International Journal of Infectious Diseases 114 (2022) 90–96

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Surging bloodstream infections and antimicrobial resistance during the first wave of COVID–19: a study in a large multihospital institution in the Paris region

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A R T I C L E I N F O

Article history:
Received 26 June 2021
Revised 22 September 2021
Accepted 15 October 2021

Keywords:
COVID-19
Blood culture
Bloodstream infection incidence
Antibiotic consumption
Antimicrobial resistance

A B S T R A C T

Objectives: This study measured the impact of the first wave of COVID-19 pandemic (COVID-19) (March–April 2020) on the incidence of bloodstream infections (BSIs) at Assistance Publique – Hôpitaux de Paris (APHP), the largest multisite public healthcare institution in France.
Methods: The number of patient admission blood cultures (BCs) collected, number of positive BCs, and antibiotic resistance and consumption were analysed retrospectively for the first quarter of 2020, and also for the first quarter of 2019 for comparison, in 25 APHP hospitals (ca. 14 000 beds).
Results: Up to a fourth of patients admitted in March–April 2020 in these hospitals had COVID-19. The BSI rate per 100 admissions increased overall by 24% in March 2020 and 115% in April 2020, and separately for the major pathogens (*Escherichia coli, Klebsiella pneumoniae*, enterococci, *Staphylococcus aureus, Pseudomonas aeruginosa*, yeasts). A sharp increase in the rate of BSIs caused by microorganisms resistant to third-generation cephalosporins (3GC) was also observed in March–April 2020, particularly in *K. pneumoniae*, enterobacterial species naturally producing inducible AmpC (*Enterobacter cloacae*...), and *P. aeruginosa*. A concomitant increase in 3GC consumption occurred.
Conclusions: The COVID-19 pandemic had a strong impact on hospital management and also unfavourable effects on severe infections, antimicrobial resistance, and laboratory work diagnostics.

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https://doi.org/10.1016/j.ijid.2021.10.034

1. Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in 2019, the world has faced an unprecedented surge of acute respiratory infections that often require intensive care and have a high case fatality rate (Khalili et al., 2020). While the demographics, clinical characteristics, and overall survival rate (Fried et al., 2020; Guan et al., 2020; Lippi et al., 2020) of hospitalized patients with COVID-19 have already been characterized in extensive reports from several parts of the word, little is known about the bacterial complications contributing to the morbidity or mortality of inpatients.

In general, it has been widely reported that patients receiving intensive care are at higher risk of hospital-acquired infections. This is due to invasive monitoring and support, exposure to multiple antibiotics, and colonization with resistant microorganisms (Maki et al., 2008). Among these nosocomial infections, bloodstream infections (BSIs) and respiratory tract infections are the most common and life-threatening (Prowle et al., 2011). Hence, it was sought to analyse the impact of the first wave of the COVID-19 pandemic and the subsequent high demand for intensive care on the epidemiology of BSIs in a large public multihospital institution in the Paris region.

2. Materials and methods

2.1. Setting

This research was conducted at Assistance Publique – Hôpitaux de Paris (APHP), a multihospital institution covering the Paris region (the 12 million inhabitants of the city of Paris, its suburbs, and the surrounding counties). APHP is the largest hospital institution in France. It provides a total of approximately 20 000 beds and admits around 1.4 million patients per year. Approximately 14 000 (70%) of these beds are distributed among 25 hospitals, including 18 acute care hospitals and seven rehabilitation/long-term care hospitals (see list in the **Supplementary Material**). These hospitals are served by laboratories of bacteriology that all use the same laboratory information system (LIS), allowing standardized data extraction and combined analysis. The research was conducted in these 25 hospitals.

2.2. Study period

The study covers the 4-month period from January to the end of April 2020 and also the same 4-month period in 2019 as the control. The March–April 2020 period corresponds to the rise and development of the first COVID-19 epidemic wave in the Paris region; this is referred to as the 'COVID-19 period'.

