overt malnutrition in a marginal malnourished child within a few days (1). Moreover, prolonged fasting may lead to hypoglycemia, an important complication of shigellosis associated with a very high case-fatality rate (19).

Antimicrobial therapy has become the mainstay in the management of shigellosis since the availability of the sulfonamides (20-22), and a number of different classes of antimicrobials have been evaluated in its treatment since then (23). Drugs evaluated to be effective in the treatment of shigellosis include tetracyclines; chloramphenicol; β-lactam agents ampicillin, pivmecillinam and ceftriaxone; trimethoprim-sulfamethoxazole; a newer macrolide, azithromycin; and the quinolones including nalidixic acid, ciprofloxacin, enoxacin, pefloxacin and ofloxacin. Aminoglycosides, polymyxins, furazolidone, and β-lactams such as cephalexin, cefamandole, and cefixime are the drugs evaluated to be ineffective in the management of shigellosis (23).

Role of antimicrobial therapy for shigellosis

The objectives for use of antimicrobial agents in the management of infectious diseases include (i) reduction in deaths, (ii) shortening the duration of illness, (iii) shortening the duration of excretion of pathogens and thereby reduce infection transmission, and (iv) prevention of complications,

Results of well-designed, controlled clinical trials clearly indicates the usefulness of effective agents in shortening the duration of illness (23). Since inflammation and gut ulceration in shigellosis begins in the rectosigmoid area and progresses proximally (24), it is conceivable that treatment with an effective antimicrobial will be useful in arresting the infection as well as its further progression, resulting in early resolution of fever, anorexia and abdominal pain. They, in turn, will decrease the metabolic demand, increase intake of food, increase absorption of nutrients, resolve the acute phase response and resumption of protein synthesis for growth, and lessen the loss of endogenous protein- all contributing to
decreased nutritional consequences of the disease.

Results of controlled clinical trials also indicate the role of effective antimicrobial therapy in significantly shortening the duration of fecal excretion of *Shigella* (23). This is an important objective since a very low infective dose of *Shigella* (25, 26), compared to other enteric pathogens, facilitates its person to person transmission which is also reflected by its higher secondary attack rates (1).

Despite lack of evidence from case-control studies, there is a general consensus that antimicrobial therapy is also useful in reducing deaths from shigellosis. Higher case-fatality rates from shigellosis in the pre-antibiotic era, and also prior to institution of effective antimicrobial therapy during early epidemics, and reduced deaths observed during the later part of epidemics when an effective therapy is instituted, provides indirect evidence that antimicrobials are useful in reducing deaths (7, 27, 28). However, better understanding of the disease process including its pathophysiology, and improvement in the fluid, electrolyte and dietary management must have had contributed to reduced deaths in the antibiotic era. On the other hand, ascertainment bias and change in the age-specific attack rates during an epidemic may explain reduced case-fatality later during an epidemic (23). However, the association of ineffective antimicrobial therapy and higher deaths and decline in the case-fatality associated with institution of effective antimicrobial therapy years after the beginning of epidemic, as observed in Africa (29), provides evidence that effective antimicrobial therapy can reduce deaths from shigellosis. Observation of deaths in association with ineffective therapy, but not with effective antimicrobial therapy provides further support (23).

It is reasonable to expect that early, effective antimicrobial therapy should reduce the frequency of complications, particularly those seen later during the course of the illness (23, 30). Early initiation of antimicrobial therapy has also been incriminated to be associated with increased risk for development of hemolytic uremic syndrome (HUS), an important complication of shigellosis, particularly when the infections are caused by *S. dysenteriae* type 1 (31). However, a causal relation is difficult to establish since *S. dysenteriae* type 1 infections are not only associated with more severe disease as well as development of HUS, but are also more likely to be treated early with an antimicrobial agent. On the other hand, the possibility of increased risk for development of HUS in association with ineffective antimicrobial therapy can’t be ignored since such drugs may provide survival advantage to drug-resistant *Shigella* by eliminating susceptible colonic flora leading to more severe disease. In the treatment of infections due to enterohemorrhagic *Escherichia coli* which is also
associated with HUS, although some studies have observed an association between antimicrobial therapy and development of HUS, others have failed to observe such as association (32-34).

