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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

COVID-19 and Children

By Micaela A. Witte and Philip R. Fischer, MD, DTM&H

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Ms. Witte and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: In China, children of all ages have been infected with SARS-CoV-2 and seem to follow a relatively mild clinical course.

SOURCE: Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020. doi: 10.1542/peds.2020-0702. [Epub ahead of print].

In early December 2019, the virus that would come to be known as SARS-CoV-2 started its spread from Hubei province throughout China and eventually the world. By March 2, 2020, there were 80,174 cases of COVID-19 in China alone, with incidence rates growing globally. While research has begun to characterize the epidemiology and clinical features of COVID-19 in adult patients, few studies have examined the epidemiological characteristics in pediatric patients.

Dong and colleagues studied 2,141 patients younger than 18 years of age with suspected (65.9%) or confirmed (34.1%) COVID-19 reported to the Chinese Center for Disease Control and Prevention between Jan. 16 and Feb. 8, 2020, to characterize the epidemiological factors and transmission patterns in pediatric patients with COVID-19. Children were characterized as having suspected COVID-19 if they were high risk (i.e., exposed to a known COVID-19 case) and had at least two of the following features: symptoms (i.e., upper respiratory symptoms, digestive symptoms, fever, or fatigue); laboratory abnormalities (i.e., normal or decreased white blood cell count, increased lymphocyte count, or increased C-reactive protein); or abnormal chest X-ray. Children with medium risk (i.e., those who lived in an epidemic area or community with reported COVID-19 cases) or low risk (i.e., those who lived in a non-epidemic area with no reported COVID-19 cases) were classified as

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having suspected COVID-19 by the same features after ruling out other causes of respiratory infections. Pediatric patients were classified as having confirmed COVID-19 if a nasal, pharyngeal, or blood sample either tested positive for SARS-CoV-2 nucleic acid using real time polymerase chain reaction (RT-PCR) or exhibited highly homologous genetic sequencing with SARS-CoV-2.

The demographic data, location, date of symptom onset, and date of diagnosis were recorded for all confirmed and suspected COVID-19 pediatric cases. In addition, each pediatric case was classified by severity: asymptomatic (i.e., positive SARS-CoV-2 nucleic test without clinical symptoms or chest imaging abnormalities); mild (i.e., symptoms of upper respiratory tract infection or digestive symptoms without auscultory or chest imaging abnormalities); moderate (i.e., lung lesions on chest imaging or more severe respiratory symptoms, such as pneumonia without hypoxemia); severe (i.e., respiratory symptoms that progress to central cyanosis with oxygen saturation less than 92%); and critical (i.e., acute respiratory distress, shock, encephalopathy, myocardial injury, acute kidney injury, or coagulation dysfunction).

A descriptive analysis showed that the median age of these patients was 7 years, and 1,213 patients were male (56.6%). The median time from the onset of symptoms to diagnosis was two days, with most diagnosed within the first week of symptoms. Only 5.9% were classified as severe to critical cases, compared with data showing 18.5% severe to critical cases in adults. Of these severe and critical pediatric cases, 83.2% were suspected cases, with only 16.8% confirmed cases. Furthermore, 4.4% of children were completely asymptomatic.

Young children seemed to be more severely affected than older children, with severe and critical cases making up a larger percentage of their total COVID-19 cases. Specifically, the percentage of severe and critical cases by age range was 10.6% in those < 1 year, 7.3% in those 1-5 years, 4.2% in those 6-10 years, 4.1% in those 11-15 years, and 3.0% in those 16-18 years. There was only one reported death: a 14-year-old boy on Feb. 7. (No further details were given about this individual.)

Modeling of spatial distribution showed the spread from Hubei Province to surrounding areas over time, with the exception of Heilongjiang Province. Furthermore, 45.9% of all pediatric COVID-19 cases were reported in Hubei Province, and 18.5% of all cases were reported in the six bordering provinces.

Modeling of temporal distribution showed a rapid increase in symptom onset since Dec. 26 that peaked around Feb. 1 and was followed by a gradual decline. Diagnoses have continued to rise since Jan. 20, when the first case was diagnosed. On average, the peak in diagnosis lagged behind symptom onset by two to seven days.

In summary, Dong and colleagues found that COVID-19 cases have been reported in all pediatric age groups, with the majority of cases following an asymptomatic to moderate clinical course. The spatial and temporal distribution of these COVID-19 pediatric cases from Hubei Province is similar to that of adult cases.

