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Review

Clostridioides difficile infections in Saudi Arabia: Where are we standing?

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ABSTRACT

Clostridioides difficile infections (CDIs) are infamous healthcare-associated infections for causing watery diarrhea to long-term hospitalized patients with a high mortality rate. Epidemiological reports from western countries showed up-trending pattern in the number of CDIs cases. It is becoming immensely challenging for routine diagnostic protocols to detect CDIs accurately with short turnaround time. In Saudi Arabia, there is a paucity of data about CDIs' prevalence, recurrence rate, methods of screening and mortality rate. Nevertheless, a growing number of cases with similar virulence strains and comparable antibiotic resistance pattern to the western countries counterparts reported data were also detected. This review aims to present the status of CDIs' diagnosis and incidence rate in Saudi Arabia based on current literature.

Contents

1. Introduction

Clostridioides difficile (*C. difficile*) is a Gram-positive, spore-forming, highly antibiotic-resistant bacteria, mainly known to cause healthcare-associated infectious diarrhea identified as *Clostridioides difficile* Infection (CDI) (Burnham and Carroll, 2013). The CDIs showed a high mortality rate within 30 days after positive stool samples (Freeman et al., 2010). In 2007, healthcare institutions in the United States (US) had reported 14,000 deaths due to CDIs-induced gastroenteritis (Hall et al., 2012). Epidemiological reports from the US, Canada, and Europe showed an incidence of 50 to 90 cases per 100,000 population between 2009 and 2011 (Chitnis et al., 2013); however, the incidence trended up to a rate of 145 per 100,000 during 2017 (Guh et al., 2020). There is no published study of CDI prevalence on a national level in Saudi Arabia, yet, the few published literature of single-center studies reported low rate of CDIs (Aljafel et al., 2020; Al-Tawfiq et al., 2020; Qutub et al., 2019). One of these studies was able to detect an increasing trend of healthcare-associated CDIs from 17% in 2001 to 20% in 2018 out of all suspected diarrhea samples tested (Al-Tawfiq et al., 2020).

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1.1 Clostridioides difficile virulence strains

The most hypervirulent strain detected during last decade was the North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis type B1, polymerase chain reaction ribotype 027, (NAP1/B1/027) and also referred to as ribotype 027 (RT027) which is also highly resistant to fluoroquinolones and metronidazole (Fatima and Aziz, 2019; Freeman et al., 2018). This strain has caused outbreaks in Europe and USA which brought the attention to CDI testing practice in hospitals, in terms of accuracy, specificity, and comprehensiveness as well as testing novel treatment options (Alhifany et al., 2019; Guh et al., 2020).

This hypervirulent strain RT027 was detected in four patients in a tertiary care center in Riyadh, one of them developed toxic megacolon and deceased even after prolonged treatment with metronidazole and oral vancomycin (Alzahrani and Johani, 2013). Alzahrani *et al.* (2013) concluded that the detection of RT027 strain in Saudi Arabia few years after it was first identified in USA, Canada and Europe, supports the assumption that the CDIs incidence in Saudi Arabia is also similar to the western countries' counterparts. The low reported incidence of CDIs in Saudi Arabia has been questioned and attributed to the undertesting and underdiagnosing due to either the inconsistent supply of polymerase chain reaction (PCR) testing equipment in many healthcare institutions or the double coverage and the overutilization of anaerobic antibiotics (Alcalá et al., 2015; Aljafel et al., 2020; Al-Tawfiq et al., 2020; Al-Tawfiq and Abed, 2010). Regardless of the reasons behind the under-reporting of CDIs in Saudi Arabia, it is very clear that we lack epidemiological and surveillance studies and the exact incidence of CDIs and their complications in Saudi Arabia and the Gulf Cooperation Council (GCC) countries are still unknown.

