Derna Academy Journal for Applied Sciences

E-ISSN: 3006-3159

DAJAS

The Impact of Clostridium Difficile Infection in the UK Hospitals

Fatma S.H.Abad [1], Sabrien E B Aboubakr[2] , Asmai S.H.Mohammed [3]

[1,2,3] Faculty of Medical Technology, Laboratory Medicine Department, University of Tobruk- Libya

*Corresponding author: E-mail addresses: fatma.abad@tu.edu.ly

Volume: 2 **Issue: 2** **Page Number: 211 - 219**

Keywords:
C. difficile Infections, Diarrhea, Healthcare, Strain

Received: 25\11\2024
Accepted: 25\12\2025
Published: 10\12\2024

DOI: https://doi.org/10.71147/j80a5a66

ABSTRACT

Clostridioides difficile *(C. difficile)* is a bacterium responsible for causing severe diarrhoea and more critical intestinal issues such as colitis. In the UK, C. difficile infections (CDI) are a major concern, especially within healthcare environments. Between April 2020 and March 2021, the annual rate of CDI was reported at 22.2 per 100,000 people, a number that has remained fairly consistent since 2013. C. difficile infections are commonly linked to the use of antibiotics, which can upset the natural balance of gut bacteria, allowing *C. difficile* to thrive. Older adults and individuals with weakened immune systems are particularly vulnerable. Effective infection prevention and control strategies, along with proper management of antibiotic use, are essential for controlling and decreasing the occurrence of CDI in the UK, another strain of the *C. difficile* that has been known as NAP1/027 has risen lately. This new strain tends to bring more serious infections. Hospitals enforce stringent infection prevention and control protocols to manage and lower CDI cases. Nevertheless, the rise of new, more aggressive strains and the bacteria's capacity to adapt to their surroundings necessitate ongoing vigilance and monitoring. This review will discuss *Clostridium difficile* problems in the UK hospitals from various aspects.

1. INTRODUCTION

C. difficile is responsible for illnesses ranging from mild diarrhea to severe conditions such as pseudomembranous colitis, intestinal inflammation, and toxic megacolon (Sayedy et al., 2010; Tang et al., 2016), see figure 1. *Clostridium difficile* is a spore-forming, gram-positive anaerobic bacillus that generates toxins A and B, which significantly contribute to mucosal damage and the formation of pseudomembranes (Rineh et al., 2014) This bacterium was first identified in the fecal matter of a healthy newborn in 1935 (Lessa et al., 2012).

For many years, until 1978, *Clostridium difficile* was thought to be harmless, but a pivotal diagnostic insight by Bartlett et al. (1978) revealed its potential as a source of cytotoxins in patients suffering from pseudomembranous colitis. The infection from *Clostridium difficile* impacts the digestive system, with cases most frequently occurring in healthcare environments (Enoch & Aliyu, 2012). It typically affects patients undergoing antibiotic treatment. Symptoms that range from mild to severe, includeincludeing diarrhea, high fever above 100.4 degrees Fahrenheit, and painful abdominal cramps, indicate the onset of the infection (Czepiel et al., 2019). An infection from *Clostridium difficile* can lead to life-threatening issues, such as severe bowel swelling due to gas accumulation, known as toxic megacolon (Bhargava et al., 2024; Sayedy et al., 2010). The spread occurs primarily through the fecal-oral route, though some studies suggest possible airborne transmission (Best et al., 2010). Spores can exit an infected person through fecal matter and can survive on surfaces for up to a week. Contact with contaminated surfaces followed by touching the mouth or nose can lead to the ingestion of spores (Shen, 2020). Generally, healthy people do not experience health issues from these bacteria; however, the use of certain antibiotics can disrupt the natural balance of gut flora, which normally provides protection against *Clostridium difficile* infections (Piccioni et al., 2022). This disruption allows the ingested bacteria to proliferate and produce toxins, leading to infection symptoms. Mild *Clostridium difficile* infections can often be managed by discontinuing the broad-spectrum antibiotics responsible for the disruption (Johanesen et al., 2015).

