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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Extensive Loss of Health at Six Months in Survivors of COVID-19

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

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SYNOPSIS: A cohort study from the U.S. Department of Veterans Affairs found many survivors of COVID-19 had significant loss of health six months after their acute illness, with greater risk associated with severity of the acute infection.

SOURCE: Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021; Apr 22. doi: 10.1038/s41586-021-03553-9. [Online ahead of print].

Most individuals with COVID-19 experience a full recovery. However, a significant minority do not and instead experience long-lasting symptoms, for which the etiology remains poorly understood. Therefore, Al-Aly and colleagues sought to comprehensively analyze the post-acute sequelae of COVID-19 using a high-dimensional approach.

The study included a cohort of 73,435 patients from the Veterans Health Administration (VHA) with COVID-19 who survived at least the first 30 days after a COVID-19 diagnosis and who were not hospitalized. These patients were compared to a control group of 4,990,835 VHA patients who did not have COVID-19 and were not hospitalized. More than 99.99% of standardized differences between the two groups were < 0.1 after adjustment, indicating that their baseline characteristics were similar. The investigators also evaluated the risk of death associated with 379 diagnoses (based on ICD-10 codes), 380 medication classes, and 62 laboratory tests beyond the first 30 days from COVID-19 diagnosis.

After the first 30 days of illness, COVID-19 survivors had a higher risk of dying (hazard ratio [HR], 1.59; range 1.46-1.73). The most commonly affected organ system for COVID-19 sequelae was the respiratory tract (28.51 per 1,000 COVID-19 patients at six months). There was an increased

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Infectious Disease [ALERT]

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incidence of bronchodilator use (22.23 per 1,000 COVID-19 patients at six months), antitussive and expectorant use (12.83), anti-asthmatic use (8.87), and steroid use (7.65). An excess burden of nervous system disorders was found, including nervous system signs and symptoms (14.32 per 1,000 COVID-19 patients at six months) and headaches (4.10). Mental health problems were more frequent as well, including sleep-wake disorders (14.53 per 1,000 COVID-19 patients at six months), anxiety and fear-related disorders (5.42), and trauma and stress-related disorders (8.93). The led to an excess burden of incident use of antidepressants (7.83) and benzodiazepines, sedatives, and anxiolytics (22.23).

Many COVID-19 survivors had cardiovascular sequelae as a result of their infection, including cardiac dysrhythmias (8.41 per 1,000 COVID-19 patients at six months), circulatory signs and symptoms (6.65), chest pain (10.08), coronary atherosclerosis (4.38), and heart failure (3.94). Gastrointestinal issues included esophageal disorders (6.90), abdominal pain (5.73), and an increased use of laxatives (9.22) and antidiarrheal agents (2.87). An excess burden in incident acute pulmonary embolism (2.63 per 1,000 COVID-19 patients at six months) and use of anticoagulants (16.43) was found. Finally, there was an excess burden of poor general well-being in the COVID-19 survivors. They had increased malaise and fatigue (12.64 per 1,000 COVID-19 patients at six months), muscle disorders (5.73), and musculoskeletal pain (13.89). Abnormal laboratory values included decreased hemoglobin (31.03 per 1,000 COVID-19 patients at six months), decreased hematocrit levels (30.73), decreased serum albumin (6.44), and increased alanine aminotransferase (7.62).

Next, the investigators compared COVID-19 survivors who were hospitalized (n = 13,654) to subjects with influenza who survived at least 30 days after hospitalization (n = 13,997). Similar to the preceding findings, the COVID-19 survivors had a higher burden of pulmonary and extrapulmonary sequelae, including neurologic disorders (19.78 per 1,000 hospitalized COVID-19 patients at six months), mental health disorders (7.75 [4.72, 10.10]), metabolic disorders (43.53), cardiovascular disorders (17.92), gastrointestinal disorders (19.28), coagulation disorders(14.31), pulmonary embolism (18.31), and malaise and fatigue (36.49).

Finally, the investigators used the receipt of influenza vaccination in odd and even months as a negative control. They tested the association between receipt of influenza vaccination in even months (n = 762,039) compared to odd months (n = 599,981) with all 821 of the analyzed high-dimensional clinical outcomes in the study. None of the associations reached the threshold of statistical significance.

■ COMMENTARY

Post-acute COVID-19 syndrome, also known as long COVID, is now recognized as a multi-organ disease with a multitude of symptoms. The study by Al-Aly and colleagues is important because it quantifies the risk survivors of COVID-19 have for negative effects on their health six months after their acute illness. Although the idea is not proven, many experts believe that an overactive immune response to the acute COVID-19 infection, rather than ongoing viral replication, is the underlying biological mechanism.

