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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

COVID-19 Vaccination and Myocarditis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Receipt of a COVID-19 mRNA vaccine is associated with a small but real risk of development of myocarditis, predominantly in young males. The vast majority of cases are mild, self-limited, and require no intervention.

SOURCES: Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 2021; Oct 6. doi: 10.1056/NEJMoa2109730. [Online ahead of print].

Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 2021; Oct 6. doi: 10.1056/NEJMoa2110737. [Online ahead of print].

Israel initiated an effective national program of immunization against COVID-19 with the BNT162b2 mRNA vaccine produced by Pfizer/BioNTech shortly after it became available and, by May 31, 2021, 5.1 million people had been fully vaccinated. With early reports of myocarditis occurring in association with receipt of the vaccine, the Ministry of Health initiated an active surveillance program and they now report the results covering the period of Dec. 30, 2020, through May 31, 2021.

As reported by Mevorach and colleagues, the surveillance program identified 142 cases, all but six of which were deemed to represent definite or probable myocarditis. During the same time period, 101 cases of myocarditis were identified among individuals who had never received the vaccine, but 29 of these had confirmed COVID-19. Of the 136 definite/probable cases, 91% of whom were male and 76% < 30 years of age, 129 (95%) presented with only mild symptoms. However, one case was fulminant, and that patient died. Nineteen (14%) of the 136 presented after the first vaccine dose, while 117 (86%) did so within 30 days after the second — most within the first six days. The standardized incidence ratio (observed vs. expected) relative to historical data was 5.34 (95% confidence interval [CI], 4.48 to 6.40), but in males 16-19 years of age, it was 13.60 (95% CI, 9.30 to 19.20). The incidence

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Infectious Disease [ALERT]

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rate ratio (comparing fully vaccinated to unvaccinated individuals) 30 days after dose 2 was 2.35 (95% CI, 1.10 to 5.02) overall but, among males 16-19 years of age, it was 8.96 (95% CI, 4.50 to 17.83), with myocarditis occurring in one of the 6,637 patients in this group.

Separately, Witberg and colleagues examined the database of the largest healthcare organization in Israel and identified 54 cases of myocarditis among more than 2.5 million BNT162b2 mRNA vaccine recipients during Dec. 20, 2020, through May 24, 2021. To be counted, cases had to occur within 42 days after the first vaccine dose (and, thus, up to approximately 21 days after the second dose). Of the 54 cases, 41 were mild, 12 were intermediate in severity, and one, with cardiogenic shock, was fulminant. The median age of the patients was 27 years, and 94% were male. Sixty-nine percent occurred after the second vaccine dose, with a large proportion occurring in the seven days after the dose, but with cases continuing to occur for the full subsequent 21 days of observation. Fourteen patients had echocardiographic evidence of left ventricular dysfunction at the time of admission, but this had resolved in four patients at the time of discharge and in another five patients on follow-up. The overall incidence per 100,000 recipients of at least one vaccine dose was 2.13 (95% CI, 1.56 to 2.70), but in males 16-29 years of age, it was 10.69 (95% CI, 6.93 to 14.46).

■ COMMENTARY

Each of these studies from Israel, one using data from the largest healthcare organization in the country and the other using national surveillance data, came to the same conclusions. Although their estimates vary to some extent, it is evident that myocarditis may be an adverse effect of this mRNA vaccine, most often within a week after the second dose, and that the highest risk occurs in young males. Nonetheless, with some exceptions, the episodes of cardiac inflammation are mild, resolve quickly, and no intervention is required — although at least one related death was recorded among the total of 190 cases in the combined series.

Nonetheless, Sweden, Norway, and Finland have put the use of the Moderna vaccine on hold in individuals younger than 30 years of age while further evaluating the data.

Myocarditis, which also may occur after receipt of the Moderna mRNA vaccine, mRNA-1273, should be suspected in patients with acute onset of chest pain, shortness of breath, or palpitations.[1] If a diagnosis is made, consideration should be given to testing for alternative causes, such as acute viral infection, including with SARS-CoV-2. Cases of post-vaccination myocarditis or pericarditis should be reported through the Vaccine Adverse Event Reporting System.[2] ■

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2. Vaccine Adverse Event Reporting System (VAERS). https://vaers.hhs.gov/reportevent.html

ABSTRACT & COMMENTARY

Prophylactic Probiotics Do Not Reduce the Risk for Developing Ventilator-Associated Pneumonia

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

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SYNOPSIS: A multicenter, randomized, placebo-controlled clinical trial found the use of prophylactic probiotics did not reduce the risk for developing ventilator-associated pneumonia or improve other outcomes for intensive care unit patients, compared to placebo.

