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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Ebola in Democratic Republic of the Congo: Confronting Potential Disaster

By Stan Deresinski, MD, FACP, FIDSA, FESCMID

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: The second largest outbreak of Ebola virus infection has come under control.

SOURCE: Aruna A, Mbala P, Minikulu L, et al. Ebola virus disease outbreak — Democratic Republic of the Congo, August 2018–November 2019. *MMWR Morb Mortal Wkly Rep* 2019;68:1162-1165.

In August 2018, the Democratic Republic of the Congo (DRC) officially declared an outbreak of Ebola and, six weeks later, the World Health Organization designated the outbreak involving North Kivu province and Ituri a public health emergency of international concern. By Nov. 17, 2019, this had become the second largest documented outbreak of Ebola in West Africa, with 3,296 cases and 2,196 (67%) deaths. The largest previous outbreak was the 2014-2016 epidemic, with 28,600 cases and 11,325 deaths.

The recognition that the outbreak was of international concern was the result of two observations. Cases occurred in Uganda after members of a family had traveled from that country to DRC to attend the funeral of another family member who had died due to Ebola virus infection. These were the first-ever cases of the Zaire Ebola strain infection in Uganda and the first case of Ebola since 2013. Also, a small number of cases occurred in Goma, the capital of North Kivu province on the border with Rwanda, with a population of as many as 2 million people.

Among the interventions was a novel one: the use of an investigational vaccine (since approved), with primary use in a ring vaccination strategy

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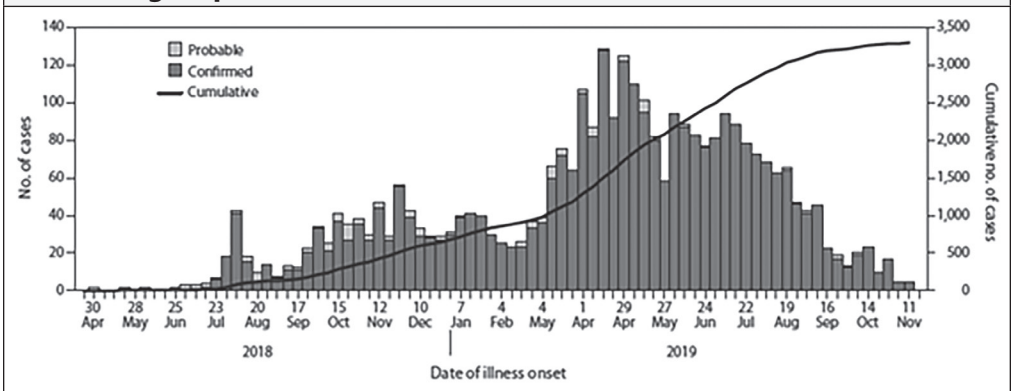
Figure 1: Confirmed and Probable Cases of Ebola Virus Disease, By Week of Illness Onset and Cumulative Number of Cases — Democratic Republic of the Congo, April 30, 2018–Nov. 17, 2019



Source: Centers for Disease Control and Prevention

focusing on recent primary and secondary contacts of Ebola virus infection. It also was provided to healthcare and front-line workers. At the same time, four investigational therapeutics were administered in a clinical trial to patients with proven disease.

■ COMMENTARY

Any Ebola outbreak is a fearful event. In this case, residents and healthcare workers must have felt that they had crossed the River Styx and descended into lowest level of Hades. One could have despaired because of, among other things, the very limited existing infrastructure, ongoing armed conflict among rebel groups and DRC armed forces, and attacks on civilians by militant groups. At the same time, the breakdown led to a loss of any residual trust in authority. Individuals avoided or delayed seeking care for fear of, e.g., acquiring infection within healthcare facilities.

The experimental vaccine, which was administered to more than a quarter of a million individuals, proved to be highly effective. Although cases continue to occur,[1] **use of the vaccine** likely contributed to the eventual control of the outbreak. (*See Figure 1.*) ■

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ABSTRACT & COMMENTARY

Preventing Ebola Virus Infection

By Stan Deresinski, MD, FACP, FIDSA, FESCMID

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: In a scientific/public health triumph, the first vaccine for the prevention of Ebola virus infection has been approved. If administered prior to 10 days after exposure, its protective efficacy is 100%.

SOURCE: U.S. Food & Drug Administration. First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. Dec. 19, 2019. Available at: https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health. Accessed Jan. 10, 2020.

