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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Virus, Variants, Vaccines

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The emergence of SARS-CoV-2 variants may compromise the efficacy of current vaccines.

The Inevitability of Viral Mutations and Emergence of Important Variants

Once SARS-CoV-2 emerged as a disease of humans in November 2019, the emergence of variants of this virus was an inevitability. SARS-CoV-2 has been reported to have an estimated median mutation rate of 1.12×10^{-3} mutations per site-year (95% confidence interval [CI], 9.86×10^{-4} to 1.85×10^{-4}).[1,2] This actually is less than for some other ribonucleic acid (RNA) viruses, as a consequence of the fact that, unlike many of the others, it has a proofreading mechanism. Thus, it is estimated that SARS-CoV-2 accumulates only two nucleotide changes per month in its genome — a rate of change about half that of influenza and one-quarter that of human immunodeficiency virus. Nonetheless, the unrestrained global replication of SARS-CoV-2 in the face of the selective pressure exerted by the immune system constantly generates enormous numbers of mutation. To possibly make matters worse, it has been suggested recently that, in addition to point mutations and deletions, recombination may occur in this virus.

Viral variants can become dominant only if they have an advantage over other forms of the virus. One important such advantage is increased transmissibility, a characteristic that provides the capability of more rapid spread. This spread potentially may affect not only non-immune populations but possibly also populations with some degree of pre-existing immunity acquired as a result of either prior natural infection or immunization. The consequences of the ability to evade such immunity is the continuation or even worsening of the pandemic.

Some Important Emergent SARS-CoV-2 Variants

A variant strain with a D614G in the viral spike protein associated with increased replication efficiency and transmissibility emerged in March or April 2020 and "took over" from the original Wuhan strain, becoming globally dominant.[1-4] The emergence in the United

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Kingdom in August 2020 of a variant now called B.1.1.7 has further alerted the world to the possibility of its spread and potential consequences. B.1.1.7, which has 17 unique mutations, including three that affect the receptor binding domain of the viral spike protein with N501Y believed to be associated with increased transmissibility, has become a dominant strain in the United Kingdom and has since been detected in the United States (where it is doubling in frequency every 1.5 weeks) and other countries. Its E484K mutation is believed to contribute to resistance to immune clearance of the virus. Laboratory and animal studies suggest increased transmissibility, and epidemiologic studies appear to confirm this. Furthermore, the possibility of an associated increased mortality rate in individuals infected with B.1.1.7 has been raised, although confirmation is necessary.

Another variant, B.1.351 with multiple mutations in the spike protein, emerged in South Africa in October 2020 and has been detected subsequently in other countries, including the United States. Antibody elicited by mRNA-1273m demonstrated significantly (six- to ninefold) reduced potency relative to its effect on B.1.1.7. Furthermore, one study found that antibody from individuals previously infected naturally with SARS-CoV-2 containing the prevalent D614G mutation, but with none of the spike mutations of B.1.351, had significantly reduced neutralizing potency against B.1.351, with IC50s that were six- to 200-fold higher. This suggests that prior infection with the original strain failed to provide full immunity to the new variant. Furthermore, this is consistent with the finding in the Novavax vaccine trial that 30% of placebo recipients had serological evidence of infection prior to enrollment (presumably with the then-prevalent strain of virus), and the rate of subsequent infection did not differ significantly between those with prior infection and those who were seronegative at study entry. B.1.1.7, B.1351, and P1 share some common mutations, such as N501Y and D614G, which are believed to be associated with increased viral transmission.

Two variants of concern have been identified in Brazil — P1, which is dominant in Manaus, and P2, seen throughout the country. P1, which has been detected in the United States, contains three mutations in the spike protein receptor binding domain: K417T, E484K, and N501Y.

Another variant, L452R (CAL-20C), which like the others carries an N501Y mutation, was first seen in Denmark but then emerged in California in the spring and summer of 2020 and began to be detected with increasing frequency in November 2020. Studies performed at the University of California San Francisco detected L452R in 3.8% of samples in mid-December but in 25% by early to mid-January. By early February, this variant accounted for one-third of SARS-CoV-2 isolates sequenced at Stanford. In addition, L452R was associated with a large outbreak at the San Jose Kaiser hospital. The transmissibility and clinical characteristics are yet to be determined, as is the efficacy of vaccines in protection against it.

SARS-CoV-2 Variants and Vaccine Efficacy

The emergence of these variants has raised concern about the efficacy of vaccines.[5,6] Fortunately, evidence indicates that antibody elicited in response to either the Pfizer mRNA vaccine, BNT162b2, or the Moderna mRNA vaccine, mRNA-1273m, effectively neutralizes B.1.1.7 (the U.K. variant) in vitro. With the Pfizer vaccine, there is reported to be an approximately 20% decrease in the potency against B.1.351 of the elicited antibody, but experience with influenza virus suggests that this is not a biologically significant loss of activity. The investigational two-dose Novavax vaccine, NVX-CoV2373, is reported to have 89% efficacy in the United Kingdom despite > 50% of infections having been caused by the B.1.1.7 variant. The AstraZeneca vaccine is reported to be effective against symptomatic infection with B.1.1.7 despite the presence of lower neutralizing antibody levels compared to those elicited against the pre-variant strain of the virus. It is reported to effectively prevent severe infection with B.1.351 but to have a lesser effect in preventing mild to moderate infection. As a result of this limited efficacy, South Africa announced on Feb. 7, 2021, that it is suspending its vaccination program with the AstraZeneca vaccine.

