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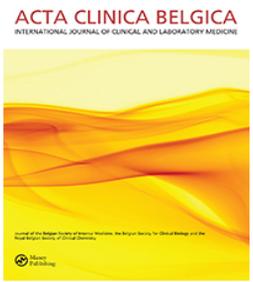

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Antibiotic use in patients with Coronavirus disease 2019 (COVID-19): outcomes and associated factors

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ABSTRACT

Objectives: To characterise the factors, outcomes and infections associated with antibiotic use in COVID-19 patients.

Methods: Records of patients with RT-PCR-confirmed COVID-19, hospitalized at the CHU Charleroi (Belgium) between 11 March and 3 May 3 2020, were retrospectively reviewed. Factors associated with antibiotic treatment, outcomes and bacterial infections were analysed.

Results: Among the 164 hospitalized COVID-19 patients (median age 60.5 years [IQR] 46–79), twenty-five (15.2%) were admitted to the ICU. Twenty-six (15.9%) died in the hospital. One hundred (61%) received antibiotic treatment. Combination therapies with macrolides were more common in the early part of the study period (26/67, 38.8%). Twenty-eight patients (17.1%) had a confirmed infection, mostly of the urinary tract (18/28, 64.3%). Only 2 (1.2%) had a documented respiratory coinfection. Six of the 7 ICU infections (85.7%) were superinfections. Gram-negative bacteria were most frequently isolated. In multivariate analysis, six factors were associated with antibiotic use: being hospitalized in the ICU (OR: 4.59; 95% CI 1.07–19.71), age > 65 years (OR: 4.16; 95% CI 1.72–10.05), arrival from a nursing home (OR: 4.59; 95% CI 1.11–19.71), diabetes (OR: 4.35; 95% CI 1.26–14.93), bilateral consolidation on chest CT (OR: 9.92; 95% CI 2.40–41.06) and a C-reactive protein level > 60 mg/L (OR:2.46; 95% CI 1.13–5.37). Antibiotic treatment did not reduce the length of stay or the mortality rate.

Conclusion: Antibiotics have been overused during the COVID-19 pandemic, despite a low rate of coinfections . Integrating the antimicrobial stewardship (AMS) programme into the COVID-19 response is essential.

KEYWORDS
Antimicrobial stewardship; antibiotic use; coinfections; coronavirus disease 2019

Introduction

Coronavirus disease 2019 (COVID-19) spread rapidly worldwide after the first cases were identified in December 2019 in China. The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [1]. In Belgium, the first wave of the epidemic spread in March 2020 and on 16 January 2021, Belgium ranks second in the world among countries most severely affected by COVID-19, with 178.18 deaths per 100,000 inhabitants [2,3].

A high percentage of patients hospitalized for COVID-19 worldwide have received antibiotics (56.6–72%), although bacterial coinfections associated with COVID-19 appear to be infrequent, approximately 4% of non-ICU patients and 14% of ICU patients [4–7].

Currently, regardless of the COVID-19 pandemic, the aetiological diagnosis of community-acquired pneumonia (CAP) remains a challenge [8,9].

High values of inflammatory biomarkers, a high fever and chest CT scan features observed in patients with COVID-19 may suggest respiratory bacterial coinfection, probably leading to the overuse of antibiotics [4–7].

The macrolide antibiotic class was evaluated in several studies as a treatment for COVID-19, in particular the combination of azithromycin (AZ) and hydroxychloroquine (HCQ), which may further encourage their use during the COVID-19 pandemic [10–13].

The main objective of this retrospective study was to determine the risk factors associated with antibiotic use in non-ICU and ICU COVID-19 patients and to assess the impact of antimicrobial therapy on the length of the hospital stay, secondary ICU admission and in-hospital mortality to facilitate the development of a specific antimicrobial stewardship (AMS) programme. Second, we describe COVID-19 associated infections in non-ICU and ICUs patients.

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Material and methods

Setting

The Charleroi University Hospital Centre (CHU Charleroi) is a tertiary hospital located in Charleroi (Belgium) with 1,374 beds (including 44 intensive care beds) and an annual number of 44,190 admissions.

Study design

This retrospective study included all non-ICU and ICU COVID-19 patients aged ≥ 16 years old hospitalized between 11 March 2020, and 3 May 2020. The exclusion criteria was critically ill patients who were transferred from other hospitals for extracorporeal membrane oxygenation (ECMO) treatment.

