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Shigellosis update: Advancing antibiotic resistance, investment empowered vaccine development and green bananas

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Abstract

Purpose of review—Shigella is the principal cause of clinical dysentery and an important cause of morbidity and mortality among children in impoverished regions. The purpose of this review is to present key findings in the areas of epidemiology, disease control, and treatment of shigellosis.

Recent findings—Recent research activity has advanced the understanding of the epidemiology and host pathogen interactions. Increased investment and activity in the area of vaccine development has lead to a diversification of candidates and ongoing technical advances yet continues to yield disappointing results in clinical trials in endemic populations and among the most relevant age groups (children under two years of age). The description of the rapid spread of quinolone resistance requires monitoring to ensure appropriate case management, particularly in Southeast Asia. The evaluation of adjunctive nutritional therapy in endemic areas has supported the use of green bananas in shortening the duration of Shigella dysentery and persistent diarrhea due to Shigella as well as improving weight gain in early convalescence.

Summary—Despite a great level in activity in basic sciences, there continues to be a large gap in the ability to translate these findings into disease control measures or therapeutic options for individuals living in areas in which shigellosis is endemic.

Keywords

Shigella; dysentery; diarrhea

Introduction

Diarrhea is a principal cause of morbidity and mortality in children living in poverty in the developing world. Improved case management of acute dehydrating diarrhea through the use of oral rehydration therapy has increased the relative contribution of dysentery and persistent diarrhea as to the present day burden of diarrheal disease. Shigella is the enteric infection

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most consistently associated with the clinical dysentery syndrome [1], prolonged episodes of acute diarrhea and the development of persistent diarrhea. Episodes of shigellosis may result in protein losing enteropathy [2] and subsequent linear growth shortfalls in children [3]. Shigella is also an important cause of traveler's diarrhea and diarrhea in military units. *Shigella dysenteriae* 1 is also still the cause of large outbreaks of disease with high mortality rates in displaced persons [4]. These factors, taken in hand with the progressive emergence of antibiotic resistance to Shigella have long made this organism a priority for vaccine development by the World Health Organization through the initiative for vaccine research. This interest has received recently complemented by funding for vaccine development from the Bill & Melinda Gates Foundation. Funding in the basic sciences and pathogenesis remains strong as *Shigella flexneri* is one of the most studied pathogens and a key model organism used to understand the type III secretion apparatus [5], intracellular persistence [6], and antiapostosis factors [7].

Epidemiology

Shigellosis results from the exposure to low inoculums of Shigella dysenteriae, Shigella flexneri, Shigella boydii and *Shigella sonnei.* In highly endemic areas, peak infection rates occur in the second year of life. Although there is evidence of protective immunity following natural infection, the existence of 46 serotypes, despite a measure of cross reactivity between O antigens, means that children routinely experience multiple episodes of shigellosis in early childhood in areas where transmission is intense.

Shigella has shown a poorly explained temporal procession in serogroup dominance. At the beginning of the 20th century, *Shigella dysenteriae* was the dominant group, in the 1930s and 1940s, *Shigella flexneri* replaced *Shigella dysenteriae* as the dominant serogroup in the absence of epidemics. Epidemiologic transition, seen first in Israel, Argentina, and now being described in Vietnam[8] has consistently favored the emergence of *S. sonnei* as the dominant serogroup, although the reason for this is not clear. In the United States, shigellosis appears to be decreasing in incidence. It is the third most frequent FoodNet pathogen in sentinel states with a population based incidence of 3.99/100,000, but rates in 2009 were found to be significantly decreased from incidence rates in between 1996-1998 [9]. It is unclear if this represents a temporary dip in incidence or if represents the beginning of a durable trend.

