Relias Media
From Relias

Vol. 40, Issue 11, August 2021
ReliasMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

MIS-C: Steroids and/or IVIG?

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SYNOPSIS: Multisystem inflammatory syndrome in children (MIS-C) can be a devastating post-COVID-19 complication, but treatment seems effective. High-dose steroids and intravenous immune globulin (IVIG) are commonly used, although new studies give conflicting findings as to whether it is best to use both treatments together.

SOURCES: McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med* 2021;385:11-22.

Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children — initial therapy and outcomes. *N Engl J Med* 2021;385:23-34.

Two similar studies reported simultaneously in the *New England Journal of Medicine* gave very different results as to whether the combination of steroids and intravenous immune globulin (IVIG) is better than the use of a single agent as initial treatment of multisystem inflammatory syndrome in children (MIS-C). McArdle and colleagues found no difference in outcomes whether patients received steroids or IVIG or both, while Son and colleagues found that adding steroids to IVIG was more effective in reducing the risk of subsequent cardiovascular dysfunction.

For 16 months now, a rare but potentially serious inflammatory syndrome has been reported in children following infection with SARS-CoV-2. Initially, the condition seemed to be a Kawasaki-like disease, and the condition now called MIS-C has been more completely characterized, while remaining poorly understood. The condition typically occurs two to six weeks after infection with SARS-CoV-2, whether or not the patient was symptomatic or ill with COVID-19. Fever, abdominal pain, vomiting, and fatigue are common; organ failure with shock is possible; extreme elevation of levels of inflammatory

Financial Disclosure: None of the planners of this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Infectious Disease [ALERT]

***Infectious Disease Alert*, (ISSN 0739-7348), is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Infectious Disease Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.**

GST Registration Number: R128870672.

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markers is common. Treatment often requires inotropic support. Similarities to Kawasaki disease (often with conjunctivitis and rash, sometimes with coronary aneurysms) prompted therapeutic trials of IVIG. The associated inflammatory findings suggestive of a cytokine storm prompted trials of steroids. Children usually recovered — without randomized, blinded, controlled studies guiding treatment decisions.

McArdle and colleagues invited pediatricians from around the world to submit data about patients with presumed post-COVID inflammatory illnesses through a web-based data collection tool. Based on the number of patients receiving various treatments, they categorized patients related to initial treatment with IVIG, IVIG and steroids, or steroids alone. From June 2020 into February 2021, clinicians from 81 hospitals in 34 countries submitted patient information. A total of 614 individuals were included, and the majority (81%) met Centers for Disease Control and Prevention (CDC) criteria for a diagnosis of MIS-C. (Thirty-seven percent of patients concurrently met criteria for a diagnosis of Kawasaki disease.)

Of these 614 patients, 40% were treated initially with IVIG alone, 34% with IVIG plus steroids, and 16% with steroids alone. (Others received other immunomodulation alone or as combinations of treatments.) The need for new inotropic support or mechanical ventilation more than two days after initiation of treatment was not different based on what the initial treatment had been. Reductions in disease severity following treatment also were not different based on the type of initial treatment used. These similar outcomes were found whether or not the patients met formal MIS-C diagnostic criteria. Neither left ventricular dysfunction nor biomarker/inflammatory levels varied based on the initial treatment modality given. Two percent of patients, equally mixed between treatment groups, died.

Son and colleagues analyzed surveillance data from 58 U.S. hospitals from March through October 2020. Inclusion was based on meeting six criteria, as detailed by the CDC: serious illness prompting hospitalization, age younger than 21 years, fever for at least 24 hours, laboratory evidence of inflammation, involvement of at least two organ systems, and confirmed SARS-CoV-2 infection or association with an infected person. Patients were categorized based on the treatment their treating physicians used. Outcomes (at least two days after initiation of treatment) were followed.

Of 596 eligible patients admitted to one of the 58 participating hospitals during the study period, 518 (87%) received at least one immunomodulating therapy. The median age of subjects was 8.7 years (range, 0-20.9), 42% were female, 35% were Black and/or Hispanic, and 75% had been healthy previously. The majority had five or more organ systems involved, and 38% met diagnostic criteria for Kawasaki disease (either complete or incomplete). The patients who received IVIG alone tended to be younger and to meet criteria for a Kawasaki disease diagnosis. Overall, 2% of patients died.

Of the 518 children who received an immunomodulating treatment sometime during the hospitalization, 17% received IVIG only, 47% received IVIG and a steroid (usually methylprednisolone 2 mg/kg/day), 21% received IVIG and a steroid and a biologic agent (such as anakinra), and 16% received some other combination of treatments. (For treatment initially at the time of hospitalization, IVIG alone was most common [37%], with almost as many [30%] receiving IVIG and a steroid; fewer patients were initially treated with a biologic agent.) Sicker patients tended to receive multiple immunomodulating treatments; 47% of patients received vasopressors. Propensity score matching was used to try to account for some of the confounding factors.