Patients

All patients hospitalized in non-ICUs received standard care. According to the Belgian treatment guidelines for COVID-19, the off-label use of HCQ sulfate was allowed [14]. No other investigational drugs or off-label drugs (including systemic corticosteroids) were administered. Antibiotics were prescribed according to the judgment of the clinician, and no specific antibiotic stewardship or bacteriological programme were put in place during the epidemic. No antiviral drugs were administered, except for acyclovir prophylaxis in patients with haematological disorders and the HIV treatment.

Data collection

We collected data from the electronic records on demographics, comorbidities, COVID-19 disease severity, laboratory test results, radiological examination results, immunosuppressive drug use, HCQ use, antibiotic treatments, length of hospital stay, immediate or secondary ICU admission, invasive mechanical ventilation, ECMO and in-hospital and ICU mortality rates. The study period lasted 7 weeks, and for the analysis of antibiotic treatments, that period was divided into 2 subperiods (11 March – 5 April and 6 April – 3 May), according to the progressive increase in the understanding of COVID-19 gained by the clinicians, which could have led to a possible change in the management of COVID-19 over time. The Age-adjusted Charlson Comorbidity Index (AACI) was calculated retrospectively for every patient. Laboratory parameters were noted on admission and on the day of antibiotic treatment. We recorded the levels of white blood cells, lymphocytes, neutrophils and C-reactive protein as inflammatory parameters. Patients immediately or secondarily admitted to the ICU were considered as ICU patients and never admitted to ICU as non-ICU patients.

Definitions

COVID-19 was diagnosed in patients with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab sample or sample of bronchoalveolar lavage fluid (BAL) who had symptoms of upper or lower respiratory tract infection (including anosmia and ageusia), diarrhoea, altered mental status or thromboembolism without other cause. COVID-19 has been classified into 4 categories of disease severity. Mild disease is defined by the absence of dyspnoea, while moderate COVID-19 is defined by the presence of dyspnoea without signs of severe disease. Severe disease is defined as a basic respiratory rate (RR) $\geq$ 30, oxygen saturation on ambient air (Sat O2) ≤ 93% or a ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) (PaO2/FiO2) ≤ 300 mmHg. Critical disease was defined as acute respiratory distress syndrome (ARDS) or a severe disease with sepsis or multi-organ failure.

Each antibiotic given for at least 24 hours was recorded during the hospital stay. Duration of antibiotic therapy was defined as the interval between the first day of antibiotic administration until the end of antimicrobial treatment. A bacterial, viral or fungal infection documented by a microbiological sample, antigen detection or molecular biological test during the hospital stay and deemed compatible with an active infection by the clinician was considered an infection. They were considered coinfections if they occured within 48 hours of admission to hospital and as superinfections if they occurred later.

Laboratory methods

From 11 to 23 March 2020, samples were sent to the National Reference Centre for Coronaviruses (UZ Leuven, Belgium), and from 24 March 2020, technical tests were carried out on site to detect SARS-CoV-2 RNA. Due to the worldwide shortage of extraction kits, a laboratory RT-PCR technique developed by the University of Namur was implemented during the first phase of the epidemic [15]. All results with a cycle threshold (Ct) <40 were considered positive. Where commercial extraction kits were available, the Seegene® Allplex 2019-nCoV kit, which targeted the E, N, and RdRP genes, was used, preceded by extraction on m2000sp (Abbott Molecular®), and samples with a Ct value < 40 were considered positive. Influenza/RSV PCR was performed with the Xpert® Xpress Flu/RSV kit (GeneXpert® Cepheid). Urine samples were used for the antigen detection of *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* (Abbot BinaxNow® *Legionella* antigen card, Abbot BinaxNow® *Streptococcus pneumoniae* antigen card, respectively). In samples of BAL fluid, the detection of respiratory pathogens was carried out using TaqMan Array Card

technology (QuantStudio 12 K Flex Thermo Fischer Scientific real-time PCR system). Microbiological samples were cultured according to the standard quantitative culture method (NCCLS), and speciation of the isolates was performed by MALDI-TOF MS (BioTyper; Brucker Daltonics, Bremen, Germany). Antimicrobial sensitivities were determined by the Clinical and Laboratory Standards Institute (CLSI) 2016 criteria. No serum galactomannan test was performed as a screening test for aspergillosis. Respiratory virus PCR panels were not routinely performed, as they are not reimbursed in the Belgian system. Serological tests for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were not performed routinely, and PCR tests for these pathogens were only requested for BAL samples.

