



Chinese clinical practice guidelines for acute infectious diarrhea in children

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Abstract

Background The guidelines addressed the evidence-based indications for the management of children with acute infectious diarrhea in Chinese pediatric population.

Data sources The experts group of evidence development put forward clinical problems, collects evidence, forms preliminary recommendations, and then uses open-ended discussions to form recommendations. The literature review was done for developing this guideline in databases including PubMed, Cochrane, EMBASE, China Biomedical Database, and Chinese Journal Full-text Database up to June 2013. Search the topic “acute diarrhea” or “enteritis” and “adolescent” or “child” or “Pediatric patient” or “Baby” or “Infant”.

Results For the treatment of mild, moderate dehydration, hypotonic oral rehydration solutions (ORS) are strongly recommended. Intravenous (IV) rehydration is recommended for severe dehydration, with a mixture of alkali-containing dextrose sodium solution. Nasogastric feeding tube rehydration is used for children with severe dehydration without IV infusion conditions with ORS solution. Regular feeding should resume as soon as possible after oral rehydration or IV rehydration. The lactose-free diet can shorten the diarrhea duration. Zinc supplements are recommended in children with acute infectious diarrhea. *Saccharomyces boulardii* and *Lactobacillus Rhamnus* are recommended to be used in acute watery diarrhea. *Saccharomyces boulardii* is recommended in children with antibiotic-associated diarrhea as well. Montmorillonite and Racecadotril (acetorphan) can improve the symptoms of diarrhea or shorten the course of acute watery diarrhea. Antibiotics are recommended with dysenteric-like diarrhea, suspected cholera with severe dehydration, immunodeficiency, and premature delivery children with chronic underlying disease; otherwise, antibiotics are not recommended.

Conclusion The principles of the most controversial treatments with of acute infectious disease are reaching to a consensus in China.

Keywords Children · Diarrhea · Dehydration · Infection · Rehydration · Treatment · Probiotics

Introduction

Infectious diarrhea is a global infectious disease with a high incidence and widespread epidemics, which is a serious public health challenge to humans, especially to children. In China, according to the household survey data of some provinces, the overall incidence of diarrhea is 0.17–0.70 episodes per person-year, and that for children under 5 years is 2.50–3.38 episodes per person-year [1]. Acute infectious

diarrhea is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations. Clinically, it can diagnosed with or without vomiting, nausea, fever, abdominal pain and other symptoms. In children, it is commonly caused by viruses and bacterial infections. Rotavirus and norovirus are the most common viral infections which lead to acute diarrhea. The bacterial pathogens include *Escherichia coli*, *Campylobacter* spp., *Salmonella enterica*, and *Shigella* spp., et al. There are two peak seasons of acute infectious diarrhea: summer and autumn–winter seasons. In the summer season (from June to August), the main pathogens are diarrhea-causing *E. coli* and dysentery bacilli; and for the autumn–winter season

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(from October to December), the main pathogen is rotavirus. Regardless of the causes of acute infectious diarrhea, the main treatment methods are fluid replacement including oral rehydration and intravenous rehydration (IV) for preventing and correcting water and electrolyte disorders and acid–base imbalance, diet therapy and pharmacological treatment.

The guideline was developed by an expert working group composed of pediatric gastroenterology, pediatric infectious disease and epidemiology experts under the organization of Academic Group of Pediatric gastroenterology of Chinese Pediatrics Association. The guideline provides recommendations for diagnosis, management and prevention of acute infectious diarrhea in children. For most controversial treatments, including the fluid selection in rehydration of children with acute diarrhea, severe dehydration, lactose-free diet, antibiotics and non-specific antidiarrheal drugs (probiotics, montmorillonite, racecadotril, etc.), we put forward clinical problems, search the literatures for the proposed clinical problems, collect evidence, apply evidence-based methods for evidence evaluation to form preliminary recommendations, and then use open-ended discussions to solicit expert opinions to form recommendations. A comprehensive thorough literature review was done for developing this guideline in databases including PubMed, Cochrane, EMBASE, China Biomedical Database (CBM), and Chinese Journal Full-text Database up to June 2013. Chinese search topic “Acute Diarrhea” or “Enteritis” and “adolescent” or “Child” or “Pediatric patient” or “Baby” or “Infant”, search PubMed for (“Diarrhea/therapy” [Mesh] OR “Gastroenteritis/therapy” [Mesh]) AND (English[lang] OR Chinese[Lang]) AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms]), search EMBASE and Cochrane library, qualify keywords: (diarrhea, diarrhoea, gastroenteritis, limit to Child:birth-18 years, limit language in Chinese or English, and based on a recently published systematic reviews, evidence-based guidelines, and high-quality clinical trials.

