Multidrug-Resistant Infections

The Underlying Threat of Multidrug-Resistant Pathogens in the COVID-19 Era

Over half of patients admitted with positive SARS-CoV-2 testing received antibiotics, but evidence of bacterial infection is uncovered in far fewer cases. We may already be seeing the effects of antibiotic overprescribing.

by Eli Goshorn, MD

During the COVID-19 pandemic, hospitals witnessed mixed results in the onset of methicillin-resistant Staphylococcus aureus (MRSA) colonizations; whereas, some medical centers saw increases, others observed decreases of MRSA among inpatients.

Recognizing and treating sepsis promptly saves lives. Some suggest that every patient admitted to the hospital for COVID-19 has sepsis secondary to COVID-19 infection. Conventional

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Emerging & Re-Emerging Infections

Considering Mandatory COVID-19 Vaccination Policies for Students

by JESSICA MALATY RIVERA, MS, and KATRINE WALLACE, PHD

A

mid the emergence of SARS-CoV-2 variants such as Omicron and its more transmissible sibling, BA.2, it is the strong recommendation of both the American Academy of Pediatrics,

Stewardship & Prevention

COVID-19 Impact on Antimicrobial Stewardship: Consequences and Silver Linings

by Anna Zhou, PharmD, BCIDP; Richelle L. Guerrero-Wooley, MD; and Karen Tan, PharmD, BCIDP

The COVID-19 pandemic has resulted in almost 470 million confirmed cases and over 6 million deaths worldwide. Consequently, health care providers (HCPs) in both outpatient and inpatient settings have had to adjust their workflow and keep up-to-date with
Two Years of COVID-19: What Have We Learned?

In the spring of 2020, Americans witnessed the beginning of the COVID-19 pandemic. Little did we know at the time, it would touch everyone’s lives. The ensuing months brought a collective despair as more people succumbed to the virus and as clinicians and investigators grappled with treatment and trying to navigate the evolving research.

Two years later, we are still dealing with the effects of it. Although the virus is evolving and our knowledge of it is changing, we have learned some important lessons along the way.

As such, Contagion® has dedicated this entire issue to discussing COVID-19 through the perspective of being 2 years in. Our authors have provided insights on lessons learned and important issues we still need to sort out.

For the former, Renslow Sherer, MD, and his coauthors discuss how our experiences with HIV can help inform our next steps in the development of best care and prevention practices for people with COVID-19. For the latter, epidemiologists Jessica Malaty Rivera, MS, and Katrine Wallace, PhD, have a thoughtful discussion of COVID-19 vaccination policies for students.

We are 2 years in, but we are still not completely out of the woods. Although we are in a period of relative quiet when it comes to caseloads, people are still getting COVID-19, and at this writing, confusion is ongoing over masking.

Nonetheless, I hope you find this issue filled with insights on this topic that remains a part of our lives, 2 years and counting.

Thank you for your continued support of the publication, and please be sure to reach out to our editors with ideas and feedback on all things Contagion® and on how we can continue to improve and serve your needs to help you provide optimal care.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®
EDITOR-IN-CHIEF LETTER

An Issue About COVID-19

I just had the refreshing experience of my first in-person infectious diseases meeting since 2019. It was wonderful catching up with colleagues and friends that I haven’t seen in years, but it was also nice to talk infectious disease outside of COVID-19.

Well, I’m afraid that this edition of Contagion® is dedicated to just that. We are marking over 2 years since the disease began its domination of our lives, inboxes, and literature. Each Contagion® section is dedicated to this topic.

In Acute Infections, Maureen McElligott, MD; Alice Gallo de Moraes, MD; and Kelly Cavcutt, MD, describe the complex issues that sepsis in patients with COVID-19 represents. Although much has been learned about this issue, complications with antibiotic use, infection control, and appropriate use and interpretation of laboratory results remain issues that clinicians in the intensive care unit confront.

In Multidrug-Resistant Infections, Eli Goshorn, MD, describes the continued issue of multidrug-resistant organisms in patients with COVID-19 and the often-contrary literature around the topic.

For HIV, Jina Saltzman, PA-C; Caroline Teter, PA-C; Renslow Sherer, MD; and David Pitrik, MD, write an intriguing comparison of what HIV teaches us about COVID-19. I believe you will enjoy the perspective they bring, using a retrospective lens to remind us of history’s lessons and how they inform the future. I appreciate this—as the need to learn and take notes during the beginning of the pandemic was the first editor-in-chief column that I wrote about COVID-19.

In Antimicrobial Stewardship and Prevention, Anna Zhou, PharmD, BCIDP; Richelle L. Guerrero-Wooley, MD; and Karen Tan, PharmD, describe the multitude of impacts that COVID-19 has had on antimicrobial stewardship programs (ASP). They take us through both the obvious (burnout) and subtle (multidisciplinary collaboration) effects resulting from working on the pandemic together. If anyone has the bandwidth to conduct a before-and-after survey of what ASPs look like after the peak phases of the pandemic pass, it could be revealing.

In Emerging and Re-emerging Infections, Jessica Malaty Rivera, MS, and Katrine Wallace, PhD, discuss mandatory vaccine policies for students. This topic may heat up in the future as vaccines hopefully become available for young children soon and as emergency use authorizations for other age groups become full approvals.

Finally, for News and Breakthroughs, I wrote about the experience of developing treatment guidelines for COVID-19 “on the fly.” This piece covers not only how it was (and is) done, but also how to read and use the guidelines from the Infectious Diseases Society of America by hopefully providing a translation from “ guideline-ese” to English.

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS
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Regdanvimab—A New Attack of the (Mono)Clones

by MONICA V. MAHONEY, PHARM.D., BCPS, BCIDP, FCCP†

As new variants of the SARS-CoV-2 virus emerge, it is imperative that novel, active therapeutics are available for treatment or prevention. Regdanvimab (CT-P59) is a neutralizing antibody that was studied in a phase 2/3 trial (NCT04602000) in outpatients with mild to moderate infections of COVID-19. Results from part 1 of the study, regarding SARS-CoV-2 suppression and patient effects for 180 days after administration, are currently available.

Patients were enrolled between October and December 2020 if they were 18 years or older, had an oxygen saturation of greater than 94% on room air, did not require supplemental oxygen, and received a diagnosis of mild to moderate COVID-19. Patients were within 7 days of symptom onset and within 48 hours of fever, cough, shortness of breath, sore throat, body aches, or headache. Patients were randomized to regdanvimab 40 mg/kg, regdanvimab 80 mg/kg, or placebo. The study drug was infused intravenously over 90 minutes. The primary end points were time to conversion to negative nasopharyngeal swab (day 28) and time to clinical recovery (day 14). Secondary end points included requiring hospitalization and/or requiring oxygen therapy and/or death due to COVID-19. Sample size estimates predicted 100 patients in each arm to achieve statistical significance with 80% power.

Baseline demographic and disease characteristics were well matched. Patients were mostly white adults aged 51 to 52 years old, with 88% enrolled from European countries. Approximately 55% to 60% had moderate COVID-19, with 88% enrolled from European countries. Most patients were white adults aged 51 to 52 years old, with 88% enrolled from European countries. Approximately 55% to 60% had moderate disease, with 70% possessing risk factors for progression to severe disease.

There were no differences among groups for time to conversion to negative polymerase chain reaction, set at a threshold of less than 2.33 log10 copies/mL. When the threshold was set to less than 3.0 log10 copies/mL, the regdanvimab groups achieved negativity approximately 3 days faster. Additionally, more participants in the regdanvimab groups achieved negative conversion by days 14 and 28 than those in the placebo group. Median time to recovery was shorter in the regdanvimab groups than those in the placebo group (5.7 vs 8.8 days).

Regdanvimab reduced the proportion of patients who required hospital admission, supplemental oxygenation, and rescue therapy. The medications were well tolerated, with similar proportions reported in each group (25%-30%) and no all-cause mortalities. Low percentages (4.5%-6.7%) were attributed to the study drug, and no participant discontinued therapy because of adverse effects. One infusion-related reaction was reported in the regdanvimab 40 mg/kg group and 2 were reported in the placebo group.

These results are promising, but as this study was conducted prior to the authorization of vaccines, the entire study population was unvaccinated. The benefits seen in a vaccinated population can be assumed to be fewer. This was also prior to the emergence of several virulent strains, such as Delta and Omicron. Additional in vitro simulations predict regdanvimab would retain activity against Delta but not Omicron.

Regdanvimab may have limited use against current circulating strains, but this pandemic has proven it is nearly impossible to predict the next iteration of the virus. A mutation may create a variant that is once again susceptible to some of the previous therapeutics. Therefore, the results of part 2 of this study and the phase 3 portion that examines the clinical effects of regdanvimab are eagerly awaited.

If proven effective against future SARS-CoV-2 variants and authorized to treat COVID-19, regdanvimab would expand the options available to clinicians and patients. However, administration may be challenging. Because regdanvimab is intended for outpatients, developing protocols and finding locations where patients with active COVID-19 infections can acquire this intravenous infusion is key. Finding clinicians who can administer the product may also be a challenge, as the health care workforce has been stretched thin. Although the 9th Amendment to the Public Readiness and Emergency Preparedness (PREP) Act authorized pharmacists to administer approved COVID-19 therapeutics, they were limited to oral, intramuscular, or subcutaneous routes of administration. Even if regdanvimab was proven to be effective, pharmacists would be barred from ordering and administering this therapy.

References are available at ContagionLive.com.

