was prohibited for at least 1 hour after medication. The same milkylike color of medication prevented the discrimination of if any vomitus.

Third, we investigated whether nonintervention was not inferior to pharmacotherapy in reducing BPD/death. The sample size was calculated using the ibuprofen group as the standard arm, with a 35% expected outcome. The nonintervention approach was not inferior to ibuprofen administration with respect to the incidence of BPD/death because it did not surpass the prespecified 20% noninferiority margin (nonintervention group vs ibuprofen group: 44% vs 51%, lower limit of the 95% CI: −0.09; greater than the noninferiority margin of −0.2).1

Lastly, although the relatively large margin might be a limitation of this trial, the rationale for choosing a 20% margin in this trial was as follows. For statistical reasoning, the 20% noninferiority margin was defined on the basis of the lower limits of the 95% CI (19.8-20.2) for the difference in the BPD/death incidence between the nonintervention (18 of 51 [35%]) and treatment (49 of 89 [55%]) groups in our historical data.4 For clinical judgement, because developing BPD/death could be affected by not only PDA management but also diverse and complex host factors and variations in clinical practice, we assumed that a noninferiority margin of 20% would be clinically acceptable, despite the risk of falsely justifying the efficacy of the nonintervention approach over pharmacologic treatment. To summarize, the nonintervention was not inferior to oral ibuprofen for closing PDA and reducing the BPD/death.

Se In Sung, MD, PhD
Myung Hee Lee, PhD
Won Soon Park, MD, PhD

Author Affiliations: Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (Sung, Park); Statistics and Data Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (Lee).

Corresponding Author: Won Soon Park, MD, PhD, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea (wonspark@sku.edu)


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Why Is Antibiotic Treatment Rarely Performed in COVID-19-Positive Children Admitted in Pediatric Intensive Care Units?

To the Editor Shekerdemian et al1 reported 48 coronavirus disease 2019–positive children (median age, 13 years) admitted to pediatric intensive care units in the US and Canada. Overall, 83% of children were not treated with antibiotics, and 17% had been treated with azithromycin. We deeply reflected on this, especially considering that 83% were also affected by severe comorbidities.

In acute diseases affecting the lungs, such as sepsis or acute respiratory distress syndrome, the lung microbiota is enriched in intestinal bacteria, such as Bacteroidetes and Enterobacteriaceae, triggering a dangerous proinflammatory vicious circle (more gut in the lung).2 In fact, the gut becomes hyperpermeable (leaky gut) and bacteria can move through the colon wall and reach the lung (hypothesis of intestinal lymph), promoting inflammation (with an increase in inflammation markers, such as interleukins 6 and 8, associated with an increased alveolus-capillary permeability), infection, and acute lung damage.3

Recent data suggest a close correlation between the pulmonary microbiota and intensive care unit hospitalization.4 In particular, changes occurring in the lung microbiota can help to predict if and to what extent critically ill patients will respond to the treatment. In a recent study of 91 adult patients, only those colonized in the lung by Enterobacteriaceae in the gut were admitted to the intensive care unit. In addition, patients showing a high number of bacteria in the lungs, and especially a prevalence of typical (good) lung bacteria, showed a better outcome 1 day after intensive care unit hospitalization for respiratory distress syndrome (globally requiring fewer days of ventilation). Contrarily, the presence of 2 groups of bacteria normally colonizing the gut (Lachnospiraceae and Enterobacteriaceae) was common in the lung microbiota of patients with the worst outcome.4

In conclusion, it can be deduced that the bacterial species found in the lung can be predictive of the outcomes. What remains to be understood is whether it is possible to modify the lung microbiota, both to prevent and to treat lung damage. The pathways regarding the gut-lung axis are not fully clear, but it is well known that respiratory tract infections can complicate with gastrointestinal dysfunctions and the other way around: this phenomenon can be also observed in patients with coronavirus disease 2019 infection, as shown in studies performed on cats.5

The action of angiotensin-converting enzyme 2 is influenced by the intestinal microbiota. We believe that for a better outcome, a course of antibiotics effective on intestinal bacteria could be considered, particularly in critically ill children undergoing enteralchelation intubation.3
Vassilios Fanos, MD
Flaminia Bardanzellu, MD
Maria Antonietta Marcialis, MD

**Author Affiliations:** Neonatal Intensive Care Unit, Department of Surgical Sciences, AOUM and University of Cagliari, Monserrato, Italy.

