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Scientific letters

Is there a relationship between the polimerase chain reaction cycle threshold and the risk of severe *Clostridium difficile* infection?☆

¿Existe relación entre el ciclo umbral de la reacción en cadena de la polimerasa y el riesgo de infección grave por Clostridium difficile?

Dear Editor,

Clostridium difficile infection (CDI), the leading cause of nosocomial diarrhoea, is associated with increased patient mortality and healthcare costs.[1,2] In addition, it has been observed that 12–18% of patients may progress to serious disease and 20% may have recurrences.[3] Given these significant percentages, it is necessary to gain insight into which patients have CDI that is likely to follow a poor clinical course in order to select a suitable treatment and prevent mortality. Various risk factors for predicting the infection's seriousness, mortality and recurrence have been examined; however, no consensus has been reached. At present, the clinical criteria that are collected during the CDI episode are insufficient to predict the course of the infectious episode.[4] Therefore, prior studies have assessed microbiological data so as to improve the prognosis and clinical course of CDI.[5,6] These data include the link between the real-time PCR cycle threshold (Ct) and mortality,[7] which would constitute an objective and early method.

The goal of this study was to evaluate the role of PCR Ct with a prognosis of clinical severity as a potential predictive marker of a poor clinical course for CDI.

We conducted a retrospective study at our hospital in 62 patients with microbiological detection of *C. difficile* (CD) in faeces using the Xpert® *C. difficile* system (GeneXpert, Cepheid, Sunnyvale, CA, United States) between January 2015 and December 2016. To this end, we enrolled in the study patients with samples of diarrhoeal faeces with suspected CDI that had been processed according to the established protocol (3-step algorithm) based on glutamate dehydrogenase immunochromatography (Wampole® C. DIFF QUIK CHEK®, Alere), toxin detection (Wampole® TOX A/B QUIK CHEK®, Alere) and real-time PCR (Xpert™ *C. difficile*) the same day they arrived at the microbiology department, having been stored at 2–8 °C until they were processed. Samples were collected in a sterile bottle with no transport medium.

Serious CDI was defined, according to the criteria of the SHEA-IDSA, as the presence of at least 2 of the following factors: signs and symptoms of serious colitis due to CD, admission to an intensive care unit, age >65 years, leukocytosis in excess of 10,000 cells/mm³,

Table 1
Clinical and epidemiological data for the groups studied.

Clinical data	Group with clinical criteria for serious disease (n = 42)	Group without clinical criteria for serious disease (n = 20)	p Value
Sex (males), n (%)	19 (45)	6 (30)	0.44
Age >65 years, (years) (%)	30 (71)	6 (30)	0.09
Length of stay from admission date to CDI diagnosis date, (days)	14 ± 20	17 ± 21	–
Length of stay from CDI diagnosis date to discharge date, (days)	19 ± 30	26 ± 32	–
Prior admission (3 months), n (%)	18 (43)	13 (65)	0.35
Institutionalisation, n (%)	3 (7)	0 (0)	0.23
Intensive care unit admission, n (%)	2 (5)	0 (0)	0.33
Leukocytosis >10,000 cells/ml, n (%)	29 (69)	0 (0)	0.0005
Neutrophilia >7500 cells/ml, n (%)	29 (69)	2 (10)	0.0058
Creatinine >1.5 times baseline level, n (%)	10 (24)	1 (5)	0.11
Fever >° 38.5 C, n (%)	6 (14)	2 (10)	0.67
>10 diarrhoeal stools per day, n (%)	4 (9)	0 (0)	0.17
Severe colitis, n (%)	18 (43)	1 (5)	0.018
Peritonitis, n (%)	1 (2)	0 (0)	0.49
Recurrence	11 (26)	4 (20)	–
Paralytic ileus, n (%)	0 (0)	0 (0)	–
Death during episode, n (%)[a]	8 (19)	2 (10)	0.43
Death after 30 days, n (%)[a]	2 (5)	1 (5)	0.96
Ct	27 ± 4	29 ± 14	0.23

CDI: *Clostridium difficile* infection; Ct: threshold cycle.