A very complete molecular investigation into the *Shigella flexneri*, initially described as variant serotype X (later termed 200217), first described in 2001 but rapidly became the most prevalent serotype in 8 of 11 provinces under surveillance in China significantly added to our understanding of the dissemination and spread of isolates [10]. Full genome sequencing was done one isolate and comparative genomics of extended multilocus sequence typing (MLST) was done on 37 serotype X variants and 74 isolates of other serotypes from provinces under surveillance as well as reference strains 2457T, Sf301, and Sf8401. Sixty-nine of the 74 strains representing other serotypes also had the same MLST strain type, which wasidentical but distinct from reference strains 2457T, Sf301, and Sf8401. This work was complemented by pulsed field gel analysis on 655 isolates from eleven provinces which demonstrated 154 pulse types, 24 of which were displayed by more than

one serotype. One pulsetype described over 30% of these isolates. The interpretation of this extensive investigation which employed a variety of techniques that allow for the view of the epidemic to occur through a variety of lenses, is that the predominant sequence type (ST91 represented by 200217) has been circulating in China prior to its recognition. For reasons that are not clear, it rapidly expanded and underwent multiple serotype switching events and acquired the resistance to multiple antibiotics during its spread. The importance of this finding is not to be understated-generally serotypes are used as markers of clonality (not sensitive ones, but markers nonetheless). That assumption would clearly be in error in this epidemic- serotype switching was well documented (an estimate of >30 such events occurred) and allowed the spread of this new distinct strain. Furthermore, the careful documentation of this switching has sobering implications for vaccine development, as the foundation of the success of a vaccine based on O-antigens requires the temporal stability of principal serotypes (assuming the vaccine is polyvalent, as is generally considered to be a prerequisite).

Pathogenesis

The detailed understanding of the more than 30 effectors of the type III secretion system continue to be expanded upon and clarified (for recent detailed reviews see [5;6] and [11]) and a key mechanism of host recognition of organisms with type III secretion systems was elucidated [12]. Recently the understanding of the host pathogen interaction has included greater study of factors that decrease intestinal epithelial turnover thru anti-apoptotic factors such as the soluble form of pilus protein FimA [7], and basement membrane adherence, mediated by OspE [13]. The interaction of the host defenses and Shigella pathogensis is also an area of expanded activity (se Ashida[14]) including the demonstration of enhanced epithelial infection of *Shigella flexneri* upon interaction with factors liberated during neutrophil degranulation [15], the downregulation of the host immune system via OspB and OspF's interaction with the retinoblastoma protein [16], and IpaH9.8s downregulation of NF-kappaB mediated immune response [17]. Additional important contributions included a human explant model for the study of early steps in Shigella infection [18] and a flouresence microscopic technique to allow for the evaluation of intracellular vacuole trafficking and activity [19] both of which will be useful platforms to expand our understanding of host pathogen interactions.

Treatment

The progressive development of antibiotic resistance in Shigella isolates is not new. Ampicillin and trimethoprim-sulfamethoxazole, once affordable mainstays of therapy have long ago lost efficacy in most Shigella endemic regions. Nalidixic acid was an alternative for a brief period only as resistance rapidly developed in Asia. Ciprofloxacin was a highly effective alternative, despite the reservations of its use in children, but resistant Shigella resistant to Ciprofloxacin is increasingly common in India and in traveler's returning from India [20] and a recent report from Banglore described an increase of resistance from 0-48% in a five year period between 2002 and 2007[21]. Flouroquinolone resistant strains from the region were found to have mutations in gyrA and parC and had developed an active efflux system [22]. Ceftriaxone offers an alternative, but there are recent reports of Shigella

resistant to ceftriaxone from India [23] and Vietnam [24] and Shigella resistant to Azithromycin has also been reported [25].