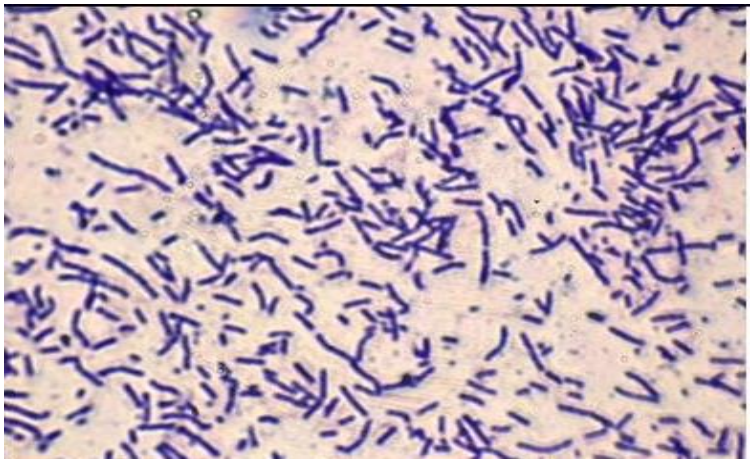

Fig. 1 Illustrates the description of *Clostridium difficile*; gram positive bacteria with spore forming (Mona et al., 2015).

2. *Clostridium difficile* is a problem in hospitals in the United Kingdom or not?

Indeed, *Clostridium difficile (C. difficile)* remains a major concern in hospitals across the UK. Despite efforts to manage its spread, *C. difficile* infections (CDI) still present challenges, especially within healthcare environments. According to the UK Health Security Agency, the rate of CDI has remained fairly stable since 2013, with an annual incidence of 22.2 per 100,000 population recorded from April 2020 to March 2021(UKHSA, 2020-2021). Moreover, in 2024, UK hospitals have experienced a significant rise in *Clostridioides difficile* (*C. difficile*) infections. The most recent quarterly report from the UK Health Security Agency (UKHSA, 2024) indicates that the overall incidence rate of *C. difficile* infections increased by 17.6% during the second quarter of 2024, climbing from 28.4 to 33.4 per 100,000 populations compared to the same period last year. This rise underscores the persistent challenge of controlling and preventing *C. difficile* infections within healthcare environments. To tackle this problem, it is crucial to implement improved infection control strategies, antibiotic management, and strict hygiene protocols. Furthermore, *Clostridioides difficile* is a major contributor to infections associated with healthcare settings, and *Clostridioides difficile* infection (CDI) is becoming an increasing issue for not only those infected but also for healthcare systems and public health across the globe (Guh et al., 2020). Many patients face not only an initial infection but also recurring episodes, complicating treatment due to the limited available options. In response, public health authorities worldwide have been implementing strategies to monitor and address CDI, including mandatory surveillance and annual case targets. For example, in the UK, Public Health England establishes yearly targets for healthcare providers, and institutions that exceed these targets face financial penalties. Antimicrobial resistance remains one of the most pressing global health challenges. The likelihood of developing CDI increases with the number of antibiotics prescribed their dosages, and the length of exposure (Stevens et al., 2011). Due to prescribers' training and practices, antibiotics are often over-prescribed. Therefore, enhancing knowledge about antibiotics and promoting responsible prescribing is crucial for reducing CDI risk.

Additionally, it is important to focus on implementing antimicrobial stewardship programs to mitigate the worsening issue of global antibiotic resistance (Finn et al., 2021).

3. Hand-washing and control on antibiotic prescriptions of NHS to eradicate the disease.

According to Enoch and Aliyu (2012), alcohol based sanitizers are not effective enough to eliminate *Clostridium difficile* spores, using soap and water is the best way of dislodging bacteria from hands. It is important that health care staff, as well as members of public coming in contact with individuals suspected of having *Clostridium difficile* infection maintain good levels of hand hygiene (Kiersnowska et al., 2021). Wearing personal protective equipment when looking after patients or handling specimens of patients having *Clostridium difficile* associated infection can reduce or eliminate the spread of spores (D'Agata et al., 2021). Similarly, early detection and isolation of suspected or confirmed patients is recommended to reduce the episodes of hand to mouth spread and airborne transmission of disease (Kociolek et al., 2023). It can serve as an effective strategy for keeping environmental contamination under control. A health care environment requires decontamination; detergents may not be as effective as chlorine-containing disinfectants (Dancer, 2014). Therefore, chlorine-containing compounds must be used to decontaminate the environment. Moreover, use of hydrogen peroxide vapors is also emerging as an effective alternative decontamination technique.