SOURCE: Johnstone J, Meade M, Lauzier F, et al; Prevention of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) Investigators and the Canadian Critical Care Trials Group. Effect of probiotics on incident ventilator-associated pneumonia in critically ill patients: A randomized clinical trial. *JAMA* 2021;326:1024-1033.

The development of ventilator-associated pneumonia (VAP) leads to significant morbidity, mortality, and increased healthcare costs. Previous studies have shown that prophylactic probiotics may reduce the risk of VAP. Therefore, Johnstone and colleagues sought to determine whether the probiotic *Lactobacillus rhamnosus* GG reduced the risk for VAP and other detrimental outcomes in patients admitted to the intensive care unit (ICU), compared to placebo.

The study was a randomized, placebo-controlled clinical trial that included 44 ICUs from the United States, Canada, and Saudi Arabia. Inclusion criteria were age at least 18 years and the expectation of mechanical ventilation for at least 72 hours. Patients were excluded if they had been on mechanical ventilation for more than 72 hours, were immunocompromised, were at increased risk of endovascular infection, had severe pancreatitis, had plans for palliation, or if they had a percutaneous enteral feeding tube or were unable to receive enteral medication. Patients were randomized 1:1 to receive either *Lactobacillus rhamnosus* GG 1×10^{10} colony forming units or an identical enteral placebo twice daily. The study product was given for up to 60 days or until discharge from the ICU. Also, the probiotic was discontinued if *Lactobacillus* spp. was isolated from a sterile culture site or if it was the predominant organism isolated in a culture from a nonsterile site.

The primary endpoint of the study was the development of VAP. This was defined as the presence of a new, progressive, or persistent infiltrate on chest imaging after at least two days of mechanical ventilation, along with any two of the following: fever (temperature > 38°C) or hypothermia (temperature < 36°C); white blood cell count $> 10 \times 10^6$/L or $< 3 \times 10^6$/L; and purulent sputum. There were 20 secondary endpoints, including *Clostridioides difficile* infection, length of hospital stay, length of mechanical ventilation, and death occurring during the hospitalization. Any cultures that were positive for *Lactobacillus* then had strain genotyping to determine whether it was the strain of *L. rhamnosus* GG used in the study.

There were 1,318 patients who received the probiotic and 1,332 who received placebo. The average age of all the patients was 59 years, 1,063 (40%) were women, and 2,027 (76.5%) had a medical admitting diagnosis. The study product was administered for a median of nine days in both groups. In the probiotic group, 289 of 1,318 (21.9%) developed VAP compared to 284 of 1,332 (21.3%) in the placebo group (hazard ratio [HR], 1.03; 95% confidence interval [CI], -2.5% to 3.7%; $P = 0.73$). Subgroup analysis did not find any effect modification based on age, frailty status, prior use of antibiotics, diagnosis category (medical, surgical, or trauma), or comorbid infection. There were no significant differences between the two groups regarding secondary outcomes, including the development of *C. difficile* infection (2.4% in probiotic group vs. 2.1% in the placebo group, $P = 0.60$). Sixteen patients had *Lactobacillus* spp. isolated in a culture, of which 12 isolates were available for sequencing. Of these, all 12 were confirmed as *L. rhamnosus* GG.

[The authors should be commended for their pragmatic investigation, which is an important contribution to the scientific literature on ventilator-associated pneumonia and answers a frequent clinical conundrum.]

■ COMMENTARY

Using probiotics to prevent VAP and other adverse outcomes in the ICU is an appealing concept. Indeed, probiotics are relatively inexpensive and generally perceived to be a low-risk intervention for most ICU patients. Unfortunately, the study by Johnstone et al is another example of a clinical approach that appeared promising based on preliminary research, but did not hold up under the scrutiny of a rigorously designed randomized clinical trial. The authors should be commended for their pragmatic investigation, which is an important contribution to the scientific literature on VAP and answers a frequent clinical conundrum.

Although not useful in preventing VAP, probiotics appear the have the potential for patient harm. It is possible that the dysbiosis present in ICU patients is too advanced for probiotics, at least *L. rhamnosus* GG, to overcome. Impaired gut integrity likely is the

central factor that allowed *Lactobacillus* to spread to sterile sites, such as the bloodstream. Notably, bacteremia due to *Lactobacillus* spp. can lead to increased mortality, especially in patients with underlying comorbidities.

