



Hospital-acquired infective endocarditis during Covid-19 pandemic

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ABSTRACT

Background: The COVID pandemic has had a major impact on healthcare in hospitals, including the diagnosis and treatment of infections. Hospital-acquired infective endocarditis (HAIE) is a severe complication of medical procedures that has shown a progressive increase in recent years.

Objectives: To determine whether the incidence of HAIE during the first two months of the epidemic (March–April 2020) was higher than previously observed and to describe the clinical characteristics of these cases. The probability of the studied event (HAIE) during the study period was calculated by Poisson distribution.

Results: Four cases of HAIE were diagnosed in our institution during the study period. The incidence of HAIE during the study period was 2/patient-month and 0.3/patient-month during the same calendar months in the previous 5 years ($p=0.033$). Two cases presented during admission for COVID-19 with pulmonary involvement treated with methylprednisolone and tocilizumab. The other two cases were admitted to the hospital during the epidemic. All cases underwent central venous and urinary catheterization during admission. The etiology of HAIE was *Enterococcus faecalis* (2 cases), *Staphylococcus aureus* and *Candida albicans* (one case each). A source of infection was identified in three cases (central venous catheter, peripheral venous catheter, sternal wound infection, respectively). One patient was operated on. Two patients died during hospital admission.

Conclusions: The incidence of HAIE during COVID-19 pandemic in our institution was higher than usual. In order to reduce the risk of this serious infection, optimal catheter

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care and early treatment of every local infection should be prioritized during coronavirus outbreaks.

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Introduction

The COVID pandemic has had a major impact on healthcare in hospitals, including the diagnosis and treatment of infections [1–3]. In order to reduce the spread of SARS-Cov-2 to patients and hospital staff, priority has been given to the care of life-threatening diseases over non-urgent conditions. In addition, restrictions to the performance of various diagnostic procedures and invasive treatments have been recommended [4,5]. Experience with prior epidemics has been useful to point out some infection-related issues such as the difficulties to comply both with the use of personal protective equipment (PPE) and the preventive measures for nosocomial infections, as well as the delay in the collection of microbiological cultures and misinterpretation of symptoms and results of diagnostic tests [6–8].

Hospital-acquired infective endocarditis (HAIE) is a severe complication of medical procedures that has shown a progressive increase in recent years [9–11]. This progression has been linked to the aging of patients, increased use of venous catheters, parenteral nutrition, hemodialysis, implantation of cardiac devices or cardiac surgery [10–12]. To date, no studies have been reported that examine the relationship between the COVID-19 outbreak and the risk of HAIE.

The aim of the study was to determine whether the incidence of HAIE during the first two months of the epidemic was higher than previously observed and to describe the clinical characteristics of these cases.

Methods

We conducted a prospective study of consecutive adult patients with definitive or possible HAIE admitted to our hospital from March 1 to April 30, 2020. Our institution is a 630-bed teaching hospital that serves as a reference hospital for cardiac surgery and heart transplantation in Madrid (Spain). As COVID-19 patient rooms were progressively established, we moved from nursing patients in single rooms before the pandemic to utilizing cohort bays as incidence of COVID-19 rose. However, the ratio of one nurse for every eight patients and the conventional measures to prevent nosocomial infection (in addition to the specific measures motivated by this viral infection) were maintained. Furthermore, during the study period there were no transfers of patients from other hospitals for endocarditis surgery and only urgent cardiac surgeries were performed due to the shortage of beds in the surgical ICU. The average monthly hospital stay during the study period was 16,726, while in the months of March and April of the previous five years it was 15,456. Since the end of February 2020 there has been a progressive reduction in the number of patients admitted for reasons other than SARS-Cov-2 infection.

Our hospital has an endocarditis team composed of different specialists who actively seek out cases of IE by reviewing patients with fever (infectious disease department) and the

information reported daily through microbiology (blood cultures) and cardiology (echocardiography findings). The team meets every one to two weeks to decide on the management of these patients. This task was maintained during the COVID-19 pandemic, although transesophageal echocardiography (TEE) was limited to cases with high suspicion of IE.

IE was defined as per the modified Duke criteria [13]. HAIE was defined as either IE manifesting > 48 hours after hospital admission or IE acquired in association with an invasive procedure performed within month prior to diagnosis [14]. Microbiological diagnosis was based on blood or valve culture. Transthoracic echocardiography and TEE were performed in patients with clinical or microbiological suspicion of IE according to European guidelines in order to confirm or rule out valve dysfunction and intracardiac complications such as abscesses, vegetations, pseudoaneurysms or fistulae [15]. Antibiotic therapy and surgical indications followed the 2015 European Guidelines [15]. SARS-CoV-2 was detected by a real-time PCR assay targeting E-gene, RdRP-gene and N-gene, performed with the protocol previously reported by the WHO (https://www.who.int/docs/default-source/coronaviruse/uscdcr-pcr-panel-for-detection-instructions.pdf?sfvrsn=3aa07934_2).