Chest imaging

During the first weeks of the epidemic, imaging was carried out using chest X-rays for logistical purposes to minimize the risk of transmission of SARS-CoV-2. Due to the rapid implementation of infection control protocols, chest X-ray was replaced by chest CT scans. The images were acquired by spiral acquisition and then reconstructed into multiplanar images (Siemens Definition AS, Siemens Healthcare, Erlangen, Germany) and analysed by a radiologist. To assess the extent of lung damage, the radiologist was assisted by artificial intelligence software (AIS), icolung (Icometrix®, Leuven, Belgium), but the final quantification was determined by the radiologist.

Statistical analysis

Variables are presented as the median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Three separate logistic regression analyses were performed. The first analysed the clinical characteristics prompting antibiotic therapy, the second the radiological characteristics of patients who received antibiotics and the third the factors associated with an increased risk of mortality. The first and third analyses were carried out on the whole cohort and the second on the subcohort in which a chest CT was performed.

Odds ratios (ORs) and 95% confidence intervals (CIs) are shown. Variables were included in the multivariate analysis if they were significantly associated in the univariate analysis ($p < 0.05$). Statistical significance was set at a p-value < 0.05. Statistical analyses were performed with SPSS version 26 (IBM Corporate, Bois-Colombes, France).

Results

Baseline characteristics

The baseline characteristics are summarized in Table 1.

From 11 March 2020 to 3 May 2020, 164 COVID-19 patients were hospitalized, 139 in non-ICUs (84.8%) and 25 (15.2%) in ICUs. Ten (6.1%) patients were immediately admitted to the ICU and 15/164 (9.1%) were secondarily transferred to the ICU. The median age was 60.5 years (interquartile range [IQR], 46–79 years) and 83 (50.6%) were women. Patients who received antibiotics (100/164, 61%) were older than those who did not receive antibiotics (64/164, 39%), (median age 67.5 years [IQR, 54–81] vs. 52 years [IQR, 37–61, $p < 0.001$]), were more frequently admitted from nursing homes (27% vs. 4.7%, $p< 0.001$), had more comorbidities (chronic cardiac disease [32% vs. 15.6%, $p = 0.019$], diabetes [30% vs. 10.9%, $p = 0.003$]), and had a higher median AACI score (5 [IQR 3–7] vs. 2 [IQR 0–5], $p < 0.001$). Patients who received antibiotic treatment also had a more severe COVID-19 illness (46% vs. 28.1%, $p = 0.022$) or a more critical illness (7% vs. 0%, $p = 0.043$). All the mechanically ventilated in the ICU received antibiotics ($p = 0.006$).

Chest CT scans were performed significantly more frequently in the antibiotic group (82/100, 82%) than in the nonantibiotic group (39/64, 60.9%, $p = 0.003$). When the proportion of affected lung parenchyma was quantified, 18/70 (25.7%) patients in the antibiotic group had at least 50% affected lung parenchyma compared to 1/35 (2.8%) in the nonantibiotic group ($p = 0.003$). Bilateral consolidations (BC) were observed significantly more often on chest CT in the antibiotic group than in the nonantibiotic group (37/82 [45.1%] vs. 4/39 [10.2%], $p< 0.001$).

The median level of C-reactive protein was significantly higher in the antibiotic group than in the nonantibiotic group (89 mg/L [IQR 44.5–154.5] vs 32 mg/L [IQR 16.3–60], $p < 0.001$).

The off-label use of HCQ was prescribed to 54/100 (54%) of patients in the antibiotic group compared with 29/64 (45.3%) of patients in the nonantibiotic group, but the difference was not statistically significant.

No significant differences in median white blood cell and lymphocyte counts were observed between the two groups (data not shown).

Variables associated with antibiotic treatment: univariate and multivariate analyses

The results of the univariate and multivariate analyses are summarized in Table 2.

Multivariate analysis

In the binary logistic regression, 6 characteristics were associated with antibiotic treatment: an age ≥ 65 years,

Table 1. Baseline characteristics of 164 COVID-19 patients hospitalized in non-ICUs and ICUs.