Clearly with these recent descriptions, regional antibiotic susceptibility patterns has to be given greater importance in order to ensure adequate case management. The adequate dissemination of this information to relevant providers who are often non-physicians (nurses, pharmacists, health care workers) in impoverished areas is a frequently overlooked step in the implementation of effective antibiotic therapy. At a regional or national level, antibiotic recommendations for Shigella and dysentery (treatment for dysentery in cases where stool culture is not available should be targeted at Shigella) should be adapted centrally and likely input into the integrated management of childhood illness treatment protocol. In the absence of local data, the recommendations from the World Health Organization should be followed [26]. A recent review of the efficacy of this treatment estimates that this treatment is still efficacious, although the emergence of new more resistant strains that were not known during the time that studies conducted during the window of this analysis of 99% is a likely overestimate [27]. First line therapy is Ciprofloxacin (in all age groups, including pediatrics), second line is Pivmecillinam (where available), Ceftriaxone, or Azithromycin. Azithromycin has the added advantage of also treating most isolates of Campylobacter, a second major cause of dysenteric diarrhea in children under the age of two years [28]. Children under the age of five in endemic areas should also receive zinc 10 mg/day if 0-6 months of age and 20mg/day for children over the age of six months. Treatment aimed at cases in non-endemic areas has also recently been reviewed and is similar although Azithromycin was favored as first line treatment in children [29].

Nutritional therapy is also warranted in shigellosis. The relationship between undernutrition and Shigellosis is strong-undernutrition significantly increases the incidence of shigellosis and is also associated with more severe disease [28;30]. In endemic areas nutritional therapy should be considered as adjunct therapy that is guided by the treatment team. In a recent Venezuelan study of children recovering from persistent diarrhea in which Shigella was one of the principal underlying etiologies, a trial of isocaloric feeds with yogurt and green bananas showed increased weight gain and decreased diarrheal duration in the green plantain group [31]. This work was complemented by a clinical trial of green bananas as adjunctive therapy in male children with Shigella and dysentery [32]. All children received Ciprofloxacin, and children receiving green bananas had an increased percent of clinical cure at day 5 from 67 to 85%, decreased stool myeloperoxidase activity at day 5, and decreased number of stools/day starting 3 days following the initiation of therapy. Green bananas are widely available and affordable in endemic areas of Asia, Africa, and South America where shigellosis is endemic. The evidence would now support their specific recommendation in the management of children over the age of six months in endemic areas where they are available. This is the only recent good news in Shigella therapy at a time where antibiotic resistance is threatening currently recommended treatment strategies.

Post infectious complications

There was a recent growing interest in the post infectious complications of Shigellosis including reactive arthritis [33;34] and post-infectious irritable bowel syndrome[35]. Reactive arthritis is the common term to the inflammatory sequelae following infection with Shigella, Campylobacter, Salmonella, Yersinia or Chlamydia (see [36] for recent review). Although there is evidence that these infections are associated with a spondyloarthropathy, particularly severe in HLAB27+ individuals, there is no precise definition of the disease, which may include arthritis (predominantly in the joints of the lower extremities), enthesopathy, inflammatory lower back pain, dactylitis, and less frequently urethritis and conjunctivitis. The criteria derived from the 1995 International Workshop on Reactive Arthritis [37] are considered inadequate by many authors, and there is a general consensus that improvements are needed. Beyond the lack of a clear clinical or laboratory parameter for case definition is the small number of studies done in US and European populations, not in populations where the disease is endemic. Regardless of definition, there is clear evidence that a small portion of individuals with dysentery do go on to develop a chronic progressive spondyloarthropathy, the management of which is classically challenging if it does not respond to first line non steroidal anti-inflammatory agents or second line disease modifying agents such as methotrexate or azathioprine. There is some anecdotal evidence of the successful use of infliximab in the treatment of chronic reactive arthritis resistant to these therapies although results from randomized clinical trials are not available [38]. The rising interest in arthritis following natural infections with Shigella was sufficient to trigger the assembly of an expert panel to analyze this possible adverse effect with the development of Shigella vaccines under development [34]. It was concluded that the risk was likely offset by disease burden reduction in highly endemic areas, but called for Phase I subjects to be screened for HLA-B27 and excluded if positive. Additionally the panel concluded that future Phase 2 and Phase 3 trials have follow-on surveillance to evaluate the incidence of reactive arthritis.

