Journal of General Practice
ISSN: 2329-9126

Choi and Hector, J Gen Practice 2015, S1:1
DOI: 10.4172/2329-9126.S1-004

Research Article Open Access

Updated Management of *Clostridium difficile* Infections in Post-Acute Care Settings

Myunghan Choi[1,*] and Melvin Hector[2]

[1]*Acute and Post-acute Hospitalist, Mountain Vista Medical Center Mesa, AZ Research consultant, Transplant Center and Advanced Liver Disease, Good Samaritan Medical Center, Phoenix, AZ, USA*

[2]*Clinical Associate Professor, College of Medicine University of Arizona Post-acute Care Hospitalist IPC Healthcare Inc., AZ, USA*

[*]Corresponding author: Myunghan Choi, Acute and Post-acute hospitalist, Mountain Vista Medical Center Mesa, AZ Research Consultant, Transplant Center and Advanced Liver Disease, Good Samaritan Medical Center, Phoenix, AZ, USA, Tel: 5209097654; E-mail: myunghan.choi@gmail.com

Receiving date: May 25 2015; **Accepted date:** June 12 2015; **Published date:** June 16 2015

Abstract

Clostridium difficile (*C. difficile*) is a formidable pathogen causing various symptoms ranging from asymptomatic colonization to fulminant colitis among the elderly. *C. difficile* associated mortality rate has quadrupled in the last five years. A recent 10 year-literature review was conducted to determine a practical approach for elderly patients with *C. difficile* infection (CDI) in post-acute settings (PAS). Risk factors for CDI include antibiotic use, age over 65 years old, a prior history of CDI, institutionalization, and use of protein pump inhibitors (PPIs) or H-2 blockers. Diagnostic testing to confirm CDI can be challenging because of the relatively low sensitivity of most commercially available tests. Strategies for the cost-effective management and prevention of CDI include surveillance of at-risk patients with appropriate testing, contact precaution of suspected patients, discontinuation of PPIs or H-2 blockers in selected patients, use of probiotics, and antibiotic stewardship. Treatment and management should be individualized based on risk factors, symptom severity, comorbidities, and history of prior CDI.

Keywords: *Clostridium difficile* infection; Elderly patients; Post-acute care

Background

Clostridium difficile (*C. difficile*) is a formidable pathogen causing various symptoms ranging from asymptomatic colonization to fulminant colitis [1]. The incidence of *C. difficile* related infection (CDI) is alarming, as the CDI-associated mortality rate has quadrupled from 5.7 per million population in 1999 to 23.7 per million population in 2004, with high mortality rates among elderly patients [1-3]. Even with appropriate therapy, approximately 20% of patients with an initial episode of CDI develop a second episode, and 60% of patients with two recurrences develop additional recurrences [4]. The CDI-associated direct annual medical costs in acute care settings have been estimated at $4.8 billion in 2008 [5]. Elderly patients in post-acute care settings (PAS) often develop CDI 2-4 weeks after discharge from hospitals [6-9]. Healthcare providers in PAS face the challenge of effective management of patients at risk for CDI to effectively treat and prevent further spread of the disease [9]. The aim of this paper is to provide healthcare providers with updated CDI information for practical management including diagnosis and management for elderly patients with CDI in PAS.

Risk factors

Broad spectrum antibiotic use has emerged as the primary risk factor for the development of CDI in various healthcare settings. In addition, persons with compromised immune systems and predisposing medical conditions are more vulnerable to CDI, with the risk increasing in patients with any or multiple antibiotic exposures, use of protein pump inhibitors (PPIs)/H-2 blockers, gastrointestinal surgery, long length of stay in healthcare settings, serious underlying illness, immune-compromised conditions, and age over 65 [2-4]. The most commonly identified risk factors of CDI are listed in Table 1.

Factors
Active diarrhea 3 times/day*
Age 65
Fever 38.5º C (101.3 F)
WBC 15,000
Recent antibiotic therapy Recent GI surgery Recent chemo or radiation therapy Use of PPIs eGFR ≤ 30 History of CDI Recent hospitalization
*Must be an included risk factor to diagnose CDI

Table 1: Risk factors contributing CDI.

Pathogenesis

C. difficile is a Gram-positive spore-forming anaerobic bacillus; the spore is heat-stable and able to survive months to years, even in harsh environments. *C. difficile* is present in the stools of 5% of healthy adults in the U.S. Its spores can traverse the acidic stomach and then quickly germinate into the vegetative form in the small intestine. In this vegetative form, *C. difficile* produces toxins A and B which

activate the release of cytokines from monocytes which in turn damage human intestinal epithelial cells causing colonic inflammation [10,11].