The use of IVIG plus steroids yielded a significant lower risk (0.56) of cardiac dysfunction as compared to treatment with IVIG alone, and it also was associated with less subsequent escalation of care to include additional immunomodulating modalities. Acknowledging the obvious limitations of a non-randomized study, the authors' careful analysis did show benefit in initial treatment of MIS-C with combined IVIG and steroids.

■ COMMENTARY

MIS-C is a rare and incompletely understood complication of SARS-CoV-2 infection. In the United States, MIS-C occurs in approximately 5.1 children per 1 million person months (and 316 per 1 million identified SARS-CoV-2 infections).[1] It is relatively more common in younger than in older children, and it is more common in Black, Hispanic, and Asian persons than in whites.[1]

The two divergent observational studies described provide some basis for encouragement. Despite the need for inpatient and, often, intensive care with inotropes and ventilation, most children recovered, and only 2% died. In an editorial commentary accompanying these two papers, Roberta DeBiasi cites an even more optimistic figure of less than 1% of children with MIS-C dying in the United States.[2] Treatment, including whatever immunomodulation is employed, seems to help children recover.

Of course, there were many factors making these two studies dissimilar: variations in treating physician management decisions, patients included, location, time (with resulting variations in viral variants in circulation), and statistical analyses. The divergent findings in the studies are not surprising. And, whether one or another solo or combination management regimen is best, children with critical life-threatening illness did recover with immunomodulatory treatment. As DeBiasi said, a lack of data to say which modality is best should not be interpreted as a lack of efficacy of the treatments.[2]

Other investigators continue to evaluate possible treatments of MIS-C. A nationwide study in France involving 111 children with MIS-C showed that those who received IVIG and steroids, as compared to IVIG alone, had less treatment failure, less requirement for new hemodynamic support with inotropes, and less subsequent development of left ventricular dysfunction.[3]

Over the months of the Son study, solo treatment became less common, and combined therapies became more common. Even while awaiting more definitive data, it is reasonable that a child sick enough to be hospitalized with MIS-C be given IVIG and steroids; escalation to a biologic, such as anakinra, or even plasmapheresis can be considered when the illness worsens or recovery stalls. Eventually, there will be more data about which virus and patient factors can be used at the time of presentation to predict which treatment regimen would be most efficacious. And, as vaccination becomes available for children and as the pandemic wanes, perhaps MIS-C also will become even more rare. ■

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3. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA* 2021;325:855-864.

ABSTRACT & COMMENTARY

COVID-19 Vaccination: The Heart of the Matter

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The occurrence of myocarditis after receipt of COVID-19 mRNA vaccines is most frequent in young males and generally is benign, with rapid resolution with only supportive care. Careful analysis indicates that the benefit of vaccination outweighs the risk in all groups for whom the vaccine is recommended — including young males.

SOURCE: Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977-982.

From December 2020, when the Food and Drug Administration (FDA) issued Emergency Use Authorization for the use of Moderna and Pfizer-BioNTech mRNA COVID-19 vaccines, through June 11, 2021, approximately 296 million doses were administered in the United States, including 52 million doses given to individuals 12-29 years of age. Within that interval, beginning Dec. 29, 1,226 reports of

post-vaccination myocarditis were reported to the Vaccine Adverse Event Reporting System (VAERS). The median age of those reported was 26 years (range, 12-94 years), with a median onset three days after vaccination. The majority were 30 years of age, and most of this younger group were male.

A further review of 323 patients who met Centers for Disease Control and Prevention (CDC) definitions for myocarditis, pericarditis, or myopericarditis was performed. All but 4% of these were hospitalized. The median age was 19 years, and 291 of the 323 were male. The median interval between vaccination and onset was two days (range, 0-40 days), with 92% having onset within seven days. The clinical course was mild, with no deaths and with 95% discharged from the hospital at the time of review.

For males 12-29 years of age, the myocarditis reporting rate occurring within seven days of a second vaccine dose was 40.6 per million, while it was 2.4 per million for males > 30 years of age. The rates for women in these age groups were 4.2 and 1.0 per million, respectively. The groups with the highest rates were males 12-17 years of age (62.8 per million) and males 18-24 years of age (50.5 per million).

Analysis led to the conclusion that the benefits associated with the prevention of COVID-19 outweighed the risk of myocarditis in all groups for whom vaccination has been recommended. Focusing on males 12-29 years of age, receiving both vaccine doses was associated with 39-47 cases of myocarditis but with prevention of 11,000 COVID-19 cases, 560 hospitalizations, 138 intensive care unit (ICU) admissions, and six deaths. It also should be noted that this analysis did not take into account the prevention of "long COVID."