Table. Primary and Secondary Outcomes of Regdanvimab vs Placebo in Mild to Moderate COVID-19 in Outpatients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Regdanvimab 40 mg/kg (n = 100)</th>
<th>Regdanvimab 80 mg/kg (n = 103)</th>
<th>Regdanvimab groups combined (n = 203)</th>
<th>Placebo (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end points: Negative PCR to day 28 (threshold, 2.33 log10 copies/mL)</td>
<td>12.8 (9.0-12.9)</td>
<td>11.9 (8.9-12.9)</td>
<td>12.7 (9.0-12.8)</td>
<td>12.9 (12.7-13.9)</td>
</tr>
<tr>
<td>Time to negative result, median (95% CI), days</td>
<td>5.3 (4.0-6.8)</td>
<td>6.2 (5.5-7.9)</td>
<td>5.7 (5.2-6.8)</td>
<td>8.8 (6.8-11.6)</td>
</tr>
<tr>
<td>Recovery by day 7, n/N (%)</td>
<td>53/94 (56.4)</td>
<td>46/92 (50.0)</td>
<td>99/186 (53.2)</td>
<td>37/99 (37.4)</td>
</tr>
<tr>
<td>Recovery by day 14, n/N (%)</td>
<td>72/94 (76.6)</td>
<td>72/92 (78.3)</td>
<td>144/186 (77.4)</td>
<td>63/99 (63.6)</td>
</tr>
<tr>
<td>Recovery by day 28, n/N (%)</td>
<td>82/94 (87.2)</td>
<td>79/92 (85.9)</td>
<td>161/186 (86.6)</td>
<td>71/99 (71.7)</td>
</tr>
<tr>
<td>Secondary end points:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring hospitalization or oxygen therapy, n (%)</td>
<td>4 (4.0)</td>
<td>5 (4.9)</td>
<td>9 (4.4)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Hospital admission, n (%)</td>
<td>4 (4.0)</td>
<td>5 (4.9)</td>
<td>9 (4.4)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Oxygen therapy, n (%)</td>
<td>4 (4.0)</td>
<td>4 (3.9)</td>
<td>8 (3.9)</td>
<td>9 (8.7)</td>
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<tr>
<td>Mechanical ventilation, n (%)</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (0.5)</td>
<td>0</td>
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<tr>
<td>Rescue therapy, n (%)</td>
<td>7 (7.0)</td>
<td>11 (10.7)</td>
<td>18 (8.9)</td>
<td>15 (14.4)</td>
</tr>
<tr>
<td>ICU transfer, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>All-cause mortality, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Any adverse event, n (%)</td>
<td>31 (29.5)</td>
<td>27 (24.5)</td>
<td>58 (27.0)</td>
<td>34 (30.9)</td>
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<tr>
<td>Adverse event leading to discontinuation, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related adverse event, n (%)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

ICU, intensive care unit; PCR, polymerase chain reaction.
Pharmacotherapy Options for COVID-19: Does Fluvoxamine Have a Place in Therapy?

by SHANE J. SOFTY

Availability of COVID-19 vaccinations has been an issue for many regions of the world affected by the pandemic.1 Barriers to access and concerns over the vaccination continue to enable the development of viral mutations, whereas overall rates of vaccination have continued to stall.1 The need for safe and effective treatment against the various strains of COVID-19 increase, and investigators continue to assess various pharmacologic options. Antivirals and immunologic therapies that had shown efficacy in trials have continued to diminish in efficacy as mutations emerge.2 Other pharmacologic options studied have failed to show any clinical benefit for patients.3 Finding medications that have clinical efficacy continues to be of the highest importance.

Reis and colleagues evaluated the clinical efficacy of fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) and a c-1 receptor agonist, at reducing the progression of COVID-19 to hospitalization.4 The appeal of medications in these classes include the widespread availability and affordability of these agents, alongside the well-documented safety profile.5 It is hypothesized that fluvoxamine could prove efficacious because of its anti-inflammatory and possible antiviral effects.6 A smaller, placebo-controlled trial found that higher-dosed fluvoxamine reduced hospitalizations and requirements in supplemental oxygen among mildly symptomatic, outpatient adults.7

The TOGETHER trial (NCT04727424) evaluated several repurposed pharmacologic therapies against COVID-19 in a multiarm, 1-to-1, placebo-controlled, double-blinded, randomized clinical trial among 11 sites in Brazil. Patients met criteria for inclusion if they were older than 18 years of age, had a positive SARS-CoV-2 diagnostic test at screening or within the previous 7 days, and had presented to an outpatient care clinic for COVID-19 symptoms, beginning within the previous 7 days. Patients were required to be unvaccinated and have a high-risk condition, including diabetes, hypertension requiring medication, cardiovascular disease, certain respiratory conditions (including asthma and smoking), a body mass index greater than 30 kg/m², stage 4 or 5 chronic kidney disease, immunosuppression, or current or recent cancer. Patients were excluded if they required hospitalization for COVID-19, had an illness caused by other viral pathogens, had an inability to use SSRIs, or had dyspnea attributed to another acute or chronic lung disease, such as decompensated chronic obstructive pulmonary disease.8

Patients were randomly assigned to start fluvoxamine 100 mg twice a day for 10 days or matching placebo, along with standard-of-care therapies for symptom management in both arms. The primary outcome of interest was a composite endpoint of medical admission to a hospital setting for COVID-19, defined as an observation period lasting 6 or more hours in the emergency department or any referral for hospitalization within 28 days of randomization. Secondary end points of interest included associated times of disease progression or resolution, safety and tolerability of the trial medication, and clinical monitoring of disease severity.9 A total of 1497 participants were recruited and randomized to fluvoxamine (n = 741) or placebo (n = 756). Patients were randomized, on average, at 3.8 days of symptoms (standard deviation, 1.87). The study’s intention-to-treat analysis found a significant reduction in the primary composite end point, attributed to the need for retention in the emergency setting for at least 6 hours (Table). The calculated number needed to treat (NNT) was 20 patients. All other secondary end points were unchanged compared with placebo. Rates of treatment-emergent adverse events did not differ significantly between fluvoxamine and placebo.4

The authors concluded that fluvoxamine may have a place in therapy for the management of outpatient, unvaccinated adults with COVID-19 infection to reduce the progression to hospitalization.4 The authors also call on subsequent research to establish whether these effects are an SSRI-class effect or related to fluvoxamine alone.4 Although fluvoxamine shows some statistical significance in reducing hospital setting visits, it appears this clinical benefit is limited to unvaccinated patients requiring extended stays in the emergency department, not those admitted to the hospital. Rates of hospitalization and death did not differ in the intention-to-treatment population, although there was a statistical decrease in death in the per-protocol population.5 Some retrospective reviews have found reduction in mortality, but the benefit appears modest in this analysis.7 A recent commentary on outpatient therapeutics estimated that at a 5% risk of hospitalization, fluvoxamine had the lowest NNT at 80 patients and lowest total drug cost of $1122.8 There are also differences in the prescribing patterns of antidepressants in different parts of the world that would influence the generalizability of this trial.9,10 SSRIs continue to show promise for partial management of COVID-19, and ongoing clinical trials will help identify its place in therapy.11

References are available at ContagionLive.com.
The first study to estimate how the COVID-19 pandemic affected life expectancy found that global life expectancy declined by 0.92 years from 2019 to 2020 and 0.72 years from 2020 to 2021. The study was authored by Patrick Heuveline, PhD, a professor of sociology and associate director of California Center for Population Research at UCLA in Los Angeles, and published in Population and Development Review. Heuveline reported that this was the first decrease since the United Nations (UN) began estimating life expectancy in 1950. From 1950 to 2019, decreases in mortality were rare and localized, such as in Cambodia in the 1970s or Rwanda in the 1990s; however, these were counterbalanced by mortality increases elsewhere.

Period life expectancy at birth is commonly used to indicate mortality conditions. The COVID-19 pandemic was the first time that yearly life expectancy declined by more than 2 years in at least 50 countries. The UN estimated that from 1950 to 2019, global life expectancy increased 45.7 years without interruption, at an average increase of 0.39 years annually. The smallest gain was during the AIDS pandemic, during which annual increases dropped to 0.2 years.

The world’s life expectancy appeared to stabilize in the last quarter of 2021, although Heuveline noted, “The plateau in global life expectancy reached during the last quarter of 2021 is far from a global trend and results instead from a diminishing impact of the pandemic in some countries and a still-increasing impact on some other countries.”

Data were not reliably recorded for all countries, with most high-quality vital statistics coming from approximately 40 upper-middle-income to high-income countries and, thus, skewing the results. “While imperfect, extant estimates suggest that the number of excess deaths might be 2 to 4 times the number of deaths officially attributed to COVID-19,” Heuveline wrote. “The bulk of these excess deaths likely occurred outside of Europe and the other high-income nations, in which the mortality impact of the pandemic has been extensively documented.” Indeed, Heuveline’s research showed that COVID-19 may have had a greater impact on Asian and African countries, specifically Egypt, India, Kazakhstan, Lebanon, South Africa, Tunisia, and the Philippines, vs Western European nations like Italy, Spain, and the United Kingdom.

“The COVID-19 pandemic was the first time that yearly life expectancy declined by more than 2 years in at least 50 countries.”

Because the UN had anticipated a 0.18-year gain in global life expectancy from 2019 to 2020, the COVID-19 pandemic resulted in life expectancy being a full 2 years lower than its expected level. Because COVID-19 mortalities are still increasing in some populations, even as they decrease in others, Heuveline concluded, “It would certainly appear unwise at this point to claim that the impact of the pandemic on the global life expectancy has peaked.”
Data Show “Long COVID” Affecting More Women Than Men

By TODD SHRYOCK

An analysis from FAIR Health Inc and Morning Consult shows a wide gender divide when it comes to suffering from “long COVID,” with women and girls making up 60% of privately insured patients with long-haul COVID-19. Researchers, however, don’t understand why this gender dynamic exists.

The data don’t reflect the racial or ethnic breakdown of long-COVID cases, but lawmakers, patient advocates, and clinicians are concerned that people of color could be disproportionately affected by the condition.

The Biden administration has taken note, releasing a government-wide action plan for long COVID that includes efforts to account for its impact on hard-hit, high-risk populations.

Yet without official data, there are still more questions than answers on why certain groups are being affected by long COVID. The FAIR Health analysis highlights that doctors and researchers are only beginning to scrape the surface in measuring the toll that long COVID is taking on Americans.

An estimated 23 million Americans have been marked by long COVID, a nebulous illness with a wide range of symptoms that can linger for months, or even years, after someone first gets COVID-19. In addition, new, exclusive data show that although some patients are affected more than others, the condition is taking a toll across ages and genders.

Among the privately insured, nearly 35% of long-COVID patients are aged 36 to 50 years and approximately 32% are aged 51 to 64 years, the claims data show. Notably, approximately 1 in 10 privately insured long-COVID patients are younger than 23 years.

A Third of Patients With COVID-19 Report Persistent Symptoms 6 Months After Illness

By JONNA LORENZ

Approximately 33% of patients with COVID-19 still experience persistent symptoms an average of 6 months after the onset of their illness, according to findings from a small study by the University of Washington.

The longitudinal, prospective cohort study, published in JAMA Network Open, included 177 people who completed follow-up questionnaires between 31 and 300 days after illness onset at an average of 169 days.

“The primary take-home message is that even in relatively young, healthy individuals and even in those who have a mild case of COVID-19, symptoms can last for months after infection and can adversely impact quality of life,” coauthor Denise J. McCulloch, MD, MPH, infectious disease fellow at the University of Washington, told Contagion®.

Most of those surveyed—150 (84.7%)—were outpatients who reported mild symptoms, 11 (6.2%) were asymptomatic, and 16 (9%) were hospitalized with moderate or severe illness.

People 65 years and older were most likely to report persistent symptoms (43.3% of 30 patients), followed by those aged 40 to 64 years (30.1% of 83) and those aged 18 to 39 years (26.6% of 64).