On Dec. 19, 2019, the U.S. Food and Drug Administration (FDA) announced the approval of the first FDA-approved vaccine (rVSV-ZEBOV, Ervebo), for the prevention of Ebola virus disease (EVD) in individuals 18 years of age and older. In 2018, the World Health Organization began using Ervebo while it was still considered investigational and was provided under an expanded access program in attempts to deal with the ongoing outbreak in the Democratic Republic of the Congo. Ervebo, which is administered as a single injection, is a live attenuated vesicular stomatitis virus vaccine engineered to present an Ebola envelope glycoprotein.

Previously, Ervebo had demonstrated efficacy in a trial in Guinea in a clustered (ring) study that randomized contacts of cases as well as contacts of contacts to receive immediate vaccination or vaccination delayed for 21 days. The vaccine had 100% efficacy in preventing Ebola cases occurring with onset more than 10 days after its administration. While no Ebola cases occurred then among the 2,108 subjects with immediate vaccination, 10 cases occurred in the 1,429 subjects whose vaccination was delayed. The vaccine is well tolerated, although 70% of recipients reported injection site pain, while 37% and 34% complained of headache and feverishness, respectively.

Several other vaccines remain in clinical trials. In the meantime, the manufacturer (Merck) has a stockpile of 190,000 doses and has plans to make another 650,000 doses available over the next 18 months. ■

ABSTRACT & COMMENTARY

Treating Ebola Virus Infection

By Stan Deresinski, MD, FACP, FIDSA, FESCMID

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Two monoclonal antibody preparations have been demonstrated to significantly reduce mortality in patients with Ebola virus infection.

SOURCE: Mulangu S, Dodd LE, Davey RT Jr, et al; PALM Consortium Study Team. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293-2303.

In a study in the Democratic Republic of the Congo (DRC), patients with documented Ebola virus infection were randomized to one of four experimental intravenous therapies. These were ZMapp (a combination of three monoclonal antibodies), remdesivir (a nucleotide analog inhibitor of RNA polymerase), mAb114 (a monoclonal antibody derived from a survivor of Ebola), and REGN-EB3 (a mix of three human IgG1 monoclonal antibodies). The last arm was added to the trial partway through. Based on the negative results of a previous trial that found minimal benefit, ZMapp was considered to be a control arm.

The data safety monitoring board interrupted enrollment after 681 patients when an interim analysis found that mAb114 and REGN-EB3 were superior to the other two treatments with respect to mortality. Death at 28 days occurred in 61/174 (35.1%) and 52/155 (33.5%) in the MAb114 and REGN-EB3 groups, respectively, with each statistically superior to ZMapp. Remdesivir did not differ significantly from ZMapp. There was an 11% increase in the odds of death for each day of symptoms before trial enrollment. High baseline viral load, as well as elevated creatinine and alanine aminotransferase levels, also were associated with increased mortality.

■ COMMENTARY

The development of effective therapeutics for the treatment of Ebola virus infection is a triumph. The ability to overcome the obstacles to conducting this trial successfully in conflict-ridden DRC was nothing short of amazing. In addition, the demonstration of efficacy perhaps opens the door to treatment of other emerging virus infections. However, the downside is the cost of monoclonal antibody therapies and the need for intravenous administration. Despite their efficacy, approximately one-third of patients died. Fortunately, the recent development of an effective vaccine to prevent Ebola infection, if widely implemented, has the capability of reducing the number of future cases of this often-lethal disease. ■

ABSTRACT & COMMENTARY

Impact of Infectious Disease Consultation for Candidemia

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Dr. Watkins reports no financial relationships relevant to this field of study.

SYNOPSIS: A retrospective cohort study found that infectious disease consultation for patients with candidemia resulted in lower 90-day mortality. This was likely a result of strong adherence to guideline- and evidence-based management and the low number of patients who were not treated.

SOURCE: Mejia-Chew C, O'Halloran JA, Olsen MA, et al. Effect of infectious disease consultation on mortality and treatment of patients with *Candida* bloodstream infections: A retrospective, cohort study. *Lancet Infect Dis* 2019;19:1336-1344.

Infectious disease (ID) consultation has been shown to improve outcomes for *Staphylococcus aureus* bacteremia, including decreased mortality.[1] Mejia-Chew and colleagues sought to determine whether ID consultation would improve mortality similarly in patients with candidemia, as well as what specific aspects of management were associated with patients who did and did not receive ID consultation.