2.3. Patient data

The number of patients admitted to the 25 hospitals during the two 4-month periods (January–April), as well as the number of patients present each day in these hospitals in March and April 2020 with virologically proven COVID-19 (based on a positive RT-PCR), were obtained from the central APHP administration.

2.4. Blood sample data processing

Data on blood cultures were extracted from the LIS of the laboratories serving these 25 hospitals and merged in a relational SQL-queryable database. A blood culture (BC) set was defined as the combination of one aerobic and one anaerobic blood culture bottle drawn through the same puncture. A positive BC set was defined as microbial growth in at least one of the two bottles.

A clinically significant episode of BSI was defined as a positive BC set growing a recognized pathogen (https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-HAI-ICU-protocol.pdf). Bacteria belonging to the commensal skin microbiota (coagulase-negative staphylococci, corynebacteria, and propionibacteria) growing in BC sets are generally defined as contaminants, except in specific individual patient clinical situations (Beekmann et al., 2005; https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-HAI-ICU-protocol.pdf). These BCs were not included in the study since clinical data were not available in the LIS. To remove duplicates, only one BSI episode was counted when several BC sets were positive with the same microorganism for a given patient.

Details of antimicrobial resistance (AMR) were extracted from the LIS, as explained above. All of the involved laboratories participate in the national accreditation process (COFRAC), including internal and external quality assessment programmes, and use the European Committee on Antimicrobial Susceptibility Testing (EUCAST) European quality standards for antimicrobial susceptibility testing (https://eucast.org/clinical_breakpoints/).

2.5. Antibiotic consumption

The consumption of third-generation cephalosporins (3GC; including cefotaxime, ceftriaxone, and ceftazidime), a group of antibiotics largely used for treating serious bacterial infections in hospital settings, was recorded for the 4-month periods of January–April 2019 and January–April 2020 by the central APHP pharmacy and converted into the defined daily dose (DDD) using the World Health Organization (WHO) definitions (https://www.whocc.no/ddd/definition_and_general_considera/).

2.6. Statistical analysis

Rate ratios and their confidence intervals were computed using Poisson models, with a linear time trend to account for possible changes in rate over time, independent of the COVID-19 pandemic. To account for multiple analyses, 99% confidence intervals (99% CI) were used.

3. Results

3.1. Patients

The rise of the COVID-19 pandemic was observed at the beginning of March 2020 in the Paris region. It peaked at the beginning of April and declined until the end of that month (https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-23-avril-2020). Correspondingly, the number of COVID-19 inpatients present in APHP hospitals increased progressively in March, reached a plateau between April 4 and April 14, and decreased steadily during the second fortnight of that month. During the plateau period, between 4700 and 4800 COVID-19 inpatients were present at APHP, among which between 1000 and 1100 were in intensive care units (ICUs) (Figure 1). During this plateau period, COVID-19 patients represented as much as a quarter of all patients present at APHP. To deal with the massive influx of adult COVID-19 patients, the organization of the APHP hospitals was modified extensively. Some medical units were dedicated entirely to the admission of COVID-19 patients who did not require intensive care. The capacity of ICU beds for adults was multiplied by 2.6 by converting post-surgery recovery rooms, operating theatres, and even some paediatric ICUs. Other beds were closed, particularly