There were some limitations to the study. First, it is uncertain whether the results would have been similar if a different probiotic was chosen. Second, no sampling of pulmonary or gastrointestinal microbiota was performed prior to the administration of the study product. Finally, VAP is an imprecise diagnosis with no universal reference definition. How this affected the results, if at all, is unclear.

Until further evidence emerges, clinicians should not prescribe *L. rhamnosus* GG to prevent VAP in patients admitted to the ICU. Whether there are other, as yet undetermined, benefits for probiotics in the ICU setting remains to be elucidated. ■

ABSTRACT & COMMENTARY

IDWeek 2021: Baricitinib for COVID-19 Patients Receiving Invasive Mechanical Ventilation or ECMO

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Baricitinib significantly reduced mortality in patients with COVID-19 receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

SOURCE: Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus standard of care for hospitalized adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: Results of a randomized, placebo-controlled trial. Abstract LB3. IDWeek 2021.

In the large adaptive ACTT-2 trial, baricitinib (a selective JAK-1 inhibitor) plus remdesivir was superior to remdesivir alone in the treatment of hospitalized patients with COVID-19, approximately one-fifth of whom received glucocorticoids.[1] However, although improved outcomes were demonstrated in patients receiving high-flow oxygen or noninvasive ventilation, no such benefit occurred in those receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at the time of enrollment. The rate ratio for recovery in that group was only 1.08 (95% confidence interval [CI], 0.59 to 1.97).

In COV-BARRIER, another large multicenter trial, baricitinib failed to achieve a statistically significant improvement relative to placebo in meeting the primary endpoint, which was the proportion progressing to noninvasive ventilation, invasive mechanical ventilation, or death by 28 days.[2] Although failing to improve the composite endpoint, the 28-day mortality was significantly lower in baricitinib recipients, with a difference of 4.8% (95% CI, -8.0% to -1.9%) and a hazard ratio (HR) of 0.56 (95% CI, 0.41 to 0.77). Nineteen percent of patients in the study received remdesivir and 79% received corticosteroids.

Ely et al presented the results of a substudy of COV-BARRIER at IDWeek, examining outcomes in just the patients who were receiving invasive mechanical ventilation or ECMO at study entry. When compared to placebo, baricitinib administration significantly reduced all-cause 28-day mortality (39.2% vs. 58.0%, respectively; HR = 0.54; 95% CI, 0.31, 0.96; P = 0.030; relative risk [RR] = 0.68; 95% CI, 0.45, 1.02) in these patients. The mortality benefit persisted to day 60 (45.1% vs. 62.0%; HR = 0.56; 95% CI, 0.33, 0.97; P = 0.027; RR = 0.73; 95% CI, 0.50, 1.06), and the number needed to treat to prevent one death was six.

■ COMMENTARY

Baricitinib inhibits the JAK1/JAK2 tyrosine kinase-associated intracellular signaling pathways of several pro-inflammatory cytokines, including interleukin-2, interleukin-6, interleukin-10, interferon gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF). In addition, it is reported to impair SARS-CoV-2 cell entry.

Perhaps somehow anticipating the results of the substudy of COV-BARRIER, the Food and Drug Administration, on Nov. 19, 2020, issued an Emergency Use Authorization for the use of

baricitinib in combination with remdesivir in hospitalized adults and children 2 years of age and older with COVID-19 who require supplemental oxygen, invasive mechanical ventilation (IMV), or ECMO.

The current National Institutes of Health guideline (as of Oct. 9, 2021) includes a recommendation to give baricitinib or tocilizumab, in addition to dexamethasone with or without remdesivir, to recently hospitalized ("For example, within three days of hospital admission") patients with rapidly increasing oxygen need (requiring high-flow oxygen or noninvasive ventilation) and signs of inflammation. For patients receiving IMV or ECMO, the guideline recommends dexamethasone and, for those within 24 hours of intensive care unit admission, the recommendation is to give tocilizumab (or sarilumab if tocilizumab is unavailable or infeasible), and it does not recommend baricitinib in this patient subset.[3] Perhaps this recommendation will change when the data presented by Ely and colleagues is examined more fully. ■

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ABSTRACT & COMMENTARY

IDWeek 2021: Gram-Negative Bacteremia: Are Follow-Up Blood Cultures Routinely Necessary?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A study of significantly immunocompromised patients with gram-negative bacteremia concluded that the routine use of follow-up blood cultures to document clearance is not warranted.