According to the Department of Health, 30% reduction in *Clostridium difficile* associated infection was observed in 2011 , as a result of introducing mandatory surveillance measures to keep the infection in control at all times (Duerden, 2011). It is identified that the Health Act 2006 imposes strict accountability on health care practitioners and hospital managers to ensure that the required measures are implemented by themselves and all the other staff members (Enoch & Aliyu, 2012). This measure is required to ensure safety of vulnerable patients in health care settings and health care providers. However, the emergence of new strains of *Clostridium difficile* called NAP1/027 has resulted in episodes of severe infection (Fatima & Aziz, 2019). Over 600 strains of *Clostridium difficile* has been identified through ribotyping. Ribotype 027 is commonly associated with high mortality and morbidity rates in the UK (Taori et al., 2013). This strain produces higher levels of toxins (Valiente et al., 2014). This is the result of dramatic changes in the epidemiology of *Clostridium difficile* associated infections. This strain also shows higher levels of resistance to fluoroquinolones and for this reason; it is a problem for health setting in the United Kingdom (Ghose, 2013). Moreover, prevalence of infection in different environments points at the bacteria's ability to modify its functionality and content in accordance to the environmental changes. This also means that the UK health care settings can experience the emergence of more pathogenic strains in future. This finding is line with the findings presented in a report by the Public Health England (2013). According to this report, ribotypes 002, 005, 014/020 and 015 are the newly emerging strains of *Clostridium difficile* in England, Northern Ireland and Scotland (Wiuff et al., 2011). Their association with infections in humans is evident from 2008 and since then, the number of cases has increased. These changes in the epidemiology and microbiology of *Clostridium difficile* infections suggests that it is still a problem for UK health care settings, despite, of the decrease in the number of infections caused by ribotype 027 since April 2007 (Herbert et al., 2019).

4. Diagnosis and detections

Stool testing is a crucial diagnostic tool for identifying infections (Carroll & Mizusawa, 2020). One of the main benefits of stool culture is its ability to identify the specific strain responsible for an outbreak. However, results typically take 2-5 days, and the process is quite labor-intensive (Kuijper et al., 2006). The cytotoxin assay, considered the gold standard for diagnosis, is known for its high sensitivity and specificity, but results are also slow, taking about 24-48 hours (Kendrick, 2018).). Additionally, this method is costly and not the most effective in terms of cost or time (Planche et al., 2013), and it only detects toxin B. The ELISA toxin test serves as another diagnostic method, providing quicker results in 2-6 hours and being easier to perform with high specificity. However, it has been criticized by healthcare providers for its lower sensitivity in detecting toxins (Singh et al., 2024). New diagnostic methods are being evaluated to potentially replace ELISA. According to Sandlund et al. (2019), the Nucleic Acid Amplification Test (NAAT), such as polymerase chain reaction (PCR), offers 100% sensitivity but can lack specificity at times. It may also produce false positives and is intended to detect the toxin B gene. PCR is expected to eventually take the place of ELISA in diagnosing infections (Singh et al., 2022). The latex agglutination assay for detecting glutamate dehydrogenase (GDH), an enzyme produced by all species of Clostridium, is an expensive but easily performed technique. However, it is heavily criticized for its poor sensitivity and specificity compared to the cytotoxin assay. This can lead to mixed results, causing confusion and potentially leading to ineffective treatment choices for patients (Girinathan et al., 2014).

Blood tests are also performed to count white blood cells, as an elevated white blood cell count often indicates a severe *Clostridium difficile* infection.

Blood tests can also detect mineral imbalances due to dehydration. To assess potential complications in the colon, a colon examination is conducted either directly via colonoscopy or indirectly through a CT scan (Frickenstein et al., 2019) Colonoscopy involves inserting a flexible tube with a camera into the rectum and colon to evaluate the disease's impact. A CT scan provides X-ray images from different angles to study the colon's condition in detail. Research indicates that managing a *Clostridium difficile* infection requires identifying the infection and discontinuing the causative antibiotics. Table 1 shows the advantages, disadvantages and targets of the different methods used for the diagnosis of *Clostridium difficile* infection.

