GLOBAL TASK FORCE ON CHOLERA CONTROL

Interim Technical Note
Use of antibiotics for the treatment and control of cholera
Revised October 2022

Cholera is an acute diarrhoeal disease caused by the ingestion of food or water contaminated with the bacterium *V. cholerae*. It has a short incubation period of a few hours to 5 days. It is endemic in some countries, frequently showing seasonal variations in the number of reported cases. Cholera also has the potential to cause explosive outbreaks which may be localized or may expand to large geographic areas.

The vast majority of people infected with *V. cholerae* will remain asymptomatic, but will still shed the bacteria in their feces for 1-10 days post infection. Of those who develop symptoms, approximately 80% will show mild to moderate symptoms, and the remaining 20% will have severe disease.

Indications for Antibiotic use

Cholera is an easily treatable disease. Rapid access to appropriate rehydration is the mainstay of therapy for the full clinical spectrum of cholera cases. Those with mild to moderate symptoms can be treated successfully with prompt administration of oral rehydration solution (ORS) and in children by providing zinc in addition to ORS. Patients diagnosed with severe dehydration require administration of intravenous fluids, with ORS also administered as soon as oral intake is possible. In these very sick patients and in those with high purging[1] or significant co-morbidities or conditions (e.g., severe acute malnutrition (SAM), pregnancy) or other high risk groups (e.g. age over 60 years), appropriate antibiotics are recommended to diminish the duration and volume of diarrhoea and reduce the duration of *V. cholerae* shedding. The use of antibiotics in treatment of cholera patients with severe dehydration is supported by several studies that show antibiotics can reduce the duration of diarrhoea by 1.5 days, decrease the volume of stool by up to 50 percent and lessen the length of shedding of *V. cholerae* to one to two days.[1] Only a small number of studies included moderately dehydrated patients and there is no available data on the effectiveness of antibiotics in this subgroup. [2,3]

One major concern that governs recommendations for antibiotic use is the risk of antibiotic resistance resulting from overuse in those patients who are unlikely to benefit with an illness that is self-limited and, in the vast majority of cases, resolves with appropriate supportive care alone. This is particularly important now that resistance to all classes of drugs used for *V. cholerae* has been documented and no

[1] The suggested definition of "high purging" is at least one stool per hour on average over the first 4 hours of observed rehydration. This is an indication that oral therapy might not be sufficient to keep up with diarrhoeal losses, risking severe dehydration and its complications.

new antibiotics are currently in development for *V. cholerae.* At the same time, the effect of targeted antibiotic use in cholera on the resistance profile of those potentially pathogenic enteric bacteria also present at the time of treatment is unknown.

Choice of antibiotic

The antibiotic options for cholera are the tetracyclines, fluoroquinolones and macrolides. Most *V. cholerae* are resistant to chloramphenicol, co-trimoxazole and furazolidone which are therefore no longer used and will not be discussed further.[4] The rationale for choosing an antibiotic should be based on efficacy, safety, feasibility, availability, cost and local resistance patterns. All the classes of antibiotics used for cholera are also used for other indications which add to the overall antibiotic pressure on the development of resistance.

Tetracyclines. Tetracyclines are the antibiotics for which there is the most clinical experience for cholera and several clinical trials have shown their efficacy. The two antibiotics from this class that are used for cholera are tetracycline and doxycycline. Tetracyclines are widely used for other indications because of the broad spectrum of activity, low toxicity and easy availability.

Several trials have directly compared tetracycline with doxycycline and showed no significant differences in clinical outcome. Other studies comparing tetracycline and doxycycline to quinolones (ciprofloxacin and norfloxacin) also did not show any statistical difference in outcome. [1] There are no clinical studies comparing the efficacy of tetracyclines and macrolides. Resistance to tetracycline and doxycycline has been documented and there is cross-resistance between the two antibiotics, although *V. cholerae* strains circulating in recent years have been sensitive to doxycycline (vs tetracycline). [5–10] The mechanism of resistance to tetracyclines is plasmid mediated which facilitates the development of resistance between different bacteria and resistance to tetracyclines in bacteria such as *V. cholerae* can easily spread to other bacteria in the environment.

