Letters

Vassilios Fanos, MD
Flavinia Bardanzellu, MD
Maria Antonietta Marcialis, MD

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

Corresponding Author: Flavinia Bardanzellu, MD, Neonatal Intensive Care Unit, Department of Surgical Sciences, AOU 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 remarks 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,1 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 (lsheker@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 Mahraj et al1 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 Mahraj 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 Mahraj et al1 and adjust our current doses of pragmatic best-evidence doses of hydroxychloroquine and remdesivir as 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. Verscheijden, MSc
Tjitske M. van der Zanden, BSc


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In Reply We would like to thank de Wildt and colleagues for their thoughtful commentary pertaining to our recently published article.1 We agree with the authors, who stressed the importance of translating these model-based dosing regimens toward clinical practice. Additionally, we would like to highlight the critical urgency for prospective randomized clinical trials evaluating the pharmacokinetics, safety, and efficacy of investigational treatments for coronavirus disease 2019 (COVID-19) in children. Such clinical investigations are essential to bridge the gap between simulation-based analyses and clinical practice.

Our model-based investigation was supported by the Pediatric Trials Network (PTN), which represents a consortium of more than 100 clinical research sites across the United States. A primary objective of the PTN is to provide an environment and appropriate infrastructure to support the development of investigations that promote safe and effective drug use in children. Capitalizing on this infrastructure, the PTN has rapidly initiated a clinical study protocol to evaluate the pharmacokinetics, safety, and efficacy of investigational treatments for COVID-19 in children. This protocol is administered under the pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care study (PTN POPS; NCT04278404).2 Based on its opportunistic design, in which children who receive specific drugs of interest as part of their standard medical care are enrolled, the PTN POPS study has successfully been used to collect pharmacokinetic data from more than 3600 children on more than 80 drugs of interest. Pediatric patients receiving investigational COVID-19 treatments by their health care professional are eligible for recruitment into the PTN POPS study. Blood samples collected during the course of routine medical care will be quantitatively analyzed for each drug of interest. The study will also collect information on patient outcomes and adverse drug reactions. Prospective study results will provide a basis to evaluate model-based pharmacokinetic predictions, as well as the safety and efficacy of different investigational treatments for COVID-19 in children. This study will play a critical role to substantiate use of our proposed model-based dosing regimens for routine clinical practice.

In responding to the current pandemic, we must ensure children, who have historically been underrepresented within medical research, are not again left behind. Through collaborative research networks that permit for the rapid development of pediatric clinical investigations, model-based dosing regimens can be systemically evaluated and expeditiously adopted into clinical practice.

Anil R. Maharaj, PhD
Christoph P. Hornik, MD, PhD, MPH
Michael Cohen-Wolkowiez, MD, PhD

Author Affiliations: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada (Maharaj); Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina (Hornik, Cohen-Wolkowiez); Duke Clinical Research Institute, Durham, North Carolina (Hornik, Cohen-Wolkowiez).

Corresponding Author: Michael Cohen-Wolkowiez, MD, PhD, Department of Pediatrics, Duke University School of Medicine, Durham, NC 27705 (michael.cohenwolkowiez@duke.edu).


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