Table 1 shows the main advantages and drawbacks of each test with the important thing the sensitivity and specificity (Di Bella et al., 2013).

Diagnostic test	*Pros*	*Cons*
Culture	High sensitivity Able to isolate the strain	Long time for results (>7 days) A second test is necessary to look for toxin production Labour intensive
Cell-culture cytotoxicity assay	Moderate/high sensitivity High specificity	48-72 h turn-around time Requires expert laboratory personnel Labour intensive
TcdA and/or TcdB detection (EIA)	High specificity Low cost Rapid and easy to perform	Low sensitivity
GDH detection (EIA)	High sensitivity Good as screening test	Cannot distinguish between toxigenic and non-toxigenic strains Cannot distinguish between active disease and colonisation
Nucleic acid amplification tests (PCR)	High sensitivitity and specificity Rapid Can identify NAP1/027/BI strains	High cost Requires expert laboratory personnel Sometimes "too sensitive"
Colonoscopy	Enables the diagnosis of pseudomembranous colitis if present Allows exclusion of concomitant disorders (i.e. IBD)	Low sensitivity Invasive test Risk of bowel perforation High cost
Imaging (CT, X-ray)	Non-invasive Allows recognition of possible complications of CDI	Indirect diagnostic tools Low sensitivity Low specificity

CDI: Clostridium difficile infection; EIA: enzyme immunoassay; GDH: glutamate dehydrogenase; CT: computed tomography, IBD: inflammatory bowel disease; PCR: polymerase chain reaction; TcdA: toxin A; TcdB: toxin B.

Significant efforts have been undertaken to combat the spread of *Clostridium difficile* infection (CDI) in healthcare settings. Although infection rates have notably decreased, particularly in the UK, CDI remains the leading healthcare-associated infection affecting the elderly (Islam et al., 2012). According to Islam et al. (2012) preventing the transmission and infection of *Clostridium difficile* continues to be a formidable challenge in the UK, largely due to antibiotic misuse. Although much remains to be accomplished, there has been a new level of collaboration and organization focused on prevention. Patients, long-term care residents, and their families are increasingly involved in care decisions. Education for patients and caregivers, along with healthcare professional training, continues to advance, fostering new strategies to tackle the issue. Collaborative efforts between environmental services professionals and infection prevention experts have led to improvements in environmental assessment, cleaning, disinfection, monitoring, and evaluation.

There is also a growing recognition of the importance of using antimicrobials judiciously. The prevention of CDI necessitates a team approach.

5. Treatment

To address severe infection cases, antibiotics such as vancomycin and metronidazole may be administered, typically leading to infection resolution within 7 to 10 days (Shen & Surawicz, 2008). However, infections often recur in patients, and in serious instances, surgical intervention may be necessary to remove the infected or damaged sections of the bowel. Additionally, live organisms like Saccharomyces are utilized, referred to as immunoglobulin and probiotics (Pelleschi, 2008). Fecal transplantation, also known as donor stool transplant, is considered a recurring treatment for *Clostridium difficile* infection (Brandt, 2012; Rohlke & Stollman, 2012). Pelleschi (2008) notes that surgery may be required to save lives in cases of pseudomembranous colitis. *Clostridium difficile* remains a significant issue in UK hospitals, necessitating strict monitoring and other preventive strategies outlined in the recommendations section of the review. The transmission of this organism is quite common and easily occurs; for example, if surfaces are contaminated and individuals touch them before contacting their bodies, the organism can be ingested. Furthermore, *clostridium difficile* spores can survive for extended periods, facilitating further transmission

6. Recommendations for the prevention of *Clostridium difficile* outbreaks in the future

Based on the findings of this review given below are some recommendations for the prevention of *C. difficile* outbreaks in different environments such as health care settings, where vulnerable patients taking antibiotics are present.

