MULTIPLE-DRUG-RESISTANT SALMONELLA

Pages with reference to book, From 212 To 215

Raymond A. Smego Jr (Departments of Medicine, Community Health Sciences, The Aga Khan University Medical College, Karachi, Pakistan.)
ZalifIquar A. Bhutta (Departments of Pediatrics, The Aga Khan University Medical College, Karachi, Pakistan.)

Since demonstration of its efficacy in 1948[1] chloramphenicol has been the drug of choice for salmonellosis. Over the last two decades, however, emerging drug resistance among salmonella has become an issue of international concern and has necessitated revision of traditional treatment approaches. The therapy of serious Salmonella infections such as enteric fever, bacteremia, meningitis, osteomyelitis and the chronic carrier state is complicated in many parts of the world by the increasing, persistent and high-level resistance among Salmonella species to clinically useful antimicrobial agents such as chloram. phenicol, ampicillin and tnmethoprim-sulfamethoxazole (TMP-SMX). The search is under way for efficacious, safe and affordable treatment alternatives for resistant salmonellosis.
Enteric fever continues to be a serious public health problem in many parts of the developing world. [2,3] While reliable systems of reporting in the West indicate a decreasing incidence of enteric fever, accurate epidemiologic data are not available from the third world. Using data on the incidence of typhoid fever in control cohorts of recent typhoid vaccine trials in India, Egypt and Chile and from data collected in Indonesia by active surveillance of bacteriologically confirmed cases, one recent calculation arrived at an annual estimate of 12.5 million cases in the world (excluding China) (540 cases per 100,000 population of the developing world), of which nearly 7 million cases occur per year in South and East Asia[4]. Seroepidemiologic studies from geographic areas where notification is not based upon bacteriologic confirmation support a high estimated prevalence of enteric fever in much of the developing world. Persons at highest risk of infection are pre-school and school-age children and of major concern in Pakistan is the emergence of multidrug resistant typhoid n these age-groups[5]. Chioramphenicol-resistant strains of S. typhi have been reported sporadically and from epidemics around the world and may be endemic in many countries of Southeast Asia[6,7]. More worrisome, however, are reports of simultaneous plasmidspecified[8] resistance to chioramphenicol, ampicillin and sulfonamides as occurred in the outbreak of typhoid fever in central Mexico in 1972 involving more than 10,000 cases and with many fatalities[9,10] Multidrug-resistant S. typhi and S. paratyphi strains have recently been reported in Karachi[11]
S. typhünurium and other non-typhoidal Salmonella serotypes most commonly implicated in human disease are also developing multiple-drug resistance at an alarming rate. [6,7,12,13] Such species include S. heidelberg, S. newport, S. saint-paul, S. panama and S. Wein. Large outbreaks of disease caused by organisms resistant to the three clinically useful antibiotics have occurred in both industrialized and developing countries[6,7] Multiple-drug resistant S. zyphimurium in India has increased from 26.6% during 1972-77 to 90% during 1978-80. [14] These clinically resistant Salmonella have characteristically been associated with extensive and protracted epidemics and are now prevalent throughout much of Asia and the Middle East. [6,15] Hospital outbreaks in pediatric wards or neonatal units have been frequent. In contrast to common-source contamination usually associated with Salmonella outbreaks, many of these epidemics of drug-resistant cases have resulted from person.to-person spread. [15]
The selective pressure of unrestricted antimicrobial usage in most developing countries has contributed to the genesis of resistant Salmonella. Mounting evidence in the West suggests that the addition of antibiotics to farm animal feed for growth promotion may lead to drug-resistant strains capable of causing human disease[6,16]. As yet, there is no documentation of animal involvement either in the