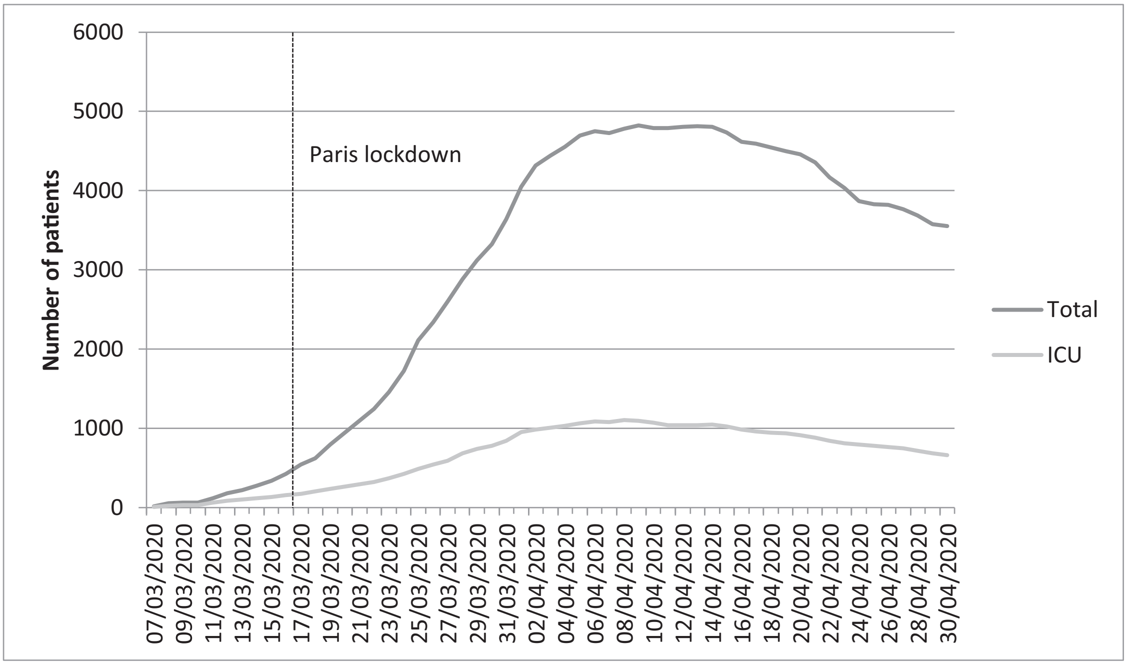

Figure 1. Change in the number of patients with COVID-19 presenting daily during March and April 2020 at Assistance Publique – Hôpitaux de Paris (APHP).

Table 1
Blood cultures and bloodstream infections during the 4-month period (January–April) in 2019 and 2020 in the 25 hospitals of Assistance Publique – Hôpitaux de Paris (APHP)

	January		February		March		April	
	2019	2020	2019	2020	2019	2020[a]	2019	2020[a]
Number of admitted patients	99 467	97 873	90 417	88 369	93 711	74 633	95 414	48 086
Number of blood culture sets collected per 100 admitted patients	24.7	22.7	25.2	23.4	23.7	36.2	20.9	53.3
Number of positive blood culture sets per 100 admitted patients	3.1	2.9	3	3	2.9	4	2.6	7.5
BSIs per 100 admitted patients	1.08	1.09	1.01	1.01	1.05	1.29	1.01	2.25
Escherichia coli	0.25	0.25	0.25	0.24	0.28	0.30	0.25	0.37
Enterococci	0.12	0.10	0.10	0.09	0.12	0.16	0.11	0.38
Streptococci	0.16	0.15	0.12	0.14	0.14	0.16	0.14	0.26
Staphylococcus aureus	0.13	0.13	0.14	0.12	0.12	0.14	0.11	0.28
Klebsiella spp	0.10	0.10	0.10	0.10	0.10	0.12	0.11	0.25
Enterobacteriaceae naturally producing inducible AmpC[b]	0.08	0.09	0.09	0.10	0.07	0.12	0.07	0.22
Non fermentative gram-negative bacilli including *Pseudomonas aeruginosa*	0.11	0.11	0.13	0.11	0.11	0.12	0.11	0.27
Yeasts	0.04	0.02	0.04	0.03	0.03	0.06	0.04	0.11
BSIs with 3CG-resistant microorganisms per 100 admitted patients								
ESBL-producing *Klebsiella* spp	0.04	0.03	0.03	0.02	0.02	0.04	0.03	0.09
Cefotaxime-resistant *Enterobacteriaceae* naturally producing inducible AmpC[b]	0.01	0.02	0.02	0.02	0.02	0.02	0.01	0.05
Ceftazidime-resistant non-fermentative gram-negative bacilli including *Pseudomonas aeruginosa*	0.02	0.02	0.02	0.01	0.02	0.01	0.02	0.03
Methicillin-resistant *Staphylococcus aureus*	0.02	0.02	0.02	0.02	0.01	0.02	0.01	0.03
Enterococci (intrinsic resistance)	0.12	0.10	0.10	0.09	0.12	0.16	0.11	0.38
Yeasts (intrinsic resistance)	0.04	0.02	0.04	0.03	0.03	0.06	0.04	0.11