Deep Dive: Deep Dive into Pre-Exposure Prophylaxis Monoclonal Antibodies

Monoclonal antibodies have become a beacon of hope for patients at high risk of COVID-19 who may not have a full response to the vaccines, or for whom vaccination isn’t an option.
Taking It as It Comes: Creating Evidence-Based Guidelines During a Rapidly Changing Pandemic

By JASON GALLAGHER, EDITOR IN CHIEF, PHARM.D, FCCP, FIDP, FIDSA, BCPS

COVID-19 has been quite an educator. One of its lessons has been a work in progress on how clinicians keep up-to-date on best practices while dealing with the sheer volume of studies about the disease. Fortunately, many groups have created guidelines to treat COVID-19, including individual hospitals, government organizations like the National Institutes of Health, and professional organizations such as the Infectious Diseases Society of America (IDSA). No organization can claim a “best” guideline, but because I have had the experience of serving on the IDSA guideline panel for the past 2 years, I would like to explain how these guidelines have been developed “on the fly” and how the recommendations are formulated.

HOW THEY ARE DONE

The IDSA guideline panel consists of a mix of clinicians and methodologists. The clinicians are a mix of physicians and pharmacists, with expertise in infectious diseases, microbiology, pediatrics, and critical care. The methodologists serve as experts in research design and analysis and construct the evidence summaries for clinical questions as they develop. Some of these questions are natural, such as when novel therapies are made available by emergency-use authorization or when arms or analyses of landmark trials are completed. Others are prompted by panel members themselves. Meetings occur on a generally biweekly basis using video conferencing software.

The literature evaluated is primarily randomized controlled trials (RCTs) when they are available, but other types of studies are considered when RCTs are not available or when the alternative design appropriately supplements RCTs, such as real-world safety studies. Peer-reviewed publications are, unsurprisingly, preferred, but the panel also evaluates data in preprints. When press releases are the only data available, preliminary assessments are made, sometimes with the benefit of additional data.

The methodologists create evidence summaries and synthesize clinical questions by PICO format (population, intervention, comparison, and outcomes) using GRADE (grading of recommendations assessment, development, and evaluation working group) methodology. If data from more than 1 trial are available with comparable outcomes, the data are analyzed together. This evidence is reviewed by panelists before meetings and discussed during them, often leading to a recommendation.

Only clinical panelists vote on recommendations, and the language is specific (Table). The term “recommend” is a strong one, made only when the panel believes that both the evidence is of sufficient quality and that the recommendation could be reasonably adapted into policies. The term “suggest” is used when the evidence is not sufficiently strong to justify a recommendation (such as due to fragility of the effect found) or when the intervention is one that patients may reasonably refuse. Thus far, the high threshold for a recommendation has limited this level to only one positive recommendation—the use of glucocorticoids for patients with critical COVID-19 disease.

Admittedly, the guidelines are not the most user friendly. Because COVID-19 is a novel disease and each therapeutic has been studied compared with standard of care, each PICO is written as a comparison between the agent and not receiving the agent. This makes many of the recommendations read as binary, without the nuances that clinicians consider in their patient evaluations. Clinical questions are more along the lines of “How should I treat this patient with COVID-19 who requires supplemental oxygen?” than “Should remdesivir (Veklury) or not remdesivir be given to patients who require supplemental oxygen?” With few exceptions, COVID-19 therapies have not been studied comparatively, so choosing therapies to preferentially recommend is difficult and is done, instead, by strength of evidence and quality of data.

Another area in which miscommunications occur is in the use of therapies in combination. As the science of studying therapies during the pandemic has progressed, combination therapies have been studied more frequently as comparisons with standard-of-care regimens, strengthening the ability to recommend them. However, important deficits in the knowledge base about combination therapies remain, and the guidelines largely eschew recommendations about them where those deficits exist. Because the guidelines take an evidence-based approach, recommendations are dependent on the evidence generated.

The guidelines are quite long, keep growing, and will hopefully continue to grow with the evaluation of successful therapies. Most people look no further than the recommendations and possibly the remarks, but reading the narrative is important when these recommendations do not line up with preexisting expectations or are not sufficiently clear. The evidence summary shows the data the panel used to determine its recommendation and is included near the end of each section, showing not only the data from the studies themselves, but the determination of the strength of those data, the risk of bias from the study design(s), and the certainty that the effects seen are real.

How to Read Them

“With few exceptions, COVID-19 therapies have not been studied comparatively, so choosing therapies to preferentially recommend is difficult and is done, instead, by strength of evidence and quality of data.”
Clinicians commonly note that “guidelines are not rules” but that people often treat them that way. The oft-mentioned phrase in guidelines that they do not substitute for clinical judgment is important though, in ways that I did not appreciate before serving on the guideline panel. First and most obviously, not every patient’s nuance will make it into a clinical trial. The recommendations made are for the broad base of patients with COVID-19—and plenty of exceptions exist. For example, patients with deficient antibody response may benefit from antiviral and antibody therapies in later stages of disease than the majority of patients enrolled in studies.

It is also important for guideline readers to realize that therapies that are not explicitly recommended in guidelines may have utility for some patients. For a therapy to reach the level of a guideline recommendation, it needs a sufficient evidence base for a judgment to be rendered. Now that effective therapeutics exist, if a promising but incompletely studied therapy is recommended before sufficient evidence justifies its use, then people may utilize it in lieu of one with greater evidence, potentially causing harm. However, that does not mean those therapies are not good choices for individual patients, and the lack of a recommendation for them does not mean they should be avoided.

Finally, the panel is careful to avoid making recommendations against therapies when clinical trials are continuing to explore their utility. Negative recommendations are made when the totality of evidence leads to a conclusion that a therapy is ineffective. However, new evidence can change a recommendation, particularly when populations studied are refined to those most likely to benefit.

DIFFICULTIES WITH THE GUIDELINES PROCESS
Creating guidelines during a pandemic has been a continuous work in progress. Although the guidelines are a living document, parts can inevitably grow stale as the pace of SARS-CoV-2 and COVID-19 therapies change. A notable example of this is the recommendation for neutralizing antibody therapies, for which literature evaluated becomes out-of-date quickly as variants evolve and become less (or more) susceptible to various monoclonal antibodies. To date, the panel has taken the position of recommending that local variants are considered when these therapies are chosen instead of trying to keep up with the rapid changes being seen. Another major challenge is keeping up with the sheer volume of literature generated about COVID-19 therapy. Fortunately, the methodologists consistently review for updates, and most major studies and therapies receive the attention of multiple panel members as well.

SUMMARY
The guidelines are a document that, although not without flaws, have hopefully helped guide treatment decisions that have aided numerous patients with COVID-19. The panelists are some of the most dedicated people with whom I have had the pleasure of working, and they are committed to the improvement of our collective work.

References are available at ContagionLive.com.
Opposing Forces During COVID-19: Perspective From the ICU

Conflicting priorities of infection control, antimicrobial stewardship, and critical care make the management of sepsis secondary to SARS-CoV-2 infection challenging.

(continued from cover page)

Maureen McElligott, MD; Alice Gallo de Moraes, MD; and Kelly Cawcutt, MD, MS

Conventional sepsis has focused heavily on bacterial infections, providing less guidance regarding the management of viral infections, including COVID-19.

wisdom has taught us that antibiotics are ineffective for viral infections, but conventional sepsis has focused heavily on bacterial infections, providing less guidance regarding the management of viral infections, including COVID-19.

DIAGNOSIS OF PNEUMONIA

Classically, pneumonia is diagnosed based on clinical symptoms coupled with a new infiltrate on an imaging study; however, this alone does not distinguish viral from bacterial pneumonia, particularly in COVID-19 infection. Early on, it was particularly challenging to determine if COVID-19 infection with or without secondary bacterial pneumonia was present due to the lag time in results from COVID-19 tests. This challenge continues to be exacerbated in hospital courses complicated by acute respiratory distress syndrome, pulmonary embolism, volume overload, and risk of nosocomial infection.

Consequently, antibiotics are often administered amid diagnostic uncertainty for refractory hypoxia and fevers because it remains difficult to determine if the cause is bacterial colonization, ventilator-associated pneumonia, a pulmonary embolism, or simply worsening COVID-19 when a patient is too unstable to travel for more definitive chest imaging.

Bronchoalveolar lavage would have been a welcome tool to evaluate for infection, but this was frequently limited...
due to risk of aerosol generation and the potential transmission of COVID-19, particularly early in the pandemic when personal protective equipment was limited and transmission was not fully understood. Instead, we relied on chest x-rays, blood cultures, urinalyses, sputum cultures, and tracheal aspirates to identify a possible infection.

**ISSUES WITH SEPSIS MANAGEMENT/SURVIVING SEPSIS GUIDELINES**

Earlier versions of the Surviving Sepsis Campaign COVID-19 guidelines recommended administering 30 mL/kg of crystalloid in patients with septic shock and elevated blood lactate levels. However, fluid resuscitation in some patients resulted in volume overload with resultant pulmonary edema, which increased the complexity of providing supportive care, particularly among those with acute respiratory distress syndrome. The Surviving Sepsis Campaign guidelines for COVID-19 primarily were composed of 9 strong recommendations, 6 of which were centered on principles of ventilation, along with many weak recommendations. Even with the updated guidelines, no guidance was given on the use of antibiotics in patients with COVID-19.

Many clinicians underestimated the impact of hypoxia on serum lactate levels in COVID-19 infection and overvalued procalcitonin, leading to the overuse of antibiotics. The role of procalcitonin in COVID-19 infection remains unclear. Although procalcitonin levels are generally low in viral infections, they can be a marker of disease severity in COVID-19, leading to potentially inappropriate antibiotic use. Treating hypoxia with oxygen in the absence of antibiotics normalized serum lactate levels in many patients, and subsequently, many critical care clinicians have learned the importance of individualizing patient care for septic patients.

**HOSPITAL-ACQUIRED INFECTIONS IN THE INTENSIVE CARE UNIT (ICU)**

The COVID-19 pandemic has been an intellectual and emotional rollercoaster: large volumes of patients overwhelming the health care system, fear of contracting COVID-19, a plethora of published papers to keep up with, supply chain shortages, burned-out health care workers, and countless patient deaths despite our best efforts.

Removing invasive lines (which were utilized longer than normal due to prolonged mechanical ventilation and prone positioning) and urinary catheters was deprioritized as we emphasized convenience amid a stretched health care workforce: reliable intravenous access for antibiotics, sedation, vasopressors, more timely labs, accurate intake and output to prevent volume overload in patients with acute respiratory distress syndrome, and even rectal tubes to preserve personal protective equipment.

Several retrospective studies have demonstrated how common ventilator-associated pneumonia is in ICU patients with severe COVID-19. As hospital COVID-19 cases surged, there were significant increases in the prevalence of central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), ventilator-associated events, and methicillin-resistant *Staphylococcus aureus* bacteremia. Burnout was associated with hospital infections even before the pandemic. Typical practices and resources to monitor and prevent the development of hospital-acquired infections (HAIs) were necessarily redirected to the COVID-19 response, increasing the risk for the development of HAIs.