**Determinants of effective antimicrobials**

Despite performing a large number of clinical trials evaluating a number of effective and ineffective antimicrobials belonging to various classes (23, 35, 36), the determinants of efficacy are yet to be fully elucidated.

Better efficacy and longer duration of usefulness of bactericidal drugs such as ampicillin, trimethoprim-sulfamethoxazole, pivmecillinam, ceftriaxone and newer quinolones compared to bacteriostatic agents such as sulfonamides and tetracyclines, and rapid emergence of resistance to the latter indicates the advantage of bactericidal over bacteriostatic drugs. Rapid emergence of resistance to chloramphenicol, a bactericidal agent, can be explained by the fact that the mechanisms of resistance, decrease permeability and efflux, is similar to that of tetracyclines. Similarly, rapid development of resistance to nalidixic acid, another bactericidal drug, can be explained by higher frequency of mutation, higher MIC relative to serum concentration, and higher protein binding with possible lower tissue concentration of this drug. Generally higher MIC of *S. dysenteriae* type 1 over others serotypes of *Shigella* is likely to be an important factor for its better efficiency in acquiring antimicrobial resistance (37).

The pathogenesis of shigellosis involve multiplication of the pathogen within colonic epithelial cells and their spread to the adjacent cells. Thus, the serum concentration is likely to be more important than the luminal concentration of a drug in determining its efficacy in the treatment of shigellosis (23). This view is supported by superior efficacy of systemic drugs such as ampicillin and trimethoprim-sulfamethoxazole compared to non-or poorly-absorbable drugs such as sulfonamides, furazolidone, gentamicin, streptomycin, neomycin and polymyxins (23). However, amoxicillin, which has better oral bioavailability than ampicillin, has been evaluated to be ineffective in the treatment of shigellosis. Although poor activity of amoxicillin in serum and inactivation of the drug by β-lactam-producing intestinal flora are possible explanation for this discrepancy (23), this may also indicate that luminal concentration of a drug is also an important determinant. Optimal luminal concentration of a drug may also be important in the prevention of proximal extension of infection (24).

Although serum concentration is used as an indicator for in vitro efficacy of a drug, the concentration and activity of drugs at the site of
interest is perhaps the best predictor of their efficacy. This is supported by demonstration of clinical efficacy of azithromycin in the treatment of shigellosis in adults (38), despite its lower serum concentrations relative to the MIC of the infecting strains of *Shigella*; the tissue and intracellular concentrations of this newer macrolide is about 100 times the achievable extracellular concentrations (39, 40).

The MIC and MBC are measures of potency of drugs. The ratio of MBC over MIC, and the ratio of drug concentrations at the site of importance over the MIC are important determinants of their efficacy—higher the ratio the better will be the efficacy. This is supported by the observation that ciprofloxacin, a drug effective in the treatment of shigellosis, even when the infections are caused by multidrug-resistant strains of *Shigella*, exerts bactericidal effect at only 4 times the MIC as opposed to 10 times required for many \( \beta \)-lactams, and that the ratio of the peak serum concentration over the MIC after a standard dose of the drug are much in excess of 4 (37, 41).

Lastly, a drug which is active both in the stationary as well as in the log phases of growth is likely to have additional advantage, as demonstrated by excellent clinical and bacteriologic efficacy of ciprofloxacin in the treatment of shigellosis.

Thus, it may be summarized that to have potentials for being effective as well as delaying the emergence of resistant *Shigella*, an antimicrobial should, (i) have rapid bactericidal activity, preferably with post-antibiotic effect, (ii) achieve adequate serum and luminal, and more importantly tissue concentrations, (iii) have excellent potency with high serum to MIC ratio, and (iv) possess characteristics which do not favor emergence of plasmid-mediated resistance.