Furthermore, although a single dose of the Johnson & Johnson Ad26 vaccine (which will be reviewed by the U.S. Food and

Drug Administration [FDA] on Feb. 26) demonstrated protective efficacies against symptomatic COVID-19 at 28 days of 72% (85% against severe disease and 100% against hospitalization or death) in a trial in the United States, it was less effective at 66% in Latin America and 57% in South Africa. This provided strong evidence of its reduced efficacy in countries with prevalent viral variants. One or more of the mutations in P1 likely account for the limited efficacy of the investigational Sinovac vaccine in Brazil, which may be as low as 50%. Vaccine efficacy against the L452R California variant has not been reported.

Additional variants of concern will continue to emerge and, in some cases, dominate. As a consequence, careful genotypic surveillance is critical. The adverse effects of some variants on the efficacy of naturally acquired or vaccine-acquired immunity is of obvious concern, and plans to address this are ongoing. Moderna has indicated that it plans Phase I trials evaluating two different strategies designed to deal with B.1.351. In one, a booster dose of the existing vaccine will be administered, while in the other, boosting will be achieved with an altered vaccine that incorporates the variant's mutations.

An important question is: How long would it take to have a new vaccine available to counter variants? Jennifer Haller received the first dose of the Moderna vaccine 66 days after scientists in the United States were able to view the published genetic code of SARS-CoV-2. If modification of a vaccine is required to deal with variants, the vaccine itself presumably could be developed in a matter of weeks. Subsequent testing would be truncated, involving smaller numbers of patients than did the parent vaccine, and the initial use of a surrogate, such as the development of neutralizing antibody, could be considered as sufficient for initial authorization. Subsequent studies could examine other more traditional endpoints.

SARS-COV-2 Variants: Other Considerations

The emergence of variants causes additional complicating issues. Thus, the FDA has warned of the potential for leading to falsely negative diagnostic polymerase chain reaction (PCR) results with some manufacturers' tests, and concern also has been raised about the potential lack of efficacy of some therapeutic monoclonal antibodies.

It is clear that SARS-CoV-2 will never disappear and that humanity will have to control it and live with it with the critical aid of effective vaccines. It also seems likely that this will involve an ongoing struggle with continual surveillance for the emergence of "escape mutants" and the potential need to modify vaccines accordingly. ■

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ABSTRACT & COMMENTARY

Getting to the Super Bowl: Lessons from the NFL on Controlling COVID-19

By Stan Deresinski, MD, FACP, FIDSA

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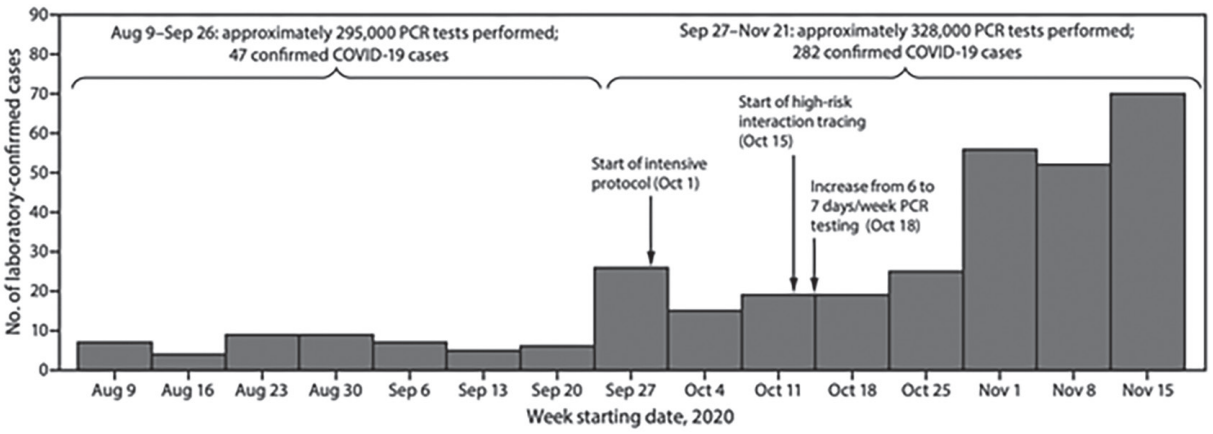
SYNOPSIS: Aggressive implementation of mitigation procedures with continual evaluations and adjustments allowed the National Football League to complete their season with minimal COVID-19 transmission.

SOURCE: Mack CD, Wasserman EB, Perrine CG, et al. Implementation and evolution of mitigation measures, testing, and contact tracing in the National Football League, August 9-November 21, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:130-135.