**ANTIBIOTIC USE**

In some hospitals, the use of a multiplex pneumonia panel provided an opportunity to avoid inappropriate initiation of antibiotics for negative polymerase chain reaction (PCR) results, initiate targeted antimicrobial therapy for positive PCR results, and enable more rapid de-escalation and discontinuation of antibiotics if the pneumonia panel was negative prior to the finalization of sputum cultures. Sometimes starting, broadening, or continuing antibiotics felt like the only tool available to attempt to save a patient on maximum ventilator settings in multiorgan failure, even though it was unclear if antibiotics would help.

In a systematic review, the prevalence of antibiotic prescribing in patients with COVID-19 was 74.6%, but estimated bacterial coinfection was only 8.6%, suggesting a high risk of unnecessary antibiotic use in COVID-19. Unsurprisingly, increased age, increased severity of illness, and mechanical ventilation were all associated with increased antibiotic use.

Prepandemic, we rarely reached for empiric voriconazole beyond patients with solid organ or bone marrow transplants; however, finding pulmonary aspergillosis infections in patients with COVID-19 later in the course changed that for us. To this day, the combination of vancomycin and cefepime frequently started in febrile, prone patients with COVID-19 with refractory hypoxia and persistent infiltrate on chest x-rays in some ICUs is affectionately termed the portmanteau vancopime.

The conflict between trying to practice good antibiotic stewardship to reduce the potential for the development of multidrug-resistant organisms while still doing everything we thought was best for our patients to decrease mortality did not wane despite more experience caring for patients with COVID-19.
EMERGING & RE-EMERGING INFECTIONS

Considering Mandatory COVID-19 Vaccination Policies for Students

Public health and school officials need to consider strategies now, ahead of FDA approval in children.

By Jessica Malaty Rivera, MS, and Katrine Wallace, PhD

(continued from cover page)

and the CDC\(^1\) that all eligible school-aged children 5 years and older be vaccinated against COVID-19, with boosters also recommended for those 12 years and older. Starting July 1, 2022, California will be the first state in the US to mandate the COVID-19 vaccine in all schools, for all students (after FDA approval) in kindergarten through 12th grade, and for all school employees.\(^2\)

Although COVID-19 vaccine\(^4\) availability for children and adolescents\(^5\) was celebrated by many parents, others have been hesitant, especially those with younger children. As of March 30, 2022, the CDC estimates that only 34\% of children aged 5 to 11 years in the US have had at least 1 dose of the COVID-19 vaccine compared with 67\% of 12 to 15 year olds.\(^5\)

There is discourse among some parenting circles over whether kids should be vaccinated for COVID-19 at all. Some rural, conservative counties in California are reporting that they will not enforce\(^7\) the school mandates because many parents in their districts do not plan to vaccinate their children. However, the controversy surrounding pediatric COVID-19 vaccination is fueled by misconceptions: (1) the “appeal to nature fallacy,” (2) the belief that children are not affected by COVID-19, and (3) that COVID-19 vaccines are a less safe way for children to acquire immunity vs the virus itself. There are fundamental misunderstandings around the risks and benefits for both the vaccine and the virus.

MISCONCEPTION NO. 1:
THE APPEAL TO NATURE FALLACY AMONG VACCINE-HESITANT PARENTS

Humans are generally not very good at assessing risk. People tend to hold beliefs based on an appeal to nature bias,\(^8\) whereby things that occur naturally are perceived as good or better,\(^9\) and things that are man-made are seen as bad or harmful. This false dichotomy also extends to COVID-19 vaccines, especially for children. Some parents believe that allowing their children to acquire “natural immunity” from COVID-19 is safer or “better” than the immunity derived from “synthetic” or “unnatural” vaccines. But the growing body of evidence does not support this viewpoint.

MISCONCEPTION NO. 2:
COVID-19 DOES NOT AFFECT YOUNG CHILDREN

This misconception is driven by a woeful minimization of pediatric COVID-19 data. Recent prevalence estimates show that children and adolescents account for 1 in 5 US COVID-19 cases.\(^10\) Estimates of postacute sequelae SARS-CoV-2 infection\(^11\)—which refers to new, returning, or ongoing health problems experienced by people 4 or more weeks after initial coronavirus infection (colloquially referred to as “long-COVID”)—in children vary, but the lower end of the prevalence range in a recent large population-based study was 4\%.\(^12\) This percentage seems low but equates to more than 500,000 children in the US with long-COVID, given the high cumulative incidence rates of pediatric COVID-19.

Thankfully, severe COVID-19 is not as prevalent in children as adults, but it is not always predictable when severe COVID-19 will occur. Children with certain medical conditions such as obesity, diabetes, asthma, chronic lung disease, sickle cell disease, or immunosuppression are at increased risk for severe illness,\(^13\) but children without underlying medical conditions also experience severe illness and hospitalization.\(^14\) During the Omicron surge in January 2022, COVID-19 hospitalizations among children and adolescents were the highest they had ever been,\(^15\) with most admissions among unvaccinated children.\(^16\) To date, there have been nearly 8000 diagnosed cases of

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Omicron and its subvariants have presented a challenge to neutralizing antibodies derived from both the vaccine and the virus.

**CONCLUSION**  
In children, the COVID-19 vaccine predictably prevents severe SARS-CoV-2 outcomes, with minimal short-term immunogenicity reactions and very rare complications. The COVID-19 virus, on the other hand, can unpredictably cause severe infection, hospitalization, MIS-C, long-term chronic health problems, and death. Although immunity from infection and vaccines will wane over time, it is not really worth taking a chance on severe outcomes for transient immunity from infection. Thus, the vaccine is a safer way to shift pediatric COVID-19 illness to the milder end of the spectrum.  

Vaccine hesitancy fueled by the appeal to nature fallacy that natural immunity is safer than the vaccine is not new. Throughout the pandemic, the proliferation of misinformation has led to public confusion surrounding the necessity and the safety of COVID-19 vaccines for children. Social media posts presenting misleading data have caused some parents to hesitate or completely decide against getting their children vaccinated while not understanding that they are putting their children at higher risk of severe illness. Children experience a significant burden of disease for COVID-19, and any preventable severe illness or death in a child is unacceptable. To minimize the impact of COVID-19 on this population ignores the reality that children exist in larger communities. By vaccinating the youngest among us, we can help break cycles of transmission in schools as well as in multigenerational households and other shared communities. Mandating vaccines for school has been found to be associated with increased adherence with vaccination, which will protect a greater number of children from severe complications of COVID-19. ▲

References are available at ContagionLive.com.
Lessons in Resilience:
What HIV Teaches Us About COVID-19

Four lessons learned from the AIDS crisis that can be applied to the fight against our current pandemic

In Jina Saltzman, PA-C; Renslow Sherer, MD; Caroline Teter, PA-C; and David Pitrak, MD

“The farther back you look, the farther forward you are likely to see.”

—Winston Churchill

Churchill’s words of wisdom impress upon us the value of reflecting—in this case, on the AIDS crisis for guidance with COVID-19. The resilience and solidarity of health care workers who have risen to the challenges of COVID-19 have been a source of inspiration worldwide. Many health workers had never experienced caring for patients with a new and potentially fatal contagious illness before COVID-19. Yet, there were many similarities between these 2 pandemics in their early years (Table). We offer these lessons from HIV to inform our next steps in the development of best practices in care, prevention, and support for people with SARS-CoV-2 infection and other emerging pandemics in the future.

Important differences also exist between HIV and COVID-19. As of May 3, 2022, almost 1 million individuals had died from COVID-19 in the United States, and more than 700,000 people had died from HIV-related diseases.1,2 As a blood-borne and body fluid–borne pathogen, HIV affected only a small portion of the US population through sexual exposure, needle sharing, or blood products; however, HIV is more widespread worldwide due to greater heterosexual spread.3 The cumulative mortality from HIV in the US, while significant, pales vs the global toll of 37.5 million deaths.4 COVID-19, a respiratory pathogen, has affected major portions of populations globally, and the US has one of the highest national COVID-19 death rates.

Our review uses a human rights–based approach that values inclusion, fairness, and equity, eg, equal global access to antiretroviral therapies and COVID-19 vaccines. This perspective offers the best way to understand, prevent, and treat COVID-19 and to address the inequalities among vulnerable populations.5 It also defines health broadly to include adequate housing, nutrition, a healthy environment, and respect for the rights of women, LGBTQ+ persons, and communities of color. Jonathan Mann, MD, Paul Farmer, MD, and others taught us that human rights are essential in the fight against HIV and HIV stigma, and these rights are equally critical for COVID-19.6,7

LESSON 1: BE FLEXIBLE, COLLABORATE, AND THINK OUTSIDE THE BOX
The early days of AIDS were fearful: an unknown illness with no known treatment was causing young Americans to die. The majority were men who have sex with men and people who inject drugs and their sexual partners, and Black and Latino Americans were disproportionately affected. Stigma and discrimination were widespread.8 People living with HIV (PLWHIV) not only suffered medical challenges, but also had profound psychosocial needs. In response, new clinical alliances formed, bringing together health educators, pharmacists, case managers, drug and mental health counselors, and community health workers.9 These interdisciplinary teams included PLWHIV and led to innovations in treatment and research. A key lesson from HIV was that transportation, childcare, and mental health services were often as important to PLWHIV as effective medications.10

Flexibility and innovation also have been essential to the COVID-19 response. During the initial wave, hospitals quickly reorganized wards into COVID-19 units and reassigned staff to testing sites, lab services, and COVID-19 care teams.11 The care and research communities pivoted nimbly to address these changing needs; for example, multidisciplinary clinics have been developed for long COVID-19. As COVID-19 transitions from a pandemic to an endemic state, it is leaving behind a trail of social and economic devastation, with mental illness and homelessness on the rise.12 Continued collaboration and creative problem solving to support those impacted will be critical.

LESSON 2: PREVENT BURNOUT AND DEVELOP EFFECTIVE RESILIENCE STRATEGIES
Prior to combination antiretroviral therapy in 1995, the AIDS death toll was staggering.9 Due to the stigma and fear surrounding HIV, many patients died without friends and family at their bedside. Similarly, hospital visitor policies during COVID-19 limited friend and family contact to telecommunications. With COVID-19, although some health workers were reassigned due to age or underlying conditions, the majority were needed to care for the overwhelming number of patients in emergency departments, wards, and intensive care units (ICUs). Early in the HIV pandemic, many health workers refused to work with HIV patients, and a small group of committed providers cared for PLWHIV. In contrast to the tsunami of COVID-19 waves, the HIV epidemic was a relentlessly growing crisis in slow motion. Nonetheless, in both pandemics, caring for a relentless daily stream of very sick and dying patients took a major emotional toll on caregivers.

