Review

Clostridium difficile: A healthcare-associated infection of unknown significance in adults in sub-Saharan Africa

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Abstract

Background

Clostridium difficile infection (CDI) causes a high burden of disease in high-resource healthcare systems, with significant morbidity, mortality, and financial implications. CDI is a healthcare-associated infection for which the primary risk factor is antibiotic usage, and it is the leading cause of bacterial diarrhoea in HIV-infected patients in the United States. Little is known about the disease burden of CDI in sub-Saharan Africa, where HIV and healthcare-associated infections have higher prevalences, and antibiotic usage is less restricted. This article reviews published literature on CDI in sub-Saharan Africa, highlighting areas for future research.

Methods

English language publications since 1995 were identified from online databases (PubMed, Medline, Google Scholar, and SCOPUS), using combinations of keywords *"C. difficile"*, "Africa", and "HIV".

Results

Ten relevant studies were identified. There was considerable variation in methodology to assess for carriage of toxigenic *C. difficile* and its associations. Eight studies reported carriage of toxigenic *C. difficile*. Three (of three) studies found an association with antibiotic usage. One (of four) studies showed an association with HIV infection. One study showed no association with degree of immunosuppression in HIV. Two (of three) studies showed an association between carriage of toxigenic *C. difficile* and diarrhoeal illness.

Conclusions

While the carriage of toxigenic *C. difficile* is well described in sub-Saharan Africa, the impact of CDI in the region remains poorly understood and warrants further research.

Introduction

Clostridium difficile, an anaerobic gram-positive spore-forming bacterium, was first described following isolation from neonatal intestinal tissue in 1935, and was initially presumed to be a commensal organism.[1] *C. difficile* was later recognised to cause pseudomembranous colitis via toxin production, and it has since emerged as a major enteric pathogen.[2,3] Its clinical significance ranges from asymptomatic carriage to life-threatening colitis, with significant associated morbidity and mortality. *C. difficile* colonises the large bowel following ingestion of spores, which are heat and acid resistant.[4] The spores can be found in most healthcare settings and in the general environment.[5,6] Gut damage in susceptible individuals results from production of the enterotoxin TcdA, which damages the intestinal epithelium, and the cytotoxin TcdB, which has broader cellular tropism.[7] The emergence of the 027/BI/NAP1 strain, with dramatically increased cytotoxin production, is responsible for the observed increased prevalence and virulence of *C. difficile* in recent years.[8-10] This strain emerged in North America and Western Europe and rapidly disseminated worldwide.[11]

The primary risk factor for *C. difficile* infection (CDI) is antibiotic usage. CDI is known to be the cause of up to 25% of antibiotic-associated diarrhoea.[12] CDI was originally described following clindamycin use but is now known to complicate the use of many broad-spectrum antibiotics, particularly cephalosporins, co-amoxiclav, and fluoroquinolones.[3,13] Following antibiotic usage, there is an imbalance in the normal gut flora and *C. difficile* overgrowth can lead to pseudomembranous colitis in susceptible individuals.[14] Other described risk factors for CDI include hospital admission, exposure to an infected carrier, advanced age, and immunosupression.[15] The importance of proton pump inhibitors and of other interventions that reduce the gastric acid barrier in increasing susceptibility to CDI remains controversial.[16,17] There is a described relationship between CDI and HIV, wherein *C. difficile* is known to be the leading cause of bacterial diarrhoea among HIV-infected populations in the United States, but it is not clear how much this reflects increased exposure to healthcare compared to HIV-negative individuals.[18,19] Only two studies show a convincing association between CDI and low CD4 count, and interpretation of these results is difficult given the high rates of *C. difficile* colonisation in HIV-infected populations.[19-22]

While CDI has been extensively researched in well-resourced health systems, there are few published studies about CDI in sub-Saharan Africa. Healthcare-associated infections cause a greater disease burden in healthcare systems with fewer resources.[23] Furthermore, in sub-Saharan Africa there is widespread availability of broad-spectrum antibiotics and fewer controls on their usage.[24] Finally, HIV is far more prevalent in sub-Saharan Africa than in the United States or Europe. It is, therefore, possible that CDI plays an important role in diarrhoeal illness in sub-Saharan Africa, yet there are few published data on the subject. Published infection rates vary greatly, with some authors describing 0% toxigenic *C. difficile* detection in Kenya and Zambia, while the highest

published rate is from Nigeria at 43%.[25-27] The nature of the relationship between HIV and CDI in sub-Saharan Africa remains poorly understood.

