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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Emerging Options for Malaria Prevention

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SYNOPSIS: Globally, there are hundreds of millions of cases of malaria each year and nearly half a million deaths due to malaria. Current preventive strategies are only partially effective. New data suggest that combining vaccination with chemoprophylaxis is better than either intervention alone, and a small pilot study suggests that a monoclonal antibody infusion is effective in preventing malaria infections.

SOURCES: Gaudinski MR, Berkowitz NM, Idris AH, et al. A monoclonal antibody for malaria prevention. *N Engl J Med* 2021;385:803-814.

Chandramohan D, Zongo I, Sagara I, et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. *N Engl J Med* 2021;385:1005-1017.

Malaria still is incompletely controlled, especially in sub-Saharan Africa where tens of millions of people get malaria each year and about 400,000 (mostly women and young children) die of malaria. Preventive efforts have been very helpful in reducing the morbidity and mortality rates to these levels, but further improvements have stalled. Thus, additional interventions are needed.

CIS43 is a human monoclonal antibody against the circumsporozoite protein of the sporozoite stage of *Plasmodium falciparum*. Pre-clinical studies showed that it was protective against mouse malaria. CIS43 was modified to the CIS43LS form to prolong its plasma half-life. Gaudinski and a group of colleagues in America studied the safety, side effects, pharmacokinetics, and protective efficacy of intravenously or subcutaneously administered CIS43LS in 40 healthy malaria-naïve adult humans. No significant safety concerns were identified, although individual patients had dizziness, asymptomatic neutropenia, or mild elevation of the creatinine level. Antibody levels were dose-dependent, since doses varied from 5 mg to 20 mg to 40 mg per kg of body weight; levels rose during the first week after subcutaneous administration.

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Antibodies still were detectable 24 weeks after administration, and the half-life of antibodies was 56 days.

Fifteen patients underwent controlled malaria infection with bites from infected *Anopheles* mosquitoes at least four weeks after antibody administration; of these, none developed parasitemia (even up to 36 weeks after receiving CIS43LS), but five of six untreated controls developed parasitemia eight to nine days after the mosquito bites. These early data suggest that monoclonal anti-circumsporozoite antibody injection protects malaria-naïve adults from developing malaria infection for up to 36 weeks after bites from infected mosquitoes. Another study is underway in Mali, where exposure happens naturally during the rainy season instead of with controlled bites from infected mosquitoes.

Meanwhile, Chandramohan and a group of colleagues in Europe and Africa studied the effectiveness of a combination of newer (vaccination) and more established (chemoprophylaxis) means of preventing malaria. Chemoprophylaxis can be effective for individuals when it is used regularly. Vaccination with an RTS,S/AS01 vaccine has been shown to reduce the incidence of malaria in children in Africa, but with waning protection over time. With 5- to 17-month-old children in areas of Mali and Burkina Faso where malaria incidence varies seasonally, Chandramohan and colleagues compared the malaria-preventing value of vaccination (an RTS,S/AS01 vaccine) to chemoprophylaxis (sulfadoxine-pyrimethamine and amodiaquine, known to still be effective in the study areas) and to both interventions in a randomized, blinded, controlled study. A total of 6,781 children began the study, and 88% completed the three-year study.

The efficacy of vaccination was statistically similar to the efficacy of chemoprophylaxis, with approximately 30 bouts of symptomatic malaria per 100 child-years. The combination of vaccination and chemoprophylaxis was significantly better than either intervention alone, with 11 malaria events per 100 child-years. Overall, the combination treatment provided 61% protective efficacy as compared to either intervention alone. Combination treatment also was associated with fewer malaria-induced deaths, blood transfusions, and hospitalizations. Five (< 0.1) vaccinated children had fever-associated seizures within a day of vaccination but did not have any lasting sequelae. Vaccination was not inferior to chemoprophylaxis, and the combination of both interventions was significantly more effective than either intervention alone.

■ COMMENTARY

The incredible complexity of the life of *Plasmodium* parasites makes the prevention of malaria extremely challenging. Multiple approaches targeting a reduction in the incidence and severity of malaria infection have focused on various aspects of the parasite's life cycle. As demonstrated by these two papers, new strategies to prevent malaria can be novel or combined.

