J Antimicrob Chemother
doi:10.1093/jac/dkaa326

Journal of Antimicrobial Chemotherapy

Antibiotic use in patients with COVID-19: a 'snapshot' Infectious Diseases International Research Initiative (ID-IRI) survey

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Received 18 May 2020; accepted 25 June 2020

Background: Antibiotics may be indicated in patients with COVID-19 due to suspected or confirmed bacterial superinfection.

Objectives: To investigate antibiotic prescribing practices in patients with COVID-19.

Methods: We performed an international web-based survey and investigated the pattern of antibiotic use as reported by physicians involved in treatment of COVID-19. SPSS Statistics version 25 was used for data analysis.

Results: The survey was completed by 166 participants from 23 countries and 82 different hospitals. Local guidelines for antibiotic use in COVID-19 patients were reported by 61.8% ($n = 102$) of participants and for 82.9% ($n = 136$) they did not differ from local community-acquired pneumonia guidelines. Clinical presentation was recognized as the most important reason for the start of antibiotics (mean score = 4.07 and SD = 1.095 on grading scale from 1 to 5). When antibiotics were started, most respondents rated as the highest the need for coverage of atypical pathogens (mean score = 2.8 and SD = 0.99), followed by *Staphylococcus aureus* (mean score = 2.67 and SD = 1.05 on bi-modal scale, with values 1 and 2 for disagreement and values 3 and 4 for agreement). In the patients on the ward, 29.1% of respondents chose not to prescribe any antibiotic. Combination of β-lactams and macrolides or fluoroquinolones was reported by 52.4% ($n = 87$) of respondents. In patients in the ICU, piperacillin/tazobactam was the most commonly prescribed antibiotic. The mean reported duration of antibiotic treatment was 7.12 (SD = 2.44) days.

Conclusions: The study revealed widespread broad-spectrum antibiotic use in patients with COVID-19. Implementation of antimicrobial stewardship principles is warranted to mitigate the negative consequences of antibiotic therapy.

Introduction

The COVID-19 epidemic has changed the focus of healthcare around the globe. The disease is mild to moderate in 80% of diagnosed cases, roughly 20% of patients are severely ill and the disease is critical in 6% of affected patients.[1] In the subset of patients admitted to hospitals, the disease, with its clinical presentation including fever, cough and lung infiltrates, resembles bacterial pneumonia. The severity of disease, the probability of bacterial superinfection and increased workload of prescribers may lower the threshold for antibiotic use leading to overprescribing and an increase in antimicrobial resistance. In a large multicentre Chinese study, 58% of patients admitted to hospital received IV antibiotics.[2] In two smaller studies from Jiangsu and Wuhan, antibiotics were prescribed to almost all patients.[3,4] Moxifloxacin was mentioned as the most common choice in Jiangsu.[4] Another study from Wuhan reported antibiotic use in 71% of their patients.[5] Virtually nothing is known about the empirical antibiotic treatment practices in COVID-19 patients in other parts of the world. Hence,

we performed a short online survey to give an insight into the antibiotic prescribing practices in COVID-19 patients.

Methods

We developed a 16-question questionnaire. The questionnaire was originally written in English and then translated into Italian for the Italian participants. The questionnaire (Supplement S1, available as Supplementary data at *JAC* Online) collected information on the characteristics of participants, followed by questions on what influenced the decision to provide antibiotic treatment in COVID-19 patients. There were also questions on local antimicrobial guidelines in relation to COVID-19 and community-acquired pneumonia. In the final part, the participants reported up to two most common antibiotic choices for empirical treatment of COVID-19 patients in both ICU and non-ICU settings in the form of multiple-response categorical variables. They were also asked the usual duration of antibiotic treatment. The questions on the decision for antibiotic therapy used a 5-point grading scale (1 = least important and 5 = most important), while the specific pathogen coverage used a 4-point (1 = strongly disagree and 4 = strongly agree) bi-modal scale. The questionnaire was published on a customized 1KA survey[6] and distributed among the members of the Infectious Diseases International Research Initiative (ID-IRI) platform and via coordinators from seven countries. The data were collected between 7 and 28 April 2020. Two reminders were sent via the survey platform and an additional one via e-mail to the coordinators. The participation in the survey was voluntary and with no compensation. Ethical approval was not required. Free text answers with more than one response are listed in Supplement S2. SPSS Statistics version 25 was used for statistical analysis.[7]

Results

The survey was responded to by 166 participants from 23 countries and 82 different hospitals. The number of participants per country is presented in Figures 1 and 2 and Supplement S3. Most of the respondents worked in university-affiliated hospitals (n = 119/166, 71.7%), followed by state-owned general hospitals (n = 33/166, 19.9%). Over three-quarters of participants (n = 129, 78.2%) were involved in direct care of patients with COVID-19 and 49.7% (n = 82) worked as managers or supervisors of direct care. Almost one-quarter of participants (n = 38, 23.0%) were involved in local guidelines for COVID-19 care. Public health activities were reported by 3.6% of participants (n = 6) and 1.8% (n = 3) were dealing with COVID-19 microbiology diagnostics.