The National Football League (NFL) consists of 32 teams in 24 states, and the decision to proceed with playing the 2020-2021 season in the midst of the COVID-19 pandemic necessitated complex and comprehensive planning and implementation of procedures designed to control SARS-CoV-2

Figure 1: Laboratory-Confirmed* COVID-19 Cases (N = 329) and Mitigation Strategies† Implemented — National Football League, United States, August 9-November 21, 2020



Abbreviations: COVID-19 = coronavirus disease 2019; PCR = polymerase chain reaction.
* Reverse-transcription PCR tests were processed on two platforms (Roche Cobas and ThermoFisher QuantStudio) and transcription-mediated amplification on one platform (Hologic Panther Aptima)
† Twenty-nine clubs spent 431 days under the intensive protocol beginning October 1; 189 high-risk contacts of 215 cases were identified and subsequently quarantined beginning October 15.
Source: Mack CD, Wasserman EB, Perrine CG, et al. Implementation and evolution of mitigation measures, testing, and contact tracing in the National Football League, August 9-November 21, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:130-135.

transmission. A standard mitigation protocol was implemented in conjunction with the Players' Association in July. The elements of this protocol included mandated masking, frequent handwashing, facility disinfection, and restricted access to facilities, together with regular and frequent polymerase chain reaction (PCR) testing of players and staff. In addition, contact tracing was performed that was supplemented with required use of wearable proximity devices while within club environments. Testing, with 24-hour turnarounds, initially was performed on players and most staff six days per week.

Initially, fewer than 10 cases of COVID-19 were detected each week, but then 41 cases were detected between Sept. 27 and Oct. 10, with 21 of these occurring at a single club resulting in the closure of their facilities. This led to league-wide implementation of a more intensive protocol, which was put in place for one week whenever a positive test was confirmed. Constant evaluation and adjustments were made. Overall, from Aug. 9 to Nov. 21, 623,000 PCR tests were performed on approximately 11,440 players and staff. During that time, 329 laboratory-confirmed cases of COVID-19 were detected, representing approximately 2.9% of the monitored population.

■ COMMENTARY

Despite the COVID-19 pandemic, Super Bowl LV was played on Feb. 7, 2021. The ability to accomplish this took, as indicated by the summary above, an enormous amount of effort and resource utilization at significant cost. This effort demonstrated that the mitigation efforts are effective and that intensification of the protocol was associated with decreased exposure and transmissions within the facilities and that this was accomplished at a time during which there was significantly increasing community transmission of COVID-19 throughout the United States.

In addition to once again demonstrating the benefit of various mitigation procedures in reducing transmission of SARS-CoV-2 infection, this experience developed new information that affected national policy. As an example, the observation that transmission could occur despite < 15 minutes of cumulative interaction (potential exposure) led to revision of the definition of high-risk contact that takes into account, in addition to duration and proximity of interaction, assessment of mask use and of ventilation. In the course of the activity, the importance of contact tracing was obvious, but the difficulty of characterization of individual risk also became apparent.

Nonetheless, implementation of postexposure quarantine after high-risk exposure, together with testing and enforcement of intensive mitigation protocols specific to the environment and circumstance, proved highly effective. The NFL did have its Super Bowl in the middle of a COVID-19 pandemic — to the chagrin of Kansas City and the delight of Tampa. ■

ABSTRACT & COMMENTARY

Unexpected Pediatric Benefits of the COVID-19 Pandemic

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: Despite the global tragedy of the COVID-19 pandemic, clinical experience suggests that there also have been some favorable indirect effects of pandemic-induced lockdowns on pediatric health. Specifically, there are lower rates of unscheduled primary care visits, emergency department visits, and hospitalizations for medical problems – without an increase in incompletely managed serious diseases.

SOURCE: Williams TC, MacRae C, Swann OV, et al. Indirect effects of the COVID-19 pandemic on paediatric healthcare use and severe disease: A retrospective national cohort study. *Arch Dis Child* 2021; Jan. 15. doi 10.1136/archdischild-2020-321008. [Online ahead of print].

Despite the extensive impact of the COVID-19 pandemic, children, as compared to adults, have been affected less severely. Nonetheless, there have been concerns that lockdown measures might have prompted delays in care-seeking with a resultant worsening of serious pediatric conditions.

The first case of infection with SARS-CoV-2 in Scotland was identified on March 1, 2020, and a U.K.-wide lockdown began on March 23. The lockdown measures were eased on May 29, and schools were opened on Aug. 12. The "natural experiment" of the pandemic provided an opportunity to determine influences of COVID-19 on pediatric use of emergent healthcare and on severe pediatric disease.

Williams and colleagues used Scotland's complete national data sets to compare pediatric care and illness from March 23 to Aug. 9, 2020, with that of previous years. Theirs was a retrospective, population-based analysis of all emergent pediatric care and specifically included data from both of Scotland's pediatric intensive care units. The study was limited to children from birth to 14 years of age.

Unscheduled after-hours primary care visits were reduced by 64% during the five-month-long lockdown, as compared to the same parts of 2016 through 2019 ($P < 0.001$). Emergency department visits dropped by half ($P < 0.001$). Hospital admissions for medical conditions dropped by about half ($P < 0.001$), but hospital admissions for surgical admissions did not change significantly.

As a clue to the seriousness of clinical situations when presenting to emergency departments, Williams looked at the proportion of emergency department visits that prompted hospital admission. During the first week of the lockdown, there was an increased rate of admission following emergency department visits, but the admission rate quickly dropped to baseline after that.

There also was a reduction in the number/rate of emergent admissions for pediatric intensive care that required mechanical ventilation, but there was no increase in the severity scores displayed by patients at admission. Death rates were similar in the lockdown months of 2020 as during the same parts of the 2016-2019 years.

