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An introduction to Shigellosis and strategies against potent drug

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Abstract

Shigellosis is a global human health problem caused by *Shigella* species spreading through highly contaminated food and water. Four species of *Shigella* i.e. *S. dysenteriae, S. flexneri, S. boydii and S. sonnei* are able to cause the disease. Worldwide, 90 million cases of shigellosis have been reported according to the World Health Organization. In order to control fatality of shigellosis different strategies have been used to develop broadspectrum antibiotics and multivalent vaccines which may reduce mortality rate.

Key-Words: Shigellosis, Shigella, vaccines, facultative anaerobe, antibiotics, Immunity

Introduction

Shigellosis, an acute gastrointestinal infection caused by *Shigella* species spread via contact with the contaminated fecal matter and by consumption of contaminated food, water and fomites. Around 90 million cases of shigellosis have been reported each year, according to the World Health Organization and 108,000 deaths due to severe infection, most of which occur in the developing world and affect children under the 5 years of age. In the United States, 14,000 shigellosis cases are reported annually, with most cases occurring among children ages 1 to 4 years(Kweon MN, 2008).In 2010, annual shigellosis mortality was estimated at 123,000 deaths (8.5 percent of all deaths attributed to diarrhea) and approximately 1 percent of all deaths in children 28 days to 5 years of age (Lozano et al, 2012). In Africa and South Asia it was observed from analysis of registered case of shigellosis and stool culture data projects that Shigella may contribute to an additional 40,000 deaths per year among age-groups older than five years (Lamberti et al, 2014). According to analysis in 2010that shigellosis was much more commonamong peoples than cholera and typhoid (Kotloff et al, 1999). Travelers and deployed military service members visiting Shigella-endemic areas also frequently suffer from shigellosis (Murray et al, 2010; Vos et al, 2010). General Symptoms include diarrhoea, abdominal pain, fever, nausea and vomiting.

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In healthy adults, the infection generally resolved on its own in five to seven days, but if left untreated, can lead to hospitalization or death, especially among young children and adults with weakened immune system and have low concentration of maternal antibody(Edwards, 1999).The genus *Shigella* is divided into four subgroups that for medical purposes continue to be treated as species: *Shigella dysenteriae*,*Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei* (Bopp et al., 2003; Chin, 2000). Out of four species of *Shigella*, *Shigella boydii* infection has been rarely reported in developed countries and is generally observed in those individuals who have travelled from developed to developing regions and soldiers serving under field conditions are also at an increased risk to develop *shigellosis*(Janda & Abbott, 1998). Nowadays there is no effective treatment and preventive measure available against severe cases of shigellosis. Drug resistant bacterium has been observed due to this reason a potent and effective drug hard to find. In order to design potential drug crucial protein of particular species of *Shigella* will have to be target and find complementary ligand to inhibit exponential growth of bacteria which may be beneficial to eradicate widespread disease. Innovative strategies which have to be develop in this direction including broad spectrum antibiotics and vaccines against particular serotype which could provide some relief to rescue from this dreadful disease.

General features on *Shigella*

Shigella is a well-known gram negative, non-sporulating, facultative anaerobe, rod shaped human pathogen and causes diseases such as diarrhea and bacillary dysentery. *Shigella* is highly invasive in the

colon and the rectum, and is able to proliferate in the host cell cytoplasm, triggering an inflammatory reaction. Infections with *Shigella* species cause approximately 600 000 deaths worldwide annually. Two-thirds of all cases and most of the deaths occur among children under 10 years of age(Chin, 2000).It is more prominent in developing countries and rarecases have been observed in highly developed countries due to proper sanitation and excellent medical care.

Structurally, *Shigella* is Gram-negative non-motile bacteria. It is believed from previous research that *Shigella* speciesare non-motile but some evidence support that they do in fact have monopolar flagella of about 10 microns in length and 12-14 nm in diameter. But for spreading infection in gastrointestinal tract, flagella are not necessary.In different species of *Shigella*, the gene which is responsible for flagella were found to be different and is one of the main reason of genetic diversity among the species among the species.(GironJa, 1995).

The metabolic action of *S. boydii* follows anaerobic pathways as it entered in the intestine but outside the host body it utilizes the aerobic pathways for its survival(Prema et al, 2005). On the basis of biochemical test *S.boydii* is typically non-motile, oxidase negative and catalase positive (Holt et al, 1994).