Oxford Evidence Classification [2] and Sackett’s [3] criteria were used to grade the strength of our recommendations and the quality of the evidence.

The quality of evidences is graded into four levels. A: Evidence from a systematic review or meta-analysis of a homogeneous randomized controlled trial (RCT) or single RCT; B: evidence from multiple high-quality cohort studies, multiple high-quality cohort studies, single high-quality case–control studies or poor-quality single randomized controlled trials; C: evidence from large sample cases, poor-quality single cohort studies or case–control studies; D: evidence from expert opinions.

The strength of recommendations depends on both the level of evidence and the trade-offs between advantages and disadvantages [4]. Highly recommended: evidence level A or B, and the benefits are very obvious; Recommendation:

evidence level B and the benefits are obvious, or high-quality research (evidence level C) is not possible under certain conditions but the benefits are obvious; considered: with suspicious evidence quality or beneficial is not obvious; Not recommended: lack of evidence and the benefits are not obvious.

Diagnosis [5]

Diagnosis of acute diarrhea

Evaluation is based on stool character and frequency of evacuations. According to the complaints from the parents and caregivers, the diagnosis can be made with or without abdominal pain, vomiting, and bloating, according to the change of stool character (lean water, mushy, mucus and pus stool) and the increase of stool frequency. The duration of the disease is within 2 weeks.

Assessment of dehydration

Assessment of the presence or absence of dehydration and electrolyte disturbance is important in children with diarrhea. The indexing and evaluation of the degree of dehydration are shown in Table 1. For moderate and severe dehydration, potassium, sodium, chlorine and blood gas analysis should be taken as soon as possible.

Identification of watery diarrhea and dysentery-like diarrhea

Watery diarrhea and dysentery-like diarrhea are differentiated according to routine examination of the feces. Watery diarrhea is non-inflammatory, and without white blood cells in the feces, mostly caused by virus or toxin-producing bacterial infections; feces of inflammatory diarrhea are mixed with mucus blood and pus, and mostly caused by invasive bacterial infection.

Pathogen of diarrhea

The possible pathogens can be suspected based on character of fecal, season of onset, age of onset, and prevalence. For acute infectious diarrhea, maintaining adequate blood volume and correcting fluid–electrolyte and acid–base imbalance precedes the diagnosis of the pathogen. For patients with normal immune function and acute watery diarrhea occurring within 24 h, stool culture is not required. Microbiological examination is required for patients with dehydration, fever or with blood and pus in feces.

Table 1 Assessment of the degree of dehydration

| Degree of dehydration | Mild | Moderate | Severe |
|---|---------------------------|--------------------------|--|
| Loss of body fluid (percent of body weight) | 3–5% | 5–10% | > 10% |
| Mental | Slightly worse | Irritability | Lethargy, coma |
| Skin turgor | Normal, slightly decrease | Decrease | Markedly decrease, pinching the skin back ≥ 2 s |
| Mucosa membranes | Slightly dry, thirsty | Dry | Obviously dry |
| Front, eyes | Slightly sunken | Sunken | Extremely sunken |
| Extremity temperature | Normal | Slightly cold | Extremely cold |
| Urine output | Slightly decrease | Obviously decrease | No urine |
| Pulse | Normal | Pulse increase | Tachycardia |
| Blood pressure | Normal | Normal or slightly lower | Hypotension |

Treatment

Rehydration therapy

- Recommendation** Oral rehydration using WHO-oral rehydration solution (ORS) or hypotonic ORS is recommended for mild or moderate dehydration (evidence level A). Nasal feeding tube rehydration can be used under conditions without IV infusion (evidence level B).