The authors appropriately pointed out that there was a reduction in the use of emergent medical care services during the lockdown but that there was no population-based evidence that children had negative outcomes related to the reduced use of emergency care. Wallace used the data, as summarized earlier, to claim that the reduction in the need for emergency care likely was linked to a reduction in the incidence of respiratory infections and, perhaps, a higher threshold for seeking care for common illnesses. Reassuringly, Wallace also emphasized that there was not widespread evidence of children delaying care to the point of presenting with more severe illnesses. They also noted that medical illnesses were less common during the pandemic even though surgical problems continued as before.

■ COMMENTARY

There is no doubt that the COVID-19 pandemic is a global tragedy. The loss of life and health is staggering. Since the beginning of the pandemic, though, it seemed clear that children were less severely affected by SARS-CoV-2 than were and are adults.

Anecdotally, pediatric hospitalists noticed a marked reduction in hospitalizations with the onset of lockdowns, social distancing, and masking in response

to the COVID-19 pandemic. Although some children still developed serious illness, there seemed to be many fewer children ill with febrile illnesses, including those caused by respiratory and gastrointestinal infections. Logically, it seemed that measures instituted to reduce the spread of SARS-CoV-2 also were effective in reducing the spread of other common infections.

Now, data are emerging that support and clarify the indirect yet favorable effects of the pandemic on child health. Williams and colleagues in Scotland documented significant reductions in rates of emergency care, without an associated increase in more severe disease (as would be seen if the reduction in emergency care was merely the result of reduced use of services rather than to a reduced need for services). Perhaps one of the favorable health outcomes in the post-pandemic era will be improved health with less need for acute medical care because of ongoing implementation of personal protective measures that reduce the spread of pathogens.

Of course, the Scottish data are subject to interpretation and might not be representative of what is occurring elsewhere. Pines and colleagues characterized pediatric care in U.S. emergency departments using data from more than 2 million episodes of care.[1] Adult non-COVID emergency care visits dropped by 60% in early 2020 as compared to 2019, and pediatric visits dropped even more (74% drop for children younger than 10 years of age, 67% drop for children aged 14 to 17 years).[1] The declines in care utilization were seen across all types of visits, but especially with non-COVID infections; serious pediatric conditions, including appendicitis, dropped by 22%.[1]

Why was medical care used less frequently? Williams and colleagues credit the reduced care use to reduced illnesses. Corroboration for this idea comes from experiences during the pandemic with milder illnesses as well. In Italy, 102 children known to be susceptible to otitis media were followed remotely when in-person visits seemed unwise.[2] There was notable clinical improvement in 82% of children with fewer bouts of otitis and less antibiotic use as compared to the previous year.[2] In the 27% of children who were evaluated face-to-face (actually, eye-to-ear), 89% had normal middle ear evaluations.[2] Although some of the improvement could have been due to the increasing age of the children, it does seem like upper airway infections and illnesses, like emergency care utilization, have decreased significantly during the era of pandemic-induced restrictions.

Pines and colleagues think that some patients actually might have avoided necessary care for ill children.[1] They saw fewer serious conditions than in a previous year and wondered if some children were not getting needed care, perhaps because of concern for COVID-19 exposure.[1] However, contrary data come from Germany, where the rates of appendicitis went down 13% from pre-pandemic months to otherwise similar months during lockdowns.[3] In that study, most of the reduction was of uncomplicated appendicitis (suggesting that some uncomplicated appendicitis might resolve even without medical care), while the rates of complicated appendicitis remained fairly stable.[3] Is childhood appendicitis different in the United States? In New York, children presenting with acute appendicitis during the pandemic had more severe disease and had worse outcomes than those presenting in 2019.[4]

There also are legitimate concerns that avoidance of routine pediatric care might put children at risk of otherwise preventable illnesses. In Singapore, for instance, there was a marked decrease (26% to 74% in various settings) in uptake of measles vaccine during the pandemic, leaving the population at risk of measles outbreaks.[5] There were similar decreases in pneumococcal vaccine coverage.[5]

Are there favorable pediatric outcomes related to the COVID-19 pandemic? Yes, there clearly are reduced rates of respiratory and gastrointestinal infections causing hospitalization. There likely is less non-judicious use of antibiotics for minor infections, and there is less emergency care for several conditions. Of course, there is a risk that some children might delay necessary medical care, and there is a risk that lowered immunization coverage might open populations to new outbreaks of preventable diseases, such as measles and invasive pneumococcal infections. ■

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ABSTRACT & COMMENTARY

Oral Moxifloxacin vs. Intravenous Ertapenem Followed by Oral Levofloxacin and Metronidazole for Acute Appendicitis

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

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SYNOPSIS: A randomized controlled clinical trial found that a seven-day course of oral moxifloxacin was not noninferior to two days of intravenous ertapenem followed by five days of levofloxacin and metronidazole in adults with uncomplicated acute appendicitis.

SOURCE: Sippola S, Haijanen J, Grönroos J, et al. Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: The APPAC II randomized clinical trial. *JAMA* 2021;325:353-362.

There is high quality evidence, including randomized clinical trials and guidelines, that antibiotic therapy can be an effective alternative to surgery in cases of acute uncomplicated appendicitis. However, the optimal regimen remains to be determined. Sippola and colleagues hypothesized that oral antibiotics alone would be as effective as intravenous antibiotics followed by oral antibiotics in the management of acute uncomplicated appendicitis.

