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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Vitamin D and COVID-19?

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; Department of Pediatrics, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates

SYNOPSIS: Low levels of vitamin D are associated with in-hospital mortality in patients with COVID-19, but causality is not yet known.

SOURCE: Angelidi AM, Belanger MJ, Lorinsky MK, et al. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: A cohort of COVID-19 hospitalized patients. *Mayo Clin Proc* 2021;96:875-886.

Vitamin D has immunomodulatory properties as well as anti-inflammatory activity. In fact, vitamin D deficiency has been associated with both an elevated risk of acute respiratory infection and worse clinical outcomes following critical illnesses. Vitamin D deficiency also is associated with problems, such as obesity, older age, and cardiac disease, that are risk factors for bad outcomes with COVID-19. Thus, investigators have wondered if vitamin D deficiency (and potential treatment) might influence the clinical course of COVID-19.

Angelidi and colleagues performed a retrospective study of adults who were hospitalized at one of two hospitals (one in Boston and one in New York) with COVID-19 from February to mid-May 2020. They reviewed records and compared patient data to 25-hydroxyvitamin D levels determined either at the time of hospital admission or within the preceding six months.

A total of 144 patients were included in the study: 79 with vitamin D levels of less than 30 ng/mL and 65 with levels of 30 ng/mL or higher. The median age was 66 years. Overall, 44% of subjects were male, and 42% were non-Hispanic Blacks. The median body mass index was 29. More than 90% of included individuals had at least one significant medical comorbidity, with hypertension (74%), hyperlipidemia (55%), and diabetes (44%) being especially common. Cough, dyspnea, fever, and/or malaise were presenting symptoms in most of the patients. Steroids were used in the management

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Infectious Disease [ALERT]

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of 24% of patients, antivirals were used in 10%, an antibiotic (usually azithromycin) was used in 72%, and hydroxychloroquine was used in 44%. Treatment included oxygen in 64% of patients and mechanical ventilation in 27%; 39% of patients required intensive care. In-hospital mortality was 18%.

Mortality was higher (25% vs. 9%) in patients with low (< 30 ng/mL) vs. higher 25-hydroxyvitamin D levels. The timing (during the six months prior to admission vs. during the hospitalization) of vitamin D testing was not related to mortality. Of dozens of variables, only vitamin D level, age, malignancy, and chronic obstructive pulmonary disease were associated with an increased risk of in-hospital death with COVID-19. Doing careful statistical analysis, researchers found hypovitaminosis D was strongly associated with in-hospital mortality, even independent of medical comorbidities. The inverse association between vitamin D level and mortality was present whether 20 ng/mL or 30 ng/mL was used as the cut-off (thus, whether there was vitamin D deficiency or insufficiency).

■ COMMENTARY

Angelidi and colleagues carefully and convincingly showed that low vitamin D levels are associated with mortality in patients hospitalized with COVID-19. Of course, this association does not necessarily imply causality, and it does not prove that either preventive or therapeutic vitamin D administration would alter mortality.

Low vitamin D levels have previously been associated with other factors that give risk for poor outcomes with COVID-19, including obesity and diabetes. However, in Angelidi's careful analysis, low vitamin D levels were independently associated with in-hospital mortality from COVID-19. There likely is either a causal impact of hypovitaminosis on the course of COVID-19 or there are other unmeasured variables, such as outdoor activity, that link both hypovitaminosis D and death from COVID without the vitamin D level directly affecting the course of COVID-19.

Hypovitaminosis D does seem causally related to other respiratory infections, even if a causal link has yet to be proven for COVID-19. Low vitamin D levels are seen more commonly in patients with acute respiratory infection than in healthy controls, and vitamin D does have an effect on immune functioning.[1] However, studies of vitamin D supplementation to prevent respiratory infections have yielded mixed results.[1] A new meta-analysis of studies of vitamin D as prevention for acute respiratory infection in children aged 1 to 15 years showed a significant (P = 0.018) but modest (odds ratio, 0.92, with 95% confidence interval, 0.86 to 0.99) effect when supplements of 400 IU/day to 1,000 IU/day were administered for up to 12 months.[1]

It is important to consider the timing of effects of intervention. Whether vitamin D provides protection against acquiring SARS-CoV-2 or other respiratory pathogens, different mechanisms of action could be necessary for vitamin D to be effective therapeutically. Griffin and colleagues recently summarized the various stages of COVID-19 and eloquently reviewed potential effects of various interventions at various times before, during, and after the actual infection.[2]