The study was a retrospective cohort analysis that included patients ≥ 18 years of age diagnosed with candidemia between Jan. 1, 2002, and Dec. 31, 2015, from a single tertiary referral center in St. Louis. Patients who died within the first 24 hours of the index blood culture with *Candida* spp. were excluded, since an ID consultation would have been difficult to obtain in that time frame. ID consultation was defined to include patients who received the consultation 24 hours before and up to seven days after the index blood culture collection date. For patients who did not receive treatment, three categories were established: culture regarded as a contaminant, clinician unaware, and patient left the hospital against medical advice (AMA) before treatment could be started. The primary outcome measured was the 90-day all-cause mortality in patients with candidemia who received ID consultation vs. those who did not.

The analysis included 1,691 patients. Of these, 776 (45.9%) received an ID consultation and 915 (54.1%) did not. Over time, the proportion of patients with ID consultations increased. More patients in the ID consultation group were admitted to the intensive care unit (ICU) (16% vs. 10%). There was no difference between the two groups in the species of *Candida* that was isolated or in the selection of the initial antifungal agent. The rate of non-treatment was lower in the ID consultation group (13/776, 2%) than in the no-consultation group (128/915, 14%; $P < 0.0001$). The reasons for no treatment in the ID consultation group were that the culture was thought to be a contaminant in four patients, the culture results were unknown to the treating physician in eight patients, and one patient left AMA.

Nonpharmacological management differed between the two groups. Central line removal was more common in the ID consultation group (76% vs. 59%), as was the use of echocardiography (56% vs. 33%) and ophthalmological evaluation (53% vs. 17%). The 90-day mortality was lower in the ID consultation group (29% vs. 51%; $P < 0.0001$). Of the 141 untreated patients, 94 (67%) were dead by day 90. ID consultation was associated with a hazard ratio (HR) of 0.81 by the propensity-score model (95% confidence interval, 0.73-0.91; $P < 0.0001$), which translated to a 19% survival benefit.

■ COMMENTARY

Candidemia is associated with high mortality, making appropriate management crucial for patient survival. This is evident in the present study with the finding that 67% of patients with candidemia who were not treated died within 90 days. Although it is likely that not all of these deaths can be attributed to the candidiasis, this grim result highlights the seriousness of *Candida* in the bloodstream. Therefore, it is disconcerting that in four cases of candidemia, the ID consultant thought it was a contaminant, and no treatment was given. Clearly, this is a quality improvement situation where peer-to-peer feedback is needed.

The Infectious Diseases Society of America guidelines provide evidence-based recommendations for the management of patients with candidemia.[2] The key factors include source control, such as catheter removal; prompt initiation of antifungal therapy; appropriate duration of therapy; and the need for medical interventions, such as an ophthalmological evaluation and cardiac imaging. Indeed, following the guidelines has been shown previously to lead to improved patient outcomes.[3] Presumably, most ID consultants are well-versed on the guidelines, and adherence to them likely explains the improvement in mortality observed in the study by Mejia-Chew and colleagues.

The main strength of the study is the size of the cohort, which is the largest to explore the association between ID consultation and mortality in patients with candidemia. However, there are a few limitations to note. First, like all retrospective analyses, it may have been influenced by unmeasured confounding variables. Second, since it was conducted at a single center, the results might not be generalizable to other settings. For example, it is more common outside of the United States for clinical microbiologists to play a more active role in advising physicians who are managing patients with serious infections, such as candidemia. Finally, selection bias could have affected the results, as some patient populations were underrepresented in each group.

ID consultants play a crucial role in the management of patients with candidemia. As the study by Mejia-Chew and colleagues demonstrates, ID consultation leads to improved 90-day mortality and, therefore, should be the standard of care for all patients with candidemia. ■

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ABSTRACT & COMMENTARY

Tafenoquine for Malaria Prevention and Relapse Treatment

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Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Tafenoquine is effective for the prevention of all species of malaria and can be used to prevent relapse of *Plasmodium vivax* and *Plasmodium ovale*. G6PD status should be evaluated prior to use.

SOURCE: Haston JC, Hwang J, Tan KR. Guidance for using tafenoquine for prevention and antirelapse therapy for malaria — United States, 2019. *MMWR Morb Mortal Wkly Rep* 2019;68:1062-1068.