Classically, antibiotics of the tetracyclines class are not recommended for pregnant women because of the potential toxicity to the fetus and for children less than eight years of age because of the potential for tooth discoloration. However, a recent systematic review of the use of doxycycline in pregnant women and young children shows that the safety profile of doxycycline differs from tetracycline and there was no correlation between the use of doxycycline and teratogenic effects or dental discoloration. In this review, the authors mention that the side effects associated with tetracycline have been carried over to doxycycline as a ‘class effect’; however, doxycycline has less calcium binding capacity than tetracycline and therefore is less likely to cause tooth discoloration. The current dosage for doxycycline is also much smaller than analogous tetracycline dosage and the duration of treatment is shorter. [11]

Fluoroquinolones. Fluoroquinolones are alternative agents in areas where tetracycline resistance is common, with efficacy comparable to tetracyclines. [3,16,17]. There is however growing resistance to fluoroquinolones in Asia and Africa. [12–14] A study done in Bangladesh over a ten-year period showed an 83 fold increase in the minimum inhibitory concentration (MIC) of ciprofloxacin.[15] The reduced susceptibility is also seen in more recent circulating strains.[8]

The safety concern for use of fluoroquinolones among children and pregnant women are its effect on joints, cartilage and long bone. These potential adverse effects in pregnancy have only been observed in animal studies. A recent meta-analysis and observational cohort study in humans showed that teratogenic effects have not been observed. [18,19] Several studies have reviewed the musculoskeletal adverse events in children following use of ciprofloxacin and showed that they are the most commonly reported adverse events, but there is no evidence that the effects are sustained [20], nor that they occur after single dose treatment.

Macrolides. Macrolides have shown efficacy in adults and children with cholera. [12,14,21–24]. Resistance to erythromycin has been documented in recent years, especially in south Asia. [25–27] Few cases of resistance to azithromycin have been reported, including in Bangladesh where the drug has been used as first line treatment for cholera since 2005. Regular testing of cholera patients in Bangladesh showed <1% resistance to azithromycin.[25] Azithromycin is considered the last line of antibiotic to which nearly all *V. cholerae* strains are still sensitive has a good safety profile with no contraindications for children or pregnant women. Erythromycin can cause significant gastrointestinal side effects that impede its effectiveness and cannot be used as single-dose therapy.[12,22,28]

Given that all antibiotics used against cholera have had documented resistance, the choice of empiric antibiotic should be guided by sensitivity to the local *V. cholerae* strain. When documented to be susceptible, doxycycline is the first choice of treatment for all patients: adults, including pregnant women, and children. Ciprofloxacin or azithromycin can be used as alternatives in situations where there is doxycycline resistance (Table 1). Erythromycin and tetracycline are less preferred options.

Ease of administration and cost. Single dose antibiotics, such as doxycycline, ciprofloxacin and azithromycin are generally preferred since they simplify drug administration and ensure better patient compliance, as compared to tetracycline and erythromycin, which must be taken several times a day for three days.

Cost is another consideration for governments and health facilities. Price per course of treatment based on an international price indicator guides are under $0.10 for doxycycline, tetracycline and generic ciprofloxacin, $0.50 for erythromycin and $0.70 for azithromycin. [29]

Which antibiotic should be used and who should receive it?

The antibiotic of choice in any individual context should be guided by the following principles:

- Antibiotics use should be selective and target those patients most likely to benefit clinically
- Current or recent evidence that the predominant circulating cholera strain remains sensitive to the selected antibiotic. Where feasible, regular monitoring of cultured cholera strains for evolution in antibiotic resistance is recommended during an outbreak.
- Antibiotics with proven single-dose efficacy are highly preferred to multi-dose regimens.
- Availability, cost, and ease of implementation are taken into consideration.

RECOMMENDATIONS

Table 1. GTFCC Case Management Working Group recommendations on use of antibiotics

Indication: ➢ Suspected cholera patients hospitalized with severe dehydration and ➢ Regardless of degree of dehydration: high purging or failure of first 4 hour course of rehydration therapy or coexisting conditions (e.g. pregnancy) or co-morbidities (e.g., SAM, HIV) or other risk factors (e.g. age over 60 years) that pose elevated risk in cholera illness,		
	First-line drug choice and dose (if local strain sensitive)	**Alternative drug choices**
Adults, including pregnant women	**Doxycycline 300 mg p.o. single dose**	**Azithromycin:** 1 g p.o. single dose or **Ciprofloxacin:** 1 g p.o. single dose
Children <12 years old	**Doxycycline:** 2-4 mg/kg p.o. single dose	**Azithromycin:** 20 mg/kg (max 1g) p.o. single dose or Ciprofloxacin: 20 mg/kg (max 1g) p.o. single dose

Case definition for suspected cholera:

- *In areas where a cholera outbreak has not been declared: Any patient aged 2 years and older presenting with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea.*
- *In areas where a cholera outbreak is declared: any person presenting with or dying from acute watery diarrhoea.*

NOTE: all children from 6 months to 5 years of age with diarrhoea regardless of cause or degree of dehydration should receive zinc sulfate[2], 20 mg p.o. per day for 10 days. Zinc sulfate has been demonstrated to reduce diarrhoea volume and duration without risk of resistance.

