was prohibited for at least 1 hour after medication. The same
milksilk 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 noninter-
tervention approach was not inferior to ibuprofen administra-
tion with respect to the incidence of BPD/death because it did
not surpass the prespecified 20% noninferiority margin (non-
tervention 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 limi-
tation of this trial, the rationale for choosing a 20% margin in
this trial was as follows. For statistical reasoning, the 20% non-
inferiority 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 clini-
cally acceptable, despite the risk of falsely justifying the effi-
cacy of the nonintervention approach over pharmacologic
treatment. To summarize, the nonintervention was not infe-
tior to oral ibuprofen for closing PDA and reducing the BPD/
death.

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patent ductus arteriosus in preterm infants a systematic review and

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

To the Editor Shekerdemian et al 1 reported 48 coronavirus dis-
eease 2019-positive children (median age, 13 years) admitted
to pediatric intensive care units in the US and Canada. Over-
all, 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 se-
vere comorbidities.

In acute diseases affecting the lungs, such as sepsis or acute
respiratory distress syndrome, the lung microbiota is en-
riched in intestinal bacteria, such as Bacteroidetes and En-
terobacteriaceae, triggering a dangerous proinflammatory vi-
cious 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 in-
creased alveolus-capillary permeability), infection, and acute
lung damage. 3

Recent data suggest a close correlation between the pul-
monary 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 re-
spond 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, pa-
tients showing a high number of bacteria in the lungs, and es-
pecially a prevalence of typical (good) lung bacteria, showed
a better outcome 1 day after intensive care unit hospitaliza-
tion for respiratory distress syndrome (globally requiring fewer
days of ventilation). Contrarily, the presence of 2 groups of bac-
teria normally colonizing the gut (Lachnospiraceae and En-
terobacteriaceae) was common in the lung microbiota of pa-
tients with the worst outcome. 4

In conclusion, it can be deduced that the bacterial spe-
cies 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 dam-
age. 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 pa-
tients with coronavirus disease 2019 infection, as shown in
studies performed on cats. 5

The action of angiotensin-converting enzyme 2 is influ-
enced by the intestinal microbiota. We believe that for a bet-
er outcome, a course of antibiotics effective on intestinal bac-
teria could be considered, particularly in critically ill children
undergoing endotracheal intubation. 3
Letters

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3. Fanos V, Pintus MC, Pintus R, Marcialis MA. Lung microbiota in the acute respiratory disease 2019 (COVID-19). While they correctly state about the pertinence 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. 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, similar to the approach taken by Maharaj et al. 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. 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 al 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.

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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.

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