**Antimicrobial Resistance of Shigella**

Like management of other infectious diseases, the concerns on antimicrobial therapy for shigellosis include cost of therapy and adverse effects, and most importantly, the emergence of resistant strains (42-44). This problem has been noted, without any exception, with all antimicrobial agents introduced in the management of shigellosis. It is, however, the emergence and spread of multi-resistant *Shigella* which is now the major concern. The rapidity of emergence of antimicrobial resistance among *Shigella* has been observed to be influenced by the species and serotypes of *Shigella* as well as drug characteristics, among others.
1. Emergence of drug-resistant Shigella

Absorbable sulfonamides are more effective than the non-absorbable ones (8, 9, 20-22), and the combination drug, trimethoprim-sulfamethoxazole, remained useful in the treatment of shigellosis for decades (23, 45-47). Emergence of sulfonamide-resistant strains were reported from different geographic locations within a very short time of their introduction in the clinical practice; such strains have also been associated with epidemics among prisoners of the Korean war (8, 9, 48, 49), and S. dyaenteriae type 1 has been the most efficient in acquiring resistance followed by S. flexneri and S. sonnei (8).

Tetracyclines are among the early antimicrobial agents introduced in clinical practice, and they were effective against sulfonamide-resistant strains of Shigella (23, 49), however, emergence of tetracycline-resistant strains of S. dysenteriae type 1 and S. flexneri quickly followed; emergence of multiply-resistant strains and development of during-therapy emergence of resistance were also noted (8).

Chloramphenicol has also been effective against sulfonamide-resistant strains of Shigella (8). Resistance to chloramphenicol was first reported among epidemic strains of Shigella; one study in Israel not only observed a rapid increase in the resistance among Shigella but also cross-resistance to tetracycline and sulfonamides (8).

Among β-lactam agents, ampicillin, pivmecillinam and ceftriaxone are effective in the treatment of shigellosis (23, 30, 50, 51). Ampicillin remained useful until the emergence of resistant epidemic strains of S. sonnei and S. dysenteriae type 1 in North and Central America, Asia, Africa and Europe (52-61). Pivmecillinam and ceftriaxone are also effective in the management of shigellosis caused by strains multiply-resistant to ampicillin, trimethoprim-sulfamethoxazole and nalidixic acid (50, 51). Resistance to ceftriaxone is not yet a problem, however, availability only in parental formulation and higher cost of the drug precludes its routine use in the developing countries. Increasing frequency of resistance to pivmecillinam, with wide variations in the pattern of resistance in different localities not far apart, has been reported from Bangladesh (62, 63).

A newer macrolide, azithromycin, has recently been found to be effective in the treatment of shigellosis in adults (38). It is likely that the drug will also be effective in children, however, controlled clinical trails are required to prove its efficacy in the treatment of childhood shigellosis.

Nalidixic acid, an older quinolones, and more potent newer fluoroquinolones such as ciprofloxacin, norfloxacin, pefloxacin and enoxacin are all effective in the treatment of shigellosis, and a single-dose therapy for shigellosis is also possible with norfloxacin or ciprofloxacin.
when the infections are caused by strains other than *S. dysenteriae* type 1 (37, 41, 64-68). There is a concern on the use of newer quinolones in children due to their arthropathogenic potentials (69), however, results of a recent study indicate that a 5-day course of ciprofloxacin suspension is safe for use in children with shigellosis (70). As with treatment of urinary tract infections, nalidixic acid-resistant strains of *Shigella* emerged within a very short time of its introduction in the management of shigellosis, and *S. dysenteriae* type 1 is the most efficient in acquiring resistance to this drugs; such strains have been observed to exhibit cross-resistance to a number of agents including tetracycline, chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (55, 63).