1.2 The current diagnostic protocols for CDIs

Conventional culture and toxigenic culture methods (by isolating the bacterial cells and detecting toxins) are the gold standard for diagnosis of CDIs. However, they require long processing time, resources such as proper testing media, and trained technicians (Carey-Ann and Carroll, 2013). When commercially available enzyme immunoassays (EIAs) emerged, it became widely used and easy to perform; however, they have low sensitivity. Thus in developed countries the PCR technique, which is considered a nucleic acid amplification test (NAAT), became the standard method in the diagnostic protocols for detecting CDIs due it its high sensitivity and analytical specificity (Burnham and Carroll, 2013). The single-step using NAAT is widely preferred protocol for many small healthcare institutions around the world, because it demands less labor and provides quicker results (Burnham and Carroll, 2013; McDonald et al., 2018). The main downside of this single step technique is that it may detects gene encoding the toxin rather than the actual toxins which may lead to the over-diagnosis of CDIs, knowing that up to 21% of hospitalized patients are asymptomatically colonized with *C. difficile* (Guh et al., 2020; Truong et al., 2017). On the other hand, the two-step algorithm for the detection of CDIs utilize EIAs for toxins detection and then confirming the positive cases with the NAAT (Cohen et al., 2010; Wong et al., 2017). Hence, Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recommended a multi-step protocol using glutamate dehydrogenase (GDH) antigen/toxin A/B combined with NAAT as the most accurate method for CDIs diagnosis (McDonald et al., 2018).

Laboratories that perform multiplex system such as GeneXpert® PCR assay which used closed cartridge-based system for nucleic acid extraction, amplification and detection reduced the chance for contamination and false-positive results. GeneXpert® PCR assay detects most of *C. difficile* strains including hypervirulent RT027 strain by targeting the gene tcdC gene that is responsible for increasing toxin production and pathogenicity.

1.3 Management of CDIs

The main trigger for CDIs is the use of antibiotics, mainly fluoroquinolones, clindamycin, broad spectrum cephalosporines and penicillins (Leffler and Lamont, 2015). Hence, the first step toward management of CDIs is to cease the offending antibacterial agent (McDonald et al., 2018). Moreover, CDIs can be contracted by being in close contact with infected patients or handling their gadgets mainly due to the spore-forming ability of the *C. difficile* that are sanitized only by soap and water (Vonberg et al., 2008). Hence, contact precautions with CDIs-infected patients is a must. Antibiotic treatment with intravenous or oral metronidazole (which is known for treating anaerobic bacterial infections) vancomycin (a glycopeptide antibiotic effective in CDIs when given orally only) or oral fidoxamycin remain the standard of care for initial episodes and subsequent recurrences, however, innovative adjunctive therapies such as fecal microbiota transplantation and bezlotoxumab have been proven effective in treating recurrent CDIs (Alhifany et al., 2019; McDonald et al., 2018).

1.4 Litereture search

A litereture search of Medline, via Pubmed, Scopus and Google scholar databases was conducted using key words '*Clostridium difficile*', '*Clostridium difficile* infection', '*Clostridioides difficile*' '*Clostridioides difficile* infections' and 'Saudi Arabia'. The search covered the period of time from inception until March 30th 2020. Fig. 1

