

Personal Perspectives

Rational use of antibiotics

Calvin M. Kunin, M.D.
Professor of Internal Medicine
Ohio State University School of Medicine

A WHO Expert Committee has endorsed the concept of "reserve antibiotics" in formulating recommendations for the biennial revision of the Model List of Essential Drugs (1). They recommend that the third generation cephalosporins, quinolones and vancomycin should be conserved to reduce the risk of resistance to them and to contain costs. They point out that many common infectious diseases can still be treated effectively with older agents and more selective use of the newer agents could be accomplished if locally relevant information on antibiotic susceptibility were available. The Expert Committee emphasized the urgent need for governments to set up reference laboratories to obtain timely information concerning emergence of resistant microorganisms.

These recommendations are in concert with the WHO report on antimicrobial resistance (2) and a Task Force on Antibiotic Use and Antibiotic Use Worldwide sponsored by the Fogerty International Center of the National Institutes of Health (3). The Newsletter of the Alliance for the Prudent Use of Antibiotics provides timely information on patterns of resistance to antibiotics in developing countries. The Rockefeller Foundation has committed resources to global surveillance of use of antibiotics through its International Clinical Epidemiology Network (INCLIN).

It is apparent that there are enormous problems with resistant bacteria in developing countries. There have been extensive outbreaks of chloramphenicol-resistant typhoid fever in Mexico (4), sulfonamide-resistant meningococcal infections which spread rapidly throughout the world (5), and penicillin-resistant pneumococci in South Africa (6) and Spain (7). The current pandemic of beta lactamase-producing, multiple-resistant gonococci appears to have originated in south-east Asia and Africa (8). Travellers in developing countries who take prophylactic antibiotics are at increased risk of enteric

colonization with indigenous resistant bacteria (9) and may not be protected from multiple-resistant strains of *Shigella flexneri* in Brazil (10) or *Shigella dysenteriae* in Mexico (11). Widespread resistance of enterobacteria to trimethoprim has been described in Chile (12) and Nigeria (13). Beta-lactamase resistance among *Haemophilus influenzae* is a major problem. In a large US collaborative study, ampicillin resistance was detected in 20 per cent of strains (14). Very little is known concerning the prevalence of these strains in developing countries.

Two-thirds of the world's population live in the developing nations of Asia, Africa and South America. Most of these populations exist under conditions of poverty, inadequate medical care, poor sanitation and nutrition (15). Bacterial infectious diseases account for much of the morbidity and mortality, particularly among young children (16-18). Effective antimicrobial therapy is limited by a large reservoir of antibiotic-resistant bacteria. This appears to be related to selective pressure exerted by extensive use of antibiotics. Spread of resistant strains is augmented by plasmid-mediated resistance and by crowding and poor sanitation.

Acute lower respiratory infections and diarrhoeal diseases among infants in developing countries tend to be much more severe and potentially more lethal than in developed nations. Prompt administration of penicillin, chloramphenicol or trimethoprim/sulfamethoxazole (19) may be life-saving for infants with acute lower respiratory infections while diarrhoeal diseases respond best to oral rehydration. Tomson and Sterky (20) found in a survey of 75 pharmacies in three Asian countries that only 16 gave appropriate advice concerning use of oral rehydration for diarrhoea in infants. Most others dispensed combination products containing kaolin and pectin with furazolidone, neomycin, sulfonamides or dihydrostreptomycin and "antimotility" agents. Use of tetracyclines, to which the organisms are likely to be resistant, rather than oral hydration, accounted for over 50 per cent of the drug costs to treat diarrhoeal disease in Indonesian children (21).

Antimicrobial agents can be purchased in most of the developing nations in local pharmacies as over-the-counter preparations, without prescription.

Although this practice makes drugs more accessible to the population, there is a growing body of information which indicates that antimicrobial agents are often sold in quantities and for indications for which they will be ineffective and that this might be conducive to development of resistance (22-25). The issue of underdosing of antibiotics is a major problem. In a district of Manila, almost 90 per cent of purchases were for 10 or less tablets or capsules (24). These findings are similar to those reported in a rural community in Bangladesh in which about half the purchases were in quantities which fulfilled the requirements for a single day's dose (22). A similar situation has been described in Nigeria (23). In contrast, a study of outpatient use of antibiotics in a US community reported an average of 46 units per prescription (26).

The aim to rationalize the use of antibiotics clearly holds policy implications at every level of health care. Can, for instance, reasonable guidelines be devised for empiric use of antibiotics for the treatment of severe lower respiratory infection or diarrhoeal disease in children without knowing the responsible organisms and their susceptibility to antibiotics?