acquisition or dissemination of multi-resistant strains in the third world. There is presently no consensus as to the optimal alternative treatment regimen for multiresistant Salmonella. Newer generation cephalosporins and quinolones are classes of antirnicrobials that possess special bacteriologic and pharmacologic properties and offer promise in the treatment of resistant salmonellosis. The potent activity, low toxicity, prolonged serum half-lives and good tissue penetration of the cephalosporins and the oral convenienöe of the quinolones are attractive features. High biliary concentrations achieved by these agents and possible penetration into choleliths suggests potential efficacy in eradicating the chronic carrier state. Third generation cephalosporins have superior in vitro activity against Enterobacteriaceae, including Salmonella. Against S. typhi, the third generation cephalosporins are two to twelve times more active than ampicillin and up to 500 times more active than chloramphenicol[17] For non-typhoidalSalmonella species, these new agents are up to 400 times more active than ampicillin or chioramphenicol.

Another new class of antimicrobials, the quinolones, are also being studied. These agents are related to nalidixic acid and are inhibitors of DNA gyrase and other enzymes. These agents include ciprofloxacin, norfioxacin, enoxacin, pefloxacin, amifloxacin and ofloxacin. Demonstration of their bactericidal activity against Enterobacteriaceae in cerebrospinal fluid, bone and intestinal tract suggests that they may be useful in the treatment of invasive Salmonella disease[7].

Other newer agents with in vitro bactericidal activity Salmonella include aztreonam, a monobactam antibiotic with excellent activity against gramnegative bacilli[18] iniipenem, a carbapenem[19] the fixed combination of amoxicillin plus clavulanic acid[20] and fosfomycin[21].

Clinical experience with new agents in the treatment of systemic salmonellosis is limited. In view of the usual discrepancy between ‘In vitro activity and therapeutic efficacy against salmonellosis, clinical extrapolation for candidate agents is generally not warranted, but preliminary animal and human studies are encouraging for several of these drugs. Ceftriaxone, moxalactam, cefotaxime and cefmenoxime were all effective in protecting mice given lethal doses of S. typhi and S. Schottmuelleri[22] Cefotaxime and moxalactam were both superior to ampicillin in the treatment of S. typhimurium infections in mice[23] .Ceftriaxone was significantly effective in reducing the bacterial burden within the reticuloendothelial system where salmonellae reside intracellularly. In a rabbit model for S. panama meningitis ceftriaxone, imipenem and ciprofloxacin were superior to ampicilin, chioramphenicol and TMP-SMX in sterilizing CSF[24].

Several case reports have found newer second and third generation cephalosporins clinically useful in treating Salmonella meningitis in humans, while others have reported treatment failures due to difficulty in sterilizing CSF and a tendency toward recurrences[6]. Additional controlled studies are needed to determine the role of these agents in the treatment of Salmonella meningitis.

A recent randomized comparative trial involving[25] children found cefoperazone as effective as chioramphenicol in the treatment of severe typhoid fever, as judged by the mean number of days until defervescence, mean number of days to the first negative blood culture after initiation of antibiotic treatment and the case-fatality rate25. In a dose-fmding study from Mexico, ceftriaxone in dosages of 3-4gm per day was found to be effective when given daily or twice daily in producing rapid clinical improvement and sterilization of blood cultures by 24 hours; no relapses occurred among 20 patients[26]. Similarly, ceftria.xone in a dose of 50-60mg/kg every 12 hours cured 13 of 14 cases of bacteremic typhoid fever[27]. In a study comparing once-daily N ceftriaxone administered for 7 days with IV or P0 chloramphenkol given for 14 days treatment outcomes were similar for both agents although diarrhea resolved earlier and patients more rapidly cleared their bacteremia in the ceftriaxonetreated group[28]. In 38 patients with culture-proven typhoid fever, oral ciprofloxacin administered every 12 hours for 14 days resulted in favourable clinical and bacteriologic outcomes[29].

Despite the potential advantages of the third generation cephalosporins, their cost and the need for

parenteral therapy limits their widespread use. Orally administered newer agents would appear to offer a more practical therapeutic alternative. Prospective, controlled studies are warranted to evaluate the clinical efficacy of potentially useful agents in the treatment of multidrug resistant salmonellosis. A multi-center, comparative trial of ceftriaxone versus fosfomycin is currently being initiated by the Departments of Medicine and Pediatrics at The Aga Khan University Hospital.