Baseline characteristics (*n*= 164)	All (*n*= 164)	Non- antibiotics group (*n*= 64)	Antibiotics group (*n*= 100)	p-value
Age, years, median (IQR)	60.5 (46–79)	52 (37–61)	67.5 (54–81)	<0.001
Female, no. (%)	83 (50.6)	33 (51.5)	50 (50)	0.944
Hospitalization Unit, no (%)				
Non-ICU	139 (84.8)	60(93.7)	79 (79)	0.546
Immediate ICU admission	10 (6.1)	3 (4.7)	7 (7)	0.546
Secondary admission at ICU	15 (9.1)	1 (1.6)	14 (14)	0.119
Total ICU	25 (15.2)	4 (6.1)	21 (21)	0.01
Body temperature (°C) at admission, median (IQR)	37 (36.1–38)	36.9 (36–37.8)	37 (36.3–38.1)	0.22
Patient origin – no. (%)				
Outpatient	117 (71.3)	49 (76.6)	68 (68)	0.275
Transfer from a hospital	11 (6.7)	7 (10.9)	4 (4)	0.111*
Nursing Home	30 (18.3)	3 (4.7)	27 (27)	<0.001
Living in a community	6 (3.6)	5 (7.8)	1 (1)	0.034*
Comorbidities, no, (%)	126 (76.8)	44 (68.7)	82 (82)	0.05
Active malignancy	9 (5.5)	1 (1.6)	8 (8)	0.092*
Chronic cardiac disease	42 (25.6)	10 (15.6)	32 (32)	0.019
Arterial hypertension	90 (54.9)	28 (43.75)	62 (62)	0.031
Moderate to severe chronic kidney disease	16 (9.8)	7 (10.9)	9 (9)	0.683
Chronic pulmonary disease	27 (16.5)	11 (17.2)	16 (16)	0.841
Diabetes	37 (22.6)	7 (10.9)	30 (30)	0.003
Obesity	62 (37.8)	26 (40.6)	36 (36)	0.551
Immunosuppressive therapy or HIV	13 (7.9)	5 (7.8)	8 (8)	1*
Age-adjusted Charlson comorbidity index (AACI), median (IQR)	4 (1–6)	2 (0–5)	5 (3–7)	<0.001
COVID-19 Clinical Severity Status at hospital admission time				
Mild	16 (9.8)	12 (18.7)	4 (4)	0.002
Moderate	77 (47)	34 (53.1)	43 (43)	0.205
Severe	64 (39)	18 (28.1)	46 (46)	0.022
Critical	7 (4.3)	0 (0)	7 (7)	0.043
Patients with specific Oxygen supplementation during ICU stay, no/patients (%)				
Non-invasive ventilation	2 (1.2)	1 (1.6)	1 (1)	0.312*
Invasive mechanical ventilation	15 (9.1)	0 (0)	15 (15)	0.006
ECMO	3 (1.8)	0 (0)	3(3)	1
Chest CT performed at admission time, no. (%)	121 (73.8)	39 (60.9)	82 (82)	0.003
Pattern of lung changes on chest CT scan at hospital admission time, -no (% chest CT scan)				
Ground glass opacity	109 (90)	35(89.7)	74 (90.2)	0.931
Local patchy shadowing	23 (19)	11 (28.2)	12 (14.6)	0.075
Crazy paving	30 (24.8)	8 (20.5)	22 (26.8)	0.452
Bilateral consolidations	41 (33.9)	4 (10.2)	37 (45.1)	<0001
Pleural effusion – no. (%)	5 (4.1)	1 (2.6)	4 (4.9)	1
Pulmonary Embolism	2 (1.7)	0 (0)	2 (2.4)	NA
Lobar consolidation	9 (7.4)	1 (2.6)	8 (9.7)	0.268
Percentage of lung parenchyma affected no. (%)				
<25%	51/105 (48.6)	20/35 (57.1)	31/70 (44.3)	0.225
>25 < 50%	35/105 (33.3)	14/35 (41.2)	21/70 (30)	0.312
≥ 50%	19/105(18.1)	1/35 (2.8)	18/70 (25.7)	0.003
C-Reactive protein level (mg/L) at hospital admission time, median (IQR)	56 (22–115)	32 (16.3–60)	89 (44.5–154.5)	<0.001
Hydroxychloroquine Sulfate treatment-no (%)	83 (50.6)	29 (45.3)	54 (54)	0.278

IQR: Interquartile range; no: number; COVID-19:coronavirus disease 2019; ECMO: extra corporeal membrane oxygenation; NA: not applicable; * Fischer exact test

arriving from a nursing home, diabetes, ICU stay and a C-reactive protein level ≥ 60 mg/L. BC was the only radiological factor associated with antibiotic use among patients on whom a Chest CT scan was performed.

Outcome

The outcomes are summarized in Table 3.

Secondary admission to the ICU was more common among patients in the antibiotic group than among those in the nonantibiotic group (14/100 [14%] vs. 1/64 [1.6%], p = 0.006).

