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Antibiotic-Associated Diarrhoea: Pharmacotherapeutic and Preventive Aspects in Children

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Abstract

Objective: Putting in perspectives the important information in the literature on therapeutics and prevention of antibiotic-associated diarrhoea (AAD) in children**.**

Resource and Design: Systematic review of literature.

Salient Features: Most important first-aid measure in AAD is withdrawal of the offending antibiotic. Supportive measures to maintain fluid and electrolyte balance and nutrition too are important. As a therapeutic measure (as and when warranted), metronidazole (preferably oral) should be considered the preferred drug. Ornidazole or nitazoxanide may be given as an alternative to metronidazole. In cases not responding to first-line drug, vancomycin is recommended as such or in combination with the first-line drug. Good food and water hygiene, meticulous hand-washing and proper environmental cleaning is helpful. Incorporation of probiotics may have both a preventive and therapeutic role.

Future Perspective: A vaccine against C. difficile, already developed, needs further evaluation.

Conclusion: Judicious use of antibiotics is the most important preventive measure in AAD. Treatment modalities include withdrawal of the offending agent and administration of metronidazole, ornidazole or nitazoxanide. In case of poor response, vancomycin yields gratifying response. At times, rifampicin or Cholestyramine may be combined with vancomycin. In an occasional case still showing poor response, a pharmacological option is to use fidaxomicin (a very expensive agent) which is very effective against the usual etiologic agent, Cl. difficile.

Keywords: Antibiotic-associated diarrhea; *C.difficil;* C. difficile-associated colitis C; difficile-associated diarrhea; *C. perfringen;* Fidaxomicin; Metronidazole; Nitazoxanide; Ornidazole; Probiotics*; S. aureus*; Vaccine; Vancomycin

Abbreviations: AAD: Antibiotic-Associated Diarrhea; MDR: Multidrug-Resistant

Background

Over the past several decades, availability of a multitude of antimicrobials has revolutionized the

scenario of the infectious diseases with a welcome increase in man's lifespan [1]. However, widespread use of antibiotics, often irrational, may lead to appearance of multidrug-resistant (MDR) strains and emerging and re-emerging opportunistic infections [1,2]. By and large, all antibiotic have the inherent property of provoking diarrhoea-like manifestations, usually by interference with the normal flora of the gastrointestinal tract [2-6], more so during infancy and childhood. Incidence varies from 5-25 % [3]. Pseudo membranous colitis associated with *C. difficile* occurs in 10 to 20% of all AAD cases and in 60-90% of the severe AAD cases. It is also termed "C. difficile-associated diarrhea" or "C. difficile-associated colitis".

Administration of an antibiotic for a longer duration is more likely to cause AAD as compared to shorter duration [7-15]. According to one observation, every other child on antibiotic(s) usually develops some sort of loose motion which may not strictly conform to the definition of diarrhea [16]. Only in a small proportion of cases, these may well be severe enough to cause concerning most instances, diarrhea is mild, resolving without any treatment whatsoever. There is no noteworthy adverse effect on the health status of the child. In those with moderate diarrhea, usually a sheer discontinuation of the offending antibiotic works; only a small proportion needs drug therapy. In others, it may be fulminate and bloody, often refractory to discontinuation of the offending antibiotic and even additional therapeutic and supportive measures. In between the two extremes, different grades of diarrhea with or without blood may be seen [17-20].

Therapeutic Approach

Immediate Measures

Immediate withdrawal of the antibiotic(s) (provided that it is workable) and offering supportive treatment in the form of fluid and electrolyte replacement and adequate nutrition should be the first and foremost approach.

Pharmacotherapy

Standard Drugs: Table 1 presents a summary of the drugs useful in AAD [1,2,13-20].

Unsatisfactory response within 48 to 72 hours and severe illness are accepted indications for oral metronidazole in high doses (20–50 mg/kg/day) or oral vancomycin (20–40 mg/kg/day) should be added for 7 to 10 days.

There is a considerable consensus that oral metronidazole should be the preferred agent since it is economical and yet very effective. Moreover, it cuts down the emergence of vancomycin-resistant enterococci, which can become a problem in hospitalized children. F response to metrondazole is poor; it may be substituted by vancomycin. Such drugs as ornidazole, and nitazoxanide may be as effective as metronidazole and can easily be used as a substitute.

