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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Children Hospitalized with SARS-CoV-2

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SYNOPSIS: Two different studies published last month give a clear, consistent finding: About three-fourths of children hospitalized with SARS-CoV-2 do not have severe COVID-19-related illness but are merely identified as infected when subjected to screening tests. Surveys reporting the number or incidence of SARS-CoV-2-infected hospitalized children likely overestimate the actual burden of disease.

SOURCES: Webb NE, Osburn TS. Characteristics of hospitalized children positive for SARS-CoV-2: Experience of a large center. *Hosp Pediatr* 2021;11:e133-e141.

Kushner LE, Schroeder AR, Kim J, Mathew R. "For COVID" or "with COVID": Classification of SARS-CoV-2 hospitalizations in children. *Hosp Pediatr* 2021;11:e151-e155.

The severity of illness with COVID-19 is classified in various ways, and hospitalized children often are automatically categorized as having severe disease. However, widespread screening for SARS-CoV-2 in hospitalized children makes it possible that children hospitalized for conditions unrelated to COVID-19 who are incidentally infected, with no symptoms attributable to the viral infection, might be reported as having "severe COVID-19 disease." Two separate studies looking at the spectrum of disease severity of children hospitalized with SARS-CoV-2 infection were reported in the August 2021 issue of *Hospital Pediatrics*. Similarly designed and with similar findings, these reports help clarify the extent of illness due to this infection.

First, Webb and Osburn studied SARS-CoV-2-positive children at a central California tertiary children's hospital that has a referral population of 1.3 million children, 75% of whom have government-funded healthcare, and a majority of whom are identified as Hispanic. They retrospectively reviewed documentation about all patients younger than 22 years of age hospitalized with a positive SARS-CoV-2

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antigen test (usually polymerase chain reaction) from May through September 2020; universal SARS-CoV-2 testing of all admitted patients was done during this time period. A total of 163 patients were identified and evaluated. Patients were assumed to have an incidental SARS-CoV-2 infection unrelated to the reason for hospitalization if they had no fever, no respiratory symptoms, and no gastrointestinal symptoms. Infections were categorized as "potentially symptomatic" if they were associated with fever or respiratory symptoms or gastrointestinal symptoms but without a requirement for respiratory support; this group included patients with diabetic ketoacidosis, appendicitis, and fever during the neonatal period with an admission to treat with antibiotics while ruling out serious bacterial infection. Patients were categorized as "significantly symptomatic" if they had respiratory or cardiac findings consistent with COVID-19 requiring respiratory support and/or intensive care.

Some other patients (17 of 163 overall infected patients in the study) were categorized by physician diagnosis (following Centers for Disease Control and Prevention [CDC] diagnostic criteria] as having multisystem inflammatory syndrome in children (MIS-C). The patients with MIS-C were excluded from subsequent analysis for the purposes of this paper, leaving 146 patients for evaluation. Overall, 58 (40%) of the 146 patients with acute SARS-CoV-2 infection were deemed to be "incidentally infected" (11 with a fracture, seven with seizures), 68 (47%) were deemed to be potentially symptomatic (with 25 of the 68 having appendicitis), and just 20 (14%) were deemed significantly symptomatic.

Significantly symptomatic patients were of statistically similar age (average 11 years) to those with incidental infection or potentially symptomatic infection (8 years). Approximately 90% of significantly symptomatic patients (and half of other patients) had medical comorbidities. There were four deaths among studied patients, with only one of the deaths being attributable to COVID-19. The "incidentally infected" and "potentially symptomatic" groups were similar for essentially all statistical analyses.

Second, Kushner and colleagues did a similar retrospective study, but from May 2020 to February 2021 (thus, including the winter respiratory season) and including only patients younger than 18 years of age (not 22 years, as in the other study) at a university-based quaternary children's hospital in northern California. They initially categorized patients as asymptomatic if they had no symptoms consistent with CDC descriptions of COVID-19, mild/moderate if they had symptoms attributable to COVID-19 but did not require supplemental oxygen, severe if they required extra oxygen but not pressure respiratory support, and critical if they required ventilation support or had sepsis or multi-organ failure. The investigators subsequently categorized patients as to whether COVID-19 was likely or unlikely to have prompted a need for hospitalization. A total of 117 patients were included in the study cohort, 71% of whom identified as Latino, 16% of whom were immunocompromised, and 27% of whom required intensive care unit admission related to SARS-CoV-2. There were no deaths during the study period, but one included patient died of COVID complications shortly after data collection was completed. For 55% of patients, COVID-19 was deemed to be the "likely" cause of hospitalization. Of the 117 total patients, 39% were "asymptomatic" (related to the SARS-CoV-2 infection), 28% had mild/moderate symptoms, 8% had severe illness, and 13% had critical illness; 12% had MIS-C.

Both research groups agreed that basing assessments of the extent by which COVID-19 is affecting children solely on the number of patients hospitalized with SARS-CoV-2 infection is inappropriate. Although their classification systems were slightly different, they each showed similar rates of SARS-CoV-2-positive children being hospitalized for reasons totally separate from having COVID-19.