It is impossible to formulate rational policies for selection of essential antimicrobial agents in a given region without systematic, representative, ongoing surveillance of patterns of resistance. There is a clear need for a representative, global system which will provide early warnings of occurrence of resistant bacteria, and which is capable of tracing the origin and spread by modern methods of plasmid and other resistance markers.

Can antibiotics be prescribed rationally in a sophisticated hospital without a well conceived formulary and the support of an adequate microbiology department?

Modern antibiotics are available to patients in tertiary care hospitals in the more rapidly industrializing countries. There is considerable evidence that nosocomial infections with resistant organisms are common and that antibiotic use is often inappropriate (27). The Infectious Diseases Society of America has prepared guidelines for improving use of antimicrobial agents in hospitals (28). Four areas are emphasized. These include:

1. A well structured formulary containing all essential drugs, obtained at the lowest cost and avoiding redundant agents.
 2. Microbiology laboratory support with ongoing surveillance of antimicrobial resistance.
 3. Studies of patterns of use of antibiotics by the medical staff.
 4. Measures for improving usage.
- It is recommended that each hospital should have an antimicrobial agents team composed of a physician knowledgeable in infectious diseases, an infection control practitioner, a clinical microbiologist and a clinical pharmacist. Their functions are to monitor antimicrobial use and resistance, to formulate policies and develop programmes to improve usage in the institution. Although hospitals in developing countries may not have all the necessary resources, they should strive toward these goals. Nothing less should be expected in urban hospitals in the more affluent, rapidly developing countries.
- There are no simple means of improving the use of antibiotics in developing countries given the constraints of widespread poverty, severe infectious diseases and lack of knowledge among the populations concerning optimal use of antimicrobial agents. Several steps are mandatory if the situation is to be improved (3). These include:
1. Raising standards of living of the populations to decrease the burden of infectious diseases through provision of sanitation, immunization, nutrition and education.
 2. Instituting an organized national system for regulating the importation and local production of essential agents and for deterring the marketing of inappropriate or ineffective products.
 3. Providing unadulterated, effective agents at a cost that is reasonable for the population with the greatest need.
 4. Providing an efficient distribution network that ensures availability of effective agents.
 5. Providing a system of medical care that can diagnose and manage infectious diseases with a reasonable level of certainty in the absence of highly-sophisticated technology.
 6. Establishing community surveillance and laboratory systems that can detect emergence of resistant micro-organisms and provide assistance to health care workers in the selection of the most effective agents at a reasonable cost.

7. Develop an understanding of the diversity of beliefs, customs, and folklore concerning health and disease among the population that is served.
8. Instituting a system of education for health care professionals that provides training relevant to the medical care needs of the population and includes an understanding of management-oriented disease classification based on critical clinical signs.

The issue of appropriate use of antibiotics and other drugs is far too complex to place the entire blame on overzealous promotion by the pharmaceutical industry (29, 30). There is considerable evidence that prescribing practices by physicians are faulty both in developed and developing countries. This is compounded by drug-seeking behaviour not only by poorly informed people, but by professionals who should know better.

Antibiotics deserve their place as one of the most powerful pillars of modern medical care. The issues of their availability, selection and proper use are of critical importance to all of us in the global community (31).