BSI, bloodstream infection; 3CG, third-generation cephalosporin; ESBL, extended-spectrum beta-lactamase.
[a] COVID-19 period.
[b] Enterobacter cloacae, Enterobacter aerogenes, Serratia spp.

in surgery, since non-urgent surgical procedures were largely postponed. In these cases, the corresponding personnel were redeployed to take care of the COVID-19 patients. Consequently, the overall number of patients admitted to the 25 hospitals decreased during the COVID-19 period (Table 1).

3.2. Blood cultures

Data on the 185 132 BC sets taken during the periods of January–April 2019 and January–April 2020 in the 25 hospitals were reviewed. There was a dramatic increase in the number of BCs collected during the COVID-19 period, i.e. 42.9 BCs per 100 admissions during March–April 2020 versus 23.6 BCs per 100 admissions during January–April 2019 (Table 1). This increase was more precisely assessed by computing the rate ratios of BCs per 100 admissions; the rate ratio was 1.6 in March 2020 and 2.37 in April 2020. This represents an increase of 60% (99% CI 56–63%) in March and 137% (99% CI 131–142%) in April 2020 in comparison to the rates recorded in the periods January–April 2019 and January–February 2020 (Figure 2). A similar increase in the rate ratio of positive BCs per 100 admissions occurred during the COVID-19 period (Figure 2). The proportion of positivity remained stable across all periods.

3.3. Microbial pathogens isolated from bloodstream infections

When considering only clinically significant microorganisms recovered from positive BCs, the rate ratio of BSIs per 100 admissions

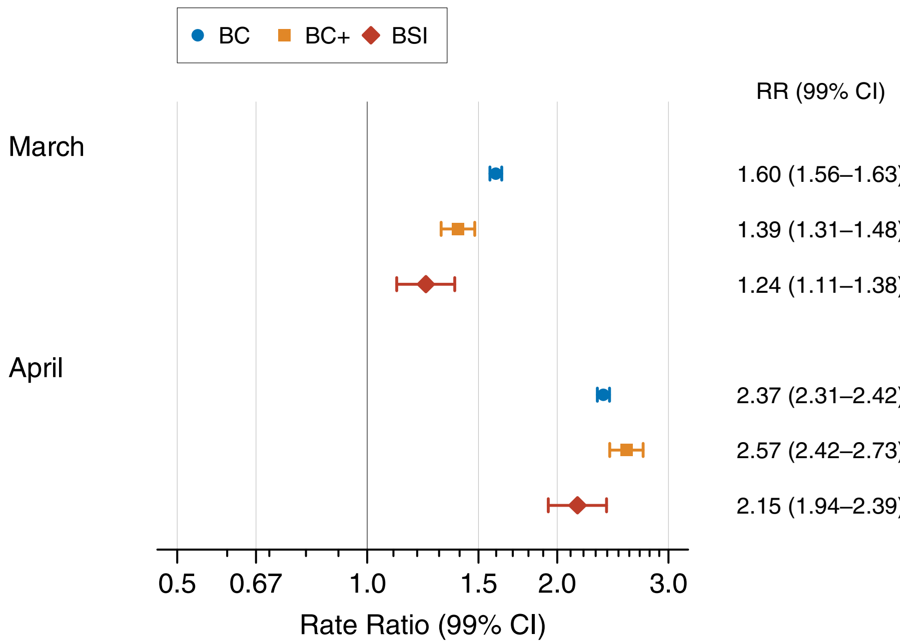

Figure 2. Rate ratios of blood cultures collected (BC), positive blood cultures (BC+), and bloodstream infections (BSI) per 100 admissions in March and April 2020 compared to expected values; 99% confidence intervals are provided.

increased by 24% (99% CI 11–38%) in March 2020 and 115% (99% CI 94–139%) in April 2020 in comparison with the rates in January–April 2019 and January–February 2020 (Figure 2).