The study was a randomized controlled clinical trial conducted at nine hospitals in Finland. Adult patients older than 18 years of age who had uncomplicated acute appendicitis that was confirmed by computed tomography (CT) imaging were included. Uncomplicated acute appendicitis was defined as an appendiceal diameter > 6 mm with a thickened, contrast-enhanced wall, peri-appendiceal edema, and/or minor fluid collection, and the absence of criteria for complicated appendicitis (i.e., presence of appendicolith, perforation, abscess, or tumor). Exclusion criteria included age < 18 years or > 60 years, pregnancy or lactation, allergy to intravenous (IV) contrast dye or study antibiotic therapy, kidney failure, type 2 diabetes and use of metformin, severe systemic illness such as malignancy, or complicated appendicitis.

Participants were randomized 1:1 to receive either oral moxifloxacin 400 mg once a day for seven days or IV ertapenem 1 g IV daily followed by five days of oral levofloxacin 500 mg daily and metronidazole 500 mg three times daily, with treatment begun in the emergency department. Patients who were suspected by a surgeon to not be responding underwent laparoscopic appendectomy. Outcomes were assessed daily in the hospital and after discharge by telephone at one week, two months, and one year. The primary endpoint was treatment success at one year, defined as resolution of acute appendicitis without the need for surgical intervention and no recurrent appendicitis.

The primary analysis included 583 patients, with 295 in the oral moxifloxacin group (oral group) and 288 in the IV ertapenem followed by oral antibiotics group (IV/oral group). Baseline characteristics were similar between the two groups, with a mean age of 36 years (standard deviation, 12 years), and 43.9% were women. The treatment success for the oral group was 70.2% (one-sided 95% confidence interval [CI], 65% to ∞) at one year compared to 73% (one-sided 95% CI, 69.5% to ∞) in the IV/oral group. For the primary outcome, the analysis determined a difference of -3.6% (one-sided 95% CI, -9.7% to ∞; $P = 0.26$ for noninferiority) between the two groups. Thus, the CI difference exceeded the predefined noninferiority definition of a lower limit of -6%, indicating oral therapy was not noninferior to IV/oral therapy. There were no significant differences between the groups in length of hospital stay or reported pain. No patients died within the one-year hospital follow-up period. Regarding adverse events, two patients in the oral group discontinued treatment (one patient developed eczema with facial swelling and one developed blurry vision), while five in the IV/oral group reported prolonged diarrhea at two months that resolved by one year.

■ COMMENTARY

Avoiding surgery with acute uncomplicated appendicitis while still achieving a desirable outcome is a worthwhile goal. Antibiotic therapy has emerged as an effective alternative to traditional appendectomy, with little apparent risk or downside. Indeed, studies have shown that patients who ultimately develop recurrent appendicitis and undergo later appendectomy do not experience any adverse outcomes related to the delay. Therefore, the study by Sippola and colleagues is

important because it adds to the body of evidence about antibiotic treatment options for acute uncomplicated appendicitis.

Oral moxifloxacin did not reach the predetermined goal of noninferiority compared to IV ertapenem followed by oral levofloxacin and metronidazole. Nevertheless, the majority of patients (70.2%) in the moxifloxacin group were able to avoid surgery. This can be interpreted in a positive light, however, from the perspective of reduced healthcare costs and complications, such as post-operative infection and anesthesia-related adverse events.

So why did moxifloxacin not fare as well as ertapenem followed by levofloxacin and metronidazole? Perhaps some cases of appendicitis were caused by quinolone-resistant *Enterobacteriaceae*, and two days of ertapenem was sufficient enough to kill a critical threshold of pathogens. This hypothesis is supported by a previous study that found treatment with oral amoxicillin-clavulanate led to inferior outcomes because of the presence of nonsusceptible *Escherichia coli*. Alternatively, and less likely, perhaps some as-yet-undetermined mechanism leads to synergy between levofloxacin and metronidazole, making them more effective in acute uncomplicated appendicitis than moxifloxacin.

The study had a few limitations. First, it was conducted in a Scandinavian country and the participants were relatively young (mean age, 36 years), which limits the generalizability to other settings. Second, the noninferiority definition of 6% was rather arbitrary. Finally, the duration of symptoms was shorter in the oral moxifloxacin group (median 18 hours) compared to the IV/oral group (median 22 hours), which may have been a confounding factor.

At present, oral moxifloxacin should not be used as therapy for acute uncomplicated appendicitis. Other treatment regimens, especially oral ones, should be investigated further in randomized clinical trials. It is hoped that the appendectomy for acute uncomplicated appendicitis will become a rarity in the not-so-distant future. ■

ABSTRACT & COMMENTARY

Ventricular Assist Device Infections: More Questions Than Answers?

By Stan Deresinski, MD, FACP, FIDSA

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SYNOPSIS: Almost two-fifths of patients with left ventricular assist devices develop associated infections. The optimal appropriate management remains to be determined.

SOURCE: Blanco-Guzman MO, Wang X, Vader JM, et al. Epidemiology of left ventricular assist device infections: Findings from a large nonregistry cohort. *Clin Infect Dis* 2021;72:190-197.

Blanco-Guzman and colleagues retrospectively reviewed cases of left ventricular assist device (VAD) infections seen at a single center from 2009 to 2015. Of the 455 who had had continuous flow left VAD placement during that time, 174 patients (38.6%) developed infection — an incidence of 36.9 per 100 patient-years of VAD support. Infections occurred 5-2,266 days (median 150 days) after placement. The infections were considered VAD-specific and VAD-related in 146 (83.9%) and 28 (16.1%), respectively. VAD-specific infections involved the device hardware or the body surfaces containing the hardware and included those involving the pump or cannula, driveline, or pocket. VAD-related infections are those — including endocarditis, mediastinitis, and bloodstream infections (BSI) — that can occur in the absence of the device, but that are seen more commonly in patients with VADs.