SOURCE: Groft L, Mease J, Bork J, et al. Follow-up blood culture practices for gram-negative bloodstream infections in immunocompromised hosts at a large academic medical center. Abstract 62. IDWeek 2021.

Although follow-up blood cultures (FUBC) to evaluate the microbiologic effectiveness of antimicrobial therapy are recommended in patients with bloodstream infection with either *Staphylococcus aureus* or *Candida* species, their usefulness in patients with gram-negative bacteremia has been questioned.[1] Groft and colleagues took this question a step further by examining the yield of FUBC obtained 24 hours to seven days after the initial positive culture in a particularly at-risk subset of patients with gram-negative bacteremia — those with significant immunocompromise. Patients included had an active malignancy, solid organ or hematopoietic cell transplant, or absolute neutrophil count < 1,000/mm^3.

FUBC were obtained for 129 (88.4%) of 146 patients. One-third of the infections were caused by *Escherichia coli*, 23.3% by *Pseudomonas aeruginosa*, and 21.9% by *Klebsiella pneumoniae*.

Only 17.8% of patients had a urinary tract source, while approximately one-half had a gastrointestinal or intraabdominal source, and one-tenth arose from a central venous access device. FUBC was positive with the same organism as the index isolate in only two cases (1.4%) — and both were febrile at the time. Thus, the number of patients needed to test to detect one case of persistent bacteremia was 71.4.

In contrast, some authors have concluded that FUBC are of value in patients with gram-negative bacteremia.

Canzoneri and colleagues reported their retrospective experience with FUBC in 2017.[1] Their positivity

rate on repeat culture was higher than that found by Croft et al, with eight (5.7%) of 140 patients having positive repeats. None of the eight died. Furthermore, six of the eight were febrile at the time the repeat culture was obtained. They concluded by stating caution against the routine practice of repeating blood cultures in patients with gram-negative bacteremia.

On the basis of a literature review, Cogliati Dezza concluded that FUBC could be of value in critically ill patients, those with endovascular and/or non-eradicable source of infection, isolation of a multidrug-resistant pathogen, end-stage renal disease, and immunodeficiencies, and that in such circumstances, the result could alter management.[2]

However, the study by Croft et al strongly supports the conclusion that routine FUBC, in the absence of additional specific risk factors, is not warranted in patients with gram-negative bacteremia — even in those with severe immunocompromise — and should be performed only in selected patients with specific indications. ■

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ABSTRACT & COMMENTARY

IDWeek 2021: Skipping Along with *Staphylococcus aureus*

By Stan Deresinski, MD, FACP, FIDSA

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SYNOPSIS: A single set of blood cultures may be inadequate to document clearance of *Staphylococcus aureus* bacteremia in some patients.

SOURCE: Go JRU, Baddour LM, Lahr B, et al. The skip phenomenon in *Staphylococcus aureus* bacteremia: Clinical associations. Abstract 9. IDWeek 2021.

Follow-up blood cultures are recommended for documentation of clearance of *Staphylococcus aureus* bacteremia. For methicillin-resistant *S. aureus* (MRSA) bacteremia, the 2011 Infectious Diseases Society of America (IDSA) guideline states that, "Additional blood cultures 2-4 days after initial positive cultures and as needed thereafter are recommended to document clearance of bacteremia."[1] The presence of negative blood cultures performed on specimens obtained two to four days after the initial set are among the requirements for considering the bacteremia to be uncomplicated.

However, repeating follow-up blood cultures only once appears to be insufficient. Fiala and colleagues at the Mayo Clinic reported in 2019 that fluctuating blood culture results — a skip phenomenon — was identified in 29 (4%) of 757 cases of *S. aureus* bacteremia for whom follow-up cultures were obtained.[2] They distinguished this from breakthrough bacteremia, which they indicate refers to continuous or new-onset bacteremia while receiving appropriate antibiotics but does not require documentation of initial clearance of bacteria from the bloodstream. This phenomenon also had been reported by others.

A Mayo group now reports identifying the skip phenomenon in 25 (5.1%) of 495 patients, with significantly increased risks in injection drug users, patients with automatic implantable cardiac defibrillators, and those with community onset of infection. The median duration and grade of bacteremia, frequency of complicated bacteremia, and endocarditis all were greater in those with the skip phenomenon.