A recent placebo-controlled study of high-dose vitamin D as treatment of established COVID-19 infection included 236 hospitalized adults in multiple centers in Brazil (mean age 56 years, mean 25-hydroxyvitamin D level 21 ng/mL at entry into the study, with 20 ng/mL being the upper limit of "deficiency").[3] Vitamin D levels increased significantly with treatment, and no significant adverse events were noted.[3] However, hospital length-of-stay, need for intensive care, need for mechanical ventilation, and mortality were not altered by vitamin D treatment.[3]

Thus, these new data remind us that hypovitaminosis D is at least associated with respiratory infections, but that preventive supplementation only modestly reduces the risk of acquiring infection (in children for non-COVID-19 infection), and therapeutic administration of

vitamin D does not alter the course of adults being hospitalized with COVID-19. Vitamin D generally is safe in the preventive and therapeutic doses used, but further convincing data will be required before vitamin D is recommended to either prevent or treat COVID-19.

Two years ago, Hu and colleagues reported that patients with chronic hepatitis B had lower vitamin D levels than did healthy controls, and among hepatitis B patients, viral loads were inversely correlated with vitamin D level.[4] Vitamin D also has been proposed for the prevention and treatment of a variety of other conditions, including diabetes, multiple sclerosis, and cognitive decline. Observational studies are supportive, but systematic reviews and randomized controlled trials are lacking.[5]

Although it seems reasonable to supplement individuals with or at risk of hypovitaminosis D to maintain a "normal" vitamin D level,[6] definitive studies do not yet support widespread recommendations to use vitamin D specifically to prevent or treat these other conditions.[5] ■

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ABSTRACT & COMMENTARY

Children Are Not Major Spreaders of COVID-19 in Schools

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

Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

SYNOPSIS: A surveillance study from Singapore found a very low risk of COVID-19 transmission for children in schools, especially preschools.

SOURCE: Yung CF, Kam K, Nadua KD, et al. Novel coronavirus 2019 transmission risk in educational settings. *Clin Infect Dis* 2021;72:1055-1058.

Although children generally have less severe illness due to novel coronavirus disease 2019 (COVID-19) compared to other age groups, cases of severe illness and the development of multisystem inflammatory syndrome in children (MIS-C) are concerning to healthcare providers and parents alike. The risks associated with transmission of COVID-19 in children have not been fully elucidated. Therefore, Yung and colleagues aimed to identify these risks in schools to better inform public health control policies.

The study was conducted using a comprehensive nationwide surveillance program in Singapore. In February and March 2020, three potential COVID-19 seeding incidences occurred in three separate educational settings: two preschools and one secondary school. Students with a close contact were placed into quarantine for 14 days from the exposure. Those in quarantine who developed fever or respiratory symptoms were admitted to the hospital and needed at least two negative nasopharyngeal (NP) swabs taken on two separate days to be discharged. Schools were not routinely closed when a positive case was detected, but other containment measures were implemented, such as canceling extracurricular activities, performing terminal cleaning, and staggering recess breaks. However, one of the preschools was closed for 14 days after several staff members tested positive.

In the first incidence, a 12-year-old student attending a secondary school became infected by a family member. The student attended school on the first day of symptoms, then was diagnosed with COVID-19 and hospitalized. Eight students (mean

age 12.8 years) who were close contacts (i.e., in the same classroom) developed symptoms, and all subsequently tested negative for COVID-19. In the second incidence, a 5-year-old also became infected by a family member and attended preschool on the first day of symptoms. Thirty-four preschool students (mean age 4.9 years) developed symptoms during the incubation period and were tested for COVID-19, all of whom were negative. The third incidence involved a cluster of 16 adult staff members at a preschool. Seventy-seven children (73% of the total enrollees, mean age 4.1 years) were evaluated, of whom eight were symptomatic and 69 were asymptomatic. All tested negative for COVID-19. The remaining 27% who were not tested did not develop any symptoms while under close monitoring and quarantine.

In all three instances, approximately 40% of symptomatic individuals were tested by multiplex polymerase chain reaction (PCR) for other viral pathogens. Approximately half were positive for rhinovirus, adenovirus, or metapneumovirus.

■ COMMENTARY

The major finding of the study by Yung et al was that no documented cases of COVID-19 transmission occurred in children from two preschools and one secondary school following exposure to symptomatic individuals. This suggests that the risk of transmission for children in these settings is low. Indeed, children appear to be at less risk for COVID-19 than for other viral illnesses, such as influenza. Although the underlying mechanism for the reduced risk of COVID-19 infection in children seen in this and other studies remains uncertain, one possible explanation is that young children express fewer ACE2 genes. The spike protein of SARS-CoV-2 binds to the ACE2 receptor on respiratory epithelial cells prior to entry.[1] Thus, children might be less susceptible to SARS-CoV-2 on a cellular level. However, recent reports have shown an increase in affinity for ACE2 receptors by SARS-CoV-2 variants, including the B.1.1.7 and B.1.351 strains.[2] How this will affect the risk of infection by novel coronavirus variants in children remains to be determined.