When computed according to bacterial species, the increase in the rate of BSIs per 100 admissions in April 2020 ranged between 46% (*Escherichia coli* and anaerobes) and 254% (enterococci) (Table 1).

The rates of clinically significant BSIs with an organism resistant to 3GC per 100 admissions increased during the COVID-19 period, particularly in April 2020. That month saw an increase in *Klebsiella pneumoniae* producing extended-spectrum beta-lactamase (ESBL) (3.3-fold), cefotaxime-resistant isolates of enterobacteria naturally producing inducible AmpC (*Enterobacter cloacae, Klebsiella aerogenes*, *Serratia* spp, etc.) (2.7-fold, likely through cephalosporinase overproduction), and ceftazidime-resistant strains of *Pseudomonas aeruginosa* (2.4-fold), as well as of other non-fermenting gram-negative bacilli (1.5-fold) and methicillin-resistant *Staphylococcus aureus* (1.6-fold) (Table 1). This increase also concerned organisms that are naturally resistant to 3GC, e.g., enterococci (3.5-fold) and yeasts (3.3-fold).

3.4. Consumption of third–generation cephalosporins (3GC)

A sharp increase (DDD per 100 admissions) in the consumption of 3GC, mostly of cefotaxime, occurred in the 25 hospitals during the COVID-19 period. In March the increase was 131% and in April it was 148%, as compared with baseline consumption during the periods January–April 2019 and January–February 2020 (Figure 3).

4. Discussion

This study showed a surge in blood culturing, BSIs, antibiotic resistance, and antibiotic use during the first wave of the COVID-19 pandemic (March–April 2020) in 25 hospitals in the Paris region, the region with the highest number of COVID-19 cases in France at that time (https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-23-avril-2020). It appears that this is the first study to show the global impact of the COVID-19 pandemic on such a broad scale (25 hospitals in a region of 12 million inhabitants).

During the first wave of the COVID-19 pandemic, the rate ratios of blood culture collection per 100 admissions increased in the 25 hospitals by 60% in March 2020 and 137% in April 2020. The same trend was observed when using rates of 1000 patient-days as an indicator (data not shown). A sharp increase in blood culturing during the COVID-19 pandemic was also reported in January through March 2020 in five hospitals in New York City, overwhelming local laboratory capacity and leading to a decrease in the duration of bottle incubation in order to free space in the automated systems (Sepulveda et al., 2020). In contrast, no variation in BCs was observed during the first wave of COVID-19 in five London hospitals (Denny et al., 2021).

Concomitantly to the increase in clinical samples, there was an increase in the number of infections. Indeed, the rate ratio of BSIs per 100 admissions increased by 24% in March 2020 and 115% in April 2020. Such an increase was also observed during a separate analysis of the major pathogens (*E. coli, K. pneumoniae*, enterococci, *S. aureus, P. aeruginosa*, yeasts, etc.). These findings are in line with the results of several single-centres studies in China, Italy, and Switzerland, which found that COVID-19 ICU patients are at a high risk of developing BSIs (Cataldo et al., 2020; Søgaard et al., 2021; Zhang et al., 2020). Conversely, a study conducted in six tertiary care hospitals in Sweden and the London study did not find a high proportion of positive BCs with clinically relevant organisms during the COVID-19 epidemics, but the incidences of BSI were not reported (Denny et al., 2021; Søgaard et al., 2021). In fact, an increase in BSIs associated with an influx of COVID-19 patients is not surprising, since serious bacterial and fungal infections, including BSIs, frequently occur during the hospital stays of severely ill patients (Bassetti et al., 2016; https://www.health.org.uk/news-and-comment/blogs/covid-19-five-dimensions-of-impact). In the 25 hospitals included in the present study, the number of ICU beds used to treat severely ill COVID-19 patients increased by 260%. This accounts for up to a quarter of the COVID-19 inpatients present in APHP hospitals, clearly indicating the severity of their status. The more severe the condition of the patient, the more