Sometimes other viral illnesses can produce post-infectious sequelae, but COVID-19 appears to be unique in this regard in terms of the number of symptoms and their duration. The Centers for Disease Control and Prevention (CDC) is conducting multi-year studies to investigate post-COVID conditions further.[1]

There are a few limitations to the study. First, the investigators used a database from the VHA, so males were overrepresented in the patient population. Second, the impact of SARS-CoV-2 variant strains and widespread vaccination on long-term symptoms remains to be elucidated. Finally, with high-dimensional data sets, the number of features can exceed the number of observations, thus increasing the risk for confounding.

As more people survive COVID-19, many will need additional follow-up and care. Since this will burden an already stretched

healthcare system further, additional studies are needed urgently to help inform future health system planning. ■

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ABSTRACT & COMMENTARY

Bacteremic Urinary Tract Infection in the Elderly — Sometimes It's a Guessing Game

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: In elderly patients with bacteremic urinary tract infection (UTI), symptoms of UTI were present in only one-third of patients, only four-fifths had fever, and just three-fifths had an early diagnosis of UTI.

SOURCE: Laborde C, Bador J, Hacquin A, et al. Atypical presentation of bacteremic urinary tract infection in older patients: Frequency and prognostic impact. *Diagnostics (Basel)* 2021;11:523.

Laborde and colleagues retrospectively evaluated the symptoms present in inpatients at the Dijon University hospital in patients 75 years of age or older who proved to have bacteremia and bacteriuria caused by the same gram-negative bacillus over a one-year period. They identified 105 such patients who had a mean age of 85.3 years and 61.9% of whom were women. Approximately one-fifth of them had a chronic urinary catheter. Infection was community-acquired in 49.5% of patients, hospital-acquired in 24.8%, and was acquired while residing in a long-term care facility in 25.7%. Patient falls were reported in 21 patients (20%), and reduction in an activity of daily living score was identified in 17 (16.2%).

Symptoms or signs of urinary tract infection (UTI) were present in 38 patients (36.2%), fever (> 38.3° C) was present in 61 patients (59.8%), and signs of sepsis were present at the time of blood culture phlebotomy in 85 patients (81.6%). Women were significantly less likely than men to have symptoms of UTI (44.7% vs. 71.6%; $P = 0.01$). A clinical diagnosis of UTI was made in only 58% of the entire cohort. The 90-day mortality was 23.6%. Independent predictors of lesser mortality were fever at presentation and early diagnosis of UTI — but the presence or absence of UTI symptoms was not associated with prognosis.

■ COMMENTARY

Dealing with suspected or proven UTI in the elderly, particularly residents of long-term care facilities, is a persistently perplexing problem. The frequent lack of urinary symptoms in bacteremic UTI has been identified previously. On the one hand, we are faced with the problem of overuse of urinalyses and urine cultures together with an inability to unequivocally distinguish UTI from urinary bacterial colonization in many instances. On the other hand, we have to deal with the fact that potentially life-threatening UTI may be present in the absence of localizing symptoms in the elderly. Thus, in this retrospective analysis of elderly patients with bacteremic UTI, symptoms of UTI were present in only one-third, and only four-fifths had fever and just three-fifths had an early diagnosis of UTI — with early diagnosis associated with better outcomes.

[Dealing with suspected or proven UTI in the elderly ... is a persistently perplexing problem.]

Does altered mental status warrant evaluation and, if so, how do you distinguish such changes that commonly occur as a result of "sundowning" or of medications? The routine examination of urine in such cases will lead to overprescribing and contribute to the problem of antibiotic resistance that is so prevalent in many long-term care facilities.

As clinicians recommending care for these patients, we, thus, are caught on the horns of a dilemma — one with which we do not seem to be making much progress in its resolution. ■

ABSTRACT & COMMENTARY

Staphylococcal Prosthetic Valve Endocarditis: Drop the Rifampin? And the Gentamicin?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: In a retrospective study, the investigators failed to find evidence of benefit of adjunctive rifampin therapy in patients with staphylococcal prosthetic valve endocarditis.

SOURCE: Le Bot A, Lecomte R, Gazeau P, et al. Is rifampin use associated with better outcome in staphylococcal prosthetic valve endocarditis? A multicenter retrospective study. *Clin Infect Dis* 2021;72:e249-e255.

Le Bot and colleagues retrospectively examined 180 episodes of prosthetic valve endocarditis (PVE) managed at three French referral centers from 2000-2018 to evaluate the role of adjunctive rifampin therapy, which was administered during 101 episodes (56.1%). The mean age was 70.4 years, and approximately three-fourths were male. A bioprosthesis was affected in 111 patients (61.7%). Cerebral emboli occurred in 53 patients (29.4%).

