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Brief Original Article

Clostridioides difficile infections: Epidemiology, correlations and treatment in a Lebanese cohort with use of ATLAS scoring

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Abstract

Introduction: The objectives of the present study were to investigate epidemiology, correlations, severity, and therapeutic response of *Clostridioides difficile* infections in a Lebanese tertiary care hospital.

Methodology: In this retrospective cohort study, patients having at least one positive *Clostridioides difficile* test (antigen glutamate dehydrogenase/GDH with toxins, or PCR) were studied.

Results: Among 58 patients, 20 (34.5%) and 53 (91.4%) had positive antigen GDH and toxins, respectively. PCR was performed in 25 (43.1%) patients without any positive ribotype 027. Fifteen (25.9%) patients were immunocompromised, 35 (60.3%) patients received antibiotics prior to the infection and 34 (58.6%) on proton pump inhibitors. Fifty-four (93%) patients had a resolution of their symptoms after a mean period of 4.2 days of treatment. Twenty-two (38%) participants were treated with oral vancomycin, 11 (19%) with intravenous metronidazole and 23 (39.6%) with both antibiotics. Resolution of symptoms was significantly more rapid with monotherapy ($p = 0.007$) with no significant difference between vancomycin and metronidazole ($p = 0.413$). A positive correlation was found between ATLAS score and delay to symptoms resolution ($r = 0.553$; $p < 0.001$; $N = 54$), as well as between ATLAS score and prevalence of complications ($p = 0.003$).

Conclusions: History of treatment with antibiotics, proton pump inhibitors, and hospital admission during the previous year were prevalent among our patient cohort. Rates of symptomatic resolution were similar with monotherapy and dual therapy.

Key words: ATLAS score; *Clostridioides difficile*; pseudomembranous colitis; Middle East; outcome; treatment.

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Introduction

Clostridioides difficile (*C. difficile*) infection is one of the most common healthcare associated infections worldwide. It can manifest with variable symptoms, mainly diarrhea, and it is responsible for significant morbidity and mortality. *C. difficile*, previously named *Clostridium difficile,* is named so due to the difficulty of isolating it. It is a gram positive, spore forming and toxin-producing anaerobe [1].

Fast identification of the infection is critical to ensure early treatment and prevent contagion. Discontinuation of antibiotics and treating the infection are effective in most cases [2]. However, a significant minority of patients develops complications requiring surgical management. Multiple criteria should be assessed to confirm treatment success [3]. *C. difficile* colonizes the digestive tract and becomes pathogenic when the normal flora is altered [4].

During the last decade, increase in *C. difficile* infection prevalence has been noted, with an emergence of new resistant strains. Liberal use of antibiotics has favored its dissemination. Current estimations report 500 000 cases of *C. difficile* infection yearly in the United States, with a medical cost approaching 1.1 billion dollars [5]. However, reported rates of *C. difficile* infections in the Middle East varies among studies [6,7].

No study has used the ATLAS score in a Middle Eastern population. This study included patients diagnosed with *C. difficile* infection in a Lebanese tertiary care hospital, and its primary endpoint was to assess the ATLAS score in this population, as well as the epidemiology, correlations and therapeutic attitude.

Methodology

After obtaining the Saint Joseph University's ethical and hospital committee's approvals, data was

collected from archived medical files and microbiology laboratory records (using the ICD-10-CM code "A04.7"). Search was conducted from November 2016 to November 2017. Patient with confirmed C. *difficile* infection during the studied period were included. Patients younger than 18 years old, or not admitted during the studied period were excluded. Information collected included age, sex, relevant past medical history (hospitalization in the past year, previous *C. difficile* infection, antibiotic, proton pump inhibitor intake and immunosuppression), symptoms, type and duration of treatment, duration between onset of treatment and clinical improvement. Serum creatinine and albumin levels upon diagnosis were also collected to calculate the ATLAS score [8]. Lastly, occurrence of complications was noted.

The targeted population tested for *C. difficile* and diagnosis were according to the definition of the IDSA guidelines [9]. Clinical improvement was defined as the resolution of fever and diarrhea. Immunosuppression was defined by the presence of any of the following: use of any type of immunosuppressor, corticosteroids (prednisone ≥ 7.5 mg for 4 weeks or more, or its equivalent), chemotherapy, HIV positive or the presence of an autoimmune/systemic diseases.

SPSS statistical software (Windows, version 22, Chicago, IL, USA) was used for statistical analysis of data. Statistical threshold used corresponds to p-value < 0.05. Effectives and percentages were used for qualitative variables whereas mean and standard deviation were used for quantitative variables. Spearman's correlation coefficient was used to study the link between the ATLAS score and the number of days till resolution of symptoms. Kruskal-Wallis test was used to compare mean duration till resolution of symptoms according to ATLAS score. Fisher's exact test was used to compare the presence of complications according to the ATLAS score, as well as to study the association between the ATLAS score and type of antibiotic therapy. Kruskal-Wallis test was used to compare the mean duration till resolution of symptoms according to monotherapy versus dual therapy.

Table 1. Reasons for admission.