■ COMMENTARY

During a recent television interview, I was asked why scientists initially said that children were not adversely affected by COVID-19 and if the Delta variant was the reason children are being so severely affected now. The questions pointed out how misuse of data can lead

to inappropriate conclusions. First, just because children are less often severely sick with COVID-19 than are adults, that did not mean that children were never adversely affected. Second, related to the Delta variant or not, widespread screening reveals that many children are infected (often without symptoms), but it still is inappropriate to assign COVID-19 as the cause of hospitalization in all hospitalized children who happen to be infected.

Yes, children can be infected by SARS-CoV-2. Yes, many children infected by SARS-CoV-2 remain asymptomatic of their infection, even if they happen to be hospitalized for appendicitis or a fracture during the time they are asymptomatically infected. Yes, infected children can get sick when infected by SARS-CoV-2. Yes, children can die of COVID-19, even though at lower rates than seen in adults.

The data from these two new studies do make it clear that focusing on the rates at which hospitalized children are SARS-CoV-2-infected will overestimate the severity and impact of the pandemic. Many children identified by universal inpatient screening as infected by SARS-CoV-2 are not symptomatic with COVID-19 and are not hospitalized because of their coronavirus infection. Whichever categorization scheme is used, 40% to 50% of children hospitalized with SARS-CoV-2 infection are not hospitalized because of or for that infection. Only 10% to 20% of pediatric patients hospitalized with SARS-CoV-2 infection are critically ill (either with the acute infection or with MIS-C). These data can help us better understand and explain the impact of the ongoing pandemic on children.

Another way to characterize the severity of COVID-19 in children would be to report on only the hospitalized children who seemed to clinicians to be hospitalized because of their SARS-CoV-2 infection and not merely due to an incidental infection that was not causing symptoms. Such was the case of another recent multicenter study.[1] That retrospective study included 874 children (younger than 18 years of age) admitted from February 2020 to January 2021 to one of 51 collaborating hospitals with symptoms referable to COVID-19. The median length of stay was four days, with 46% requiring intensive care. Overall, 1.4% did not survive the illness. Children requiring intensive care were older (10 vs. 6 years), heavier (body mass index [BMI] 20.1 vs. 18.9), or had MIS-C (44% vs. 15%). Asthma was a common comorbidity in children requiring intensive care for COVID-19. ■

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ABSTRACT & COMMENTARY

Neutrophil Extracellular Traps and COVID-19

By Dean L. Winslow, MD, FACP, FIDSA, FPIDS

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SYNOPSIS: Neutrophil extracellular traps (NETs) contribute to immune-mediated inflammation and thrombosis. Donor neutrophils were stimulated with plasma from patients hospitalized with COVID-19. R406 (metabolically active component of fostamatinib) abrogated release of NETs in vitro.

SOURCE: Strich JR, Ramos-Benitez MJ, Randazzo D, et al. Fostamatinib inhibits neutrophils extracellular traps induced by COVID-19 patient plasma: A potential therapeutic. *J Infec Dis* 2021;223:981-984.

Plasma was obtained from seven healthy donors and seven COVID-19 patients (six hospitalized at the National Institues of Health Clinical Center and from one patient hospitalized at University of Maryland Hospital who was receiving extracorporeal membrane oxygenation [ECMO] support). Neutrophils were isolated from one healthy donor. Cells were plated in microtiter plates at 20,000 cells/mL, incubated at 37°C, and then stimulated with either normal plasma or plasma from the COVID-19 patients. Neutrophil extracellular trap (NET) formation was measured by labeling of released extracellular deoxyribonucleic acid (DNA), which was visualized by fluorescent microscopy and quantitated by relative fluorescent units (RFU). For inhibition experiments, R406 was preincubated with the healthy neutrophils at either

1 µM or 4 µM for 30 minutes prior to stimulation with plasma.

Kinetics of NETs formation showed a gradual increase over six hours when stimulated by serum from COVID-19 patients, which was approximately 10 times greater than that seen with normal serum. Preincubation of neutrophils with R406 dramatically reduced NETs release triggered by COVID-19 patient plasma at all time points, but did not alter NETosis induced by phorbol myristate ester (PMA).

■ COMMENTARY

Those of us who, since last February, have been caring for patients with COVID-19 who are ill enough to require hospitalization have been quite impressed with the degree of inflammation and activation of coagulation in these patients, as evidenced by dramatically elevated levels of C-reactive protein (CRP) and D-dimer levels. We learned early on that these patients all require at least prophylactic doses of anticoagulants, and to have a high index of suspicion for clinical deep venous thrombosis and pulmonary thromboembolism requiring therapeutic anticoagulation.

