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RISK FACTORS, COMPLICATIONS, MANAGEMENT AND CLINICAL OUTCOME OF NOSOCOMIAL DIARRHEA IN MEDICAL ICU

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ABSTRACT

WHO defines diarrhea as the passage of 3 loose stools per day. A Bristol score of 6 or 7 is also classified as diarrhea". The incidence of diarrhea in intensive care unit ranges from 2- 95%. Diarrheal episodes of duration less than 14 days is acute diarrhea if it is greater than 14 days then it is persistent diarrhea and a chronic diarrhea is of duration greater than 30 days. Both infectious and noninfectious etiology accounts for diarrhea. The infectious causes can be bacterial, viral and protozoal, Non-infectious diarrhea can be disease, medication and diet related. The major complications associated with diarrhea in critically ill patients are Skin breakdown, electrolyte abnormalities, nutritional deficiencies, metabolic acidosis, hemodynamic instability, severe dehydration. Discontinuation of provoking medications, antidiarrheals, probiotics, metronidazole and vancomycin specifically in clostridium difficile induced diarrhea are the treatment option employed for the management of diarrhea Diarrheal patients in the intensive care unit are also seen to have a rise in morbidity rates. High rates of nosocomial co-infections are associated with certain bacteria that leads to diarrhea which when untreated escalates the morbidity and mortality rates. Diarrhea affects adversely multiple clinical outcome such as hospital mortality rates and length of stay.

INTRODUCTION

In an intensive care unit patients who are seriously ill and those who need special care preponderate. Occurrence of diarrhea among these crowd is a significant concern. "WHO defines diarrhea as the passage of 3 loose stools per day. A Bristol score of 6 or 7 is also classified as diarrhea". The incidence of diarrhea in ICU ranges from 2- 95%. Diarrheal episodes of duration less than 14 days is acute diarrhea if it is greater than 14 days then it is persistent diarrhea and a chronic diarrhea is of duration greater than 30 days.[1] Both infectious and noninfectious etiology accounts for diarrhea. The infectious causes can be bacterial, viral and protozoal which includes *clostridium difficile, Klebsiella oxytoca, clostridium perfringens, staphylococcus aureus, shigella, norovirus, rotavirus, adeno virus, entamoeba histolytica*.[2] Non-infectious diarrhea can be disease, medication and diet related. Disease related diarrhea includes specific intolerances, endocrine disorders, tumors, bile acid malabsorption, intoxication and chronic malassimilation. Use of medications like antibiotics, antineoplastic, laxatives, H_2 receptor blockers, proton pump inhibitors, prokinetics and hyperosmolar oral liquid preparations are likely to cause diarrhea .[3]Diarrhea is one of the major interrupting factors in tube fed and orally fed patients. The major complications associated with diarrhea in critically ill patients are skin breakdown, electrolyte abnormalities, nutritional deficiencies, metabolic acidosis, hemodynamic instability and severe dehydration.[3,4] *clostridium difficile* contribute to more severe complications like toxic mega colon, pseudomembranous colitis, complete ileus.[5,6] The mortality and morbidity rate is up turned by all these above stated factors and also contribute to the prolonging of hospital and medical ICU stay.

Risk factors of diarrhea in the intensive care unit

Increased age and a high APACHE II score[7,8,9,10] is a predisposing factor for diarrhea. Even though there is no association with diagnosis and diarrhea chronic disease like lactose, sorbitol, fructose intolerance and celiac disease thyroid disease diabetes, zollinger Ellison syndrome, inflammatory bowel disease, bile acid malabsorption, intoxication,[7,8,11] are associated with diarrheal incidence. Hyperthyroidism being one of the culprit for diarrheal episodes in critically ill patient, 25% of total population go through mild to moderate diarrhea. 45-85% of people with celiac disease have diarrhea as a GI symptom.[12] Even though the exact mechanism contributing to diabetes induced diarrhea remains

unknown around 20% of patient diagnosed with diabetic mellitus had shown diarrheal episodes.[13,14] Zollinger Ellison syndrome (ZES) is another factor contributing to diarrhea with an incidence rate of 73% .50 – 80% of patients on the chemotherapeutic regimen suffer from chemotherapy induced diarrhea.[15]

