Antibiotic–Associated Diarrhoea: An Overview

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Introduction

The term, antibiotic-associated diarrhoea (AAD), is defined as the diarrhoea that has no other known cause than antibiotic therapy given concurrently or discontinued at the most 4 weeks preceding it. It is encountered in a considerable proportion of children who are treated with one or the other antimicrobial [1-4]. In most cases diarrhea is mild, resolving without any treatment whatsoever. In this group, there is no noteworthy adverse effect on the health status of the child. Those with moderate diarrhea may have an impact on their health status and usually need sheer discontinuation of the offending antibiotic for redressal of the problem; of course, some respond only when specific ant-AAD agent is administered. In a relatively, smaller group, AAD may be fulminant and bloody, often refractory to discontinuation of the offending antibiotic and even additional therapeutic and supportive measures. Pseudomembranous colitis, in-variably secondary to *C. difficile* infection, occurs in 10 to 20% of all AAD cases and most of the severe AAD cases.

Overall incidence of AAD varies from 5 - 25%. The patients administered with an antibiotic for a short duration are less likely to develop AAD as compared to those on longer duration [1-9].

Other sementics for the entity include antibiotic-related diarrhoe and antibiotic-induced diarrhoe.

Incidence/Frequency

Every other pediatric subject put on an antibiotic develops some loose consistency of motions of variable magnitude. In a proportion of the cases, these may well be severe enough to cause concern [10-16]. According to one estimate, on an average, overall risk of ADD varies from 5 to 25% with different antibiotics [3]. Pseudomembranous colitis associated with *C. difficile* occurs in 10 to 20% of all AAD cases and most of the severe AAD cases. Since, usually, *C. difficile* is the etiologic agent in severe AAD, it is also termed "*C. difficile*-asso-ciated diarrhea/colitis". Truly speaking, the term, PMC should be reserved for the advanced stage of the disease in which bloody stools, secondary to development of pseudomembrane, are characteristically seen.

Though clindamycin and lincomycin are known to have a high potential for causing AAD, in our series of nearly 350 children with AAD, these antibiotics were responsible for it in just 2% of the cases [10]. Reason: These antibiotics were employed in only a small number of cases. However, their extraordinary potentiality for causing AAD receives support from the observation that every third child treated with them developed AAD in our series.

Etiologic Considerations

Major risk factors are listed in box 1.

- Such antibiotics as clindamycin, expanded-spectrum penicillins and cephalosporins
- Immunologic susceptibility as indicated by absent serum levels of toxin A IgG antibodies
- Hospitalization

Box 1: Risk factors for Cl. difficile infection in children.

Fundamentally, all antibiotics are capable of causing diarrhea. Nonetheless, some antibiotics are high-risk while others are low-risk (Box 2).

High-risk
- Clindamycin
- Lincomycin
- Ampicillin
- Amoxicillin
- Macrolides, especially azithromycin
- Cephalosporins

Low-risk
- Penicillin
- Cotrimoxazole
- Ciprofloxacin
- Ureidopenicillins

Certain antibiotics, say clindamycin, lincomycin, ampicillin, amoxycillin, cephalosporins (cefixime, cefpodoxime), methotrexate, anti-viral agents, etc. when administered orally, may particularly cause serious disease in the form of pseudomembranous colitis.

Very rarely, even vancomycin and metronidazole, which are employed for treatment of PMC, may cause this condition [1]. Though clindamycin was the first antibiotic blamed for severe diarrhoea (PMC), most cases appear to be secondary to ampicillin, amoxycillin and cephalosporins because of a very extensive use of these agents in clinical practice.

The three pathogens incriminated in the etiology of AAD are:

1. *Cl. difficile*
2. *Cl. perfringens*
3. *Staphylococcus aureus*
4. *Candida* species

This may be emphasized that in most instances of severe AAD, *Cl. difficile* is the etiologic pathogen.

Pathogenesis [10-13]

The growth of a spore-forming gram-positive anaerobic bacillus, *Cl. difficile*, which is ubiquitous in the environment in the soil, is invariably responsible for the PMC. It is normally found in 70% neonates, 20 to 50% infants and only 3% of adolescents and adults. It

is by no means invasive. Most of its strains are toxic, producing two toxins which cause a plethora of adverse effects as shown in box 3.

> - Inflammation
>
> - Loss of protein
>
> - Exaggerated peristalsis
>
> - Hemorrhages
>
> - Enhanced fluid and electrolyte secretions
>
> - Cytotoxicity
>
> *C. difficile* accounts for 10 - 20% of all cases of AAD, most cases of antibiotic-associated colitis, and virtually all cases of PMC.