Twenty-six (15.9%) patients died in the hospital. In-hospital mortality was higher in the antibiotic group (23/100 [23%] vs. 3/64 [4.7%], p = 0.002). Mortality in ICU was higher in the antibiotic group (5/21, 23.8% vs 0/4, 0%) but the difference was not statistically significant.

Regarding non-ICU patients, the median length of hospital stay was significantly longer in the antibiotic group than in the nonantibiotic group (10 days [7–15] vs 6 days [4–9], p≤ 0.001) Similar results were observed for the median ICU length of stay (11 days [6–15] vs 3 days [3,4], p = 0.019).

Antibiotic use was associated with an increased risk of in-hospital mortality (OR:4.55; 95% CI 1.50–13.87) (data not shown). However, this association was not significant in the multivariate analysis once the clinical severity of COVID-19 and the AACI score were taken

into account (adjusted OR: 3.47; 95% CI 0.81–11.49). Likewise, the use of HCQ was associated with a reduced risk of mortality (OR: 0.30; 95% CI 0.12–0.76) but disappeared in the multivariate analysis (adjusted OR: 0.44; CI 0.15–1.35).

Characteristics of antibiotic treatment during the study period

The characteristics of antibiotic treatment are summarized in Table 4.

During the study period, 100/164 (61%) patients received antibiotics specifically 21/25 (84%) ICU patients and 79/139 (56.8%) non -ICU patients, with no statistical difference for all cohort between the first and second subperiods (67/107, 62.6% vs 33/57, 57.9%, p = 0.55).

The most frequently prescribed antibiotics were β – lactam+β– lactamases inhibitors (BL-BLIs) (86/100, 86%). Amoxicillin ±clavulanic acid and combination therapies with macrolides were prescribed significantly more frequently in the first subperiod than in the second subperiod (41/67, 62.2% vs 11/33, 33.3%, p = 0.013 and 26/67[38.8%] vs. 4/33 [12.1%], p = 0.029, respectively).

Characteristics of infections in COVID-19 patients

The characteristics of infections are summarized in Table 5.

Twenty-eight patients (28/164, 17.1%) had a confirmed infection, including 21/139 (15.1%) non-ICU patients and 7/25 (28%) ICU patients. Nineteen (19/28, 67.9%) infections were diagnosed within 48 hours and these were considered coinfections. Additionally, 9/28 (32.1%) were diagnosed more than 2 days after admission and these were considered superinfections and were found mostly among ICU patients (6/7, 85.7%). Six bacterial respiratory infections were documented among the 164 patients (3.6%), but only 2 were coinfections (2/164, 1.2%).

The most frequent source of infection was urinary tract infections (UTIs) [18/28, 64.3%]). UTIs were coinfections in 15/18 (83.3%) patients, and a source of 4 secondary bacteraemia cases. Superinfections occurred in 3 (3/139, 2.2%) non- ICU patients, one case of hospital acquired pneumonia (HAP), one UTI and one 'other infection'. Six superinfections were identified among the 25 ICU patients (6/25, 24%) including UTI (2/25, 8%), HAP (1/25, 4%), and one (4%) COVID-19-associated pulmonary aspergillosis (CAPA) infection.

Table 2. Univariate and multivariate analyses of factors associated with antibiotic use in COVID-19 patients hospitalized in non-ICUs and ICUs.

Clinical and laboratory characteristics associated with antibiotic use in COVID-19 patients				
Variable	**Univariate analysis Odds ratio (95% CI)**	**p value**	**Multivariate analysis adjusted Odds ratio (95% CI)**	**p value**
Age > 65 years	5.03 (2.47–10.26)	<0.001	4.16 (1.72–10.05)	0.002
Nursing home	7.52 (2.18–26)	<0.001	4.59 (1.11–19.71)	0.041
Arterial hypertension	2.1 (1.11–3.97)	0.02	0.56 (0.22 – 1.43)	0.23
Diabetes	3.49 (1.43–4.75)	0.004	4.35(1.26–14.93)	0.024
AACI>3	4.71 (2.40–9.29)	<0.001	1.53 (0.47–4.99)	0.482
Severe or critical disease	2.88 (1.47–5.64)	0.002	1.34 (0.57–3.18)	0.5
ICU Stay	3.99 (1.3–12.23)	0.01	4.59 (1.07–19.71)	0.008
C-reactive protein >60 mg/L	3.24 (1.67–6.27)	<0.001	2.46 (1.13–5.37)	0.024
Radiological characteristics associated with antibiotic use in COVID-19				
Bilateral consolidation	7.2 (2.34–22.1)	<0.001	9.92 (2.40 – 41.06)	0.002
Lung parenchyma affected:		0.225	NA	NA
<25%	0.61 (0.28–1.36)	0.31	NA	NA
>25 < 50%	0.651	0.02	2.81 (0.3–26.95)	0.365
≥50%	10.8 (1.39–84.1)			

AACI: age-adjusted Charlson comorbidity index; CI: confidence interval; ICU: intensive care unit; NA: not applicable

Table 3. Clinical outcomes among COVID-19 patients hospitalized in non-ICUs and ICUs.