Summary Oral rehydration is as effective as intravenous infusion, and oral rehydration is not only an effective and also cost-effective treatment for acute infectious diarrhea [6, 7]. It is strongly recommended for preventing dehydration and treating mild or moderate dehydration. The components of WHO-ORS are: sodium 90 mmol/L, potassium 20 mmol/L, glucose 111 mmol/L, with a total osmotic pressure of 311 mOsm/L. In May 2002, WHO recommended a new hypotonic ORS: sodium 75 mmol/L, potassium 20 mmol/L, glucose 75 mmol/L, and with a total osmotic pressure of 245 mOsm/L. The solution contains 2.6 g sodium chloride, 1.5 g potassium chloride, 2.9 g sodium citrate, and 13.5 g anhydrous glucose per liter. Both WHO-ORS and hypotonic ORS are effective. In China, we highly recommend hypotonic ORS.

For children without dehydration, children should be given extra fluids to prevent dehydration; give ORS or other clean drinking water; give extra fluids after each loose stool (<6 months, 50 mL; 6 months to 2 years old, 100 mL; 2–10 years old, 150 mL; patients over 10 years old are free to drink as needed) until diarrhea stops. For children with mild–moderate dehydration, give ORS at a dosage: dosage (mL) = body weight (kg) \times (50–75), served within 4 h. Assessing dehydration status after 4 h, and selecting the appropriate treatment.

- Recommendation** IV rehydration is used for severe dehydration (evidence level A), and the IV fluid solu-

tion is made with a mixture of alkali-containing dextrose sodium solution (evidence level C).

Summary IV rehydration is strongly recommended for acute diarrhea with severe dehydration [4, 8, 9] (Table 2, for specific methods). During rehydration, assess dehydration status of the child every 1–2 hours. If there are no improvements, accelerate the rate of IV rehydration.

Acute diarrhea causes reduced sodium and water absorption or increased secretion. A large amount of water, electrolytes and alkaline substances are lost from the intestinal tract, resulting in decreased body fluids, blood volume and alkaline substances. At present, no strong evidence indicates that severe dehydration of acute diarrhea can cause stress hyperglycemia. On the contrary, 5% dextrose-containing fluids can reduce the occurrence of hypoglycemia (evidence level C). The use of alkali-containing dextrose sodium solution for acute diarrhea with severe dehydration has significant benefits. Therefore, we recommend using a mixed solution of alkali-containing dextrose solution in the treatment of acute infectious diarrhea with severe dehydration. Specifically, the first stage is to give IV bonus with 2:1 isotonic sodium-containing solution to rapidly increase blood volume, improve circulation and renal function, and then re-evaluate dehydration status. If the condition is not improved, additional boluses of isotonic solution is needed. Choose the appropriate solution according to dehydration properties (isotonic dehydration with 2:3:1

Table 2 Intravenous infusion time with different age of acute diarrhea patient

| Age | First stage (20 mL/kg) | Second stage (80 mL/kg) |
|----------------|------------------------|-------------------------|
| < 12 mon | 1 h | 6 h |
| 12 mon–5 y old | 1 h | 5 h |

solution, hypotonic dehydration with 4:3:2 solution) to supplement the deficit fluid. And first supplement with 2/3 of the amounts of deficit fluid. The specific ratios of 2:1 isotonic solution, 2:3:1 solution, 4:3:2 solutions are listed in Table 3. The above-mentioned IV rehydration fluids solution does not contain potassium. Therefore, when the child urinates, potassium should be supplemented at a concentration of 0.2%, no higher than 0.3%. Oral ORS should be given as soon as the child can drink: usually 3–4 h after IV rehydration for infants and 1–2 h after IV rehydration for children.

If without conditions of IV treatment, ORS solution can be given via nasogastric feeding tube at a speed of 20 mL/kg/h; the total volume cannot exceed 80 mL/kg. Assess dehydration status every 1–2 h.

Diet treatment

Recommendation Resume feeding as soon as possible, which can improve intestinal osmotic pressure caused by infections, shorten the duration of diarrhea, improve the nutritional status of children (evidence level A), and lactose-free diet can shorten the diarrhea duration of children (evidence level B).