Box 3: *Adverse effects of Cl. difficile.*

Enterotoxin (toxin A) acts on the intestinal mucosa to produce diarrhea. Cytotoxin (toxin B) enhances vascular permeability in low doses, but in higher doses it may prove lethal. Toxin B is 1,000 times more powerful and have 100 fold greater enzymatic activity than toxin A. Occasional strains of the pathogen may produce only one or neither toxin. The significant mechanisms of production of diarrhea by *C. difficile* are listed in box 4.

> - Overgrowth of the organisms with suppression of normal gut flora by antibiotics
>
> - Interaction of the organisms with other flora of the gut
>
> - Actual triggering of production of the toxin by organisms by the antibiotics
>
> - Production of enzyme, beta-lactamases, by resistant organisms, which inactivate antibiotics and facilitate growth of *C. difficil*e.

Box 4: *Mechanism of production of diarrheal symptoms by C. difficile.*

Majority of pediatric AAD is not due to *C. difficile* though it is an important cause of severe AAD in the form of PMC. *S. aureus, Clostridium perfringens*, and *Klebsiella oxytoca* are other pathogens identified as potential causes of *C. difficile*-negative AAD in the form of hemorrhagic colitis when predominant in stool samples, should also be considered a possible etiologic agent for AAD.

Four stages of AAD may be recognized based on picture of the colonic mucosa (Box 5). Most children suffer from, stage II, which is characterized by mild erythema and edema of the colonic mucosa. Some fecal leukocytes can be detected in around half of the cases whereas a large number of red cells in feces are almost a rule. Histopathology of PMC nodules/plaques reveals mushroom-like lesion with massive fibrin, red cells and leukocytes.

> Stage One: Normal appearance
>
> Stage Two: Mild erythema and edema
>
> Stage Three: Granular, friable or hemorrhagic mucosa
>
> Stage Four: Pseudomembrane formation.

Box 5: *Stages of AAD based on appearance of colon*
(on recto-sigmoidoscopy/colonoscopy).

Pathophysiology [12-15]

Box 6 lists the several postulations that have been put forward to explain the pathophysiology of PMC.

- Changes in intestinal microbial flora

- Direct effects of antibiotics and their metabolites

- Localized Schwartzman reaction

- Hypersensitivity reaction

- Intravascular coagulopathy

- Elaboration of toxins by intestinal flora and production of enzyme, beta lactamase, by resistant organisms, which inactivate antibiotics and facilitate growth of *C. difficile*.

Box 6: *Various postulations for pathophysiology of pseudomembranous colitis.*

The so-called 'pseudomembranous nodules' (also termed 'plaques') develop in rectum, sigmoid colon or distal colon. In some cases, these may be noticed in cecum and transverse colon only. The lesions appear as greyish-white exudates that are surrounded by edematous and erythematous inflammatory response. These are only weakly adherent to the underlying tissue.

Until recently, it was held that *C. difficil*e does not cause diarrhea unless the subject is administered an antibiotic. However, strains of *C. difficile* (around 8%) have been recognized that cause diarrhea even without preceding antibiotic administration.

Convincing evidence is available that any factor that disrupts the normal bowel flora (antibiotics) or bowel motility (bowel stasis, Hirschsprung disease, bowel surgery) predisposes to *C. difficile*-associated diarrhea. Uremia, anesthesia and dietary changes also render the child vulnerable to pseudomembranous colitis. Today, there is evidence that *Staphylococcus aureus* and *C. perfringen*s too are capable of causing AAD.

Clinical Presentation [7,10,11]

Clinical picture is variable, ranging from mild self-limited diarrhea through explosive watery diarrhea with occasional blood to severe hemorrhagic colitis with classical picture of blood and mucus accompanied by toxemia. The child with toxemia may have pyrexia, cramps, abdominal pain, nausea and vomiting, dehydration with dyselectrolytemia, protein-losing enteropathy, and hypoalbuminemia. Infrequently, toxic megacolon, colonic perforation, peritonitis and shock my complicate, occasionally culminating as death.

Interestingly, manifestations may occur several days and even two or three (up to four 4) weeks subsequent to discontinuation of therapy with offending antibiotic(s). Occasionally, manifestations may occur within hours of starting the implicated antibiotic.

Diagnosis [7,10,11,16]

High index of suspicion in a patient with significant diarrhea or colitis in the setting of prior or current antibiotic therapy remains critical in the diagnosis of AAD [3].

Diagnosis is established by demonstrating *C. difficile* or its toxins in the stools (usually the latter).