Malaria parasites rely on mosquito vectors to sustain their existence. *Anopheles* breed near water, bite from dusk to dawn, and live for several weeks. Reduction of standing water around residences reduces the number of breeding mosquitoes near where people sleep. However, large puddles are not required, and even a few drops of water between the leaves and stalks of plants can support insect breeding. Screened windows, air conditioning, and bed nets (especially those impregnated with an insecticide such as permethrin) block access of mosquitoes to sleeping humans. DEET and picaridin in concentrations of 20% to 30% are effective as topical repellents on exposed skin for four to six hours (but not usually all night). Genetically altered and Wolbachia-infected mosquitoes can, to some degree, displace malaria-transmitting mosquitoes in some areas.[1]

Decades ago, DDT (dichloro-diphenyl-trichloroethane) was dispersed widely to kill mosquitoes; this was somewhat effective, but resistance developed (of mosquitoes to DDT and of societies to the adverse ecological effects of widespread application of DDT). Now, application of DDT and related compounds on the walls of homes provides some safe and lasting local reduction in mosquito populations.

In humans, there are four main stages of *Plasmodium*'s life: sporozoites, hepatic schizonts, blood schizonts, and gametocytes; each has been targeted by various medications and vaccines. Sporozoites travel from the site of a mosquito bite through the bloodstream to the liver and are cleared from the blood within 30 to 60 minutes of the bite. Sporozoites are targeted by some prospective malaria vaccines, including the RTS,S/AS01 vaccine used in Chandramohan et al's study. The monoclonal antibody used in Gaudinski et al's study targeted a sporozoite protein that is needed for sporozoite motility and hepatocyte invasion.

Hepatic schizonts develop in the liver and then disperse short-lived merozoites from the liver into the bloodstream a week or so later (or much longer, such as with the dormant hypnozoites of *P. vivax*). Hepatic schizonts are attacked by a limited number of malaria medications, including primaquine and atovaquone-proguanil. After being released from hepatic schizonts into the blood, merozoites invade red cells to form blood schizonts. For days, with repeated rupture and release and reinfection, parasitemia builds and persists — and is responsible for the clinical symptoms of acute malaria. Some candidate vaccines target merozoites to prevent them from penetrating red blood cells, and most anti-malarial medications (including the amodiaquine and sulfadoxine-pyrimethamine used in Chandramohan et al's study) target blood stages of malaria.

Finally, some parasites in the blood become gametocytes, the fertile forms of the parasite that then are taken up by another *Anopheles* mosquito with a subsequent blood meal to continue the life cycle through mosquitoes. "Transmission-blocking vaccines" are those that attack gametocyte function; new data offer hope that monoclonal antibodies also can block gametocytes from transmitting infection back to mosquitoes.[2]

[The incredible complexity of the life of *Plasmodium* parasites makes the prevention of malaria extremely challenging.]

Clearly, multifaceted approaches to the prevention of malaria still are required. Vaccines and chemoprophylaxis can help many children, but more children can be helped by combining these interventions. Novel monoclonal antibody therapy holds great potential for the prevention of malaria in travelers and, with repeated doses, for residents of malaria-endemic areas. With implementation of all available as well as emerging interventions, there is potential to save the lives of the 400,000 women and children currently dying of malaria each year. ■

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ABSTRACT & COMMENTARY

Environmental Shedding of MRSA Is Far Greater than from Multidrug-Resistant Gram-Negative Bacilli

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

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SYNOPSIS: An observational cohort study found shedding of methicillin-resistant *Staphylococcus aureus* by colonized patients outside hospital rooms or during outpatient clinic visits occurred more often than in those colonized by multidrug-resistant gram-negative bacilli.

SOURCE: Alhmidi H, Cadnum JL, Koganti S, et al. Shedding of methicillin-resistant *Staphylococcus aureus* and multidrug-resistant gram-negative bacilli during outpatient appointments and procedures outside hospital rooms. *Am J Infect Control* 2021;49:991-994.