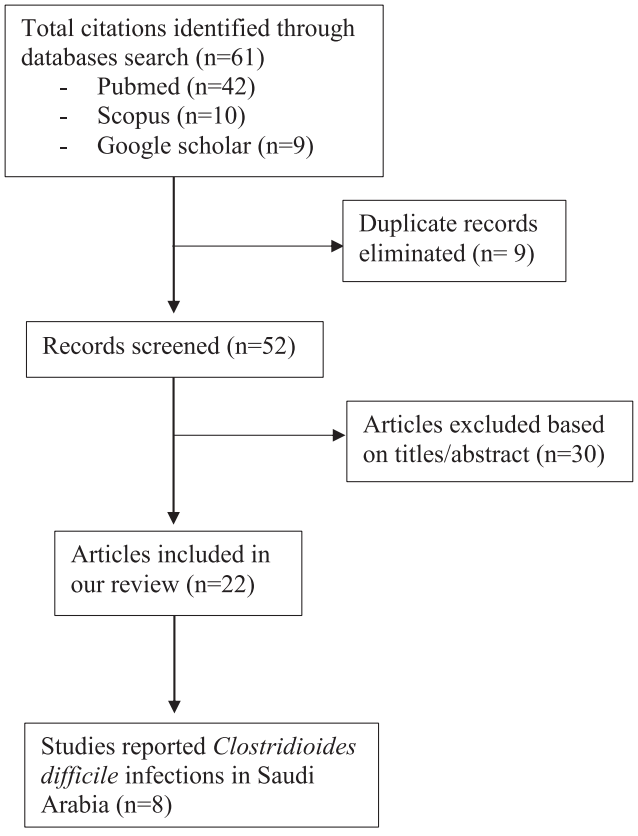

Fig. 1. Summary of the research method used in this review to explore *Clostridioides difficile* infections' diagnostic protocols, management and prevalence in Saudi Arabia.

Table 1
Highlights From Published Diagnostic Protocols of *Clostridioides difficile* Infections (CDIs) in Saudi Arabia.

Study protocol		CDIs' Incidence rate	Location of study	Reference
Single-step				
	Enzyme immunoassay testing (EIA)		Dhahran	(Al-Tawfiq and Abed, 2010);
		2.4** in 2007 and 1.7** in 2008		(Aljafel et al., 2020);
		8.4%	Jeddah	(Alnimr et al., 2019)
		0.03*	Dammam	
	Nucleic acid amplification tests (NAATs)	0.22*	Dhahran	(Al-Tawfiq et al., 2020)
		0.03*	Dammam	(Alnimr et al., 2019)
Two-step				
	Nucleic acid amplification tests (NAATs) & culture in selective medium	13.7%	Aljubail	(Shajan et al., 2014)
	Enzyme immunoassay testing (EIA) then confirmed by PCR testing such as GeneXpert multiplex PCR system.	5.54%	Jeddah	(Qutub et al., 2019)
		3.5**	Riyadh	(Alzouby et al., 2020);
		14.8%	Riyadh	(Senok et al., 2017)

Incidence rate (*per 1000 patients-day, **per 10,000 patients-day).

summarizes the search method used to determine the relevant literature.

2. CDIs diagnostic protocols, management, and prevalence data in Saudi Arabia

Despite the high incidence of CDIs globally, there is a controversial data regarding the incidence rate of CDIs and the prevalent strains in Saudi Arabia. In 2010, 913 stools specimens from a single center were screened for CDI using EIA and the incidence rate was determined at 4.6% (Al-Tawfiq and Abed, 2010). The same center reconducted the study again in 2019 and reported a 5.2% incidence rate out of 10,995 tested stool samples between 2001 and 2018 by using NAATs' testing protocol (Table 1) (Al-Tawfiq et al., 2020). Worth mentioning that this center is located in the eastern region of Saudi Arabia that is exclusively serving oil refinery workers and their families which limit their results' external validity.

On the other hand, two recently published studies reported an 8.4% and 10% incidence from two tertiary hospitals, King Abdulaziz University-affiliated hospital in Jeddah and King Faisal specialist hospital in Riyadh, respectively (Aljafel et al., 2020; Qutub et al., 2019). Nevertheless, the study from Jeddah reported CDIs' results based on EIA testing only which has 88% sensitivity, without further confirmatory testing (Aljafel et al., 2020). The other study, from Riyadh, utilized PCR as an affirmative step for specimens with discrepancy results after the initial immunoassay test, yet, the center is considered a specialist healthcare institution which limit their results' external validity (Qutub et al., 2019). Another study performed a six months surveillance at a Military hospital in Riyadh in 2015 which identified 106 episodes of CDIs by using EIA confirmed by PCR testing (Table 1) (Alzouby et al., 2020). They concluded that the incidence rate of CDIs is 3.5 per 10,000 patients which is still considered below global rate. Another study by Alnimr et al. (2019) conducted at a hospital in Eastern region of Saudi Arabia which reported short turnaround time and reduction in the number of CDI's tests ordered when GeneXpert® PCR was used (Alnimr et al., 2019). The study reported that the use of metronidazole and vancomycin therapies for treating suspected *C. difficile* patients declined after shifting the testing procedures from EIA to GeneXpert®. Another retrospective study that was conducted in a small private hospital in the Eastern region of Saudi Arabia has analyzed 146 samples using both DNA amplification and culture in a selective media (Shajan et al., 2014). Two-step algorithm testing protocol using GHD antigen and/or toxin by EIA combined with GeneXpert® was performed in a study after collecting 210 stool samples from large educational hospital in Riyadh (Senok et al., 2017). The study determined the superiority of the PCR testing over EIA alone and suggested using the molecular testing as a confirmatory test after EIA assays (Senok et al., 2017). The data reported from the latter two studies were collected over one-year. Other than the above-mentioned articles, (Table1) there were no single or multi-center studies in Saudi Arabia reported in the literature about the utilization and outcomes of multi-step detection methods for CDIs.