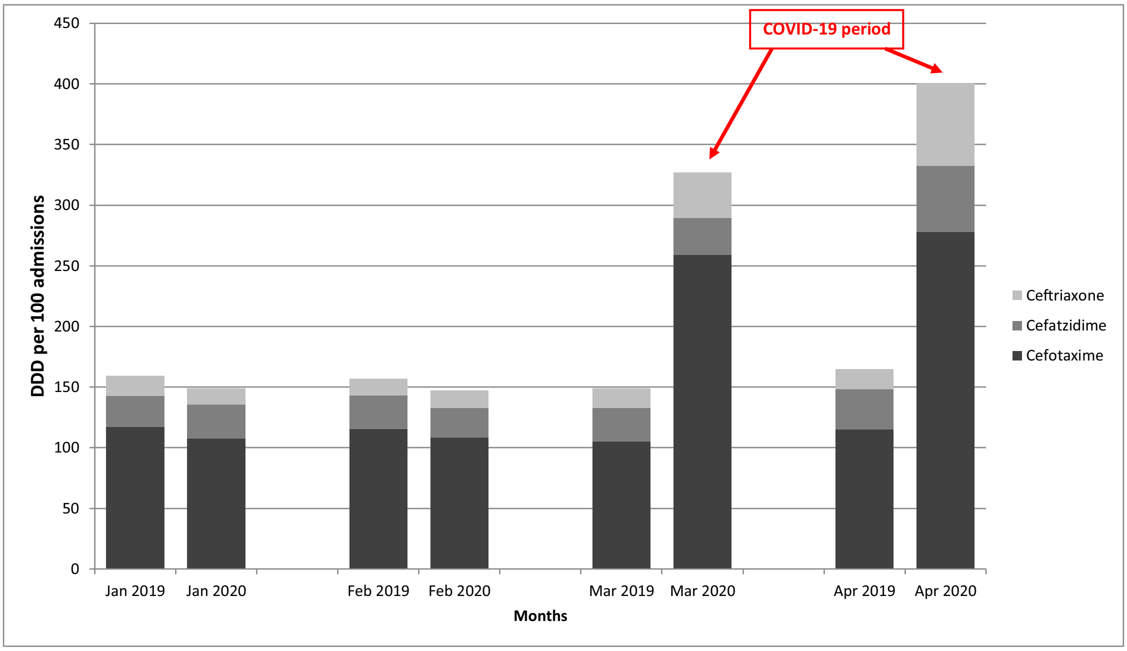

Figure 3. Monthly consumption of third-generation cephalosporins, expressed as the defined daily dose (DDD) per 100 admissions, during the first 4 months of the years 2019 and 2020 in the 25 hospitals of Assistance Publique – Hôpitaux de Paris (APHP).

often invasive procedures are carried out, therefore leading to more infections and more diagnostic tests. It should be noted that at least two in three of the BSIs diagnosed in March and April 2020 in this study could be considered as hospital-acquired based on the time interval between patient admission and BCs.

Moreover, this study found an increase not only in the rate of BSIs, but also in the rate of BSIs caused by microorganisms resistant to 3GC, as compared to a reference period. Several authors have warned of the possible negative impact of the COVID-19 pandemic on AMR (Cantón et al., 2020; Monnet and Harbarth, 2020). Taking resistance to 3GC as an indicator of antibiotic resistance is justified for several reasons. Indeed, 3GC are a major class of injectable antibiotics used widely for severely ill patients in a hospital setting and recommended in the Surviving Sepsis Campaign guidelines for the management of critically ill adults with COVID-19 (Alhazzani et al., 2020). These drugs are among the main indicators of use both at the European level as well as worldwide to assess antibiotic consumption and resistance (https://apps.who.int/iris/bitstream/handle/10665/279656/9789241515061-eng.pdf; https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf). The observed increase concerned mainly gram-negative species resistant via ESBL production and cephalosporinase overproduction (*Klebsiella, Enterobacter, Pseudomonas*), species known to cause hospital-acquired infections. We confirm on a large scale the findings of other reports in smaller settings showing an increase in multiresistant gram-negative species during the COVID-19 epidemic (Arcari et al., 2021; Belvisi et al., 2021). In addition, we also report an increase in the rate of BSIs caused by *S. aureus* with acquired resistance to methicillin and cephalosporins (MRSA), as well as enterococci and yeasts, two types of microorganism characterized by their natural resistance to 3GC.