2. Mechanisms of action and resistance

The mechanism of resistance of antimicrobials are often related to their mechanisms of action. Antimicrobials may act by interfering with the metabolic pathways of susceptible organisms either by inhibiting enzyme systems or by competing with the substrates for synthesis of nutrients essential for growth or multiplication of bacteria. Trimethoprim and sulfonamides act by impairing two different steps of bacterial folic acid synthesis- the former inhibits the enzyme dihydrofolate reductase and the latter competes with para-aminobenzoic acid (PABA) for binding with the enzyme dihydropteroate. Sulfonamides are bacteriostatic, however, in combination with trimethoprim it produces a sequential and additive, bactericidal effect (71). Resistance to sulfonamides may be chromosomal or plasmid-mediated, and the mechanisms include increased production of PABA, reduced permeability, and more importantly decreased sensitivity of dihydropteroate to the drug (71). Resistance to trimethoprim is most often plasmid-mediated, and the mechanisms include increased synthesis of dihydrofolate, synthesis of the enzyme with less affinity for the drug, and reduced drug permeability (71).

Tetracylines, chloramphenicol and macrolides inhibit bacterial protein synthesis by binding to their 30S, 50S and 50S ribosomal subunits respectively (71). While tetracyclines exert a bacteriostatic effect, chloramphenicol is bactericidal for susceptible organisms, and macrolides may exert either a bacteriostatic or a bactericidal effect depending on characteristics of drugs as well as bacterial density and growth phase (71). Resistance to tetracycline is usually plasmid-mediated, and the mechanisms include reduced permeability, and more importantly, rapid efflux of the drug using the “primary” or the “secondary” pumps (42, 72). Resistance to tetracyclines may also be due to modification with reduced sensitivity of the binding site of the drug on 30S ribosome and efflux of the drug by
secondary pump mediated by \textit{tet M} and \textit{tet O} genes (42, 72-74). Resistance to chloramphenicol may be natural or acquired. Natural resistance to this drug is mediated by decreased permeation or efflux by secondary (PMF) pumps encoded by \textit{bmr} and \textit{norA} genes, and the acquired, plasmid-mediated resistance may be mediated by decreased permeation, and more importantly, due to acetylation and inactivation of the drug by Chloramphenicol Acetyltransferase (CAT)- an enzyme which may be inducible or constitutively expressed on chromosomes or transposons (42, 75, 76). Natural or intrinsic resistance of \textit{Enterobacteriaceae} to macrolides is due to decreased accumulation resulting either from decreased permeability or active efflux of the drug (71). A number of bacterial enzymes, most importantly rRNA methylase, may modify the target site to decrease their affinity for the drug. Expression of rRNA may be constitutive or inducible, and location of the gene expression of this enzyme on transposons and plasmids, in addition to their expression on chromosomes, may facilitate their transfer to other bacteria (77). A number of other enzymes e.g. acetyltransferase, phosphotransferase, hydrolase and esterases may also inactivate macrolides (42, 77).

Bactericidal agents, \(\beta\)-lactams and quinolones, interfere with growth or multiplication of susceptible bacterium. \(\beta\)-lactam agents (penicillins and cephalosporins) reduce production of peptidoglycan, required for bacterial cell wall formation, through their action on penicillin binding proteins (PBP) (78). Their bactericidal effect is exerted either by osmotic effect, or by unregulated activity of bacterial autolysins (79) which is dependent on drug characteristics as well as species and strain of bacteria (80). Essential PBP (1s, 2, and 3) are the targets for growth-inhibiting effect, and non-essential PBP 5, either alone or in combination with others, is considered to be the target(s) for bactericidal activity of the \(\beta\)-lactams (81). It has been observed that saturation of two of the three essential PBP are required for clear bactericidal effect, and the highest bactericidal effect has been observed with saturation of all three PBP (80-82). Bacteria may become resistant to \(\beta\)-lactams through production of \(\beta\)-lactamases, enzymes which hydrolyse the \(\beta\)-lactam ring to render the drugs inactive; modification of the PBP to render them less sensitive to the drugs; and through alterations in the porin channels to reduce drug permeability (71, 83, 84). Additionally, bacteria may become “tolerant” to these agents, a condition where the MBC is substantially increased without any change in the MIC, and the phenomenon is believed to be a consequence of decreased production of bacterial autolysin (71).