The etiologic agent was *Staphylococcus aureus* in 114 episodes (63.3%), and 17 (14.9%) of these were methicillin-resistant. The remaining 66 episodes (36.7%) were due to coagulase negative staphylococci (CoNS), 39 (59.0%) of which were methicillin-resistant.

All patients received antibiotics intravenously as recommended by international (U.S. and European) guidelines: cefazolin or an antistaphylococcal penicillin with gentamicin for methicillin-susceptible infection and, for those that were methicillin-resistant, a glycopeptide or daptomycin with gentamicin.[1] The baseline characteristics of those who did and did not receive rifampin were similar, with the exception of the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), which was etiologic in 14/64 (21.9%) and 3/50 (6.0%), respectively ($P = 0.04$). No isolate was rifampin-resistant. Rifampin was initiated a median of seven days after diagnosis of PVE at a median dose of 1,200 mg per day for a median duration of 33 days. However, it was discontinued in 31 (30.9%) patients because of severe adverse events, the most frequent of which was hepatotoxicity in 11 patients. Fifty-one (28.3%) patients underwent valve surgery, 94% of them within 60 days of diagnosis of PVE.

The overall in-hospital mortality was 23.6%, increasing to 35.4% at 12 months with no significant difference related to use of rifampin, with the exception of hospital length of stay, which was nine days longer among rifampin recipients. Relapse occurred in 6/101 (5.9%) rifampin recipients and 7/79 (8.5%; $P = 0.65$) of those who did not receive rifampin. None of the six relapse isolates associated with rifampin therapy were resistant to this rifamycin. Only three factors were independently and significantly associated with greater 12-month mortality: cerebral emboli, definite endocarditis by Duke criteria, and MRSA infection.

■ COMMENTARY

Guidelines of both the American Heart Association and the European Society for Cardiology recommend that staphylococcal PVE be treated with a triple antibiotic combination. They each recommend intravenous (IV) cefazolin or an antistaphylococcal penicillin for methicillin-susceptible infections or either a glycopeptide or daptomycin for those caused by methicillin-resistant organisms, either combined with IV gentamicin for the first two weeks with rifampin for the entire six-week duration of therapy — and state that these are Class I recommendations. This three-drug recommendation may have arisen originally from a report of small numbers of patients with methicillin-resistant CoNS PVE, with most of the patients having undergone valve replacement and, thus, making the results uninterpretable — as I indicated in a review a dozen years ago.[2] Furthermore, my interpretation of the use of gentamicin for these infections is that it clearly adds toxicity in the absence of demonstrated clinical benefit. This is consistent with a report by the Spanish Collaboration on Endocarditis.[3]

Le Bot and colleagues, reviewing the most recent literature regarding the use of rifampin, together with their own experience, reach a similar conclusion, as do Galar et al.[1] Remember — "primum non nocere" — drop the rifampin and gentamicin. ■

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ABSTRACT & COMMENTARY

Childhood Diarrhea — Judicious Use of Diagnostic Tests

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: In the United States, rapid diagnostic testing for panels of potential gastrointestinal pathogens in children increases the yield of identifying rare pathogens, but, overall, does not change length of stay for hospitalized patients or reduce hospital charges.

SOURCE: Cotter JM, Thomas J, Birkholz M, et al. Clinical impact of a diagnostic gastrointestinal panel in children. *Pediatrics* 2021;147:e2020036954.

Globally, diarrheal disease is the second leading cause of preschool-age mortality. In the United States alone, hundreds of millions of dollars are spent each year to manage children with gastroenteritis. Nonetheless, most episodes of diarrhea in children resolve spontaneously with adequate hydration and do not require specific etiology-directed treatment. Thus, early diagnosis of severe, treatable, and potentially lethal causes of diarrhea would be helpful — both to target helpful disease-limiting therapies appropriately and to avoid inappropriate use of unhelpful antimicrobial agents.

During the past several years, advances in molecular diagnosis of pathogens have prompted the development of test panels that rapidly identify the presence/absence of dozens of pathogens (including viruses, bacteria, and parasites) in stool samples. At the same time, though, there have been questions about the value of these relatively expensive tests in clinical practice. Now, Cotter and colleagues provide data about the clinical utility of these panels, as compared to traditional stool testing, in identifying pathogens, and about the effect of this testing in altering patient outcomes in a large population of children.