In a recent case control study of children in Italy[39] with diarrhea caused by Salmonella, Shigella or Campylobacter there was a significant association with these bacteria and the development of a gastrointestinal disorder in 87% cases significant with IBS case definitions. Remarkably, 43% (6 of 14) of children with prior Shigella infections were found to have symptoms of post-infectious gastrointestinal disease, whereas symptoms were present in only 11% of control subjects. Haagsma et al [35] published a report of post infectious inflammatory bowel syndrome developing in 9% if patients with prior Campylobacter, Salmonella, or Shigella infections in the Netherlands. Despite the differences in patient populations and prevalence, both suggest that lasting effects of shigellosis occurs frequently following invasive diarrhea in the developed world.

Developments in Shigella vaccines

The increased investment in Shigella vaccines has stimulated the development of candidate vaccines from multiple groups. Predominant among new candidates are polysaccharide conjugates, synthetic conjugates, invasion complex based, and live attenuated vaccines (recently reviewed in [40;41]).

Despite a thorough understanding of Shigella O antigen structure [42] and improved techniques for enhancing immunogenicity of the polysaccharide unit there was disappointing news from a field trial of Shigella conjugates in a pediatric population in Israel [43]. This trial included the evaluation of both a *Shigella sonnei* conjugate and a *Shigella flexneri*-2a conjugate. There was no efficacy in 1-2 year old children, the key age group infected in highly endemic areas, whereas the vaccine demonstrated an efficacy of 71.1% in 3-4 year olds. The *S. flexneri* results were limited by the occurrence of only 7 documented cases of *S. flexneri* 2a infection in 1315 children, so no efficacy information was able to be obtained. It is hoped that improved techniques for enhancing immugenicity of the polysaccharide unit [44] will bring improved protection to the most relevant age groups. Synthetic conjugates allows for improved standardization and avoids the risk of LPS contamination and a synthetic *S. flexneri*-2a conjugate has recently shown immunogenicity in mice and offers an alternate strategy [45], albeit in very early stages of development. Similarly advances are being made in the purification and evaluation of candidates from major outer membrane proteins (MOMPs) of *Shigella flexneri* 2a which is an important development offering the hope of a candidate which is more likely to be cross-reactive[46]. Invasin complex based vaccines (Invaplex), a purified extract of *Shigella flexneri*-2a containing LPS including IpaB and IpaC, is an alternative approach that has also demonstrated immugenicity in early trials [47]. Lastly, a second generation virG(iscA) *Shigella sonnei* live attenuated candidate vaccine more highly attenuated via the loss of ShET-1, ShET-2, and MsbB2 (which makes the lipid A portion of LPS less endotoxic) have been shown to be immugenic in guinea pigs and are hoped to be less reactogenic when moved forward into human trials[48].

These advances are important, but are far from what is needed to adequately protect communities from shigellosis in the developing world. For example, in a highly endemic area in Peru where the incidence of shigellosis is 0.34 episodes per child-year[28] in children under the age of five a vaccine that conferred complete protection against *S. flexneri* 2a would prevent 34.3% of the cases of *S. flexneri*, but only 22.3% of the cases of Shigella. Alternatively a vaccine conferring 100 efficacy and *Shigella flexneri* 2a, 3a, and 6 would protect children against 72.6% of the incident cases of shigellosis caused by *S. flexneri*, but only 47.5% of all cases of shigellosis. Clearly, we are still far from a vaccine offering coverage that would have a major impact on shigellosis burdens in children in the developing world.

Conclusion

In the near future, the key measures to control the burden of disease from shigellosis will be improved access to water and sanitation, access to education for women, and the control of undernutrition in children in endemic areas. Improved case management is also critical and should include regional monitoring of antibiotic resistance and the inclusion of treatment flow charts with specific antimicrobials specified that have been demonstrated to be effective *in vitro* in the region. This information must be included into management guidelines (such as the integrated management of childhood illness) available to local clinicians, and non-clinician attendants (nurses, pharmacists, health care workers) in endemic areas. Adjuvant therapy with nutritional supplementation following shigellosis, or dysentery, should include

nutritional therapy, including zinc. In areas where green bananas are available, caregivers should be encouraged to include them as a staple in the treatment and early rehabilitation period.

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