The study had some limitations. First, the interval between the timing of sample collection and the last exposure ranged from five to 11 days. However, the authors noted it was unlikely that the timing of sample collection would have missed infected cases because the duration of PCR detection for COVID-19 is long in children. Second, only three sites were included in the study, which limits the generalizability to other settings. Third, as mentioned earlier, the study was conducted before the emergence of novel SARS-CoV-2 variants, which have increased transmissibility compared to the original strain. Fourth, it is well known that COVID-19 can lead to a myriad of symptoms, not just respiratory ones, that the exposed children were being monitored for. Finally, adolescents were not included in the analysis and, therefore, the findings should not be extrapolated to this age group.

A targeted strategy of keeping symptomatic children away from school may be effective in preventing COVID-19 transmission, rather than blanket school closures. Allowing schools to remain open has important downstream effects, such as alleviating parents from having to miss work because of homebound children. It appears that the focus should be on adult staff members at preschools and secondary schools, rather than children, to reduce the spread of COVID-19 in these settings. Thus, COVID-19 vaccination of preschool and secondary school staff is strongly encouraged. ■

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ABSTRACT & COMMENTARY

Response to COVID-19 Vaccination in Solid Organ Transplant Recipients

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The apparent immunogenicity of available SARS-CoV-2 messenger ribonucleic acid vaccines is markedly reduced in solid organ transplant recipients, providing concern that they may not provide protection from symptomatic COVID-19 in many.

SOURCES: Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA* 2021; Mar 15:e214385. doi: 10.1001/jama.2021.4385. [Online ahead of print].

Chavarot N, Ouedrani A, Marion O, et al. Poor anti-SARS-CoV-2 humoral and T-cell responses after 2 injections of mRNA vaccine in kidney transplant recipients treated with belatacept. *Transplantation* 2021; Apr 8. doi: 10.1097/TP.0000000000003784. [Online ahead of print].

Boyarsky and colleagues examined the antibody response to receipt of a COVID-19 messenger ribonucleic acid (mRNA) vaccine in 436 solid organ transplant recipients (SOT). Their median age was 55.9 years, 61% were women, and 89% were white. A median of 6.2 years after transplantation, approximately half of the patients received the BNT162b2 vaccine from Pfizer-BioNTech, while the other half of them received mRNA-1273 from Moderna. Eighty-three percent were taking tacrolimus, while 54% were taking corticosteroids, and 66% were taking mycophenylate. Less than 10% were taking azathioprine, sirolimus, or everolimus.

Serum antibody was tested a median of 20 days after administration of the first vaccine dose. The antibody tests used detected spike protein antigens and have been demonstrated to correlate with neutralizing activity. Antibody was detectable in only 76 subjects (17%; 95% confidence interval [CI], 14% to 21%). Older age and receipt of an antimetabolite immunosuppressant (mycophenylate or azathioprine) each were associated with reduced responses, as was receipt of BNT162b2 compared to mRNA-1273.

Chavarot and colleagues examined serological and cellular immune responses to vaccination with BNT162b2 of renal transplant recipients who had received, together with other immunosuppressives, abatacept, a monoclonal antibody directed at the coreceptor molecule CTLA4 — and found even poorer responses. Two-thirds of the 101 patients were men, and the median interval since transplantation was 59 months. The Abbott and Wantai tests were used, each at separate clinics. These detect antigens in the receptor binding domain of SARS-CoV-2 and have reported sensitivities of 97% and 90%, respectively. Antibody was detected in only two subjects (2.0%) 28 days after the first dose and in only two of 35 (5.7%) tested one month after the second dose. T-cell responses, as determined by an IFN- γ release assay by EliSpot in response to SARS-CoV-2 spike antigens, were observed in two of 40 patients (5.0%) at day 28, and seven of 23 patients (30.4%) at day 60.

■ COMMENTARY

These brief studies demonstrate that the available SARS-CoV-2 mRNA vaccines have markedly reduced immunogenicity in solid organ transplant recipients when compared to the general population cohorts in clinical trials in whom seropositivity has been reported to result in 100% of mRNA-1273 and BNT162b2 single-dose recipients by days 15 and 21, respectively. Perhaps more disturbing, in the study by Chavarot and colleagues, the second dose of BNT162b2 did not result in significantly improved antibody response rates, with only 5.0% being seropositive. Furthermore, in that same study, only 5.0% had evidence of T-cell immunity after the first dose, although this increased to 30.4% at two months. However, it must be kept in mind that the patients in that study differed from many other SOT recipients in that they were all receiving abatacept — although whether this was determinative is not known.