■ COMMENTARY

In a review of 72,314 COVID-19 cases on Feb. 11, 2020, the Chinese Center for Disease Control and Prevention found that only 1% of all patients were younger than 10 years of age.[1] This reduced vulnerability to infection has been echoed in other studies. For example, a recent report found that of 1,391 children exposed to SARS-CoV-2 and later tested, only 171 (12.3%) were positive for infection.[2]

Currently, it is unknown whether neonates are at risk of vertical transmission. In four recently published studies, only L. Zeng and colleagues reported neonates with positive SARS-CoV-2 testing after delivery to SARS-CoV-2 positive mothers (three out of 33 infants).[3-6] Despite this relatively low rate of positive testing, two studies found that neonates had elevated levels of SARS-CoV-2 antibodies. Specifically, the infant in the case study conducted by Dong and colleagues was positive for both SARS-CoV-2 immunoglobulin G (IgG) and immunoglobulin M (IgM) despite

negative SARS-CoV-2 PCR tests.[5] Similarly, two of the six neonates studied by H. Zeng and colleagues were positive for both SARS-CoV-2 IgG and IgM, and three were positive for IgG.[6] Whether a positive SARS-CoV-2 IgM represents a response to infection or is simply a false positive has not been determined yet.

Furthermore, children who do become infected with SARS-CoV-2 seem to follow a mild course. In the report by Lu and colleagues, 39 (22.8%) of the confirmed COVID-19 cases were completely asymptomatic, although 12 (30.8%) of these children had ground glass opacity on imaging. Only three (1.8%) children (one with intussusception, one with hydronephrosis, and one with leukemia on chemotherapy) had severe symptoms requiring intensive care and ventilation, with one reported death (the child with intussusception).[2] Similar findings have been reported in other Chinese provinces, with one study finding 13% of children (n = 31) to be asymptomatic and another finding 28% asymptomatic. In both of these studies, the remaining children reported mild to moderate symptoms, although six children required supplemental oxygen.[7,8]

Because many of the children with COVID-19 in these reports were suspected cases without confirmatory testing, it is possible that the true population of COVID-19 cases was even milder than reported. This potential case contamination also may explain the discrepancy in the current article by Dong and colleagues, which reported 83% of the severe to critical cases in suspected cases, while only 17% in confirmed cases. Information regarding other risk factors, such as underlying pulmonary pathology and immunocompromised conditions, would further inform conclusions from these data, since these children may be affected disproportionately.[9]

In addition to reduced susceptibility and milder infection, children with SARS-CoV-2 infection may present differently. For example, children with COVID-19 have been shown to have elevated procalcitonin levels, a finding that has not been reported in adults.[3,7,8,10] Specifically, Xia and colleagues found that 80% of affected pediatric patients had elevations in procalcitonin, and Qui and colleagues found that procalcitonin levels greater than 0.5 ng/mL predicted a more aggressive clinical course.[8,10] Furthermore, Xia and colleagues found that 50% of patients had consolidation with halos reported on imaging. The authors believe this finding may be related to coinfection, since 40% of patients were infected with at least one other pathogen (i.e., cytomegalovirus, influenza A, influenza B, respiratory syncytial virus, or mycoplasma).[10] Supportively, in an earlier study conducted in Norway, 68.1% of hospitalized children with coronavirus were infected with at least one other pathogen.[11]

These features suggest a modified response to infection in children. However, the mechanism for a different and generally mild COVID-19 course in the pediatric population is not well understood. Dong and colleagues hypothesized that it may have to do with social factors, such as children being more likely to stay home and, thus, having less exposure. They also listed potential physiological factors, such as children having immature ACE2 enzymes, which are thought to serve as receptors for SARS-CoV-2, and a more active immune system with higher antibody levels due to a higher frequency of infection.

With the large proportion of asymptomatic cases, children may greatly affect viral transmission.[2,7] Furthermore, research conducted by Jiehao and colleagues found that children may have prolonged nasal and fecal shedding of SARS-CoV-2. Specifically, the average length of time for continued SARS-CoV-2 RNA on nasopharyngeal swab after symptom onset was 12 days. At the time of their publication, the five out of six patients who initially tested positive for fecal SARS-CoV-2 RNA continued to test positive on days 18-30 after symptom onset.[12]

The work of Dong and colleagues provides valuable information regarding the spread and severity of COVID-19 in the pediatric population. Specifically, through their large sample of patients, they were able to track many of the COVID-19 pediatric cases in China and quantify the severity of their symptoms. However, more research regarding the susceptibility, physiologic response, and treatment of SARS-CoV-2 in children is needed. ■

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ABSTRACT & COMMENTARY

Malaria Prophylaxis During Pregnancy

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: In a retrospective study of American military women involving 50 treated with atovaquone-proguanil and 156 exposed to mefloquine, no increase in risk of fetal loss or adverse infant outcomes was identified. Atovaquone-proguanil seems safe for use in pregnancy, but data are limited.

SOURCE: Gutman JR, Hall C, Khodr ZG, et al. Atovaquone-proguanil exposure in pregnancy and risk for adverse fetal and infant outcomes: A retrospective analysis. *Travel Med Infect Dis* 2019;32:101519.

