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Co-infections and antimicrobial use among hospitalized COVID-19 patients in Punjab, Pakistan: findings from a multicenter, point prevalence survey

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ABSTRACT

There are reports of high rates of antibiotic prescribing among hospitalized patients with COVID-19 around the world. To date, however, there are few reports of prescribing in relation to COVID-19 in Pakistan. Herein, we describe a point prevalence survey of antibiotic prescribing amongst patients hospitalized with suspected or proven COVID-19 in Pakistan. A Point Prevalence Survey (PPS) was undertaken in seven tertiary care health facilities in Punjab Provence, Pakistan. Baseline information about antimicrobial use according to the World Health Organization (WHO) standardized methodology was collected on a single day between 5th and 30 April 2021. A total of 617 patients' records were reviewed and 578 (97.3%) were documented to be receiving an antibiotic on the day of the survey. The majority (84.9%) were COVID-19 PCR positive, 61.1% were male and 34.9% were age 36 to 44 years. One quarter presented with severe disease, and cardiovascular disease was the major comorbidity in 13%. Secondary bacterial infection or co-infection (bacterial infection concurrent with COVID-19) was identified in only 1.4%. On the day of the survey, a mean of 1.7 antibiotics was prescribed per patient and 85.4% antibiotics were recorded as being prescribed for 'prophylaxis'. The most frequently prescribed antibiotics were azithromycin (35.6%), ceftriaxone (32.9%) and meropenem (7.6%). The majority (96.3%) of the antibiotics were empirical and all were from WHO Watch or Reserve categories. Overall, a very high consumption of antibiotics in patients hospitalized with suspected or proven COVID-19 was observed in Pakistan and this is concerning in view of already high rates of antimicrobial resistance in the region. Antimicrobial stewardship programs need to urgently address unnecessary prescribing in the context of COVID-19 infection.

KEYWORDS

Hospitalized; Covid-19; antimicrobial; use; surveillance; Punjab; Pakistan

1. Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic in March 2020 by the World Health Organization (WHO) [1]. An initial lack of proven medicines to treat patients with COVID-19, concerns regarding potential bacterial co-infection or secondary bacterial infection, and clinical/diagnostic overlap with bacterial respiratory tract infections have been associated with multiple reports of very high antibiotic use in hospitalized patients with COVID-19 [2–6]. A small number of hospitals have reported lower antibiotic prescribing rates among patients with COVID-19 [7–11]. Despite high rates of antibiotic prescribing in the context of COVID-19, only 3.5%–14.3% of the hospitalized COVID-19 patients (including those in critical care units) have been shown to have bacterial co-infection or secondary infection [2,4].

Unnecessary antimicrobial prescribing in patients with COVID-19, more generally, is a concern due to the increasing antimicrobial resistance (AMR) risk with associated increases in morbidity, mortality and health care and societal costs [12–16]. The annual economic cost of AMR may be as high as $0.33–1.2 trillion by 2050 unless addressed [17]. Currently, more than 700,000 deaths globally are reported per year due to AMR, with a projected increase to 10 million deaths over the next three decades with Asian countries sharing approximately half of this mortality [18]. Adverse events following the unnecessary use of antimicrobial agents is another concern for patients and physicians, and the incidence has been reported as high as 30% of the hospitalized patients [19,20].

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In 2015, WHO devised the Global Action Plan (GAP) on AMR, which clearly outlined the need for knowledge strengthening through research and surveillance to optimize the rational use of antimicrobial agents [21]. Moreover, in 2018, a standardized methodology was developed by the WHO to obtain baseline information about the use of antibiotics among hospitalized patients by reviewing their medical records during a specific time by means of point prevalence surveys (PPS) [22]. We are aware that a number of PPS studies have previously been conducted in Pakistan including those contained within systematic reviews [23–27]. We are also aware of concerns with high rates of resistance to common antibiotics including the cephalosporins and fluoroquinolones in Pakistan [28,29]. Overall, antibiotic consumption in hospitals in Pakistan has been documented to increase in the context of the pandemic and this is of significant concern given the already high antibiotic use observed in hospitals in Pakistan [30]. A recent study also highlighted the alarming situation of AMR in Pakistan before and during the current pandemic that may adversely affect health care provision in the country [31]. We are, however, unaware of any PPS conducted to date in Pakistan among those hospitalized with suspected or confirmed COVID-19. Consequently, we sought to address this by conducting a multicenter PPS among patients hospitalized for suspected or confirmed COVID-19 in the Punjab Province of Pakistan. Patient specific data is important to inform the implementation of the Pakistan National Action Plan to reduce AMR [32–34].