In yet more critical situations (toxic megacolon, adynamic ileus), the two drugs (metronidazole and vancomycin) may well be given simultaneously (intravenously). Alternatively, vancomycin may well be substituted with a tetracycline in older children. Response to treatment, as a rule is excellent, usually over 70 to 95%. However, a proportion of patients (say 5 to 30%) are likely to have a recurrence within 1 to 2 week. Another course of therapy usually resolves their problem.

In our experience, even children with severe AAD (including pseudo membranous colitis) show gratifying response to metronidazole. Institution of vancomycin or metronidazole plus vancomycin therapy is necessitated in only an occasional case.

The experience with a relatively new agent, fidaxomicin, (though recommended for *Clostridium difficile* associated diarrhoea as a good substitute for vancomycin) remains limited in AAD as such [21]. The drug is the most expensive antibiotic at present costing US$ 1500-2000 per course of 7-10 days. The dose is 6-8 mg/kg/day in 2 divided doses for children and 400mg/day in 2 divided doses for adolescents [22].

Drug	Dosage	ADRs	Remarks
Metronidazole	20-40 mg/kg/day (PO) in 2-3 divided doses) 21 mg/kg/day (IV)	Metallic taste	Economical, usually quite effective, safe
Ornidazole	30-40 mg/kg/day (PO) n 2-3 divided doses	Gastrointestinal disturbance, headache, vertigo, rash	Quite effective; needs to be avoded in hepatobiliary and renal diseases

Nitazoxanide	14 mg/kg/day (PO) in 2 divided doses	Gastrointestinal disturbance, headache	For better absorption, needs to taken with food.
Vancomycin	40-50 mg/kg/day (PO, IV)	May per se cause diarrhea; red man syndrome	Expensive but very effective; recommended in severe colitis unresponsive to metronidazole, ornidazole or nitazoxanide
Fidaxomicin	4-6 mg/kg/day (PO,V) n 2 divided doses	Gastrointestinal disturbances(ncludng diarrhoea), rash	Very expensve; may be used in cases refractory to vancomycin, vancomycnplus metronidazole, vancomycin plus rifampicin, vancomycin plus cholestyramine
Rifampicin	10-20 mg/kg/day (PO) q 12-24 h	Hepatotoxicity, discoloration of urine	Usually, administered in combination wth vancomycn. Caution: Orange-colored urine; avoid in pre or coexisting liver disease
Cholestyramine	240 mg/kg/day (PO) in 3 divided doses	Hyperchloremic acidosis, vomiting, constipation, abdominal distention/ discomfort/ pain, malabsorption, skin rash, deficiency of vitamin A, D, E and K	An antilipemic drug; nonabsorbable; its favorable outcome in AAD is by binding the luminal *C. difficile* toxins A and B. Usually, administered in combination wth vancomycn

Table 1: Summary of drugs recommended for treatment of AAD.

Role of Probiotics [23-37]: Probiotics are friendly or health-enhancing microorganisms consumed as a food or dietary supplement. Yoghurt and fermented milks are the most common foods that serve as probiotics. Dietary supplements serving as probiotics are available as powder, tablets and capsules. Whereas their important role in rotavirus diarrhea stands by and large established [26], their beneficial effect in AAD is very likely as a consequence of restoration of the normal gut flora, direct effect on the *C. difficile* colitis, or both.

Nonpathogenic organisms employed in the therapy of AAD are listed in Table 2.

Lactobacilli: *L. acidophillus* (readily available, economic though less potent), *L. bulgaricus* L. GG (most potent, but expensive)
Bifidobacterium longum
Enterococcus faecium
Streptococcus thermophilus
Saccharomyces boulardii

Table 2: Probiotics employed in treatment of AAD

Resistant Cases

A small group of patients continue to have further recurrence(s) despite the aforesaid therapy. It is in order to give trials of oral cholestyramine, rifampicin (along with vancomycin), bacitracin, immune globulin, probiotics (*lactobacilli* and *bifidobacteriu*m species) for reconstitution of bowel flora, and baker's yeast. Even instillation of fecal flora by tube feeding or enemas has been recommended [23,30]. Such a desperate situation seldom occurs.