Gestational malaria is associated with significant risks to both the mother and the baby. Travel by pregnant women to malaria-endemic areas is not always avoidable. Chloroquine has been used widely in pregnancy without evidence of adverse effects, but it is ineffective against the malaria found in many parts of the world. Mefloquine is thought to be safe in pregnancy, but resistance is increasing. The typical expert advice is to avoid atovaquone-proguanil during pregnancy because of an uncertain safety profile, but the actual risks are unknown.

Gutman and colleagues reviewed data from 198,164 pregnancies of U.S. military women from 2003 to 2014. During that time, 50 women received atovaquone-proguanil during pregnancy, 156 received mefloquine, and 131 received chloroquine. Those who received atovaquone-proguanil were older and more likely to be in the first trimester of pregnancy (since the treatment policy was not to use atovaquone-proguanil when the woman was known to be pregnant).

Women receiving atovaquone-proguanil or mefloquine demonstrated no increased risk of either pregnancy loss (spontaneous abortion, stillbirth) or adverse infant outcome (preterm birth, small for gestational age, large for gestational age, or birth defects). Although the differences were not statistically significant, miscarriage and stillbirth were seen in 28% of women treated with atovaquone-proguanil and 16% of those treated with mefloquine. Pregnancy loss was seen in 6.1% of women treated with chloroquine. Statistically, the use of chloroquine was protective against pregnancy loss.

The authors summarized their findings by saying that a true assessment of the safety of atovaquone-proguanil was not possible with the small number of women included in the study. They suggested that further observational studies be done but, because of concerns for risk, they do not advocate for a randomized prospective study.

■ COMMENTARY

Pregnant women are at particular risk of contracting malaria. With pregnancy, women produce more exhaled carbon dioxide and release different concentrations of transcutaneous substances, making them more attractive to mosquito chemoreceptors.[1] In addition, related to pregnancy-induced changes in immunity and specific parasite-placenta interactions, pregnant women are at risk of severe malaria and serious consequences of malarial infection.[2]

Malaria is dangerous for pregnant women and their babies. Mothers risk pregnancy loss, severe illness, anemia, premature labor, and death.[1] Babies born to women with gestational malaria are at increased risk

of congenital malaria, low birthweight, neonatal fever, neonatal death, infantile anemia, infantile malaria, and death during the first year of life.[3]

Thus, it is wise to try to prevent malaria during pregnancy.[4] For women who must be in areas where malaria is endemic, mosquito bites should be avoided by wisely using insecticide-impregnated clothing to cover skin, insect repellents such as diethyl-meta-toluamide (DEET) or picaridin, and insecticide-impregnated bed nets. Behaviorally, pregnant women also can try to stay away from areas where *Anopheles* mosquitoes are active, especially during evening and night hours. In addition, because of the risk of malaria and its severe consequences, they should take chemoprophylaxis.

There are several sorts of malarial prevention medications.[4,5] Chloroquine remains effective in parts of Central America but not in most other malarial areas of the world. Mefloquine is effective in most malarial areas, but it does cause bothersome side effects (nausea, unpleasant dreams) in nearly one-fifth of those who take it. It should not be used in those with active seizure disorders, cardiac rhythm disturbances, and psychiatric conditions. Atovaquone-proguanil is expensive but usually is well-tolerated and was the focus of Gutman's study. Doxycycline usually is avoided during pregnancy because of concerns about altered bone and tooth development in the growing fetus, but experts in some countries accept its use, when truly necessary, during pregnancy.[5] Finally, primaquine (like the new similar medication tafenoquine, see the February 2020 issue of *Infectious Disease Alert*) can be used to prevent malaria, but it carries a risk of triggering hemolysis in those with glucose-6-phosphate dehydrogenase deficiency (such as untested but affected fetuses). This summary of malaria preventive treatments serves as a reminder that atovaquone-proguanil, although incompletely tested, is the only agent without significant, proven risk (even though it is expensive). Thus, it was very helpful for Gutman and colleagues to try to determine through a retrospective observational study if atovaquone-proguanil actually is safe in pregnancy.

Previously, a study of 149 Danish women inadvertently exposed to atovaquone-proguanil during early pregnancy showed no unusual risk of birth defects.[6] A retrospective review and a systematic review provided some (incompletely conclusive) optimism for the safety of atovaquone-proguanil.[7,8]

How should we interpret and apply the findings of the new study by Gutman and colleagues? Certainly, we can agree with the authors that the number of subjects was small and that a significant risk still could exist below the level of statistical significance of this study. Further studies are warranted.

At the same time, there are reasons to believe that the increased incidence of fetal loss with atovaquone-proguanil (28%) vs. mefloquine (16%) was not only statistically insignificant but, even if it is significant in larger studies, it likely is related to separate factors. First, the women in Gutman's study who received atovaquone-proguanil were older overall than the women who received mefloquine, and twice as many were older than 35 years of age. Older age during pregnancy can be associated with increased risks.