Clinical manifestations

Clinical presentation of CDI varies, ranging from asymptomatic colonization to mild diarrhea to toxic megacolon and fulminant colitis leading to multi-organ failure and death. The most common clinical symptoms of CDI include watery diarrhea (more than 3 times a day), fever, loss of appetite, nausea with/without vomiting, abdominal pain, and/or tenderness [3]. Complications of CDI, if not treated, may include pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis, and even death [3].

Antibiotics and CDI

Exposure to antibiotics, even a single dose, is strongly associated with development of CDI with a prevalence rate ranging from 15% to 89% [12-14]. Although any single antibiotic can contribute to CDI, the most common antibiotics that cause the change in bacterial milieu leading to the pathologic emergence of predominantly *C. difficile* bacteria in the bowel are penicillin, clindamycin, beta lactams, fluoroquinolones, and cephalosporins [15]. Indications for which antibiotics are prescribed in PAS are superfluous. The leading infectious indications for unnecessary antimicrobial use are suspected urinary tract infections and pneumonia [16]. While treating patients with antibiotics is critically necessary, prescribing the least broad spectrum that will work for the shortest effective period is essential in order to reduce the prevalence of CDI, especially for the elderly and those who are immune compromised.

Clinical guidelines are becoming increasingly accepted as a means of directing clinicians' practice for prompt antibiotic usage for patients who have certain threshold lab values and who may still asymptomatic. Providers should consider an individualized plan when ordering antibiotics because there are no guidelines or hospital protocols that can be sufficiently specific to apply to all clinical situations. Once diagnostic testing rules out the suspected infection, initiated antibiotics must be promptly discontinued or the spectrum of antibiotic coverage should be narrowed if possible. National evidence-based guidelines could be modified using the anti-microbial biograms (susceptibility test reports for the determination of sensitivity of bacteria to given antibiotics minimal inhibitory concentration) of the local laboratory or facility.

Proton pump inhibitors (PPIs) and CDI

PPI use has grown significantly, especially with the recent availability of over-the- counter preparations. More than 119 million prescriptions were written for PPIs in 2009, creating a 13.5 billion dollars/year market in the U.S., not including those purchased without a prescription [17]. PPIs such as pantoprazole, omeprazole, lansoprazole, etc are often used indiscriminately without a documented medical need and for far longer than intended [18]. Potential side effects include osteopenia, vitamin B-12 deficiency, increased enteric infection risk, and hypomagnesemia [19,20]. The most commonly reported side effect of long term use of PPIs is diarrhea, which is the most frequent reason for their discontinuation. The association between PPIs and CDI has received significant attention. PPIs may contribute to the development of CDI by suppressing gastric acid which may increase the risk of nosocomial infection [21,22]. PPIs can also contribute to bacterial overgrowth that increase the levels of unconjugated bile salts that in turn support the conversion of *C. difficile* spores into the more virulent vegetative forms [22], and increase bacterial load in the stomach due to loss of gastric acid protection and decreasing gastric mucous viscosity with long term PPI use [23-25]. Other studies have demonstrated an association between anti-secretory therapy and increased risk of CDI, with a greater risk for PPI therapy than with H2 blockers [26-28]. Additionally, the risk for recurrent CDI was increased by 42% in co-therapy with PPIs during CDI treatment [29]. PPIs, in short, exert a multitude of influences that create a preferential environment for *C. difficile* proliferation and subsequent toxin production, particularly in the setting of previous antibiotic use, which suggests the discontinuation of PPIs for patients with CDI to prevent symptom exacerbation and recurrent CDI.

Providers in hospitals put patients on PPIs for prophylaxis against the development of stress ulcers, reflux, or gastritis. When these patients are discharged to PAS, the PPIs are generally continued unless medication reconciliation is thoroughly reviewed. This practice is unlikely to change until providers understand that the risk of significant gastrointestinal side effects is much lower than that of CDI. Many cases of dyspepsia or reflux resolve on their own. Lifestyle modifications including smaller meals throughout the day, weight reduction, smoking cessation, alcohol and caffeine avoidance, and stress reduction may be useful in many cases. The preponderance of data suggests that PPI use must be carefully monitored, especially in immune-compromised, chronically ill elderly patients and any patients with life-threatening CDI.

