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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Drug Sensitivity to *Salmonella typhi*: Coming Full Circle

Chawla V, Chandra RK, Bhujwala RA, Ghai OP. A comparative trial of hetacillin and chloramphenicol in typhoid fever. *J Pediatr* 1970;77:471-3.

In 1970, Chawla et al were concerned about the “rampant use” of chloramphenicol for treatment of typhoid fever owing to its serious toxic effects. They studied hetacillin (a synthetic derivative of 6-aminopenicillanic acid) as a safer alternative and concluded that it had comparable efficacy with fewer side effects.

Fifty years later, typhoid fever remains a public health problem, especially in developing countries, causing approximately 11 to 21 million cases and 128 000 to 161 000 deaths annually, with the peak incidence in children aged 5 to <15 years. Up to the 1970s, chloramphenicol was widely used to treat enteric fever. It was replaced by ampicillin and trimethoprim-sulfamethoxazole due to the emergence of resistant strains. In the early 1980s, there was a rapid emergence of IncHI1 plasmid-mediated resistance to all 3 drugs, in multidrug-resistant strains. This prompted the use of fluoroquinolones, which were highly efficacious.

The late 1990s witnessed decreased sensitivity to fluoroquinolones (primarily ciprofloxacin and ofloxacin) mainly via chromosomal mutations and emergence of intermediate and fully insensitive strains, such as nalidixic acid-resistant *Salmonella typhi*, especially in Asia. Third-generation cephalosporins have since replaced fluoroquinolones for empirical therapy of typhoid. The addition of azithromycin to cephalosporins may be warranted in clinically nonresponsive patients.^{1,2} Recently, *S. typhi* strain H58, which is resistant to 3 primary drugs, fluoroquinolones and cephalosporins, has emerged in certain pockets of the Indian subcontinent, especially Pakistan, since 2016; these strains are now labeled as extensively drug-resistant.³ Alarming, sporadic cases of azithromycin resistance have also started to appear in the same geographical region. An interesting twist: due to decreased use, sensitivity to chloramphenicol, ampicillin, and co-trimoxazole is reemerging in some regions, including India.

The journey portrayed by the bacilli shows extreme variability in sensitivity pattern based on geographical region, prevalent strains, and antibiotic usage profiles. Stringent and continual microbiological surveillance and appropriate antibiotic stewardship need to be integrated into the global strategy against typhoid to address antimicrobial resistance.

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