■ COMMENTARY

These observations indicate that to demonstrate clearance of *S. aureus* bacteremia, reliance on a single set of blood cultures on a single day clearly is insufficient. It can be speculated that cases considered to represent relapse of bacteremia are, in fact, examples of persistent bacteremia unless sufficient negative cultures have been documented. However, the interval between repeat cultures and the number required to reliably detect the skip phenomenon

are unclear, but it may be necessary to perform the cultures on multiple days. ■

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ABSTRACT & COMMENTARY

Can Antibiotics Lead to Colon Cancer?

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: Swedish researchers saw an association between frequent antibiotic use and proximal colorectal cancer.

SOURCE: Lu SSM, Mohammed Z, Häggström C, et al. Antibiotic use and subsequent risk of colon cancer: A Swedish nationwide population-based study. *J Natl Cancer Inst* 2021; Sep 1:djab125. doi: 10.1093/jnci/djab125. [Online ahead of print].

A nationwide, population-based study in Sweden was conducted with a matched, case-controlled design. Data were collected from national registers where information was gathered from 2005 to 2016. The authors studied 40,545 cases of colorectal cancer with 202,720 controls, noting frequent antibiotic use was associated with a higher risk of proximal colon cancer (odds ratio, 1.17; 95% confidence interval, 1.05-1.31). The most common offending antibiotics were quinolones and sulfonamides with or without trimethoprim. There was an inverse association with rectal cancer in women.

Other investigators have found a relationship between antibiotic use and colorectal cancer.[1,2] The composition and function of the gut microbiome are believed to play a role in colorectal cancer development.[3,4] Antibiotics disrupt the gut microbiome and may result in dysbiosis, hindering the anti-inflammatory effects of some bacteria and producing more pathogenic bacteria.

■ COMMENTARY

Clinicians have come to better understand the risks of antibiotics and the importance of the gut microbiome. The rise in colorectal cancer cases among younger adults has led to calls to start screening patients at a younger age. Consider why this is happening. Dietary factors certainly play a role, especially consuming processed carbohydrates and meat. The potential role of antibiotics in causing colorectal cancer is poorly recognized. Association is not causation, but this study and other investigations raise concern. Anytime clinicians use antibiotics, especially repeatedly, consider the risk-benefit ratio and realize these drugs can cause harm. Diverticulitis is one example of a common inflammatory condition that may not require antibiotics in uncomplicated cases.[5,6] ■

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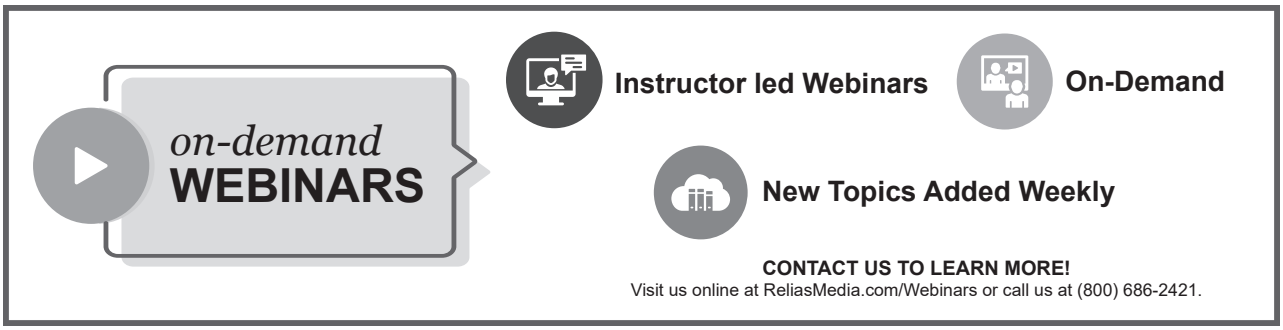

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ABSTRACT & COMMENTARY

Bacillus cereus Causing an Anthrax-Like Pneumonia

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: *Bacillus cereus* group organisms may cause a rapidly fatal pulmonary infection consistent with anthrax.

SOURCE: Dawson P, Schrodt CA, Feldmann K, et al. Notes from the field: Fatal anthrax pneumonia in welders and other metalworkers caused by *Bacillus cereus* group bacteria containing anthrax toxin genes — U.S. Gulf Coast States, 1994–2020. *MMWR Morb Mortal Wkly Rep* 2021;70:1453-1454.

