Multidrug-Resistant Plague

Since the number of plague cases notified to the World Health Organization has increased and because, having been quiescent for many years, plague has reappeared in epidemic form in several countries including India, Malawi and Mozambique during 1994 while the number of enzootic foci is gradually expanding in some countries, plague is now considered a re-emerging disease. For instance, in the United States the number of states reporting human plague increased from 3 in the 1950s to 13 in the 1990s. Isolates of Yersinia pestis, the causative agent of plague, typically show susceptibility to antibiotics used against gram-negative bacteria. A report by Gallimand et al. 1997 concerns a 16-year-old boy in Madagascar who, during 1995, developed a febrile illness which initially was diagnosed as malaria and treated as such with quinine. Three days later, a right inguinal bubo, hyperpyrexia (41°C), delirium and prostration suggested that the patient suffered from plague which was subsequently confirmed by isolation of Yersinia pestis (strain 17/95) from bubo aspirate. He recovered on treatment with twice daily intramuscular streptomycin (2 g daily for 4 days) and oral trimethoprim-sulfamethoxazole (TMP/SMZ) (2 g daily for 10 days). Disk agar diffusion tests showed that the Y. pestis isolate was resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, tetracycline, minocycline and sulfonamides. It was susceptible to trimethoprim, cephalosporins, other aminoglycosides, and quinolones. It is thought that the patient's recovery was most likely due to the action of trimethoprim despite an absence of synergistic activity by sulfamethoxazole. The observed multidrug-resistance found to be mediated by a single plasmid which, in vitro, was readily transferred between Y. pestis 17/95 and E. coli and from 17/95 to other isolates of Y. pestis. This finding is of great concern.

An editorial by Dennis and Hughes 1997 raises several issues arising from the above finding of a multidrug-resistant Y. pestis isolate from a patient in Madagascar. One of these concerns the source of the plasmid in question. Rats, the main reservoir hosts of plague in Madagascar, are omnivorous and live in a fecally contaminated environment. It is suggested that transfer of a resistance plasmid from multidrug-resistant human fecal flora to Y. pestis is therefore more likely to occur in such rats than in fleas (vectors of plague) or in patients with plague. If that is indeed the case, there could be substantial public health implications. The authors emphasize that emerging and re-emerging infections in one region can have serious global implications. Another question concerns the appropriate responses by health authorities to multidrug-resistant plague. These center on a need for more information, especially regarding the potential for spread of resistant Y. pestis in its natural cycle. Research should focus also on determining drug resistance patterns in other plague foci and on evaluating alternative antibiotics, such as the fluoroquinolones for therapeutic and prophylactic purposes.

In this context, a recently published study by Frean et al. 1996 noted that, in practice, treatment of plague still relies mainly on the use of streptomycin, tetracycline and chloramphenicol. In view of the serious and highly fatal complications of plague such as septicemia, pneumonia and meningitis, these authors also regard the range of commonly used antimicrobials as rather limited and needing supplementation with newer antibiotics. Clinically, the sulfonamides, TMP/SMZ, kanamycin and ampicillin have been less effective, or more toxic. These workers therefore assayed 100 northern Namibian, human Y. pestis isolates in vitro against 14 antimicrobial drugs which included those commonly used in the treatment and/or prophylaxis of plague and several that are new or under investigation. As expected, among the drugs that have previously been used to treat plague, they found all isolates to be susceptible to streptomycin, TMP/SMZ, chloramphenicol, tetracycline, doxycycline and amoxicillin. Ceftoxime and the fluoroquinolones levofloxacin and ofloxacin were highly active against all the Y. pestis isolates tested and, among the newer drugs, this was valid also for faropenem and the ketolide RU004. However, the authors draw attention to a Russian study which reported the emergence of quinolone resistance in a virulent Y. pestis strain following its exposure to a single dose of nalidixic acid. Clearly, more studies are needed.

Reference