The quinolones act by blocking the activity of the bacterial DNA in a dose-dependent fashion (71), and they are active in the log phase as well
as in the stationary phase of growth of bacterium. Resistance to quinolones is mediated by chromosomal mutation, and plasmid-mediated resistance has not been reported. The mechanism of resistance include changes in either of the subunits of the bacterial DNA gyrase (A or B), and *nal B*-encoded mutation resulting in reduced drug permeability where the bacterium also exhibits cross-resistance to other classes of antibiotics (85-87). The frequency of the in vitro resistance of *Enterobacteriaceae* to fluoroquinolones is lower than that of nalidixic acid (88), however, it remains to be seen what happens with increasing selection pressure; development of resistance to ciprofloxacin has been already been noted among strains of *Campylobacter jejuni* (89, 90).

3. Multidrug resistance

In this form of resistance, pathogens exhibiting resistance to one class of drug also exhibit resistance to unrelated classes of drugs. This phenomenon, first described in association with chemotherapy for cancer, is now a major problem in the management of infectious diseases including shigellosis, and is a consequence of efflux of drugs by primary efflux pump encoded by *mdr1* (42). Emergence of multi-drug resistance *Shigella* was noted since the early days of antimicrobial therapy, and this problem is particularly noted during epidemics—during an epidemic in Israel, strains of *S. flexneri* were observed to be multiply-resistant to sulfonamides, tetracyclines and chloramphenicol (8). In the seventies and eighties, multiply-resistant strains of *S. sonnei* and *S. dysenteriae* type 1 exhibiting resistance to subsequently introduced drugs such as ampicillin, trimethoprim-sulfamethoxazole and nalidixic acid have been associated with epidemics and foreign travel (52, 54, 58, 59, 61, 91-93). In 1994, 24,000 people were killed during a major epidemic among the Rwandan refugees in Goma, Zaire which was caused by strains of *S. dysenteriae* type 1 multiply-resistant to ampicillin, trimethoprim-sulfamethoxazole and nalidixic acid (7). Although less common, multidrug resistance has also been observed among endemic strains of *S. flexneri* in Navajo reservation in the USA (94), and in Thailand (95). In another endemic country, Bangladesh, all species of *Shigella* are currently multiply-resistant to ampicillin, trimethoprim-sulfamethoxazole and nalidixic acid, and some strains are additionally resistant to pivmecillinam (63).

**Addressing the problem of antimicrobial resistance among Shigella**

Microorganisms are remarkable in acquiring resistance to antimicrobial agents irrespective of their classes. Thus, as for other infectious diseases, the final solution to the problem of antimicrobial resistance of *Shigella*
will reside on implementation of specific and non-specific preventive measures such as immunization, and improved water supply and sanitation along with establishment of effective health education programs. The advantage of non-specific preventive measures are that they have potentials to reduce the incidence of shigellosis as well as other diarrheal diseases, and may also influence incidences of other infectious diseases. However, an effective vaccine for prevention of shigellosis has yet to be available, and establishment of effective prevention programs will take a considerable time in the developing countries.

**Interim measures**

Until effective, specific and/or non-specific preventive programs are established, antimicrobial therapy will remain as the mainstay in the management of shigellosis. It will, therefore, be important to consider measures for delaying emergence of antimicrobial resistance, and develop guidelines for appropriate antimicrobial therapy. The following issues are important in this regard:

1. **Better understanding on the determinants and mechanisms of resistance**
   Defining of strategies for slowing down or reversing the emergence of antimicrobial-resistant *Shigella* will require a clear understanding of the mechanisms and determinants of resistance which are complicated by interplay of a number of microbial, host and antimicrobial factors. Studies are also necessary to understand the mechanism and magnitude of the problem of multi-drug resistance, particularly among *S. dysenteriae* type 1 which is the most efficient in developing antimicrobial resistance.