The gold standard is the cytotoxin assay, which detects as little as 10 pg of toxin, but is inconvenient for many hospital laboratories and requires 24 - 48 hours for results.

From the practical and feasibility angle, today the most commonly used test is enzyme immunoassay (EIA) for detection of toxin A or toxin A+B; the latter are preferred because 1 - 2% of cases involve strains of *C. difficile* that produce only toxin B. The EIA test is somewhat less sensitive than the cytotoxin assay. The ground reality is that application of (EIA) for detection of *C. difficile* has turned out to be a highly sensitive and specific method for diagnosis of PMC, giving results in just 3 hours. This should be considered the method of choice, and, perhaps, the gold-standard test, for rapid diagnosis of *C. difficile*-induced diarrhea. On rectosigmoidoscopy/colonoscopy, the usual findings are mucosal edema, friability and ulceration of varying grades. Pseudomembranous nodules/plaques are seen in advanced cases only. Infrequently, these observations spare the rectum and the sigmoid colon, but may be seen proximal colon.

However, we strongly feel that this investigation should be reserved for atypical cases in resource-poor regions.

Differential Diagnosis [17]

Differential diagnosis of AAD is from diarrhea due to

- *Shigella, Salmonella*,
- Inflammatory bowel disease,
- Neutropenic colitis/typhlitis,
- Malabsorption
- Bloody diarrhea due to parasites such as *L. giardia, E. histolytica, H. nana, S. stercoralis* and *T. trichiura*.

For dependable diagnosis of AAD, it is appropriate that these causes of diarrhea are excluded. Nevertheless, coexistence of one or more of these factors plus the AAD is not unusual in resource-limited communities.

Management

As a therapeutic measure (as and when considered warranted), metronidazole should be considered the preferred drug.10 Alternatively, ornidazole or nitazoxanide may be given. The superior, though expensive, alternative is vancomycin. At times, the two drugs may be given simultaneously. Also, vancomycin may be given in combination with rifampicin or cholestyramine in cases showing unsatisfactory response to first-line drugs. The new drug, fidaxomicin, though very effective, needs to be used as a last resort. Fidaxomicin, a narrow-spectrum macrolide is superior to vancomycin in achieving clinical cure and is associated with fewer recurrences of CDAD compared with vancomycin [18]. Moreover there is a good safety profile. All these considerations make fidaxomicin an attractive therapeutic option in treating refractory AAD, especially CDAD which is invariable secondary to *Cl. difficile* infection. Unfortunately, this drug is extremely expensive to be afforded by most patients.

Box 7 presents a suggested approach to management of AED.

Before embarking on pointed therapy, decide if it indeed is diarrhoea or a sheer slight change in consistency of stools without any health impact. No intervention needed. Moreover, determine if it is mild diarrhoea, moderate diarrhoea or severe diarrhoea as such and/or with bloody stools.

Step I. Withdraw the offending antibiotic and provide supportive care with extra fluids and balanced diet.

Step II: No response: Start metronidazole.

Step III : No response: Add vancomycin OR give only vancomycin as such

Step IV: No response: Along with vancomycin , add rifampin or cholestyramine

Step V: No response: Treat with Judicious use of antibiotics is the most important preventive measure. Probiotics may be helpful both in treatment and prevention. A vaccine against *C. difficile*, though already developed, needs further evaluation. (very expensive)

***Box 7:** Suggested therapeutic approach to AAD in a nutshell.*

Judicious use of antibiotics is the most important preventive measure. Probiotics may be helpful in prevention [17-19]. A vaccine against *C. difficile*, though already developed, needs further evaluation [19-21].

Summary and Conclusions

By and large, each and every antibiotic has the inherent property of provoking diarrhea-like manifestations, usually by interference with the normal ecosystem of the gastrointestinal tract. The problem is more frequent in infancy and childhood. Most likely antibiotics involved in causing AAD include clindamycin, lincomycin, ampicillin, amoxycillin, cephalosporins and azithromycin. Low-risk antibiotics include cotrimoxazole, ureidopenicillin and ciprofloxacin.

In most cases diarrhea is mild, resolving without any treatment whatsoever.. Those with moderate diarrhea need discontinuation of the offending antibiotic as such along with anti-AAD drugs like metronidazole. In about one-fourth cases of AAD, diarrhoea may be fulminant and bloody, often continuing despite withdrawal of the offending antibiotic and even additional therapeutic and supportive measures. Such agents as metronidazole and or vancomycin are usually indicated in them. Fidaxomicin may be warranted in very frequent situations.

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