Ideally, CDI diagnosis should rely on stool positive results as well as clinical symptoms; however, all of the previously cited studies in Saudi Arabia defined their positive results only on laboratory testing of unformed stools, without integrating their findings with patients' symptoms.

Clinical symptoms and unformed stool samples tested with multi-step algorithm (GDH plus toxin and NAAT) was highly recommended protocol for detecting CDIs by IDSA 2017 guideline (McDonald et al., 2018). There are only two records in the literature reported an improvement in the detection and management of CDIs after the implementation of an institutional protocols for ordering *C. difficile* tests, prepared by experts in two tertiary hospitals in Saudi Arabia (Aljafel et al., 2020; Alzouby et al., 2020). Furthermore, they reported that by following such internal tailored protocols lead to a decline of unnecessary testing of asymptomatic patients and consequently decline in healthcare cost.

Similar to global reports, antibiotics' overutilization has been reported to be highly associated with CDIs in Saudi Arabia. Alzouby et al. (2019) concluded that the use of three courses of antibiotics, including carbapenems in particular, is an independent predisposing factor for CDIs in the Military hospital in Riyadh (Alzouby et al., 2020). Another study conducted in Dhahran hospital, published in 2010, showed that 61% of patients with positive *C. difficile* stool sample received antibiotics within three months period prior to the infection (Al-Tawfiq and Abed, 2010). They reported that most common antibiotics used among patients with CDIs were cephalosporins and fluoroquinolones. On the other hand, there is a paucity of data about the management outcomes of CDIs in Saudi Arabia (Aljafel et al., 2020).

2.1. Further testing: antimicrobial susceptibility testing for CDIs

Global studies showed a reduced susceptibility of *C. difficile* RT027 strain to antibiotics (Freeman et al., 2018). In Saudi Arabia, no study performed susceptibility testing for isolated *C. difficile* strains for research purposes and there has been no reports of such tests conducted as a routine practice in hospitals in Saudi Arabia (Alzouby et al., 2020). Susceptibility data of *C. difficile* strains to antibiotics is an important factor for better estimating the

virulence and predicting management plans for health-care and community CDIs (Peng et al., 2017). Therefore, it is very valuable to include susceptibility data of *C. difficile* in future studies and as a routine testing procedure in hospitals to be part of their antibiograms. Combining the NAAT testing with antimicrobial susceptibility testing of *C. difficile* would provide better understanding for the researchers and treating physicians about the pattern of *C. difficile* virulence strains and best approach for empirical treatment.

3. Conclusion

This review demonstrates that CDI incidence rate was explored in limited number of healthcare institutions in Saudi Arabia. Published studies were based on single-center settings that are lacking institutional protocols for detecting, screening, and managing CDIs. Published literature are missing a comprehensive reporting of laboratory results and clinical information. Furthermore, the reported statistical records for incidence rates were not complying to the IDSA guidelines for some studies and we found multiple discrepancies in the reported numbers in others. Hence, we recommend the implementation of a unified testing and screening algorithm, combining clinical symptoms with multi-step testing (GDH plus toxin and NAAT) and susceptibility results of *C. difficile* isolated strains to antibiotics, for better detection and managing of CDIs and accurate epidemiological data reporting on a national level.

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