At our institution, most patients ill enough to be hospitalized are treated with remdesivir (which shortens recovery time but has a modest effect on mortality), and those with significant supplemental oxygen requirement are treated with dexamethasone (which has been shown to reduce mortality in moderately to severely ill patients).[1] Other modalities to target inflammation more selectively, such as blocking interleukin-6 (IL-6) with tocalizumab or Janus kinase 1 and 2 with baricitinib, appear to have a more modest effect than dexamethasone but may have additive benefit.[2,3] The demonstration of the likely contribution of NETs to inflammation and coagulation and the demonstration that R406, an inhibitor of spleen tyrosine kinase and NETs activation, works in cell culture, suggests that inhibition of this pathway may be worthy of study in patients. ■

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ABSTRACT & COMMENTARY

Updated Sexually Transmitted Infection Guidelines

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The Centers for Disease Control and Prevention has updated their recommendations for the treatment of several sexually transmitted infections, including gonorrhea, trichomoniasis, bacterial vaginosis, pelvic inflammatory disease, and those due to *Chlamydia trachomatis* and *Mycoplasma genitalium*.

SOURCE: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep* 2021;70:1-187.

The Centers for Disease Control and Prevention (CDC) has updated their 2015 guidelines for the treatment of sexually transmitted infections, and some of the changes are reviewed here.

Gonorrhea. Progressively reduced antibiotic susceptibility and concerns about altering the microbiome have led to a recommendation to discard dual therapy and instead to increase the dose of ceftriaxone monotherapy to a single 500-mg intramuscular (IM) dose (1,000 mg for individuals weighing > 150 kg). If ceftriaxone is unavailable, alternative regimens that can be used are a single 800-mg oral dose of cefixime or 500 mg IM gentamicin together with azithromycin 2 grams by mouth as single doses. Patients with pharyngeal infection should have a test of cure at seven to 14 days post-treatment.

***Chlamydia trachomatis* infection.** The preferred treatment is doxycycline in a dose of 100 mg by mouth twice daily for seven days. Alternative regimens are azithromycin 1 gram orally as a single dose, which may be preferred for patients in whom adherence to a multidose regimen may be problematic, or levofloxacin 500 mg orally daily for seven days. If

single-dose azithromycin is used, a test of cure should be considered at four weeks, at least in cases of rectal infection.

Pelvic inflammatory disease (PID). Empiric treatment of PID required coverage against *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and other likely pathogens, including anaerobes, with the last consideration leading to a recommendation to add metronidazole to all regimens. Thus, the currently recommended regimen is single-dose ceftriaxone (1,000 mg IM) together with doxycycline (100 mg orally twice daily for 14 days) and metronidazole (500 mg orally twice daily for 14 days).

Trichomoniasis. Although there has been no change in the recommendation of metronidazole given as a single oral dose of 2 grams to men, the recommendation for females now is 500 mg twice daily for seven days with the aim of reducing persistent infections. Tinidazole as a single 2-gram oral dose is an alternative treatment for both males and females.

***Mycoplasma genitalium* infection.** Infection with this organism can be documented by a Food and Drug Administration (FDA)-approved nucleic acid amplification test (NAAT), but its treatment is complicated by increasing antimicrobial resistance in the face of frequent unavailability of resistance testing. If antimicrobial susceptibility is unknown because of unavailability of such testing, the CDC recommends doxycycline 100 mg orally twice daily for seven days, followed by moxifloxacin 400 mg once daily for seven days. If testing is available and the organism is susceptible to macrolides, the recommended regimen is doxycycline 100 mg orally two times/day for seven days, followed by azithromycin 1 g orally initial dose, followed by 500 mg orally once daily for three additional days (2.5 g total). If it is resistant to macrolide antibiotics instead, doxycycline 100 mg orally two times/day for seven days, followed by moxifloxacin 400 mg orally once daily for seven days.

Bacterial vaginosis. The CDC lists three preferred regimens from which to choose: metronidazole 500 mg orally twice daily for seven days, or metronidazole gel 0.75% one full applicator (5 g) intravaginally once a day for five days, or clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for seven days.

■ COMMENTARY

In addition to these antimicrobial treatment recommendations, the CDC provides additional statements regarding epidemiology, vaccination, and testing for various sexually transmitted infections. These include an expanded list of risk factors that direct testing for syphilis in pregnancy, alignment of their recommendations for human papillomavirus vaccination with those of the Advisory Committee on Immunization Practices, recommendation of universal hepatitis C virus testing, and serologic testing for diagnosis of genital herpes simplex infection.

The number of reported cases of sexually transmitted disease reached a new high for the sixth consecutive year in 2019 and, despite the appearance of COVID-19, the CDC reported a few months ago that "preliminary data suggest that many of these concerning trends continued in 2020, when much of the country experienced major disruptions to sexually transmitted disease testing and treatment services due to the COVID-19 pandemic."[1] ■

REFERENCE

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ABSTRACT & COMMENTARY

COVID-19: Effective Post-Exposure Prophylaxis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Subcutaneous administration of a combination of anti-SARS-COV-2 antibodies effectively prevented COVID-19 in most household contacts of cases.

SOURCE: O'Brien MP, Forleo-Neto E, Musser BJ, et al; Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. *N Engl J Med* 2021; Aug 4. doi: 10.1056/NEJMoa2109682. [Online ahead of print].