The immune response to natural SARS-CoV-2 infection in immunnosuppressed patients also is of interest, and some studies have found that antibody and cellular immune responses were similar to those of a non-immunosuppressed control group. In a study by the same group responsible for the paper reviewed here, SARS-CoV-2 infection resulted in the development of antibody to the viral spike protein in 78% after a median of 98 days.[1] Favà et al found that solid organ transplant recipients had serologic and cellular immune responses similar to those of a control population, although with a delay in some.[2] These results seem consistent with a number of reports that, despite their immunosuppressive therapy, the outcome of COVID-19 in solid organ transplant recipients is similar to that of patients not receiving such therapy. In fact, immunosuppressive agents (dexamethasone, baricitinib, and perhaps tocilizumab) have been demonstrated to provide clinical benefit in selected patients with COVID-19. We have a lot to learn.

Overall, the available data indicate that surviving COVID-19 in immunosuppressed patients is a potent immunizing event, while receipt of an mRNA vaccine is much less so. Whether these impaired measures of immunogenicity predict lack of protection against severe COVID-19, however, remains to be seen. But I think we should maintain a high level of concern and begin thinking about alternative protective strategies in these patients. ■

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ABSTRACT & COMMENTARY

Reduced Incidence of Kawasaki Disease During the Time of COVID-19

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

Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

SYNOPSIS: Mitigation in response to COVID-19 has been associated with decreases in common childhood respiratory infections. The incidence of Kawasaki disease from April to December 2020 was significantly decreased from the same period during the previous eight years.

SOURCE: Shulman S, Geevarghese B, Kim KY, Rowley A. The impact of social distancing for COVID-19 upon diagnosis of Kawasaki disease. *J Pediatric Infect Dis Soc* 2021; Mar 23. doi: 10.1093/jpids/piab013. [Online ahead of print].

Records from the Center for Kawasaki Disease at Lurie Children's Hospital and other affiliated Chicago-area pediatric hospitals were accessed for the periods Jan. 1, 2020, until March 31, 2020 (pre-social distancing), and April 1, 2020, until Dec. 31, 2020. Data from the same periods in the years 2012 through 2019 were accessed as well.

The number of cases of Kawasaki disease (KD) diagnosed in the January to March pre-social distancing period of 2020 was 13 (95% confidence interval [CI] from 2012 to 2019: 13.0, 21.7), which is comparable to the corresponding period in 2012-2019. In contrast, the number of KD cases diagnosed from April to December 2020, the coronavirus mitigation period, was 15 cases, significantly lower than the number of cases diagnosed annually from April to December in 2012 to 2019 (2012 to 2019 mean = 46.6; 95% CI: 41.5, 51.7; $P = 0.01$). To take into account the slight decrease in KD cases from January to March 2020 compared with previous years, the authors calculated the ratio of incidence from April to December cases divided by January to March cases. Again, there was a substantial decrease in April to December cases in 2020, with the incidence ratio of 1.15 (95% CI from 2012 to 2019 ratios is 1.86, 4.15; $P = 0.008$).

■ COMMENTARY

It has long been theorized that KD may be an abnormal immune response to a variety of common childhood respiratory viral infections, perhaps preferentially affecting children who may have polygenic disposition. The finding of decreased KD incidence seen in this study is parallel to the findings of Hatoun et al for common respiratory and enteric viral and some bacterial infection diagnoses during the months of mitigation.[1] Thus, this finding supports the hypothesis that KD is triggered by a common childhood infectious respiratory agent.[2,3]

Shulman et al also looked at the possibility that the decreased number of KD cases during the April to December 2020 mitigation period was the result of parents not bringing their ill children to clinics for care. To address this, the authors examined the number of patient emergency department visits and admissions for acute pyelonephritis from 2016 to 2020. They found no decrease corresponding to the mitigation period.

Hatoun et al reported that COVID-19-related childhood mitigation social distancing measures, including the closure of schools, a stay-at-home advisory, and the use of masks, coincided with a marked reduction in diagnoses of many common infectious diseases in children.[1] The most pronounced declines were observed in infections transmitted by the respiratory route, with influenza, croup, and bronchiolitis essentially disappearing during the social distancing period.[1]

Shulman et al found that the number of cases of KD in early 2020 (January to March) was comparable to the number in the same months during the eight previous years, but that the number of KD diagnoses during the 2020 social distancing era (April to December) was very significantly lower than in the comparable period of 2012 to 2019 — less than one-third of the number previously observed ($P = 0.008$). This finding supports the hypothesis that the agent(s) of KD are transmitted via the respiratory route and that transmission of the agent(s) also is reduced by coronavirus mitigation practices.