In 2020, a 34-year-old man in Texas died as the result of a rapidly progressive pulmonary infection caused by an organism identified as *Bacillus cereus*. In that same year, a 39-year-old man survived a similar infection, also due to *B. cereus*. That patient was given anthrax antitoxin. Five additional cases, four of which were fatal, were identified by the Centers for Disease Control and Prevention (CDC) from 1994-2011.

[The strains causing severe disease, such as those reported by the CDC, have acquired plasmids encoding virulence factors closely associated with those of *Bacillus anthracis*.]

In each of the seven cases, the patients were metalworkers (five were welders) in Texas or Louisiana. Their ages ranged from 39 to 56 years, and only one was female. In one case, a soil sample from the patient's work site yielded a bacterium that genetically matched a clinical isolate from the patient.

■ COMMENTARY

Organisms of the *B. cereus* group are gram-positive, spore-forming facultative anaerobes that are widespread within the environment, with their dominant reservoir in soil and dust. They may contaminate food and cause acute vomiting and diarrhea. In addition, they may cause ocular and cutaneous infections, as well as bacteremia and endocarditis, with the latter two most often associated with injection drug use and central venous access infection.[1] Taxonomic studies indicate that *B. cereus* (now termed the *B. cereus* group) should be subdivided into nine species. Whole-genome sequence analysis identified the isolates from these patients as *Bacillus tropicus*.[2]

The strains causing severe disease, such as those reported by the CDC, have acquired plasmids encoding virulence factors closely associated with those of *Bacillus anthracis*, which carries a tripartite toxin comprised of protective antigen (PA), lethal factor (LF), and edema factor (EF).[3] PA forms membrane pores, facilitating the entrance of the other two, with LF then inhibiting protein kinase activity and inducing apoptosis, while EF also interferes with cell signaling. Also required for full virulence of *B. anthracis* is an exopolysaccharide capsule. Additional toxins have been identified in *B. cereus* strains causing lethal infection.

The reason why all the cases reviewed here occurred in only Texas and Louisiana is unknown. However, metalworking is associated with various respiratory illnesses, including an increased risk of lower tract infections and pneumonia, as well as hypersensitivity pneumonitis. The latter is believed to be caused by contamination of metalworking fluid with rapidly growing mycobacteria, such as *Mycobacterium abscessus*.[4] ■

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ABSTRACT & COMMENTARY

Malaria: At Last a Vaccine

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The World Health Organization has recommended the use of the first effective malaria vaccine.

SOURCE: World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk. Oct. 6, 2021. https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk

On Oct. 6, 2021, the World Health Organization (WHO) dramatically advanced the fight against malaria with the following statement recommending the use of the first vaccine with efficacy in the prevention of malaria due to *Plasmodium falciparum*:

"WHO recommends that in the context of comprehensive malaria control the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO. RTS,S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden."

It is estimated that the vaccine, whose development was largely funded by GlaxoSmithKline and the Gates Foundation, will cost approximately $5 per dose and that approximately 100 million doses per year will be required.[1]

Funding for implementation of widespread vaccination programs now depends on the actions of the global health community and individual governmental decisions for incorporation into their national malaria control strategies.

Although a four-shot series provides only 30% protection, modeling studies indicate that full vaccination of all children living in high-incidence countries could prevent 23,000 deaths in a year. Furthermore, even though limited, the success of this vaccine opens the path to the development of more effective vaccines. ■

REFERENCE

1. Maxmen A. Scientists hail historic malaria vaccine approval — but point to challenges ahead. *Nature* 2021; Oct. 8. doi: 10.1038/d41586-021-02755-5. [Online ahead of print].

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

A Reservoir of Pharyngeal GC

SOURCES: Barbee LA, Soge OO, Khosropour CM, et al. The duration of pharyngeal gonorrhea: A natural history study. *Clin Infect Dis* 2021;73:575-582.

Adamson PC, Klausner JD. The staying power of pharyngeal gonorrhea: Implications for public health and antimicrobial resistance. *Clin Infect Dis* 2021;73:583-585.