O'Brien and colleagues examined the efficacy of REGEN-COV administration as post-exposure prophylaxis (PEP) for prevention of asymptomatic and symptomatic COVID-19 in adult and adolescent household contacts of SARS-CoV-2-infected individuals. REGEN-COV is a combination of two monoclonal antibodies, casirivimab and imdevimab, that each bind distinct epitopes in the receptor binding domain of the viral spike protein and have neutralizing activity.

Participants were asymptomatic, ≥ 12 years of age, and were enrolled within 96 hours of a household contact being found infected with SARS-CoV-2. They were randomized to receive a single subcutaneous administration of either placebo or 1,200 mg of the monoclonals (600 mg of each). All were screened for evidence of current or past COVID-19 by polymerase chain reaction (PCR) and antibody testing, with the latter including anti-spike immunoglobulin G (IgG) and immunoglobulin A (IgA) as well as antinucleoprotein antibodies. Although all participants continued in the study, only the 1,505 who were PCR and antibody negative were included in the assessment of the primary endpoint analysis for purposes of this report — the percentage who developed symptomatic PCR-documented infection within 28 days.

The mean age was 42.9 years. Approximately one-third of patients had a body mass index (BMI) ≥ 30 and in one-eighth it was ≥ 35. Overall, 30.5% had any high-risk factor. Symptomatic SARS-CoV-2 infection occurred in 11/753 (1.5%) REGEN-COV recipients and 59/752 (7.8%) of those given placebo, for a relative risk reduction of 84% ($P < 0.001$). During weeks 2-4, two (0.3%) and 27 (3.6%) patients, respectively, developed symptomatic infection, with a relative risk reduction of 92.6%.

In combining documented asymptomatic infection with symptomatic infections, these occurred in 36/753 (4.8%) of REGEN-COV recipients and 107/752 (14.2%) of those given placebo, providing a relative risk reduction of 66.4% ($P < 0.001$). Monoclonal antibody administration also was associated with an 85.8% relative risk reduction of having a high nasopharyngeal viral load, defined as $>10^4$ ribonucleic acid (RNA) copies/mL, and the duration of having a high viral load was almost one week shorter. In patients who developed symptomatic infection, the time to resolution of symptoms was two weeks shorter in those who had received REGEN-COV.

Although monoclonals were administered subcutaneously rather than intravenously, the mean serum concentrations of casirivimab and imdevimab one day later were 22.1 mg/L and 25.8 mg/L, respectively — both above the estimated target dose for SARS-CoV-2 neutralization of 20 mg/L. The monoclonals reached peak concentrations at seven to eight days, and their mean elimination half-lives were 32.4 days and 27.0 days, respectively. At 28 days, the mean serum concentration of casirivimab was 30.4 mg/L and that of imdevimab was 24.6 mg/L.

■ COMMENTARY

Administration of the combination of casirivimab and imdevimab to at-risk outpatients with symptomatic COVID-19 has been demonstrated previously to result in an approximately 70% reduction in the incidence of hospitalization or death, rapidly reduce the viral load, and shorten the duration of symptoms.[1] That study, which clearly demonstrated therapeutic benefit, resulted in the issuance of an Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA).[2,3] Of note is that this remains the only unequivocally effective therapeutic for use in symptomatic outpatients. The study reviewed here similarly shows clear benefit in the prevention of symptomatic COVID-19 in household contacts of cases, and this resulted in the addition of this indication to the EUA.

Although the emergence of variants of SARS-CoV-2 has rendered some monoclonals ineffective, those with current significant circulation in the United States, including the Delta variant, remain susceptible to neutralization by the components of REGEN-COV. Delta also remains susceptible to neutralization by another monoclonal, sotrovimab, which similarly has received EUA for treatment of at-risk symptomatic outpatients. However, it is likely that novel variants resistant to these monoclonals will emerge eventually.

In a study evaluating the therapeutic efficacy of REGEN-COV in hospitalized patients with COVID-19, benefit was limited to those seronegative at enrollment.[4] As a consequence, it was stated by the investigators that "therapeutic use of REGEN-COV in the hospital setting may be best restricted to seronegative patients." This observation and conclusion regarding therapy of COVID-19 inpatients naturally raises the question of whether outpatient post-exposure prophylaxis also should be limited to seronegative individuals — a distinction that would require point-of-care antibody testing. However, O'Brien and colleagues stated in the discussion portion of their report that, based on an analysis that included participants who were seropositive at entry and together with the safety profile of REGEN-COV, such testing is not necessary to inform decisions about its administration in the clinic setting. That analysis is based on data presented only in the supplementary appendix. The primary endpoint of development of

symptomatic COVID-19 was reached in 5/222 (2.3%) seropositive placebo recipients and 1/235 (0.4%) of those given the monoclonal combination, yielding a relative risk reduction of 81.1%.