Finally, we have cases of AAD from recurrent Clostridium difficile infection which are rather difficult to treat. Box 1 presents an approach to therapy of established recurrent Clostridium difficile diarrhoea/ colitis.

Box 1 gives the usual pharmacotherapy in confirmed Cl. diffcle diarrhoea/colits.

Box 1: Pharmacotherapy of established recurrent *Cl. difficile* diarrhoea/colitis.

First Relapse

- 10- to 14-day course of metronidazole if symptoms are moderate
- 10- to 14-day course of vancomycin if symptoms are severe

Second Relapse

Vancomycin-taper regimen

- 125 mg every 6 hr for 10 to 14 days
- 125 mg every 12 hr for the next seven days
- 125 mg daily for the next seven days
- 125 mg every other day for the next eight days
- 125 mg every three days for the next 15 days

Third Relapse

- 10- to 14-day course of vancomycin followed by a 14-day course of oral rifaximin 400 mg twice a day

Further Options

Therapy with microorganisms, e.g., bacteriotherapy, Saccharomyces boulardii, or Lactobacillus spp. in combination with and following metronidazole or vancomycin or Intravenous immunoglobulin 400 mg/kg two or three times with a three-week interval between doses

OR

- Vancomycin 125 mg every 6 hr plus cholestyramine 4 g twice daily

OR

- Vancomycin 125 mg every 6 hr and rifampicin 600 mg twice daily.

Outcome and Prognosis

High index of suspicion, timely confrmation of diagnosis and identification, discontinuation of the suspected antibiotic and timely management are usually accompanied by a favorable outcome [32,33].

Prevention

Broadly, attention to the following measures may well be helpful in prevention of AAD [15,16]:

- Food and water hygiene
- Hand hygiene
- Proper environmental cleaning
- Judicious use of antibiotics.
- Routine use of probiotic-rich diet or as medicinal supplement, especially during the course of antibiotic administration. Enough evidence is available supporting the preventive role of *Lactobacillus GG* in AAD. According to the Working Group on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [35], using *Lactobacillus rhamnosus* GG or *Saccharomyces boulardi* for prevention of AAD. If the use of probiotics for preventing *Clostridium difficile*-associated diarrhea is considered, the Working Group suggests using *S. boulardii*. Other strains or combinations of strains have been tested, but sufficient evidence is still lacking to recommend their use.
- Prevention of AAD in PICU revolves around avoidance of overuse of antibiotics. For prevention of *C. difficile* and other agents responsible for AAD, improved hygiene (single room, private bathrooms, use of gloves and hand washing) are helpful [9,13]. In order to safeguard against nosocomial spread, contact isolation of the patients is mandatory. Else, they may spread the infection to others.

Vaccine: As a result of recent research, a vaccine against *C. difficile* is available [38-40]. However more studies need to be conducted to evaluate its consistent efficacy and safety [41].

Conclusions

First and foremost first-aid measure is withdrawal of the offending antibiotic and offering supportive measures to maintain fluid and electrolyte balance and nutrition. Good food and water hygiene, meticulous hand-washing and proper environmental cleaning is helpful. Incorporation of probiotics may have both a preventive and therapeutic role in AAD.

As a therapeutic measure (as and when considered warranted), metronidazole (preferably oral) should be considered the drug of first choice. Alternatively, ornidazole or nitazoxanide may be given. The superior, though expensive, alternative is vancomycin. At times, the two drugs may be given simultaneously. Judicious use of antibiotics is the most important preventive measure though a vaccine against *C. difficile* may well be around the corner. At tmes, rifampcn or cholestyramne may be combined with vancomycin. In an occasional case still showing poor response, a pharmacological option is to use fidaxomicin which is very effective against the usual etiologic agent, *Cl. difficile*. Unfortunately, it is far too expensive to be affordable by most families in resource-limited communities.

Take-Home Messages

- Most important first-aid measure in AAD is withdrawal of the offending antibiotic and offering supportive measures to maintain fluid and electrolyte balance and nutrition
- Probiotics may have both a preventive and therapeutic role.
- Metronidazole, ornidazole or nitazoxanide should be considered the drug of first choice in its treatment.
- Vancomycin may be considered in cases not responding to first-line drug. At times, the two drugs may be given simultaneously
- Rational use of antibiotics is the most important preventive measure.

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