Patients colonized with pathogenic bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant gram-negative bacilli (MDR-GNB), are known to shed these organisms

in their hospital rooms and during procedures. This leads to contamination of other people, environmental surfaces, and medical equipment. However, less is known about bacterial shedding outside of patient rooms, such as at outpatient clinics, during physical therapy appointments, and in the radiology department. Therefore, Alhmidi and colleagues examined environmental shedding of MRSA and MDR-GNB by colonized patients in settings outside of hospital rooms.

The study was an observational cohort study that included patients in contact precautions for MDR-GNB or MRSA. MDR-GNB were defined as an extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli or a carbapenem-resistant gram-negative bacilli. A control group of 10 patients with no history of MRSA or MDR-GNB colonization and with negative baseline cultures also was included. Culture swabs were obtained of the anterior nares to determine MRSA colonization and from the skin and perirectal area for patients with MDR-GNB. Environmental shedding was assessed outside patient rooms for inpatients and during outpatient clinic visits within three months of hospital discharge. The investigators cleaned and disinfected environmental surfaces. Then immediately after appointments, they used culture plates to recover MRSA or MDR-GNB from a standardized group of high-touch surfaces. For the first 10 appointments, they collected cultures before patients entered the room to ensure that no MRSA or MDR-GNB were recoverable.

[Less is known about bacterial shedding outside of patient rooms, such as at outpatient clinics, during physical therapy appointments, and in the radiology department.]

For patients known to be colonized with MRSA, spa typing was performed on environmental isolates. These were considered to be concordant with nares isolates if the spa type was the same. In those with MDR-GNB colonization, environmental isolates were considered concordant if the perirectal or skin isolates had the same species identification and susceptibility pattern.

There were 39 patients with MRSA colonization and 11 with MDR-GNB included in the study. The frequency of environmental shedding was significantly greater for MRSA (15/39, 38%) compared to MDR-GNB (0/11, 0%; $P = 0.02$). No MRSA or MDR-GNB were recovered from the 10 control patients. Following two outpatient appointments with MRSA-colonized patients, contamination was detected in the provider work area after a provider's hands contacted a patient without wearing gloves and did not perform hand hygiene. Spa typing was done on 10 MRSA carriers, of whom eight had the same nasal and environmental isolates identified. Finally, the presence of a wound that was culture-positive for MRSA was the only significant characteristic associated with shedding.

■ COMMENTARY

The study by Alhmidi and colleagues demonstrates the high frequency of MRSA shedding into the environment by colonized patients, particularly those with MRSA in their wounds. This provides strong evidence of the need for effective environmental decontamination in outpatient clinics and other sites where inpatient appointments occur, such as physical therapy, to reduce MRSA transmission. It also supports implementing other methods that might lead to less MRSA shedding, such as chlorhexidine bathing, patient hand hygiene, and the use of intranasal mupirocin.

Of equal importance was the finding that MDR-GNB colonization did not lead to similar environmental shedding. This calls into question the appropriateness of contact isolation for patients colonized with MDR-GNB. Contact precautions have a number of potential downsides, including patient dissatisfaction due to less interaction with hospital staff, increased hospital costs (e.g., isolation gowns and gloves), and restricted visitation. These need to be weighed against the potential of transmission of pathogenic bacteria to vulnerable patients, hospital staff members, and objects in the environment, such as medical equipment. Although the results of the study are reassuring in terms of the low risk of MDR-GNB shedding, further research is necessary to replicate this finding.

There are a few limitations to the study. First, the study was conducted at a single Veterans Affairs (VA) hospital, so the population was almost entirely older males. Thus, the results might not be generalizable to other patient groups. Second, there was a relatively small number (n = 11) of patients colonized with MDR-GNB. Third, 20% of the MRSA isolates had spa types different from concurrent nasal isolates, which raises the possibility that some MRSA isolates originated from healthcare workers or another source. Finally, healthcare workers were aware they were being observed by the investigators.

Shedding of MRSA by colonized patients can occur in other areas besides their inpatient rooms. This has important policy ramifications for infection control personnel in their efforts to reduce the transmission of MRSA in healthcare facilities. Fortunately, the risk of transmission of MDR-GNB by colonized patients shedding into the environment appears to be much lower. ■

ABSTRACT & COMMENTARY

Adjuvanted Zoster Vaccine: Persistent Protection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The adjuvanted recombinant zoster vaccine efficacy is high and persistent, with apparent plateauing at > 84% four to six years after vaccination.