Most of the respondents were specialists in infectious diseases (50.3%), intensive care (28.5%) and internal medicine (11.5%).

Existence of local guidelines for antibiotic use in patients with COVID-19 were reported by 61.8% (n = 102/166) of participants and for 82.9% (n = 136/166) they did not differ from local community-acquired pneumonia guidelines. The reported differences are included in Supplement S2.

Clinical presentation was recognized as the most important reason for the start of antibiotic therapy (mean score = 4.07 and SD = 1.095 on a scale from 1 to 5), followed by laboratory markers of inflammation (mean score = 3.99 and SD = 0.93) and radiology findings (mean score = 3.85 and SD = 1.072). Procalcitonin was rated as the most important among laboratory markers of inflammation (mean score = 3.96 and SD = 1.230 on the 5-point scale), followed by neutrophil count (mean score = 3.71 and SD = 1.039), WBC count (mean score = 3.62 and SD = 1.095) and C-reactive protein (mean score = 3.23 and SD = 1.193). Other responses are listed in Supplement S2.

On the bi-modal 4-point scale, most respondents rated as the highest the need for coverage of atypical pathogens (mean score = 2.8 and SD = 0.99), followed by *Staphylococcus aureus* (mean score = 2.67 and SD = 1.05) and *Pseudomonas aeruginosa* (mean score = 2.13 and SD = 1.07), while MRSA and fungi were not recognized as critical pathogens that should be covered empirically (mean score = 1.95 and SD = 1.02 for MRSA, mean score = 1.51 and SD = 0.83 for *Candida* spp. and mean score = 1.63 and SD = 0.92 for *Aspergillus* spp.).

Antibiotic choices for patients with COVID-19 on the ward and in the ICU are presented in Figures 1 and 2 and Supplement S2.

The mean reported usual duration of antibiotic treatment was 5 days (SD = 1.55) in North America, 5.44 days (SD = 1.67) in the UK, 6.59 days (SD = 2.11) in Spain, 6.87 days (SD = 2.09) in Portugal, 7.2 days (SD = 2.25) in Italy, 7.35 days (SD = 1.37) in Slovenia, 7.63 days (SD = 2.78) in Turkey and 8.47 days (SD = 3.04) in other countries, with a mean of 7.12 (SD = 2.44) for all countries.

Discussion

The results of our survey show that broad-spectrum antibiotic use in patients with COVID-19 is widespread. A recent survey of 203 American physicians showed that antibiotics are very commonly prescribed drugs in patients with COVID-19, second only to acetaminophen.[8] In the patients on the ward, only 29.1% of respondents chose not to prescribe an antibiotic as one of the two options. Such an approach was most common in respondents from Slovenia and was absent in North America. The decision on antibiotic use was based on clinical presentation and less so on laboratory markers or radiology. Among the laboratory markers of inflammation, responders considered procalcitonin as the most important factor to influence antibiotic prescribing decision. The percentage of elevated procalcitonin was reported to be relatively low in a large Chinese series of patients with COVID-19[2] and might be as such a good marker of bacterial superinfection. More studies are necessary in this area.[9] The flora causing bacterial superinfection in COVID-19 is currently unknown and seems to be scarce,[10] but most participants agreed that coverage of agents causing atypical pneumonia and staphylococci is warranted. The coverage of atypical pathogens is not supported by a recent report from North California, USA, showing very few cases of *Mycoplasma pneumoniae* and no infection with *Chlamydia pneumoniae*.[5] The need for an anti-staphylococcal antibiotic may reflect the experiences with bacterial superinfection in influenza that is often caused by *S. aureus*.[11] Participants mostly disagreed with antifungal treatment. In a study from Wuhan, fungi were isolated in 4% of patients and antifungals were prescribed in 15% of cases.[11]

Almost two-thirds of participants reported that they do have local guidelines for antibiotics in COVID-19, but mostly follow regular community-acquired pneumonia guidelines used in their hospitals. In contrast to scarce reports from China,[4] fluoroquinolone use was only popular in Turkey.

Piperacillin/tazobactam was reported as the most commonly used antibiotic overall. Carbapenems and combinations with fluoroquinolones predominated in Italian reports and antibiotics directed against MRSA predominated in North America.