Second, more of the atovaquone-proguanil exposed women were in their first trimester of pregnancy, and essentially all were unaware of their pregnancy at the time of treatment. Miscarriage is most common during the first trimester, and it could be that the timing of treatment (earlier, first trimester), rather than the treatment itself, could prompt the women in the atovaquone-proguanil group to have more miscarriages than those in the mefloquine group. Finally, it is not clear whether the women receiving atovaquone-proguanil might have been visiting geographical areas or participating in activities (such as brief, dangerous missions) during deployment that might have increased the risk of fetal loss separate from the medication use.

Thus, the new study from Gutman provides reassurance that even more data demonstrate no significant risk of poor outcomes related to the use of atovaquone-proguanil during pregnancy. However, that reassurance is incomplete since some risk still could exist for an individual traveler. We must mitigate risk wisely by using non-pharmacologic protection against mosquito bites and by carefully considering the risks and benefits as we make specific chemoprophylaxis recommendations for women who are pregnant or might become pregnant during travel to malarial areas.

Statistically, the finding that chloroquine protected against pregnancy loss is fascinating. The authors attributed this protection to the known anti-inflammatory properties of chloroquine. Although no one should suggest using chloroquine to prevent miscarriage, pregnant travelers to areas of the Caribbean and Central America where malaria is sensitive to chloroquine certainly can use chloroquine with confidence. ■

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ABSTRACT & COMMENTARY

Differentiating *Clostridioides difficile* Infection from Chronic Carriage in Patients with Diarrhea Through Host Inflammatory Markers

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Dr. Watkins reports no financial relationships relevant to this field of study.

SYNOPSIS: Investigators compared levels of inflammatory markers in patients with *Clostridioides difficile* infection (CDI) to those who were colonized with *it*. Several markers appeared to be able to distinguish true CDI, although a gold standard definition of CDI is needed.

SOURCE: Kelly CP, Chen X, Williams D, et al. Host immune markers distinguish *Clostridioides difficile* infection from asymptomatic carriage and non-*C. difficile* diarrhea. *Clin Infect Dis* 2020;70:1083-1093.

Diagnosing *Clostridioides difficile* infection (CDI) is a frequent conundrum. In clinical practice, diarrhea is a common symptom with myriad etiologies, and testing for CDI using nucleic acid amplification tests (NAATs) can be confounded by those who are asymptomatic carriers of *C. difficile*. Indeed, the diagnosis can be especially challenging when colonized patients have certain underlying conditions, such as inflammatory bowel disease or irritable bowel syndrome. Kelly and colleagues sought to identify specific biomarkers that differentiate a patient with CDI from one with the combination of diarrhea and *C. difficile* colonization.

The participants in the study were inpatients ages 18 years or older. They were divided into four cohorts that included presumed CDI, defined as new-onset diarrhea and a positive NAAT; a carrier-NAAT, defined as a positive NAAT without diarrhea; a negative NAAT with diarrhea; and a negative NAAT without diarrhea. The negative NAAT, no diarrhea cohort was originally screened as eligible for the carrier-NAAT cohort (i.e., admitted for less than 72 hours, received at least one dose of antibiotic within the preceding seven days, and did not have diarrhea in the 48 hours prior to stool sample submission), but the submitted stool sample tested negative by NAAT. Patients were excluded if they had a colostomy, received a drug to treat CDI for more than 24 hours in the preceding seven days, had been diagnosed with CDI in the previous six months, or had tested negative for CDI in the preceding seven days.

The investigators obtained discarded serum samples drawn within one day of the stool sample collection. They measured multiple analytes, including serum cytokines, antitoxin A and B levels, and stool levels of calprotectin, toxin A and B, and antitoxin B. Also, serum albumin values within five days before and two days after stool collection were recorded.

There were 122 stool samples in the CDI-NAAT cohort; 44 in the carrier-NAAT group; 44 in the diarrhea, negative NAAT group; and 50 in the no diarrhea, negative NAAT group. Two additional cohorts were the CDI-Tox20 (n = 79), which included subjects who were positive by both NAAT and single molecule array for toxin A + B, and carrier-Tox20 (n = 34). The demographic and baseline laboratory values were similar between all the cohorts, except

for significantly lower median albumin levels in the CDI-NAAT and CDI-Tox20 cohorts. Interestingly, the mean white blood cell (WBC) count was highest (12.5 × 10^9/L) in the no-diarrhea, NAAT negative group. Median values for 11 of the analytes were significantly greater ($P < 0.05$) in the CDI-NAAT group compared to the carrier-NAAT group. Of these, granulocyte colony-stimulating factor (GCSF) most clearly differentiated the CDI-NAAT group from the other cohorts, with an area under the receiver operating curve of 0.842. There were no significant differences in GCSF levels when the non-CDI cohorts were compared to each other. The other analytes that distinguished the CDI-NAAT cohort from the others, albeit less strongly, included IL-6, TNF-α, and IgG antitoxin A in blood, and IgA and IgG antitoxin B in stool.