■ COMMENTARY

Numerous case reports and small case series describing myocarditis after COVID-19 mRNA vaccination are appearing in the literature, and these attest to the usual apparent benign nature of this complication. As one example, Marshall and colleagues reported seven cases in adolescents. All had elevated cardiac troponin levels, and all had late enhancement of magnetic resonance imaging (MRI) images with gadolinium enhancement, a characteristic finding in myocarditis.[1] All patients recovered rapidly without apparent sequelae.

Montgomery et al described 23 cases of myocarditis identified within the U.S. Military Health System that occurred over a period during which more than 2.8 million mRNA vaccine doses had been administered.[2] All were male and their median age was 25 years (range, 20-51 years). All had elevated serum troponin, and MRI findings were consistent with myocarditis in all eight patients in whom this study was performed. Their illnesses were mild, and all had recovered or were recovering at the time the report was submitted for publication.

The benign nature of the illness described in these series is consistent with the CDC report and conclusions. As they indicate, it will be important that follow-up of these cases continues to assure the absence of any longer-term adverse effects. ■

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2. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol* 2021; Jun 29. doi: 10.1001/jamacardio.2021.2833. [Online ahead of print].

ABSTRACT & COMMENTARY

Clostridioides difficile Infection: Guideline Update

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Fidaxomicin is preferred over vancomycin for both initial and recurrent cases. Bezlotoxumab is recommended in many cases of recurrent infection and initial infection in patients at high risk of recurrence.

SOURCE: Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults. *Clin Infect Dis* 2021;Jun 24:ciab549. doi: 10.1093/cid/ciab549. [Online ahead of print].

Johnson and colleagues have provided a focused update of the 2017 Infectious Diseases Society of America — Society for Healthcare Epidemiology of America clinical practice guidelines for *Clostridioides difficile* infection (CDI). The update is limited to three new recommendations — one each dealing with the treatment of initial and recurrent infection, and one dealing with prevention of further recurrences. The following is a brief version of the changed recommendations. All are considered conditional; the first two are based on low certainty evidence and the third is based on very low certainty evidence.

- For initial episodes of CDI, fidaxomicin therapy is recommended, rather than a standard course of vancomycin.
- For recurrent episodes of CDI, fidaxomicin therapy is recommended, rather than a standard course of vancomycin.
- For patients with a recurrence in the previous six months, bezlotoxumab administration is recommended together with standard of care therapy.

■ COMMENTARY

The optimal management of CDI is an ever-evolving process. Among the knottier issues is that of diagnosis of the disease in the absence of a gold standard — and this is not addressed by the update. Nonetheless, this document provides useful guidance regarding the relative benefit of fidaxomicin over vancomycin therapy in initial and recurrent episodes of infection, as well as the use of bezlotoxumab in recurrent disease.

No change in the previous recommendation for fecal microbiota transplantation (FMT) has been made, and the "opinion of the panel" is that patients who have had a third recurrence despite appropriate therapy may be offered FMT. However, the panel points out that since 2017 there have been two Food and Drug Administration (FDA) alerts about the treatment modality: two related to transmission of antibiotic-resistant *Escherichia coli* and one raising issues regarding COVID-19.

The recommendation regarding the preference of fidaxomicin over vancomycin likely could have been made at the time of the 2017 guideline, but the major impediment undoubtedly was the remarkable cost differential between the two therapies. The very high cost of fidaxomicin persists and is addressed in the current document. For this reason, the current recommendation acknowledges the implementation of the fidaxomicin recommendation "depends upon available resources" and includes a statement that vancomycin remains an acceptable alternative. High-dose enteral vancomycin continues to be recommended for cases of fulminant CDI.

The panel noted that for those patients with a first recurrence of CDI, a tapered regimen and a pulsed regimen of vancomycin are acceptable alternatives to fidaxomicin. For patients with multiple recurrences, acceptable options for fidaxomicin are tapered and pulsed vancomycin followed by rifaximin or FMT.

In addition to the use of bezlotoxumab in those with recurrent CDI as indicated earlier, its use may be considered during initial episodes in individuals with risks for recurrence, such as severe CDI on presentation, age > 65 years, or the presence of immunocompromise. It should be noted that the monoclonal should be administered during receipt of standard of care. However, the benefit of both fidaxomicin and bezlotoxumab relates to their ability to prevent recurrent CDI and the evidence is next to nonexistent that the combination is superior in this regard to the use of either agent alone — an important consideration given the potential financial toxicity of each. ■

REFERENCE

1. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018;66:e1-e48.

ABSTRACT & COMMENTARY

Amebic Meningoencephalitis

By Stan Deresinski, MD, FACP, FIDSA

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SYNOPSIS: Primary amebic meningoencephalitis is a rarely diagnosed worldwide disease associated with exposure to fresh water that causes highly lethal, rapidly progressive central nervous system infection but may be treatable in some cases, necessitating maintenance of a high index of suspicion in appropriate cases.