The probability of the studied event (HAIE) during the study period was calculated by Poisson distribution. For this purpose, the cases of endocarditis treated in our institution during the months of March and April of the previous five years have been taken into account. For the calculation of statistical significance of the comparison of the incidence of HAIE by hospital stays, the test of the χ^2 has been performed.

Results

Four cases of HAIE were diagnosed in our institution during the study period. During the months of March and April of the previous five years (2015–2019), 23 cases of infectious endocarditis were treated in our hospital, of which 3 cases were acquired in our hospital. The 4 cases detected during the months of March and April 2020 represent an increase compared to the same months during the previous 5 years. The incidence of HAIE during the study period was 2/patient-month and 0.3/patient-month during the previous 5 years ($p=0.033$). The incidence of HAIE per 1000 days of stay during the study period was 0.119 and during the months of March and April of the previous 5 years it was 0.0194 ($p < 0.001$).

According to Duke's criteria, the first 3 cases were classified as definite IE whereas the 4th was classified as possible IE (Table 1). Case 1 was diagnosed after the patient had been hospitalized twice in the previous month, for surgical resection of urothelial carcinoma, followed by repair of iatrogenic arteriovenous fistula. Eight days later she was readmitted to a ward specifically dedicated to COVID-19 due to suspicion of having this infection. Five days after admission, IE was diagnosed in the context of moderate heart failure. Case 2 suffered

Table 1

Clinical features of patients diagnosed with HAIE during COVID-19 pandemic

Case	Decade	Time from admission (days)	Comorbidity	Risk factors ^a	Type of IE	Infection source	Clinical presentation	COVID-19 (treatment)	ETE findings	Blood cultures	Treatment	Surgery indicated	Surgery performed
1	7th	1	Carcinoma (surgery two w before)	Mitral and aortic rheumatic valvulopathy, mitral insufficiency, UC, CVC	Native	Forearm phlebitis	Fever, dyspnea, leg edema	No	Vegetation 7 mm on mitral valve	<i>Enterococcus faecalis</i>	ampicillin + ceftriaxone (4w)	No	No
2	7th	48	HTA. DMID. HCOL.	Aortic and mitral proshetic valve, sacral pressure ulcers, ICU admission, UC, CVC	Prosthetic	Sternal wound infection	Fever, thoracic pain, wound erythema and serosanguinous exudate (<i>Serratia marscerens</i> , <i>Candida albicans</i>)	No	Hypocogenic aortic perivalvular thickening (1.3 cm). Extension to mitroaortic junction and aortic root (abscess)	<i>C. albicans</i>	Anidulafungin (8w) Fluconazole (indefinitely)	Yes	No ^b
3	6th	15	Atrial fibrillation, obesity, rheumatic fever without valve functional impact	UC, CVC	Native	Unknown	Fever, dyspnea, productive cough	Yes (Tocilizumab, methylprednisolone)	Vegetation 22 mm on mitral valve. Moderate mitral insufficiency	<i>E. faecalis</i> ^c	ampicillin + ceftriaxone (6w)	Yes	Yes

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Table 1 (continued)

Case	Decade	Time from admission (days)	Comorbidity	Risk factors ^a	Type of IE	Infection source	Clinical presentation	COVID-19 (treatment)	ETE findings	Blood cultures	Treatment	Surgery indicated	Surgery performed
4	6th	20	DMID, HCOL	ICU admission, UC, CVC	Native	CVC infection	Fever, wrist arthritis, right sternoclavicular arthritis, meningitis, right infrapopliteal, DVT	Yes (Tocilizumab, methylprednisolone)	Normal	MSSA ^d	Cefazolin (6w)	No	No

F: Female, M: Male. HAIE: Hospital-acquired infective endocarditis. HTA: Hypertension. DM: Diabetes mellitus. HCOL: Hypercholesterolemia. UC: Urinary catheter. CVC: Central venous catheter. ICU: Intensive care unit.

^a Clinical factors associated with HAIE.

^b The surgical team rejected surgical treatment because of the high risk of death in the postoperative period due to the patient deteriorated condition and bad surgical prognosis.

^c *E. faecalis* grew in the blood and valve cultures.

^d MSSA grew in catheter culture, cerebrospinal fluid and in blood cultures (until the 9th day of effective treatment). DVT: Deep vein thrombosis. MSSA: Methicillin-sensitive *Staphylococcus aureus*. w: weeks.

from an aortic prosthetic IE due to *Candida albicans* acquired during admission for aortic valve surgical replacement. During the study period, surgical activity was reduced due to the SARS-CoV-2 pandemic, and the capacity of the surgical ICU was restricted to prioritize COVID-19 cases needing critical care. The surgical treatment was rejected because of the high risk of technical complications and frailty of the patient who died during hospital admission. Cases 3 and 4 presented IE after being diagnosed with COVID and treated with methylprednisolone (more than 1000 mg, each) and two doses of tocilizumab (600 mg, intravenously). Case 3 underwent surgery due to severe mitral insufficiency and evolved favorably. Case 4 presented a progressive sepsis that proved fatal despite antibiotic treatment. The patient presented several secondary foci: right costoclavicular arthritis, left wrist, several psoas abscesses, L2-L3 spondylodiscitis, lumbar anterior epidural collection and meningitis. The intervention was not considered because the TEE only showed mild mitral insufficiency without vegetations. However, it was considered that the patient most likely suffered from infectious endocarditis.