The authors performed a thorough review of the published literature (269 English language publications), examined data submitted to the U.S. Food and Drug Administration, and have released guidance for using tafenoquine for both prevention and antirelapse therapy for malaria. Randomized controlled trials of tafenoquine for prevention of malaria in the field showed comparable efficacy to mefloquine (86-100%). A randomized human challenge study demonstrated 100% efficacy of tafenoquine against the blood stage of *Plasmodium falciparum* in healthy volunteers.[1] In patients with confirmed *P. vivax* malaria, a single 300 mg dose of tafenoquine prevented relapse in 62-89% of cases. Tafenoquine was well-tolerated when used as a single dose and in multiple dosing regimens used for prophylaxis. An interesting side effect seen in one study described vortex keratopathy (whorl-like deposition of pigmented material — often medications) in approximately 90% of patients, but this did not affect visual acuity and resolved in all cases within one year.[2]

Tafenoquine (an 8-aminoquinoline like primaquine, but with a prolonged half-life in humans) is contraindicated in patients with G6PD deficiency,

pregnancy, breastfeeding (if the infant is G6PD-deficient or has unknown G6PD status), known hypersensitivity to 8-aminoquinolines, and a history of significant psychiatric disorders (mefloquine-like side effects were rarely seen in clinical trials).

The dosing recommendations for prophylaxis are to load with tafenoquine 200 mg daily for three days before departure, followed by a maintenance regimen of 200 mg weekly beginning seven days after the last loading dose, and taken for the entire duration of travel plus one additional dose after returning. For antirelapse therapy in patients being treated for *P. vivax* or *P. ovale* malaria, a single 300 mg dose should be given on the first or second day of blood stage treatment or as soon as possible after completion of blood stage therapy. For presumptive antirelapse therapy in patients who received other malaria prophylaxis regimens, a single 300 mg dose is given on the same day as the last dose of prophylaxis (or as soon as possible afterward). Of course, an antirelapse dose of tafenoquine would not be necessary if the patient received either primaquine or tafenoquine for prophylaxis.

■ COMMENTARY

Tafenoquine is an attractive option for malaria prophylaxis in adults 18 years of age or older and for antirelapse therapy for *P. vivax* or *P. ovale* in patients 16 years of age or older. The simplified dosing regimen and its good tolerability should improve adherence. An interesting publication last year showed in a SCID mouse model of babesiosis, a single dose of tafenoquine resulted in a > 90% reduction in parasitemia, suggesting that this new drug might be useful in this infection as well.[3] ■

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ABSTRACT & COMMENTARY

Pneumonia Outbreak in China

By Stan Deresinski, MD, FACP, FIDSA, FESCMID

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: A cluster of cases of pneumonia apparently caused by a novel coronavirus has emerged in China.

SOURCES: CDC Health Advisory Alert. Outbreak of Pneumonia of Unknown Etiology (PUE) in Wuhan, China. Available at: https://emergency.cdc.gov/han/HAN00424.asp. Accessed Jan. 10, 2020.

World Health Organization. WHO Statement Regarding Cluster of Pneumonia Cases in Wuhan, China. Available at: https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china. Accessed Jan. 10, 2020.

As of Jan. 5, 2020, public health authorities in China had notified the World Health Organization of 59 cases of pneumonia of unknown etiology (PUE) that had occurred in Wuhan province from Dec. 12-19, 2019. While no deaths were reported, seven (11.9%) patients were critically ill. No healthcare workers have become ill, and human-to-human transmission has not been reported. The patients are being managed in isolation, and contacts are being identified and placed under close observation.

Some of the affected patients worked at Wuhan South China Seafood City, a wholesale market where seafood, chickens, bats, marmots, and a number of wild animals are sold. The market has been closed and is undergoing cleaning and disinfection. Testing of the patients for a wide variety of known respiratory pathogens was negative, but a virus morphologically resembling a coronavirus was observed initially in one patient, and sequencing is reported to have demonstrated that it is a novel coronavirus. Subsequent nucleic acid testing identified the novel virus in 15 patients.

■ COMMENTARY

This event obviously elicits memories of the emergence of another coronavirus in China that

was linked to markets selling wild animals. Another lethal coronavirus, Middle East respiratory syndrome (MERS), has emerged more recently in the Arabian Peninsula and has been linked to exposure to camels. In addition to often being lethal, both severe acute respiratory syndrome (SARS) and MERS are readily transmitted among humans. Fortunately, the Wuhan coronavirus (so far) appears to have neither of these characteristics, although some human transmission seems possible. Two infections with this virus have been detected in patients outside Wuhan.[1] In a case identified in Thailand, the patient had visited a "fresh market" but not the one noted earlier, while a patient identified in Japan had had contact with someone with pneumonia in China. ■

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ABSTRACT & COMMENTARY

Fever of Unknown Origin Due to Cat Scratch Disease

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Disseminated cat scratch disease may present as a fever of unknown origin.