The aims of this review are to describe current published literature regarding CDI in adults in sub-Saharan Africa, and to highlight areas warranting further research.

Methods

In order to identify English-language publications since 1995 assessing CDI in adults in sub-Saharan Africa, online databases (PubMed, Medline, Google Scholar, and SCOPUS) were searched, using combinations of keywords *"C. difficile"*, "Africa", and "HIV". All relevant papers, in English, from 1995 onwards were included in the review, and their bibliographies were reviewed for relevant papers. Papers that looked for *C. difficile* in children were excluded. Papers looking at adults and children were only included if it was possible to distinguish between the two populations. In total ten relevant studies were found. Data were extracted from relevant papers using a standardised pro forma.

Results

Ten studies looked for toxigenic C. difficile carriage in sub-Saharan Africa. Of these, eight described toxigenic C. difficile carriage. Two studies from Kenya (1998) and Zambia (2000)[6] did not find carriage of toxigenic C. *difficile*.[25,26] There was considerable variation in laboratory methodology used to identify *C. difficile* and in the populations studied. Furthermore, there was wide variation in the methodology used to assess the association of CDI with recent antibiotic usage, HIV, diarrhoea, and degree of immunosuppression. Table 1 summarises current published studies of CDI in adult populations in different countries in sub-Saharan Africa.

Discussion

The majority of published studies, and all studies after the year 2000, describe carriage of toxigenic *C. difficile* in adult populations in sub-Saharan Africa. In three studies, which assessed recent antibiotic usage, there was a significant association between antibiotic usage and CDI; however, no studies were designed to implicate individual antibiotics, nor to describe the nature of antibiotic usage.[29,30,34] These findings are consistent with the well-described risk factor of antibiotic usage in high-resourced healthcare systems. In three of four studies that assessed association with HIV status, no association was found. The only study claiming an association between HIV status and CDI in adults was from Nigeria. However, it compared toxigenic *C. difficile* carriage in an entirely HIV-positive sample from an urban teaching hospital, with a control population from a different geographical region, wherein HIV status was presumed to be negative if unknown.[27] A study of adults and children in Tanzania found a significant difference in toxigenic *C. difficile* carriage between HIV-positive and HIV-negative individuals. It was not possible, however, to distinguish between adults and children in this analysis, and the number of adults in the study was low.[34] The lack of association between CDI and HIV status in adults differed from observations in high-resource healthcare systems in the United States and Europe.[18,20,21] The only study to assess the association between degree of immunosuppression in HIV and CDI was from Malawi.[31] This study showed no significant association between carriage of toxigenic *C. difficile* and severe immunosuppression (CD4+ cell counts less than 50 $\times$ 10^6/L), although numbers in this group were small. This warrants assessment in a larger study population.

A further area of uncertainty is the role that *C. difficile* plays in diarrhoeal illness, as opposed to asymptomatic infection and incidental detection, in populations studied in sub-Saharan Africa. Table 1 shows that a wide variety of laboratory methods have been used to detect *C. difficile* in the different studies, with different sensitivities and specificities. Methods that use cytotoxicity or immunogenic assays to detect *C. difficile* toxin reliably detect invasive CDI but sensitivity is variable and dependant on laboratory technique, while methods based solely on polymerase-chain-reaction (PCR) assays probably result in overdiagnosis.[35-38] Only one study used the two-step diagnostic algorithms currently recommended in many countries, using assays for faecal *C. difficile* glutamate dehydrogenase (GDH) as a screening test for presence of infection, followed by confirmatory PCR for cytotoxin genes to diagnose invasive disease potential.[35] The majority of studies assessed *C. difficile* in patients with diarrhoea and did not compare these to non-diarrhoeal controls. However, the most robust study of CDI in sub-Saharan Africa showed a clear association between detection of toxigenic *C. difficile* and symptomatic diarrhoeal illness in South Africa.[29] Another study of adults and children in Tanzania detected toxigenic *C. difficile* in 9 of 141 subjects with diarrhoea, compared to none in the stools of 109 symptom-free controls.[34] While asymptomatic carriage has been well documented and has demonstrated to contribute to ongoing transmission of *C. difficile* in well-resourced healthcare systems, its significance in sub-Saharan Africa is uncharacterised.[21,22,39,40]