Summary During acute period of diarrhea, resume food as soon as possible after oral rehydration or IV rehydration [10]. Give an age-matched diet, breast-fed infants and young children continue to breastfeed, for those fed with formula milk, low lactose or lactose-free formula is recommended [11]. For older children, diet is not limited, including cereals, meat, yogurt, fruits, and vegetables. The main purpose is to ensure enough calories. After recovery, nutrients should be supplemented. Foods containing high concentrations of monosaccharides, including carbonated drinks, jellies, canned juices, desserts and other sugary drinks, are not recommended. High-fat foods are also not recommended.

Zinc supplementation

Recommendation Zinc supplements should give for all children with acute infectious diarrhea (evidence level A).

Table 3 Simple preparation of commonly used mixed solutions

| Types of solution | 5% dextrose (mL) | 10% sodium chloride (mL) | 5% sodium bicarbonate (mL) |
|---|------------------|--------------------------|----------------------------|
| 2:1 isotonic sodium-containing solution | 500 | 30 | 47 |
| 4:3:2 solution | 500 | 20 | 33 |
| 2:3:1 solution | 500 | 15 | 24 |

Summary Zinc is lost in stool due to acute diarrhea, which causes negative zinc balance. Zinc supplements can improve the clinical prognosis of acute diarrhea and chronic diarrhea, and reduce the recurrence of diarrhea. Children with acute infectious diarrhea are recommended to be treated with zinc. (Less than 6 months: 10 mg/day; older than 6 months: 20 mg/day, for 10–14 days). Elemental zinc 20 mg equals to 100 mg of zinc sulfate and 140 mg of zinc gluconate.

Drug treatment

Probiotics [12–16]

Recommendation Several probiotics have curative effects on the treatment of acute infectious diarrhea in children, especially for watery diarrhea caused by viral infection (evidence level A), and the effect is more obvious in the early stage of the disease (evidence level B); no significant effect occurs in the treatment of invasive bacterial enteritis (evidence level A); probiotics are effective for treating antibiotic-associated diarrhea in children (evidence level D). *Saccharomyces boulardii* can shorten the duration of acute infectious diarrhea in children, reduce the duration of hospital stay (evidence level A); *Lactobacillus* GG (LGG) treatment of acute watery diarrhea shortens the duration of diarrhea (evidence level A), other *Lactobacillus* (*Lactobacillus bulgaricus*, *Lactobacillus reuteri* and *Lactobacillus acidophilus*) can shorten the duration of disease (evidence level B), and the daily dose of *Lactobacilli* is negatively correlated with the duration of disease (evidence level B); *Bifidobacterium* combined with *Lactobacillus* and *Streptococcus thermophilus* treatment for children with acute infectious diarrhea can shorten the duration of disease (evidence level C), and is effective in treating nosocomial infectious diarrhea (evidence level C); *Clostridium butyricum* may be effective in the treatment of acute diarrhea (evidence level D).

Summary Probiotics had moderate effects in treating acute infectious diarrhea in children, and it is strain- and dose dependent (dose greater than 10¹⁰–10¹¹ CFU), especially for watery diarrhea caused by certain viruses. Probiotics are recommended for acute watery diarrhea, and not recommended for inflammatory diarrhea caused by invasive bacteria. It is recommended to give probiotics in the early phase of the disease. For acute watery diarrhea, it is strongly recommended *S. boulardii*, *L. Rhamnus*, and other *Lactobacillus* (including *L. bulgaricus*, *L. reuteri* and *L. acidophilus*). *Bacillus bifidus* combined with *Lactobacillus* or *Streptococcus thermophiles* are highly recommended too. *Clostridium butyricum* can also be chosen to treat acute watery diarrhea. For antibiotic-associated diarrhea, it is recommended to use *S. boulardii*.

Montmorillonite [17–19]

Recommendation Montmorillonite is recommended for children with acute watery diarrhea, which can shorten the duration of diarrhea, reduce the frequency and amount of diarrhea, and improve the cure rate (evidence level).

Summary Montmorillonite is recommended to be used in treatment of acute infectious diarrhea (< 1-year-old children, 3 g/day, two times; > 1-year-old children, 3 g/time, three times a day).

Racecadotril [20–22]

Recommendation Racecadotril can significantly shorten the duration of acute watery diarrhea patients (evidence level B), and control diarrhea symptoms within the first 24 h (evidence level B).