a) *Clostridium difficile* spores can easily spread in the environment, for these maintaining high standards of cleanliness is critical. In order to avoid the spread of infection chlorine-based disinfectants must be used to remove those spores from the objects, devices and surfaces. Hydrogen peroxide vapors can also be used to decontaminate the environment.
b) The infection caused by *Clostridium difficile* spreads from hand to mouth. Therefore, it is very important to maintain good hand hygiene by washing hands frequently and particularly after using toilets or visiting someone in hospital, with soap and warm water to dislodge the spores. Alcohol gels are not effective against the spores.
c) In health care settings, staff members must wear gloves and disposable aprons in order to prevent the spreading of infection from one patient to another. Equipment like rectal thermometers must be cleaned using sporidical agents.
d) Hospital laboratories must have an alert system that can be developed using advance communication means and can be used to immediately notify the health care provider about the positive test result for *Clostridium difficile* infection
e) Use of antibiotics must be restricted and this can be done by offering other treatment options where it can be.
f) When somebody is suspected of having infection by *Clostridium difficile*, they should be put in isolated health care setting such as a single room. This will enable to avoid the risk of spreading the infection to others. This strategy must be used eve while the diagnostic tests are in process.
g) When the infection is confirmed, patient must be transferred to special wards where the infection can be treated effectively. However, it is important to ensure that the patient stays away from other vulnerable patients in other wards i.e. they must have their own toilet facilities which must be regularly disinfected by the cleaners.
h) The recurrence of this disease has to be managed through effective early detection strategies. Those using antibiotics and are highly susceptible of getting the infection can be offered a bowel or a blood test, in a few weeks of starting the course so that early detections can be made and treatments can be started before the disease gets worse.
i) At this present time, there is another solution and will be useful in the future which vaccination is. Therefore, if this vaccine work and people start to take it the infections of *Clostridium difficile* will be decrease and it could be a radical solution to avoid the infection (Donskey et al., 2024).

7. Conclusion

In summary, *Clostridium difficile* remains a major issue in UK hospitals. Although the number of reported cases has declined since 2007-2008, the incidence has plateaued since 2013, with an annual rate of 22.2 per 100,000 people from April 2020 to March 2021. The infection poses a significant risk of morbidity and mortality, with a 30-day all cause mortality rate estimated to be between 9% and 38%. Efforts to control and reduce *C. difficile* infections persist, emphasizing infection prevention, accurate diagnosis, and effective treatment strategies. Despite the progress made, ongoing vigilance and strict adherence to guidelines are crucial to protect vulnerable patients and healthcare workers.

8. Acknowledgments

We thank the Ministry of Higher Education and Scientific Research –Libya.

9. REFERENCES

Bartlett, J. G., Chang, T. W., Gurwith, M., Gorbach, S. L., & Onderdonk, A. B. (1978). Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med*, *298*(10), 531-534. https://doi.org/10.1056/nejm197803092981003

Best, E., Fawley, W., Parnell, P., & Wilcox, M. (2010). The Potential for Airborne Dispersal of Clostridium difficile from Symptomatic Patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *50*, 1450-1457. https://doi.org/10.1086/652648

Bhargava, A., Mahakalkar, C., Kshirsagar, S., & Yachmaneni, A. (2024). Toxic Megacolon: A Sequelae of Clostridioides difficile Infection in a Case of Necrotizing Fasciitis. *Cureus*, *16*(1), e53034. https://doi.org/10.7759/cureus.53034

Brandt, L. J. (2012). Fecal transplantation for the treatment of Clostridium difficile infection. *Gastroenterol Hepatol (N Y)*, *8*(3), 191-194.

Carroll, K. C., & Mizusawa, M. (2020). Laboratory Tests for the Diagnosis of Clostridium difficile. *Clin Colon Rectal Surg*, *33*(2), 73-81. https://doi.org/10.1055/s-0039-3400476

Czepiel, J., Dróżdż, M., Pituch, H., Kuijper, E. J., Perucki, W., Mielimonka, A., Goldman, S., Wultańska, D., Garlicki, A., & Biesiada, G. (2019). Clostridium difficile infection: review. *Eur J Clin Microbiol Infect Dis*, *38*(7), 1211-1221. https://doi.org/10.1007/s10096-019-03539-6