More than 700 drugs have diarrhea as adverse drug reaction.[16] Laxative, prokinetics, hyperosmolar oral liquid preparation, antibiotic, chemotherapy and radiation therapy beget medication related diarrhea.[1,15,16,17,18,19] Antibiotic-associated diarrhea (AAD) is due of disrupted intestinal flora that is caused by antibiotic administration. Almost all antibiotics, peculiarly those that act on anaerobes, can cause diarrhea, but the risk is higher with aminopenicillins, a combination of aminopenicillins and clavulanate, cephalosporins and clindamycin.The incidence rate of AAD varies from 5% to 35% .pipperacillin/ tazobactem combination ,carbopenams, Amikacin, ceftriaxone are the major offenders of antibiotic associated diarrhea.[8] In the incidence of AAD, enzyme inhibitor antibiotics or broad spectrum antibiotics are pre-eminent. Combination of enzyme inhibitor antibiotics with antifungals and other antibiotics will also increases the incidence of AAD.[20,21,22] Laxative abuse has been accountable for occasional cases of watery diarrhea. In addition antecedent use of laxative can upturn the risk of *clostridium difficile* infection.[23] prokinetics reduces the gastric transit time and be a factor that bring about diarrhea. Metoclopramide was associated with 32% of diarrhea during intragastric feeding in critically ill patients [19]. PPIs elevates the gastric p H levels which smoothens the path of pathogenic flora in the gastrointestinal tract. Also increased gastric p H allows conversion from the spores to vegetative cells that eventually generate toxins. PPI is also an independent risk factor for the development of CDAD. H_2 receptor antagonist can also be responsible for diarrhea as it causes hypochlorhydira.[24,25,26,27]

Clostridium difficile, Salmonella, campylobacter, pseudomonas aeruginosa, norovirus and candida albicans are the most identified Infectious causes of diarrhea [7,8,16,19] Among these clostridium difficile is responsible for 15% of the incidence [5] and is the most common pathogen that causes nosocomial diarrhea[16] Established risk factors for CDAD include the administration of almost any antimicrobial therapies, particularly repeated courses and/or broad-spectrum antibiotics such as penicillins (including b-lactamase inhibitors), cephalosporins and clindamycin. The most common culprits of clostridium difficile are fluoroquinolones, cephalosporins, and clindamycin, clarithromycin which are identified in greater than 90% of hospitalized patients who develop CDI, although most antibiotic classes have been implicated.[2,6,7] Another cause for clostridium difficile is acid suppression therapy.[20,21,22,23,28,29,30,31] A hospital stay is also an risk factor for CDAD [8] .lack of proper hand wash can ramp up the number of clostridium difficile cases.[2,6,7,31]

Enteral tube feeding is a major risk factor for the occurrence of diarrhea in the intensive care unit,[1,7,8,9,17,18,19,32] delivering more than 60% energy, combination of enteral nutrition with antibiotics or antifungals can increase the risk on diarrheal incidence[18] Diarrhea is one of the major interrupting factors in tube fed and orally fed patients. 22-26% of patients receiving enteral tube feeding shows incidence of diarrhea that disrupts the enteral nutrition management.[33]

Patients with diarrhea experience increased ICU length of stay increased ICU mortality.[7,9,16]

Complications associated with diarrhea

Complications related to Diarrhea are secondary conditions, symptoms, or other disorders that are caused by Diarrhea. Some of the major complications includes the following. The major complications associated with diarrhea in critically ill patients are Skin breakdown, electrolyte abnormalities, nutritional deficiencies, metabolic acidosis, hemodynamic instability, severe dehydration. Dehydration is found to be the leading complication associated with diarrhea. Large amount of water and electrolytes is lost with watery diarrhea leading to dehydration. This can be further compounded by vomiting. Electrolyte imbalance can be developed through dehydration, which act as another complication. Electrolytes can become imbalanced by abnormal fluid loss, as occurs in diarrhea. The fluid lost in diarrhea takes electrolytes and water out of the body, these have to be replaced. Major electrolytes lost in diarrhea include sodium and potassium. The conditions associated with electrolyte imbalance are Hypokalemia– decreased potassium in blood, as Stomach acid has a high concentration of potassium in the form of potassium chloride. Potassium is important for the production and secretion of acid, which helps in the digestion of the foods we eat. Hypernatremia and depletional hyponatremia depends on the consistency of the diarrhea. Hypernatremia occurs primarily when someone has diarrhea that is watery. Diarrhea can also be loose, unformed stool which will not have as much water content and the person may become hyponatremic. It is mainly associated with hypokalemia. Hypomagnesemia- it mainly occurs due to the decreased gastrointestinal absorption and increased renal loss. Diarrhea remains the major cause for decreased gastrointestinal absorption of magnesium. Less than the normal range leads to seizures and life threatening arrythmias.[34,35,36]