■ COMMENTARY

The current testing paradigm for CDI at many hospitals, wherein a positive NAAT test is followed by the more specific toxin assay, is being questioned increasingly. This is because of recognition that many hospitalized patients are asymptomatic carriers of toxigenic strains of *C. difficile*. Thus, it is incumbent on clinicians to recognize when patients need treatment, but importantly, when they do not. The study by Kelly and colleagues is interesting because it found several immune markers, particularly GCSF, that potentially could be developed into tests that differentiate true CDI from colonization. Notably, the patients in the carrier-NAAT cohort all were hospitalized, making it reasonable to assume they would have had elevated levels of inflammatory markers.

Yet, the study raises almost as many questions and it answers. The fundamental problem is that no gold standard exists to diagnose CDI. The authors presumed that all patients with diarrhea and a positive NAAT had true CDI, which may not have been totally accurate. Furthermore, there was not a cohort of patients with diarrhea and a positive NAAT whose diarrhea ultimately was found to be from a different etiology than CDI. Thus, we are left to wonder what their levels of inflammatory markers would have been. Another issue is the finding that serum albumin levels were lower in the CDI-NAAT cohort. How this may have affected the levels of inflammatory markers is unclear.

Developing specific laboratory tests to distinguish CDI from colonization is an important goal. Kelly and colleagues have made important progress in this regard. However, many issues remain to be elucidated, including whether the inflammatory markers they identified can be used to determine which patients will go on to develop severe, complicated, or recurrent CDI. A gold standard definition for CDI remains elusive, but we are getting closer. ■

ABSTRACT & COMMENTARY

Evaluation of 2020 Vancomycin Guidelines: Highlights, Limitations, and Obstacles

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Dr. Meng reports no financial relationships relevant to this field of study.

SYNOPSIS: The key change from the 2009 vancomycin guidelines is the switch from trough-based to area under the curve (AUC)-based dosing and monitoring. This article will highlight key differences between the 2009 and 2020 guidelines, limitations of the new guidelines, and implementation issues.

SOURCE: Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2020 Mar 19. pii: zxaa036.

The switch from trough-based dosing to area under the curve (AUC)-based dosing for vancomycin was driven by recent evidence showing that trough values are a poor surrogate for AUC values, and may lead to unnecessary nephrotoxicity when targeting trough values of 15 mg/dL to 20 mg/dL.

The 2020 guidelines now recommend targeting a vancomycin AUC to minimum inhibitory

Table 1. Comparison of 2009 and 2020 Vancomycin Guideline Recommendations (Adults)[1,2]

	2009 Guidelines[2]	2020 Guidelines[1]
Recommended monitoring parameter	Target troughs 15-20 mg/L as surrogate marker for PK/PD target ($AUC_{24}/MIC_{BMD} \geq 400$) if MIC ≤ 1 mg/L for complicated infections (bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*) Avoid troughs < 10 mg/L	Target AUC_{24}/MIC_{BMD} 400-600 in suspected or definitive serious MRSA infections (assume vancomycin MIC_{BMD} of 1 mg/L), preferably in the first 24-48 hours of therapy. Do not decrease dose if $MIC_{BMD} < 1$ mg/L.
Method of therapeutic drug monitoring	No routine monitoring of peaks Trough prior to next dose at steady state (before 4th dose)	Preferred: Bayesian software, using 1-2 vancomycin concentrations, with at least one trough, but preferable two levels Alternatively, collection of two concentrations (peak and trough), preferably during the same dosing interval, utilizing first-order PK equations
Dosing weight	Actual body weight	Actual body weight
Loading dose (complicated infections in seriously ill patients)	25-30 mg/kg	20-35 mg/kg, max: 3,000 mg Obese: 20-25 mg/kg, max 3,000 mg
Continuous infusion regimens	No recommendations	Continuous infusions as alternative if AUC cannot be achieved with intermittent dosing; target level 20-25 mg/L

PK = pharmacokinetic; PD = pharmacodynamic; AUC = area under the curve; MIC = minimum inhibitory concentration; BMD = broth microdilution; MRSA = methicillin-resistant *Staphylococcus aureus*

concentration (MIC) measured by a broth microdilution (BMD) (AUC: MIC_{BMD}) ratio of 400-600 for both adults and children. (*See Table 1.*) This narrow range balances efficacy with toxicity thresholds. Data point to increased nephrotoxicity risk at vancomycin AUCs ranging 563 mg·h/L to 1,300 mg·h/L, but converge around 650 mg·h/L.

The preferred method of estimating vancomycin AUC is by using Bayesian software programs based on one to two (preferably two) serum concentrations. Bayesian software uses individual patient data together with a population pharmacokinetic (PK) model (ideally in a similar patient population) to predict an optimal dosing regimen. Some advantages include:

- ability to use pre-steady-state vancomycin concentrations;
- fewer drug levels;
- Bayesian models continuously learn; incorporates real-time individual patient data and can inform subsequent dosing.