All included patients underwent central venous and urinary catheterization and had received systemic antibiotic treatment during the month prior to the diagnosis of HAIE. Comorbidity, risk factors, infection source, clinical presentation, TEE findings, microbiology and treatment of the patients are shown in Table 1. There were no more fatalities during the first 60 days of follow-up.

Discussion

There is a growing concern about the potentially negative impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of other infectious diseases [1–3]. Our study suggests that the risk of developing HAIE may increase during an outbreak of coronavirus infection. To reduce the risk of HAIE, efforts to improve the prevention and treatment of bacteremia and other hospital-acquired infections potentially related to HAIE should be undertaken during outbreaks of viral respiratory infections.

HAIE cases usually comprise approximately 10% of the IE cases in the literature. The characteristics of the patients included in this small series are similar to those of series published before the COVID-19 pandemic [9–12]. Advanced age, prolonged contact with the hospital, the presence of previous heart disease or invasive devices often characterize these patients. With respect to etiology, it should be noted that half of the cases were caused by *E. faecalis*. This result is in concordance with the increase in enterococcal HAIE frequency that typically affects elderly patients with prior valvular damage or invasive diapositives [16].

Our results represent a remarkable finding because, to our knowledge, no link has been reported between outbreaks of coronavirus and the increase in IE cases so far. In contrast, coinfection with bacteria and fungi is a proven fact in severe cases of COVID-19 and has been estimated at about 8–10%, with a bacteremia rate of about 6% [17–21]. Lymphopenia and immunosuppressive treatments such as corticosteroids and interleukin-6 antagonists such as tocilizumab could potentially favor this complication [18,22].

Viral pneumonia itself could be considered a risk factor for the development of IE although the occurrence of

pneumococcal endocarditis in the context of a respiratory virus pandemic is considered a rare event [23]. As has been observed in previous outbreaks, some of our patients may have suffered a delay in the diagnosis of IE due to postponement of blood culture collection, the difficulties in obtaining a TEE for fear of contagion of the viral infection and to the misinterpretation of clinical and microbiological results [7,8]. Because of the similarity in clinical presentation between COVID-19 and other infections, appropriate diagnostic tests (including blood cultures) should be promoted when patients show signs suggestive of bacteremia or endocarditis [19]. Although TEE is a high-risk procedure for transmission of CoV-SARS-2 to health-care workers, because it can generate aerosols, its use should not be restricted only to life-threatening cases, even in the context of the COVID-19 pandemic, as has been proposed [5,13]. Providing healthcare workers with the appropriate PPE and facilitating TEE in appropriate cases, a proper diagnosis of IE during outbreaks of coronavirus infection can be done.

With regard to extrinsic risk factors, our patients frequently had invasive devices that increase the risk of developing HAIE such as venous or urinary catheters [14,17]. In fact, the use of PPE could constitute an additional difficulty in the correct maintenance of these devices due to a decrease of the time dedicated to patient care [6]. In our experience, the high number of newly recruited nurses, the possible reduction in the number of patient visits attributed to the need to put on and take off PPE each time, and the impact of PPE on the tactile and visual performance of healthcare workers may have affected the quality of care. The WHO has insisted on the convenience of verifying sterile insertion in these patients and the need for removal when no longer needed [24]. Of note, cases 1, 2, and 4 presented a distinct original source of infection (peripheral catheter infection, sternal wound infection and central venous catheter infection, respectively).

The fact that the study was done in a single center and the small number of cases makes it advisable to await before acknowledging the increased risk of HAIE during coronavirus outbreaks. We recognize that several potential biases that could have influenced our results such as changes in the number and characteristics of patients at risk, ICU admissions, surgical procedures or transfer of patients from other hospitals. Larger and multicenter epidemiological studies based on designs such as time-series or healthcare evaluation studies are needed to more definitively affirm this potential increase in the incidence of HAIE during coronavirus epidemics.

In summary, we have detected an incidence of HAIE higher than usual during the first two months of the COVID-19 pandemic. In order to reduce the risk of this serious infection, it could be recommended to strengthen basic preventive measures such as optimal catheter care, early treatment of any local infection and appropriate use of diagnostic techniques (TEE) in patients with suspected IE during the peak or second waves of COVID-19.

Credit author statement

Antonio Ramos-Martínez. Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Ana Fernández-Cruz. Conceptualization, Methodology, Writing – original draft, Visualization.

Fernando Domínguez. Data curation, Writing – review & editing.

Alberto Forteza. Data curation, Supervision, Visualization. Marta Cobo. Data curation, Supervision.

Isabel Sánchez-Romero. Data curation, Visualization.

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Ethical statement

This study was approved the local Clinical Research Ethics Committee (CEIC). All patients gave their consent to participate in the study.

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Declaration of Competing Interest

None declared.

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