Hypovolemic shock is the physical and mental reaction due to reduced circulation. Reduced blood flow can be occurred due to severe diarrhea, vomiting, and dehydration. It's a life-threatening condition that results when you lose more than 20 percent (one-fifth) of your body's blood or fluid supply. This severe fluid loss

makes it impossible for the heart to pump a sufficient amount of blood to your body and finally leads to organ failure.[36,37] Metabolic acidosis- Many of the juices that are released into the gut are alkaline. These come from organs such as the pancreas and gallbladder, and the fact that they are alkaline helps to neutralize the acid from the stomach. Normally, much of the bicarbonate from these alkaline juices is absorbed back into the gut, so that only a small amount passes out of the body in stools. When a person contracts diarrhea, the amount of bicarbonate lost increases hugely as much larger quantities of stools are passed. Diarrhea usually contains large amounts of bicarbonate, this can cause an imbalance in the body's pH. Bicarbonate is alkaline, so its loss leads to a condition known as acidosis, where the blood is too acidic. For this reason, diarrhea is one of the causes of acidosis.[37,38,38] Hemodynamic instability- is defined as any instability in blood pressure which can lead to inadequate arterial blood flow to organs. it is associated with the hypovolemic condition due to diarrhea. Hypovolemia causes low cardiac output and hypotension by decreasing the preload. So it directly affects the rate of blood availability in different organs. The conditions associated with the same are Abnormal heart rate,Shortness of breath, Pulmonary congestion, Cold extremities, Peripheral cyanosis, Decreased urine output, Alternative consciousness (restlessness, loss of consciousness, confusion), Chest pain.[36,37] Fecal incontinence - is the inability to control bowel movements, causing stool (feces) to leak unexpectedly from the rectum. Also called bowel incontinence, fecal incontinence ranges from an occasional leakage of stool while passing gas to a complete loss of bowel control.it can occur temporarily during an occasional bout of diarrhea. But it can be chronic or recurring, so proper management is needed.[40]

Treatment of diarrhea in intensive care unit

AAD is defined as the diarrhea that occurs after the administration of antibiotics. It is characterized by at least 3 loose or watery stools regularly for 3 days. The use of broad-spectrum antimicrobials, the combination of three or more antibiotics as well as prolonged duration of antibiotic agents contribute to disruption of intestinal flora resulting in the increased drug resistant bacteria such as *C.difficile* leading to antibiotic associated diarrhea (AAD).[41,42]

Antibiotic associated diarrhea and clostridium difficile infection

Discontinuation of provoking antibiotic is the first measure. For uncomplicated cases of AAD, the most reasonable measure is to discontinue or change the provoking antibiotic if possible. In cases where the etiologic agent for AAD is known then specific targeted antibiotic therapy against these pathogens is recommended. If diagnostic tests for CDI is unavailable and severe or complicated CDI is suspected empirical therapy should be initiated. If the result of stool toxin assay is negative then start the individualised therapy. Discontinue antibiotic agent under use as soon as possible. Then institute supportive care including hydration and electrolyte replacement. For mild to moderate initial episode of CDI, the drug of choice is metronidazole. The recommended dosage is 500 mg 3 times daily or 250 mg four times a day for 10 to 14 days. In case of resistance to metronidazole vancomycin orally at a dosage of 125 mg 4 times daily for 10 to 14 days should be used. In case of severe CDI Vancomycin is the drug of choice and the dosage is 125 to 250 mg orally 4 times daily for 10 to 14 days. Vancomycin is given orally with or without intravenously administered metronidazole for severe complicated CDI. The vancomycin at a dose of 500 mg in 100 mL normal saline rectally every 6 hours can be used as a retention enema foe CDI.[41,43]

If intravenous management is needed, only metronidazole is effective compared to vancomycin since intravenous metronidazole will attain a moderate concentrations of the drug in the colon. The anticipated response to treatment is reduction of fever in one day and reduction of diarrheal episodes in four to five days. Vancomycin treatment is preferred only in the cases of pregnancy, lactation, intolerance to metronidazole or failure to respond to metronidazole after three to five days of treatment. In some case critically ill patients shows no response to intravenous metronidazole or oral vancomycin in such case they may require colectomy. Most of the C. difficile bacteria shows response to either of the treatment option that is vancomycin or metronidazole and the lack of a response need a prompt evaluation of compliance to the medications, an alternative diagnosis, or an assessment for ileus or toxic megacolon, since these conditions may prevent the drug from reaching the target site.[44]