One hundred forty men who have sex with men (MSM) living in Seattle were recruited for a longitudinal cohort study of pharyngeal gonorrhea (GC)/chlamydia infection. The men were asked to self-collect weekly pharyngeal and rectal swabs and complete a survey every week for 48 weeks, and specimens were tested for nucleic acid (NAAT) for GC/chlamydia. Pharyngeal and rectal specimens were collected at baseline, and those who were positive for GC waited two weeks and those who were positive for chlamydia waited three weeks following treatment before participating. Infection was defined as two consecutive positive tests, and clearance was defined as two consecutive negative tests. Participants were asked to wait for treatment so the true duration of infection could be determined.

Twenty percent failed to collect any specimens and were excluded. Nineteen of 112 MSM (16.9%) had 21 episodes of pharyngeal GC infection. The estimated median duration of infection was 16.3 weeks (95% confidence interval, 5.1-19.7 weeks) (incidence 31.7/100 person years). Sore throat was

reported in only six cases (26%), and that was only during the first one to two weeks of infection. The duration of infection was not associated with human immunodeficiency virus (HIV) status, smoking history, or a prior history of gonorrhea. Three men (15%) reported only kissing or oral-anal contact, and four men reported no oral sexual exposure at all, suggesting their infections were either passively acquired by nonsexual or environmental means, or the men misreported/forgot what they had been doing.

In addition, 22 men had single positive specimens a median of seven days after their last negative test. If these men were included in the analysis, the estimated duration of infection was closer to 10 weeks.

Previously, pharyngeal GC was believed to be a transient infection, lasting one to six weeks, seldom resulting in symptoms or significant morbidity. This study suggests the natural duration of pharyngeal GC infection may be much longer — perhaps out to four months. This implies that pharyngeal GC may serve as a much more important reservoir for community infection than previously estimated. Since it is much harder to clear pharyngeal GC with antibiotics, and antibiotic levels in the oropharynx may be sub-optimal, pharyngeal GC organisms are more likely to experience selective pressure and risk antibiotic resistance, as well as risk acquiring bits of genetic material from other organisms in the oropharynx. It is possible that serial NAAT testing overestimated the duration of infection in this study, since 5% to 10% of infections may have detectable nucleic acid tests one to two weeks following treatment (and I have observed out to four weeks).

Screening MSM for pharyngeal GC on a regular basis, even in the absence of symptoms, is an important public health measure. Performing test of cure two weeks following treatment is important to detect treatment failures. ■

Difficult-to-Treat vs. Standard Multidrug Resistance

SOURCES: Karlowsky JA, Lob SH, Raddatz J, et al. In vitro activity of imipenem/relebactam and ceftolozane/tazobactam against clinical isolates of gram-negative bacilli with difficult-to-treat resistance and multidrug-resistance phenotypes — Study for monitoring antimicrobial resistance trends, Untied States 2015-2017. *Clin Infect Dis* 2021;72:2112-2120.

Al-Hasan MN. Gram-negative bacteria with difficult-to-treat resistance: A moving target. *Clin Infect Dis* 2012;72:2121-2123.

Authors in the first article sought a comparison of Clinical and Laboratory Standards Institute (CLSI)-defined in vitro activities of imipenem/relebactam and ceftolozane/tazobactam against urinary/respiratory/intra-abdominal gram-negative isolates collected in United States hospitals from 2015-2017 in 18 states. In a unique approach, Enterobacterales isolates (10,516) and *Pseudomonas aeruginosa* isolates (2,732) were assigned to the usually defined multidrug-resistance (MDR) grouping or a novel grouping called difficult-to-treat resistance (DTR).

From an infection control standpoint, MDR has been defined as nonsusceptibility to three classes of antimicrobial agents. That distinction presumes that different types of resistance have similar therapeutic and institutional implications, and that different classes of antimicrobials have similar value in treatment, which is not the case, e.g., aminoglycosides are seldom used as first-line therapy or as a single agent for sepsis, and therefore, their "weight" in the assessment of MDR is distorted. Instead, certain types and patterns of resistance are more clinically relevant, and the introduction of newer treatment options has altered the playing field.

For example, extended-spectrum beta-lactamase (ESBL) containing-organisms are automatically considered MDR according to current criteria, but carbapenems have provided effective therapy against these isolates for more than a decade. Further, certain carbapenem-resistant isolates have limited treatment options, whereas other do not. Take most carbapenem-resistant *P. aeruginosa* (PsA): Many still are sensitive to cefepime, ceftazidime, Zosyn, and even fluoroquinolones (FQ). In contrast, carbapenem-resistant Enterobacterales often are extensively drug resistant, with fewer treatment options.