Clinical symptoms and transmission

Spreading of *Shigella* infection occurs through oral-fecal transmission which is highly invasive agent for the host.Transmission of *Shigella*is spread by direct contact with an infected person, or by eating contaminated food or drinking contaminated water. Flies may also transmit the organism (Clemens et al, 1999). Once entered in the host body, it infects the epithelial cells of the intestinal mucosa reaches through the gastrointestinal tract and starts causing irritation, inflammation and necrosis (swelling and breaking of infected cells, which spreads further invasion).After an incubation period of one to four days, patients typically present with diarrhoea characterized by the frequent passage of small liquid stools that contain visible blood, with or without mucus. Abdominal cramps and tenesmus (unproductive, painful straining) are common. Fever and anorexia are also common, but are not specific. Patients may, however, present only with acute watery diarrhoea without visible blood or mucus, and without the other symptoms described above, especially at the beginning of their illness. If dehydration occurs, it is usually moderate in degree (Cobra et al, 1996). Although most patients recover uneventfully within seven to ten days, serious complications may occur, including: metabolic abnormalities, sepsis, convulsions, rectal prolapse, toxic megacolon, intestinal perforation and haemolytic-uraemic syndrome.It has ability to infect with less than 20 cells in 12-48 hours in favorable condition (Viner et al. 2001; Greenberg et al. 2003).General symptoms of infection such as stomach cramps, high fever, mucus in feces, and bloody diarrhea due to ulceration of intestinal lining and rectumhave been observed (Grimont et al, 2007). Immunological deficient neonates and children (including human immunodeficiency virus infection) and malnutrition invite bacteria for spreading infection and other complications of shigellosis (Struelens et al. 1985; Martin et al. 1983; Viner et al. 2001; Greenberg et al. 2003).

Risk factors against shigellosis

On an average, severity of illness and risk of death are minimum by *S. sonnei* and greatest cause of shigellosis responsible by *Shigella dysentry*. Therefore, case-fatality is as high as 15% among patients suffered with *Shigella dysentry* who require to be hospitalized, and is increased by delayed arrival and treatment with inefficient antimicrobials against infection (Bennish et al, 1991).

The disease is also most likely to be severe, and the risk of death greatest, among:

- Infants and adults older than 50 years.
- Children who are not breastfed.
- Children recovering from measles.
- Malnourished children and adults.
- Any patient who develops dehydration, unconsciousness or hypo- or hyper thermia, or has a history of convulsion when first seen.

Diagnosis

Shigellosis cannot be distinguished reliably from other causes of bloody diarrhoea on the basis of clinical features alone nor in individual cases. Routine microscopy of fresh stool is a simple screening test to detect invasive bacterial diarrhoea. It is cheap, rapid and easy to perform, even in a peripheral health facility. A definitive diagnosis of Shigella infection can only be made by isolating the organism from stool and serotyping the isolate. Culture is also required to determine antimicrobial sensitivity. PCR is one of the sensitive molecular techniques to detect *Shigella*and usually it is not practically used and they do not permit determination of antimicrobial sensitivity(Lindsay, 2014). Methods to detect *Shigella* in food and in the environment are not yet standardized (Centres for disease control and prevention, 1999)

Differential diagnosis of *Shigella* is necessary confirmatory test against *shigellosis.*Some other symptoms and bloody diarrhoea that confirm

shigellosis and *enteritis* also, that caused by *Campylobacter jejuni*, enteroinvasive*Escherichia coli*, *Schistosoma*, *Salmonella* and *Entamoebahistolytica*. Direct microscopic examination of fresh stool should be used to diagnose. (Bennish et al, 1999)

Prevention

Prevention of dysentery caused by Shigella relies primarily on measures that prevent spread of the organism within the community and from person to person. These include:

- hand-washing with soap
- ensuring the availability of safe drinking water
- safely disposing of human waste
- breastfeeding of infants and young children
- safe handling and processing of food, and control of flies

These measures will not only reduce the incidence of shigellosis, but of other diarrheal diseases as well. In all cases, health education and the cooperation of the community in implementing control measures are essential (Centres for disease control and prevention, 1999).

Treatment

Treatment of *shigellosis* reducing the duration of fever, diarrhea and fecal excretion of the pathogen with the administration of antibiotic and apparently also reduces the risk of mortality rate(Varsano et al, 1991). Alternative treatment of infection may be oral rehydration and those patient suffer from severe infection should be treated with intravenous replacement of fluids and electrolytes. Primarily antibiotic treatment is generally recommended for people suffered from colitis or dysentery (Ashkenazi, 2004; Christopher et al. 2010).

The major problem, however, is the worldwide increasing antibiotic resistance of *Shigella* spp. (Chuang et al. 2006; Centers for Disease Control and Prevention, 2013).Unfortunately, resistance of Shigella to ampicillin, co-trimoxazole and nalidixic acid has become widespread and these are no longer recommended. Ciprofloxacin, formerly used as a backup drug to treat shigellosis, is now the drug of choice for all patients with bloody diarrhoea, irrespective of their age. Although quinolones have been reported to cause arthropathy in immature animals, the risk of joint damage in children appears to be minimal and is clearly outweighed by the value of these drugs for treatment of this potentially life-threatening disease (Bhattacharya et al, 2009)