2. Methods

2.1 Study design and setting

The Punjab province represents more than half of Pakistan's total population and is served by forty-nine teaching hospitals, all of which are under the administrative control of the Specialized Healthcare and Medical Education Department (SHCME). All hospitals were contacted for participation in the survey and seven (all tertiary care hospitals) agreed. The survey was conducted according to standardized WHO and European Center for Disease Control (ECDC) methodologies [22,35]. Data were gathered from the medical records of suspected and confirmed COVID-19 patients admitted to the isolation wards/units of each hospital on a single day between 5 April 2021 and 30 April 2021. Each of the COVID-19 isolation wards were divided into medical and intensive care units (ICU). As part of usual care, patients were provided with free of cost medicines, testing facilities, supplemental oxygen and mechanical ventilator support if indicated and available.

2.2 Data collection tool

The data collection tool was developed by the investigators to collect necessary information at the ward level and patient level and was adapted from the WHO Global Point Prevalence Survey (PPS) tool [22]. The type of ward (medical ward or ITU) was recorded alongside the number of beds and patients on the ward on the day of the PPS. Collected data included patients' ages and gender, comorbidities including cardiovascular disorders, diabetes mellitus, asthma/COPD and other chronic illness. Chronic illness are conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both. These conditions in our study population included neurodegenerative disorders such as Parkinson disease, kidney diseases and long-term injuries. The current status of COVID-19 (suspected or proven by RT-PCR), disease severity and the presence of any bacterial co-infection, which was determined by the blood/sputum culture, were also recorded. COVID-19 disease severity was determined by reference to guidelines issued by the ministry of National Health Services, Regulation and Coordination, Government of Pakistan [36] as follows:

•**Asymptomatic**: SARS-CoV-2 infection but without any symptom.

•**Mild**: Symptoms due to COVID-19 but without any hemodynamic disturbances and did not require oxygen therapy or any chest x ray abnormalities. The oxygen saturation in these cases must be ≥ 94%.

•**Moderate**: Those patients who have oxygen saturation below 94% but above 90% and chest x-ray with infiltrates involving < 50% of the total lung fields and were without any severe manifestations were declared as moderate cases.

•**Severe**: Severe cases were those who have fever and cough along with respiratory rate <30, severe respiratory distress, chest x-ray with infiltrates involving <50% of the total lung fields, and oxygen saturation ≤90 on room air were identified as severe cases.

•**Critical**: Presence of acute respiratory distress syndrome (ARSD) or worsening of respiratory symptoms, bilateral opacities or lung collapse in chest x-ray or CT scan and respiratory or cardiac failure were considered as critical cases.

Antibiotic prescribing data were collected including the generic name (INN: International Nonproprietary Name) of prescribed antibiotics, route of administration, stop time/dates, reason for prescribing, empiric or targeted therapy and whether culture sensitivity testing was performed before the prescribing of any antibiotic. In addition, whether the antibiotics prescribed were on the WHO Access, Watch or Reserve list with the objective of reserving the prescribing of antibiotics on the

WHO Reserve list [37,38]. Bacterial co-infection among confirmed hospitalized COVID-19 patients was identified as those bacterial infection identified in ≤2 days after hospital admission, while bacterial secondary infection among confirmed COVID-19 patients were reported in >2 days after admission microbiologically [39].

2.3 Data collection procedure

On the day of survey, investigators visited COVID-19 isolation wards at 8:00 AM and identified the medical records of the patients present at that time/date. Data were recorded on the hand written data collection forms. Clinical staff were contacted for any clarification if required. All the members of the data collection team were properly trained about data collection according to PPS methodology as well as differentiation between cases according to diseases severity.

2.4 Inclusion and exclusion criteria

All the patients with suspected or confirmed COVID-19 as recorded in the medical records present in the surveyed hospitals at 8:00 AM on the day of survey were included in the study. Patients present in hospital wards, and patients admitted after 8:00 AM were excluded from the survey.