SOURCE: Landes M, Maor Y, Mercer D, et al. Cat scratch disease presenting as fever of unknown origin is a unique clinical syndrome. *Clin Infect Dis* 2019 Nov 23. pii: ciz1137.

Landes and colleagues analyzed data obtained from a national surveillance of cat scratch disease (CSD) in Israel from 2004-2017 to characterize cases presenting with fever lasting > 14 days without a cause identified. Of the approximately 2,800 patients with CSD, 126 (4.1%) were reported to have had fever of unknown origin, but only 66 patients, 89% of whom were immunocompetent, were included in this study after various exclusions. The patients ranged in age from 3 to 88 years (median 35.5 years); 83% reported contact with felines. The median duration of fever was four weeks. In 48%, the fever occurred daily, while in 52% it had a relapsing pattern. Loss of > 5% of body weight occurred in 37.5% of the patients.

The diagnosis was confirmed by serology in 65/66 patients, and *Bartonella henselae* DNA was detected in seven patients in tissue. Investigation found involvement of one or more organ systems in 39 (59%) patients: 23 with hepatic and/or splenic lesions, 12 with ocular disease, four with multifocal osteomyelitis, and three with pneumonitis. One patient each had pericarditis, pleuritis, meningitis, and sensorineural hearing loss.

Antibiotics with possible activity against *B. henselae*, mostly azithromycin and doxycycline, were administered to 46 (70%) patients for two days to 3.5 months. The mean duration of fever was four weeks whether antibiotics were taken or not. Nonetheless, symptoms eventually resolved in 56 of the 59 patients with follow-up; the other three had ocular involvement with visual residua.

■ COMMENTARY

In classic CSD, characterized by regional lymphadenitis that is self-limited, fever may occur in up to 30% of patients, but it lasts a mean of only six days. The patients in the series described here lacked classic findings of CSD and had fever that lasted at least 14 days. This syndrome has been described before, but it has been characterized more often as disseminated or simply named by the focal sites of infection identified, such as osteomyelitis. Such focal sites were identified in 59% of the patients reported by Landes et al. One site of infection not included in this case series is heart valves; the diagnosis of *Bartonella* endocarditis often is quite difficult.

A finding of note in this series is the fact that the prolonged fever had a relapsing pattern in approximately one-half of patients. The authors pointed out that relapsing fever was characteristic of "trench fever," which is caused by *Bartonella quintana*, a louse-borne infection seen in modern times in people who are homeless in the United States and

Europe. Of course, relapsing fever also may be caused by *Borrelia* (e.g., *Borrelia hermsii* in the western United States, *Borrelia persica* in Israel) and also may be caused by lymphoma, among other things. ■

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ABSTRACT & COMMENTARY

Feeding the Microbiota: Complementary Foods Enhance Recovery in Malnourished Children by Modulating the Gut Microbiota

By Casey R. Johnson, MD, MS, and Philip R. Fischer, MD, DTM&H

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Dr. Johnson and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: In a series of studies in gnotobiotic animals and malnourished children, incomplete recovery from malnutrition is associated with immature gut microbiota, and complementary foods directed to enhance microbiotal maturity improved recovery from malnutrition.

SOURCE: Gehrig JL, Venkatesh S, Chang HW, et al. Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. *Science* 2019;365:in press. doi: 10.1126/science.aau4732.

The microbiome is a dynamic ecology of microorganisms that changes throughout the course of growth and development, especially during the weaning period. Children with acute malnutrition fail to undergo these normal patterns of change within their microbiome. Microbiota from children with severe acute malnutrition (SAM) or moderate acute malnutrition (MAM) largely reflect that of healthy but chronologically younger infants, still predominantly milk-dependent.

Current ready-to-use therapeutic foods (RUTF) and complementary foods are an important component of treatment for SAM and MAM; however, they do not afford the catch-up growth necessary to ameliorate stunting or neurocognitive delays that accompany acute malnutrition. The authors hypothesized that the microbiotal aberrations in acute malnutrition are responsible in part for failure to fully recover, and that complementary foods could be formulated to direct the microbiome toward a healthier, age-appropriate profile, further alleviating the state of persistent malnourishment and its consequences.

Stool samples from malnourished and healthy control children in Bangladesh were used to profile microbial resident communities. The authors inoculated germ-free animals with stool from children to test various formulations of microbiota-directed complementary foods (MDCF) based on culturally accepted available foods. Growth and anthropometric parameters, microbiotal changes, and plasma proteins from important signaling pathways were recorded. MDCF formulated with chickpea, soy, banana, and peanut were found to be most effective compared with controls and other formulations in aiding recovery.

