**Defined daily dose of antibiotics in elderly patients with COIVD-19 of a hospital in China**

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**Abstract**

**Background.** Defined daily doses (DDDs) are widely used to monitor the utilization of drug. This study aims to explore the clinical utilization of antibiotics in elderly patients with corona virus disease-19 (COVID-19) in order to provide guidance of clinical rational application of antibiotics.

**Methods.** A retrospective analysis method was used to statistically analyze the sales amount, anti-bacterial use density (AUD) and DDDs of antibiotics used by elderly patients with COVID-19 in the First Affiliated Hospital of Wenzhou Medical University from January to April 2020.

**Results.** A total of 63 patients were included, and of which 56 patients were treated with antibiotics. The sales amount of anti-bacterial drugs was 22.70% of total sales amount of medicine. The AUD was as high as 80.23. In addition, the special grade anti-bacterial drugs were used in large amounts, among which cefoperazone sulbactam, moxifloxacin and piperacillin tazobactam were used of top 3

**Conclusion.** The high intensity of anti-bacterial drugs uses in elderly patients with COVID-19 in this hospital might be related to the high proportion of critically ill patients, but it is important to strengthen the anti-bacterial drugs management.

**Keywords.** Defined daily dose; COVID-19; Antimicrobial consumption

**Introduction**

The current epidemic situation of corona virus disease-19 (COVID-19) remains severe. The World Health Organization (WHO) declared it as a “public health emergency of international concern” on 31 January, 2020. Elderly people with underlying diseases are more susceptible to severe illness and are admitted to the intensive care unit (ICU), and the mortality of elderly patients is higher [1]. The underlying diseases include hypertension, diabetes, cerebro-vascular disease and cardiovascular disease [2]. As disease progressed, COVID-19 patients, especially severe and critically ill patients, may suffering secondary infection caused by other pathogen.

The antibiotics empirically used for COVID-19 patients is mainly based on eradication of common pathogens from community sources. For hospital-acquired pneumonia (HAP) / ventilator-associated pneumonia (VAP) patients, the antibiotics are mainly selected the one covering pathogens from hospital sources. Moreover, it is still necessary to avoid blindly or inappropriately use of antimicrobial drugs, especially in combination with broad-spectrum antimicrobial drugs. Reliable statistics on the consumption of antibiotics is useful for performing internal evaluations and making comparisons with others [3-5]. Defined daily dose (DDD), which is determined and updated by WHO Collaborating Centre for Drug Statistics Methodology, was created to provide drug utilization statistics with ultimate goal of improving the rationale use of drug [6]. In order to understand the clinical use of antibiotics in elderly COVID-19 patients, this study analyzed the antibiotics used in elderly patients in a hospital from January to April 2020, which provides valuable information of antibiotic management and promotes the rational use of antibiotics in elderly COVID- 19 patients.

**Methods**

Data for present study were obtained from Hospital Information System of the First Affiliated Hospital of Wenzhou Medical University that provides data of antibiotic prescriptions of hospitalized elderly patients (＞60 years) diagnosed with COVID-19 from January to April 2020. Antibacterial agents in this study were defined according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. The rates of antibiotic consumption were calculated using DDDs as defined by consumption of the antibiotics/DDD. The DDD value was defined according to WHO Collaborating Centre for Drug Statistics Methodology 2019 Guidelines. In addition, the anti-bacterial use density (AUD), defined as average DDDs per 100 patients per day; defined daily cost (DDC), defined as drug cost/ DDDs, which represents the average daily cost of drug; serial number ratio, defined as drug cost rank/ DDDs rank, were used to analyze the utilization of antibiotics in the elderly COVID-19 patients.

**Results**

Demographic data of the 32 adult patients are presented in Table 1. A total of 63 hospitalized COVID-19 patients were admitted, including 40 males and 23 females, with an average age of 70.88 years. The clinical classification was determined according to the Guidelines of Diagnosis and treatment of covid-19 from National Health Commission of China. There were 26 (41.27%) cases of general type, 26 (41.27%) cases of severe ill type, and 11 (17.46%) cases of critically ill type. In addition, 56 patients were received antimicrobial therapy during hospitalization, among which the average time for the first use of antibiotics (from the day of admission) was 0.97 d, which indicated that most elderly COVID-19 patients received antimicrobial therapy immediately after admission.

The cost of antibiotics, DDDs and AUD analysis of patients were shown in Table 2. The data showed that the cost of antibiotics accounts for 22.70% of the total cost of drug consumption. The AUD of the elderly COVID-19 patients is 80.23, while the AUD of antibiotics of this hospital in 2016 is 36.34, indicating that the intensity of antibiotics use in elderly COVID-19 patients is significantly higher than the average level of AUD in the hospital. The reason of high intensity of antibiotics use may be due to the high percent of severe and critically ill patients, and most of them were combined with underling diseases, such as cardiovascular diseases and diabetes.