2.5 Approval of the study

Ethical approval was granted from the Research Ethics Committee, Department of Pharmacy Practice, the University of Lahore (UOL), Lahore (REC/DPP/FOP/38). Moreover, approval of the current study was also taken from the administration of the concerned hospital prior to data collection. As data was obtained from the medical records and drug prescription chart without patient contact, written consent was not required. Confidentiality of data was strictly maintained in line with other PPS studies conducted in Pakistan and elsewhere [23–27].

2.6 Statistical analysis

Data were entered on Microsoft Excel and Statistical Package for the Social Sciences (SPSS), version 22. Descriptive statistics were employed to present data by frequency and percentage.

3. Results

3.1 Demographic characteristics

Demographics of the study population are shown in Table 1. On the day of survey, 617 (84.2%) of the 733 COVID-19 beds in the isolation wards of the seven tertiary care hospitals were occupied. Sixty one percent were male and 78.2% were being treated in the medical wards. Most patients had comorbid illness including, cardiovascular complications (13%) and diabetes (7.5%). The majority (84.9%) were confirmed SARS-CoV-2 PCR positive and 44.8% had severe disease. Out of the total number of patients surveyed, 36 patients (6.2%) were mechanically ventilated.

Table 1. Demographic characteristics of the study participants and hospital related information

Variables	N (%)
Total bed in COVID-19 isolation ward	736
Total patients in COVID-19 isolation ward at 8:00 AM	617
Total number of patients prescribed antibiotics	578 (93.7)
Gender	
Male	335 (61.1)
Female	225 (38.9)
Age (years)	
18-25	35 (6.0)
26-35	104 (17.9)
36-45	202 (34.9)
46-55	150 (25.9)
≥56	87 (15.0)
Ward Sub-specialty	
Medical ward	452 (78.2)
Intensive care unit (ICU)	126 (21.8)
Covid status	
Negative (PCR report negative)	21 (3.6)
Suspected (PCR report waiting)	66 (11.4)
Confirmed PCR report positive)	491 (84.9)
Covid severity	
Asymptomatic	21 (3.6)
Mild	58 (10.0)
Moderate	178 (30.7)
Severe	259 (44.8)
Critical	62 (10.7)
Comorbidity	
No comorbidity	322 (31.9)
Cardiovascular	131 (13.0)
Diabetes	76 (7.5)
Asthma/COPD	35 (3.5)
Chronic illness	14 (1.4)
Presence of bacterial infection	
Yes	8 (1.4)
No	570 (98.6)

3.2 Antimicrobial prescribing

Five hundred and seventy-eight (93.7%) patients received at least one antibiotic on the day of the survey. Of those receiving antibiotics, two thirds received more than one antibiotic, two thirds received their antibiotics via the intravenous (IV) route and two thirds of antibiotics were prescribed without recording the proposed stop date in the medical records (Table 2). The majority (85.4%) were recorded as being prescribed for prophylactic use, 94.3% of the antibiotics were prescribed without documenting indication in the medical records and 96.3% were prescribed empirically. Antibiotics prescribed were all from the WHO Watch or Reserve categories and none were from the Access category. The most frequent antibiotics prescribed among the hospitalized COVID-19 patients were azithromycin (35.6%), ceftriaxone (32.9%) and meropenem (7.6%) (Table 3). Remdesivir was prescribed in 21.9% of the patients, antifungals in 2.7%

Table 2. Antimicrobials prescribed and indications detail

Variables	N (%)
Total number of prescribed antibiotics	1010
Number of antibiotics per patient	
One antibiotic	191 (33.0)
Two antibiotics	335 (57.9)
Three antibiotics	52 (8.9)
Route of administration	
Oral	325 (32.2)
Intravenous	685 (67.8)
Stop time/date	
Yes	378 (32.2)
No	632 (67.8)
Indications	
Therapeutic use	41 (4.0)
Prophylaxis use	863 (85.4)
Unknown	106 (10.4)
Reason on notes	
Yes	132 (5.7)
No	878 (94.3)
Types of therapy	
Empirical therapy	973 (96.3)
Targeted therapy	37 (3.6)
Other anti-infective agents	
Antiviral (Remdesivir)	127 (21.9)
Antifungal	16 (2.7)
Antiprotozoal	34 (5.8)

and anti-protozoal therapy in 5.8% of the surveyed patients (Table 2). Sputum samples were examined in 43 patients and 8 were positive for bacteria: *Staphylococcus aureus* in 1 patient, *Streptococcus pneumoniae* in 3, *Haemophilus influenzae* in 2 and *Pseudomonas aeruginosa* in 2 patients. None of the patients were diagnosed with secondary bacterial infections on the day of survey. Bacterial co-infection was therefore only recognized in 1.4% of the patients with suspected or proven COVID-19 receiving antibiotics on the day of the survey.