The recent EUA allows prophylactic administration of REGEN-COV to individuals at high risk of exposure because of SARS-CoV-2 infection in other individuals residing in the same institutional settings, such as nursing homes and prisons.[2,3] It also provides for monthly administration, albeit at a reduced dose, for those not expected to mount an adequate immune response to vaccination and who have ongoing exposure. Monthly administration is consistent with the pharmacokinetic data presented by O'Brien et al and summarized earlier. Although there are no publicly available data regarding prophylaxis with sotrovimab, this monoclonal is believed to have a more prolonged serum half-life as a consequence of modification of its Fc fragment, thus potentially allowing less frequent administration. The EUA allowance for REGEN-COV raises the issue of whether non-institutionalized individuals, such as organ transplant recipients, who fail to respond to vaccination also may be candidates for receipt of ongoing prophylaxis.

SUMMARY

- REGEN-COV has a high degree of efficacy as post-exposure prophylaxis for symptomatic illness in seronegative and seropositive household contacts of patients with COVID-19.
- REGEN-COV is effective in the treatment of seronegative, but not seropositive, patients hospitalized because of COVID-19. ■

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ABSTRACT & COMMENTARY

Treatment of Presumed Urinary Tract Infection in Afebrile Males: How Long Is Long Enough?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Symptom resolution after seven days of antibiotic therapy in afebrile males with presumed urinary tract infection was not inferior to 14 days of therapy.

SOURCE: Drekonja DM, Trautner B, Amundson C, et al. Effect of 7 vs 14 days of antibiotic therapy on resolution of symptoms among afebrile men with urinary tract infection: A randomized clinical trial. *JAMA* 2021;326:324-331.

Drekonja and colleagues performed a pragmatic clinical trial in afebrile male veterans with new onset of symptoms suggestive of urinary tract infection (UTI). Patients had been started on treatment with either ciprofloxacin (57%) or trimethoprim-sulfamethoxazole (TS, 43%) and were randomized before the eighth day after antibiotic initiation to continue their originally prescribed antimicrobial or to receive a placebo from days 7-14. One-half the 262 randomized patients were enrolled by mail.

In this population who received their care through Veterans Administration Medical Centers in Houston or Minneapolis, the median age was 69 years. Overall, a pretreatment urinalysis was obtained from 253 (95.0%) patients, and a pretreatment urine culture was obtained from 239 (87.9%). Of the 239, the culture detected > 100,000 colony forming units (CFU)/mL in 145 patients (60.7%), < 100,000 CFU/mL in 39 patients (16.3%), and no growth was detected in 55 patients (23.0%). Thus, almost 40% did not meet the usual criterion for significant bacteriuria, and approximately one-fifth had totally negative pretreatment cultures.

Resolution of symptoms by 14 days after completion of active antibiotic therapy, the primary outcome, occurred in 122/131(93.1%) and 111/123 (90.2%) of

the seven- and 14-day treatment groups, respectively. UTI recurrence occurred in 9.9% and 12.9%, respectively. The incidence of adverse events also did not significantly differ between the two groups.

In a post hoc analysis with stratification by the results of urine culture, there were no significant differences in symptom resolution whether the culture yielded > 100,000 CFU/mL, was positive but with < 100,000 CFU/mL, or was culture negative. Symptom resolution occurred in > 90% in each cohort, and in the group without detectable bacteriuria, this occurred in 28/30 (93.3%) of the seven-day group and 25/25 of the 14-day group.

■ COMMENTARY

This study, which took place in 2014-2019, was modestly underpowered because enrollment was discontinued when funding ran out. Furthermore, the fact that one-fifth had negative pretreatment urine cultures also affects interpretation of the results. Despite these facts and others, there was not a hint of benefit of extending treatment from seven to 14 days.

Perhaps most intriguing is the fact that symptoms resolved with antibiotic therapy as frequently in those without detectable bacteriuria as in those with high or intermediate levels of bacteriuria. Of course, there was no control group who did not receive antibiotics — something which could have shed light in the interpretation of the results.

It can be concluded from these results that seven days of antibiotic therapy is associated with a high frequency of resolution of urinary tract symptoms in afebrile males and that extending therapy for another seven days does not provide additional benefit. It also can be concluded that the etiology of new-onset urinary symptoms in patients without bacteriuria is unknown, and the fact that they resolved raises question about at least some patients with true bacteriuria. We must face the fact that our understanding of UTI in males is severely lacking. ■

ABSTRACT & COMMENTARY

Adherence to the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Does Not Lead to Improved Clinical Outcomes

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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SYNOPSIS: A longitudinal study from a single healthcare system found that adherence to the Medicare Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) resulted in some changes in process measures, but did not lead to improvements in clinical outcomes.

SOURCE: Barbash IJ, Davis BS, Yabes JG, et al. Treatment patterns and clinical outcomes after the introduction of the Medicare Sepsis Performance Measure (SEP-1). *Ann Intern Med* 2021;174:927-935.

