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Evolution of Antimicrobial Resistance in Shigella since the Turn of 21st Century, India

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Abstract : Multidrug resistant shigellae have emerged as a therapeutic challenge in India. At our 2000 bed tertiary care referral centre in Chandigarh, North India, which caters to a large population of 7 neighboring states, antibiotic resistance in Shigella is being constantly monitored. Shigellae are isolated from 3 to 5% of all stool samples. In 1990 nalidixic acid was the drug of choice as 82%, and 63% of shigellae were resistant to ampicillin and cotrimoxazole respectively. Nalidixic acid resistance emerged in 1992 and rapidly increased from 6% during 1994-98 to 86% by the turn of 21st century. In the 1990s, the WHO recommended ciprofloxacin as the drug of choice for empiric treatment of shigellosis in view of the existing high level resistance to agents like chloramphenicol, ampicillin, cotrimoxazole and nalidixic acid. First resistance to ciprofloxacin in S. flexneri at our centre appeared in 2000 and rapidly rose to 46% in 2007 (MIC>4mg/L). In between we had an outbreak of ciprofloxacin resistant S.dysenteriae serotype 1 in 2003. Therapeutic failures with ciprofloxacin occurred with both ciprofloxacin-resistant S. dysenteriae and ciprofloxacin-resistant S. flexneri. The severity of illness was more with ciprofloxacin-resistant strains. Till 2000, elsewhere in the world ciprofloxacin resistance in S. flexneri was sporadic and uncommon, though resistance to co-trimoxazole and ampicillin was common and in some areas resistance to nalidixic acid had also emerged. Fluoroquinolones due to extensive use and misuse for many other illnesses in our region are thus no longer the preferred group of drugs for managing shigellosis in India. WHO presently recommends ceftriaxone and azithromycin as alternative drugs to fluoroquinolone-resistant shigellae, however, overreliance on this group of drugs also seems to soon become questionable considering the emerging cephalosporin-resistant shigellae. We found 15.1% of S. flexneri isolates collected over a period of 9 years (2000-2009) resistant to at least one of the third-generation cephalosporins (ceftriaxone/cefotaxime). The first isolate showing ceftriaxone resistance was obtained in 2001, and we have observed an increase in number of isolates resistant to third generation cephalosporins in S. flexneri 2005 onwards. This situation has now become a therapeutic challenge in our region. The MIC values for Shigella isolates revealed a worrisome rise for ceftriaxone (MIC90:12 mg/L) and cefepime (MIC90:8 mg/L). MIC values for S. dysenteriae remained below 1 mg/L for ceftriaxone, however for cefepime, the MIC90 has raised to 4 mg/L. These infections caused by ceftriaxone-resistant S. flexneri isolates were successfully treated by azithromycin at our center. Most worrisome development in the present has been the emergence of DSA(Decreased susceptibility to azithromycin) which surfaced in 2001 and has increased from 4.3% till 2011 to 34% thereafter. We suspect plasmid-mediated resistance as we detected qnrS1-positive Shigella for the first time from the Indian subcontinent in 2 strains from 2010, indicating a relatively new appearance of this PMQR determinant among Shigella in India. This calls for a continuous and strong surveillance of antibiotic resistance across the country. The prevention of shigellosis by developing cost-effective vaccines is desirable as it will substantially reduce the morbidity associated with diarrhoea in the country

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