Following preliminary selection of MDCF formulation, breastfeeding Bangladeshi children with persistent MAM, who previously underwent stabilization and treatment for SAM, were enrolled in a double-blind, randomized, controlled trial testing the efficacy of the MDCF prototypes. Stool samples for microbiome analysis, blood draws for plasma protein and biomarker analyses, and anthropometric data were collected routinely at set intervals. The lead MDCF identified in animal studies with chickpea, soy, banana, and peanut was again most effective at increasing levels of biomarkers and growth-signaling pathways, neurodevelopment, immune function, and bone formation.

The results of the study support the hypothesis that healthy microbiota is causally linked to healthy growth and development. The model provides a precedent for developing therapeutic foods for acute malnutrition that target healthy development of the microbiome, and provides a new platform from which microbiota-directed changes in health and development can be evaluated.

■ COMMENTARY

The human microbiome functions as a kind of extra-human organ, far outnumbering the cells in a human body and exceeding the number of genes in the human genome by a factor of at least 100.[1,2] This coevolved ecosystem of microorganisms plays a complex role in supporting human health, capable of protecting the host from invading pathogens, stimulating the immune system, increasing availability of nutrients, stimulating bowel motility, and improving lipid levels in the body.[3] However, aberrations in the gut microbiota also can contribute to disease — obesity,[4,5] diabetes,[6] infections,[7] inflammatory bowel disease,[8,9] cancer,[10] and, as demonstrated in the present article, persistent malnutrition.

In their article, Gehrig and colleagues elegantly demonstrated the potential for the microbiome to be harnessed for human health improvement. Using a variety of methodologies from basic science to direct translational trials, they phenotyped the microbiome in healthy and malnourished children, established microbiota-directed prototype foods using two gnotobiotic animal models, demonstrated that the effects were dependent on having an intact microbiota, and, finally, showed physiologic and anthropomorphic superiority of their prototype foods with associated normalization of the microbiome in a double-blind, randomized, controlled trial.

The idea of using food or food ingredients to manipulate the microbiome for health benefits is an old concept that has developed more rapidly since Gibson and Roberfroid[11] proposed the concept of prebiotics. Prebiotics are defined as "selectively fermented ingredients that result in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health." These compounds occur naturally in a wide variety of foods, including several prebiotics in foods comprising the MDCF.[12,13] However, little is known about the microbiotal effects of the vast majority of foods and food ingredients globally.

Other methods directed at changing the systemic effects of the microbiota include probiotics[3] and fecal transplant.[14] These methods rely on introducing new species and/or increasing the quantity of resident microbial communities that are known to be associated with improved health. In the case of the former, generally a few well-known species are administered in large quantities, with randomized controlled trials showing moderate benefits for infectious diarrhea and irritable bowel syndrome.[15,16] The latter employs a myriad of microbial species of various unknown concentrations, and of which little is known overall, but which is taken from a healthy human subject.

The findings presented by Gehrig and colleagues reinforce the vast amount of attention that the human microbiome has received in recent years, and their work likely will inspire many future investigations. Could microbiota-directed therapeutic foods reduce hospital-acquired infections and recurrent infections such as *C. difficile*? Is there a role for microbiota-directed foods in the prevention or prolongation of time to onset of neurodegenerative changes? Could similar research affect obesity in countries where childhood obesity rates have soared in recent years? As the fields of microbiology and bioinformatics continue to excel, one should expect to learn much more about such questions and many more. In the meantime, microbiota-directed complementary foods hold potential for better preventing and treating childhood malnutrition. ■

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Updates

By Carol A. Kemper, MD, FACP

Lyme Carditis: Any AV Block of Concern

SOURCE: Marx GE, Leikauskas J, Lindstrom K, et al. Fatal Lyme carditis in New England: Two case reports. *Ann Intern Med* 2019; Oct. 22. doi: 10.7326/L19-0483. [Epub ahead of print].

In the United States, Lyme carditis is uncommon, occurring in ~1.5% to 5% of all patients with untreated acute Lyme disease, although pathologic studies suggest that cardiac involvement may be more common. Lyme disease should be included in the differential in anyone presenting with a new atrioventricular (AV) block. Ninety percent of patients with Lyme carditis present with various degrees of AV block, and 60% have some component of perimyocarditis. In one study, 44% of those who presented with first-degree AV block developed, at least temporarily, complete AV block. Generally, AV conduction abnormalities are reversible with treatment, although temporary pacing may be required. Permanent pacer placement seldom is necessary. Prolonged QT is uncommon, although it has been documented in a few pediatric cases. Congestive failure and dilated cardiomyopathy usually is a later manifestation of untreated Lyme carditis.