Two-thirds of VAD-specific infections involved the driveline, while one-third of the VAD-related infections were BSI. Local infections (driveline or pocket infections, or mediastinitis without BSI) accounted for 108 (62.1%) of the cases and endovascular infections (pump/cannula infection, endocarditis, BSI) accounted for 66 (37.9%) of the cases. Of importance, 29.2% of patients considered to have endovascular infection did not meet systemic inflammatory response syndrome (SIRS) criteria on their initial evaluation.

Computed tomography (CT) was performed on 142 patients (81.6%) and was normal in 37.7%. Driveline stranding was the most common finding, seen in 70 patients (49.3%), while a drainable fluid collection was identified in 15 patients (10.6%). Infection was caused by Gram-positive bacteria in 62.6%. Approximately

one-fifth of endovascular infections were caused by methicillin-susceptible *Staphylococcus aureus* or *Enterococcus*. Gram negatives accounted for 15% of infections and with similar frequencies in local and endovascular infections. *Candida* (all non-albicans) was associated with six infections, five of which were endovascular.

The median duration of antibiotic therapy for both local and endovascular infections was six weeks. Almost three-fourths of the 155 patients who survived to completion of their initial antibiotic therapy were started on antimicrobial suppression (84.3% with endovascular and 66.3% with local infection). Approximately one-fifth underwent a surgical procedure to control infection — most commonly driveline revision and debridement of the mediastinum or pocket. The median survival time from initiation of infection was 28 months, but it was only 14 months for those with endovascular infection compared to 35 months with local infection.

■ COMMENTARY

This study confirms the known remarkably high incidence of infection in left VAD patients, which occurred in 38.6% at a rate of 36.9 per 100 patient-years in this cohort. The majority were caused by Gram-positive organisms. *Candida* infection occurred in only six patients, five of whom had an endovascular source.

An important observation was that almost one-third with infections involving the pump, cannula, or bloodstream with or without endocarditis did not meet SIRS criteria at the time of initial evaluation, suggesting that the diagnosis often may be delayed. Almost one-third lacked fever and leukocytosis. Measurement of procalcitonin levels is not helpful during the first weeks after VAD placement since it becomes elevated, often markedly, in the absence of infection in the first days after the procedure before resolving toward normal by 14-30 days.[1]

CT scans were helpful in localizing some local infections and assisted in allowing drainage of fluid collections, but were less sensitive than desired. I would guess that positron emission tomography/CT would be a better diagnostic and localizing procedure, albeit at greater cost.

The choice of antibiotic therapy is dictated by the microbiological results, but the duration of therapy is poorly defined in many of the infections seen in association with left VADs. Even more poorly defined are the role and duration of suppressive therapy. Clearly, we need clinical trials to provide guidance in the optimal prevention and management of these infections, as well as effective means to detect infections at onset and to define their location. ■

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ABSTRACT & COMMENTARY

Clinician Alert: XDR *Salmonella* Typhi Acquired in the United States

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SYNOPSIS: Nine patients in the United States with no travel history had typhoid fever due to extensively drug-resistant *Salmonella* Typhi.

SOURCE: Centers for Disease Control and Prevention. Official Health Advisory. Extensively drug-resistant *Salmonella* Typhi infections among U.S. residents without international travel. Health Alert Network. Feb. 12, 2021, 1:00 PM ET, CDCHAN-00439.

The emergence of extensively drug-resistant (XDR) *Salmonella enterica* ssp. enterica serovar Typhi in Pakistan has led to large numbers of cases in that country.[1] In addition, cases have been seen within a number of countries in travelers from Pakistan. The Centers for Disease Control and Prevention (CDC) now reports nine cases of XDR *Salmonella* Typhi in the United States that occurred in the absence of any international travel history.

Of the 71 reports received by the CDC of patients with XDR *Salmonella enterica* ssp. enterica serovar Typhi infection as of Jan. 14, 2021, 67 had a known travel history. Culture specimens from the 71 had been obtained between February 2018 and mid-November 2020. Fifty-eight (87%) of these had traveled to Pakistan in the 30 days prior to the onset of illness. However, nine (13%) patients had not traveled outside the United States. These cases were identified in six states: three in

New York, two in California, and one each in Illinois, Maryland, New Jersey, and Texas. Positive specimens had been identified in eight of the nine during the 2020 calendar year. The antimicrobial susceptibility patterns of the nine isolates were identical to those described for XDR Typhi in Pakistan. No epidemiologic linkages among the cases were identified by the CDC.

■ COMMENTARY

International travel, especially to South Asia, is a known risk factor for infection due to enteric pathogens with resistance to a number of antibiotics. Antibiotic resistance of *Salmonella* Typhi and paratyphi recovered from travelers of worldwide origin and identified in the GeoSentinel system was described recently by Hagmann and colleagues.[2] The majority of the infections were acquired in South Asia. None of the 889 were XDR. Among the *Salmonella* Typhi for which the information was available, 65% were non-susceptible to ciprofloxacin, 50% were non-susceptible to ampicillin, 13% were non-susceptible to trimethoprim-sulfamethoxazole, 8% were non-susceptible to macrolides, 1.5% (representing only two isolates) were non-susceptible to third-generation cephalosporins. All were susceptible to carbapenems.