Outcome	Results	Non antibiotic	Antibiotics	p value
Total (N = 164)		***n = 64***	***n = 100***	
Length of hospital stay -Days, median (IQR)	9 (6–16)	6.5 (4–10)	11.5 (8–18)	0.01
In -hospital mortality, no. (%)	26 (15.9)	3 (4.7)	23 (23)	0.002
Secondary ICU admission, no (%)	15 (9.1%)	1 (1.6)	14 (14)	0.006
***Non-ICU patients (n* = 139)**		***n*= 60**	***n* = 79**	
Length of hospital stay -Days, median (IQR)	8 (5–14)	6 (4–9)	10 (7–15)	<0.001
In -hospital mortality, no. (%)	22 (14.3)	3 (1.9) 3	19 (12.3)	0.006
ICU patients (n=25)		***n* = 4**	***n*= 21**	
Length of ICU stay -Days, median (IQR)	9 (3.5–14.5)	3 (3–4)	11 (6–15)	0.019
Length of hospital stay -Days, median (IQR)	17 (12–21.5)	17 (14–18)	18 (12–22)	0.358
ICU mortality, no. (%)	5 (20)	0 (0)	5 (23.8)	0.522

IQR: interquartile range; ICU: intensive care unit

Table 4. Characteristics of antibiotic treatment among 164 COVID-19 patients hospitalized in non-ICUs and ICUs.

	All study period	March11, 2020– 5 April 2020	6 April 2020– 3 May 2020	p value
Number of patients (*N*), (n/N, %)	164	107 (65.2)	57 (34.8)	
Antimicrobial therapy, n (%)	**100 (61)**	**67 (62.6)**	**33 (57.9)**	0.55
non-ICU wards – no. (%)	79 (56.8)	49 (73.1)	30 (91)	0.22
ICU -no. (%)	21 (84)	18 (26.8)	3 (9)	0.22
Monotherapy, no (no/n, %)	71 (71)	43 (64.2)	28 (84.5)	0.27
Combination therapy, no, (%)		26 (38.8)	5 (15.1)	0.029
with clarithromycin	31 (31)	24 (35.8)	4 (12.1)	
with azithromycin	28 (28)	2 (3)	0 (0)	
with amikacin	2 (2)	0 (0)	1 (3)	
	1 (1)			
Delay between hospital admission and antibiotic initiation days, median, (IQR)	0 (0–1)	0 (0–0.25)	0 (0–1)	0.66
Duration of antibiotic therapy, days median, (IQR)	7 (4–8)	6.5 (4–8)	8 (5–10)	0.18
non-ICU stay				
ICU stay	7 (4–11)	7 (4.5–9.5)	12 (6.5–15.5)	0.58
Antibiotics prescribed, no (%)				
Temocillin	3 (3)	0 (0)	3 (9)	0.041
Amoxicillin	1 (1)	1 (1.5)	0 (0)	1
Amoxicillin + clavulanic acid	52 (52)	41 (61.2)	11 (33.3)	0.013
Piperacillin +tazobactam	34 (34)	21 (31.3)	13 (39.4)	0.63
Second generation cephalosporin	15 (15)	10 (14.9)	5 (15.2)	0.90
Third generation cephalosporin	13 (13)	9 (13.4)	4 (12.1)	1
Meropenem	6 (6)	4(6)	2 (6)	1
Ciprofloxacin	5 (5)	0 (0)	5 (15.1)	0.005
Moxifloxacin	6 (6)	3 (0)	3 (9.1)	0.42
Clarithromycin	28 (28)	24 (35.8)	4 (12.1)	0.012
Azithromycin	2 (2)	2 (3)	0 (0)	0.54
Vancomycin	1 (1)	1 (1.5)	0 (0)	1
Amikacin	1 (1)	0 (0)	1 (3)	0.34
Trimethoprim/sulfamethoxazole	2 (2)	2 (3)	0 (0)	0.54
Voriconazole	3 (3)	1 (1.5)	2 6)	0.27

Ventilator- associated pneumonia (VAP) was documented in 2/15 (2/15, 13.3%) intubated patients.