Burnout was common in the first decade of AIDS, and COVID-19 is having a similar impact. Recently, two-thirds of ICU nurses were considering leaving

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nursing due to COVID-19 burnout. To cope with burnout, AIDS caregivers established support groups, memorial services, community linkages, and a range of health worker supports. However, with COVID-19 restrictions since 2020, similar strategies have been challenging to implement. Staffing shortages and high health worker dissatisfaction with COVID-19 are an alarming call for us to learn from past experience to improve working conditions and support our workforce with wellness programs that promote resilience.

**LESSON 3: ADVOCATE AND NETWORK TO FIGHT MISINFORMATION AND TOXIC POLITICS**

Both the COVID-19 and HIV pandemics have been embroiled in toxic politics. The media stoked the public’s fear of HIV with sensationalized reporting that further stigmatized PLWHIV. Politicians demanded that PLWHIV be barred from some occupations and children with HIV be kept from school, even when science established a negligible risk of transmission. The US government’s early response to HIV was inadequate and underfunded, leaving advocacy groups such as the AIDS Coalition to Unleash Power, or ACT UP, and the AIDS Foundation of Chicago to organize grassroots campaigns to help care for PLWHIV and fight for their rights. Through community engagement and aggressive political advocacy, the Ryan White Comprehensive AIDS Resources Emergency Act was implemented to support HIV services and medications for Americans with low incomes.

Today’s polarized political landscape has resulted in a bewildering and irrational range of health policies regarding masking in schools and public spaces, vaccine mandates, and access to COVID-19 testing and therapies. Shockingly, the White House was the most common source of COVID-19 misinformation in 2020. Social media was absent in the early HIV era, but it is a virulent source of misinformation about COVID-19 that seriously hampered early efforts to prevent further spread and reduce mortalities. Our right to share in free speech and scientific advances includes the responsibility to harness social media as a powerful tool for accurate information, stigma reduction, and community engagement.

Early in the HIV epidemic, HIV clinicians, scientists, and advocates shared their experiences and research at international conferences. These meetings were invaluable for networking with the global HIV community and promoting solidarity for marginalized groups such as LGBTIQ+, women at risk, and people of color. Like HIV clinicians, health workers today should continue to network, collaborate, and share stories of inspiration and support to advocate for the safety of our patients and our own well-being and to stay up-to-date during this rapidly evolving pandemic.

**LESSON 4: PROGRESS AND SCIENTIFIC DISCOVERY ARE THE SILVER LININGS AND WAY FORWARD**

HIV and COVID-19 have attracted an astonishing volume of research interest and scientific productivity. In one survey, 40% of physicians who cared for patients with HIV reported increased levels of intellectual stimulation and career satisfaction. Similarly, a study of physicians who cared for patients with AIDS found that AIDS care also became an opportunity to connect more deeply with themselves and to enact the values of their profession. These are hopeful trends for today’s exhausted COVID-19 caregivers.

HIV research led to innumerable scientific discoveries, such as antiretroviral therapies, electron microscopy, immune modulators, genomic sequencing, and chimeric antigen receptor T-cell therapies, which changed the course of previously fatal diseases. The pace of scientific progress in all fields has greatly accelerated, as exemplified by access to almost real-time data on the number of new cases. mRNA vaccine technology and advances in pangenotypic COVID-19 vaccine research are promising future innovations.

Our world is almost unrecognizable, as fear, unease, and politically polarized battles have become the new norm. Too often, we forget the most profound of our human rights—the responsibility to remember the lessons of past pandemics and to act in the interest of public health to prevent their recurrence. In the 1990s, PLWHIV, activists, and health workers fought ferociously to demand that all lives be valued equally and insisted that lifesaving antiretroviral therapy be provided to all PLWHIV in the world. Similar voices in the COVID-19 pandemic are working to expand equal care and treatment globally and to demand equitable access to COVID-19 vaccines.

As with HIV, the battle against COVID-19 will be won with science, sound public health, and broad implementation of a human rights approach. It is essential that we achieve global equity in access to COVID-19 personal protective equipment, testing, vaccines, and treatments to overcome the scourge of COVID-19 and the inequities that it has exposed. The lessons learned from the early HIV era remain essential for both HIV and COVID-19 today: Our greatest asset is our collective strength to collaborate and advocate for effective accessible health services and policies that are based on science and the fundamental human right to dignity and health. ▲

References are available at ContagionLive.com.
The Underlying Threat of Multidrug-Resistant Pathogens in the COVID-19 Era

by Eli Goshorn, MD

Over half of patients admitted with positive SARS-CoV-2 testing received antibiotics, but evidence of bacterial infection is uncovered in far fewer cases. We may already be seeing the effects of antibiotic overprescribing in this population.
The predictions of those who study MDRO epidemiology reflected the uncertainty of the times, and 2 general tenets emerged. One highlighted an increased awareness of infection control measures among hospital staff, believing that the pandemic would drive improvements in adherence to standard practices, such as hand hygiene and use of personal protective equipment. The other cited data from the 2002 to 2004 severe acute respiratory syndrome (SARS) outbreak demonstrating stagnant and sometimes worsening isolation rates for methicillin-resistant *Staphylococcus aureus* (MRSA).\(^1^,\(^2^\) The conclusion at the time was that increased stress on health care systems from SARS led to poor compliance with existing infection control policies designed to prevent spread of MDROs. A similar lapse seemed likely to occur with the COVID-19 pandemic.

Two years later, the impact of the COVID-19 pandemic on rates of MDRO isolation is beginning to come into focus. The results of several prominent studies are summarized in the Table.\(^3^\)-\(^10^\) Taken in the context of varying pandemic responses, it is unsurprising that these early articles often reported contradictory findings. In resource-rich settings, a general decrease in isolation of MDROs was observed. For example, a case-control study at an academic center in Italy reported decreased rates of overall MDRO isolation in March to June 2020 compared with previous years. Rates of MDRO isolation were decreased among both patients with COVID-19 and patients without COVID-19, although the differences were less pronounced and not statistically significant within the COVID-19 group. This improvement was driven by a dramatic decline in MRSA isolation.\(^3^\)

A similar decrease in new-onset MRSA colonization was observed among inpatients at a large Singapore hospital after infection prevention policies aimed at COVID-19 were implemented.\(^4^\) Lower monthly MDRO rates from 2019 to 2020 were also noted in articles written by investigators at California and Australia facilities.\(^5^,\(^6^\) Reports from other regions were not as favorable for rates of MDR gram-negative pathogens. Across Japanese hospitals, Hirabayashi et al found a decrease in MRSA rates, contrasting with a relative increase in isolation of MDR *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.\(^7^\) Similar reports showcasing higher rates of MDR gram-negative acquisition among patients with COVID-19 emerged from academic centers in Baltimore, Maryland, and Terni, Italy.\(^8^,\(^9^\)

Most alarmingly, data from a hospital dedicated to COVID-19 in São Paulo, Brazil, noted a 23% increase in MDRO infections during the pandemic driven by outbreaks of both MRSA and carbapenem-resistant *Acinetobacter baumannii*.\(^10^\)

Factors associated with the increased transmission of MDRO during the pandemic include liberal antibiotic utilization, prolonged hospital courses, and individual outbreaks. Evidence from the literature demonstrates that clinicians frequently ordered empiric antibiotics for patients with COVID-19. To understand the appropriateness of this empiric prescribing, the frequency of early bacterial coinfection and superinfection in COVID-19 has been investigated. Wang et al examined microbiological specimens of all patients with a positive SARS-CoV-2 test within 48 hours of admission at 2 London hospitals, reporting a 2.7% rate of clinically important bacterial coinfection, with urinary tract infections identified as the most common infectious source.\(^11^\) A similar study performed at a Barcelona hospital found a 9.1% rate of early bacterial coinfection; however, a positive pneumococcal urine antigen accounted for 79% of coinfections.\(^12^\) These discordant results may be explained by differences in methodology. For instance, the latter study only included patients who had procalcitonin and microbiological samples collected and excluded those with positive urine cultures.

Although institutional culture plays a large role in antibiotic prescribing, reports suggest that a majority of inpatients with COVID-19 have been treated empirically for bacterial coinfection or superinfection. One study of 2 hospitals in northwest London reported that 95% of patients with COVID-19 received antimicrobial therapy at the time of admission,\(^13^\) whereas a recent systematic review by Al-Hadidi et al analyzing 141 studies and 28,093 patients reported a more palatable rate of 58.7%.\(^14^\)

Prescribing patterns were examined more closely in a retrospective observational study of patients diagnosed with COVID-19 at 716 US hospitals by Rose et al. Among these patients, 77.3% received at least 1 day of antibiotics, and 81.3% of antibiotics were started on admission. The most commonly ordered agents were antibiotics used to treat pneumonia, such as third-generation cephalosporins and macrolides. Patients admitted to critical care units were more likely to receive broad-spectrum agents such as vancomycin, piperacillin-tazobactam, cefepime, and meropenem.\(^15^\) This level of antibiotic use far exceeds estimates for >>
the burden of bacterial disease among inpatients with COVID-19.

A reasonable exception for which antimicrobial use may be justified is among patients with severe COVID-19 who require mechanical ventilation and extended intensive care unit (ICU) stays. Yang et al reported a bacterial superinfection rate of 13.5% among patients critically ill with COVID-19 in Wuhan, China.15 Investigations into the microbiology of superinfection in this population have identified a variety of culprit organisms that reflect the local epidemiology. Patients with COVID-19 in ICUs in Spain and Italy with high baseline rates of MDR Enterobacterales typically developed ventilator-associated pneumonia (VAPs), catheter-associated bloodstream infections, and urinary tract infections due to these same organisms.16-18

Resistant organisms appear to be less common in US ICUs with lower baseline rates of MDRO isolation overall. Analyzing data from a US tertiary care center, Pickens et al found that only 20.8% of patients who underwent a bronchoalveolar lavage for an initial VAP episode had bacteria resistant to standard therapy for community-acquired pneumonia.19 Regardless of the setting, isolation of MDRO occurred more frequently with prolonged hospitalizations among patients with COVID-19.

Differing between respiratory distress due to COVID-19 or bacterial pathogens is a significant challenge. Retrospective studies have found that patients with bacterial coinfection and superinfection tend to present with a higher severity of illness and require prolonged hospital courses. In aggregate, these patients show more pronounced elevations in white blood cell count and inflammatory markers.20 Procalcitonin is not a specific marker, but it may yet be useful for its high negative predictive value among patients with COVID-19.21 Unfortunately, each of these features is also commonly seen in severe COVID-19, so clinical judgment must still play the largest role in the decision to treat empirically for bacterial infection.