The XDR *Salmonella* Typhi that originated in Pakistan were characterized by resistance to ceftriaxone, ampicillin, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole. Fortunately, the isolates were susceptible to azithromycin (although some recent isolates have been resistant to azithromycin) and to carbapenems.

The CDC makes the following recommendations for empiric therapy prior to the results of susceptibility testing. If the patient has traveled to Pakistan in the previous 30 days, initiate therapy with a carbapenem or azithromycin. For those with recent travel to Iraq, since it can be anticipated that most isolates will be resistant to or have reduced susceptibility to ciprofloxacin and that some strains are resistant to ampicillin and ceftriaxone, the recommendation again is to empirically use a carbapenem or azithromycin. Most patients who have not traveled recently to Pakistan or Iraq can be given ceftriaxone. Despite this, it is necessary to keep in mind that, although currently very rare, patients without a travel history may be infected with XDR *Salmonella* Typhi — as were the nine reported by the CDC. ■

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2. Hagmann SHF, Angelo KM, Huits R, et al. Epidemiological and clinical characteristics of international travelers with enteric fever and antibiotic resistance profiles of their isolates: A GeoSentinel analysis. *Antimicrob Agents Chemother* 2020;64:e01084-20.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Outcome of Coccidioidomycosis in the Pre-Antifungal Era

SOURCE: Bays DJ, Thompson GR, Reef S, et al. Natural history of disseminated coccidioidomycosis: Examination of the VA–Armed Forces database. *Clin Infect Dis* Aug 2020; Aug. 11; ciaa1154. [Online ahead of print].

These authors describe the natural history of coccidioidomycosis before the availability of antifungal treatment in a large, healthy cohort of military veterans. The fate of non-disseminated (non-DCM), disseminated (DCM), and central nervous system (CNS) disease was observed, both with regard to the presentation of initial infection and mortality.

A total of 669 cases of cocci infection were identified in veterans diagnosed from 1955-1958 and followed through at least 1966, and in many cases for up to 10 to 30 years. Insufficient data were available for 104 patients, and another 64 were excluded for receipt of topical or systemic treatment with amphotericin during the initial period of followup through 1966. Of the remaining 531 cases, 87% were classified as non-disseminated (non-DCM, no evidence of disease outside the lungs), 8.3% had disseminated disease, and 4.7% involved the CNS (meninges/central nervous system, with or without other areas of dissemination). Overall, this was a fairly young and healthy cohort. The median age for each of the three groups was mid-30s, and most had no comorbidities or underlying pulmonary disease. Diabetes was present in 4.5%, with similar prevalence for the three groups. As expected, Black Americans and Filipinos were more likely to have disseminated infection; close to one-third of Black Americans and Filipinos in the cohort had dissemination and/or CNS involvement, and there was a trend toward increased disseminated infection in Latinos.

The outcomes of the three groups were very different. Regarding the outcome of primary infection, pulmonary

nodules occurred or developed in 39.6%, 13.6%, and 20% of those with non-DCM, DCM, and CNS disease ($P < 0.001$) — and cavitation developed in 34.2%, 9%, and 8% of those with non-DCM, DCM, and CNS disease, respectively ($P < 0.001$). This was construed as evidence of differing host immune responses between the three groups at the time of initial exposure. Note that these data were collected prior to the availability of computed tomography (the availability of which may have altered these observations).

Dissemination occurred early in the course of disease in the majority of patients, and was present at the time of initial infection or as an initial manifestation in 41% of those with DCM and 56% of those with CNS infection. Most cases of dissemination were diagnosed within two to six months of presentation. Only 28% and 36% of patients with DCM and CNS involvement, respectively, developed signs or symptoms of disseminated infection more than six months after initial diagnosis, consistent with other data suggesting antifungal therapy does not prevent the dissemination of infection.

All-cause mortality was substantial for patients with CNS disease (96%) compared with DCM patients (29.6%) and non-DCM patients (5.4%) ($P < 0.00001$). At a time before the availability of antifungal therapy, only 3/459 patients (0.65%) with non-DCM disease died as the result of their cocci infection. Two of these patients had cavitary lung disease and a third had marked elevation of cocci serology suggestive of occult disseminated infection.

PET Imaging for Fever of Unknown Origin

SOURCE: Wright WF, Auwaerter PG, Dibble EH, et al. Imaging a fever — Redefining the role of 18FDG-PET/CT in FUO investigations. *Clin Infect Dis* 2020; Aug 23;ciaa1220. [Online ahead of print].

Infectious disease physicians are at the front line for investigating fever of unknown origin (FUO), although historically only about one-third of such cases are the result of an infection. Historically, about one-third of FUO cases are secondary to malignancy, somewhere around 16% to 55% are due to noninfectious inflammatory disorders, while about 5% elude diagnosis. I liken FUO workups to peeling an onion, with an initial "layer" of laboratory and radiographic studies, followed by "layers" of subsequent studies. Depending on how quickly you peel through these layers and are able to schedule and secure results, FUO workups may take weeks before arriving at a solution.