SOURCE: Boutry C, Hastie A, Diez-Domingo J, et al; Zoster-049 Study Group. The adjuvanted recombinant zoster vaccine confers long-term protection against herpes zoster: Interim results of an extension study of the pivotal Phase III clinical trials (ZOE-50 and ZOE-70). *Clin Infect Dis* 2021;Jul 20:ciab629. doi: 10.1093/cid/ciab629. [Online ahead of print].

Boutry and colleagues reported the interim results of a follow-up study of adults > 50 years of age enrolled in two pivotal trials (ZOE-50/70) that demonstrated efficacy in the prevention of herpes zoster in adults by administration of a glycoprotein E-based adjuvanted recombinant vaccine (Shingrix). Patients participating in that study were offered, after approximately five years, entry into this long-term follow-up evaluation, and 7,413 of the original cohort of 14,648 agreed to do so.

Vaccine efficacy during the follow-up period approximately 5.1 to 7.1 years post-vaccination was 84.0% (5% confidence interval [CI], 75.9 to 89.8), with an incidence of 8.6 per 1,000 patient-years. The overall efficacy through the entire period after vaccination was 90.9% (95% CI, 88.2 to 93.2). A plateau of > 84% efficacy was reached between post-vaccination years 4 and 6. Antibody levels and T cell measures also plateaued at approximately sixfold above prevaccination levels at years 5 to 6.

■ COMMENTARY

As pointed out by the authors, Zostavax had lower levels of efficacy than seen with Shingrix in clinical trials and its efficacy diminished rapidly over time. In fact, any efficacy demonstrated with Zostavax was not statistically significant eight years after vaccination of individuals > 60 years of age. In contrast, Shingrix not only provides higher levels of protection, but its efficacy appears to have plateaued at > 84% at four to six years after vaccination.

The follow-up data of Shingrix indicates that protection provided is long-lasting and, in fact, modeling of its immunological results suggests that the measured responses will persist for at least 20 years post-vaccination. However, it must be recognized that immune correlates of protection remain uncertain. Of importance, though, is that immunosuppressive and immune-modulating therapies were not allowed during the study. ■

ABSTRACT & COMMENTARY

Well-Appearing Febrile Infants: New Guidelines for Evaluation and Management

By Neamat Ibrahim Almasri, MBBS; Maha Khalil Abass, MBChB; and Philip R. Fischer, MD

Dr. Almasri and Dr. Abass are pediatric residents at Sheikh Shakhbout Medical City in Abu Dhabi, United Arab Emirates. Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; Department of Pediatrics, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates.

SYNOPSIS: New guidelines provide specific guidance for the use of diagnostic testing, antimicrobial treatment, and ongoing care based on age for children between 8 and 60 days of age.

SOURCE: Pantell RH, Roberts KB, Adams WG, et al. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics* 2021;148:e2021052228.

Whether practicing pediatrics for 40 years or currently in training, the management of infants with fever who look well is challenging. Various practice parameters have been proposed, and care is far from standardized. In fact, the length of stay for hospitalized febrile infants varies from 30 to 100 hours at various children's hospitals.[1] Relevant to febrile infants, there have been changes in epidemiology (group B streptococcal infection is less common because of maternal screening and treatment), diagnosis (more rapid blood culture results, antigen detection, increasing use of inflammatory marker tests), and understanding of the risks of hospitalization (economic, social, infectious). Thus, the American Academy of Pediatrics convened an expert group that solicited broad input from a variety of professionals and from families while reviewing current knowledge and providing updated guidelines for the testing and treatment of febrile infants who look well.

Of note, these new guidelines apply to previously healthy term infants with rectal temperatures of greater than or equal to 38.0°C who appear to be well (other than the fever) with no indication from the history and physical exam of a site or source of infection (and no specific concern for herpesvirus infection). Because of varying risks by age, these guidelines do not deal with children during the first week of life. And, evaluation and management were customized for three different age subsets within the 8- to 60-day age range.

The expert committee suggests that these guidelines not be used for children with bronchiolitis. Children with bronchiolitis generally are very unlikely to have meningitis or bacteremia concurrently. These guidelines can be used in children younger than 1 month of age with otitis media and positive viral antigen tests, since neither otitis nor positive virus tests at this age seems to alter the risk of having meningitis or bacteremia.