SOURCE: Gharpure R, Bliton J, Goodman A, et al. Epidemiology and clinical characteristics of primary amebic meningoencephalitis caused by *Naegleria fowleri*: A global review. *Clin Infect Dis* 2021;73:e19-e27.

Gharpure and colleagues, performing a literature review as well as an examination of the Centers for Disease Control and Prevention (CDC) Free-Living Ameba surveillance data, identified 381 cases of primary amebic encephalitis (PAM) caused by *Naegleria fowleri* from 1937 through 2018. Of these, 145 cases occurred in the United States and were identified by the surveillance system and an additional 11 cases were from case reports published prior to 1962. Exposures occurred in a total of 33 countries, with the United States accounting for 41%, Pakistan accounting for 11%, and Mexico accounting for 9%. One-half or more of the diagnoses were made by direct visualization of the organism, with the remainder made by immunohistochemistry or immunofluorescence, with confirmation by polymerase chain reaction (PCR) or next generation sequencing.

Water activities were reported as likely exposures in 247 cases; nasal irrigation was reported in 9%. The water sources were lakes, ponds, or reservoirs in 45%; swimming pools in 13%; tap water in 12%; and canals, ditches, or puddles in 12%. Of the 34 cases associated with swimming pool exposure, 33 (97%) occurred before 1988. Of the 315 cases for which the information was available, 85% described the season as summer or stated it was warm or hot.

Three-fourths of patients were male, and the median age of the cohort was 14 years (range, 1 month to 85 years). Of the 256 cases for whom the presenting symptoms were recorded, these were influenza-like in 41 (16%), while the remainder had symptoms suggestive of central nervous system infection. Common symptoms and signs included fever (88%), headache (82%), nausea/vomiting (57%), altered mental status (50%), and nuchal rigidity (35%); 13% were comatose at the time of presentation. On lumbar puncture, the opening pressure was elevated in all patients, the median red blood cell count was 212 cells/μL, the median white blood cell count was 1,238 cells/μL with neutrophil predominance (median 82%), elevated protein, and low glucose.

There were 32 survivors, for a case fatality rate of 92%, but only seven of the 32 had acceptable laboratory confirmation. The median incubation period was six days (range, one to 30 days). All seven of the survivors with confirmed infection received intravenous amphotericin B (deoxycholate in at least four; the product used was not stated in the other three), and five of these also received the drug intrathecally. Six of the seven received an antifungal azole, four each received azithromycin and/or miltefosine; dexamethasone was administered to five of the patients.

■ COMMENTARY

The number of identified cases of amebic meningoencephalitis has increased over the years, most likely as the result of increased recognition. However, it has been speculated that warming related to global climate change may increase potential exposure to the thermophilic *N. fowleri*.

An interesting observation is that almost one in 10 cases were associated with nasal irrigation, which was performed for either therapeutic or religious reasons.

Although all seven survivors with confirmed PAM received amphotericin B, this drug was administered to 71% of the entire cohort — obviously failing in a very large proportion. However, treatment with potentially effective drugs depends on suspicion of the diagnosis. The authors pointed out that the definition of a probable case used in their analysis is useful in this regard: acute onset rapidly progressive meningoencephalitis with fever, headache, vomiting, and/or meningismus occurring within 14 days of freshwater exposure. The most rapid and readily available means of diagnosis is the visualization of motile trophozoites of the ameboflagellate in wet preparations of cerebrospinal fluid. The one case I have seen (decades ago in Florida) was identified initially by a laboratory technician performing a cell count using a cytometer.

The CDC can be contacted about suspected cases: https://www.cdc.gov/parasites/naegleria/diagnosis-hcp.html. ■

ABSTRACT & COMMENTARY

The Use of Proton-Pump Inhibitors and the Risk of Acquiring Community-Associated *Clostridioides difficile* Infection

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

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SYNOPSIS: A nationwide cohort study of adults in Denmark found that proton-pump inhibitor (PPI) use was associated with a moderately increased risk of community-associated *Clostridioides difficile* infection, and the risk remained elevated up to one year after PPI treatment had stopped.

SOURCE: Inghammar M, Svanström H, Voldstedlund M, et al. Proton-pump inhibitor use and the risk of community-associated *Clostridium difficile* infection. *Clin Infect Dis* 2021;72:e1084-e1089.

Several observational studies over the last 15 years have reported an association between *Clostridioides difficile* infection (CDI) and proton-pump inhibitor (PPI) use. However, many of them have been criticized for their observational design and lack of sufficient adjustment for confounding variables. One way to adjust for confounders is a relatively new type of study design called the self-controlled case-series (SCCS), which compares time periods of exposure and non-exposure within individuals, thereby controlling for all confounders that remain constant over the observation time frame. Inghammar and colleagues conducted a large nationwide study to determine the risk of community-associated CDI (CA-CDI) in adults prescribed PPIs using an SCCS design.