2. **Policies to delay the emergence of resistant strains**
   Due to limited options for antimicrobial therapy for shigellosis, it is necessary to define ways to prolong their usefulness as well as to delay emergence of resistance against them. We may consider the following options:

   2.1 **Stop using antimicrobials for treatment of shigellosis**
   The benefits of antimicrobial therapy for shigellosis is so clear that this is not a practical option.

   2.2 **Limit use of antimicrobials**
   Selective pressure of antimicrobials is an important determinant of emergence of drug-resistant organisms. Thus, reducing the selection pressure through limited use of antimicrobial will be an important strategy.
for delaying the emergence of resistant strains. We may consider the following options:

a. Limit use to only confirmed cases of shigellosis
   This is complicated by the facts that (i) an etiologic diagnosis of shigellosis can't be clinically made, and that (ii) conventional laboratory tests will not only be unable to identify all cases of *Shigella* infections but will also be expensive as well as time-consuming and thus difficult to implement, particularly in the developing countries where the magnitude of the problem is the greatest.

   It is also impolntant to recognize that making of even a presumptive diagnosis of shigellosis will require a fair understanding of the epidemiology as well as the clinical features of *Shigella* infections which may widely differ in endemic and epidemic disease, and are also influenced by microbial factors such as species and serotypes, and host factors such as age, nutritional status and immunity.

b. Limit use to high risk population
   Infancy, malnutrition, presence of dehydration and acidosis, non-breast feeding, and presence of complications such as hypoglycemia, hyponatremia, intestinal obstruction and septicemia are recognized risk factors for death (96, 97). Thus, such groups of population will benefit most from an effective antimicrobial therapy, and should be routinely treated. Disease severity is known to be more in malnourished children, and also when the infections are caused by *S. dysenteriae* type 1, although some studies failed to observe any association between case-fatality among hospitalized children and species of *Shigella* (3, 4). A strong argument for routine use of antimicrobial therapy for all clinically suspected cases of shigellosis is that deaths are not confined only to high-risk population, and that reducing disease severity and the duration of illness are also important objectives of antimicrobial therapy for shigellosis. The disease severity and deaths are both higher in epidemic disease, and thus all cases during an epidemic should be treated adequately with an effective agent. Since epidemics are often caused by multidrug resistant *Shigella*, it will be important to determine antimicrobial susceptibility of the strain of *Shigella* causing the epidemic within shortest possible time in order to define appropriate antimicrobial therapy. The case-fatality from shigellosis is higher among those with complications such as hypoglycemia, septicemia, toxic megacolon and hyponatremia. Thus, limiting use of antimicrobials for those with complications could be one strategy. However, early, effective antimicrobial therapy is considered to prevent many of the potential complications of shigellosis and deaths, and deferring antimicrobial therapy until the time of development of complications will not
be a practical approach.

c. Use effective antimicrobials in rotation

Selective pressure is an important determinant of emergence of resistant strains, and reduced use of chloramphenicol has been reported to reduce the prevalence of resistant strains of *Salmonella typhi* (63). However, antimicrobials which are useful in the treatment of shigellosis may have other indications, and thus their withdrawal from a community will not be possible.

Switching from one effective drug to another before emergence of resistant strains could be an option. However, because of diverse indications for use of the antimicrobial agents, organizational difficulties, and the need for continuous monitoring of antimicrobial susceptibility which is known to vary widely from one community to another, it will be difficult to implement this policy, particularly in the developing countries where the problem is the greatest and the use of antimicrobials is not controlled (23). Most importantly, optimal time to switch can not be reasonably determined due to inability to predict emergence of resistant strains.