Since last year, my colleagues have cared for a small number of children with COVID-19-related

multisystem inflammatory syndrome in children (MIS-C) at Lucille Packard Children's Hospital, and our Medicine service has cared for several adults at Stanford Hospital with MIS-A. The parallels to KD are striking. However, similar to the experience of Hatoun et al,[1] while we have been incredibly busy caring for COVID-19 adult patients on our wards and in our intensive care units, the reduction in hospital admissions for severe influenza and other viral respiratory infections has been dramatic. ■

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ABSTRACT & COMMENTARY

Antibiotic Therapy: How Long Is Long Enough (or too Long)?

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The Centers for Disease Control and Prevention and the American College of Physicians have provided advice on the best practice regarding the duration of antibiotic therapy for a number of common infections.

SOURCE: Lee RA, Centor RM, Humphrey LL, et al. Appropriate use of short-course antibiotics in common infections: Best practice advice from the American College of Physicians. *Ann Intern Med* 2021; Apr 6. doi: 10.7326/M20-7355 [Online ahead of print].

The Centers for Disease Control and Prevention (CDC) and the American College of Physicians have provided best practice advice addressing the duration of antibiotic therapy for a series of infections commonly encountered in the primary care setting. These infections include acute bacterial exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, uncomplicated urinary tract infections, and non-purulent cellulitis. Their recommendations are the following:

• **Acute bacterial exacerbations of chronic pulmonary disease:** five days.

They actually refer to this entity as acute bronchitis in adults with chronic obstructive pulmonary disease and describe clinical signs of bacterial infection. These are listed as "increased sputum purulence in addition to increased dyspnea and/or increased sputum volume."

• **Community-acquired pneumonia:** five days.

This recommendation refers to non-immunocompromised adults who achieve clinical stability and follows the Infectious Diseases Society of America/American Thoracic Society guideline.

• **Uncomplicated bacterial cystitis in nonpregnant adult females:** nitrofurantoin for five days, trimethoprim-sulfamethoxazole for three days, or fosfomycin as a single dose.

• **Uncomplicated pyelonephritis in nonpregnant adults:** depending on susceptibility test results — a fluoroquinolone for five to seven days, or trimethoprim-sulfamethoxazole for 14 days.

• **Non-purulent cellulitis in all adults:** an antibiotic active against streptococci for five to six days.

■ COMMENTARY

This best practice advisory is useful, but some of its recommendations are perhaps more conservative than necessary. One important example is illustrated by a very recently published randomized trial that found three days of antibiotic therapy was noninferior to eight days in hospitalized patients with moderately severe community-acquired pneumonia who achieved clinical stability after three days of therapy.[1]

On the other hand, the recommendation for the Food and Drug Administration-approved use of fosfomycin as a single dose may be insufficient in women with uncomplicated lower urinary tract infection, as shown in a recent randomized trial demonstrating this to be significantly less effective than a five-day course of nitrofurantoin.[2]

This advisory serves as a good starting point in convincing clinicians to shorten unnecessarily prolonged durations of antibiotic therapy and, thus, reduce the selective pressure leading to the evolution of antimicrobial resistance. However, there is a long way to go. ■

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ABSTRACT & COMMENTARY

Candida Endocarditis

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A review of a national administrative database examined 703 patients with *Candida* endocarditis and found the greatest risk factor for mortality was underlying liver failure, while a history of opiate abuse was associated with a reduced risk of death.

SOURCE: Huggins JP, Hohmann S, David MZ. *Candida i*nfective endocarditis: A retrospective study of patient characteristics and risk factors for death in 703 United States cases, 2015-2019. *Open Forum Infect Dis* 2020;8:ofaa628.

Using the nationwide Vizient database, Huggins and colleagues retrospectively examined information regarding 703 inpatients with *Candida* endocarditis seen at 179 clinical sites from Oct. 1, 2015, through April 30, 2019. The median number of cases per site was five (range, 1-32), and 57.2% were male.

Diabetes was present in 28.6% of patients, and 31.2% had chronic kidney disease, with 10.4% of the total cohort receiving hemodialysis. Only 14 patients (2.2%) were human immunodeficiency virus-infected, while 22 (3.1%) had undergone solid organ transplantation, and 31 (4.4%) had hematologic malignancy in either the present or the past. Hepatitis C virus infection was documented in 199 patients (27.0%), and hepatitis B virus infection was documented in 20 patients (2.8%). Fifty-five patients (7.8%) had acute or subacute liver failure, and 25 (3.6%) had documented cirrhosis. Present or past opioid abuse was documented in 213 cases (30.3%), while there was a history of use of other illicit substances in 128 cases (18.2%).