The study included Danish adults 20 years of age and older in a nationwide database diagnosed with CA-CDI between February 2010 and December 2013. A case of CA-CDI was defined based on guidelines from the Infectious Diseases Society of America as a first positive test for *C. difficile* based on culture, molecular assay, or toxin test among individuals who had symptoms in an outpatient setting or two or fewer days after hospitalization, who had no other positive CDI tests within the preceding eight weeks and had not been hospitalized in the preceding 12 weeks. PPI exposure was defined based on four timeframes: new use, defined as a PPI prescription among individuals without PPI use in the prior 365 days; current use, defined as ongoing treatment with one tablet per day of a PPI from the first day of treatment until treatment cessation; intermediate use, defined as the time period zero to six months (0-179 days) after treatment cessation; and past use, defined as six to 12 months (180-364 days) after treatment cessation.

There were 3,583 cases of CA-CDI in 3,338 individuals during the study period. The median age was 65 years (interquartile range, 44 to 80 years), and 38% were male. CA-CDI occurred in 964 individuals who currently were using PPIs, 324 cases occurred after intermediate use, 123 occurred after past use, and 2,172 occurred during time periods without use of PPIs. The adjusted incident rate ratio (IRR) was 2.03 (95% confidence interval [CI], 1.74-2.36), comparing PPI use with nonuse. The increased risk continued to be elevated in later time periods: 1.54 (CI, 1.31-1.80) for zero to six months and 1.24 (CI, 1.00-1.53) for six to 12 months after current use.

After comparing the incidence of CA-CDI during current use of PPIs with periods of nonuse, the unadjusted IRR was found to be 2.78 (95% CI, 2.40-3.22). Adjusting for hospitalization, antibiotic use, and corticosteroid use resulted in an adjusted IRR of 2.03 (95% CI, 1.74-2.36). The increased risk was reduced but still elevated in later timeframes (adjusted IRR, 1.54 [95% CI, 1.31-1.80] for zero to six months and adjusted IRR 1.24 [1.00-1.53] for six to 12 months after current use of PPIs). Estimates for the association between current use of PPIs and CA-CDI were similar with regard to sex and age.

■ COMMENTARY

Most of the previous studies that investigated the association between PPIs and CDI were done with hospitalized patients. These individuals tend to be older, sicker, and have more antibiotic exposures than patients who develop CDI in community settings. Therefore, the analysis by Inghammar and colleagues is interesting because it focused on this latter, less studied group. The key finding was the use of PPIs was associated with approximately two times the risk

for acquiring CA-CDI. The risk was reduced after PPI treatment stopped, but it remained significantly increased up to 12 months afterward.

So what should clinicians take away from this study? First, they need to realize there is increasing evidence for an association between PPI use and CDI. They should carefully assess the potential benefits of PPI use compared to the risk of CA-CDI, especially in patients with a previous history of CDI. In such cases, perhaps an alternative agent would be a better choice, or the PPI could be used but for a limited amount of time.

Second, the mechanism by which PPI use increases the risk for CDI has not yet been fully elucidated. It is believed that PPIs suppress the capacity of the normal microbiome in limiting the proliferation of *C. difficile*. Further experimental evidence is needed to test this hypothesis.

Despite the robust study design, a few limitations are worth mentioning. First, some PPIs can be purchased over the counter in Denmark, which could have led to misclassification of drug exposure. Second, although the SCCS design enables patients to be used as their own controls, which minimizes the effect of time-fixed confounders, residual confounding theoretically still is possible since there was no randomization in the study. Finally, the results of the study might not be generalizable to other populations in different geographic areas.

Definitive proof that PPIs cause CDI likely will require a randomized clinical trial. Given the relatively low incidence of CDI in the community, this would require a large number of individuals to be enrolled. Until then, clinicians need to be aware of the risks associated with PPIs and prescribe them with the best available evidence in mind. ■

ABSTRACT & COMMENTARY

Quinacrine for Refractory Giardiasis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Quinacrine is highly effective in the treatment of giardiasis that is recalcitrant to initial therapy with other agents, but patients must be warned about neuropsychiatric effects.

SOURCES: Neumayr A, Schunk M, Theunissen C, et al. Efficacy and tolerability of quinacrine monotherapy and albendazole plus chloroquine combination therapy in nitroimidazole-refractory giardiasis: A TropNet study. *Clin Infect Dis* 2021; Jun 11:ciab513. doi: 10.1093/cid/ciab513. [Online ahead of print].

Ydsten KA, Hellgren U, Asgeirsson H. Quinacrine treatment of nitroimidazole-refractory giardiasis. *J Infect Dis* 2021; May 24:jiab287. doi: 10.1093/infdis/jiab287. [Online ahead of print].