Summary Oral racecadotril is recommended to be used, which can reduce the duration and frequency of acute diarrhea in children older than 2 months, and the benefits are obvious. For children aged from 3 months to 10 years old, the most common dosage is 1.5 mg/kg, three times for 5 days or until recovery as an adjuvant treatment for oral rehydration (take before meals).

Antibiotics treatment [23–25]

Recommendation Antibiotics are not recommended to be used for diarrhea caused by viral infections, which prolongs the duration of disease (evidence level B); Antibiotics are recommended to be used in children with dysenteric-like diarrhea, suspected cholera with severe dehydration, premature infants, children with immunodeficiency disease (evidence level A); Most *Campylobacter* enteritis is self-limiting, with good prognosis. Generally, antibiotic treatment is not needed. However, patients with severe disease and prolonged disease (high fever, bloody stool, and prolonged duration of disease lasting for longer than 1 week) still need antibiotic treatments. Early use can shorten the duration of disease and the period of bacterial discharging (evidence level A); *Bacillus brasiliensis* enteritis should be treated with antibiotics (evidence level B); *E. coli* that causes diarrhea mainly has 5 categories: *Enterotoxigenic E. coli* (ETEC), *Enteropathogenic E. coli* (EPEC), *Enteroinvasive E. coli* (EIEC), *Enterohemorrhagic E. coli* (EHEC), and *Enterotoxigenic E. coli* (EAEC). The enteritis caused by ETEC, EPEC and EIEC, when presented as stools with mucus blood and pus, should use antibiotics for 5–7 days (evidence level D), including third-generation cephalosporin (evidence level C), amikacin (evidence level C), and imipenem (evidence level A) which against *E. coli* producing extended-spectrum β -lactamases (ESBLs) (evidence level A). Most of the pathogens of EHEC enteritis

are O157:H7 strains. EHEC enteritis is a self-limiting disease. Antibiotics cannot shorten the duration of disease or hospitalization. Instead, the pathogens will be dissolved and release a large amount of Shiga-like toxin, which induces hemolytic uremic syndrome (HUS); antibiotics are not recommended for mild cases. However, antibiotics (evidence level D) can be used for severe cases with high fever and poisoning symptoms; for *Klebsiella pneumoniae* enteritis is more common in children under 2 years of age, without obvious seasonality, and usually with prolonged disease duration, antibiotics should be used with a duration 1–2 weeks (evidence level A); *Clostridium difficile* is the main pathogen causing antibiotic-associated diarrhea (AAD). For patients with mild–moderate *C. difficile* associated diarrhea (CDAD), it is most effective and simple to stop the original antibacterial drugs. For those who have severe diarrhea or who cannot effectively improve diarrhea after stopping the original antibiotics, metronidazole (evidence level C) or vancomycin (evidence level D) should be used; For *Staphylococcus aureus* enteritis, it is necessary to stop general antibiotics immediately, and vancomycin (evidence level A) or linezolid (evidence level D) should be chosen; antifungal drugs will be used for fungal enteritis (evidence level D).

Summary Even if suspected with bacterial diarrhea, antibiotics are not recommended firstly, because most diarrhea caused by pathogens are self-limiting; for children with dysenteric-like diarrhea, suspected cholera with severe dehydration, immunodeficiency, premature delivery and children with chronic underlying disease, antibiotics are recommended. Regarding the usage of antibiotics, because the resistance spectrum of antibiotics is different in different regions, it can be selected according to the results of fecal culture and drug susceptibility as well as the clinical situation of the children. Specific recommendations are shown in Table 4.

Principles of treating acute infectious diarrhea at home

Children without dehydration and mild dehydration can be treated at home, and medical staffs should advise parents to stick to the following principles when treating children at home: (1) give the child enough fluid to prevent dehydration; (2) give zinc supplements; (3) resume feeding as soon as possible.