Increasingly, fluoro-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging has found a role in the investigation of FUO. Using PET/CT, my partners have diagnosed an elusive case of malignancy and another case of giant cell arteritis involving the arterial system extending from the carotids to the iliac arteries. In contrast to these successes, FDG-PET/CT was not helpful in the diagnosis of a rare case of Cogan's syndrome (a variant of giant cell arteritis), which resulted in two months of intermittent fever and hearing loss in a young woman, and another case of drug hypersensitivity syndrome with eosinophilia and systemic symptoms (DRESS), both of which remained diagnostic challenges.

There are increasing data to support the use of FDG-PET and FDG-PET/CT in FUO workup. These authors provide a review of 50 clinical studies, published between 2011-2019 (44 retrospective and six prospective studies), and examine the contribution of PET/CT imaging to the investigation of FUO. Although some studies couch their results in terms of specificity and sensitivity, the diagnostic yield of PET/CT scanning is more appropriately presented in terms of "agreement" or "non-agreement," since often there is no gold standard or reference standard for comparison. Examining pooled data, PET/CT imaging showed a percentage positive agreement in diagnostic yield of 79% to 94%, and a percentage negative agreement of 44% to 97%. The overall percent agreement varied from 54% to 94%. Further, several studies observed that the use of PET/CT achieved a speedier diagnosis and decreased the overall cost of FUO workup by at least 35% to 60% by reducing the number of diagnostic evaluations and the number of invasive evaluations. Tests that commonly were no longer required included various viral and serologic studies, bone marrow and other biopsies, endoscopies, and various ultrasound and magnetic resonance imaging (MRI) studies. Several studies also demonstrated reductions in hospital days. Overall, PET/CT was 4.6 times more useful than labeled leukocyte scanning.

More than 90% of FDG-PET/CT imaging is currently used for diagnosis, staging, and monitoring in oncology. As recently as Jan. 9, 2021, Medicare issued a decision memorandum stating inadequate supporting data to justify the cost of PET/CT in the diagnosis of various infections and inflammatory disorders, including investigations of FUO, chronic osteomyelitis, chronic hip arthroplasty infection, sarcoid, etc. This prompted certain insurance companies (e.g., Aetna) to follow suit with a similar position paper indicating their willingness to cover the cost of PET/CT for certain conditions, such as cardiac sarcoid and a long list of malignancies, but not for the investigation of FUO, aortitis/large vessel vasculitis, Takayasu's arteritis, or other noninfectious inflammatory disorders. Of course, when you order a PET/CT for your diagnostic workup, how do you know whether you are going stumble across one of the 25

malignancies listed — or something else that would not be covered? Ironically, Medicare does cover the cost of nuclear leukocyte imaging, which is more costly than PET/CT, although far less useful.

High Rates of Thromboembolism in COVID-19

SOURCE: Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. *Ann Intern Med* 2020;173:268-277.

Prospectively obtained autopsy data from a single academic center in Hamburg, Germany, revealed a significant frequency of occult thromboembolism in the first 12 consecutive COVID-19 deaths. Two of the patients died in the outpatient setting following unsuccessful cardiac resuscitation, five patients died in intensive care, and five patients had advance directives for best active care on a medical unit. The median age was 73 years, and three-fourths were men. Coronary artery disease (50%) and obesity and chronic obstructive pulmonary disease (25%) were common. The cause of death in all 12 cases was found in the lungs or pulmonary vasculature. Although venous thromboembolism (VTE) was not suspected prior to death in any of the patients, autopsy revealed that seven of the 12 patients (58%) had VTE. Four patients died of massive pulmonary embolism (PE), all derived from the deep veins of the lower extremity, and the other three had lower extremity deep vein thrombosis (DVT) without PE. D-dimers varied from 20 nmol/L to > 1,905 nmol/L, with a median of 495 nmol/L. Eight of the patients had histopathologic evidence of diffuse alveolar damage, consistent with early acute respiratory distress syndrome (ARDS), with microvascular thromboemboli, capillary congestion, and interstitial edema. In addition, six of nine men had fresh thrombosis in the prostatic venous plexus.

PE should be suspected in any COVID-19 patient with an abrupt deterioration in respiratory or hemodynamic status. Further, we have been routinely screening COVID-19 patients for upper and lower extremity thromboembolism, especially those with elevated D-dimers. Although the radiology department resists performing these noninvasive studies in the rooms of these patients in airborne and contact isolation, the yield has been surprisingly high. ■

CME QUESTIONS

1. The COVID-19 pandemic has been associated with which of the following?

a. Decreased use of pediatric emergency services

b. Increased serious childhood illnesses and infections

c. Increased rates of appendicitis in children

d. Decreased pediatric hospitalizations for surgical concerns

2. Which of the following is correct regarding SARS-CoV-2 variants?

a. SARS-CoV-2 mutants emerge with greater frequency than do those of the influenza virus.

b. SARS-CoV-2 variants have emerged in the United Kingdom, South Africa, and Brazil.

c. The Moderna and Pfizer mRNA vaccines have become ineffective in the United States because of the introduction of the U.K. variant (B.1.1.7).

d. SARS-CoV-2 variants have emerged as a result of mutation in their nucleoprotein antigens.

3. Which of the following is correct regarding the XDR *Salmonella* Typhi that emerged in Pakistan and was detected in nine individuals in the United States with no history of travel outside the country?

a. It is susceptible to ceftriaxone.

b. It is susceptible to ciprofloxacin.

c. It is susceptible to azithromycin.

d. It is susceptible to trimethoprim-sulfamethoxazole.