D'Agata, E. M. C., Apata, I. W., Booth, S., Boyce, J. M., Deaver, K., Gualandi, N., Neu, A., Nguyen, D., Novosad, S., Palevsky, P. M., & Rodgers, D. (2021). Suggestions for the prevention of Clostridioides difficile spread within outpatient hemodialysis facilities. *Kidney Int*, *99*(5), 1045-1053. https://doi.org/10.1016/j.kint.2021.02.028

Dancer, S. J. (2014). Cleaning and decontamination of the healthcare environment. *Decontamination in Hospitals and Healthcare*, 25. (cleaning detergent disinfectants infection control decontamination)

Di Bella, S., Capone, A., Musso, M., Giannella, M., Tarasi, A., Boldock, E., Taglietti, F., Campoli, C., & Petrosillo, N. (2013). Clostridium difficile infection in the elderly. *Le infezioni in medicina : rivista periodica di eziologia, epidemiologia, diagnostica, clinica e terapia delle patologie infettive*, *21*, 93-102.

Donskey, C. J., Dubberke, E. R., Klein, N. P., Liles, E. G., Szymkowiak, K., Wilcox, M. H., Lawrence, J., Bouguermouh, S., Zhang, H., Koury, K., Bailey, R., Smith, H. M., Lockhart, S., Lamberth, E., Kalina, W. V., Pride, M. W., Webber, C., Anderson, A. S., Jansen, K. U., . . . Group, o. b. o. t. C. S. (2024). CLOVER (CLOstridium difficile Vaccine Efficacy tRial) Study: A Phase 3, Randomized Trial Investigating the Efficacy and Safety of a Detoxified Toxin A/B Vaccine in Adults 50 Years and Older at Increased Risk of Clostridioides difficile Infection. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciae410

Duerden, B. I. (2011). Contribution of a government target to controlling Clostridium difficile in the NHS in England. *Anaerobe*, *17*(4), 175-179. https://doi.org/https://doi.org/10.1016/j.anaerobe.2010.12.004

Enoch, D. A., & Aliyu, S. H. (2012). Is Clostridium difficile infection still a problem for hospitals? *Cmaj*, *184*(1), 17-18. https://doi.org/10.1503/cmaj.111449

Fatima, R., & Aziz, M. (2019). The Hypervirulent Strain of Clostridium Difficile: NAP1/B1/027 - A Brief Overview. *Cureus*, *11*(1), e3977. https://doi.org/10.7759/cureus.3977

Finn, E., Andersson, F. L., & Madin-Warburton, M. (2021). Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. *BMC Infectious Diseases*, *21*(1), 456. https://doi.org/10.1186/s12879-021-06147-y

Frickenstein, A. N., Jones, M. A., Behkam, B., & McNally, L. R. (2019). Imaging Inflammation and Infection in the Gastrointestinal Tract. *Int J Mol Sci*, *21*(1). https://doi.org/10.3390/ijms21010243

Ghose, C. (2013). Clostridium difficile infection in the twenty-first century. *Emerg Microbes Infect*, *2*(9), e62. https://doi.org/10.1038/emi.2013.62

Girinathan, B. P., Braun, S. E., & Govind, R. (2014). Clostridium difficile glutamate dehydrogenase is a secreted enzyme that confers resistance to H2O2. *Microbiology (Reading)*, *160*(Pt 1), 47-55. https://doi.org/10.1099/mic.0.071365-0

Guh, A. Y., Mu, Y., Winston, L. G., Johnston, H., Olson, D., Farley, M. M., Wilson, L. E., Holzbauer, S. M., Phipps, E. C., Dumyati, G. K., Beldavs, Z. G., Kainer, M. A., Karlsson, M., Gerding, D. N., & McDonald, L. C. (2020). Trends in U.S. Burden of Clostridioides difficile Infection and Outcomes. *N Engl J Med*, *382*(14), 1320-1330. https://doi.org/10.1056/NEJMoa1910215

Herbert, R., Hatcher, J., Jauneikaite, E., Gharbi, M., d'Arc, S., Obaray, N., Rickards, T., Rebec, M., Blandy, O., Hope, R., Thomas, A., Bamford, K., Jepson, A., & Sriskandan, S. (2019). Two-year analysis of Clostridium difficile ribotypes associated with increased severity. *J Hosp Infect*, *103*(4), 388-394. https://doi.org/10.1016/j.jhin.2019.06.003