[2] *Zinc may reduce the absorption of some classes of some antibiotics including ciprofloxacin. For best effect with these classes of drugs, antibiotics should be administered 2 hours before zinc or 4-6 hours after zinc. Children receiving therapeutic food for the treatment of severe acute malnutrition do not require zinc supplementation as these foods contain sufficient zinc.*

Use of antibiotics as chemoprophylaxis

Because antibiotics decrease shedding of *V. cholerae*, it is assumed that antibiotics could have an important role in reducing transmission and interrupting an outbreak.

Mass chemoprophylaxis, defined as treatment of an entire community with an antibiotic is not recommended by WHO nor any other organization because there is no evidence of its effectiveness for outbreak control and it can lead to antibiotic resistance. [31–33] In settings where mass prophylaxis has been practiced, such as the program for eradication of trachoma with azithromycin, an increased resistance to azithromycin as well as other antibiotics in *S. pneumoniae* isolates has been documented. [34,35]

Selective chemoprophylaxis is defined by WHO as treatment of healthy but potentially infected members in the household of a cholera patient, to prevent their becoming ill. Essentially, the term is also applicable to groups or contacts of individual cases within closed settings (such as in a prison setting).[31,36] The rationale for the approach is based on the higher risk of infection among contacts of patients compared to overall community risk. [37] The single-dose antibiotics used for treatment can be used for selective chemoprophylaxis. Antibiotics, as opposed to vaccines, are effective immediately but offer little to no on-going protection.

Two studies, published in 1968 and 1978, show that selective chemoprophylaxis lowered infection rates in the first few days after antibiotic administration before returning to rates similar to contacts who were not given antibiotics. A systematic review and meta- analysis of selective chemoprophylaxis in contacts noted a reduction in clinical disease and hospitalisations in contacts who had received chemoprophylaxis, but the authors cautioned that the studies had a high risk of bias. [40]

No study has been conducted to assess selective chemoprophylaxis targeting health care workers. As they will have continuous exposure to cholera cases, repeated courses of antibiotics is impractical and may only lead to adverse effects and antibiotic resistance.

In prisons, where the risk of rapid transmission is very high, selective chemoprophylaxis has been deemed successful although few experiences have been published. [41]

During a large outbreak of cholera in Douala, Cameroon in 2004 selective chemoprophylaxis was given to household members and direct neighbours of cases. This was done in addition to household disinfection and health education. A total of 174,644 individuals, were given antibiotics. The authors concluded that while the strategy was effective to reduce transmission in contacts, it had no impact on the overall epidemic curve, probably due to massive environmental contamination (42). Antibiotic sensitivity was monitored in *V. cholerae* during the epidemic and no resistance was reported. [42].

Before selective chemoprophylaxis is recommended in any setting, more evidence is needed to assess its effectiveness as an intervention in a cholera outbreak. At a minimum, there should be consensus

agreement on the criteria on when selective chemoprophylaxis may be considered, least of which is having a system in place to monitor for development of antibiotic resistance.

Summary

1. Rehydration remains the primary therapy in the treatment of cholera

2. Antibiotic use should remain selective and should target those patients who are likely to benefit most clinically. Antibiotics should be given to suspected cholera patients who require hospitalization for severe dehydration or who have high purging or who have treatment failure following the initial 4 hours of rehydration therapy. Antibiotics should also be given to all suspected cholera patients regardless of degree of dehydration who have coexisting conditions (e.g. pregnancy) or co-morbidities (e.g. SAM, HIV) or other risk factors (e.g. age over 60 years), that pose elevated risk in cholera illness

3- There are concerns with development of antibiotic resistance and lack of new antibiotics.

4. The choice of empiric antibiotic should be guided by sensitivity to the local *V. cholerae* strain as all antibiotics used against cholera have had documented resistance. When documented to be susceptible, doxycycline is the first choice of treatment for all patients, including adults, children and pregnant women. Azithromycin or ciprofloxacin or are alternatives in situations where there is doxycycline resistance.

5. Zinc supplementation should be given to all children aged 6 months to 5 years with diarrhoea. While antibiotics can shorten the duration and volume of diarrhoea in patients with severe dehydration, zinc supplementation in children from 6 months to 5 years of age with cholera also has the same effect. Unlike antibiotic use, this medical intervention can be used widely without risk of developing resistance and should be given to all children with acute diarrhoea[3i].

6. Mass chemoprophylaxis is not recommended. There is currently insufficient evidence to evaluate the effectiveness of selective chemoprophylaxis (household contacts, enclosed communities). It is recommended that any use should be within the context of a prospective study specifically designed to measure effectiveness of antibiotic prophylaxis and development of antibiotic resistance in household contacts (i.e., sharing a meal) of a suspect cholera patient, as well as any impact of such strategy on outbreak evolution.

The evidence provided in this technical note is based on an extensive literature review conducted by WHO in 2015 and 2016.

[3] Children receiving therapeutic food for the treatment of severe acute malnutrition do not require zinc supplementation as the foods contain sufficient zinc.

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