The hierarchical management of antibiotics is the core strategy of the rationale use of antibiotics, which delays the rising trend of bacterial resistance. According to the safety, clinical efficacy, bacterial resistance and price, the antibiotics are divided into three parts, which was referred to the Chinese Guidelines for clinical application of antibiotics. The results of DDDs and AUD of different grade of antibiotics used in the elderly COVID-19 patients were shown in Table 3. The data showed that the restricted and special antibiotics accounted for 90.88% of all the antibiotics used, of which the restricted antibiotics accounts for 67.43%, indicating that the high ratio of restricted and special restricted antibiotics.

The DDDs, DDC and Serial number ratio of specific antibiotics were presented in Table 4. The largest proportion use of antibiotics is Cefoperazone and Sulbactam for injection (1g), followed by Moxifloxacin for injection (400mg), and Piperacillin and Tazobactam for injection (4.5g). The sum of DDDs of the top 3 used antibiotics accounts for 48.69% of the total DDDs, which indicated that the patients were initially covered with broad-spectrum antibiotics.

**Discussion**

The study showed a high proportion of antibiotics use during hospitalization of elderly COVID-19 patients. In addition, the DDDs of restricted and special-restricted antibiotics accounted for 90.88%, especially cefoperazone sodium sulbactam sodium for injection, moxifloxacin for injection and piperacillin and tazobactam for injection. Among the varieties of antibiotics used, broad-spectrum antibiotics accounted for a relatively high proportion. Although the hospital is a designated hospital for centralized treatment of severe and critically ill patients diagnosed with COVID-19 of the city, the proportion of severe and critically ill patients is as high as 61.9%, the rationale use and management of antibiotics should to be strengthened.

The severe or critically ill COVID-19 patients with opened trachea are often complicated with bacterial or fungal infection in the later period of hospitalization. The bacteriological surveillance may lag behind of antibiotics administration in clinical practice. Patients with potential bacterial infection should start anti-infection treatment immediately after admission, and the timely use of antibiotics can avoid the rapid progress of deterioration of disease. However, by reviewing the published literature associated with COVID-19, we found that there were few cases of COVID-19 combined with bacterial infection [2, 7], which may be related to the failure of the delivery of microbial culture samples. According to the data of 1099 patients diagnosed with COVID-19 in 522 hospitals reported by Guan et al. [2], the proportion of antibiotics consumption was 58.0% (637 / 1099), the proportion of that in severe or critically ill patients was 80.3% (139 / 173). In our study, the proportion of 63 patients diagnosed with COVID-19 who consumed antibiotics was 88.89% (56 / 63). It can be seen that the proportion of antibiotics used in the hospital was higher than others in the same period. Steven et al. [8] commented that it is necessary to conduct antimicrobial management to better support the treatment of COVID-19. The rationale use of antibiotics in patients with COVID-19, especially in severe patients, is a challenge to the current management of antibiotics.

In the early stage of COVID-19 combined with bacterial infection, moxifloxacin can be taken orally. According to the underling diseases and possible pathogens, β-lactamase compounds preparation, such as piperacillin/tazobactam, cefoperazone/sulbactam, carbapenems, linezolid, vancomycin, are available. For patients with secondary fungal infection, antifungal agents, caspofungin and voriconazole are the choice to antifungal treatment [9]. For patients with septic shock, empirical antibiotics can be used before outcome of etiological diagnosis, which should cover the most common *Enterobacteriaceae, Staphylococcus* and *Enterococcal* pathogens at the same time. If the treatment is not work, or the patient is suffering severe septic shock, carbapenem drugs can be used as first-line choice. After screening out the specific pathogen, the use of antibiotics should be adjusted immediately. With the prolongation of hospitalization in severe patients, the risk of bacterial-resistance increased gradually. Therefore, the use of antibiotics should be adjusted according to the drug sensitivity test [9]. In the current study, cefoperazone sulbactam and piperacillin tazobactam consumption ranked top 1 and top 3 of DDDs respectively, which may be related to the high percentage of secondary nosocomial pneumonia in severe and critically ill patients. In addition, the moxifloxacin tablets and injections ranked top 2 and top 4 of DDDs respectively, which may be related to the initial consumption of moxifloxacin in the early diagnosis and treatment of COVID-19.

In general, the proportion of antibiotics used by the elderly COVID-19 patients in the hospital is relatively high. Therefore, we should pay attention to the rational use of antibiotics in the treatment of COVID-19. For the patients with secondary bacterial and fungal infection of COVID-19, it is necessary to strengthen the management of the antibiotics, such as evaluating the efficacy of the patients after 48-72 hours of empirical antibacterial treatment, adjusting the antibacterial treatment plan according to the susceptibility test, to reduce the DDDs of antibiotics and unnecessary consumption of antibiotics.