Pseudomembranous colitis and CDI

Once intestinal epithelial cells are exposed to high concentrations of *C. difficile* toxins, myofibroblast cells that support wound healing are impaired, contributing to severe inflammation such as pseudomembranous colitis [30]. Symptoms of pseudomembranous colitis are not easily distinguished from CDI without pseudomembranes, but usually include bloody diarrhea, fever, and severe abdominal cramps. The combination of fever with leukocytosis was a significant independent risk factor for pseudomembranous colitis [30]. The presence of pseudomembranous colitis is strongly suggestive of toxigenic *C. difficile* infection regardless of possible negative laboratory tests results [30]. When patients manifest bloody diarrhea with fever, colonoscopy is typically recommended to rule out pseudomembranous colitis. Simple sigmoidoscopy is not recommended as a single test because 33% of pseudomembranes present only in the right colon; some gastroenterologists are reluctant to perform colonoscopy on elderly patients with current CDI symptoms due to risks of perforation [31].

Diagnostic Approach

The diagnosis of CDI is based on clinical presentation and detecting the presence of *C. difficile* or its toxins in a diarrheal stool sample. Important issues to consider when collecting stool specimens for CDI include: 1) anaerobic stool cultures do not differentiate between toxin-producing and non-toxigenic strains; 2) stool specimens should be promptly refrigerated at 2-8˚C (35.6-46.4 F) for no more than 3 days to avoid false negative results: the toxins degrade at room temperature and may be undetectable within 2 hours after collection of a stool specimen; and 3) stool specimens that are too solid to form into the shape of the container will usually be of little benefit. Stool tests are commonly used to determine the presence of *C. difficile* toxins A and

B. Since not every laboratory offers every test, Table 2 represents options considering sensitivity and specificity for *C. difficile* testing relevant to PAS. Stool culture for *C. difficile* has sensitivities ranging from 60% to 70% and specificities of 98% [12] but requires a minimum of 72 hours to complete. Repeat testing using the same test following a negative test is not recommended because the likelihood of finding a false positive test is higher than the likelihood of having missed the diagnosis with the first attempt [31].

Test name	Waiting time	Sensitivity (%)	Specificity (%)	Reference/ Comment
Stool culture	3-5 days	60-70	98	
Toxin A/B EIA	<60 min	60-80	91-95	Not recommended as a stand-alone test
NAAT	45-180min	94-100	93-99	Can be used as a stand-alone test Detects C-difficile toxin genes
PCR (*C. difficile* DNA)	<60 min	>98	>98	Molecular methods
GDH antigen with assay	70 min	90-99	99	
Toxigenic culture	7 days	64-67	99	

Table 2: Laboratory tests for CDI.

Commonly used tests in PAS are stool culture and toxin A/B EIA: these are not recommended as stand-alone tests due to low sensitivity. A strategy suggested by the 2010 Infectious Diseases Society of America guidelines on *C. difficile* supports a two-step method: 1) Glutamate dehydrogenase (GDH) as the initial screen followed by a toxigenic culture, or 2) Polymerase chain reaction (PCR) for the toxin A/B gene as the confirmatory test for GDH positive specimens only [32]. PCR assays using *C. difficile* DNA for the toxin A/B provide high sensitivity and specificity in many studies, and are commonly used test [12,13]. We recommend that providers use a PCR assay of *C. difficile* DNA as a stand-alone test in PAS. When a patient's *C. difficile* PCR assay is negative, ruling out other causes of frequent loose stools becomes important. These may include lactose intolerance, overuse of laxatives, medication-induced diarrhea, malabsorption, irritable bowel syndrome, use of PPIs, etc.

Therapeutic Interventions

Optimal treatment for CDI should be based on risk assessment, symptom severity, and comorbidities in a given patient. Once a patient is identified to be at substantial risk for CDI, consider discontinuing certain medications including unnecessary antibiotics, PPIs or H-2 blocker, immunosuppressive drugs, laxatives, and medicines that are associated with prolonging the endotoxin effect such as antidiarrheal agents. In a newly symptomatic patient, nursing staff should be allowed the freedom to send specimens for *C. difficile* DNA (PCR) testing as soon as frequent diarrheal symptoms develop, without waiting for a provider's order. An elderly person with diarrhea more than 3 times a day, abdominal pain, fever and WBC >15,000 in the appropriate setting (Table 1) should be considered to have CDI and be empirically treated while stool testing for *C. difficile* DNA (PCR) is performed.