Even though evidence-based guidelines for the management of sepsis have been developed and disseminated, morbidity and mortality for sepsis remain unacceptably high. In 2015, the Centers for Medicare and Medicaid Services (CMS) implemented the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), which requires hospitals to collect and report data on their adherence to a multi-component treatment bundle. Since then, substantial debate has occurred regarding the usefulness of SEP-1, particularly regarding whether it leads to improvement in patient survival. Therefore, Barbash and colleagues sought to determine whether adherence to SEP-1 leads to improved outcomes in hospitalized patients with community-onset sepsis.

The investigators conducted a longitudinal study using data from 11 academic and community hospitals that are part of a large healthcare system (University of Pittsburgh Medical Center Health System [UPMC]). Patients included in the study were 18 years of age or older and had community-onset sepsis and organ failure within six hours of arrival to the emergency department. SEP-1-adherent therapy was defined as intravenous (IV) antibiotics, lactate measurement, and crystalloid IV fluid administration within three hours of suspected infection, and repeated lactate

measurement and administration of a vasopressor within six hours of suspected infection. Time zero was defined as the time a fluid culture (e.g., blood, urine, respiratory, or other) was ordered. Patients were stratified into two groups for comparison: before SEP-1 (January 2013-September 2015) and after SEP-1 (January 2016-December 2017). Exclusion criteria included transfers to other institutions outside the UPMC system, hospital stays < 24 hours or > 30 days, early comfort care, and repeated encounters. The primary outcomes of interest were admission to the intensive care unit (ICU), in-hospital mortality, and discharge to home among survivors.

There were 29,051 patients in the before-SEP-1 group and 22,759 in the after-SEP-1 group. Not surprisingly, adherence in the after-SEP-1 group was much greater for three-hour lactate measurement ($P < 0.001$), antibiotic administration within three hours ($P = 0.001$), and adherence to administration of 30 mL/kg of IV fluids within three hours ($P < 0.001$). There was no meaningful difference in the rate of vasopressor administration within six hours ($P = 0.61$). A time series analysis determined that SEP-1 was associated with a 50% increase in checking lactate levels, a 10% increase in broad-spectrum antibiotic use, and a 30% increase in IV fluid administration within three hours of culture orders if the expected rate of trends that occurred before SEP-1 had continued.

Adherence to SEP-1 was not associated with statistically significant or clinically important outcomes, including admission to the ICU ($P = 0.055$), in-hospital mortality ($P = 0.87$), or discharge home ($P = 0.145$). Subgroup analysis showed a similar null effect in patients with septic shock. No statistically significant differences in the primary outcomes were found in patients requiring vasopressors before or after SEP-1. Finally, there was some evidence of ascertainment bias as a result of increased culture ordering in the after-SEP-1 group.

■ COMMENTARY

Adherence to an authoritative and widely implemented sepsis bundle based on solid clinical evidence failed to improve outcomes in patients with community-onset sepsis and septic shock. Indeed, this is an unexpected and disappointing finding. But credit should be given to Barbash and colleagues for conducting this study and reminding us that even the most rational and plausible dogma should not be above reproach.

So why did following the SEP-1 bundle not improve outcomes? There are several possible explanations. One is that we still do not have a deep enough understanding of the pathophysiology of sepsis to know how and when to intervene. Another is the inherent weakness of measuring serum lactate, which can be elevated in numerous other conditions besides sepsis and infections. This can lead to the over-administration of IV fluids that can be harmful in certain patients with comorbid illnesses, such as congestive heart failure or those on hemodialysis.

A third explanation is the possibility that many patients with sepsis were misdiagnosed. There is no gold standard definition of sepsis useful at the bedside that accurately takes into account the many nuances of how infections manifest in the human body. It also is important to remember that many infections, especially pneumonia, are caused by viruses, and large volume fluid resuscitation and broad-spectrum antibiotics are not indicated in such cases.

[Adherence to SEP-1 was not associated with statistically significant or clinically important outcomes, including admission to the intensive care unit ($P = 0.055$), in-hospital mortality ($P = 0.87$), or discharge home ($P = 0.145$).]

The study had a few limitations that should not be overlooked. First, it might have been more pragmatic to define time zero as when a fluid culture actually was collected, rather than ordered. Whether this had any impact on the findings is not clear. Second, the overall mortality was relatively low, raising the possibility that many patients were not sick enough for small increases in quality of care to make a substantial difference. Third, there was no control group to compare with the after-SEP-1 group, although this would have been difficult to construct since SEP-1 was instituted as a national policy. Finally, the study was conducted at a healthcare system well known for its high quality in emergency and critical care medicine, thus limiting the generalizability to other healthcare settings and institutions.

Should CMS require that hospitals continue to comply with SEP-1? The study by Barbash raises serious questions about the appropriateness of that policy. Further studies are warranted, especially from smaller hospitals and other geographic areas. ■

Updates

By Carol A. Kemper, MD, FACP

California Mandating Healthcare Worker COVID-19 Vaccination

In an unprecedented public health action, the California State Public Health Officer ordered on Aug. 5, 2021, all healthcare workers (HCWs) in the state to receive full COVID-19 vaccination before Sept. 30 or essentially relinquish their positions.[1] For the purposes of this order, this includes any paid or unpaid worker in an indoor facility who provides patient care or has access to patients for any reason. This order trumps the California State Governor's mandate on July 26, requiring all state workers and workers in healthcare and high-risk congregate settings either to show proof of vaccination or submit to weekly testing. Those who are unable to receive vaccination are required to wear an N95 (or similar) mask at all times while working and submit to twice-weekly SARS-CoV-2 testing.