**Declarations**

**Conflict of Interest**

All authors have no conflicts of interest to disclose

**Author’s contribution**

JP contributed to the conception and design of the work. XY, CZ and YD carried out the data analysis. XY and XW wrote the manuscript. All authors read and approved the final manuscript.

**Tables**

**Table 1. Patient Characteristics**

|  |  |
| --- | --- |
| **Characteristic** | **Valuea** |
| Age (years)  Sex | 70.88 (7.58) |
| Male | 40 (64.49%) |
| Female | 23 (26.51%) |
| Clinical classificationb |  |
| General | 26 (41.27%) |
| Severe ill | 26 (41.27%) |
| Critically ill | 11 (17.46%) |
| Number of patient use antibiotics | 56 (88.89%) |

a Values are mean (standard deviation) or No. (%)

b Determined according to the Guidelines of Diagnosis and treatment of covid-19 from National Health Commission of China

**Table 2 Sales, defined daily doses (DDDs), and antibiotic use density (AUD) of antibiotics used by elderly patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sales of antibacterial drugs /Thousand Yuan | | Total Sales of Drugs/Yuan | Sales Ratio% | Accumulative DDDs | AUD/DDDs·Hundred patients-1·Day-1 |
| 353.4 | 155.67 | 22.70% | 1010.11 | 80.23 |

**Table 3 Analysis of DDDs and AUD of different grades of antibiotics**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Non-restricted antimicrobial agents | | | | Restricted antimicrobial agents | | | | Special restricted antimicrobial agentsa | | |
| DDDs | AUD/  DDDsb | DDDsc Ratio/% | DDDs | | AUD/DDDsb | DDDsc Ratio/% | DDDs | | AUD/  DDDsb | DDDsc Ratio/% |
| 92.10 | 7.32 | 9.12 | 681.11 | | 54.10 | 67.43 | 236.90 | | 18.82 | 23.45 |

aClassfication of different grades of antimicrobial agents was referred to the Chinese Guidelines for clinical application of antimicrobial agents

bHundred Patients-1·Day-1

cAccumulative DDDs

**Table 4 Analysis of DDDs of** **specific antibiotics**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Generic name | ATC Code | Route of administration | DDDs | Sales/Thousand Yuan | DDC/Thousand Yuan | Serial number ratio |
| Cefoperazone and Sulbactam | J01DD62 | P | 189.75 | 36.6 | 1926.8 | 5.00 |
| Moxifloxacin | J01MA14 | P | 179 | 39.2 | 2191.7 | 2.00 |
| Piperacillin and Tazobactam | J01CR05 | P | 123.10 | 47.0 | 3816.4 | 1.00 |
| Moxifloxacin | J01MA14 | O | 100 | 2.2 | 215.7 | 3.50 |
| Meropenem | J01DH02 | P | 68.83 | 28.0 | 4060.8 | 1.20 |
| Ceftazidime | J01DD02 | P | 68.25 | 11.7 | 1720.0 | 1.67 |
| Imipenem and cilastatin | J01DH51 | P | 64 | 17.3 | 2700.0 | 1.29 |
| Fluconazole | J02AC01 | P | 52 | 10.2 | 1956.4 | 1.38 |
| Voriconazole | J02AC03 | P | 32.5 | 62.1 | 19112.9 | 0.11 |
| Linezolid | J01XX08 | P | 25 | 17.6 | 7022.8 | 0.80 |
| Cefixime | J01DD08 | O | 21 | 0.4 | 210.0 | 1.45 |
| Cefaclor | J01DC04 | O | 19.5 | 0.6 | 288.4 | 1.25 |
| Caspofungin | J02AX04 | P | 16 | 23.2 | 14468.8 | 0.54 |
| Vancomycin | J01XA01 | P | 12 | 5.2 | 4292.4 | 0.86 |
| Levofloxacin | J01MA12 | P | 8 | 0.1 | 112.2 | 1.20 |
| Amikacin | J01GB06 | P | 7.2 | 0.1 | 82.5 | 1.19 |
| Polymyxin B | J01XB02 | P | 7 | 48.4 | 69090.0 | 0.12 |
| Amoxicillin | J01CA04 | O | 7 | 0.04 | 42.9 | 1.11 |
| Amoxicillin and Clavulanate | J01CR02 | P | 6.40 | 0.4 | 653.3 | 0.89 |
| Daptomycin | J01XX09 | P | 3.57 | 3.4 | 9483.2 | 0.65 |

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