The medical and public health communities must anticipate future outbreaks of multidrugresistant salmonellosis, caused by both S. typhi an&nontyphoidal species. The development of effective and practical alternative therapy for resistant disease is clearly needed. An ominous possibility is that drug resistance may be associated with other factors which enhance the virulence or communicability of host strains. Further microbiologic experimentation will be required to confirm this theory. More likely, where the clinical impression is an increased severity of typhoid fever, various factors prQbably interrelate and lead to an increase in the number of persons coming into contact with larger inocula of organisms. This in turn, results in an absolute increase in typhoid cases and perhaps a higher prevalence of severe cases. Countries that report increased enteric fever severity share several characteristics including rapidly expanding populations, rapidly increasing urbanization, inadequate facilities for processing human wastes, decreasing water supplies per capita, intimate contact between human, food, and heavily contaminated water supplies and overburdened health systems[5]. Present and future control measures for salmonellosis must ensure provision of safe water supplies and effective sanitation for all.

REFERENCES

1. Woodward, T.E.,Smadel, J.E., Ley, H.L. Jr., Green, R. and Mankikar, D.S. Preliminary report on the beneficial effect of chioromycetin in the treatment of typhoid fever. Ann. Intern. Med., 1948; 29: 131.
2. Gangaxosa, E.J. Typhoid fever as a public health problem. Epidemiology and mode of transmission. Meeting of Sub-Committee on Live Oral Typhoid Vaccine, Geneva, Diairhoeal Diseases Control Programme, June 1-3, 1982.
3. WHO Scientific Woiking Group. Enteric infections due to Campylobacter, Yersinia, Salmonella, and Shigella. Bull. WHO., 1980; 58:519.
4. Edelman, R. and Levine, M.M. Summary of an international workshop on typhoid fever. Rev. Infect. DIs., 1986; 8:329.
5. Bhutta, Z.A. and Shaikh, S.A. Diagnostic difficulty in partially-treated typhoid. England, British Paediatric Association Annual Conference, 1987.
6. Editorial, unsigned. Drug resistance in Salmonellas. Lancet, 1982;1: 391.
7. Bryan, J.P., Rocha, H.' and Scheld, W.M. Problems in salmonellosis: Rationale for clinical trials with newer B-lactam agents and quinolones. Rev. Infect. Dis., 1986;8: 189.
8. Goldstein, F.W., Chumpitaz, J.C., Guevara, J.M., Papadopoulou, B., Acai, FJ., et al. Plasmid-mediated resistance to multiple antibiotics in Salmonella typhi. J. Infect. Dis., 1986; 153: 261.
9. Olarte, J., Galindo, E. Salmonella typhi resistantto chioramphenicol, ampicillin and other antimicrobial agents: Strains isolated during an extensive typhoid fever epidemic in Mexico. Antimicrob. Agents Chemother., 1973; 4:597.
10. Gonzalez.Cortez, A., Bessudo, D., Sanchez-Leyva, R., Fragoso, R., Hinajosa, M., et al. Water-borne transmission of chioramphenicol-resistant Salmonella typhi in Mexico. Lancet, 1973; 2: 605.
11. Smego, R.A. Jr., Zaidi, A.K.M., Mohammed, Z., Bhutta, Z.A. and Hafeez S. Multiply resistant Salmonella and Shigella Isolates. Safat, Kuwait, Third Kuwait International Medical Sciences Conference, 1987.
12. Koshi, G. Alarming increase in multi-chug resistant Salmonella typhimurium in Southern India. Indian J. Med. Res., 1981; 74:635.
13. Rowe, B., Frost, J.A., Threlfall, EJ. 'and Ward, L.R. Spread of a multiresistant clone of Salmonella