With that background and context, we review some of the key action statements produced by this expert group. Of course, more clarification and detail are available in the original 38-page article.

EVALUATION AND MANAGEMENT OF WELL-APPEARING FEBRILE INFANTS, AGED 8 TO 21 DAYS

During the second through fourth weeks of life, clinical and initial laboratory evaluation is unable to definitively rule out invasive bacterial infection. Thus, in a well-appearing 8- to 21-day-old infant, it is strongly recommended that clinicians obtain the following:

1. urine specimen by catheterization or suprapubic aspiration of the bladder for urinalysis and, if the urinalysis result is positive, for culture;
2. blood culture; and
3. cerebrospinal fluid for analysis (white blood cells, protein, glucose, Gram stain) and culture for bacteria.

At this age, inflammatory marker results should not have significant impact on the decisions of hospitalization and initiation of treatment. Infants in this age group should be hospitalized and monitored actively by experienced nursing staff while awaiting bacterial culture results, regardless of inflammatory marker levels.

To reduce morbidity and mortality from an anticipated bacterial infection in this age group, infants should be treated empirically with parenteral antimicrobials. The eventual duration of treatment

depends on culture results, the nature of the infection, the responsible organism, and the infant's response to the treatment. When initial cerebrospinal fluid results suggest the presence of meningitis, ampicillin and ceftazidime should be given. When initial urinalysis results suggest the presence of a urinary tract infection and when initial spinal fluid and urine results do not suggest a focus of infection, therapy with ampicillin and either ceftazidime or gentamicin is advised. When culture results are negative for 24-36 hours (or are positive only for contaminants) and infants are asymptomatic or improving with no other indication for hospitalization, parenteral antimicrobials should be discontinued, and hospitalized patients can be discharged home.

EVALUATION AND MANAGEMENT OF WELL-APPEARING FEBRILE INFANTS, AGED 22 TO 28 DAYS

During the final week of the first month of life, less aggressive testing may be considered. In well-appearing but febrile 22- to 28-day-old-infants, it is strongly recommended that clinicians obtain a blood culture and a urine specimen via catheterization or suprapubic aspiration for urinalysis. If the urinalysis is abnormal, culture should be performed. Alternatively, obtain a urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if the urinalysis result is positive, obtain a catheterization or suprapubic aspiration specimen for culture.

The recommendation of obtaining cerebrospinal fluid for analysis and culture from infants in this age group depends on the presence or absence of abnormal inflammatory markers. Inflammatory markers are considered abnormal at the following levels: procalcitonin > 0.5 ng/mL, C-reactive protein (CRP) > 20 mg/L, and absolute neutrophil count > 4,000 per mm^3 (or > 5,200 per mm^3, expert opinions vary). If any abnormal inflammatory marker result is obtained, physicians are recommended to obtain cerebrospinal fluid for analysis and culture. Thus, testing of inflammatory markers is recommended in this age group, unlike in younger infants.

The decision of hospitalization or home management can be challenging. It is strongly recommended to hospitalize and initiate parenteral antimicrobials for infants in this age group with either a positive urinalysis or a cerebrospinal fluid analysis that is suggestive of bacterial meningitis, regardless of inflammatory marker levels. Clinicians may consider parenteral antibiotics in hospitalized infants if the cerebrospinal fluid analysis is normal, urinalysis is negative, and an abnormal inflammatory marker result is obtained. An abnormal inflammatory marker result indicates a risk of bacteremia > 5%, a threshold sufficiently high to recommend empiric antimicrobial treatment in the hospital even if cerebrospinal fluid and urinalysis results are normal.

If all inflammatory marker levels are normal and the urinalysis and cerebrospinal fluid analysis do not suggest infection, the risk of bacteremia is between 1% and 2% (i.e., to prevent one necessary treatment being missed, the number needed to treat is 50 to 100). There are insufficient data to estimate precisely the risk of bacterial meningitis with a normal cerebrospinal fluid analysis, but the risk appears to be quite low. Physicians may administer parenteral antimicrobials in hospitalized infants when they have negative initial cerebrospinal fluid and urine results with no elevation of inflammatory marker levels. Clinicians may consider use of parenteral antimicrobials in infants who will be managed at home with negative urinalysis, negative cerebrospinal fluid analysis, and normal inflammatory marker levels.