Therefore, it is more relevant and useful to consider isolates that are clinically DTR and which pose a threat to your hospital environment (NMD, VIM,

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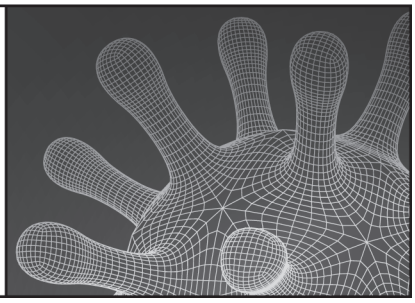

etc.). DTR then is defined as dose-limiting resistance to first-line therapeutic agents, including several newer agents, carbapenems, and FQs. Step-wise loss of susceptibility to one, two, or three first-line agents is associated more clearly with increasing treatment failure and mortality than MDR status. In one study, 43% of patients with bloodstream infection with DTR with nonsusceptibility to three first-line therapeutic agents died during the index hospitalization.

Fortunately, the availability of newer agents for gram-negative treatment is driving the re-assessment of our current concepts of MDR. In this study, among Enterobacterales, imipenem/relebactam inhibited 95.4% of all isolates, and specifically 99.4% of *Klebsiella pneumoniae* and 99.9% of *Escherichia coli*. Only *Morganella* appeared more susceptible to ertapenem and meropenem because *Morganellaceae* are intrinsically less susceptible to imipenem (and not because of carbapenemase production, so the addition of relebactam does not provide additional activity). Among Enterobacterales, 1% were considered DTR and 15.6% were MDR. Of these, imipenem/relebactam inhibited 82.4% of DTR and 92.1% of MDR (using a breakpoint minimal inhibitory concentration [MIC] ≤ 1 mcg/mL). In contrast, ceftolozane/tazobactam inhibited only 1.5% of DTR and 65.8% of MDR Enterobacterales.

Among all PsA, imipenem/relebactam and ceftolozane/tazobactam inhibited 93.9% and 94.7% of isolates, respectively (using a breakpoint MIC of ≤ 2 mcg/mL and ≤ 4 mcg/mL, respectively). Among PsA, 8.4% were considered DTR and 32.4% were MDR. Of these, imipenem/relebactam inhibited 62.2% of DTR PsA and 82.2% of MDR PsA. Further, ceftolozan/tazobactam inhibited 67.5% of DTR PsA and 84% of MDR PsA. Against all isolates of PsA, susceptibility to imipenem/relebactam was 22% points higher than to imipenem alone — suggesting that many newer strains of PsA are resistant not from constitutive resistance but because of newer beta-lactamases.

As anticipated, resistance was more common in respiratory isolates than in intra-abdominal or urinary isolates, as well as isolates collected in the intensive care unit. In U.S. hospitals, DTR PsA is more common than DTR Enterobacterales (8.4% vs. 1%), but labeling these organisms as MDR overstated the frequency of treatment-limiting options. Both imipenem/relebactam and ceftolozane/tazobactam offer effective treatment options for most MDR and DTR strains of PsA, and imipenem/relebactam provides effective treatment against most MDR and DTR Enterobacterales. ■

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CME QUESTIONS

1. Which of the following is correct regarding the impact of probiotics on the development of ventilator-associated pneumonia?

a. Patients who received placebo were more likely to develop *Clostridioides difficile* infection.

b. Subgroup analysis showed an effect from prior antibiotic use.

c. The median duration of product administration (i.e., placebo or probiotic) was nine days.

d. Several of the isolates of *Lactobacillus* from sterile sites were different from the study probiotic.

2. Which of the following is correct regarding the occurrence of myocarditis after receipt of the BNT162b COVID-19 mRNA vaccine?

a. It occurs most frequently in young males.

b. It usually is fatal.

c. It most commonly presents with an arrhythmia but is otherwise asymptomatic.

d. It occurs most often within a week after receipt of the first vaccine dose.

3. Which of the following is correct regarding *Bacillus cereus*?

a. *Bacillus cereus* is a common cause of lethal pneumonia.

b. *Bacillus cereus* may acquire toxin-encoding plasmids similar to those of *Bacillus anthracis*.

c. Lethal pneumonia caused by *Bacillus cereus* has been reported almost exclusively in females.

d. *Bacillus cereus* is not an environmental contaminant.

4. What antibiotics were implicated as a potential cause of colorectal cancer?

a. Penicillins

b. Cephalosporins

c. Quinolones

d. Macrolides

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.

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