Thirty microorganisms were isolated, including 29 bacteria such as *Escherichia coli* (15/29, 51.7%), *Pseudomonas aeruginosa* (3/29, 10.3%), *Klebsiella pneumoniae* (3/29, 10.3%), *Citrobacter koseri* (2/29, 6.9%), *Staphylococcus aureus* (2/29, 6.9%). *Proteus mirabilis, Bacteroides fragilis, Enterococcus faecalis and Streptococcus constellatus* were isolated in one case (3.5%). *Aspergillus fumigatus* was isolated by culture and PCR from the BAL of an intubated patient and *Pneumocystis jirovecii* was isolated by PCR from the BAL of another patient

Discussion

Sixty one percent of non-ICU and ICU COVID-19 patients received antimicrobial therapy, although a significantly lower proportion had confirmed bacterial infections (17.1%). In particular, documented bacterial pneumonia was present in only 6/164 (3.6%) patients and 1.2% were coinfections. This overconsumption of antibiotics is alarming, although it is consistent with the levels of antibiotic consumption in COVID-19 patients previously reported by Vaughn [5] (56.6%) and Rawson [6] (72%).

We found that COVID-19 was first managed as CAP [8]. At the time of the onset of the pandemic, the risk of bacterial coinfection was unknown, and it seems that it was substantially overestimated by clinicians. The difficulty in obtaining respiratory specimens from patients with CAP is known but it is still recommended in patients with a severe illness or of those at risk for infection with a multidrug-resistant organism (MDRO) [8]. In our study, 43.3% of COVID-19 cases were severe, but respiratory cultures were performed in only 28/164 (17%) patients, including 2 BAL cultures (1.2% of patients, [data not shown]). The lack of microbiological documentation is explained by the fact that cough is not productive and that sampling techniques generate aerosols, exposing healthcare workers to SARS-CoV-2 [4]. Only 39 (23.8%) patients underwent pneumococcal and *Legionella* pneumophila antigen detection (data not shown).

Antibiotics were most frequently prescribed at admission for a median duration of 7 days and most of the prescription were for BL-BLIs. The use of macrolides was consistent, especially during the first subperiod of the epidemic. Compared to that in the same period in 2019, the defined daily dose (DDDs)/1000 hospital-days was 2.5 higher for clarithromycin and 1.6 for AZ (data not shown). Macrolide consumption decreased during the second subperiod of the epidemic, when clinicians became familiar with COVID-19. pneumonia. The literature suggests an antiviral effect of AZ, prescribed alone or in combination with

Table 5. Infections among 164 COVID-19 patients hospitalized in non-ICUs and ICUs.

			non-ICU (*n*= 139)				ICU (*n* = 25)			
Infections	**No infections (%)**	**No infections/ No patients (%)**	**No infections**	**D1-D2**	**D3-D7**	**>D7**	**No infections**	**D1-D2**	**D3-D7**	**>D 7**
UTI	18 (64.3)	11	**15**	14	0	1	**3**	1	1	1
Secondary bacteriemia*	4*(14.3)		**3***	3*	0	0	**1***	1*	0	0
CAP	2 (7.1)	1.2	**2**	2	NA	NA	**0**	0	NA	NA
HAP	2 (7.1)	1.2	**1**	NA	1	0	**1**	NA	1	0
VAP	2 (7.1)	1.2	**NA**	NA	NA	NA	**2**	NA	1	1
Primary bacteriemia	2 (7.1)	1.2	**2**	2	0	0	**0**	0	0	0
Invasive aspergillosis	1 (3.6)	0.6	**0**	0	0	0	**1**	0	1	0
Other	1 (3.6)	0.6	**1**	0	0	1	**0**	0	0	0
Total infections/n patients (%)		**28 (17.1)**	**21(15.1)**	**18 (12.9)**	**1 (0.7)**	**2 (1.4)**	**7 (28)**	**1 (4)**	**4 (16)**	**2 (8)**

No: number; UTI: urinary tract infection; CAP: community acquired pneumonia; HAP: hospital acquired pneumonia; VAP: ventilator- associated pneumonia; D: day; NA: not applicable

HCQ, may also have had an impact on the overuse of this specific antibiotic [10–13].

We identified 6 factors associated with antibiotic prescription: older age, coming from a nursing home, diabetes, ICU stay, BC features on chest CT scan and a C-reactive protein level >60 mg/L.