In a prospective, open-label, non-randomized study at four European travel clinics belonging to the TropNet group, Neumayr and colleagues evaluated the outcomes of two different treatment regimens in patients with giardiasis who had failed one or more 5-nitroimidazole treatment courses. The patients, 57% of whom had acquired their infection in India, then were treated for five days with either quinacrine alone (100 mg three times daily) or the combination of albendazole (400 mg twice daily) plus chloroquine (155 mg twice daily). The choice of treatment was based on local availability of the drugs.

Among those for whom the data were available, monotherapy with quinacrine was associated with clinical cure in 59/72 (81%) and parasitological cure in 56/56 (100%). The combination of albendazole and chloroquine, in contrast, yielded clinical cure in 12/33 (36%) and parasitological cure in 12/25 (48%). In addition, clinical cure was achieved in all nine patients treated with quinacrine who had failed the combination therapy. Mild-to-moderate treatment-related adverse effects occurred in 45% of quinacrine and 30% of combination therapy recipients. One patient given quinacrine developed severe neuropsychiatric symptoms after his fourth day of treatment that led to a brief hospitalization and then completely resolved. One quinacrine recipient developed acute kidney injury, but this was judged to be due to dehydration resulting from diarrhea from giardiasis.

Separately, Ydsten and colleagues at the Karolinska University Hospital retrospectively examined the records of 87 patients who had failed two courses of treatment of giardiasis; 54 patients (62%) had traveled to India. Of the 87 patients, 54 (62%) had been given quinacrine (two in combination with

metronidazole) in a dose of 100 mg three times daily — most for five to seven days. After treatment, six (12%) patients had symptom persistence, while parasitological efficacy was 94%. Repeat quinacrine treatment was effective in each of the three patients who had failed their initial course. After quinacrine, the second most frequent regimen administered to patients who had failed nitroimidazole therapy was albendazole plus metronidazole, which had a 57% failure rate among the 37 patients for whom follow-up samples were available. Among the quinacrine recipients, there were no serious adverse events among seven patients with a prior diagnosis of psychiatric disorder, although one patient, in addition to headache and gastrointestinal complaints, transiently felt distracted.

■ COMMENTARY

Literature suggests that the frequency of treatment failure of giardiasis with 5-nitroimidazoles, such as metronidazole, appears to be increasing. Furthermore, evidence points to India being a source of many infections recalcitrant to treatment with those agents.

The Centers for Disease Control and Prevention states that effective treatments for initial treatment of giardiasis include metronidazole, tinidazole, and nitazoxanide, and that others include paromomycin, quinacrine, and furazolidone.[1] For treatment failures, they recommend considering combination therapy, but they do not recommend specific agents. A recent review of refractory disease points out that no randomized controlled trials addressing this problem have been performed in a quarter of a century. Based on the available information, they state that quinacrine is effective, but warn that side effects may limit its use.

Because of their design, the studies presented here cannot be considered to provide high-quality evidence. Neither was randomized, and one was retrospective. In the other, although it was prospective, treatment assignment was based on availability of the therapeutic agents. Nonetheless, the results clearly indicate that quinacrine is a highly effective agent in the treatment of giardiasis refractory to other treatments. One serious adverse event, a neuropsychiatric disturbance, occurred in 126 patients given quinacrine in the two studies, and this resolved with drug discontinuation.

That is the good news about quinacrine. The bad news is that quinacrine is available in the United States only through compounding pharmacies. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Sepsis Bundle Erodes Gains in Stewardship

SOURCE: Pakyz AL, Orndahl CM, Johns A, et al. Impact of the Centers for Medicare and Medicaid Services Sepsis Core Measure on antibiotic use. *Clin Infect Dis* 2021;72:556-565.

Beginning in October 2015, the Centers for Medicare and Medicaid Services (CMS) implemented a new policy for sepsis patients with initiation of a core measures sepsis "bundle," an important part of which was time to first antibiotic dose following a diagnosis of sepsis and the initiation of broad-spectrum antibiotics within three hours of diagnosis.

These authors assessed monthly adult antibiotic usage for 111 acute care hospitals in the one year before this policy change (October 2014 to September 2015) and following this policy change (October 2015 to June 2017). Four different categories of antibiotic use were observed, including broad-spectrum antibiotics for community-acquired infection, broad-spectrum antibiotics for nosocomial infection/multidrug-resistant organisms, the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents (such as vancomycin, daptomycin, linezolid, ceftaroline, etc.), as well as antibiotics for surgical prophylaxis.

Prior to implementation of the CMS sepsis bundle, antimicrobial usage had been diminishing gradually. Beginning in October 2015, however, an immediate 88.9% increase was observed in the overall use of antibiotics, with observed increases in all four categories. Broad-spectrum drugs for multidrug-resistant organisms and MRSA increased > 65%.