Justification for the California Department of Public Health (CDPH) mandate was based on the continued increase in cases throughout the state, with documentation of 9,300 outbreaks and 113,000 outbreak-related cases since January 2021, with evidence of increasing numbers of cases in HCWs. Despite the availability of a vaccine since early 2021, the current vaccination rate in California is ~63%, with an additional 10% with partial vaccination — certainly better than most states — but leaving one-third of California's population 12 years of age and older vulnerable to infection. Further, HCWs provide care to the most elderly and the most vulnerable in our society, who remain at the highest risk of severe disease and death.

The CDPH order allows for exemptions for qualified medical reasons and on religious grounds. Religious exemption and "personal belief against vaccination" are hot-button topics, but essentially U.S. citizens do not have a legal right to object to vaccination based on religious grounds or personal beliefs. In 1944, the U.S. Supreme Court in *Prince v. Massachusetts* ruled that the "right to practice religion freely does not include liberty to expose the community or the child to communicable disease or the latter to ill health or death." This was the principle driving measles vaccination in the Hasidic community in Brooklyn, NY, in 2018-2019 after two years of ongoing measles infections. However, politically, it has been difficult to eradicate religious exemption as an excuse to decline vaccination. Currently in the United States, all 50 states allow for medical exemption for vaccination for school-age children, and 44 states allow for religious exemption (Connecticut, California, Maine, Mississippi, New York, and West Virginia do not), although generally these exemptions apply to school-age children.

In fact, few religions have an absolute objection to vaccines, mainly the First Church of Christ, Scientist, as well as several smaller churches that rely on faith healing and prayer. These include small Christian churches, such as the Church of the First Born, End Time Ministries, Faith Tabernacle, and First Century Gospel Church, most of which are located in the southern United States. Numbers of Christian Scientists have been dwindling steadily, and as of 2009, only about 50,000 members existed across the United States (0.015% of the population).

Other religious groups opposed to vaccines but that do not prohibit their members from getting them include some Orthodox Jewish communities, some Dutch Reformed Churches, and some Amish communities, as well as some Muslim fundamentalists. Interestingly, some of the more conservative churches actually believe that vaccines are "a gift from God." Although they had a past objection to vaccines, Jehovah's Witnesses decided in 1952 that vaccines were not contrary to God's commandment or in violation of the everlasting covenant with Noah. Following an outbreak of polio in an Amish community in 2005 and the measles outbreak in 2018-2019 in the largely Orthodox Jewish community in Brooklyn, NY, some of these communities embraced vaccination, at least temporarily. But larger outbreaks of measles still continue in the Netherlands in Dutch Reformist groups.

In the United States, Muslims generally are not opposed to vaccines under the principle of necessity, meaning they are necessary for healing and cannot be prohibited by religious law. In 2017, Islamic world leaders signed the Dakar Declaration of Vaccination outlining the importance of vaccination for the protection of children, allowing parents to make their own decisions for their children. For those religions that might object based on the use of cow, pig, or fetal

tissue in the manufacture of vaccines, both Islamic organizations and Jewish scholars agree that injectable porcine gelatin is permissible, and Hindus have no theological objection to possible trace bovine material in vaccines. Catholics are decidedly pro-vaccination, even when aborted fetal tissue may have been used in vaccine manufacturing, since the vaccine recipient is not complicit in any previous act, and if there is no other alternative, it is "lawful to use these vaccines if danger to the health of children exists or to the health of the population as a whole."

This recent surge in COVID-19 cases demonstrates that the "health of the population" is at risk — and we believe this is largely preventable. HCWs might object based on ostensible religious grounds, but they have a moral obligation to their patients and their communities to get vaccinated, and a responsibility to set an example for others. In California, HCWs who decline the vaccine on the basis of religious belief are required to submit a signed declination form attesting to the religious belief (not just check a box). But the new CDPH order does not impose a "sincerely held belief" standard, nor does it require employees to provide supporting information beyond a signed affidavit (in contrast, a signed physician's letter is required for medical exemption). However, if an employer is aware of facts that provide an objective basis for questioning the sincerity of the religion/belief, the employer is justified in requesting additional supporting information.[2] Based on population statistics, healthcare facilities could reasonably anticipate one or two individuals with true religious objections out of an employee base of ~3,000 individuals.

Based on the Civil Rights Act of 1964, employers are required to accommodate religious practices. Legal precedent has allowed for religion to be defined broadly and to encompass not just organized religions but also "sincerely held beliefs." Religion under the law may encompass non-theistic and moral beliefs — such as veganism in certain circumstances — but a "sincerely held belief" has been shown legally to not include concerns about the health effects of vaccination. As of 2019, 15 states (the last available count) still allowed for personal belief/philosophical exemption.