A valve procedure was performed on 158 patients (22.5%) during their hospitialization, with no significant difference in mortality in those who did so (23.1%) and those who did not (19.3%; $P = 0.370$). Approximately one-third of procedures each involved the aortic and tricuspid valves, while in one-eighth the mitral valve was addressed. Intervention involved more than one valve in 17.1%. Almost all aortic valve and mitral valve interventions (98% and 90%, respectively) involved replacement procedures, while only 80.8% of those involving the tricuspid valve resulted in valve replacement.

Most patients received an echinocandin or fluconazole, and both were received together in 28.6%. The mortality rate prior to discharge was 16.2%. The strongest independent predictor of death was liver failure. In an adjusted analysis, a number of other predictors were associated with mortality risk, while opiate abuse was associated with a lower risk (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.2 to 0.9).

■ COMMENTARY

This study has many of the drawbacks to be predicted when the information is limited to that in an administrative database. Examples include lack of clear insight into the proportion of cases that might have involved prosthetic cardiac valves, lack of information on the *Candida* species involved, and limited insight into the precise courses of antifungal therapy.

The 2016 guideline of the Infectious Diseases Society of America recommends administration of a lipid formulation of amphotericin B with or without flucytosine, or the use of an echinocandin in high dose (caspofungin or micafungin 150 mg daily, anidulafungin 200 mg daily), with subsequent transition to fluconazole (depending on in vitro susceptibility).[1] The guideline also states that "valve replacement is recommended."

Something of note from the experience reviewed here is that the presence of liver failure was the strongest predictor of mortality. Unfortunately, there is no information regarding the direct cause of death in those patients. Also of note is the lesser mortality associated with illicit drug use, which is fortunate

since the current opiate abuse epidemic in the United States has been reported to be associated with an increased frequency of *Candida* endocarditis cases. It could be speculated that this apparent lesser mortality may be associated with younger age and also the greater frequency of tricuspid valve infection. ■

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ABSTRACT & COMMENTARY

Ebola — Sometimes it Does Not Go Away

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A patient without apparent immunodeficiency experienced a late relapse of Ebola virus disease with subsequent transmission causing 91 secondary cases. Such late relapse raises concerns regarding control of this disease.

SOURCE: Mbala-Kingebeni P, Pratt C, Mutafali-Ruffin M, et al. Ebola virus transmission initiated by relapse of systemic Ebola virus disease. *N Engl J Med* 2021;384:1240-1247.

A 25-year-old man in the Democratic Republic of Congo presented with Ebola virus disease on June 15, 2019, despite having been vaccinated against this infection six months previously. Infection was confirmed by a positive serum polymerase chain reaction (PCR) test. He was treated with an experimental monoclonal antibody preparation and subsequently discharged from the hospital after two consecutive negative PCR tests. A semen sample PCR was negative two months after presentation.

The patient had symptom recurrence beginning on Nov. 25, 2019, 149 days after he was discharged and eventually reached the Ebola treatment unit at which he had received his previous care. Human immunodeficiency virus testing was negative, but Ebola virus ribonucleic acid (RNA) was detected repeatedly in serum, and he developed multiorgan system failure and died. Ebola PCR on postmortem saliva was positive. Genomic investigation indicated virtual identity of the virus responsible for this episode and that in the initial episode, demonstrating that the infection represented a relapse. Contact tracing investigation, confirmed by genomic analysis, identified subsequent transmission from the relapse episode to 91 cases over the subsequent four months.

■ COMMENTARY

Persistent Ebola virus infection has been identified previously, with persistence of virus in semen for months and with evidence of sexual transmission after recovery from the acute infection. In addition, rare cases of recrudescent symptomatic infection also have been reported, but these have not been associated with further transmission of the virus. In this case, there was complete clinical recovery from the initial case and apparent confirmed viral clearance. Nonetheless, the viral infection relapsed, not only causing the patient's death, but leading to a large number of secondary cases.

Look-back examination found that, despite receipt of an Ebola vaccine, the patient had no detectable antibody against the virus at the time of initial presentation, although testing of a day-14 sample demonstrated that he had successfully seroconverted. Antibody was again detected eight days after the onset of his relapsed infection. The lack of antibody after vaccination has previously been known to occur in a small proportion of cases. The occurrence in this case after receipt of a therapeutic monoclonal antibody raised the question of immune escape, but the antibody retained its neutralizing activity against the virus recovered during the second episode. Finally, immunological evaluation of the patient, including whole exome sequencing, failed to identify evidence for an immune deficit.