[a] Mortality was linked to CDI in 50% (n = 5) of cases of death during the episode (4 patients had clinical criteria for serious disease) and in 33.3% (n = 1) of cases of death after 30 days (this patient had clinical criteria for serious disease).

neutrophilia >7500 cells/ml, increased creatinine ≥1.5 times the baseline value, temperature >38.5 °C, >10 diarrhoeal stools per day, paralytic ileus, peritonitis and colitis on examination through a computed tomography scan. These seriousness factors were those that were subsequently linked to the Ct. Other variables were also analysed: sex, length of stay from admission to CDI diagnosis, length of stay from CDI diagnosis to discharge, admission in the

3 months prior to CDI, institutionalisation, death during the current episode, death after 30 days and recurrence. Next, patients were divided into 2 categories: those with clinical criteria for serious CDI and those without criteria for serious CDI. The results are shown in Table 1.

Among the seriousness criteria studied, we found significant differences ($p < 0.05$) between the two groups with respect to leukocytosis >10,000 cells/ml, neutrophilia >7500 cells/ml and serious colitis. The Ct obtained was 12 ± 13 in patients with recurrence and 27 ± 13 in patients with related mortality.

Although the Ct in patients with serious CDI was lower, we were unable to demonstrate any significant differences between the two groups. Similarly, a recent study by Rao et al.[8] found no correlation between Ct values and severe CDI or mortality. However, a recent study by Reigadas et al.[3] evaluated Ct values for PCR amplification as a prognostic factor. It should be noted that our study did not have the same methodology as the above-mentioned studies. One notable limitation of our study was its limited number of samples.

Nevertheless, we wish to stress that it is important to conduct more studies to determine whether the Ct could be a good predictor of recurrence, seriousness and/or mortality in episodes of CDI, since this would be a simple, objective marker available at the time of diagnosis.

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Laura Sante*, Yanet Pedroso, Beatriz Castro, María Lecuona

Servicio de Microbiología, Parasitología y Control de la Infección, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Tenerife, Spain

* Corresponding author.
E-mail address: laurasante@hotmail.com (L. Sante).

Acute mediastinitis as a rare complication of an infectious mononucleosis☆

Mediastinitis aguda como complicación atípica de una mononucleosis infecciosa

Dear Editor,

Infectious mononucleosis (IM) is a common entity caused by different aetiological agents. The one that accounts for the most cases (90% of them) is Epstein–Barr virus (EBV). In children, primary infection usually goes unnoticed. In young adults, it is more symptomatic, featuring a typical triad of fever, cervical lymphadenopathy and odynophagia.[1]

Usually it is a self-limiting disease requiring treatment of symptoms. However, its duration and seriousness may vary considerably.[1] Complications are rare in immunocompetent adults. An increased incidence of serious cases of IM has recently been reported.[2]

We present a case of IM due to EBV with acute mediastinitis as a rare complication.

A 22-year-old woman, an active smoker with a penicillin allergy and no other prior history of interest, was admitted to our hospital due to signs and symptoms consistent with IM (general malaise, fever, myalgia and odynophagia). A physical examination revealed cervical lymphadenopathy, jaundice, splenomegaly and tonsillar hypertrophy with necrosis.

Laboratory testing revealed abnormal liver function tests (bilirubin 4.10 mg/dl; AST 458 U/l; ALT 831 U/l; AP 438 U/l and GGT 384 U/l), peripheral blood leukocytosis ($14{,}990 \times 10^9$/l) at the expense of lymphocytes (29%) and high C-reactive protein (316 mg/l). Blood cultures and serologies for cytomegalovirus; herpesvirus 6, parvovirus B_{19}; toxoplasmosis; hepatitis A, B and C; and human immunodeficiency virus were negative. However, IgM antibodies for EBV were positive (IgG antibodies were negative) and a lymphogram showed an abnormal CD4/CD8 ratio (20%/57%). Quantification of immunoglobulins showed no deficit and an abdominal ultrasound confirmed splenomegaly measuring 15.8 cm.

After 7 days had elapsed since the patient's admission, due to persistent fever and progressive dysphagia as well as onset of oedema in the submandibular and anterior cervical area, the patient underwent a cervical ultrasound and computed tomography (CT) scan (Fig. 1). This showed hypertrophic tonsils as well as collections of air and fluid in the anterior laterocervical and supraclavicular area having spread to subcutaneous fat tissue and deep spaces. Given the patient's penicillin allergy and a suspicion of serious infection, broad-spectrum empirical antibiotic therapy (imipenem) and intravenous corticosteroid therapy were started.

Due to a suspicion of spread to the mediastinum, a chest CT scan was performed (Fig. 1). This confirmed an anterior mediastinal collection measuring 70 mm × 70 mm with images of air and septa inside requiring subdrainage through 2 cervicotomies. Both were done under orotracheal intubation. This intubation had to be