Alternatively, the AUC may be calculated using two steady-state concentrations, usually a peak and trough concentration, drawn during the same dosing interval, and using first-order PK equations.

In contrast to the 2009 guidelines, the updated 2020 guidelines include expanded guidance on special populations, including obese, dialysis, and pediatric patients.

■ COMMENTARY

The generally accepted PK/pharmacodynamic (PD) parameter for vancomycin's efficacy (AUC/$MIC_{BMD} \geq 400$) is based nearly exclusively on retrospective, observational studies in methicillin-resistant *Staphyloccocus aureus* (MRSA) bacteremia, except for a few in pneumonia and one in infective endocarditis.[1] Studies on osteomyelitis and meningitis are notably missing. Thus, the 2020 guidelines only address serious infections caused by MRSA. The authors cautioned against extrapolating to infections due to methicillin-susceptible *S. aureus* (MSSA) strains, coagulase-negative staphylococci, enterococci, streptococci, and other pathogens. It is important to achieve PK/PD targets early in the course of vancomycin therapy, often prior to culture and MIC results. However, if vancomycin is continued in a patient for a non-MRSA infection, these guidelines do not directly address their management. Most patients ultimately do not have a MRSA infection. In one study on AUC-based vancomycin dosing, 42% of the study population had an infection with a gram-positive organism, but only 10% were MRSA.[5] For non-*S. aureus* isolates, investigators targeted an AUC of 400 mg·h/L regardless of the MIC. In a separate publication, the lead guideline author recommended targeting a vancomycin AUC of 400-600 mg·h/L regardless of MIC or organism treated.[6]

While Bayesian software programs allow for accurate, individualized dosing with as few as one vancomycin concentration (possible with a population PK model with richly sampled PK data from a similar population as your institution's), obstacles to implementation include high cost, specialized training required, and informatics resources to integrate software with existing electronic medical records. Many hospitals have created homegrown spreadsheet calculators to calculate AUC values based on two concentrations using the linear-trapezoid rule. Both dosing methods are accurate and precise, with a median error of < 2%.[7,8] These methods of vancomycin dosing will take additional resources to implement in the inpatient and outpatient parenteral antibiotic therapy (OPAT) setting.

The 2020 guidelines dance around the dosing issues around MRSA isolates with a vancomycin MIC_{BMD} = 2 mg/L. On one hand, they argue that automated susceptibility testing methods are imprecise, but they state that alternative therapy should be considered since AUC/MIC targets may not be safely achieved. This conflicts with Infectious Diseases Society of America (IDSA) MRSA treatment guideline recommendations that for susceptible MRSA isolates, "the patient's clinical response should determine the continued use of vancomycin, independent of the MIC."[9]

Overall, these guidelines address many of the gaps in the 2009 guidelines. Additional research is needed for optimal vancomycin dosing in patients receiving extracorporeal membrane oxygenation, those with infections of the central nervous system, and infections due to non-MRSA organisms such as *Streptococcus* spp. and coagulase-negative *Staphylococcus*. Optimal dosing regimens still are unknown for obese populations and patients with renal insufficiency.

Implementation of vancomycin appropriateness criteria and early vancomycin de-escalation efforts, such as with the use of negative nasal MRSA polymerase chain reaction in suspected MRSA pneumonia,[10] may circumvent unresolved vancomycin monitoring issues. Avoidance of vancomycin is another alternative, as emerging data suggest a promising role for early stepdown to oral antibiotics in serious gram-positive infections traditionally treated with intravenous therapy.[11-13] ■

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Updates

By Carol A. Kemper, MD, FACP

Masking Our Anxiety

SOURCE: Klompas M, Morris CA, Sinclair J, et al. Universal masking in hospitals in the Covid-19 era. *N Engl J Med* 2020. doi:10.1056/NEJMp2006372.

Sitting in the intensive care unit (ICU) last week across from one of our renal specialists, who was adjusting her mask and complaining that it sure was uncomfortable to wear all day, I inquired why she was wearing it, then. She seemed puzzled, and responded, "Because of coronavirus." I had to tell her, she was not really protecting herself, she was protecting me. She said, "So, why am I wearing it, then?"

Experts are divided as to whether all healthcare workers (HCWs) — nay, everyone on the planet — should be wearing a mask. After a local academic center announced their universal mask policy last week, our facility felt arm-twisted into proceeding with similar guidance for our HCWs to mask in clinical areas. But when is it logical to initiate such a measure for HCWs? The pros and cons for this measure are as follows:

Pros

• Psychological benefit to the wearer. This is really the whole ball game. Right or wrong, people are psychologically more *comfortable* wearing a mask right now, allowing them to better focus on their jobs, even if they are physically more *uncomfortable*. Unfortunately, masks are a component of full personal protective equipment (PPE), including gowns, gloves, and face shields, and by themselves may provide minimal protection to the wearer.

