Antibiotic associated diarrhoea

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Antibiotic associated diarrhea (AAD) is defined as diarrhea that occurs in association with the administration of antibiotics.1 The direct toxic effects of antibiotics on the intestine can alter digestive functions secondary to reduced concentrations of the normal gut bacteria or cause pathogenic bacterial overgrowth.2 Clostridium difficile is widely known to be responsible for approximately 10-20% of cases of AAD and almost all cases of pseudomembrane colitis.3 However Klebsiella oxytoca,4 enterotoxin producing Clostridium perfringens,5 Staphylococcus aureus,6 Candida species,7 Salmonella species and Pseudomonas aeruginosa8 might also contribute to the development of AAD.9

C. difficile is the major cause of AAD and colitis. C. difficile is estimated to colonize 3% of healthy adults and 15-20% of hospitalized patients.10,11 Risk factors associated with hospital acquired C. difficile associated disease include antimicrobial use, laxative use, anti-neoplastic chemotherapeutic use, renal insufficiency, advanced age (>65 yrs), gastro-intestinal surgery/procedures, severity of underlying disease, nasogastric intubation, gastric acid suppressants, duration of hospital stay, duration of antibiotic course and prolonged hospital stay.12,13

Antibiotics are the most important risk factors for C. difficile associated diarrhea (CDAD). Clindamycin was the first antibiotic implicated in the precipitation of the disease. Cephalosporins are also the common agents implicated in nosocomially acquired CDAD. In outpatient settings, antibiotics such as ampicillin, amoxicillin or amoxicillin clavulanate combination are important and common causes. Less commonly implicated antibiotics are macrolides, tetracyclines, sulphonamides, trimethoprim, chloramphenicol and penicillin. It has been established that the oral dosing is four fold more responsible in producing the disease than parenteral injections or topical therapy. The organism colonizes approximately 25% of adults recently treated with antibiotics. Antibiotic therapy accounts for 98% of all cases of CDAD.

Apart from antimicrobials, immunosuppressive drugs have been reported to be associated with the development of CDAD. Patients receiving immunosuppressive drugs are debilitated and are unable to mount an effective IgG antibody response against C. difficile toxin A, thereby increasing the risk for CDAD. With the increased use of immunosuppressive drugs, the incidence of CDAD may account for as many as 20% of CDAD patients without prior use of antibiotics. Proton pump inhibitors (PPI) inhibit the gastric acid secretion by interfering with the activity of H+/K+ ATPase of the parietal cells and may thus contribute to the pathogenesis of the CDAD by altering the intestinal flora. Thus the risk of CDAD in hospitalized patients receiving antibiotics may be compounded by exposure to PPI therapy.14

Pathogenicity- The disruption of normal colonic flora appears to be essential to the pathogenesis of C. difficile infection.15 Acquisition of C. difficile occurs by oral ingestion of spores that resist the acidity of the stomach. These spores germinate in the colon to vegetative organisms and toxin producing strains subsequently produce toxin. Toxin A and B lead to tumour necrosis factor production, proinflammatory interleukins and increased vascular permeability. This results in colitis, pseudomembrane formation and watery diarrhoea. Toxin production is associated with clinical disease in infected patients.16-18

Epidemiology- The incidence of AAD due to C. difficile is presently increasing with increase in fatalities. The global epidemic strain NAPI/B1/027 has also been reported to cause outbreaks in parts of continental Europe. This strain was found to produce greater than 16 times toxin A and 23 times toxin B in addition to the binary toxin. Presently this global strain has been reported from...
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United Kingdom, Netherlands, Belgium, France, Austria, Germany, Luxembourg, Poland, Japan, Finland etc. with increased morbidity and mortality. Apart from this, another ribotype 078, a strain frequently isolated from the intestines of pigs and calves has been observed to be increasing in Europe.14

Detection- AAD can be diagnosed clinically as well as by identification of etiological agent.14,19 Various signs and symptoms help to diagnose the disease clinically.

IDENTIFICATION OF ETIOLOGICAL AGENT

Morphology- *C. difficile* is a Gram positive bacillus with terminal elongated spores slightly wider than the bacillary body.

Culture characteristics- It is a strict anaerobe. It readily grows on selective media such as cefoxitin-cycloserine fructose agar (CCFA). The characteristic odor of the colonies is that of horse or elephant’s dung. Colonies of *C. difficile* usually show a yellow green or chartreuse fluorescence when exposed to long wave ultraviolet light on blood agar. Culture is a low cost, sensitive and good method and the organism is available for epidemiological and antibiogram typing which may be beneficial when outbreaks occur.