typhimurlum phage type 66/122 in Southeast Asia and the Middle East. Lancet, 1980; 1:1070.
14. Rangnekar, V.M., Banker, D.D. and Jhala, Hi. Antimicrobial resistance and incompatibility groups of R plasmids in Salmonella lyphimurium isolated from human sources in Bombay from 1978 to 1980. Antimicrob. Agents Chemother., 1983; 23:54.
15. Smith, S.M., Palumbo, PE. and Edelson, PJ. Salmonella stains resistant to multiple antibiotics; therapeutic implications. Pediatr. Infect. Dis., 1984; 3:455.
16. Holmberg, S.D., Osterhoim, M.T., Senger, LA. and Cohen, M.L. 'Drug-resistant Salmonella from animals fed antlinicrobials. N. EngI. I. Med., 1984; 311:617.
17. Preblud, S.R., Gill, C.J. and Campos, J.M. Bactericidal activities of chioramphenicol and eleven other antibiotics against Salmonella sps. Antimicrob. Agents Chemother., 1984; 25:327.
18. Sykes, R.B. and Bonner, D.P. Aztxeonam; the first monobactam. Am. J. Med., 1985; 78 (2A) :2.
19. Barza, M. Imipenem; first of a new class of betalactam antibiotics. Ann. Intern. Med., 1985; 103-552.
20. DeMol, P., Levy, J., Lepage, P. et a!. In Vitro comparative study of Hr 211, R015-8074 and Augmentin on Mrican multiiesistent Salmànella and Shigella (abstract /H 1305), in Programme and Abstracts of the 26th Inferscience Conference on Antimicrobial Agents and Chemotherapy. Washington, American Society for Microbiology, 1986.
21. Tones, MA., Borobio, N.y. and Perea, EJ. Synergism of fosfomycin-ampicillin and fosfomycin-chloramphenicol against Salmonella and Shigella. Curr. Chemother. ~1977; 1:671.
22. Beskid, G., Christenson, J.G., Cleeland, R., DcLorenzo, W. and Trown, P.W. In vivo activity of ceftriaxone (RO 13-9904), a new broad spectrum simisynthetic cephalosporin. Antimicrob. Agents Chemother., 1981; 20:159.
23. Anton, P.A., Kemp, J.A., Butler, T. and Jacob, M.R. Comparative efficacies of ceftriaxone, moxa lactum and ampicillin in experimental Salmonella typhimurium infection. Antimicrob. Agents Chemother., 1982; 22:3 12.
24. Bryan, J.P. and Scheld, W.M. Therapeutic evaluation of experimental Salmonella enteritidis meningitis (abstract H 666), in Program and Abstracts of the 24th Interscience Conference on Antimicrobial Agents. and Chemotherapy. Washington, American Society for Microbiology, 1984.
25. Pape, J.W., Gerdes, H., Oviol, L. and Johnson, W.D. Jr. Typhoid fever; successfnl treatment with cefoperazone. J. Infect. Dis., 1986; 153:272.
26. Macias-Hernandez, 0., Quintero, N.P., Campa-Uribe, G., Perez-Ruvalcaba, J.A., Hernandez-Bugarin, et al. Ceftriaxone in the treatment of typhoid fever: a dose.finding study (abstract H 1005), in Program and Abstracts of the rdInterscience Conference on Antimicrobial Agents and Chemotherapy. Washington, American Society for Microbiology, 1983.
27. Ti, T., Montero, E.M., Lam, F. and Lee, H. Cef triaxone therapy of bacteremic typhoid fever. Antimicrob. Agents Chemother., 1985; 28:540.
28. Islam, A., Butler, T., Nath, S.K. and Huq, N. Trial of ceftriaxone vs. chloramphenicol in typhoid fever. (abstract H166), in Program and Abstracts of the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, American Society for Microbiology, 1986.
29. Ramirez, CA., Bran, J.L. ,Meija, C.R. and Garcia, J.F. Open, Prospective study of the clinical efficacy of ciprofloxacin. Antimicrob Agents Chemother., 1985; 28:128.