4. Discussion

Multiple factors may contribute to the development of AMR in hospital settings during the current COVID-19 pandemic. LMICs are particularly at risk because of potentially poor infection prevention and control programs, disruption of routine immunization services, lack of standardized clinical microbiology laboratory facilities and suspension of national AMR surveillance and monitoring [40,41]. Disruption of these activities contribute to compromise of the implementation of antimicrobial stewardship (AMS) activities and contribute to unnecessary antibiotic consumption [42]. This survey revealed that almost all patients hospitalized with suspected or confirmed COVID-19 in this region of Pakistan were prescribed antibiotics during the second wave of the pandemic in Pakistan. It was not possible to compare with prescribing during the first wave of the pandemic in Pakistan; however, our findings were in line with multiple other studies during the first pandemic wave including a previous study from Bangladesh where all hospitalized COVID-19 patients were prescribed broad-spectrum WHO Watch and Reserve antibiotics [43,44].

It is likely that clinical uncertainty, lack of other therapeutic options, and similarities in presentation between COVID-19 pneumonia and bacterial pneumonia drove the high rates of empirical antibiotic prescribing in those hospitalized with COVID-19 during the first wave of the pandemic [45]. Subsequently multiple observational studies have shown that bacterial co-infection is a rare entity in patients with COVID-19 [4–7]. Nosocomial secondary bacterial infection may be associated with prolonged hospital stay particularly if requiring mechanical ventilation or following the use of multiple intravenous catheters or other interventions [13]. In the largest published observational study to date, bacterial infection was reported in 1107 of the 48,902 hospitalized patients with COVID-19 in the U.K. and the majority (>70%) of these infections were hospital acquired secondary infections [39].

It is essential that health care providers are vigilant about the prescription and selection of antibiotics during the pandemic. Adherence with recommendations and favoring WHO Access antibiotics when there is clinical uncertainty, coupled with using microbiological testing to guide targeted therapy, and informing early discontinuation of therapy when SARS-CoV-2 is confirmed or bacterial co-infection is disproved, will reduce unnecessary antimicrobial prescribing and minimize the risk of AMR. Health settings need to maintain and develop diagnostic testing and develop innovative testing facilities, which include multiplex

Table 3. Prescribed antibiotics according to ATC classification

Sr. No.	ATC Code	ATC class	Name of antibiotic	N (%)
1	J01FA10	Macrolides	Azithromycin	360 (35.64)
2	J01DD04	Third-generation Cephalosporins	Ceftriaxone	332 (32.87)
3	J01DH02	Carbapenems	Meropenem	77 (7.62)
4	J01MA14	Fluoroquinolones	Moxifloxacin	53 (5.24)
5	J01MA02	Fluoroquinolones	Ciprofloxacin	48 (4.75)
6	J01CR05	Piperacillin and beta-lactamase inhibitor	Piperacillin/Tazobactam	41 (4.05)
7	J01XX08	Other antibacterials	Linezolid	36 (3.56)
8	J01DD08	Third-generation Cephalosporins	Cefixime	32(3.16)
9	J01DD62	Cephoperazone and beta-lactamase inhibitor	Cephoperazone and beta-lactamase inhibitor	24 (2.37)
10	J01DE01	Fourth-generation Cephalosporins	Cefepime	7 (0.69)

testing facilities for rapid identification between bacterial and viral infections, so that effective management of COVID-19 can be achieved [46]. In resource poor settings, this of course will be challenging. Previous studies from Pakistan observed non-availability of diagnostics facilities, lack of comprehensive financial resources, and inappropriate use of antibiotics as key issues facing the Pakistani health care system while implementing the National Action Plan (NAP) to tackle AMR [47–49]. This gap needs to be addressed going forward if Pakistan is to achieve the goals established in its NAP.