Reason for admission	Total number of patients
Nondigestive infections	13
Oncologic admissions	9
Diarrhea	8
Cardiovascular diseases	8
Digestive symptoms other than diarrhea	6
General weakness, non-specific symptoms	3
Neurology admissions	3
OBGYN admissions	2
Nephrology admissions	2

Table 2. Presenting symptoms and diagnostic methods for *Clostridioides infection* in the studied population.

Characteristics	Number of patients (%)
Gastrointestinal symptoms	
Diarrhea	57 (98.3)
Loose stools	1 (1.7)
Fever	
Present	30 (51.7)
Absent	28 (48.3)
Toxins	
Positive	20 (34.5)
Negative	38 (65.5)
Antigen	
Positive	53 (91.4)
Negative	5 (8.6)
Toxins – Antigen	
Toxin Positive – Antigen Positive	16 (27.6)
Toxin Positive - Antigen Negative	4 (6.9)
Toxin Negative - Antigen Positive	37 (63.8)
Toxin Negative - Antigen Negative	1 (1.7)
PCR	
Not done	33 (56.9)
Positive	21 (36.2)
Negative	4 (6.9)
Ribotype 027	
Not done	33 (56.9)
Negative	25 (43.1)

Results

Fifty-eight participants (23 males and 35 females; sex ratio = 1.52) with a mean age of 65.28 ± 20.87 years (18-95 years) were included in the study. Only 8 (13.8%) patients were admitted for diarrhea (Reasons described in Table 1).

All patients developed diarrhea or loose stools, with (51.7%) or without fever (48.2%). Toxins and antigens were positive in 20 (34.5%) and 53 (91.4%) patients, respectively. PCR test was done in 25 (43.1%) patients. Ribotype 027 was tested in 25 (43.1%) patients. Details are presented in Table 2.

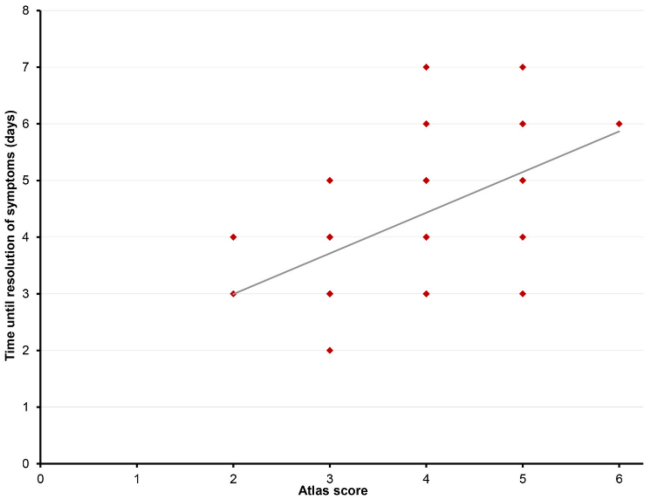
Results have shown that 15(25.9%) patients were immunocompromised, and most were receiving proton pump inhibitor therapy (58.6%) or antibiotics prior to the *C. difficile* infection episode (60.3%). The most used antibiotic prior to the episode was Amoxicillin/ clavulanic acid (34.3%). Also, 24.9% of patients had a history of one or more *C. difficile* infection episode and 84.5% were hospitalized once or more during the year prior the current episode. Details on patients are shown in Table 3.

The mean of ATLAS score was 3.74 ± 0.890 with a median of 4. Fifty-six patients with *C. difficile* infection were treated with antibiotic therapy and the most used was an association between vancomycin and metronidazole (39.7%) or monotherapy with vancomycin (37.9%). The mean course of treatment was 12.66 ± 2.134 days (range: 6-14 days) and clinical resolution of symptoms occurred after a mean of 4.20 ± 1.122 days (range: 2-7 days). Seven (12.1%) patients developed complications.

Table 3. Details on patient's characteristics.

	Number of patients (%)
Previous antibiotics use	35 (60.3)
Antibiotics	
Amoxicillin/Clavulanic acid	12 (34.3)
Quinolones	7 (20.0)
Carbapenems	4 (11.4)
Cephalosporins, 3rd generation	4 (11.4)
Trimethoprim/ sulfamethoxazole	2 (5.7)
C3G + Carbapenems	1 (2.9)
Tigecycline	1 (2.9)
Monobactam	1 (2.9)
Cephalosporins, 4th generation	1 (2.9)
Piperacillin/Tazobactam	1 (2.9)
Amoxicillin, Aminoglycoside	1 (2.9)
Proton pump inhibitors	34 (58.6)
Previous C. diff infection episode	
0	44 (75.9)
1	10 (17.2)
2	3 (5.2)
3	1 (1.7)
Hospitalization during last year	
0	9 (15.5)
1	22 (37.9)
2	17 (29.3)
3	9 (15.5)
5	1 (1.7)
Immunosuppression	15 (25.9)
Atlas score	
2	3 (5.2)
3	21 (36.2)
4	24 (41.4)
5	8 (13.8)
6	2 (3.4)
Antibiotic therapy	
None	2 (3.4)
Metronidazole	11 (19.0)
Vancomycin	22 (37.9)
Vancomycin /metronidazole	23 (39.7)
Complications	7 (12.1)
Type of complication	
Death	4
Colic distention	1
Ileus	1
Acute kidney injury	1

Figure 1. Relationship between ATLAS score and time until resolution of symptoms.