Drug selection is based on symptom severity and prior history of CDI. Metronidazole (500mg orally three times a day for 10-14 days) is the drug of choice for patients with mild or moderate CDI for the first time, and often for patients with a first recurrence. Vancomycin (125mg-250mg orally four times a day for 10-14 days) is used for patients presenting with more severe CDI and/or patients with a history of CDI with more than one recurrence. Treatment with metronidazole should be avoided for a second or more recurrence of CDI due to possible neurotoxicity or hepatotoxicity with prolonged use, although it is rare [33].

Regardless of the above recommendations, infectious disease experts often favor vancomycin because of increasing reports of failure of metronidazole for moderate to severe CDI [34]. For patients with complicated CDI (e.g., ileus or toxic megacolon), a combination of vancomycin and metronidazole is recommended in concert with appropriate surgical consultation [33-34].When patients have recurrent CDI, the symptoms usually occur 1-2 weeks after the initial treatment.

Other pharmacologic treatment options for CDI include use of fidaxomicin and rifaximin, tigecycline, rifalazil, and immunoglobulin therapy. Fidaxomicin appears to be superior to vancomycin in treating CDI because of low recurrence rate and longer mean time to recurrence [35] but its use has been low due to severe problems with fecal impaction and excessive cost [9,35]. Rifaximin is well-tolerated and especially efficacious when it is used with vancomycin, but is also quite expensive [36-37]. Tigecycline, a derivative of minocycline, is a broad spectrum antibiotic against Gram positive and Gram negative bacteria and has been used successfully in treating refractory CDI as monotherapy, or in combination with metronidazole or rifaximin [36-38].

Another consideration for the treatment of recurrent CDI is fecal transplant. Conventionally, an infusion of feces from related donors through a nasoduodenal tube was used. Recently, capsulized fecal microbiota transplantation (each patient received 15 capsules on 2 consecutive days) was successfully implemented (90% with clinical resolution of diarrhea) for patients (median age, 64.5 years) with recurrent CDI [39]. Patients with recurrent CDI despite antibiotic treatment should be considered for referral to a specialist for evaluation and possible performance of the fecal transplant.

Adjunctive therapy including probiotics and anion-binding resins in concert with vancomycin or metronidazole has been efficacious in PAS. Probiotics including Saccharomyces boulardii or Lactobacillus casei sp strain GG have been widely used and proven helpful in the treatment of antibiotic-associated CDI and other inflammatory bowel disease [32]. Probiotics may be effective for prevention of CDI because bacteria in probiotic preparations: 1) alter intestinal flora by suppressing the growth of *C. difficile*; 2) produce acids that lower the pH of the local gut environment and toxins that inhibit the growth of other bacteria; 3) inhibit adhesion and decrease invasion of pathogenic organisms to the colonic epithelium; and 4) modulate both the innate and adaptive immune systems by stimulating receptors [40-42].

Use of anion-binding resins (e.g., cholestyramine) have been advanced as being efficacious in patients due to binding of *C. difficile*

toxins and it has been suggested that they could be used along with metronidazole or vancomycin [43]. Unfortunately, on a regimen of multiple doses of antibiotics and other medicines per 24 hours, it is an imposing challenge to give resins in a time frame that does not interfere with the dosing of other drugs. The use of resins is, therefore, not typically endorsed in PAS. Immunoglobulin therapy has been associated with improvement of intestinal vascular permeability and mucosal damage in the gut against fulminant CDI symptoms but clinical evidence is so far quite limited [43].

Preventive Interventions

Contact isolation of the patient is critically important in reducing the transmission of CDI via hands and clothing of nursing staff, visitors, and providers. Wearing gloves and hand washing with soap and water are the most effective methods of reducing acquisition of CDI in PAS [44]. Contact isolation is improved with single-use items including disposable thermometers, blood pressure cuffs, and stethoscopes, and should be considered. Nurses should have standing orders to send stool specimens for CDI testing as soon as they deem it appropriate. For patients with greater than three unformed stools within 24 hours consider presumptive isolation while specimen results are pending [1]. If clinical suspicion is strong, or the patient's circumstance is high risk, begin treatment while awaiting test results. Development of a vaccination for CDI is in process, but is still in very early stages [45].

Conclusion

CDI is a serious nosocomial and community-associated infection and a frequent cause for readmission of patients from post-acute to acute care settings. A risk assessment for CDI is recommended to help guide the initiation of treatment. Each individual presents with CDI symptoms differently. Testing for *C. difficile* should be considered in patients with more than three loose stools per 24 hour-period. Stool for *C. difficile* DNA (PCR) as a stand-alone test is recommended in PAS to diagnose CDI.