Advise the parents to take the children to the hospital as soon as possible when the conditions of diarrhea are not improved or with any of the following symptoms (1) severe diarrhea, frequent stools or large amount of diarrhea; (2) cannot eat normally; (3) frequent vomiting, cannot be orally administered; (4) high fever (< 3 months old, > 38 °C; > 3 months, > 39 °C); (5) appearance of dehydration:

Table 4 Antibiotic recommendations for each pathogen

| Pathogens | Antibiotics | Dosages | Recommendation | |
|-------------------------------|--|--|--------------------|--------------------|
| <i>Scherichiacoli</i> | Cefotaxime | 50–100 mg/kg/d, 2–4 times, IV | Recommend | |
| | Ceftizoxime | 40–150 mg/kg/d, 2–3 times, IV | | |
| | Ceftriaxone | 20–100 mg/kg/d, single or 2 times, IV | | |
| | Ceftazidime | 30–100 mg/kg/d, 2–3 times, IV | | |
| | Cefixime | 5–10 mg/kg/d, 2 times, orally | | |
| | Cefoperazone | 50–150 mg/kg/d, 2–3 times, IV | | |
| | Amikacin | The first dose of 10 mg/kg, followed by 7.5 mg/kg every 12 h, or 15 mg/kg every 24 h, IM or IV | | Option |
| | Imipenem* | 30–60 mg/kg/d, severe cases can be increased to 100 mg/(kg day), the total daily amount does not exceed 2 g, 3–4 times, IV | | Recommend |
| <i>Campylobacter</i> spp | Erythromycin | 40–50 mg/kg/d, 3–4 times, orally, the total duration of treatment is 5–7 days, and the duration of treatment for severe infections is extended to 3–4 weeks | Option | |
| | Azithromycin | 10 mg/kg/d, oral or IV (for children > 6 months, < 45 kg), once a day, 3 days a week for a duration of treatment, or 5 days of therapy: 10 mg/(kg day) on the first day, halved after 4 days. Generally, 1 duration of treatment can be used, and severe cases require 2–3 duration of treatment | Recommend | |
| <i>Salmonella typhimurium</i> | Cefotaxime | 50–100 mg/kg/d, 2–4 times, IV | Option | |
| | Ceftriaxone | 20–100 mg/kg/d, single or 2 times, IV | | |
| | Ceftazidime | 30–100 mg/kg/d, 2–3 times, IV | | |
| | Cefoperazone | 50–150 mg/kg/d, 2–3 times, IV | | |
| | Piperacillin-Tazobactam | 60–150 mg/kg/d, 3–4 times, IV | | |
| | Imipenem ^a | 30–60 mg/kg/d, severe cases can be increased to 100 mg/(kg day), the total daily amount does not exceed 2 g, 3–4 times, IV | | Strongly recommend |
| <i>Klebsiella pneumonia</i> | Cefoperazone-Sulbactam | 80–160 mg/kg/d, 2–3 times, IV | Option | |
| | Imipenem | 30–60 mg/kg/d, severe cases can be increased to 100 mg/(kg day), the total daily amount does not exceed 2 g, 3–4 times, IV | Strongly recommend | |
| <i>Staphylococcus aureus</i> | (Stop the previously-used antibiotic) Vancomycin | 20–40 mg/kg/d, IV, every 12 or 8 h | Recommend | |
| | Linezolid | 10 mg/kg, IV every 8 h | Option | |
| <i>Clostridium difficile</i> | (Stop the previously-used antibiotics) Metronidazole | 30 mg/kg/d, four times | Recommend | |
| | Vancomycin | 20–40 mg/kg/d, orally, divided into four times | Recommend | |
| <i>Candida albicans</i> | Nystatin | 50,000–100,000 U/kg/d, three times, orally | Option | |
| | Fluconazole | 3 mg/kg/d, singly orally | | |
| | Clotrimazole | 25–50 mg/kg, two times, orally | | |
| | Ketoconazole | 3–5 mg/kg, single or two times, orally | | |

^aNot as the first drug choice for pediatric clinical antibiotics use, for *Escherichiacoli* producing multi-broad beta-lactamase (ESBLs) and multidrug-resistant *Salmonella typhimurium*

obvious thirsty, sunken eye, irritability and lethargy; (6) blood in the stool; (7) age < 6 months, with a history of chronic disease, and with complications.

Prevention

Precautions include improving personal hygiene and sanitation, promoting breastfeeding, active prevention and

treatment of malnutrition, rational use of antibiotics, and the use of rotavirus vaccines.

Author contributions CJ designed the manuscript, CJ and FYH drafted and revised the final manuscript. WCM carried out the evidence based methodology. All the other authors collected data and wrote one part of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors contributed equally to this paper.

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Compliance with ethical standards

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