Using results of stool tests done in the Children's Hospital Colorado microbiology laboratory from 2013 through 2017, Cotter and colleagues compared data from 24 months prior to the adoption of gastrointestinal pathogen test panels with data from one to three years after the availability of these tests in children younger than 19 years of age. (The first year of initial panel test availability was not included in the analysis since practices were transitioning at that time.) Samples came from inpatient and outpatient settings affiliated with an academic children's hospital and with three community children's hospitals. The panel used in that setting included tests for 22 different gastrointestinal pathogens.

Testing was done only on non-formed stool. Decisions to use the testing were made by clinicians and were not affected by the investigators. However, to avoid providing clinicians with "too much information" that might prompt inappropriate practice, the laboratory did not routinely report results of enteropathogenic, enteroaggregative, and enterotoxigenic *E. coli* (because of the uncertain clinical significance of these "pathogens" in the United States) or of *Clostridioides difficile* during the first year of life (because this usually represents asymptomatic colonization at this age).

A total of 12,222 stool tests were included in the study, representing 8,720 medical encounters by 6,733 individual patients. Overall, 40% of patients had a complex chronic medical condition pre-dating the acute diarrhea illness, and 60% of patients were hospitalized at the time of testing. Stool testing, per patient population size, increased by 21% during the final years of the study. More patients underwent multiple different stool tests during the era prior to panel testing (after which it became more common to do only the panel of tests).

During the two years of panel testing, stool tests were more likely to be positive (40%, as compared to 11% during the years prior to panel testing). Prior to panel testing, *C. difficile*, *Salmonella*, *Campylobacter*, Shiga toxin-producing *E. coli*, and *Giardia* were the most commonly identified pathogens. Norovirus, sapovirus, rotavirus, and adenovirus were identified more commonly with the pathogen panel testing than before. With the panel testing, 9% of patients had multiple pathogens identified concurrently. Of those with a positive panel test, 54% had a virus, 38% had *C. difficile*, 18% had other bacteria, and 5% had a parasite.

Panel test results were available to clinicians more quickly than were the previous conventional test results (four vs. 31 hours). With the panel, but not including *C. difficile*-positive patients for this analysis, antimicrobial therapy was given based on results for 3.7% of children, as compared to 1.9% with previous conventional testing.

For hospitalized children who received antimicrobial treatment based on test results, the length of stay in the hospital was shorter during the panel testing era (three vs. five days). Overall for the entire cohort of patients, though, the length of stay was not different during the pre-panel and post-panel eras. With shorter stays, the overall hospital charges were less for those with focused bacterial or parasitic treatment than for those without such treatment, but the hospital charges, overall, were not different based on the type of testing done.

[The authors ... concluded that focused gastrointestinal pathogen panel testing yielded more diagnostic information more quickly than did previous testing.]

The authors rightly concluded that focused gastrointestinal pathogen panel testing yielded more diagnostic information more quickly than did previous testing, and panel testing helped identify more children who could benefit from focused antimicrobial treatment. However, the beneficiaries of such gains represented only about 2% of the patients tested. The authors recommended that these new diagnostic tests be used judiciously, since many tests were done in generally healthy children without severe gastrointestinal disease who had low pre-test probability of requiring etiology-focused therapy.

The authors also wisely noted that the problem of unnecessary "low value" use of pathogen panels is seen when testing for central nervous system and respiratory pathogens as well. These still-new pathogen panels offer added value when used judiciously for children with high clinical suspicion of finding a treatable pathogen.

■ COMMENTARY

In an editorial accompanying the paper by Cotter and colleagues, Tarr and Tarr concluded that molecular enteric microbiology testing is "a model opportunity for diagnostic stewardship to maximize worth and minimize wasteful expense."[1] They noted that panel testing has been shown in other adult and pediatric settings to reduce unnecessary antibiotic prescriptions and, in the case of viruses being identified, to reduce unnecessary pursuit of additional tests and diagnoses.[1]

Cotter and colleagues cleverly modeled judicious use of test results by choosing not to report findings that might prompt inappropriate treatment — infections with some *E. coli* that neither require nor are altered by antimicrobial therapy and *C. difficile* in infants (who, by lacking the toxin receptor or other reasons, seem not to become symptomatic with *C. difficile* colonization). Whether by decree of the laboratory or by education of clinicians, efforts should be made to prevent "positive" findings of test panels from triggering unhelpful treatment.

So, which children are most likely to benefit from gastrointestinal pathogen panel testing? Results are most likely to helpfully alter treatment for children with acute grossly bloody diarrhea and those whose illness includes severe abdominal pain and/or high fever.[1]

We face similar concerns while dealing with patients with lower respiratory tract infections. In that setting, care could be altered with rapid access to tests identifying influenza (for which specific medication might be indicated) and respiratory syncytial virus (which might prompt fewer radiographs looking for evidence of bacterial pneumonia).[2] However, knowledge about the presence or absence of other viral pathogens might not alter treatment decisions. Observational studies can document potential benefits of such testing, but "real world" cost effectiveness data are necessary to determine which patients in which settings actually should undergo such testing.[2] ■

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ABSTRACT & COMMENTARY

Blood Culture Contamination — Risks and Adverse Effects

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: In addition to identifying several patient risk factors for contamination of blood culture specimens, the authors also highlighted various adverse clinical and financial adverse effects.