Before discharging patients to long term care facilities (LTC) or assisted living facilities, patients are sometimes requested to have negative test results for *C. difficile* by the accepting facility; repeat testing following a positive test for evidence of "cure", however, is not a recommended strategy because patients may carry toxigenic *C. difficile* for months after treatment and clinical resolution. Completion of CDI treatment is a clinical decision determined by identifying formed stools, or cessation of diarrhea in an asymptomatic patient.

Factors involved for the cost effective management and prevention of CDI include awareness of CDI, antibiotic stewardship, environmental sequestration, discontinuation of PPIs in selected patients, and use of probiotics if necessary. Treatment and management information provided in this study should be individualized based on risk factors, symptom severity, comorbidities, history of prior CDIs and their implication.

Acknowledgments

We would like to thank: Donna Velasquez, PhD, FNP, FAANP; Meaghan Dirksen, BA in Global studies at the Arizona State University; Gregory Stevenson, MSN, NP at the VA hospital in Tucson, AZ; Randy Odero, MD; Hosu Chang, Arizona State University; and Jean Chang, BS for their contribution.

References

1. http://www.cdc.gov/HAI/organisms/cdiff/Cdiff_infect.html.
2. Redelings MD, Sorvillo F, Mascola L (2007) Increase in Clostridium difficile-related mortality rates, United States, 1999-2004.Emerg Infect Dis 13: 1417-1419.
3. Al-Abed YA, Gray EA, Rothnie ND (2010) Outcomes of emergency colectomy for fulminant Clostridium difficile colitis.Surgeon 8: 330-333.
4. Kachrimanidou M, Malisiovas N (2011) Clostridium difficile infection: a comprehensive review. Crit Rev Microbiol 37: 178-187.
5. Dubberke ER, Olsen MA (2012) Burden of Clostridium difficile on the healthcare system. Clin Infect Dis 55 Suppl 2: S88-92.
6. Laffan AM, Bellantoni MF, Greenough WB 3rd, Zenilman JM (2006) Burden of Clostridium difficile-associated diarrhea in a long-term care facility. J Am Geriatr Soc 54: 1068-1073.
7. Chang HT, Krezolek K, Johnson S, Parada JP, Evans CT, et al. (2007) Onset of symptoms and time to diagnosis of Clostridium difficile-associated disease following discharge from an acute care hospital. Infection Control and Hospital Epidemiology 28: 926-931.
8. Mylotte JM (2008) Surveillance for Clostridium difficile-associated diarrhea in long-term care facilities: what you get is not what you see. Infect Control Hosp Epidemiol 29: 760-763.
9. Mylotte JM, Russell S, Sackett B, Vallone M, Antalek M (2013) Surveillance for Clostridium difficile infection in nursing homes. J Am Geriatr Soc 61: 122-125.
10. Hampton T (2011) C. difficile test approved. The Journal of the American Medical Association 305: 2056-20562011;305: 2056-2056305:2056-2056.
11. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, et al. (2004) Outcome after colectomy for Clostridium difficile colitis.Dis Colon Rectum 47: 1620-1626.
12. Carroll KC (2011) Tests for the diagnosis of Clostridium difficile infection: the next generation. Anaerobe 17: 170-174.
13. Simor AE (2010) Diagnosis, management, and prevention of Clostridium difficile infection in long-term care facilities: a review. J Am Geriatr Soc 58: 1556-1564.
14. Cartman ST, Heap JT, Kuehne SA, Cockayne A, Minton NP (2010) The emergence of 'hypervirulence' in Clostridium difficile. Int J Med Microbiol 300: 387-395.
15. Lesperance K, Causey MW, Spencer M, Steele SR (2011) The morbidity of Clostridium difficile infection after elective colonic resection-results from a national population database. Am J Surg 201: 141-148.
16. Shaughnessy MK, Amundson WH, Kuskowski MA, DeCarolis DD, Johnson JR, et al. (2013) Unnecessary antimicrobial use in patients with current or recent Clostridium difficile infection. Infect Control Hosp Epidemiol 34: 109-116.
17. Sheen E, Triadafilopoulos G (2011) Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci 56: 931-950.
18. Heidelbaugh JJ, Goldberg KL, Inadomi JM (2010) Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. Am J Manag Care 16: e228-234.
19. Chen J, Yuan YC, Leontiadis GI, Howden CW (2012) Recent safety concerns with proton pump inhibitors. J Clin Gastroenterol 46: 93-114.
20. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH (2000) Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Alimentary Pharmacology & Therapeutics 46: 651-668.
21. Dial S, Delaney JAC, Barkun AN, Suissa S (2005) Use of gastric acid-suppressive agents and the risk of community acquired Clostridium difficile associated disease. The Journal of the American Medical Association 294: 2989–2995.
22. Oake N, Taljaard M, van Walraven C, Wilson K, Roth V, et al. (2010) The effect of hospital-acquired Clostridium difficile infection on in-hospital mortality. Arch Intern Med 170: 1804-1810.

