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Consumption of antibiotics at an Italian university hospital during the early months of the COVID-19 pandemic: Were all antibiotic prescriptions appropriate?

To the Editor

Although coronavirus disease-19 (COVID-19) is caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), broad-spectrum antibiotics are frequently given to COVID-19 patients presenting with fever, cough and lung infiltrates that resemble bacterial pneumonia, but are actually typical manifestations of mild-severe SARS-CoV-2 infection [1].

An Italian study conducted during the early months of the epidemic at a COVID-19 referral centre in Milan, Italy, found that two out of three COVID-19 patients received at least one antibiotic course during their hospital stay [2], and the proportion was even higher (80 %) at a hospital in Barcelona, Spain, [3].

We have now assessed the impact of the COVID-19 outbreak on antibiotic consumption at Luigi Sacco Hospital, a 500-bed university hospital whose 75-bed Infectious Diseases Department was the first COVID-19 referral centre identified in the metropolitan area of Milan, and discuss the possible inappropriate use of antibiotics in the light of emerging evidence of superimposed bacterial infections in patients affected by SARS-CoV-2.

The first COVID-19 patients were admitted to our hospital on 21 February 2020, after which the entire hospital was converted to receive further patients in 328-bed general wards and a 30-bed ICU reaching the maximum capacity by 5 April 2020. The use of antibiotics during March and April 2020 was examined using the Anatomical Therapeutic Chemical (ATC) classification, and the data were compared with those of January-February 2020, January-April 2019, and January-April 2018. Monthly antibiotic consumption was calculated on the basis of defined daily doses (DDD) and normalised per 100 occupied bed days. The normality of the DDD values in the pre-epidemic periods was confirmed using the Shapiro-Wilk normality test, and mean values with standard deviations (SDs) were calculated. Monthly antibiotic consumption in March and April 2020 was compared with that in the pre-epidemic periods, and a change was assumed if the DDD values were more than two SDs from the mean.

Overall antibiotic consumption in March and April 2020 was not different from that in the pre-epidemic period (Fig. 1) but, when considering the antibiotics used to treat community-acquired pneumonia (CAP), it was found that the mean consumption of azithromycin and ceftriaxone in March 2020 was almost double the mean pre-epidemic DDD (15.66 and 20.31 vs 6.14 [SD = 1.6] and 10.55 [SD = 1.3] per 100 bed days), but normalised during April 2020.

The marked increase in the use of azithromycin and ceftriaxone in the early weeks of the COVID-19 epidemic in Italy is similar to that observed by Nestler *et al.* at an 865-bed urban academic medical centre in Virginia, USA, in April 2020 when the epidemic exploded there [4]. A large study carried out at 84 facilities of the Veterans' Health

Administration in the USA also found a significant increase in antibiotic consumption during the period January–May 2020, with the largest increase being observed in the case of the antibiotics used to treat CAP and broad-spectrum antibiotics in general [5].

Ceftriaxone and azithromycin are commonly used to treat CAP, and their increased use in COVID-19 patients may reflect initial concerns regarding possible disease complications due to bacterial superinfections, as has been previously described in the case of influenza and other viral respiratory infection. However, emerging data indicate that community-acquired co-infections are relatively infrequent in hospitalised COVID-19 patients (approximately 3% in a study by Gracia-Vidal *et al.* and 3.5 % in a meta-analysis by Langford *et al.*) [3,6], and so the routine use of broad-spectrum antibiotics for this purpose may far exceed the actual need and unnecessarily expose the patients to unwanted side effects.

It must be mentioned that azithromycin was widely used in combination with hydroxychloroquine in early COVID-19 clinical trials because of its potential anti-inflammatory properties and antiviral activity, although the results suggest that azithromycin does not offer any survival benefit.

Furthermore, the emergency caused by the dramatic surge of COVID-19 cases severely challenged the ability of hospitals to implement or maintain antimicrobial stewardship (AMS) programmes to help physicians reduce inappropriate antibiotic use. AMS requires trained personnel and dedicated infrastructures, and it is clear that these were undermined by the reallocation of resources required by the ongoing epidemic.