Unexpectedly, antibiotic use for surgical prophylaxis significantly increased 284%. Use continued to increase incrementally every month for the next three years.

The rush to administer antibiotics within three hours of sepsis diagnosis has led to less discriminate use of antibiotics. The bundle itself presents only certain antibiotic options, and some agents are not even listed. It is estimated that at least one-third of sepsis diagnoses are due to noninfectious causes, such as acute pancreatitis, acute hypersensitivity reactions, and diabetic ketoacidosis, for which antibiotics may not be necessary. This is because sepsis is a physiological state, which may not be caused by an infection at all. And yet, as long as the hospital has satisfied their sepsis bundle goal, no one seems to care that CMS policy is directly counter to antimicrobial stewardship goals and the critical reduction of antimicrobial resistance. Notably, credit for the bundle is given in an "all or none" manner, meaning even if you sagely decide to implement everything in the bundle except the (perhaps unnecessary) antibiotics, you get zero credit for thinking.

Studies examining the use of antibacterials have observed that, once antibiotics are started in the emergency department (ED), too often they are continued for complex reasons. First, antibiotics begun in the ED often are not immediately re-evaluated by the admitting physician, who may be reluctant to disrupt the initial choice of antibiotics. Second, a gap of up to 24 hours may occur before the physician picking up the case the next day begins to tackle the process of re-evaluating the initial choice of antibiotic. Third, a gap of 24-72 hours occurs before micro data are available, and physicians may be reluctant to stop antibiotics without those data. How many times have I heard "wait at least 48 to 72 hours for negative cultures before stopping antibiotics."

Medical teams, especially in teaching hospitals, function in a more collaborative approach (meaning that no one person "owns" the decision) and often take the path of least resistance, waiting for clinical outcomes and specific micro data before making decisions. Surgical teams, which round early in the morning when neither micro data nor antimicrobial stewardship pharmacists are available, are poorly prepared to make decisions about antibiotics during rapid-fire morning rounds. Rather, "lesser" decisions (such as antibiotics) are delegated to a junior member of the surgical team, who is more worried about negative outcomes and making the wrong decision. So, difficult decisions about antibiotics often are deferred, again leading to more prolonged use of antibiotics. ■

Asymptomatic Transmission of COVID-19 in Households

SOURCE: Ng OT, Marimuthu K, Koh V, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: A retrospective cohort study. *Lancet* 2021;21:333-343.

Early on during the COVID-19 pandemic, Singapore adopted a comprehensive approach to prevention, diagnosis, and management of COVID-19, with clear guidance for the community and recommendations for mask wearing and social distancing. A network of 800 public health and community clinics was activated to quickly perform contact tracing and quarantine of contacts in the home and in the workplace and to test contacts who developed symptoms, with a medical leave plan for those who became ill. From Jan. 23 to April 3, 2020, 13,026 close contacts were identified, including 1,863 household contacts (with 578 distinct contact groups), 2,319 work contacts (with 225 distinct contact groups), 3,588 social contacts (with 346 distinct contact groups), 2,626 transportation contacts, and 2,630 other contacts.

Of these, a total of 468 (26.3%) household contacts, 332 (14.9%) work contacts, and 458 (13.1%) social contacts were polymerase chain reaction (PCR) tested based on the presence of symptoms. A total of 188 cases were identified as secondary cases based on symptom-driven PCR screening, and another 7,582 completed quarantine without a COVID-19 diagnosis. Based on symptom-based screening, the secondary attack rate was 5.9% for household contacts, 1.3% for work contacts, and 1.3% for social contacts. Cases clearly clustered together within certain households and a few work groups; 86.3% of household contact groups and 91.6% of work contact groups had no apparent secondary cases based on symptom-based PCR screening.

Convalescent serologic testing was performed in 30% of household contacts, 9% of work contacts, and 11.8% of social contacts who completed quarantine without a COVID-19 diagnosis. An additional 5.5% of household contacts, 2.5% of work contacts, and 2.1% of social contacts were identified as secondary cases based on positive serology. Among these, two-thirds were asymptomatic and one-third had developed symptoms but had tested SARS-CoV-2 PCR negative.

Activities that increased the risk of transmission included sharing a bedroom, sharing a vehicle, or being spoken to by a COVID-19 PCR-positive person for > 30 minutes. Indirect contact, sharing objects or

equipment, sharing a bathroom, and sharing a meal were not associated with SARS-CoV-2 transmission.

Secondary transmission was much more likely to individuals within households (11.4%) than in the workplace (3.8%) or social situations (3.4%), and infections clearly clustered in some households and a few workplaces. Efforts to control secondary transmission should be given to households and those contact groups where any case of secondary transmission has already been identified. Symptom-based PCR screening of contacts missed nearly half of those who developed secondary infection. At least one-third of secondary transmission cases remained asymptomatic. ■

When Is Hand Hygiene Personally Protective?