SOURCE: Klucher JM, Davis K, Lakkad M, et al. Risk factors and clinical outcomes associated with blood culture contamination. *Infect Control Hosp Epidemiol* 2021; Apr 26:1-7. doi: 10.1017/ice.2021.111. [Online ahead of print].

Klucher and colleagues examined risk factors for blood culture contamination as well as clinical outcomes associated with such contamination at a single center in Little Rock, AR, in 2014-2018. Only 2% of specimens for culture were drawn through central venous access devices. During that time, 1,504 (10.9%) of 13,782 blood cultures were true positives. Of the remaining, 1,012 (7.3%) were considered contaminated and 11,266 (81.7%) were negative — these served as cases and controls, respectively.

Multivariate analysis identified the following independent risk factors for contamination: increasing age, Black race, increasing body mass index (BMI), chronic obstructive pulmonary disease (COPD), paralysis, and sepsis with septic shock on presentation. The presence of metastatic cancer was protective. "Code sepsis" cases were associated with a numerically greater risk of contamination.

Blood culture contamination was associated on multivariate analysis with a one day longer length of hospital stay (7.9 days vs. 6.6 days), greater duration of antibiotic administration (6.2 days vs. 5.2 days), greater hospital charges ($35,008 vs. $28,875), higher rate of acute kidney injury (26.7% vs. 26.3%), higher frequency of ordered transthoracic echocardiograms (27.4% vs. 19.2%), and increased in-hospital mortality (8.0% vs. 4.6%). Individual antibiotics were not included in the multivariate model, but, on univariate analysis, blood culture contamination was associated with more frequent and prolonged vancomycin use.

■ COMMENTARY

It is no surprise that blood culture contamination leads to unnecessary antibiotic administration, but, as reported here, it leads to an additional array of negative effects. These include the ordering of additional laboratory tests, such as further blood cultures and transthoracic echocardiograms, the occurrence of acute kidney injury, prolongation of hospital stay, and increased costs. Another effect in some cases is unnecessary hospitalizations in patients discharged from the emergency department and then recalled when the laboratory reports the blood culture result.

The authors pointed out that identification of patient characteristics associated with an increased risk of blood culture contamination may allow focusing on them in attempts to reduce the rate. Among the methods employed to avoid contamination is the use of phlebotomy teams. However, in this study, and as is true at many hospitals, blood cultures were obtained by nurses in the emergency department. Another method is avoidance of central line draws. In this study, only 2% were obtained from this site. Enforcement of the use of sterile collection techniques is critical, and feedback of contamination rates to individual phlebotomists may be useful.

[Enforcement of the use of sterile collection techniques is critical, and feedback of contamination rates to individual phlebotomists may be useful.]

Another approach for which there is evidence of benefit is the use of diversion devices, which are a response to evidence that it is the initial 1 mL to 2 mL that often is the source of culture contamination. Such a device actively diverts and sequesters a small amount of the initial recovered blood, with blood for culture collected via a separate flow path. ■

ABSTRACT & COMMENTARY

Nocardia Brain Abscess

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A review of 24 cases of *Nocardia* brain abscess, two-fifths of which occurred in apparently non-immunocompromised hosts, had variable outcomes, but antibiotic therapy was effective in most.

SOURCE: Corsini Campioli C, Castillo Almeida NE, O'Horo JC, et al. Clinical presentation, management, and outcomes of patients with brain abscess due to *Nocardia* species. *Open Forum Infect Dis* 2021;8:ofab067.

Corsini Campioli and colleagues reviewed the cases of adults with brain abscesses caused by *Nocardia* spp. seen from Jan. 1, 2009, to June 30, 2020, at the Mayo Clinic in Rochester, MN. The 24 cases represented 9.7% of the 247 brain abscess patients. The median age of the cases was 65 years and 75% were male. Comorbidities were frequent, including chronic kidney disease (45.8%), hypertension (33.3%), and diabetes mellitus (29.1%). Approximately one-half had malignancies. Three (12.5%) were recipients of hematopoietic stem cell transplants and seven (29.1%) had undergone solid organ transplantation (SOT), with a median interval from transplantation to diagnosis of *Nocardia* brain abscess of 876 days. Nine patients had received a median 10 mg daily dose of prednisone for more than two weeks and seven patients (9.2%) had received other immunomodulatory therapies. Two infections were the result of central nervous system trauma. Four transplant patients were receiving trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii* pneumonia.