Outbreaks among patients admitted to COVID-19–dedicated wards have also been cited for increased MDRO rates. Factors associated with outbreaks include a medication room mistakenly excluded from terminal cleaning, flawed proning protocols, double-occupancy rooms, and a team nursing model in which multiple nurses shared direct care responsibilities over a large group of patients.22,23 Taken together, poor staff compliance with infection control appears to be a key determinant of outbreak settings.

This is concerning, as nurses and patient care technicians are experiencing unprecedented levels of burnout and job departures. It was recently reported that 18% of US health care workers resigned during the pandemic, with an additional 31% considering leaving their positions.24 Frontline workers in understaffed settings may find themselves in situations in which they don’t have time to comply with infection control measures while also providing essential bedside care.

A potential blueprint for reducing antibiotic use can be found within reports from centers that have successfully managed antibiotic prescribing among patients with COVID-19. Highly engaged antimicrobial stewardship practices were a commonly reported theme. At a center in Tokyo, Murakami et al demonstrated an overall decrease in antibiotic days of therapy per 1000 patient days to below pre-pandemic levels by April 2021, despite a 39.7% spike in intravenous antibiotic use at the time of the emergency declaration.25 In Tel Aviv, Henig et al reported significant decreases in the proportion of patients who received antibiotics in COVID-19 wards relative to pre-pandemic rates in 2019, from 44.9% to 30.2% during the June to November 2020 wave and 50.1% to 30.5% during the December 2020 to March 2021 wave. These results were achieved through the development and frequent updating of institution-specific guidelines that addressed bacterial therapy and the involvement of an infectious disease specialist in weekday rounds.26 Seaton et al reported a 38.3% rate of antibiotic use among patients with COVID-19 across 15 Scottish hospitals and explicitly attributed the success to the impact of antimicrobial stewardship.27

At the outset of the pandemic, many hoped that increased visibility and emphasis on infection control measures would lead to a decrease in rates of MDRO isolation. The data we have now paint a more uneven picture, with some groups reporting improvement and others stagnation. Patients hospitalized with COVID-19 receive antibiotics at a rate far in excess of the observed burden of bacterial illness, and this is likely contributing to gram-negative resistance in this population.

Assessing a patient with COVID-19 for superimposed bacterial infection often presents a diagnostic challenge, and fearful providers frequently prescribe empiric therapy. It is imperative that we standardize our approach to antibacterial therapy in this population and decrease antibiotic use among these patients. To accomplish this, we must empower antimicrobial stewardship programs, which are best equipped to address the problem. We must also take measures to address the impending hospital staffing crisis and ensure that frontline workers have the support they need so that infection prevention does not compete with direct patient care.

Acting now will allow us to expand pandemic-era improvements in MDRO isolation beyond the most resource-rich settings and—in the case of the hardest-hit areas—prevent stagnation from deteriorating into an antibiotic-resistance crisis. ▲

**TABLE. Studies Examining MDRO Isolation During the COVID-19 Pandemic**

<table>
<thead>
<tr>
<th>CITATION (YEAR)</th>
<th>HOSPITAL/POPULATION</th>
<th>NOTABLE FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berdivneva et al (2021)</td>
<td>Academic center/Rome, Italy</td>
<td>Decrease in overall incidence of MDR bacteria from 41.4% of discharges in 2019 to 19.2% among patients without COVID-19 and 29.2% among patients with COVID-19 in 2020—driven mostly by drop in MRSA isolation (15.4% to 4.2% non-COVID-19 and 10.6% COVID-19)</td>
</tr>
<tr>
<td>Bork et al (2021)</td>
<td>Academic center/ Baltimore, Maryland</td>
<td>MDR gram-negative incidence for patients with COVID-19 was 68 per 10,000 patient days vs 17 hospital wide. Overall, MDR gram-negative incidence rate did not vary significantly between 2019 and 2020. Antibiotic use increased 30% in 2020 during the pandemic onset period vs the same period of the previous year.</td>
</tr>
<tr>
<td>Cole and Barnard (2021)</td>
<td>Community hospital/ Los Angeles, California</td>
<td>35% decrease in prevalence of MRSA, ESBL, and VRE from specimens collected on or after hospital day 4 between first and second quarter 2020.</td>
</tr>
<tr>
<td>Hirabayashi et al (2021)</td>
<td>Various hospital/ Japan</td>
<td>Between second quarter 2019 and second quarter 2020, MRSA isolation decreased by 13.5% and penicillin-resistant Streptococcus pneumoniae by 59.6%. No significant change in rates of isolation occurred for third-generation cephalosporin-resistant Escherichia coli and carbapenem-resistant Pseudomonas aeruginosa. Third-generation cephalosporin-resistant Klebsiella pneumoniae increased by 14.4%.</td>
</tr>
<tr>
<td>Madden et al (2021)</td>
<td>Academic center/ Charlottesville, Virginia</td>
<td>28% decrease in MRSA acquisition during pandemic months</td>
</tr>
<tr>
<td>Moso et al (2021)</td>
<td>Academic center/ Melbourne, Australia</td>
<td>Mean decrease of 0.77 MDRO isolates/1000 patient days when directly comparing individual months between 2019 and 2020. 54% of patients with COVID-19 received empiric antibiotics.</td>
</tr>
<tr>
<td>Polly et al (2022)</td>
<td>COVID-19 dedicated academic center/ São Paulo, Brazil</td>
<td>23% increase in MDRO infections during pandemic, driven by outbreaks of MRSA and CRAB</td>
</tr>
<tr>
<td>Tiri et al (2020)</td>
<td>Academic center/Terni, Italy</td>
<td>CRE acquisition rate in a COVID-19–dedicated ICU increased from 6.7% to 50% during pandemic.</td>
</tr>
<tr>
<td>Wee et al (2021)</td>
<td>Academic center/ Singapore</td>
<td>Hospital-wide MRSA acquisition rates decreased by 46% in the 7-month period after introduction of pandemic infection prevention measures relative to the preceding 2 years. Health care–associated MRSA bacteremia rates decreased by 69%. Rates were stable for CRE and MDR Pseudomonas aeruginosa.</td>
</tr>
</tbody>
</table>

CRAB, carbapenem-resistant Acinetobacter baumannii; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamases; ICU, intensive care unit; MDR, multidrug-resistant; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococci.
COVID-19 Impact on Antimicrobial Stewardship: Consequences and Silver Linings

This crisis has united multidisciplinary groups and laid the foundation to better equip the health care workforce for future pandemics.

(continued from cover page)

COVID-19 literature, emergency-use authorizations, and treatment recommendations. Amid the uncertainty, infectious diseases (ID) clinicians, especially those leading antimicrobial stewardship programs (ASPs), have taken on additional leadership roles to organize and maintain their institutions’ COVID-19 treatment guidelines.

The negative impacts of COVID-19 cannot be understated, such as the tremendous toll on the health care community and the potential impact of exacerbating resistance due to overuse of empiric antimicrobials; however, silver linings deserve to be highlighted. These include renewed recognition of the versatile skill set of ID specialists, as well as the opportunity to strengthen multidisciplinary working relationships.

In this article, we will review both the negative and positive effects of COVID-19 and its impact on ASP workload.

INCREASED BURNOUT

Burnout among HCPs was a topic of concern prior to the COVID-19 pandemic and was associated with reductions in patient satisfaction, waning provider empathy, and increased medical errors. Since December 2019, there has been a heightened awareness of how the pandemic has contributed to HCP burnout; however, the true prevalence of burnout among HCPs is unknown.

A study conducted in the United Kingdom attempted to estimate burnout rates through a questionnaire, which included variables validated by established measures such as the Copenhagen Burnout Inventory. Almost 80% of the UK participants (424/539) reported moderate to severe burnout. Conversely, in a Japanese study led by Matsuo et al, 31% (98/312) of HCPs reported burnout. Additionally, when compared with physicians, burnout prevalence was almost 5 times higher for nurses (odds ratio [OR], 4.9; 95% CI, 2.2-11.2) and pharmacists (OR, 4.9; 95% CI, 1.3-19.2), 6 times higher for laboratory medical technicians (OR, 6.1; 95% CI, 2.0-18.5), and 16 times higher for radiological technicians (OR, 16.4; 95% CI, 4.3-61.6).

Patient demographics, including younger age, female sex, and presence of comorbid conditions including preexisting depression, may also increase the risk for burnout.

Recognizing burnout among our HCPs is the first step in providing interventions to reduce burnout, such as maintaining open communication with coworkers and supervisors about job stress, increasing sense of self-control by keeping a consistent daily routine, and engaging in mindfulness techniques.

Resources to support HCPs should be offered to prevent burnout, such as the tools provided on the CDC’s Support for Public Health Workers and Health Professionals website.

ANTIMICROBIAL OVERUTILIZATION

Another repercussion of COVID-19 is the potential exacerbation of antimicrobial resistance due to antimicrobial overuse. Unnecessary empiric antibiotic use was commonly reported early in the COVID-19 pandemic, despite low reported rates of bacterial coinfection—approximately 8% to 19% of adult patients hospitalized for COVID-19.

A review of early COVID-19 prescribing trends found that 25% to 70% of patients who were severely ill with COVID-19 were empirically started on antibiotics to cover for possible community-acquired bacterial pneumonia (CAP). Continuation of unnecessary antibiotic therapy during hospitalization is also an issue because approximately 15% to 24% of patients hospitalized with COVID-19 will acquire a secondary bacterial infection.

Therefore, ASP efforts to monitor antimicrobial overuse increased because patients required case-by-case evaluation to assess the need for initiating and continuing antimicrobial therapy.
Recognizing the Value of Antimicrobial Stewardship Expertise

Due to the worldwide and profound impact of COVID-19, both the public and the health care sector looked toward the expertise of ID clinicians to lead them through the pandemic. On a national level, the Society of Infectious Diseases Pharmacists (SIDP) provided clinicians and patients with valuable, real-time information and useful tools about therapeutics, vaccines, and more.17

SIDP’s YouTube channel, which houses over 30 COVID-19 videos with more than 160,000 views (as of April 2022), showcased evidence-based reviews of COVID-19 therapeutics provided by ID pharmacy experts. SIDP’s Breakpoints podcast also shared stories from those on the front lines and their approach to addressing relevant issues. COVID-19 gave ID pharmacists, who were already equipped to handle the ever-changing demands of the health care system, an opportunity to further demonstrate their value.

The negative impacts of COVID-19 cannot be understated, such as the tremendous toll on the health care community and the potential impact of exacerbating resistance due to overuse of empiric antimicrobials.

AsPs were also paramount in the fight against the pandemic. Throughout the country, they led the efforts within their own institutions to discuss rapidly changing information, create COVID-19 treatment guidelines, and provide education. Additionally, AsPs were presented with a unique opportunity to utilize existing knowledge and skill sets to optimize and intervene on inappropriate antimicrobial usage. Various stewardship groups have shared their approach to integrating COVID-19 into their daily clinical practice, some of which include maintaining the COVID-19 treatment guidelines and utilizing molecular diagnostic tools to help differentiate viral and bacterial pneumonia.