Infants can be managed at home when the following criteria are met: 1) the urinalysis is normal; 2) no tested inflammatory maker level is abnormal; 3) cerebrospinal fluid analysis is normal or enterovirus-positive; 4) verbal and written instructions have been given for monitoring during the period of time at home; 5) follow-up plans have been created and are in place for reevaluation in 24 hours; and 6) plans have been created and are in place in case the patient's clinical status changes, including a method of communication between the family and providers and access to emergency medical care.

Whether a decision was made for hospitalization or home management, it is recommended to stop parenteral antimicrobials when all cultures are negative after 24 to 36 hours and if the infant still looks clinically well. On the other hand, when blood, cerebrospinal fluid, or urine bacterial cultures are positive, infants should be treated with antimicrobials for the duration that is indicated by the nature of infection, causative agent, and clinical response of the infant. When cerebrospinal fluid is suggestive of bacterial meningitis, parenteral ampicillin and ceftazidime, in combination, are the first-choice antibiotics. Parenteral ceftriaxone has been shown to be effective against urinary tract infection and bacteremia with no other focus identified.

EVALUATION AND MANAGEMENT OF WELL-APPEARING INFANTS, AGED 29 TO 60 DAYS

At this age, a urinalysis should be done. If the urinalysis is abnormal, urine obtained via

catherization or suprapubic aspiration should be cultured. Blood culture should be done, and inflammatory markers should be tested. Cerebrospinal fluid analysis and culture are not necessarily needed if the urinalysis and inflammatory marker testing are normal. Absolute neutrophil counts are helpful but are not as accurate as the newer inflammatory markers CRP and procalcitonin.

Parenteral antimicrobial therapy with ceftriaxone or ceftazidime and vancomycin (for the possibility of resistant *S. pneumococcus*) should be administered if the cerebrospinal fluid analysis suggests the presence of meningitis and may be administered if an inflammatory marker result is elevated in the absence of abnormal urine and cerebrospinal fluid results. Oral antimicrobial therapy (cephalexin or cefixime) should be provided if the urinalysis suggests infection and cerebrospinal fluid and inflammatory marker results are normal. Pending culture results, antimicrobial therapy is not necessarily required if the urinalysis is not suggestive of infection, the cerebrospinal fluid results are normal (or enterovirus-positive), and all inflammatory markers tested yield normal results. As for children in the previously described age group, observation at home is possible with follow-up plans established if the urinalysis, cerebrospinal fluid results, and inflammatory marker tests all are normal. Antimicrobial therapy should be stopped, and the child should be discharged from the hospital (if hospitalized) if cultures are negative at 24 to 36 hours and the child is doing well with no other indication for hospitalization and antibiotic treatment. Urinary tract infection (with other test results normal and the child improving) can be treated with oral antimicrobial therapy.

CONCLUSION

These expert recommendations are reasonable and are based on solid evidence. And, they are novel. Knowing and experiencing extreme variations in the care of febrile well-appearing infants in and between different pediatric centers, we believe that application of these recommendations will reduce invasive testing, target the use of CRP and calcitonin testing and interpretation, reduce initiation of antibiotic therapy, minimize the duration of presumptive antibiotic treatments, and result in better outcomes for children. ■

REFERENCE

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ABSTRACT & COMMENTARY

SARS-CoV-2 Rapid Antigen Testing in a Nursing Home Outbreak

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

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SYNOPSIS: Rapid antigen testing was accurate in detecting SARS-CoV-2 antigen when compared to polymerase chain reaction.

SOURCE: McKay SL, Tobolowsky FA, Moritz ED, et al; CDC Infection Prevention and Control Team and the CDC COVID-19 Surge Laboratory Group. Performance evaluation of serial SARS-CoV-2 rapid antigen testing during a nursing home outbreak. *Ann Intern Med* 2021;174:945-951.