One-third of the patients had more than one brain abscess. Cutaneous nocardiosis was present in 12.5%, and 37.5% had pulmonary involvement, with the latter being present in 71% of the immunocompromised patients but in only 29% of those without known immunocompromise.

The diagnosis was confirmed by culture of brain abscess material in all 24 patients, and the most frequent isolate was *Nocardia farcinica*, which accounted for nine cases (37.5%). *Nocardia* was isolated in blood culture from only three patients, although all had had blood cultures.

Various antimicrobials were used alone or in combination with trimethoprim-sulfamethoxazole, to which all 24 isolates were susceptible. Corticosteroids, most often dexamethasone, were initially administered to 10 patients (41.6%). The median duration of parenteral administration of antibiotics was 21 days, and all received at least two antibiotics (counting trimethoprim-sulfamethoxazole as one) for the first six weeks of therapy. Subsequently, 10 patients received monotherapy at some point, with most receiving at least one orally administered antibiotic, most often trimethoprim-sulfamethoxazole and/or linezolid.

Seven patients (29.1%) died after a median interval of 169 days after diagnosis, but four of these deaths were related to comorbidities. Complete clinical and radiographic resolution was achieved by 14 patients (58.3%), while two survived with permanent neurological deficits and one had disease progression ultimately requiring surgical intervention.

■ COMMENTARY

Resistance to trimethoprim-sulfamethoxazole generally is rare and it remains the antimicrobial of choice for the treatment of nocardiosis, including cases of brain abscess. Reports indicate that susceptibility is maintained even in cases in which this infection arises in patients receiving prophylactic doses of trimethoprim-sulfamethoxazole — something that was true in four patients in the series reviewed here. This lack of the emergence of resistance may be the result of the use of low, infrequently administered doses that exert limited selective pressure — or to non-compliance with prophylaxis. At any rate, it is recommended that initial therapy in such patients should include trimethoprim-sulfamethoxazole. Other antibiotics to which *Nocardia* frequently are susceptible include amikacin, imipenem, linezolid, ceftriaxone, and minocycline. Patients with histories of trimethoprim-sulfamethoxazole allergy may undergo testing and, if indicated, desensitization.

Generally, it is recommended that combination therapy be administered intravenously initially and then for approximately six weeks, after which including orally administered agents can be considered. It should be noted that these recommendations generally are based on low-quality evidence. For SOT

patients with cerebral nocardiosis, the Infectious Diseases Community of Practice of the American Society of Transplantation recommends, largely based on expert opinion alone, initial intravenous therapy with imipenem, amikacin, and trimethoprim-sulfamethoxazole.[1] They recommend that alternative individual agents that may be substituted in the regimen include linezolid, ceftriaxone, cefotaxime, or minocycline. ■

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ABSTRACT & COMMENTARY

Cytomegalovirus Viremia in Liver Transplant Recipients

By Joseph F. John, MD, FACP, FIDSA, FSHEA

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SYNOPSIS: Cytomegalovirus (CMV) viremia emerges in the majority of CMV seronegative recipients of liver transplants from CMV seropositive donors, most often within the first post-transplant month. The only independent risk factor identified was increasing donor age.

SOURCE: Singh N, Winston DJ, Razonable RR, et al. Risk factors for cytomegalovirus viremia following liver transplantation with a seropositive donor and seronegative recipient receiving antiviral therapy. *J Infect Dis* 2021;223:1073-1077.

Singh and colleagues previously reported a randomized controlled trial in cytomegalovirus (CMV) seronegative patients who received liver transplants from seropositive donors (D+R-) that found that the use of preemptive valganciclovir was associated with fewer episodes of CMV disease when compared to its prophylactic administration.[1] The trigger for initiation of preemptive valganciclovir was the occurrence of CMV viremia at any level as detected with a sensitive polymerase chain reaction (PCR). Now the same group has published a post hoc analysis evaluating the risk factors for the occurrence of that viremia in those assigned to preemptive therapy.

The final analysis included 94 patients who had weekly tests for CMV viremia totalling 1,197 blood samples. Of these, 79 (84%) developed viremia during the 100 days after transplantation, with a mean interval of 24.5 days to the first positive result. The cumulative incidences of viremia among these 79 patients were 20%, 44%, and 70% by two, three, and four weeks, respectively. The only factor identified as an independent risk factor for the development of viremia was greater donor age, with an odds ratio of 2.20 for each quartile increase in donor age (95% confidence interval [CI], 1.07 to 4.52; $P = 0.031$).