Creation of institution-specific COVID-19 treatment guidelines provide frontline providers with the most up-to-date recommendations. When coupled with education, the employment of institution-specific guidelines has been shown to reduce unnecessary use of empiric antibiotics. In a single-center, quasi-experimental study, education and recommendations were provided to COVID-19 providers. Implementation of a COVID-19 treatment guideline with provider education resulted in a significant reduction in empiric CABP antibiotics for patients with COVID-19 (74.5% preintervention vs 42% postintervention; P <.001).13

Molecular respiratory tests may also be used as a stewardship tool for COVID-19 patients when a bacterial coinfection or secondary infection is suspected. Three studies evaluated the microbiological performance of BioFire FilmArray pneumonia panels, including the pneumonia panel and pneumonia-plus panel, in critically ill patients with COVID-19.14-16 High rates of test sensitivity (89.3%-100%) were reported across all studies, supporting the use of this rapid diagnostic test for ruling out bacterial coinfection.

AsPs can assist with interpretation of polymerase chain reaction–based test results and help guide appropriate antimicrobial use in COVID-19 patients.

Strengthening Multidisciplinary Working Relationships

Initially, AsPs were charged with assuming the burden of the COVID-19 response. A Twitter poll surveying the infectious diseases community and AsPs noted that 30% of respondents were directly involved with the COVID-19 response in their health systems.17

Additionally, Mazdeysna et al provided an outline based on traditional AsPs and the extra responsibilities a program might assume in response to COVID-19.18 These include creating COVID-19 guidelines, expanding prior authorization restrictions to drugs with mixed evidence (eg, ivermectin and lopinavir/ritonavir), and providing education on the constantly changing recommendations.18 The authors mention that AsPs also have an opportunity to assist with disaster response and preparedness against emerging pathogens by collaborating with infection control.19 However, there is still a paucity of data regarding how the multidisciplinary working relationship among ID specialists, ASP, and other departments has grown in response to COVID-19.

Specifically, at Loma Linda University Medical Center in California, the multidisciplinary working relationship has expanded between the ID specialists, especially ASP specialists, and various groups. Due to the unique experimental nature of many COVID-19 therapeutics, the ID pharmacists have strengthened their working relationship with the investigational drug pharmacists. The ASP specialists took ownership to review data regarding treatment and creation of inpatient COVID-19 guidelines. Drugs that were previously used to treat rheumatological diseases were repurposed to treat patients who were critically ill with COVID-19. ASP specialists worked closely with the critical-care physician group to create stringent guidelines for the appropriate use of these agents. When new oral antivirals were granted emergency use authorization, prompt collaboration between the ASP and information technology ensued to create order sets and note templates. Additionally, ASP specialists also collaborated with outpatient providers, including emergency department and ambulatory care providers, to ensure proper use and equitable allocation of new antivirals.

Conclusion

Reflecting on the impact of the COVID-19 pandemic on HCPs and AsPs, both negative and positive aspects can be felt. The burnout experience shared by many HCPs is an ongoing issue that needs further research to not only address the limited number of solutions, but also techniques to effectively employ those solutions. Additionally, the long-term impact of the initial overutilization of antimicrobials on the development of future antimicrobial resistance is yet to be determined. However, there has been renewed appreciation for ID specialists, especially ASP specialists, and their unique skill set, which has enabled them to navigate the ever-changing landscape of COVID-19 management. Ultimately, COVID-19 has united multidisciplinary groups in this shared experience and laid the foundation to better equip the health care workforce for future pandemics. ▲
COVID-19 Expectations on the Rollout of the Booster Shots

by GINA BATTAGLIA, PHD

COVID-19 booster shots play a critical role in protecting against infection, hospitalization, and death related to COVID-19 infection, according to infectious disease experts who participated in a recent Contagion® Peer Exchange panel, moderated by Peter Salgo, MD, professor of medicine and anesthesiology, Columbia University Vagelos College of Physicians and Surgeons, New York City, New York. However, the panelists added that achieving herd immunity with vaccination may be difficult with the widespread vaccine hesitancy and lack of access to vaccines in developing countries. The panelists reviewed the importance of COVID-19 booster shots for promoting durable immunity, the benefits of COVID-19 vaccination on the individual and public health levels, and the role of booster shots in protecting against new virus variants.

THE IMPORTANCE OF COVID-19 BOOSTER SHOTS

The purpose of the COVID-19 booster is to potentiate the immune system and provide an additional layer of protection from infection, hospitalization, and death, according to Donald Alcendor, PhD, associate professor of microbiology and immunology at Meharry Medical College and adjunct associate professor of pathology, microbiology, and immunology at Vanderbilt University School of Medicine in Nashville, TN. Salgo said that the public may question if the need for booster shots will ever end, but Angela Rasmussen, PhD, research scientist III at the Vaccine and Infectious Disease Organization in Saskatchewan, Canada, noted that vaccines for many other diseases (such as measles, poliomyelitis, and hepatitis B virus infection) have multiple-shot regimens and that the optimal dosing regimen for the COVID-19 vaccines remains to be seen.

“The probability correctly that we will get to a point where you've been sufficiently boosted, that you have very responsive protective long-term–memory immunity to this virus,” Rasmussen said. “Because these vaccines were expedited to the clinic, we don't really know what the optimal dosing regimen is, but I think it’s very unlikely that we're going to be needing COVID-19 boosters every 6 months for the rest of our lives.”

Rasmussen added that although the mRNA technology platform used with SARS-CoV-2 vaccines is unique, the fundamental effects of these vaccines on the immune system are similar to those of vaccines with other technology platforms such as adenovirus vectors.

“They expose your immune system to the antigen, in this case the spike protein from SARS-CoV-2, the same way that a protein subunit vaccine would and the same way that an inactivated virus would,” she said. “I don’t that there's anything fundamentally different to this technology that would necessitate constant boosters. The data that we do have suggest that there are immune responses to both the mRNA and the adenovirus-vectorized vaccines that are compatible with long-term–memory immunity.”

Jeff Goad, PharmD, MPH, associate dean of academic affairs, professor and chair of the Department of Pharmacy Practice at Chapman University School of Pharmacy, in Irvine, CA, added that natural disease has not been shown to lead to long-term immunity and that vaccination will be important to possibly achieve herd immunity.

“What we’re seeing is that the human is just not able to develop a long-lasting response, whether we’re using vaccine or natural disease,” he said. “When you start talking about the role of the booster and how many we may need moving forward, a lot of it has to do with how well we do with getting the primary series in and now getting the booster in 6 months later because vaccination to herd immunity is going to be critical moving forward.”

HOW COVID-19 BOOSTER SHOTS AFFECT IMMUNITY

The effectiveness of COVID-19 vaccines should be looked at on both the public health and individual levels, according to Jason Gallagher, PharmD, clinical

“The question really is: At what point do you need to deliver those boosters to make sure that everybody is safe? At what point is it urgently needed?”

–Angela Rasmussen, PhD
professor, clinical specialist, infectious diseases, and director of the PGY2 Residency in Infectious Diseases Pharmacy at the Temple University School of Pharmacy, in Philadelphia, PA. He said that although “there’s no doubt” about the benefits of a booster following the initial 2-dose regimen from an individual standpoint, providing countries and individuals with their first vaccine doses is the ideal strategy from the public health standpoint. Additionally, the deployment of the vaccines amid a pandemic to try to change its trajectory is unprecedented, Gallagher noted. “We are learning as we go,” he said.

Alcendor said that the vaccine has “yet to let us down” in accomplishing its primary goals of protecting against severe disease, hospitalizations, and death. However, he noted that he has observed a “tremendous amount” of vaccine hesitancy and resistance in several areas of the country, such as in the rural counties of Tennessee where he lives, that is likely to persist and may eliminate the possibility of achieving herd immunity with vaccination.

“We are also dealing with antivaxxers who are putting out misinformation and helping support conspiracy theories around [ill-founded] ideas about vaccine efficacy and safety,” Alcendor said. “We are getting breakthrough infections, and we are getting the evolution of variants that we don’t know if we can control with existing immunity, so we are in a holding place when it comes to herd immunity.”

Alcendor added that even if a country such as the United States has a high vaccination rate, global vaccination is necessary to ensure widespread protection. He said that the low vaccine availability in developing countries, such as those in Africa, is a critical barrier that needs to be addressed.

“Those countries cannot afford vaccine contracts. Vaccine contracts are paid for before the vaccine is even made,” he said. “You’re looking at rich countries having more than 60% of the vaccine supply. What you need to do is this: You need to bring vaccine manufacturing and distribution local to those communities, and that must be done through public-private partnership with vaccine companies and the governments. The World Health Organization must be involved.”

ARE COVID-19 BOOSTER SHOTS NECESSARY?

The panelists agreed that booster shots are necessary, and Rasmussen added that turning down a booster shot in countries of high vaccine access, such as the United States or Canada, does not increase vaccine access to other countries in need.

“I think that the boosters may be necessary for everybody for long-term immunity,” she said. “Are they necessary now to prevent the severe disease that Donald [Alcendor] was talking about earlier? For a lot of people, probably not. Are these really 3-shot vaccine regimens, at least for the mRNA vaccines, and a 2-dose regimen for the adenovirus-vectorized vaccines? I do think that they are. The question really is: At what point do you need to deliver those boosters to make sure that everybody is safe? At what point is it urgently needed? I would argue that in people who are low risk for severe COVID-19, boosters are not urgently needed, even though long term they may be needed for that duration of immunity.”

Alcendor added that the push to provide boosters in the United States was likely prompted by data from Israel showing the occurrence of breakthrough infections and decreases in antibody levels over time, but he noted that the effects of T-cell or cell-mediated immunity on the immune response against COVID-19 infection is often overlooked. According to Alcendor, T cells play a critical role in B cell differentiation and synthesis of antibodies, as well as activation of cytotoxic T cells and improving their ability to kill infected cells.

“We are using antibody levels as a surrogate marker for immunity,” Alcendor said. “We never talk about T-cell or cell-mediated immunity as a clear marker that must be looked at.”

However, Goad countered that higher antibody levels may be important for protection against new variants, such as the Omicron variant, that are likely to continue to develop in countries with limited access to vaccination.

“Without...changing the makeup of the vaccines, we can also overwhelm the virus by a higher antibody titer that we’re getting with the booster,” he said. “There may be some protection here that we’re overlooking, especially with new variants coming out.”

Access the videos
Scan the QR code by hovering the camera from your smartphone to watch the full videos at ContagionLive.com.
COVID-19 vaccination, though highly effective against severe or fatal disease, does not offer full protection against infection. Currently 3 COVID-19 vaccines are available in the US: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Johnson & Johnson-Janssen (JNJ-78436735). One study, presented in April at the Society for Healthcare Epidemiology of America 2022 Conference, explored the demographic characteristics and disease outcomes of COVID-19 breakthrough infections by type of vaccine received.