It is interesting to note that, like Nestler *et al.* [4], we observed a rapid reversal of azithromycin and ceftriaxone consumption to pre-epidemic values and, albeit in the absence of published reports and clear guidelines, it can be speculated that increasing knowledge of COVID-19 led us to reconsider the empirical use of antibiotics to treat CAP [3]. In our opinion, the main opportunity for reducing inappropriate antibiotic consumption is at the time of hospital admission, when a pre-hospital prescription of empiric antibiotic treatment can be censured or a new prescription avoided in the absence of clear signs of superimposed infection. In this scenario, the principles of AMS should be borne in mind and the collection of microbiological samples should be the standard for ensuring the appropriate use of antibiotics.

In conclusion, in the current context of overloaded front-line physicians, the risk of over-prescribing antibiotics is still real. It is therefore important to continue research in this field in order to develop clear recommendations concerning the use of antibiotics in COVID-19 patients, and every effort should be made to ensure effective hospital AMS programmes that can mitigate the harm caused by their inappropriate use, including antimicrobial resistance.

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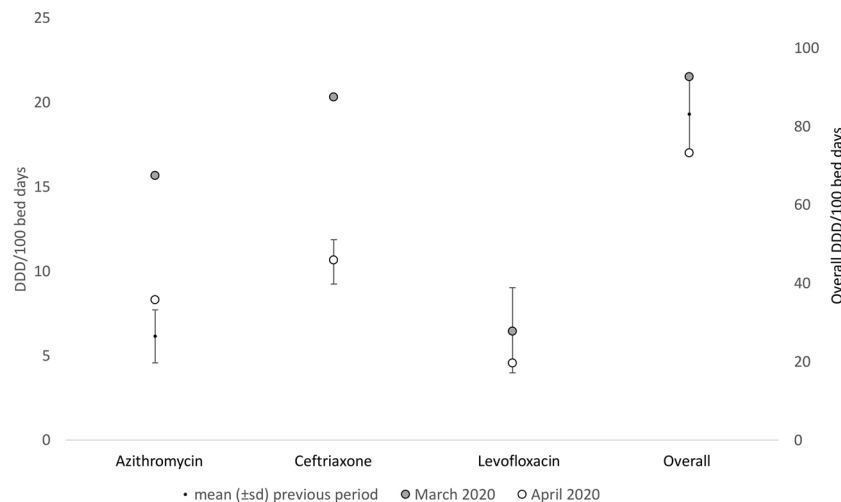


Fig. 1. Antibiotic consumption during the SARS-CoV-2 pandemic months of March and April 2020, and mean antibiotic consumption in the pre-pandemic period, expressed as DDD per 100 bed days.

DDD, defined daily dose; SD, standard deviation.

Authors' contributions

All of the authors were involved in writing this letter, approved the final version as submitted, and have agreed to be accountable for all aspects of it.

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References

- [1] G. Abelenda-Alonso, A. Padullés, A. Rombauts, et al., Antibiotic prescription during the COVID-19 pandemic: a biphasic pattern [published correction appears in *Infect Control Hosp Epidemiol.* 2020 Nov;41(11):1373], *Infect. Control Hosp. Epidemiol.* 41 (11) (2020) 1371–1372.
- [2] A. Giacomelli, A.L. Ridolfo, L. Milazzo, et al., 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study, *Pharmacol. Res.* 158 (2020), 104931.
- [3] C. Garcia-Vidal, G. Sanjuan, E. Moreno-García, et al., Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study [published online ahead of print, 2020 Jul 31], *Clin. Microbiol. Infect.* 27 (1) (2021) 83–88, <https://doi.org/10.1016/j.cmi.2020.07.041>.
- [4] M.J. Nestler, E. Godbout, K. Lee, et al., Impact of COVID-19 on pneumonia-focused antibiotic use at an academic medical center [published online ahead of print, 2020 Jul 23], *Infect. Control Hosp. Epidemiol.* (2020) 1–3.
- [5] T.D. Dieringer, D. Furukawa, C.J. Graber, et al., Inpatient antibiotic utilization in the Veterans' Health Administration during the coronavirus disease 2019 (COVID-19) pandemic [published online ahead of print, 2020 Oct 20], *Infect. Control Hosp. Epidemiol.* (2020) 1–3.

- [6] B.J. Langford, M. So, S. Raybardhan, et al., Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis, *Clin. Microbiol. Infect.* 26 (12) (2020) 1622–1629.

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