The reported duration of antibiotic therapy in COVID-19 patients was 5 days in the UK and North America, and 7 or

	Country								
	Turkey *n*=46 27.7%	Portugal *n*=25 15.1%	Slovenia *n*=23 13.9%	Spain *n*=22 13.3%	other *n*=19 11.4%	Italy *n*=11 6.6%	North America* *n*=11 6.6%	UK *n*=9 5%	total *n*=166 100%
We do not routinely prescribe antibiotics to the patients in the ward	19.6	40.0	54.5	22.7	31.6	18.2	0	44.4	29.1
Non-pseudomonal β-lactam+β-lactamase inhibitor	0	32.0	50.0	4.5	15.8	9.1	0	0	15.8
Non-pseudomonal β-lactam+β-lactamase inhibitor+macrolide	17.4	48.0	22.7	0	21.1	27.3	0	33.3	21.2
Non-pseudomonal β-lactam+β-lactamase inhibitor+fluoroquinolone	4.3	0	0	4.5	5.3	0	0	0	2.4
Fluoroquinolone	30.4	0	4.5	9.1	10.5	0	0	11.1	12.1
Ceftriaxone/cefotaxime	15.2	0	9.1	13.6	10.5	0	27.3	0	10.3
Ceftriaxone/cefotaxime+macrolide	32.6	12.0	0	45.5	15.8	27.3	63.6	33.3	26.7
Ceftriaxone/cefotaxime+fluoroquinolone	2.2	0	0	9.1	5.3	0	0	0	2.4
Anti-pseudomonal β-lactam	4.3	4.0	13.6	4.5	5.3	0	0	0	4.8
Anti-pseudomonal β-lactam+fluoroquinolone	2.2	0	0	0	0	0	0	0	0.6
Antipseudomonal β-lactam+macrolide	2.2	4.0	0	0	10.5	27.3	9.1	0	4.8
Ceftaroline	0	0	0	0	0	0	0	0	0
Ceftaroline combined with other antibiotics	0	0	0	0	0	0	0	0	0
Other	2.2	4.0	0	4.5	10.5	0	27.3	0	4.8

Figure 1. Percentage of participants prescribing the given group of antibiotics on the ward. Multiple-response categorical variables (up to two responses). Darker colours indicate higher percentages. *USA and Canada.

even 8 in Italy and other non-specified countries with few respondents, respectively.

Recently, a group of authors, members of the ESCMID Study Group for Antimicrobial Stewardship (ESGAP), published a paper warning against non-critical use of antibiotics in COVID-19 patients with some practical recommendations.[12] Some of the findings in our study, such as coverage of atypicals and the duration of treatment, are very much in disagreement with their

	Country								
	Turkey *n*=46 27.7%	Portugal *n*=25 15.1%	Slovenia *n*=23 13.9%	Spain *n*=22 13.3%	other *n*=19 11.4%	Italy *n*=11 6.6%	North America* *n*=11 6.6%	UK *n*=9 5%	total *n*=166 100%
Anti-staphylococcal penicillin+fluoroquinolone	2.2	0	0	0	0	0	0	0	0.6
Ceftriaxone or cefotaxime	10.9	47.6	14.3	47.6	23.5	10.0	40.0	11.1	24.5
Anti-pseudomonal cephalosporin	4.3	0	28.6	4.8	0	10.0	30.0	0	8.4
Ceftaroline	0	0	0	4.8	0	0	0	0	0.6
Piperacillin/tazobactam	63.0	47.6	81.0	23.8	35.3	50.0	1.0	55.6	50.3
Carbapenem	17.4	4.8	9.5	19.0	17.6	30.0	10.0	0	14.2
Fluoroquinolone	4.3	0	0	0	0	0	0	0	1.3
β-Lactam+aminoglycoside	0	4.8	4.8	0	5.9	0	0	11.1	2.6
β-Lactam+fluoroquinolone	0	0	0	14.3	23.5	40.0	0	0	21.3
β-Lactam+colistin	2.2	0	0	0	11.8	0	0	0	1.9
Other	2.2	28.6	19.0	28.6	11.8	20.0	70.0**	33.3	20.0

Figure 2. Percentage of participants prescribing the given group of antibiotics in the ICU. Multiple-response categorical variables (up to two responses). Darker colours indicate higher percentages. *USA and Canada. **'Other' groups of antibiotics prescribed in North America: azithromycin, vancomycin, cefepime+linezolid, ceftriaxone+azithromycin and vancomycin+cefepime.

recommendations. In the current situation with COVID-19 patients overloading our wards and limited knowledge on the aetiology and diagnosis of superinfection more precise guidelines do not seem to be feasible. At the same time we have to be aware of the collateral and long-term consequences of increased use of broad-spectrum antibiotics. Implementation of antimicrobial stewardship principles in COVID-19 patients is urgently needed to mitigate the harm.

Our study has several limitations. The survey was very short, taking into account the workload of physicians caring for COVID-19 patients. The number of respondents is relatively small for the same reason. We used different media to distribute the survey, so we were not able to define the response rate.

At the same time, the report is the first one (to the best of our knowledge) to investigate the antibiotic prescribing practices in patients with COVID-19. Most of the participants were involved in treatment of COVID-19 patients and the report covered a total of 82 COVID-19 hospitals. The study is a real-time and first-hand picture on what is going on in antibiotic prescribing in COVID-19 patients and a stimulus for much-needed research in this field.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Supplementary data

Supplements S1 to S3 are available as Supplementary data at *JAC* Online.

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