The investigators included a total of 85 fully vaccinated patients with a documented COVID-19 breakthrough infection from February to September 2021. Breakthrough infection was defined as SARS-CoV-2 detection greater than or equal to 14 days after receiving all initial doses of an authorized COVID-19 vaccine. The investigators collected patient demographics and hospitalization information, such as length of stay and oxygen needs.

Participants were recruited from 2 hospitals in Southeast Michigan and classified by nonsevere, severe, or critical disease. Patients were classified as severe if their oxygen saturation level was less than or equal to 94% on room air or if they required supplemental oxygen, and they were classified as critical if they developed respiratory failure, including requiring mechanical ventilation or extracorporeal membrane oxygenation.

A total of 85 breakthrough infections were identified in the study cohort. The average age of the patients was 69.9 years and 51.8% were female. Severe disease (n = 73; 85.9%) was the most common type of breakthrough infection, followed by nonsevere disease (n = 7; 8.24%). A total of 9 (10.6%) deaths occurred in the cohort.

Most patients received the Pfizer-BioNTech (n = 38; 44.7%) or Moderna (n = 35; 41.2%) vaccine. Severe illness was more common among participants who received a Pfizer-BioNTech vaccination regimen (n = 33/73; 45.2%), and patients with critical disease were more likely to have received the Moderna vaccine (n = 4/5; 80.0%).

Moderna vaccine recipients had the longest time in between COVID-19 infection and vaccination (181.9 ± 43.1 days), and Janssen vaccine recipients had the shortest time between testing positive and receiving the vaccine (91.0 ± 61.1 days). The investigators concluded that COVID-19 breakthrough infections were uncommon among fully vaccinated persons but increased with time after vaccination.

Study Assesses Risk of COVID-19 Breakthrough Infections by Vaccine Received

By NINA COSDON

**People Living With HIV Have Higher COVID-19–Related Hospitalization, Mortality**

By JOHN PARKINSON

Striking the right balance between addressing the needs of patient who have infections and addressing antimicrobial stewardship can be challenging for providers caring for patients at end of life (EOL). Without the benefit of a specified treatment protocol for EOL, practitioners are left to use their own judgment to decide how to proceed.

Certainly, practitioners want to keep their patients’ best interests in mind, especially comfort as a priority. In one survey, an overwhelming majority of practitioners said they prescribed medicines to their patients in almost all EOL situations. In fact, 88% to 100% of physicians started patients at EOL on antibiotics in all situations, except for when the patients exhibited advanced dementia (45%).

A group of investigators decided to examine the estimated antibiotic use during the last 6 months of life for patients under hospice or palliative care. These investigators wanted to identify potential time points in the EOL period during which antimicrobial stewardship interventions could be targeted for maximal benefit. This large, retrospective, national cohort study was done during a 5-year period (2014-2019) with Veterans Affairs (VA) patients who had been hospitalized within 6 months prior to death.

The investigators used electronic medical records data to collect demographics, comorbid conditions, and duration of inpatient antibiotics administered, as well as outpatient antibiotics dispensed. They used a propensity score-matched cohort analysis to compare antibiotic use between patients placed into palliative care or hospice and patients not receiving palliative care or hospice. Repeated-measures analysis of variance and repeated-measures linear regression methods were used to analyze difference in differences of days of therapy between the 2 cohorts.

“Overall, 77% (18,296/23,746) of hospice patients and 80% (71,812/89,768) of palliative care patients received at least one antibiotic, while 69% (95,167/138,308) of those not placed in hospice or not receiving palliative care received antibiotics,” the investigators reported.

In addition, in the cohort analysis, the investigators compared patients placed into hospice or palliative care to propensity score–matched controls. Those in palliative care were associated with a 11% absolute increase in prescribing antibiotics and those in hospice were associated with a 4% absolute increase during the 7 to 14 days post entry vs pre-entry.

“We observed that patients receiving EOL care have high levels of antibiotic exposure across VA population, particularly on entry to hospice or during admissions when they receive palliative care consultation,” the investigators concluded.
Community-Acquired *Candida glabrata* Empyema: An Atypical Diagnosis Not to Miss

by SARA RENDELL, PHD; DANIEL ESCOBAR, MD; NAASHA TALATI, MD, MSCR; and RANDI SILIBOVSKY, MD

**FINAL DIAGNOSIS**

*Candida glabrata* empyema

**HISTORY OF PRESENT ILLNESS**

A 65-year-old woman presented complaining of 2 weeks of sudden-onset dyspnea, cough, and left-sided pleuritic chest pain. Review of systems was notable for increased thirst, polydipsia, polyuria, and nocturia. She denied preceding gastrointestinal or upper respiratory symptoms, although she complained of some nausea and heartburn. She described "white fluffy stuff" on her tongue, accompanied by xerostomia, and diminished taste over the same time period. She denied weight loss or sick contacts. During the 10 days prior to admission, her shortness of breath and chest pain worsened, and she presented to the hospital.

**PAST MEDICAL HISTORY**

She had a 16-year history of steroid-dependent sarcoidosis and no known history of diabetes, prior surgeries, or malignancies.

**KEY MEDICATIONS**

She was on a course of 20 mg of prednisone daily for 3 consecutive months for pulmonary sarcoidosis, which was tapered to 10 mg daily 3 weeks prior to admission.

**EPIDEMIOLOGICAL HISTORY**

The patient was born in the US. She had no history of intravenous drug use, was a current smoker with a 16 pack-year history, and drank 1 to 6 units of alcohol weekly. She was up-to-date with pneumococcal vaccination, had not traveled in 6 months, and had 1 house cat with no other animal exposures.

**PHYSICAL EXAMINATION**

On admission she was afebrile (98.3 °F), tachycardic (110 beats per minute), hypertensive (92/57 mm Hg), and tachypneic (28 breaths per minute). Her oxygen saturation was 95% on room air. She was fully oriented but drowsy and complaining of pain in her left chest. She had oral thrush. She had no jugular venous distention. Her heart sounds were regular rate and rhythm without murmurs, rubs, or gallops. The lung examination revealed diminished breath sounds bilaterally, with marked diminishment to the axilla on the left side. She had left upper flank tenderness to palpation. Her abdomen was soft without tenderness or distention. She had no axillary, supraclavicular, or cervical lymphadenopathy. She had no rashes, no joint tenderness or swelling, and no lower limb edema.

**STUDIES**

Laboratory tests revealed a leukocytosis with neutrophilic predominance: 23.8 k/mm3 wbc (normal, 4.5-11 k/mm3), 93% neutrophils, and 0.9% bands. Her blood glucose level was markedly elevated at 973 mg/dL (normal, 70-140 mg/dL), and her electrolytes and blood gas were consistent with diabetic ketoacidosis with respiratory compensation. Her creatinine level was 1.89 mg/dL (baseline, 1.1 mg/dL), and her liver function tests were within normal limits. An electrocardiogram revealed no ischemic changes, and serially repeated troponins were negative. The HIV test, rapid respiratory viral panel, COVID-19 polymerase chain reaction test, methicillin-resistant *Staphylococcus aureus* nasal swab, and *Legionella* urine antigen were negative. Urinalysis was positive for ketones and negative for nitrites and leukocyte esterase and only 1 to 2 white blood cells.

A chest x-ray and computed tomography of the chest with contrast (Figures 1, 2, and 3) showed a large, loculated left-sided pleural effusion, no evidence of esophageal rupture, stable hilar adenopathy, no mediastinitis, and no mass.

**CLINICAL COURSE**

She was admitted to the hospital with diabetic ketoacidosis secondary to sepsis, likely from a complicated pneumonia. She received intravenous fluids, electrolyte repletion, and an insulin drip, and she was started on azithromycin and celepime.

**DIAGNOSTIC PROCEDURES**

Interventional radiology performed fluoroscopy-guided diagnostic thoracentesis for fluid analysis. The pleural fluid studies revealed an exudative effusion. Laboratory values were as follows: lactate dehydrogenase, 1352 U/L (normal, <140 U/L); total protein, 4.6 g/dL (normal, <1-2 g/dL); glucose, 165 mg/dL; white blood cells, 1381/μL (normal, <1000) (64% neutrophils); red blood cells, 502 x 106/μL (normal, <50). The pleural fluid Gram stain was negative, and both routine and fungal cultures grew multiple colonies of *Candida glabrata* at 72 hours. Two chest tubes were placed for source control; repeat fluid culture was also positive for *C glabrata*, which revealed susceptibility to micafungin (minimum inhibitory concentration [MIC], 0.015 μg/ml), dose-dependent susceptibility to fluconazole (MIC, 16), and susceptibility to voriconazole (MIC, 0.5 μg/ml). Anaerobic cultures were negative. Blood cultures were negative. Fluid cytology did not yield malignant cells. Ophthalmology found no evidence of ocular involvement on the dilated exam. To further search for an etiology of the fungal empyema, we performed a barium study and esopha-gastroduodenoscopy, which showed no evidence of esophageal perforation or other pathology.

**TREATMENT AND FOLLOW-UP**

Two cycles of chest tube drainage with fibrinolysis achieved moderate...
improvement. She was treated with caspofungin for 28 days. Her chest tubes were removed 2 weeks prior to completion of antifungal therapy. At 3-month follow-up, she remained asymptomatic without recurrence of pleural effusion.

**DISCUSSION**

Definitive diagnosis of fungal empyema should be made based on isolation of fungal species from exudative pleural fluid studies obtained via thoracentesis, clinical presentation consistent with pleural infection (fever, leukocytosis, dyspnea), and isolation of the same organism from pleural fluid on another occasion or from another specimen (including blood culture). Confirmed *Candida* empyema thoracis, especially in patients without evidence of candidemia, most commonly occurs in the setting of esophageal disease, especially rupture or recent chest surgery. Although this patient had none of these common risk factors associated with *Candida* empyema, she did have other factors predisposing her to fungal colonization and subsequent infection.

Although this patient had none of these common risk factors associated with *Candida* empyema, she did have other factors predisposing her to fungal colonization and subsequent infection.

**SUMMARY**

Community-acquired *Candida* empyema thoracis is rare. Diabetes mellitus and prolonged corticosteroid use both predispose to fungal overgrowth. In patients with these risk factors, transient fungemia or translocation may seed the pleural space. A diagnosis of *Candida* empyema thoracis should be considered despite a lack of commonly associated risk factors (such as recent surgical intervention, esophageal malignancy, or perforation) when isolated on multiple cultures obtained on different occasions. This infection is associated with a high mortality and must be managed with prompt drainage and targeted antifungal therapy.

References are available at ContagionLive.com
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