Aside from ciprofloxacin and some other fluoroquinolones, pivmecillinam (amdinocillinpivoxil) and ceftriaxone are currently the only antimicrobials that are usually effective for treatment of multi-resistant strains of Shigella in all age groups. Azithromycin is also considered an alternative for treatment of adults. However, Use of these alternative drugs is currently limited by their high cost (pivmecillinam, azithromycin), rapid development of resistance (azithromycin), their formulation (injectable for ceftriaxone, four times a day for pivmecillinam), and limited data on efficacy (ceftriaxone, azithromycin). They should only be used when local strains of Shigella are known to be resistant to ciprofloxacin (Bhattacharya et al, 2009; WHO, 2005)

Severe cases and other patients at increased risk of death should be referred to hospital or a specialized treatment centre. Because outpatients may also become severely ill or die, they must also be treated with an antimicrobial and reviewed after two days of treatment to ensure they are improving. Important signs of improvement are less fever, less blood in the stool, less frequent stools and improved appetite (sack et al, 2001). If their illness is not improving within two days, or worsens, they should be hospitalized. Patients treated at home should be given clear instructions regarding disinfection of clothing, personal articles and their immediate environment. An individual file should be created for each patient admitted to a health facility. This should remain with the patient until discharge. It should include information on the diagnosis, clinical symptoms on admission, and progress during hospitalization. Health education messages should be provided to all patients (Keusch et al, 1998; World Health Organization, 2005)

Supportive care: (World Health Organization 2005**)**

a) Rehydration

- Oral rehydration is usually sufficient
- Ringer's lactate solution is preferred for intravenous rehydration

b) Feeding

- Continued feeding is imperative
- Frequent small meals
- An extra meal each day for at least two weeks for convalescent children

c) Other supportive care

- Anti-pyretic for fever
- Analgesic for pain
- Zinc supplementation for 10-14 days for children up to five years of age

Approaches for the development of effective drug against *shigellosis*

In order to attain such a safe and efficacious treatment against bacterial infection, two basic approaches followed.One is the combining the efficacious serotype-targeted vaccines and next approach is the binding of ligand with the particular target protein to

achieve protection against *Shigella* strain.Various innovative strategies have been developed and some are ongoing process to achieve this ultimate goal. In this regard most of the drugs against infection become effective for short duration and then species become drug resistant against homologous serotype(Mel et al, 1974; Meitert et al. 1984).Although antibiotics are the standard care for shigellosis patients, antibiotic-resistantbacteriumisbecomingcommon.Therefore,itisur gentlynecessarytodevelop asafeandeffective*Shigella*vaccine. In this regard, researchers are doing their studies towards inducing good immune response which may be beneficial for multivalent *Shigella* vaccine and in the direction of antibiotic study,potent drug target may be used to develop broad spectrum antibiotics which would widely effective against disease related to bacterial species.

In this direction current relentless efforts and approaches are developed by the researchers. Out of these, one of the good strategiesrecently is being discussed. According toAshida et al, 2015, that bacteria use to manipulate inflammatory outputs of host-cell responses such as cell death, membrane trafficking, and innate and adaptive immune response in whichmanipulation in the host immune response by delivering effector protein viathetypeIIIsecretion system (T3SS) that enable bacterial evasion from host immune systems. These pathogens are able to efficiently colonize the intestinal epithelium.As a result bacterial infection evokes host defense systems that would restrict and eliminate bacteria (Parsot. C, 2009)

Once *Shigella* invades and replicates within host cells, the innate immune system ,andtransmits variousalarm signals to th erest of theimmune system, and ultimately triggers inflammation (Raqib et al, 2002). Inflammation, which is accompanied by inflammatory cytokinesecretion, neutrophil recruitment, andmassive tissuedestruction, isthehall mark of the host innate Immune response that eventually restricts andeliminates bacterial infection (Konradt et al, 2011).However, many bacterial pathogens, including *Shigella*, deliver a subset of T3SS effectors that manipulate host innate immune responses, thereby promoting bacterial colonizationand survival (Ashida et al, 2011) Shigella targets T and B cells and manipulates adaptive immunity against Shigella infection, thereby preventing antibody-mediated lasting immunity and promoting bacterial infection (Wassef et al, 1989).However, the interactions between Shigella and adaptive immuneresponse, such as T and B lymphocytes, have not been thoroughly investigated but it may also one of the strategies for promoting infection against bacteria.Therefore, several recent studies have shown that host adaptive immunity is targeted and subverted by ShigellaT3SS effectors. (Ashida et al, 2015)

Conclusion

In the conclusion of this review, *Shigella* is one of the important pathogens responsible for diarrheal diseases and bacillary dysentery occurring globally. To reduce the rate of mortality and morbidity researchers are practicing to achieve effective and potent broad spectrum drug against *shigellosis*. Therefore, the discovery of new *Shigella* strategies will not only provide a new understanding but also facilitate development to new type of anntibacterial drugs that target bacterial effectors and bacterial live vaccines to overcomebacterialinfections. I hope that such relentless work in this direction will lead to safe and efficacious treatment against this pathogen and willprovide such a safe life for humanity.

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