2.3 Appropriate use of effective antimicrobials

Administration of antimicrobials without indication, or their use in inadequate dose or duration, and decreased patient compliance are among the factors known to facilitate emergence of resistant strains. This is a global problem, however, the magnitude is more in the developing countries where promotion of appropriate use of antimicrobial agents will be a formidable task (63).

2.4 Single-dose therapy

A single-dose therapy for shigellosis will not only be most cost effective, but will also have the advantage of best possible patient compliance-one of the important determinants of emergence of resistant pathogens. Single-dose therapy for shigellosis has been possible with tetracycline and ampicillin, and the former was also effective when the infections were caused by in vitro resistant strains. The possible explanation for this observation is that with a large, single-dose, it was possible to attain a concentration of the drug at the site of interest that exceeded the in vitro MIC of the organisms. This indicates the advantage of determining MIC over disc diffusion method in determining antimicrobial susceptibility, although the later is easy to perform and less expensive. When the MIC is elevated to a level which can be attained by increasing the drug dose not exceeding the safety margin, it may be an option for prolonging the usefulness of the drugs. This will, however, require a clear understanding
of the pharmacokinetics and toxicity of the agent concerned. Two newer quinolones, norfloxacin and ciprofloxacin are effective in the treatment of shigellosis when administered in a single-dose, except when the infections were caused by \textit{S. dysenteriae} type 1. Thus, in localities where infections due to \textit{S. dysenteriae} are either absent or uncommon, a single-dose treatment with agents with proven efficacy may help delay the emergence of resistant strains.

2.5 Therapy with carefully selected agents

Selection of an ideal agent will require a good understanding of the attributes of drugs which will make the organisms less likely develop resistance to them. Review of the past experience on antimicrobial therapy for shigellosis may be useful in this regard. An ideal antimicrobial with potentials for being most effective and at the same time likely to delay the emergence of resistant \textit{Shigella}, in addition to being safe and less expensive, should (i) be rapidly bactericidal, preferably with post-antibiotic effect, (ii) achieve adequate serum and luminal, and more importantly, tissue concentrations, and (iii) have excellent potency with high serum to MIC ratio. Spread of resistant is facilitated when the mechanism of resistance is encoded on plasmids, hence, use of drugs to which resistance is not plasmid-mediated could be another way of delaying emergence of resistant strains.

3. Other options

Delayed emergence of resistant strains to trimethoprim-sulfamethoxazole may, at least in part, be explained by inhibition of folic acid synthesis at two different steps producing an additive effect. Similarly, saturation of more than one PBPs with two or more different $\beta$-lactam agents have been shown to produce better bactericidal effect. Thus, one option for delaying emergence of resistance would be to use a combination of drugs with different mechanisms of action.

Efforts may also be taken to develop drugs to offset or counteract resistance mechanisms. This approach has been successfully utilized in the development of reversible and irreversible inhibitors of group 1 and 2 $\beta$-lactamases such as cloxacillin and sulbactum, and tazobactum; \textit{CAT}s inhibitors; macrolide analogues with greater affinity for methylated RNA; agents to block \textit{mdrl}-encoded efflux through direct inhibition of the efflux ATPase (42,74); inhibitor of \textit{norA}-mediated efflux; tetracycline analogues capable of inhibiting the \textit{tetA}- and \textit{tetB}-mediated efflux of tetracyclines; and naturally occurring pump inhibitors (98).

Lastly, development of more effective drugs will require better
understanding of the resistance mechanisms in *Shigella*. This will require close collaboration between the drug designers, pharmaceutical chemists and scientists. Many pharmaceuticals capable of undertaking such projects are located in the developed countries where the magnitude of the problem is not as great as in the developing countries, and consequently there may not be great interest for development of such drugs. However, the developing countries constitute a huge market for anti-infectives, and even with low profit/unit of drug the total profit is likely to be significant. Furthermore, the pharmaceuticals with their available expertise and resources, have a moral obligation to collaborate with others in tackling the problem of antimicrobial resistance.

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