SOURCE: Chang NN, Reisinger HS, Schweizer ML, et al. Hand hygiene compliance at critical points of care. *Clin Infect Dis* 2021;72:814-820.

Hand hygiene remains the most effective method for preventing healthcare-associated infections (HAI). Healthcare data often focus on hand hygiene on entry to or exit from a patient room and not on healthcare worker (HCW) behavior between patient care tasks. These authors used secondary data analysis from the STAR*ICU trial to examine HCW behavior during the process of patient care, breaking down the care into "care sequences" and identifying "task pairs" — two consecutive tasks and the intervening hand hygiene opportunity.

Patient care tasks were categorized as either non-contaminating or contaminating, meaning more likely to contaminate HCW hands. Non-contaminating tasks included sterile tasks, device-blood (opening, connecting, injecting, etc., using an intravascular device and not in contact with mucous membrane or nonintact skin), device-other, patient (touching patient skin or a closed wound), and environment (items or surfaces in the environment). In contrast, contaminating tasks included blood or body fluid (with the potential for exposure to blood or body fluid), contaminated respiratory tract, oral, nose, or eye care; contaminated urinary catheter care, contaminated wound or wound drain care, and contaminated elimination. Tasks were defined further as critical if they were more likely to be associated with a higher risk of patient infection. Some tasks could be both contaminating and critical, depending on their position in the task pair. Multiple logistic regression analysis using repeated measures was used to examine associations between hand hygiene compliance, the type of patient care task, the order of the task, and the workload. The data were adjusted for HCW type and whether the patient was in standard, contact, or airborne isolation.

The study identified 28,826 task sequences with 42,349 hand hygiene opportunities. Critical tasks occurred significantly more often for patients in isolation than those in standard precautions. Overall, hand hygiene compliance was 43.2% before critical tasks and 38.1% before non-critical tasks. However, after adjusting for HCW type, glove use, and isolation precautions, HCWs were slightly less likely to perform hand hygiene before critical tasks compared with other tasks (adjusted odds ratio [OR], 0.97). Overall hand hygiene was 62.7% after contaminated tasks and 35% after other tasks (adjusted OR, 1.12).

HCWs tended to move from tasks that had relatively lower risk to patients to those tasks with higher risks for patients, rather than vice versa. However, they were less likely to perform hand hygiene when moving from tasks with lower risk to patients to those with higher risk, even when those subsequent tasks were considered critical. Hand hygiene decreased with increasing workload. An increase in workload was associated with increased odds of performing critical tasks. Hand hygiene also was performed more often when the patient was in isolation than during standard precautions. Nurses provided both critical and contaminating tasks more than physicians or other HCWs, and their hand hygiene generally was better than that of either physicians or other HCWs. Individuals who performed hand hygiene were more likely to practice it consistently throughout the process of patient care. In other words, for certain individuals, hand hygiene has become embedded in their routine.

The authors concluded that even though HCWs were more likely to order their work from less critical to more critical tasks, they appeared to perceive this approach as posing less of a risk to patients, rather than starting with the most critical tasks for the patient and moving to less critical tasks. This observation suggests that HCWs do not understand the rationale for hand hygiene as intended to prevent HAI, having more to do with their preferred work flow and less to do to with minimizing risks to patients. All HCWs were significantly more likely to perform hand hygiene after contaminating tasks, suggesting that they were more concerned about contaminating themselves.

The emphasis on personal protective equipment appears to have conveyed the wrong message to HCWs, who misunderstand the purpose of hand hygiene as protective to patients. HCWs choose to perform hand hygiene more often following a task than before a task, and when performing contaminating tasks than at critical moments during

patient care. Hand hygiene was performed more often when the patient was in isolation, although hand hygiene and HAI are just as important for patients in standard precautions. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding multisystem inflammatory syndrome in children?

a. It is diagnosed based on SARS-CoV-2 positivity and cardiac dysfunction.

b. It is best treated with intravenous immune globulin without a second concurrent immunomodulatory agent.

c. It is seen in about 10% of children who previously had COVID-19 and has a mortality rate of 10% to 15%.

d. It is similar in some features to Kawasaki disease.

2. Which of the following is correct regarding myocarditis occurring after administration of an mRNA vaccine against COVID-19?

a. The median age of its occurrence in recipients was 8 years.

b. The median interval between vaccination and onset of symptoms was nine days.

c. The mortality rate is 17%.

d. The highest incidence occurred in males 12-17 years of age.

3. Which of the following is correct regarding amebic meningoencephalitis?

a. It is caused by *Balamuthia mandrillaris*.

b. The dominant presentation is with a brain abscess.

c. The cerebrospinal fluid demonstrates neutrophilic predominance.

d. The cerebrospinal fluid opening pressure is low.

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.