0021-7557/12/88-04/366
Jornal de Pediatria

Antibiotic therapy in acute diarrhea associated with *Shigella*: what is the best option?

Dear Editor,

Nunes et al.[1] highlight the finding of 77.1% of bacterial resistance in *Shigella* samples isolated from children with acute diarrhea in Teresina, state of Piauí, Brazil.[1]

International and national guidelines recommend antibiotics as a supplementary measure in the treatment of children with acute diarrhea and blood in stool (dysentery presumably caused by *Shigella*),[2-4] respecting the profile of regional sensibility to antimicrobials.[2,3] However, usually antimicrobials are prescribed before the results of coproculture and antibiogram are available. In Brazil, combined trimethoprim-sulfamethoxazole therapy is recommended for diarrhea caused by *Shigella*.[4]

The World Health Organization (WHO)[2] recommends the use of ciprofloxacin at any age.

As options, other fluoroquinolones are suggested, as well as ceftriaxone in cases of multidrug resistance. Azithromycin is an alternative option in adults.[2] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[3] recommends azithromycin as a first choice, and third-generation cephalosporin (ceftriaxone), nalidixic acid, and fluoroquinolones as alternative options. Fluoroquinolones are reserved for patients over 17 years old.[3] Neither WHO[2] nor ESPGHAN[3] recommend the use of trimethoprim-sulfamethoxazole.

The Office of Health Surveillance of the Brazilian Ministry of Health[4] recommends trimethoprim-sulfamethoxazole as the first choice in severe cases of *Shigella* infection. The prescription of quinolones is reserved for cases of bacterial resistance and is contraindicated in children and pregnant women.[4]

In this context, in 2011, we decided to conduct a literature review in the MEDLINE and LILACS databases on the susceptibility to trimethoprim-sulfamethoxazole of *Shigella* samples isolated in Brazil. Five articles were retrieved, published between 1995 and 2006[5-9]; all of them had antibiograms performed by the disk method.

The *Shigella* samples analyzed in those articles,[5-9] together with the ones analyzed in the article published in Jornal de Pediatria,[1] totalize 658. Of these, 86.6% (570/658) were resistant to trimethoprim-sulfamethoxazole. Resistance to other antibiotics was as follows: 50.0% (330/658) for ampicillin, 7.0% (47/658) for ceftriaxone, 4.7% (22/465) for nalidixic acid, and 1.0% (6/552) for ciprofloxacin. Thus, considering in vitro sensitivity results, it is possible to infer that the trimethoprim-sulfamethoxazole association should not be used to treat infections by *Shigella*. As a result, one question remains: what is the best antimicrobial available to treat *Shigella* infections?

Considering that the samples of *Shigella* in Brazil were not tested for azithromycin and that about 90% were resistant to trimethoprim-sulfamethoxazole, it can be concluded that the best therapeutic options are nalidixic acid (55 mg/kg/day divided into four oral doses) and ceftriaxone (50-100 mg/kg/day intravenously or intramuscularly for 3-5 days). WHO recommends the use of ciprofloxacin rather than nalidixic acid due to its low cost (open patent), ease of administration (two rather than four oral doses), absence of quinolone-induced arthropathy seen in animals but not in humans, and also because nalidixic acid-resistant *Shigella* strains may show cross-resistance to ciprofloxacin and other quinolones in areas where nalidixic acid is used as the first choice. However, ciprofloxacin has not been approved for pediatric use in Brazil.

In our experience, especially in hospitalized cases with acute dysentery, ceftriaxone has been used for a few years already.

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Marina H. C. Carrari
Pediatrician. Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.

Soraia Tahan
Physician. PhD, Disciplina de Gastroenterologia Pediátrica, Departamento de Pediatria, UNIFESP, São Paulo, SP, Brazil. Professor, Instituto de Pesquisa Unolab, Departamento de Ciências da Saúde, Centro Universitário Fundação e Instituto de Educação de Osasco (UNIFIEO), Osasco, SP, Brazil.

Mauro B. Morais
Associate professor, tenured professor and chief, Disciplina de Gastroenterologia Pediátrica, Departamento de Pediatria, UNIFESP, São Paulo, SP, Brazil.