The authors noted that two other patients, in addition to the one described, who are known to have relapsed after an acute Ebola virus infection, had received antibody-based treatment. They pointed out that administration of convalescent plasma also has been associated with cases of relapse of Argentinian hemorrhagic fever. The underlying reasons for such occurrences remain obscure, but they may raise questions regarding the use of therapeutic monoclonals in other viral infections, such as COVID-19. ■

Updates

By Carol A. Kemper, MD, FACP

Aussie Flesh-Eating Disease

SOURCE: Buruli ulcer – Australia: (VI) increasing incidence. ProMED-mail post, Feb. 24, 2021. www.promedmail.org

An increasing number of Australians and travelers to Australia are being diagnosed with Buruli ulcer, raising public health concerns and prompting more extensive spraying for mosquitoes in the suburbs of Melbourne and along coastal areas of Victoria. Buruli ulcer, sometimes called Bairnsdale ulcer in Australia, where it is a nationally reportable disease, is caused by *Mycobacterium ulcerans*. It starts as a painless papule or pimple and slowly ulcerates and expands over several months, causing local tissue destruction, and potentially involving muscle, nerve, and even bone. Notably, the lesions are painless and without fever — making them distinct from a local cellulitis. The organism requires low temperatures for growth (29-33°C), so it generally results in infection on the extremities; rarely, the face is involved.

Globally, Australia has the third highest number of cases of Buruli ulcer, after Ghana and Nigeria, although many cases around the world likely go unreported. The infection has been reported from 33 countries, including countries in sub-Saharan Africa and Southeast Asia, Mexico, Peru, and Papua New Guinea. The disease has been present in Australia for decades, although it is being reported from previously unaffected and more affluent areas, including the suburbs of Melbourne, the coastal areas just east of Melbourne in Frankston and the Mornington Peninsula, as well as (going the other direction from Melbourne) the Greater Geelong, and the shire of East Gippsland. A handful of cases also have been observed in northern Queensland and near Darwin. Although 65 cases were reported in Australia in 2013 and 106 cases were reported in 2015, a total of 340 cases were reported in 2018. That the infection is affecting individuals living in suburbs and more affluent areas has garnered attention in the press and by health officials. The increase in cases also prompted a re-evaluation of the case definition, which previously required the isolation of the organism in culture or polymerase chain reaction (PCR) confirmation, and likely was resulting in under-reporting. A group of Australian clinicians, laboratory experts, and public health officials gathered in 2019 and drafted a new case definition, which allows for an expert clinical diagnosis without bacteriological confirmation.[1]

Buruli ulcer generally is considered a tropical disease, and the reasons for the observed increase in cases in Australia and other countries, such as Benin and Liberia, are not clear. The ecological niche for the organism and the transmission pathway are not known. In most countries, stagnate or slowly moving bodies of water and coastal salt marshes are considered risk factors, with certain species of mosquito as the likely vector. Epidemiological surveys in Australia have found the organism in the pelleted feces of possums, although these animals are not considered to be the source of human infection. Transmission is only rarely human-to-human. Fortunately, if the infection is recognized early, it generally responds well to an eight-week course of rifampin and clarithromycin (or rifampin and streptomycin). More extensive lesions may require skin grafting or even amputation. ■

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1. Betts JM, Tay EL, Johnson PDR, et al. Buruli ulcer: A new case definition for Victoria. *Commun Dis Intell* 2018;44:1-7. https://www1.health.gov.au/internet/main/publishing.nsf/Content/8FA6078276359430CA257BF0001A4C42/$File/buruli_ulcer_a_new_case_definition_for_victoria.pdf

Misleading Imaging in COVID

SOURCES: Nawwar AA, Searle J, Green C, Lyburn ID. Infection control of COVID-19. Surgical mask-related facial cutaneous artifact on FDG Pet/CT. *Clin Nucl Med* 2021;46:e221-e223.

Xu G, Lu Y. COVID-19 mRNA vaccination-induced lymphadenopathy mimics lymphoma progression on FDG PET/CT. *Clin Nuc Med* 2021;46: 353-354.

These two articles highlight the challenges of diagnostic testing at a time when all of us are being tested by an entirely new disease, COVID-19. Fluorodeoxyglucose-positron emission tomography computed tomography (FDG PET/CT) imaging obtained for staging of mantle cell lymphoma in a 56-year-old man revealed avid uptake in sub-diaphragmatic lymph nodes and the face, raising concerns about possible facial skin involvement. Cutaneous involvement would be unusual, but possible, with mantle cell lymphoma. The avidity extended from the bridge of the nose to the mandible. And yet, there was no apparent abnormality on

corresponding CT and nothing found clinically. It was concluded that the man's facemask must have resulted in build-up of local blood flow or increased heat and humidity to the facial tissues under the mask, yielding falsely positive results on PET imaging.