Toxin assay- Various methods are available to detect toxins in the fecal samples.

Tissue culture- Tissue culture has been regarded as the gold standard in laboratory diagnosis of *C. difficile* toxin because of its high specificity and sensitivity.

Enzyme Immunoassays- Enzyme-linked immuno-sorbent assays (ELISA) are available to detect either toxin A alone or both toxins A and B in stool specimens. Both enterotoxins A and cytotoxin B of *C. difficile* are thought to be important for development of symptomatic disease. However toxin A is a potent enterotoxin in the intestine than toxin B. ELISAs that detect only toxin A may miss out on toxins from isolates of A B+ strains. Thus , ELISAs that detect both toxin A and B are recommended to detect these atypical isolates.

Latex Agglutination Tests (LAT)- Commercially available latex agglutination test is a rapid method. It is known to detect a nontoxic marker antigen of *C. difficile* and therefore frequently results in false positive reactions. Now, commercial LAT is less frequently available and has been replaced by ELISA.

Counter Immunoelectrophoresis- It is used only for research purposes.

Dot Immunobinding Assays- The reagents used are expensive and unaffordable for routine use.

Polymerase Chain Reaction - The polymerase chain reaction technique is used to detect enterotoxin or toxin B gene in isolates or feces and has sensitivity similar to cytotoxin testing.

Serotyping- There is a correlation between serogroups and toxigenicity. The serotyping of each *C. difficile* strain can be done by ELISA. However initial culturing for recovery of isolates is required. This approach is useful for epidemiological typing. Most serotypes belonging to A, C, G, H and S are considered toxigenic.

MANAGEMENT20

The recommendations are-

- Stop all antimicrobials.
- Attention to fluid replacement and electrolyte balance is also very vital.
- Both metronidazole and vancomycin are effective.
- If there is no response to metronidazole, patient should be treated by oral vancomycin.
- Oral therapy is preferred, but if the patient cannot tolerate oral medication, antibiotics can be given by nasogastric tube.

The increase in the rate of incidence, mortality and morbidity due to CDAD over the past decade has stimulated a search for newer adjunctive therapeutic management apart from the standard treatment given i.e. probiotics and prebiotics, fecotherapy, adsorbents, immunoglobulin therapy and others.

PREVENTION AND INFECTION CONTROL MEASURES21,22

Primary prevention involves measures to ensure that the patients should not become susceptible to *C. difficile* infection through disruption of their commensal gut flora, because this is the main defence against *C. difficile* associated disease. Primary prevention can be efficiently done by observing proper infection control protocols, appropriate antibiotic policies, hand hygiene, patient and staff education and thorough environmental cleaning, especially of toilet areas.
Secondary prevention is the prevention of further spread of *C. difficile* infection, once a case has already reported in a hospital ward. The following are the elements of secondary prevention:

- Wash hands with soap and hot water after every patient contact.
- Wear disposable gloves and aprons when handling body fluids.
- Clean patient equipment after use.
- Thoroughly clean non-critical equipment and surfaces daily to reduce environment spore load. Clean all surfaces and equipment carefully with a detergent and a hospital grade disinfectant or chlorine bleach because *C. difficile* spores can survive routine household disinfectants. Since usual hospital cleaning agents and alcohol based hand disinfectants are ineffective against *C. difficile*, the preferred alternatives are hypochlorite solution (1:10 mixture of household bleach to water) and either soap or chlorhexidine for hand hygiene.
- Restrict admission to the unit.
- Immediately clean up faeces on the floor with detergents and water using disposable cloth or mops.
- If a patient has diarrhea in bed, clean the patient and gather the linen carefully, put it in a plastic bag and treat it as infected. Send it to laundry immediately.

CONCLUSION

Antibiotic associated diarrhea is a common problem now a days. The most common organism is *C. difficile*. The infection spreads quickly because it is very difficult to eradicate the spores from the wards. The emergence of a hypervirulent *C. difficile* strain circulating globally is a great public health challenge. Thus, active and aggressive surveillance activity is the key to reduce incidence of antibiotic associated diarrhea. Management of risk factors by infection control education, training and practice are required to contain the global epidemic.

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