Our study showed a significantly positive correlation between ATLAS score and the time needed to achieve clinical resolution of symptoms ($r = 0.553$; $p < 0.001$; $N = 54$). With a higher ATLAS score, the time needed to achieve clinical resolution of symptoms after starting treatment was significantly longer ($p < 0.001$) as shown in Figure 1.

Occurrence of complications was significantly associated to ATLAS score ($p = 0.003$). Out of the patients presenting with complications, 71% had a score of 5 and 28.6% had a score of 6. Out of the 7 complications, 4 patients died (3 of them had a score of 4 and one a score of 6).

Antibiotic choice was correlated to ATLAS score ($p < 0.001$). Patients with a low score (< 4) were treated with monotherapy, with the use of metronidazole particularly and patients with higher scores (≥ 4) were treated with dual therapy. Dual therapy was used in patients with higher scores, explaining the longer duration to recovery and symptoms resolution.

Time to recovery was significantly longer in patients treated with dual antibiotic therapy than with monotherapy ($p = 0.007$). No significant difference in time to recovery was seen between metronidazole and vancomycin ($p = 0.413$).

Discussion

Many studies have been carried out worldwide to investigate *C. difficile* infections, but these are lacking in the Middle East and Lebanon. Studies from the Middle East showed variable prevalence for this infection [10]: Shehabi *et al*. [11] reported 9.7% in Jordan, Rotimi *et al*. [12] found a less than 10% prevalence of hospital acquired *C. difficile*

infection/colonization in Kuwait, and Moukhaiber *et al*. [13] found that 30 out 88 (65.2%) of stool samples examined of patients admitted to a tertiary care center in Lebanon, were positive for C. difficile.

To our knowledge, this is the first study to use the ATLAS score in this population. The average age was comparable to one study in the literature, showing a mean age of 67 years for a total of 15,461 patients [14**]**. Also, the percentage of women (60.2% in our study) was comparable to that of this same study. A history of antibiotic therapy and proton pump inhibitor use were associated with *C. difficile* infection according to this study. A study from Jordan showed that most patients with *C. difficile* infections were on one or more board spectrum antibiotic which is comparable to our study [15]. Therefore, limiting unnecessary antibiotic prescription remains the most important method for reducing the risk of such infection [10]. Proton pump inhibitors usage have a proven association with *C. difficile* infection as several studies and meta-analyses showed [10,16]. Using proton pump inhibitors only when indicated can therefore decrease the incidence and the recurrence of this infection.

Most patients in this study had at least one hospitalization during the year preceding the current *C. difficile* infection, which is consistent with the data from worldwide studies, showing that each hospital stay increases the risk of infection, with a higher risk when the stay is longer. Another study from Lebanon showed two third of *C difficile* infected patients were hospitalized in the previous weeks. Hygiene measures are therefore essential to prevent the transmission of such infections [17]: patients isolation, hand washing with soap and water and educating the patient and staff.

ATLAS score predicts the severity and clinical course of *C. difficile* infection [8]. This score also predicted the length of hospital stay after the diagnosis and the time needed until symptomatic recovery after treatment [18]. We found a positive correlation between this score and the time needed to recover. Studies have proved that with higher scores, comes a higher time needed to symptomatic recovery and patient discharge [19]. Complication rate is also significantly higher when ATLAS score is higher and choice of antibiotic therapy depends on the score, even if the physician is not familiar with the score [17]. Using this score was easy with no significant additional costs on the patient. Compared to the severity classification of the IDSA guidelines, ATLAS score may be more objective, standardized and may anticipate a potential complication of *C. difficile* infection.

Antibiotic therapy was initiated to some patients in this study without confirming diagnosis, only when the clinical suspicion was high, and PCR test could not be done. This practice has proved to have significant shorter times to initiate effective antimicrobial therapy and implement contact precautions [20].

This study highlights the importance of clinical and laboratory tests to diagnose *C. difficile* infection and to efficiently begin treatment. It is also the first study to use the ATLAS score in this population. However, this is a wide period monocentric study with a small population conducted on medical records, which could involve selection and documentation bias. It lacks consistency in microbiological test used. This study lacks comparative control group to assess the impact of risk factors on CDI development and the effect of CDI antibiotic therapy on outcomes.

Conclusions

Prior antibiotics, proton pump inhibitors intake, and history of hospitalization within the previous year are most prevalent among our patient cohort. ATLAS score is a good predictor of infection severity, its complications, time of hospital stay and choice of antibiotic therapy. Dual therapy is not always superior to monotherapy in terms of symptomatic recovery, and ATLAS score should guide the treatment.

Authors' contribution

JC: conceptualization and editing; RW, EH, MC, NC, GS: writing - review and editing; HD: writing – initial draft.

Ethics approval

Authorization by the ethical committee of the Saint Joseph University, Beirut, Lebanon for data processing and publication was obtained.

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