Islam, J., Cohen, J., Rajkumar, C., & Llewelyn, M. J. (2012). Probiotics for the prevention and treatment of Clostridium difficile in older patients. *Age and Ageing*, *41*(6), 706-711. https://doi.org/10.1093/ageing/afs077

Johanesen, P. A., Mackin, K. E., Hutton, M. L., Awad, M. M., Larcombe, S., Amy, J. M., & Lyras, D. (2015). Disruption of the Gut Microbiome: Clostridium difficile Infection and the Threat of Antibiotic Resistance. *Genes (Basel)*, *6*(4), 1347-1360. https://doi.org/10.3390/genes6041347

Kendrick, K. (2018). Laboratory diagnosis of Clostridium difficile infection. *Journal of Laboratory and Precision Medicine*, *3*. https://jlpm.amegroups.org/article/view/4254

Kiersnowska, Z. M., Lemiech-Mirowska, E., Semczuk, K., Michałkiewicz, M., Sierocka, A., & Marczak, M. (2021). Level of Knowledge of Medical Staff on the Basis of the Survey in Terms of Risk Management, Associated with Clostridioides difficile Infections. *Int J Environ Res Public Health*, *18*(13). https://doi.org/10.3390/ijerph18137060

Kociolek, L. K., Gerding, D. N., Carrico, R., Carling, P., Donskey, C. J., Dumyati, G., Kuhar, D. T., Loo, V. G., Maragakis, L. L., Pogorzelska-Maziarz, M., Sandora, T. J., Weber, D. J., Yokoe, D., & Dubberke, E. R. (2023). Strategies to prevent Clostridioides difficile infections in acute-care hospitals: 2022 Update. *Infect Control Hosp Epidemiol*, *44*(4), 527-549. https://doi.org/10.1017/ice.2023.18

Kuijper, E. J., Coignard, B., & Tüll, P. (2006). Emergence of Clostridium difficile-associated disease in North America and Europe. *Clinical Microbiology and Infection*, *12*, 2-18. https://doi.org/https://doi.org/10.1111/j.1469-0691.2006.01580.x

Lessa, F. C., Gould, C. V., & McDonald, L. C. (2012). Current status of Clostridium difficile infection epidemiology. *Clin Infect Dis*, *55 Suppl 2*(Suppl 2), S65-70. https://doi.org/10.1093/cid/cis319

Mona, T., Al, M., Yusif, L., Mahdi, Turkey, M., Luma, A.-M., Mahdi, Y., & Al-Musawi, M. (2015). Isolation and Identification of Clostridium difficile from Antibiotic- Associated Diarrhea and Colitis in Iraqi children, using API20A Isolation and Identification of Clostridium difficile from Antibiotic-Associated Diarrhea and Colitis in Iraqi children, using API20A Anaerobic system. *journal of the college of basic education*, *21*, 57-68. https://doi.org/10.35950/cbej.v21i87.8852

Pelleschi, M. E. (2008). Clostridium difficile–Associated Disease: Diagnosis, Prevention, Treatment, and Nursing Care. *Critical Care Nurse*, *28*(1), 27-35. https://doi.org/10.4037/ccn2008.28.1.27

Piccioni, A., Rosa, F., Manca, F., Pignataro, G., Zanza, C., Savioli, G., Covino, M., Ojetti, V., Gasbarrini, A., Franceschi, F., & Candelli, M. (2022). Gut Microbiota and Clostridium difficile: What We Know and the New Frontiers. *Int J Mol Sci*, *23*(21). https://doi.org/10.3390/ijms232113323

Planche, T. D., Davies, K. A., Coen, P. G., Finney, J. M., Monahan, I. M., Morris, K. A., O'Connor, L., Oakley, S. J., Pope, C. F., Wren, M. W., Shetty, N. P., Crook, D. W., & Wilcox, M. H. (2013). Differences in outcome according to Clostridium difficile testing method: a prospective multicentre diagnostic validation study of C difficile infection. *Lancet Infect Dis*, *13*(11), 936-945. https://doi.org/10.1016/s1473-3099(13)70200-7