■ COMMENTARY

This study shows that CMV viremia is very common after transplantation of a CMV-positive liver into a CMV-negative recipient. The value of the study is to alert clinicians that a CMV syndrome could occur as early as two weeks from infection propagated by a CMV-positive donor and will be detected, on average, about three weeks after transplantation.

The study does not address the adverse effects of new infection in recipients, but it did find that the rates of rejection were no higher in recipients with viremia than those without viremia. The authors suggested that immune senescence is responsible for the higher rates of viremia in older patients, as noted in earlier studies of healthy seropositive patients. What is not known, as stressed by the authors, is what variables in donors may contribute to the rate of viremia in recipients — a facet that should be studied further.

Dr. Nina Singh in Pittsburgh has a long and illustrious career in transplant infectious diseases. Along with her multicenter colleagues, she again has opened a window of opportunity with this observation in liver transplantation. This study was conducted with National Institute of Allergy and Infectious Diseases/National Institutes of Health oversight and can be found at ClinicalTrials.gov, registration number NCT01552369. ■

REFERENCE

1. Singh N, Winston DJ, Razonable RR, et al. Effect of preemptive therapy vs antiviral prophylaxis on cytomegalovirus disease in seronegative liver transplant recipients with seropositive donors: A randomized clinical trial. *JAMA* 2020;323:1378-1387.

Updates

By Carol A. Kemper, MD, FACP

Party Affiliation and Social Distancing

SOURCE: Leventhal A, Hongying D, et al. Association of political party affiliation with physical distancing among young adults during the COVID-19 pandemic. *JAMA Intern Med* 2021;181:399-403.

Disparate public health messaging from political officials, news media, and internet outlets has occurred throughout the COVID-19 pandemic in the United States. Some have wanted to ascribe lower rates of compliance with public health guidance to political affiliation.

These authors examined the political affiliation of a group of young adults, aged 18 to 25 years, mostly residing in Los Angeles County, with their compliance with physical distancing guidelines and risk activities for COVID-19 infection between May 18 and Aug. 3, 2020. The cohort (n = 3,396) was recruited originally in high school in 2013 as part of an existing health behavior survey. Of those with currently valid contact information, 2,179 (67.5%) agreed to participate in this study. The mean age of the participants was 21.2 years, 61% were female, and 84.8% lived in Los Angeles County. Political party affiliation was collapsed into four categories: Democrat (43.1%), Republican (7.2%), Independent/other (15.8%), or don't know/declined to answer (34%). Questions regarding physical distancing (sometimes/rarely vs. always/usually/have not been in public places) were given a binary outcome (0 or 1). Engaging in four different kinds of social/recreational activities (visiting a public venue, e.g., a mall, attending or hosting a party > 10 people, or going to a restaurant) also were given binary scores (1 or 0), which were summed as continuous outcomes.

Those who identified as Republican were twice as likely to engage in social/recreational activities as Democrats (mean standard deviation [SD] 3.6 vs. 1.9, $P < 0.001$), and somewhat more likely than either Independents/other (mean SD 2.2) or those who don't know/declined to state (mean SD 2.2) (both $P < 0.001$). Participants identifying as Republicans also were significantly more likely to engage in infrequent physical distancing (24.3%) compared with any of the other three groups (Democrats [5.2%], Independent/other [6.6%] or don't know/decline to state [5.7%]; each comparison, $P < 0.001$). The proportion of participants who perceived a risk of contracting COVID-19 or a chance of dying of COVID-19 was no different between any of the groups. Further, substance use, impulsivity, and delinquency scores (as measured by inventory impulsivity scales or a sum of generally bad behavior in 9th grade) also had no apparent relationship with a willingness to disregard social distancing and to engage in social/recreational activities.

The psychology of behavior is difficult to pin down. We once participated in study of safer sex behavior involving five medical centers on the West Coast. I was struck that none of our ongoing, repetitive, safe sex messaging, T-shirts, posters, and free condoms made much of a difference in either the frequency of safer sex or the number of partners. But one fundamental finding was that outcomes differed depending on where people fell on the pessimism vs. optimism personality scales. Only those classified as "pessimists" actually believed that bad things could happen to them and were willing to modify their behavior, whereas those scoring higher on the "optimism" scale only saw the future as getting better, regardless. So perhaps mask wearers are simply more pessimistic about the future? ■

Ethnicity and Occupation as Risk Factors for COVID Infection

SOURCE: Pathela P, Crawley A, Weiss D, et al. Seroprevalence of SARS-CoV-2 following the largest initial epidemic wave in the United States: Findings from New York City, May 13-July 21, 2020. *J Infect Dis* 2021; Apr 9:jiab200. doi: 10.1093/infdis/jiab200. [Online ahead of print].