No conflicts of interest declared concerning the publication of this letter.

http://dx.doi.org/10.2223/JPED.2220

Authors' reply

Dear Editor,

There is a consensus that, although shigellosis is often self-limited and successfully treated with fluid and electrolyte replacement therapy only, more severe cases of dysentery require the administration of antimicrobials, especially undernourished patients or those with a compromised immune system. In fact, the World Health Organization recommends early establishment of antibiotic therapy directed against *Shigella* for individuals with inflammatory diarrhea.[1]

In Brazil, the Ministry of Health still recommends the trimethoprim-sulfamethoxazole association as the first choice treatment for patients with shigellosis whenever the use of antimicrobial drugs is indicated. In cases of bacterial resistance, quinolones should be used, but these are non indicated for pregnant woman and children.[2]

Carrari et al.[3] described the use of ceftriaxone for the treatment of patients hospitalized with dysentery, given the high rates of trimethoprim-sulfamethoxazole resistance found by those authors. Indeed, a high prevalence of *Shigella* samples that are resistant to this association of antimicrobials has been observed in different regions of Brazil.[4-8] Thus, considering the great possibility of therapy failure when trimethoprim-sulfamethoxazole association is employed for patients with *Shigella* dysentery, other options should be considered.

In Brazil, *S. sonnei* and *S. flexneri* are almost exclusively observed. Our results corroborate data found in the literature, which show that the distribution of *Shigella* species in different Brazilian regions is uneven. We observed a predominance (≈ 80%) of *S. flexneri* among children with shigellosis in Teresina,[9] while in Belo Horizonte, *S. sonnei* was associated with almost 90% of the cases.[10]

In addition, our experience points to differences in the antimicrobial susceptibility profiles of *S. sonnei* and *S. flexneri*. All samples included in our study groups were susceptible to nalidixic acid, ceftriaxone, and ciprofloxacin. Regarding trimethoprim-sulfamethoxazole and ampicillin, rates of about 85 and 100% were observed for S. sonnei, and of 50 and 70% for *S. flexneri*, in southeastern and northeastern Brazil, respectively. Ampicillin resistance, in turn, was not found in any sample of *S. sonnei* and in approximately 65% of *S. flexneri* strains in the state of Piauí; in Minas Gerais, resistance rates of approximately 15 and 100% were observed for *S. sonnei* and *S. flexneri*, respectively.[9,10]

According to the recommendation of the Brazilian Ministry of Health, antimicrobial drugs should be indicated for the treatment of patients with shigellosis regardless of diagnostic confirmation via coproculture and antibiogram.[2] Taking into consideration that, in most cases, treatment is initiated prior to a result of a coproculture – a poorly sensitive, expensive and time-consuming test – and thus without the establishment of the antimicrobial susceptibility profile of the etiologic agent in question, safe treatment options, based on local epidemiological data, should be adopted.

In this scenario, nalidixic acid, ceftriaxone, and ciprofloxacin emerge as suitable options; treatment definition should be based on the particularities of each patient. Ceftriaxone is available only in an parenteral formulation, and therefore it is more suitable for hospitalized patients; however, the high cost of this antimicrobial and the scarcity of data pointing to its efficacy limit its use.[1] Moreover, nalidixic acid and ciprofloxacin are recommended for outpatient treatment. With regard to ciprofloxacin, although there is not a consensus,[1] the Brazilian Ministry of Health imposes restrictions on its use in children.[2] Finally, nalidixic acid has been shown to have a low therapeutic efficacy, even when susceptibility of the etiologic agent is confirmed in vitro.[1]

In view of the above, as mentioned by Nunes et al.,[9] indeed the use of sulfamethoxazole-trimethoprim for the empirical treatment of patients with dysentery in Brazil is not appropriate and should be restricted to cases for which antimicrobial susceptibility results are available. These data also suggest that the recommendation of the Ministry of Health regarding the use of this antimicrobial for the treatment of patients with shigellosis should be revised.

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Mireille Ângela Bernardes Sousa
PhD, Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais (UFMG) e Hermes Pardini, Belo Horizonte, MG, Brazil.

Maria do Rosário Conceição Moura Nunes
PhD, Departamento de Parasitologia e Microbiologia, Instituto de Ciências da Saúde, Universidade Federal do Piauí, Teresina, PI, Brazil.

Edilberto Nogueira Mendes
MD, PhD, Departamento de Propedêutica Complementar, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.

Luciano Amedée Péret-Filho
MD, Departamento de Pediatria, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.

Francisco José Penna
MD, Departamento de Pediatria, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.

Paula Prazeres Magalhães
PhD, Departamento de Microbiologia, Instituto de Ciências Biológicas, UFMG, Belo Horizonte, MG, Brazil.

No conflicts of interest declared concerning the publication of this letter.

http://dx.doi.org/10.2223/JPED.2221