Rineh, A., Kelso, M. J., Vatansever, F., Tegos, G. P., & Hamblin, M. R. (2014). Clostridium difficile infection: molecular pathogenesis and novel therapeutics. *Expert Rev Anti Infect Ther*, *12*(1), 131-150. https://doi.org/10.1586/14787210.2014.866515

Rohlke, F., & Stollman, N. (2012). Fecal microbiota transplantation in relapsing Clostridium difficile infection. *Therap Adv Gastroenterol*, *5*(6), 403-420. https://doi.org/10.1177/1756283x12453637

Sandlund, J., Mills, R., Griego-Fullbright, C., Wagner, A., Estis, J., Bartolome, A., Almazan, A., Tam, S., Biscocho, S., Abusali, S., Nolan, N., Bishop, J. J., Todd, J., & Young, S. (2019). Laboratory comparison between cell cytotoxicity neutralization assay and ultrasensitive single molecule counting technology for detection of Clostridioides difficile toxins A and B, PCR, enzyme immunoassays, and multistep algorithms. *Diagnostic Microbiology and Infectious Disease*, *95*(1), 20-24. https://doi.org/https://doi.org/10.1016/j.diagmicrobio.2019.04.002

Sayedy, L., Kothari, D., & Richards, R. J. (2010). Toxic megacolon associated Clostridium difficile colitis. *World J Gastrointest Endosc*, *2*(8), 293-297. https://doi.org/10.4253/wjge.v2.i8.293

Shen, A. (2020). Clostridioides difficile Spores: Bile Acid Sensors and Trojan Horses of Transmission. *Clin Colon Rectal Surg*, *33*(2), 58-66. https://doi.org/10.1055/s-0040-1701230

Shen, E. P., & Surawicz, C. M. (2008). Current Treatment Options for Severe Clostridium difficile-associated Disease. *Gastroenterol Hepatol (N Y)*, *4*(2), 134-139.

Singh, K. B., Khouri, A., Singh, D., Prieto, J., Dutta, P., Nnadozie, M. C., Clanton, C., Morrison, E., & Sonnier, W. (2024). Testing and Diagnosis of Clostridioides difficile Infection in Special Scenarios: A Systematic Review. *Cureus*, *16*(4), e59016. https://doi.org/10.7759/cureus.59016

Singh, S., Newton-Foot, M., Nel, P., & Pienaar, C. (2022). Comparison of commercial assays and two-step approach to detect Clostridioides difficile in South Africa. *Afr J Lab Med*, *11*(1), 1809. https://doi.org/10.4102/ajlm.v11i1.1809

Stevens, V., Dumyati, G., Fine, L. S., Fisher, S. G., & van Wijngaarden, E. (2011). Cumulative Antibiotic Exposures Over Time and the Risk of Clostridium difficile Infection. *Clinical Infectious Diseases*, *53*(1), 42-48. https://doi.org/10.1093/cid/cir301

Tang, D. M., Urrunaga, N. H., & Von Rosenvinge, E. C. (2016). Pseudomembranous colitis: Not always <em>Clostridium difficile</em&gt. *Cleveland Clinic Journal of Medicine*, *83*(5), 361. https://doi.org/10.3949/ccjm.83a.14183

Taori, S. K., Wroe, A., & Poxton, I. R. (2013). Clostridium difficile infections in South East Scotland: mortality and recurrence in a region without PCR ribotype 027. *Journal of Medical Microbiology*, *62*(9), 1468-1477. https://doi.org/https://doi.org/10.1099/jmm.0.061093-0

UKHSA. (2020-2021). *'Annual epidemiological commentary: Gram-negative bacteraemia,*

MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financia. UKHSA. Retrieved 05 Dec 2024

Valiente, E., Cairns, M. D., & Wren, B. W. (2014). The Clostridium difficile PCR ribotype 027 lineage: a pathogen on the move. *Clinical Microbiology and Infection*, *20*(5), 396-404. https://doi.org/https://doi.org/10.1111/1469-0691.12619

Wiuff, C., Brown, D., Mather, H., Banks, A. L., Eastaway, A., & Coia, J. (2011). The epidemiology of Clostridium difficile in Scotland. *The Journal of infection*, *62*, 271-279. https://doi.org/10.1016/j.jinf.2011.01.015