A large serosurvey of COVID-19 antibody was conducted in a convenience sample of 52,941 New Yorkers following the first surge of COVID-19 infection in that city in the spring of 2020. Free antibody testing (using the Liaison SARS-CoV-2 S1/S2 assay, DiaSorin, Saluggia, Italy) was offered to New York City residents 18 years of age or older during May 13 to July 21, 2020. The project was advertised through the media, local channels, and the internet, although recruitment was done online, where participants scheduled an appointment for testing and completed a survey. Approximately 14.3% of participants did not have a fully completed survey and were excluded, leaving 45,367 participants. Non-Hispanic whites (908/100,000 residents) and Staten Island residents (2,512/100,000) were disproportionately

represented compared with people 65 years of age or older (260/100,000), non-Hispanic Blacks (236/100,000), and those residing in Brooklyn, the Bronx, or other poorer neighborhoods (all below 460/100,000). Men and women were similarly recruited for participation.

Nearly one-quarter of the participants (23.6%) had antibodies to SARS-CoV-2. If this figure is extrapolated, it implies that more than 1.5 million New Yorkers had COVID-19 infection during the first wave of infection in that city. Hispanics and non-Hispanic Blacks had the highest prevalence of antibody (35.3% and 33.5%, respectively) compared with Asians/Pacific Islanders (20.2%) and non-Hispanic whites (16%). Geographically, the highest prevalence of antibody was found in the Bronx (37%) and other poorer neighborhoods (35.3%), compared with Manhattan (19.4%) and Staten Island (21%). At the time of the survey, about 72% of participants were employed. Antibodies were observed in 27.4% of those who worked outside the home compared with 22.2% of those who did not work outside the home. Seroprevalence was observed in 31.6% of essential workers, 30% of healthcare workers, and 20% of those in education, compared with 23.8% of those who were not working.

Roughly two-thirds of participants (60%) provided a history of symptoms of COVID-like illness (CLI). This observation suggests that study recruitment was perhaps skewed toward those individuals interested in confirming previous infection. Approximately one-third (34%) of those reporting CLI symptoms were seropositive, compared with 21% of participants with no CLI who were seropositive. Of all the key CLI symptoms observed, loss of taste or smell was the most strongly associated with the presence of antibody.

New York City Public Health officials concluded these data show how certain groups of people were disproportionately affected by the epidemic, in part because they were working in the front-line lower-paying jobs in healthcare, grocery stores, and transit with higher levels of exposure. However, unemployment also was seen as a risk factor for COVID-19 infection in this survey. Poorer neighborhoods and households with increased numbers of people were also disproportionately hit harder.

Interestingly, in the southern San Francisco Bay Area, the Asian/Pacific Islander community was disproportionately affected for some of the same reasons — in our area, they tend to take the positions in skilled nursing facilities and as home health aides, and also live in multigenerational households. COVID-19 infection literally ripped through our local skilled nursing facilities, sometimes infecting the entire resident population and most of the workers within weeks with a single SARS-CoV-2 strain. However, I believe this says more about the lack of good infection prevention practices and ability to quickly test and cohort the sick in these kinds of facilities than the ethnicity of the workers or their pay.

One important finding in this study was the lack of participation of the elderly. Although 61% of participants were 18-44 years of age, only 7% were 65 years of age or older. Strategies for recruiting the elderly for COVID-19 studies and vaccination programs must overcome their lack of computer skills and ability to enlist online. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **Which of the following is correct regarding the adverse sequelae of COVID-19 survivors in the Veterans Health Administration study at six months?**

   a. The respiratory tract was the most frequently affected organ system.

   b. Cardiovascular symptoms were absent.

   c. Mortality was not greater than that seen in non-COVID-19 patients.

   d. The frequency of adverse sequelae did not differ from that seen in patients who had had influenza rather than COVID-19.

2. **Which of the following is correct regarding the results of the study of staphylococcal prosthetic valve endocarditis by Le Bot and colleagues?**

   a. Rifampin was only effective when given in doses four times greater than standard dosing.

   b. Rifampin was effective when given with vancomycin but not with beta-lactams.

   c. Rifampin use was the only factor independently significantly associated with reduced mortality.

   d. Rifampin was discontinued in almost one-third of patients because of adverse effects.

3. **Multiple gastrointestinal pathogen panels are most useful for diagnostic testing in which children?**

   a. Children with mild acute watery diarrhea

   b. Children with grossly bloody diarrhea

   c. Children with a history of recent antibiotic use

   d. Children in outpatient settings

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.