Only one study on CDI in South Africa described complications (other than diarrhoea) and prognosis.[33] There was an observed 66.7% mortality rate for patients with CDI and diarrhoea. However, there was no statistical difference in mortality between patients with or without *C. difficile*, nor in length of stay and intensive care admission. Twelve percent of patients with CDI required colectomy, a finding that was significantly associated with the presence of toxigenic *C. difficile*. The presence of toxigenic *C. difficile* has been described in sub-Saharan Africa, but its disease burden and clinical significance, particularly in areas of high HIV prevalence, remain poorly understood.

Conclusions

There are relatively few studies on CDI in sub-Saharan Africa, but toxigenic *C. difficile* has been detected in the majority of studies designed to look for it in the region, where it has been consistently associated with antibiotic usage. Further in-depth research is needed to define the epidemiology of CDI in sub-Saharan Africa in order to clarify the extent of colonisation within communities and among hospitalised populations, the extent to which CDI is associated with HIV and CD4 count, and its role in contributing to morbidity and mortality.

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Table 1: Published studies on CDI in adults in sub-Saharan Africa, 1995 to present

Author	Year	Country	Setting	Controls	Diagnostic test for CDI	Sample size (adults)	CDI detection rate (adults)	Antibiotic association	HIV association
Mwachari[25]	1998	Kenya	HIV positive adult inpatients with chronic diarrhoea	n/a	Cytotoxicity assay	75	0%	n/a	n/a
Germani[28]	1998	Central African Republic	Adults presenting to hospital with diarrhoea	HIV positive and negative non-diarrhoeal adult inpatients	Cytotoxicity assay	430	0.7%	n/a	n/a
Zulu[26]	2000	Zambia	HIV positive adult inpatients	n/a	ELISA for toxin A	68	0%	n/a	n/a
Samie[29]	2008	South Africa	Adults and children in hospital and community with diarrhoea	HIV positive and negative non-diarrhoeal adult in hospital and community	PCR for cytotoxin genes	135	17.8%	Yes	No
Onwuema[27]	2011	Nigeria	Adults and children in hospital and community with diarrhoea	HIV negative (or unknown) adults in the community	EIA for toxin A and B	140	4.3% (community) to 43.5% (inpatient)	n/a	Yes
Rajabally[30]	2013	South Africa	Adult inpatients with diarrhoea	n/a	EIA for toxin A	643	9.2%	Yes	No
Beadsworth[31]	2014	Malawi	Adult inpatients with diarrhoea	HIV positive and negative non-diarrhoeal adult inpatients	ELISA for toxin A and B	206	13.6%	n/a	No
Simango[32]	2014	Zimbabwe	Adults and children in community with diarrhoea	n/a	Culture and EIA for toxin A and B	159	6.9%	n/a	n/a
Kullin[33]	2015	South Africa	Adults in hospital and community with diarrhoea	n/a	PCR for cytotoxin genes	156	16%	n/a	n/a
Seugendo[34]	2015	Tanzania	Adults and children inpatients with diarrhoea	Non-diarrhoeal adults in community	Rapid test for GDH and PCR for cytotoxin genes	33	9.1%	Yes	Yes

CDI = *Clostridium difficile infection;* ELISA = Enzyme-linked immunosorbent assay; PCR= polymerase chain reaction; EIA = Enzyme immunoassay; n/a = not assessed; GDH = glutamate dehydrogenase (*Clostridium difficile*-specific)

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