**Corresponding Author:** Flaminia Bardanzellu, MD, Neonatal Intensive Care Unit, Department of Surgical Sciences, AOUM and University of Cagliari, SS 554 km 4,500, 09042 Monserrato, Italy (bardanzellu.flaminia@virgilio.it).

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In Reply We thank Fanos and colleagues for their comments regarding our article and specifically referring to the lack of antibiotic use in our cohort of pediatric patients hospitalized with coronavirus disease 2019 (COVID-19). While they correctly state that alterations in gut permeability and subsequent disturbances in the pulmonary microbiome may contribute to severity of lung injury in patients with acute respiratory distress syndrome, we would like to point out that they may have misinterpreted the specific aims of our investigation.

As described in the Methods section of our article, our objective was to describe pharmacotherapies targeted at modulating the clinical effects of COVID-19 (ie, hydroxychloroquine, azithromycin, remdesivir, and tocilizumab) and not to explore or report antibacterial coverage. Thus, in the Results, where we included a paragraph entitled Targeted Therapies, and in the Discussion, we specifically described only antiviral or immunomodulating therapies. These included hydroxychloroquine and azithromycin that were both being widely used to enhance clearance of severe acute respiratory syndrome coronavirus 2 early in the COVID-19 pandemic, as well as remdesivir and tocilizumab.

Lara S. Shekerdemian, MD, ChB, MD, MHA
Jeffrey P. Burns, MD, MPH

**Author Affiliations:** Texas Children’s Hospital, Baylor College of Medicine, Houston (Shekerdemian); Harvard Medical School, Boston, Massachusetts (Burns).

**Corresponding Author:** Lara S. Shekerdemian, MB, ChB, MD, MHA, Texas Children’s Hospital, 6651 Main St, Houston, TX 77030 (lissheker@texaschildrens.org).

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**Rapid Implementation of Model-Based Dosing Recommendations During the Coronavirus Disease 2019 Pandemic**

To the Editor With great interest, we read the article by Maharaj et al and the accompanying Editorial by Watt.2 We can only applaud the authors, the Pediatric Trial Network, and the journal for showing the pediatric community the added value of modeling and simulation in situations where pediatric data are scarce. We would like to take the opportunity to stress the importance of translating these model-based dosing guidelines to clinical care. Most pediatricians are not familiar with pharmacokinetic articles and may be hesitant to use simulated doses from scientific publications in real-life clinic.

Chloroquine, hydroxychloroquine, and remdesivir were recommended at the start of the pandemic by the Dutch Centre for Infectious Disease Control for both adults and children. Because specific dosing guidelines for children were missing, the Dutch Paediatric Formulary, the nationwide resource for pediatric drug doses, assessed the risk-benefit for pediatric use based on peer-reviewed pediatric malaria and Ebola virus studies, (limited) adult data from patients with coronavirus disease 2019, the adult coronavirus disease 2019 dosing advice, and expert opinion.3 Doses were next published on our website to ensure access to prescribing physicians.

In addition, supported by a recent Bill & Melinda Gates Foundation grant, we used physiologically based pharmacokinetic modeling for the recommendation of pediatric chloroquine doses,4 similar to the approach taken by Maharaj et al.1 As published pediatric pharmacokinetic data were available from studies in patients with malaria, we verified our model for children as young as 6 months old. Two weeks after the publication of the pragmatic best-evidence dose, we replaced the dosing advice with the model-based dose on both our own and on our international affiliates websites.5 Moreover, the European Network of Paediatric Research at the European Medicines Agency shared our dose advice with its members after acceptance of the peer-reviewed publication.

We will now use the above decision framework to evaluate the published doses by Maharaj et al1 and adjust our current doses of pragmatic best-evidence doses of hydroxychloroquine and remdesivir when needed. We hope others will take our example and thereby ensure physicians across the globe have access to pragmatic yet evidence-based dosing information to treat children with the highest chance of an effective and safe therapy. We are curious to learn from the authors how the Pediatric Trials Network supports implementation of dosing recommendations in real-life clinical care.

Saskia N. de Wildt, MD, PhD
Laurens F. M. Verscheidjen, MSc
Tjitske M. van der Zanden, BSc

Letters