Finally, concomitantly to the rise in BSI and resistance, a sharp increase in 3GC consumption was observed. Similar increases in broad-spectrum beta-lactams, and particularly 3GC, have been reported during the COVID-19 pandemic in different countries, but always in a single facility, which may not be representative (Abelenda-Alonso et al., 2020; Bork et al., 2020; Giacomelli et al., 2021; Nestler et al., 2020). The intensive use of 3GC is known to exert a selective pressure on enterobacteria with acquired resistance to these antibiotics, either through ESBL production or cephalosporinase overproduction (Mizrahi et al., 2020; Padmini et al., 2017), as well as on naturally resistant organisms such as yeasts (Arendrup, 2010) and enterococci (García-Solache and Rice, 2019). This dual impact is not surprising since a strong correlation between the rates of natural and acquired resistance in BSIs has been established in recent research in European countries (Jarlier et al., 2019).

Despite the strengths of this study, which covers a large set of regional hospitals, several limitations should be acknowledged. First, the scale of the study, which dealt with the approximately 120 000 patients admitted in March and April 2020, made an analysis at the individual level (invasive procedures, antibiotic prescriptions…) impossible. The research therefore captured the overall impact of the COVID-19 pandemic, without patient stratification, on four indicators in the 25 hospitals. More specifically, stratification of BCs and BSIs by COVID-19 status was not performed because of the lack of a unified comprehensive clinical and microbiological database. Second, the study focused on BSIs because the bacteriological results of BCs are relatively simple to interpret. Other major types of infection, such as lower respiratory tract infections, would have been of interest in the context of COVID-19 pulmonary involvement. However, these infections are difficult to assess based simply on bacteriological results without an analysis of clinical data, which are not available in LIS (see above). Similarly, the lack of individual data on indwelling catheters or other invasive procedures made the identification of ‘true’ BSIs due to skin commensal species (coagulase-negative staphylococci, etc.) impossible. Third, we did not evaluate other factors such as nursing staff ratios or staff expertise, which could have affected BSI rates in a more complex context (Amarsy et al., 2021; Robert et al., 2000).

Upheaval in hospital organization has been reported in many countries where the health system has been overwhelmed by the spread of COVID-19 (Grasselli et al., 2020; https://www.health.org.uk/news-and-comment/blogs/covid-19-five-dimensions-of-impact). Health care systems can rapidly become compromised in the case of an explosive outbreak of an emerging infection (Crawford et al., 2016; Elston et al., 2017; Nuzzo et al., 2019) or in the case of conflicts and natural disasters (López Tagle and Santana Nazarit, 2011; Roberts et al., 2003).

The collateral effects of the COVID-19 crisis on BSIs, AMR, and antibiotic consumption have not been reported simultaneously and at the scale of a large region. Comprehensive studies in more focused populations will be needed to assess the respective contributions of risk factors to BSIs and increases in antibiotic resistance during the pandemic. A combination of responsible use of antimicrobials and adequate hygiene measures should be used in order to minimize the risk of unfavourable outcomes following another sudden crisis of a similar magnitude.

Acknowledgements

The authors thank Christophe Leroy, in charge of the SI-VIC data centre at APHP, for providing information on the COVID-19 patients presenting daily at APHP hospitals.

Declarations

Funding: None.

Ethical approval: This study did not require any specific ethical approval, as it used data that were extracted anonymously according to current French regulations. All patients admitted to APHP hospitals are informed about the potential use of their data for research purposes.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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