All patients with suspected or confirmed COVID-19 in our survey received WHO Watch or Reserve broad-spectrum antibiotics despite a lack of confirmatory bacterial infection. The indication for antibiotic prescribing was also poorly documented in our survey, potentially adding to high rates of prescription. Unnecessary antibiotic prescription by physicians has been identified as a major ongoing challenge in the implementation of the NAP of Pakistan against AMR [50], and it is likely that this inappropriate use has been heightened by the COVID-19 pandemic. Similar findings have been reported in India where high rates of WHO Watch and Reserve antibiotics were used despite a paucity of documented bacterial infections amongst hospitalized COVID-19 patients [51]. Overall, our survey reported that azithromycin, third generation cephalosporins and meropenem were the most frequently prescribed antibiotics for patients with actual or suspected COVID-19 although other Watch and Reserve antibiotics were also frequently prescribed (Table 3). These findings mirror those of Mustafa et al (2021), who found an appreciable increase in antibiotic consumption during the current COVID-19 pandemic among five hospitals in the Punjab province, particularly for azithromycin and ceftriaxone in the context of COVID-19 [30]. Similar findings were documented in India where carbapenems and third generation cephalosporins were the most common classes of antibiotics prescribed among COVID-19 patients [51]. Another study from Singapore highlighted amoxicillin as the most frequent antibiotic in hospitalized patients with COVID-19 followed by piperacillin/tazobactam and cephalosporins [10]. In contrast to our findings, a further study in Singapore illustrated that co-amoxiclav was the frequently prescribed antibiotic in COVID-19 patients [52].

These findings are in contrast to a previous PPS from Scotland during the first wave of the pandemic where only 38% of the hospitalized confirmed COVID-19 patients were prescribed at least one antibiotic on the day of survey, with the majority of antibiotics from the WHO Access category with good documentation of the reason for a prescription [13]. Another recent study reported from Singapore also demonstrated very low prevalence of antibiotics (6%) among hospitalized COVID-19 suspected and confirmed patients with the majority of antibiotics prescribed with justification in the medical records [10]. These provide guidance for healthcare professionals treating COVID-19 patients in hospitals in Pakistan.

There are a number of limitations with our study. First, this survey was limited to seven tertiary hospitals in the Punjab province, and we were unable to include the remaining teaching hospitals in the region. It is therefore uncertain if this is a true representation of prescribing in the region. Moreover, the median duration of hospital stays of COVID-19 patients was not recorded by the investigators on the day of survey, which could affect antibiotics prescription. Further private sector hospitals were not included in this survey, and so, practice cannot be extrapolated for that sector of health care. Diagnosis of bacterial infection may also have been underestimated due to limitations in microbiological sampling and diagnostic resources. Notwithstanding these limitations, we believe this survey to be a reasonable representation of prescribing in hospitals in Pakistan in the context of COVID-19, providing guidance for the future as Pakistan seeks to reduce current high rates of AMR.

5. Conclusion and Recommendations

This PPS study has shown excessive and largely unjustified antimicrobial use amongst patients hospitalized with suspected or proven COVID-19 in the Punjab province of Pakistan. High rates of broad spectrum WHO Watch and Reserve antibiotic prescribing are also concerning as this will fuel growth in AMR rates during the current pandemic. Consequently, there is an urgent need to institute AMS strategies in the context of COVID-19 in the Punjab Provence of Pakistan and likely across Pakistan, which should be part of the ongoing NAP activities. Avoidance of empirical antibiotics in community onset COVID-19 at presentation to hospital, promotion of WHO Access antibiotics when there is clinical uncertainty, rapid transition from IV to oral therapy, short duration therapy and early discontinuation of antibiotics if SARS-CoV-2 are confirmed or, if bacterial infection is concluded to be unlikely, are the key AMS principles in COVID-19. Reducing clinical uncertainty through improved use of microbiological diagnostics is also essential particularly in patients in a critical care setting where secondary infections are more common. Local AMS efforts should be coordinated nationally and should be supported by a strong educational program, surveillance of antimicrobial use and AMR and allocation of necessary financial and human resources. A multi-sectorial approach engaging all the

stakeholders is essential to develop robust antimicrobial stewardship programs going forward. We will be following this up in the future.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Z.U.M. was responsible for the study concept. M.S.S., M.N.I, S.A.B and S.K. lead the organized data collection procedure. Z.U.M. and M.S. were involved in data analysis, interpretation of results and manuscript writing. B.G and R.A.S critically reviewed and edited the manuscript and contributed to data analysis. All authors read it carefully before submission.

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