These two case reports document the fairly rapid progression of conduction defects in untreated Lyme carditis. A 49-year-old woman from Massachusetts developed a flu-like illness with a headache and required parenteral fluids. Two weeks later, she developed syncope, and an electrocardiogram (ECG) showed AV dissociation. Laboratory studies and cardiac home event monitoring were ordered. She was presumptively prescribed doxycycline, but before she could take her first dose, she died of ventricular tachycardia, detected on the home monitor.

Another case involved a 57-year-old man from Vermont with erythema migrans consistent with disseminated Lyme. An ECG showed first-degree AV block with a PR interval of 220 msec. Laboratory studies were ordered, which were positive for *Borrelia burgdorferi* by ELISA and Western blot. Twelve days later, before treatment was initiated, the man was found unresponsive and died. Postmortem examination in both cases revealed pancarditis with immunohistochemical evidence of *Borrelia*, and spirochetes were visualized in cardiac tissue from the first case.

Lyme carditis should be considered in anyone presenting with new AV conduction disorder, regardless of age, but especially if a young person presents with AV block. If cardiac Lyme is suspected, laboratory testing for Lyme, an ECG, chest radiograph, and echocardiogram are appropriate next steps. Close monitoring with telemetry is recommended for those with PR interval > 300 msec, as progression to complete AV block or dissociative rhythm is common and may occur quickly.

Syphilis Screening in Pregnancy a Must

SOURCE: Umapathi KK, Thavamani A, Chotikanatis K. Incidence trends, risk factors, mortality and healthcare utilization in congenital syphilis-related hospitalizations in the United States: A nationwide population analysis. *Ped Infect Dis J* 2019;38:1126-1130.

Cases of congenital syphilis (CS) in the United States continue to escalate, precipitated by our evolving syphilis epidemic. CS results in significant neonatal morbidity and mortality, and frequent permanent disability in survivors. Untreated CS results in a 40% risk of intrauterine demise, miscarriage, or neonatal death. According to Centers for Disease Control and Prevention (CDC) data, CS cases have increased steadily since 2013, when 362 cases were reported, to 918 cases in 2017, and to a whopping 1,306 cases in 2018. Of these, 70% were reported from five states: Florida, California, Arizona, Texas, and Louisiana.

This survey examined national trends in hospitalization and healthcare utilization related to CS from 2009 to 2016, based on data abstracted from the Agency for Healthcare Research and Quality for hospital stays for patients younger than 21 years of age, as well as the National Inpatient Sample (NIS). During the seven-year study period, a total of 5,912 CS-related hospitalizations in infants < 12 months of age were examined. Of these, 47% were African-American and 29% were Hispanic. A higher number of CS-related hospitalizations was associated with public insurance or no insurance (88%), and low median income. The majority were hospitalized in the South (59%) or the Western United States (21%). Excluding stillbirths, the mortality rate among hospitalizations was 0.54%, with 32 deaths.

The mean length of hospital stay was 12 days. Hospital charges, adjusted for inflation, significantly

increased over the years, reaching in $58,500 per hospitalization in 2016, which is significantly higher compared with other hospitalizations for the same age group. This means that more than $120 million was spent on CS-related hospitalizations in the United States in 2016. Note that the number of CS-related hospitalizations is significantly higher than the number of CS cases reported by the CDC. This could result from more frequent hospitalization in affected cases, although more likely it includes CS cases not reported to the public health system.

All but six states mandate syphilis screening during pregnancy. While the requirements for screening vary among states, most recommend screening on presentation for the first prenatal exam (84%).[1] The CDC and other advisory bodies recommend screening at 28 weeks gestation and again at delivery in higher-risk women. However, only eight states (15.7%) require screening at delivery, and five require it only if the woman is at "high risk." Six states do not require screening for syphilis during pregnancy, including Iowa, Ohio, Minnesota, Mississippi, New Hampshire, and Wisconsin. Hawaii and Maine provide no specific requirements as to when testing should be done. Changing these laws to mandatory prenatal screening for all women at presentation and again in the third trimester, with mandatory public health reporting, would go a long way to limiting the end effects of this epidemic on neonates. Attempts to reduce spending for public health and STD treatment in the United States since 2003 have precipitated an even costlier public health crisis.

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Deferring INH Until Postpartum in HIV-Positive Women

SOURCE: Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *N Engl J Med* 2019;381:1333-1346.