23. Nerandzic MM, Pultz MJ, Donskey CJ (2009) Examination of potential mechanisms to explain the association between proton pump inhibitors and Clostridium difficile infection. Antimicrob Agents Chemother 53: 4133-4137.
24. Goddard AF, Spiller RC (1996) The effect of omeprazole on gastric juice viscosity, pH and bacterial counts. Aliment Pharmacol Ther 10: 105-109.
25. Klingensmith ME, Neville LJ, Delpire E, Wolfe MM, Soybel DI (1999) Gastrin-mediated effects of omeprazole on rat colon mucosa. Surgery 126: 272-278.
26. Kuehn BM (2012) Reflux drugs linked to C. difficile-related diarrhea. JAMA 307: 1014.
27. Howell MD, Novack V, Grgurich P, Soulliard D, Novack L, et al. (2010) Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med 170: 784-790.
28. Ben-Horin S, Margalit M, Bossuyt P, Maul J, Shapira Y, et al. (2010) Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and Clostridium difficile infection. J Crohns Colitis 4: 194-198.
29. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA (2010) Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 170: 772-778.
30. Arora G, Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G (2009) Risk of perforation from a colonoscopy in adults: a large population-based study. Gastrointest Endosc 69: 654-664.
31. Quinn CD, Sefers SE, Babiker W, Alcabasa R, He Y, et al. (2010) C diff Quik Chek complete enzyme immunoassay provides a reliable first-line method for detection of Clostridium difficile in stool specimens. Journal of Clinical Microbiology 48: e603-e605.
32. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, et al. (2010) Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infection Control and Hospital Epidemiology 31: 431-455.
33. Cocanour CS (2011) Best strategies in recurrent or persistent Clostridium difficile infection. Surg Infect (Larchmt) 12: 235-239.
34. Pakyz AL, Carroll NV, Harpe SE, Oinonen M, Polk RE (2010) Increase in use of vancomycin for Clostridium difficile infection in US hospitals. Infect Control Hosp Epidemiol 31: 867-868.
35. Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, et al. (2012) Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis 55 Suppl 2: S104-109.
36. Mattila E, Arkkila P, Mattila PS, Tarkka E, Tissari P, et al. (2013) Rifaximin in the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther 37: 122-128.
37. Lao D, Chang T, Gomez E (2012) Refractory Clostridium difficile infection successfully treated with tigecycline, rifaximin, and vancomycin. Case Reports in Medicine.
38. Anton PM, O'Brien M, Kokkotou E, Eisenstein B, Michaelis A, et al. (2004) Rifalazil treats and prevents relapse of clostridium difficile-associated diarrhea in hamsters. Antimicrob Agents Chemother 48: 3975-3979.
39. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, et al. (2014) Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. The Journal of the American Medical Association 312: 1772-1778.
40. Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, et al. (2008) Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. The Journal of Infectious Disease 197: 435-438.
41. Kalliomäki MA, Walker WA (2005) Physiologic and pathologic interactions of bacteria with gastrointestinal epithelium. Gastroenterol Clin North Am 34: 383-399, vii.
42. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, et al. (2012) Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 307: 1959-1969.
43. Saito T, Kimura S, Tateda K, Mori N, Hosono N, et al. (2011) Evidence of intravenous immunoglobulin as a critical supportive therapy against Clostridium difficile toxin-mediated lethality in mice. J Antimicrob Chemother 66: 1096-1099.
44. Stone SP, Fuller C, Savage J, Cookson B, Hayward A, et al. (2012) Evaluation of the national Cleanyourhands campaign to reduce Staphylococcus aureus bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. The British Medical Journal 344: e3005-3024.
45. Aboudola S, Kotloff KL, Kyne L, Warny M, Kelly EC, et al. (2003) Clostridium difficile vaccine and serum immunoglobulin G antibody response to toxin A. Infect Immun 71: 1608-1610.

This article was originally published in a special issue, entitled: **"Patient Care"**, Edited by Faisal Alnasir, Arabian Gulf University, Bahrain