FDG PET/CT scanning was obtained in a 72-year-old man, also with mantle cell lymphoma, who had achieved complete remission in response to chemotherapy. Serial follow-up PET/CTs had been unremarkable for recurrent lymphoma — until 10 months post-treatment, when a PET/CT revealed a cluster of highly avid left axillary lymph nodes, concerning for recurrent cancer. But the images also revealed less explicable uptake in the left deltoid muscle and surrounding soft tissues, until it was determined the patient had undergone COVID mRNA vaccination two days earlier. Vaccine-induced soft tissue inflammation, myositis, lymphadenopathy, and even bone edema have been misinterpreted previously on magnetic resonance imaging and PET/CT. ■

Abstruse 2021 CLABSI Case Definition

SOURCE: National Healthcare Safety Network (NHSM) Patient Safety Component Manual. January 2021. https://www.cdc.gov/nhsn/pdfs/psc-manual/pcsmanual_current.pdf

The reduction of hospital-acquired infection (HAI) is a priority for us all. Our facility has spent a decade successfully working to reduce our rates of catheter-associated bloodstream infections (CLABSI), hospital-acquired *Clostridioides difficile* infection (HO-CDI), and catheter-associated urinary tract infections (CAUTI). Series of tiered best-practice interventions to prevent HAI have been implemented thoughtfully, with welcome results for HO-CDI and CAUTI. However, despite our best efforts, the number of reported CLABSI has increased — not improved. After in-depth clinical investigation and root cause analysis of each case, I believe most of these CLABSI events are an artifact of the National Healthcare Safety Network (NHSN) case definition.

The NHSN Patient Safety Component Manual definition of CLABSI is presented in an increasingly complex and abstruse 42-page document called the "Device-associated Module." Hospitals are required to abide by this document, but I cannot imagine how the usual hospital infection prevention staff could begin to implement this document, and the statistical section requires an advanced degree. I have read it through several times, and I do not get it. The module goes to great lengths to define bloodstream infections, with a sub-definition of mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI), which in turn describes three subcategories of MBI-LCBI with a series of tiered requirements. Presumably, this complexity is an attempt to prevent hospitals from omitting some bloodstream infections as CLABSI.

However, in the process of attempting to create a series of requirements that are appropriately inclusive, the case definition has become so complex as to be specious — and appears to be artifactually creating more device-related infections than it correctly identifies. For example, as an infectious disease (ID) specialist with years of experience, I would regard perhaps at most one of our NHSN-defined CLABSI events as a "true" CLABSI, even when viewed in a critical light. The other so-called CLABSIs are either artifacts of contaminated blood draws obtained from peripherally inserted central catheter (PICC) lines, or bacteremias in cancer patients with existing Medi-ports. The most illegitimate "CLABSI events" occurred in three cancer patients with existing Medi-ports, each of whom developed gram-negative bacteremia. The first of these developed chemotherapy-induced febrile neutropenia, and blood cultures yielded *Klebsiella* spp. Urine cultures yielded the same organism, with a colony count of 30,000 CFU/mL to 50,000 CFU/mL. This inexplicably failed to meet criteria as a "secondary source," although in the setting of frank neutropenia, this presents an obvious risk. However, because no "secondary source" could be confirmed, this case was classified as a CLABSI. Two other patients had severe malignant bowel obstruction, confirmed both clinically and radiographically, but again no "secondary source" for infection, with a documented paired culture, could be confirmed (simply because a "source" culture could not be reasonably obtained without an invasive procedure). All three gram-negative bacteremias were treated successfully with 10- to 14-day courses of antibiotics, and the ports were not removed and showed no further evidence of infection. The ID consultants involved in the care of these patients did not define or code these cases as device-related infections, and the devices were not removed, as certainly would be indicated for a true gram-negative device-related infection. If you wish to identify a device-related bloodstream infection, why not look at the ID consultant's notes and treatment?

The government has the responsibility to create and apply regulations that naturally achieve important objectives without causing undue harm. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **Vitamin D administration has proven effectiveness in:**

   a. preventing respiratory infections in children.

   b. treating COVID-19 in adults.

   c. treating chronic hepatitis B.

   d. preventing multiple sclerosis.

2. **The reported antibody response rate of solid organ transplant recipients after administration of one of the available messenger ribonucleic acid (mRNA) vaccines is approximately:**

   a. 1% to 20%.

   b. 21% to 40%.

   c. 41% to 60%.

   d. 61% to 80%.

3. **Which of the following is correct regarding the recent Centers for Disease Control and Prevention/American College of Physicians recommendation for the usual duration of antibiotic therapy for the following common infections?**

   a. Bacterial exacerbation of chronic obstructive lung disease: 14 days

   b. Community-acquired pneumonia in non-immunocompromised adults: five days

   c. Non-purulent cellulitis in adults: 10 days

   d. Uncomplicated cystitis in nonpregnant adult females: nitrofurantoin for seven days

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.