One of the complication of antibiotic treatment is relapse. Small percent of patients may have more than six relapses. Relapse is defined by the reappearance of symptoms 3 to 21 days after metronidazole or vancomycin is discontinued. These relapse cases respond to another course of antibiotics in standard doses for 10 days. Other potential options include alternative antimicrobial agents such as fidaxomicin, nitazoxanide, monoclonal antibody, intravenous IgG, the use of C. difficile toxoid vaccine or fecal transplantation.[41,44]

Bacitracin 500 mg every 6th hourly for 7-10 days can be one of the choice for the treatment of antibiotic-associated colitis and diarrhea caused by Clostridium difficile. Bacitracin, being less expensive and more readily available, it can be used in place of vancomycin with bad taste and high cost. It can also be used for the management of diarrhea that relapsed after initial response to vancomycin therapy.[45]

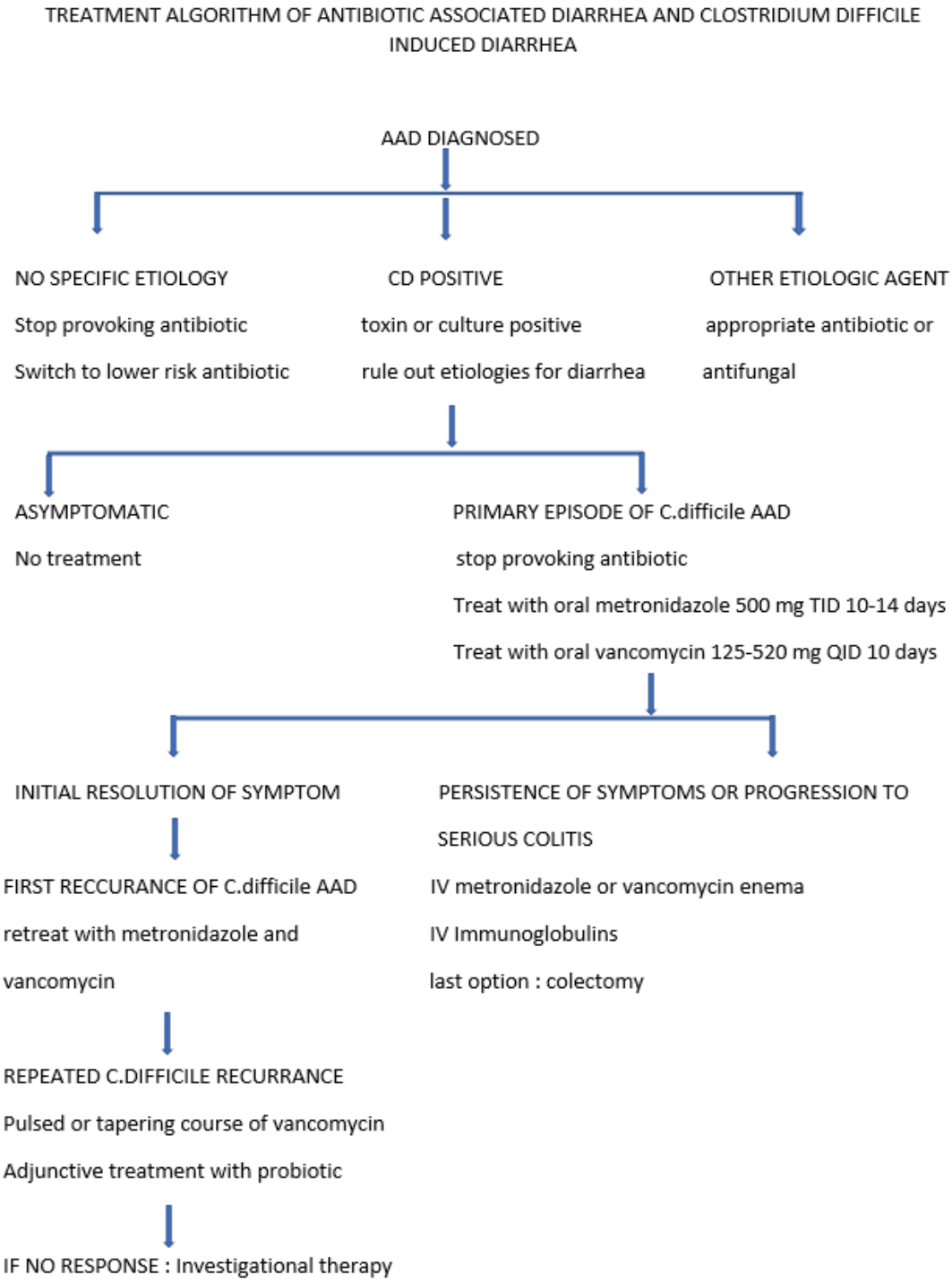

Fig. 1: Management of antibiotic associated diarrhea.