References

1. Reserve antibiotics. *WHO Drug Information*, **3**: 165-166 (1989).
2. Antimicrobial resistance. Report of a WHO Working Group. *Bulletin of the World Health Organization*, **61**: 383-394 (1983).
3. Kunin, C.M., Lipton, H.L., Tupasi, T. et al. Social, behavioural and practical factors affecting antibiotic use worldwide: Report of task force 4. *Reviews of Infectious Diseases*, **9** (Supplement 3): S270-S285 (1987).
4. Olarte, J., Galindo, E. *Salmonella typhi* resistant to chloramphenicol, ampicillin and other antimicrobial agents: strains isolated during an extensive typhoid fever epidemic in Mexico. *Antimicrobial Agents and Chemotherapy*, **4**: 597-601 (1973).
5. Morre, P.S., Schwartz, B., Reeves, M.W. et al. Intercontinental spread of an epidemic group-A *Neisseria meningitidis* strain. *Lancet*, **2**: 260-262 (1989).
6. Appelbaum, P.C. Worldwide development of antibiotic resistance in pneumococci. *European Journal of Clinical Microbiology*, **6**: 367-377 (1987).
7. Casal, J., Fenoll, A., Vicioso, M.D. et al. Increase in resistance to penicillin in pneumococci in Spain. *Lancet*, **1**: 735 (1989).
8. Brunton, J.L., Clare, D., Meier, M.A. Molecular epidemiology of antibiotic-resistant plasmids of *Hemophilus* species and *Neisseria gonorrhoeae*. *Reviews of Infectious Diseases*, **8**: 713-724 (1986).
9. Murray, B.E., Rensimer, E.R., DuPont, H.L. Emergence of high level trimethoprim resistance in fecal *Escherichia coli* during oral administration of trimethoprim or trimethoprim-sulfamethoxazole. *New England Journal of Medicine*, **306**: 130-135 (1982).
10. Tiemens, K.M., Shipley, P.L., Correia, R.A. et al. Sulfamethoxazole-trimethoprim-resistant *Shigella flexneri* in North-eastern Brazil. *Antimicrobial Agents and Chemotherapy*, **25**: 653-654 (1983).
11. Parsonnet, J., Gerber, A.R., Greene, K.D. et al. *Shigella dysenteriae* type 1 infections in US travellers to Mexico, 1988. *Lancet*, **2**: 543-545 (1989).
12. Urbina, R., Prado, V., Canelo, E. Trimethoprim resistance in enterobacteria in Chile. *Journal of Antimicrobial Chemotherapy*, **23**: 143-149 (1989).
13. Lamikanra, A., Ndep, R.B. Trimethoprim resistance in urinary tract pathogens in two Nigerian hospitals. *Journal of Antimicrobial Chemotherapy*, **23**: 151-154 (1989).
14. Doem, G.V., Jorgensen, J.H., Thomsberry, C. et al. National collaborative study of the prevalence of antimicrobial resistance among clinical isolates of *Haemophilus influenzae*. *Antimicrobial Agents and Chemotherapy*, **32**: 180-185 (1988).
15. Walsh, J.A., Warren, K.S. Selective primary health care: an interim strategy for disease control in developing countries. *New England Journal of Medicine*, **301**: 967-974 (1979).
16. Grant, J.P. *The state of the world's children 1984*. Oxford: United Nations Children's Fund and Oxford University Press (1983).
17. Riley, I., Carrad, E., Gratten, H. et al. The status of research on acute respiratory infections in children in Papua New Guinea. *Pediatric Research*, **17**: 1041-1043 (1983).
18. Snyder, J.D., Merson, M.H. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bulletin of the World Health Organization*, **60**: 605-613 (1982).
19. Campbell, H., Forgie, I.M., Lloyd-Evans, N. et al. Trial of co-trimoxazole versus procaine penicillin in young Gambian children. *Lancet*, **2**: 1182-1184 (1988).
20. Thomson, G., Sterky, G. Self-prescribing by way of pharmacies in three Asian developing countries. *Lancet*, **2**: 620-621 (1986).

-
21. Lerman, S.J., Shapard, D.S., Cash, R.A. Treatment of diarrhoea in Indonesian children: what it costs and who pays for it. *Lancet*, **2**: 651-654 (1985).
22. Hossein, M.M., Glass, R.I., Khan, M.R. Antibiotic use in a rural community in Bangladesh. *International Journal of Epidemiology*, **11**: 402-405 (1982).
23. Montefiore, D.G., Osoba, A.O. Antibiotic use in Nigeria. *Alliance for the Prudent Use of Antibiotics Newsletter*, **3**: 1-7 (1985).
24. Lansang, M.A., Lucas-Aquino, R., Tupasi, T. et al. Purchase of antibiotics without prescription in Manila, the Philippines. Inappropriate choices and doses. *Journal of Clinical Epidemiology*, **43**: 61-67 (1990).
25. Thamlikitkul, V. Antibiotic dispensing by drug store personnel in Bangkok, Thailand. *Journal of Antimicrobial Chemotherapy*, **21**: 125-131 (1988).
26. Stolley, P.D., Becker, M.H., McEvilla, J.D. et al. Drug prescribing and use in an American community. *Annals of Internal Medicine*, **76**: 537-540 (1972).
27. Aswapokee, N., Vaithayapichet, S., Heller, R.F. Pattern of antibiotic use in medical wards of a university hospital, Bangkok, Thailand. *Reviews of Infectious Diseases*, **12**: 136-141 (1990).
28. Marr, J.J., Mofefet, H.L., Kunin, C.M. Guidelines for improving the use of antimicrobial agents in hospitals: a statement of the Infectious Diseases Society of America. *Journal of Infectious Diseases*, **157**: 869-876 (1988).
29. Greenhalgh, T. Drug marketing in the Third World: beneath the cosmetic reforms. *Lancet*, **1**: 1318-1320 (1986).
30. Hosking, G. Drug marketing in the Third World. *Lancet*, **2**: 164 (1986).
31. Kunin, C.M., Staehr Johansen, K., Worning, A.M. et al. Report of a symposium on use and abuse of antibiotics worldwide. *Reviews of Infectious Diseases*, **12**: 12-19 (1990).
-