• By wearing a mask, you are helping to protect those around you. Data suggest that a mask reduces the risk of potential transmission from an asymptomatic or minimally symptomatic HCW to fellow workers and patients, although it is unclear to what degree such individuals may contribute to overall transmission.

• Reduced stigmatization for those wearing a mask who come to work with minimal or ambiguous symptoms. At least they feel more *comfortable* donning a mask if everyone else is.

Cons

• Masks are a valuable resource. Until sufficient masks are available for every HCW, every day, they should be conserved for more necessary duties.

• Is it rational (or even ethical) for me to wear a mask every day to work when colleagues in New York are at risk for running out of PPE? I do not feel *comfortable* with this.

• Masks are *uncomfortable*. Data suggest mask wearers touch their face and mask more often than those without a mask. And, requiring employees to don a mask only in clinical areas guarantees they will be donning and doffing that mask all day, putting it down on a surface, or stuffing it in their pocket during lunch. Like clothing, I bet by the end of the shift, that mask will be covered with various bacteria, viruses, etc.

• If the goal is to reduce transmission to other employees, why is it recommended to remove the mask in nonclinical areas?

• On the other hand, if the goal is to reduce transmission to patients, then why are many hospital workers with limited or no contact with patients wearing a mask?

• Will it be practice or policy for HCWs to wear a mask in the healthcare environment? Is this one more thing a hospital is supposed to enforce? Just as there are some HCWs who desperately want to wear a mask, there are some who do not. Can you force them to wear a mask?

I do not see where personal comfort enters into this discussion. Good healthcare must be rational and based on sound principles, not fear. There must be some balance between the prevalence of disease in the population, the risk of transmission from asymptomatic individuals, and disease severity that leads to this decision. It feels like this decision is just masking our anxiety.

Is it Luck or Genetics?

SOURCE: Deng X, Gu W, Federman S, et al. A genomic survey of SARS-CoV-2 reveals multiple introductions into Northern California without a predominant lineage. https://doi.org/10.1101/2020.03.27.20044925.

On Feb. 26, 2020, our facility, located in Santa Clara County, CA, diagnosed the second case in the United States of community-acquired SARS-CoV-2 infection in a 68-year-old woman, admitted to the intensive care unit (ICU) five days earlier with progressive respiratory failure. This case prompted the Centers for Disease Control and Prevention (CDC) to expand testing to hospitalized patients with acute respiratory failure of uncertain cause (e.g., no known exposure by travel or close contact with another patient with confirmed SARS-CoV-2). The patient had been cared for in our ICU for five days,

requiring bilevel positive airway pressure (BiPAP) with no precautions. A total of 82 staff were exposed to this patient, many of whom had high-risk exposure, including 32 nurses, 14 respiratory therapists, and eight physicians (including two intensivists, one pulmonologist, and several hospitalists). Only one of these individuals (1.2%), a nurse in the step-down ICU unit who cared for the patient on her first night of admission, subsequently developed symptoms on day 9 post-exposure, and tested positive for SARS-CoV-2. No one in her family developed symptoms or became positive. Two other staff who were exposed to the patient developed some symptoms (upper respiratory infection symptoms in one, and sore throat in the other) and both tested negative.

Since then, none of our healthcare staff have been diagnosed with SARS-CoV-2 infection related to a known workplace exposure, although sporadic exposures here and at other facilities have occurred (we are surprised at how many healthcare workers [HCWs] work in multiple facilities.) Stanford Occupational Health recently performed SARS-CoV-2 nasopharyngeal testing on 1,200 of their staff with their home-based assay, and 2.8% were positive, with most exposed at home within family clusters.

How have we been so lucky in our area with such minimal HCW exposure? Our local experience seems different from that described in Washington state or New York — or Italy — where reports of HCW infection seem more frequent. Washington experienced the first large community outbreak of infection, extending from their first identified case on Jan. 19 in a patient from Wuhan, China. This outbreak had serious consequences for HCWs at a local nursing facility. Since then, the vast majority of cases in Washington state have shared a strain of SARS-CoV-2 now recognized as the WA1 lineage, consistent with persistent community transmission of this dominant viral strain.

Perhaps the answer is there is more than one strain of SARS-CoV-2 in circulation in different areas, and some are more transmissible than others. Deng and colleagues analyzed nasal swab specimens from 29 patients diagnosed with SARS-CoV-2 infection throughout Northern California between Feb. 3 and March 15, 2020. The 29 individuals came from nine different counties, including San Francisco, San Mateo, Santa Clara, Sonoma, and Solana counties. Nine samples came from passengers and crew aboard two Princess cruises in February and March. Fourteen of the samples came from people without a source of transmission by travel history or an identified confirmed contact. Three samples came from Solano County, including the first case of community transmission with respiratory failure of uncertain cause and two HCWs; a husband and wife in San Mateo with infection; another case from San Mateo in a recent traveler from Switzerland; a cluster of five cases in Santa Clara County thought to be related to workplace exposure over a two-week period; one case in Sonoma; and several others. Metagenomics sequencing with spiked primer enrichment was used to enrich and assemble viral genomes directly from the clinical specimens, and these were compared phylogenetically with 342 SARS-CoV-2 genomes logged into the GISAID as of March 17.