As the result of measles outbreaks in Disneyland in 2014 and repeated outbreaks of pertussis in schools, health officials lobbied the California state legislature to remove the personal belief clause as an exemption for existing vaccine requirements (e.g., for entry to private or public elementary and secondary schools and daycare centers), resulting in Senate bill 277 in 2015.[3] This had an immediate successful effect on vaccination rates in school kids throughout California (parents can choose to home school their children if not vaccinated). However, the senate bill did "allow exemption from future immunization requirements deemed appropriate by the State Department of Public Health for either medical reasons or personal beliefs." Legal experts say the bill does include a clause allowing CDPH to mandate new vaccines for "any other disease deemed appropriate by the department ... in order to achieve total immunization for appropriate age groups against disease." Sounds like there might be a legal battle ahead.

It is hoped that this public health order will not lead to a critical shortage of HCWs in the state. Following dismissal of an employee lawsuit in June 2021, when Houston Methodist Hospital mandated COVID-19 vaccination, 178 employees were suspended for two weeks and 150 employees lost their jobs. ■

REFERENCES

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Seasonal Coronavirus in Stem Cell Transplant

SOURCE: Pinana JL, Xhaard A, Tridello G, et al. Seasonal human coronavirus respiratory tract infection in recipients of allogeneic hematopoietic stem cell transplantation. *J Infect Dis* 2021;233:1564-1575.

From 2012-2018 (pre-COVID-19), these authors examined the clinical characteristics, risk factors, and morbidity for seasonal human coronavirus (HCoV) infections in a cohort of allo-hematopoietic stem cell transplant recipients (HSCT) obtained from the Spanish and European bone marrow transplant registries. A total of 402 allo-HSCT recipients developed 449 episodes of upper and lower respiratory tract infection from seasonal HCoV, as demonstrated by a positive polymerase chain reaction (PCR). These included NL63, 229E, OC43, and HKU1. Upper respiratory tract infection (URTI) was defined as one or more upper respiratory symptoms (pharyngitis, rhinorrhea, sinusitis, otitis) without chest radiographic or computed tomographic evidence of pneumonia. Seasonal HCoV infection occurred a median of 222 days after transplantation. URTI occurred in 73%, and the remainder had probable/confirmed lower respiratory tract infection (LRTI). Hospitalization was required in 18% and admission to the intensive

care unit (ICU) was required in 3%. Supplemental oxygen was required in 13%.

All-cause mortality for the entire cohort was 7% at three months and 16% for those with LRTI. Three conditions at the time of seasonal HCoV infection were associated with increased mortality, including neutropenia, corticosteroid use, and ICU admission.

Although seasonal HCoV infections were observed throughout the year, most (83%) occurred during the cold months of late December to March, and OC43 was the most frequent subtype observed (38%). The Alphacoronavirus genus (NL63 and 229E) predominated in 2012-2013 and Betacoronavirus (OC43 and HKU1) predominated in 2014-2018. There was a trend toward higher mortality in those infected with Betacoronavirus group than the Alphacoronavirus group. Two or more seasonal HCoV subtypes were detected simultaneously in 15 cases (3%).

Although corticosteroids have become a mainstay of treatment of COVID-19, their use in this group of patients was associated with higher mortality, although this may simply be a marker of disease severity. The amount of corticosteroids employed was not specified. As observed many times with COVID-19 infection, chest computed tomography scans are more sensitive for LRTI, and chest radiographics alone may miss evidence of pneumonia. ■

CME QUESTIONS

1. **Of children hospitalized with SARS-CoV-2-positive test results:**

   a. nearly all are significantly symptomatic with COVID-19.

   b. about half have no symptoms related to the SARS-CoV-2 infection.

   c. about half require intensive care.

   d. nearly 15% die.

2. **Which of the following is correct regarding the updated 2021 Centers for Disease Control and Prevention guidelines for management of sexually transmitted infection?**

   a. Women with trichomoniasis should be treated with a single 2-gram dose of metronidazole.

   b. The preferred treatment for *Chlamydia trachomatis* infection is doxycycline 100 mg twice daily for seven days plus a single 1-gram dose of azithromycin.

   c. Gonorrhea should be treated with a combination of ceftriaxone and doxycycline.

   d. Empiric treatment of pelvic inflammatory disease should consist of the combination of ceftriaxone as a single dose, doxycycline 100 mg twice daily for 14 days, and metronidazole 500 mg twice daily for 14 days.

3. **Which of the following is correct regarding the combination of the two monoclonal antibodies, casitivimab and imdevimab, under Emergency Use Authorization?**

   a. It is effective in the prevention of SARS-CoV-2 infection in household contacts of infected individuals.

   b. It is ineffective against the Delta variant of the virus.

   c. It must be given intravenously.

   d. Anaphylaxis occurs in 10% of recipients.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.