Older age and nursing home residency are probably explained by the fact that the prompt administration of antibiotics is crucial in severe CAP, as severe CAP is associated with a high in-hospital mortality rate of 25–50% and that elderly patients with respiratory infections are at risk of severe illness requiring ICU management [19,20]. In addition, US data on in-hospital mortality in COVID-19 patients showed a range from 35% for patients aged 70–79 years to more than 60% for patients aged 80–89 years [4].

Diabetic status has previously been described as a risk factor for pneumococcal pneumonia and for contracting and dying from various infections [21,22]. These data probably led to a higher rate of prescription of antibiotics among these patients, who were more susceptible to bacterial infections.

A C-reactive protein level greater than 60 mg/L is considered a criterion for differentiating between CAP of bacterial or viral origin, which probably explains why we identified an increase in C-reactive protein value as a risk factor for receiving an antibiotic [9].

The severity of COVID-19 is driven by the inflammatory response and not by superinfections in contrast to influenza [23]. AMS and clinical algorithms for initiating antibiotics in patients admitted to the ICU with COVID-19 are essential. We also observed a probable case of CAPA in an intubated patient, who was treated with voriconazole.

BC on chest CT scans is the sixth risk factor that we identified for the prescription of antibiotics. Chest CT appeared as a diagnostic tool in the first wave of the COVID-19 pandemic because the SARS-CoV-2 RT-PCR turnaround time sometimes exceeded 36 hours. During the study period, approximately 30% of patients were managed by frontline providers who were less familiar with the management of pneumonia (data not shown). In a previous study of viral pneumonia caused by common respiratory viruses, Shiley et al. [24] showed that radiological images were often the reason for the misdiagnosis of bacterial aspiration pneumonia. However, in our study, chest CT may have been performed more frequently in patients with severe COVID-19 or among those perceived to be at high risk of bacterial infection, which may have resulted in an overestimation of the role of this pattern in the prescription of antibiotics.

In terms of outcomes, antibiotic treatment did not reduce the length of stay, the number of secondary ICU admissions or in-hospital mortality. Hospital mortality was higher in the group of COVID-19 patients treated with antibiotics, probably due to confounding factors such as older age, higher AACI score, and more severe disease.

In our study, infections were identified in 17.1% of the patients and were mainly urinary tract infections (64.3%). This rate of infections is higher than that published in the literature, but if we consider only bacterial pneumonia coinfections, the rate drops to 1.2%, which is similar to other published data [5–-7,25-28]. Coinfections of urinary origin were probably overestimated in nursing home patients, with a high frequency of asymptomatic bacteriuria, which could have been misdiagnosed as a urinary tract infection.

In Spain, Garcia-Vidal et al. [25] showed an equally low coinfection rate of 3.1%, mainly due to *S. pneumoniae* and *S. aureus*, in contrast to this study, in which no cases of coinfection with *S. pneumoniae* were documented and *S. aureus* infections were superinfections.

Only one CAPA case was documented, but only 2 (1.2%) BAL procedures were performed in all patients (data not shown). In addition, no systematic screen with galactomannan serum antigen was performed.

The antimicrobial management team (AMT) was not included in our hospital's epidemic management plan as was the case in other hospitals [29]. The problem of antibiotic resistance was not considered as a possible consequence of the pandemic. In

addition, AMS has also been difficult to achieve due to infection control policies and a shortage of personal protective equipment (PPE), making it difficult for infectious disease specialists to exchange information face-to-face with other specialists. These barriers to AMS also contributed to the overuse of antibiotics during this period [30].

AMS strategies must adapt to this emerging disease as suggested by Seaton [31]. A daily re-assessment of the need for antibiotics seems essential given the lack of identified clinical benefit and the exposure of these patients to the acquisition of MDRO.

Our study has several limitations due to its retrospective and monocentric design. The empirical use of antibiotics at admission may have led to an underestimation of existing bacterial coinfections by treating them without identifying them. We did not perform MDRO monitoring or review the patient files for antibiotic toxicities; therefore, we could not report the negative impacts of antibiotic overuse.

In conclusion, the role of empirical antimicrobial therapy in the COVID-19 patients hospitalized in non-ICUs and ICUs appears to be very limited. The potential benefits must be carefully balanced against the risk of side effects, the development of MDRO and the exposure of health care workers to SARS-CoV-2 when administering the antibiotics to the patient. Integrating the AMS programme into the COVID-19 response is essential.

Ethical approval

The study was approved by the local ethics committee on 13 May 2020 (CCB: B3250000019).

Patient consent is not required for this type of retrospective study in Belgium.

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