Interestingly, the nine sequenced genomes from crew members and passengers aboard the two Princess cruise ships clustered within the WA1 lineage. Virus from the infected passengers on the second cruise shared two mutations with virus obtained from a passenger on the first cruise, suggesting that virus was passed from passengers to crew, and then on to passengers on the second cruise. Their WA1 virus appeared to originate in Washington state.

The three Solano cases had their own distinct cluster, separate from the WA1 lineage, confirming transmission of infection from the patient to the two HCWs. The husband and wife in San Mateo County shared their own virus, which was distinct from other recognized clusters. Several other cases and their contacts were more closely related to non-WA1 ancestral SARS-CoV-2 lineages observed in China. In contrast, the strain from the single San Mateo County traveler from Switzerland fell into sequences commonly seen in Europe. Interestingly, three further viral genomes from Northern California patients also fell within a viral lineage observed in Europe, including an individual recently returned from a trip to New York.

The Santa Clara County cluster was surprising. Three of the employees in the building each had a distinct strain of virus; one of these shared their virus with two household contacts, and these three made their own cluster distinct from any of the other strains observed in the database. This indicates that three genetically distinct SARS-CoV-2 viruses were introduced into the same building within a two- to three-week period. Virus from a patient in Solano County fell within this distinct cluster of three cases, although no recognizable link could be established between these individuals.

In contrast to the dominant WA1 virus circulating in Washington state, this phylogenetic data beautifully demonstrates that at least eight different lineages of SARS-CoV-2 were identified in individuals diagnosed during a six-week period in February and March in Northern California. This strongly suggests the separate introduction of multiple different strains

throughout the Bay Area and Northern California counties. In contrast, the dominant strain in Washington is the WA1 strain with sustained community transmission, and obviously has involved HCWs. This must be a more transmissible strain. The WA1 strain has become distinctly recognizable by its three key single nucleotide variants, and is now being observed in other states, such as Utah, Illinois, and Minnesota. It would be of interest to re-examine a larger number of samples from individuals in Northern California to see if some of these observed strains were epidemiological dead-ends.

Neurologic Infection from SARS-CoV-2

SOURCE: Poyiadji N, Shahin G, Nourjaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020. doi: 10.1148/radiol.2020201187.

Cases of suspected neurologic involvement from SARS-CoV-2 have been few. Many clinicians involved in the treatment of the earliest cases of SARS-CoV-2 have described unremarkable spinal taps and negative central nervous system imaging, even in patients with altered mental status.

One case stands out: A 55-year-old airline attendant was admitted to the hospital in Detroit with three days of fever, cough, and altered mental status. An initial CXR was unremarkable, and all relevant bacterial and viral studies were negative. During the initial course of hospitalization, a nasopharyngeal swab for SARS-CoV-2 was positive. A traumatic lumbar puncture was difficult to interpret, but viral studies for varicella zoster virus, herpes simplex virus, and West Nile virus were negative. Magnetic resonance imaging showed dramatic changes with T2 Flair hyperintensity within the medial temporal lobes and thalami with evidence of focal areas of hemorrhage and rim enhancement. It is believed this is the first case of acute necrotizing hemorrhagic encephalopathy from SARS-CoV-2 infection. I understand she eventually developed evidence of progressive respiratory involvement and radiographic abnormalities. ■

CME QUESTIONS

1. Which of the following statements is true regarding COVID-19 in children?

a. It is less severe than in adults.

b. It is more contagious than in adults.

c. It is rarely asymptomatic.

d. It is never fatal.

2. Which of the following is correct regarding the new guideline on vancomycin therapeutic drug monitoring?

a. The measurement of trough concentrations remains the preferred method.

b. The use of the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio is not readily adaptable for use in hospitals.

c. If AUC estimation is performed, an AUC/MIC (with the MIC measured by broth microdilution) of 400-600 should be targeted.

d. Targeting an AUC/MIC ratio of 400-600 is associated with greater nephrotoxicity than simple use of trough concentrations.

3. Which of the following is correct?

a. The detection of *Clostridioides difficile* toxin gene in the stool of a patient with diarrhea is definitive demonstration that the organism is causing infection rather than simple colonization.

b. There remains no gold standard for routine diagnosis of *Clostridioides difficile* infection.

c. In the study by Kelly et al, the mean peripheral white blood cell count was highest in the group with diarrhea and a positive test for *Clostridioides difficile* toxin gene.

d. In the study by Kelly et al, the serum biomarker with the greatest correlation with presumed *Clostridioides difficile* infection was granulocyte colony-stimulating factor.

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