The World Health Organization (WHO) provides general recommendations for treatment with antiretroviral therapy and pre-emptive isoniazid (INH) therapy in HIV-positive pregnant women at risk for tuberculosis (TB). However, there has been a lack of information on the safety and tolerance of INH during pregnancy, and the optimal timing of INH in such women has not been established. These questions were examined in this large-scale, double-blind, placebo-controlled trial of INH chemoprophylaxis in HIV-positive pregnant women, most of whom were receiving antiretroviral therapy.

The project was conducted at 13 clinical sites in eight different countries at risk for TB infection. Women were randomly assigned to standard INH treatment for 28 weeks, beginning during pregnancy, or to deferred treatment at 12 weeks following delivery. Eligible women included those between 14 and 34 weeks of gestation, who weighed at least 35 kg, who had fairly normal cell counts, and who had liver enzymes no more than 1.25 times the upper limit of normal within 30 days of entry, and with no recent known exposure to TB, no prior treatment for TB, and no diagnosis of hepatitis or neuropathy within the previous year. Evidence of latent TB at entry was not a requirement, although about 30% had a positive Interferon-Gamma Release Assay (IGRA) at entry. The primary outcome of the study was a composite safety outcome of grade 3 or higher adverse events or permanent discontinuation of therapy because of side effects. Patients were followed every four weeks through 48 weeks post-delivery.

A total of 956 pregnant women were recruited for study. The median age was 29 years, 90.5% were Black African, the median CD4 count was 493 cells/mL, and all but one were receiving highly active antiretroviral therapy (HAART); 85% were receiving a regimen containing efavirenz. Nearly one-fifth (17.9%) discontinued the trial prematurely, including 8.9% who were lost to follow-up and six who died. Before the study, primary outcomes were estimated to occur in about 5% of participants, but, in fact, were much higher than anticipated, occurring in 15.1% of the early treatment group and 15.2% of the deferred treatment group. The intent-to-treat analysis showed no significant differences in the incidence of grade 3 or higher adverse events between the early treatment group vs. the deferred group (incidence rate 34.95 vs. 31.26 per 100 person-years, P = NS). The incident rate of hepatotoxicity was similar between the two groups (incident rate 5.8 in the early treatment group vs. 6.7 per 100 person-years in the deferred treatment group, P = NS). Six women died, including two in the early treatment group and four in the deferred treatment group. All six deaths occurred postpartum, and four of the deaths were due to liver failure. All four were receiving combination efavirenz-tenofovir-emtricitabine at the time of death, and two women had received INH. Active TB developed in six women (three in each group).

There were 926 deliveries. Adverse pregnancy outcomes were significantly higher in the early treatment group than in the deferred treatment group (23.6% vs. 17%, P = 0.01). This included stillbirths, spontaneous abortion, low birth weight, preterm delivery, or congenital abnormalities in an

infant. A composite score for severe adverse pregnancy events was similar between the groups.

This large-scale study of pregnant HIV-positive women shows that INH preventive therapy administered during pregnancy was non-inferior to deferred treatment three months post-delivery, although the risks of INH treatment when started during pregnancy (after the first trimester) appeared to be greater. Grade 3 or higher maternal adverse events were three times higher than anticipated (~15%), especially during the postpartum period in both treatment groups, regardless of whether INH was initiated during pregnancy or deferred until three months after delivery. There also was a higher than expected risk of adverse pregnancy outcomes in those receiving INH during pregnancy, although pregnant women in the early treatment group did not begin INH until at least week 14 of pregnancy. Although the study was conducted in countries endemic for TB, the number of cases of active TB occurring during study was low. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. In the trial in Guinea, what was the efficacy of the Ebola vaccine (rVSV-ZEBOV or Ervebo) in preventing Ebola virus disease in case contacts beginning 10 days after vaccine receipt?

a. 25%

b. 50%

c. 75%

d. 100%

2. Which of the following statements is correct regarding tafenoquine?

a. Tafenoquine is safe in patients with G6PD deficiency.

b. Relative to primaquine, tafenoquine has a prolonged serum half-life.

c. Tafenoquine is an effective agent for prevention of malaria but ineffective as an antirelapse agent in *Plasmodium vivax* infection.

d. Tafenoquine causes an ocular lesion (vortex keratopathy) and causes irreversible visual loss.

3. Which of the following is correct regarding patients with cat scratch disease considered by Landes et al to have fever of unknown origin?

a. Approximately one-half had daily fever.

b. A relapsing fever pattern was not observed.

c. Focal sites of infection were absent.

d. Antibiotic administration was associated with a dramatically reduced duration of fever.

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.