Probiotics

Many studies supported the use of probiotics for prevention of antibiotic associated diarrhea. Concomitant use of probiotic along with two or more antibiotics and PPIs is helpful in reducing the antibiotic-associated gastrointestinal side effects.

Probiotics should be species specific, should be of human origin , should survive the gastric acid barrier, digestive enzymes, and bile acids and then travel down the small intestine into the colon to proliferate there. The dose of probiotics should preferably be greater than 10 billion cfu/gm in adults to maintain their viability and concentration and have adequate shelf life for its effectiveness.

Probiotics enhances mucosal barrier function by secreting mucins, produce colonization resistance increase production of secretory immunoglobulin A (IgA), produce a balanced T-helper cell response, and increases production of interleukin 10 there by developing immunologic tolerance to antigens and

protection from potential pathogens. Probiotics also reduce the incidence of recurrent CDI when used adjunctively with high-dose vancomycin.

Single strain probiotics used for treating AAD include Lactobacillus GG , Saccharomyces Boulardii . And multi strain probiotics include L. Casei, S. Thermophilus, and L. Bulgaricus.[41]

Tube fed induced diarrhea

The incidence of diarrhea in tube-fed ill patients are associated with multiple factors including hypoalbuminemia, hyperosmolar or high-fat formulas and antibiotics. Fiber supplementation can be used for the treatment of tube feeding related diarrhea.[46,47]

A change in the enteral feeding formula may sometimes needed to reduce osmolality, caloric density, residue content, nutrient content or presence of lactose in patients with diarrhea. Small-peptide formulas, fibre-containing formulas or elemental formulas can be helpful in reducing tube fed associated diarrhea. Elemental formulas and peptide-based formulas are higher in CHO and lower in fat as compared to standard formulas.[48]

Prevention measures

The most important prevention measures include measures for patients, visitors, and health care workers along with environmental cleaning, restrictions on antimicrobial agents and the use of selected probiotics.

Infection usually spreads through the fecal-oral route. A patient-isolation room with a dedicated toilet is crucial, lid-down flushing is recommended. Hand washing with soap and warm water is indicated for patients, visitors, and health care providers. Contact precautions should be maintained throughout the period of diarrhea. Disposable medical equipments should be used. Chlorinated agents should be used for effective room cleaning and disinfection. PPIs and antiperistaltic medications should be discontinued.

It is necessary to reduce the frequency and duration of antimicrobials as an attempt to lessen the incidence of CDI. An antimicrobial stewardship program should be initiated.[41]

Financial implications

Financial importance are closely related to diarrhea associated with ICU stay as they develops in there due to various reasons like antibiotic treatments , hospital acquired infections, enteral feeding and other complications associated with the primary disease condition. Also the total payment for the primary treatments will includes the measures taken to manage the diarrheal conditions which is found to be undesirable in financial outcome. The important fact is that there are no genuine studies relating to financial implications of diarrhea. Hence proper research studies should be considered to overcome and manage this cause.

Outcome

Diarrhea is a frequent concern in the intensive care unit patients that can be managed with rigorous multi – disciplinary effect. Severity of complications may lead to mortality. There is an increase in intensive care unit crude mortality rates in patients contracted with diarrhea. It is worth noting that this shoot up in mortality rate leads to a rise in the ICU and hospital stay. When attributable length of hospital stay due to diarrhea increases the baseline risk of death increases. There is a soar noted in the intensity of workload among the healthcare workers especially the nursing sector.

Diarrheal patients in the intensive care unit are also seen to have a rise in morbidity rates. High rates of nosocomial co-infections are associated with certain bacteria that leads to diarrhea which when untreated escalates the morbidity and mortality rates. Diarrhea affects adversely multiple clinical outcome such as hospital mortality rates and length of stay. Increased length of stay has a high influence of treatment interruptions due to diarrheal episodes as certain medicines have to be stopped to bring loose stools under control for the betterment of the patient. As there is a confounding increase in mortality there is an indirect involvement in the rise of length of stay.

Diarrheal episodes in patients often cause the healthcare workers to work extra which gives a burden to them. There are treatment interruptions in Diarrheal patients as certain drugs has to be withdrawn or stopped which in turn affects their treatment outcomes. Antibiotic withdrawal is also done in certain cases to control diarrheal episodes.[1,8,9,10,16,17,18,49,50]

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