The objective of this study was to determine the efficacy and role of rapid antigen testing for SARS-CoV-2 infection during a nursing home outbreak. The time period was October and November 2020, with the first case identified on Oct. 7, 2020. During just a 13-day period, all staff and patients were tested up to three times if they were at the facility on the day of testing. The Abbott BinaxNOW COVID-19 Ag Card was used to perform antigen testing. Along with rapid antigen testing of samples from each nare, a reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 analysis also was done to determine the relative usefulness of a rapid antigen test. Results showed that 107 staff and 127 residents took part in at least one round of testing, and there were 234 total participants. Among residents, the median age was 75 years; 43% were female and 60% were Black. During the three testing periods, 522 paired specimens, including 388 from persons who were not tested previously, were tested.

The percentage positive agreement (PPA) and the percentage negative agreement (PNA) were

determined for each sample, and the antigen test had an 84% to 99% PPA and a near 100% PNA. When antigen was compared to RT-PCR, 133 of 532 paired samples (21%) were positive by one of the methods. Of those who were positive, 64% were positive by both methods. Only 33 of 113 were RT-PCR positive and antigen negative. Of all the 532 paired samples, the PPA between antigen and PCR was 69% and the PNA was 98%. For those people who were not positive previously, the PPA was 63%. Importantly, for all groups, the PNA between antigen and PCR remained near 100%.

Virus culture was not particularly sensitive in detection of virus in antigen-positive subjects. Viral cultures were positive when tested for only 21% of positive specimens. Viral culture was attempted only for subjects who were considered likely to have positive cultures, i.e., those with a cycle threshold (CT) of < 34.

Antigen performed best with early infections compared to late infections, with PPA 86% in early infection and 51% in late infection. Antigen positivity generally related to lower CT values.

■ COMMENTARY

This study in a Georgia nursing home population among residents who had been infected and those who had not showed that rapid antigen testing was useful in detecting infected persons. It was not quite as good as RT-PCR, but good enough to be used in the setting of such healthcare facilities. The critical issue is whether rapid antigen testing can be used to identify those residents or patients within health facilities who need to be cohorted or receive early treatment with, e.g., monoclonal antibodies to reduce disease progression and virus spread. The Abbott BinasNOW antigen kit was used in this study, and it will be interesting to see if newer antigen methodology can improve on the data reported in this article.

Because antigen testing was more sensitive, perhaps fortuitously, in early vs. late infection, future studies can focus on just how early rapid antigen testing could be used to reduce subsequent spread. The proliferation of virus likely peaks between two to four days, thus suggesting to the hospital epidemiologist that tools like point prevalence surveys at a given frequency, say weekly, may detect additional infected persons in facilities like this Georgia nursing home.

False positives were stated to number only eight at a time when PNA was 98%. Several of those false positives were in residents who had previously positive results by PCR.

Rapid COVID-19 antigen detection likely will assume more use because of ease of use, low cost, and reliability that a negative result correlates very well with more expensive time-consuming tests. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Pyrethroids Losing Activity Against Mosquitoes

SOURCE: Keïta M, Sogoba N, Kané F, et al. Multiple resistance mechanisms to pyrethroids insecticides in *Anopheles gambiae sensu lato* population from Mali, West Africa. *J Infect Dis* 2021;223(Suppl 2):S81-S90.

Pyrethroid-impregnated mosquito netting and indoor dusting/spraying have been critical steps in malaria control in Africa. The increased use of these measures, coupled with indiscriminate agricultural use, has increased the selection pressure on mosquito vectors, with loss of pyrethroid activity in some areas. Using the World Health Organization standard bioassay to assess *Anopheles gambiae sensu lato* susceptibility to pyrethroids, these authors examined both phenotypic and genotypic resistance mechanisms in three different health districts in Mali, West Africa.

High frequencies of phenotypic resistance to both deltamethrin and permethrin was found in *Anopheles gambiae s.l.* in multiple locations, with only 13% to 41% mortality observed. Susceptibility to deltamethrin could be partially restored by the addition of piperonyl butoxide (PBO) (a P450 cytochrome inhibitor) and, to a lesser degree, two other metabolic inhibitors, suggesting the presence of three different metabolic resistance pathways.

Taqman SNP genotyping assays for targeted markers showed a high prevalence of previously recognized *Kdr_W* resistant alleles at all of the study sites, including a high frequency of L1014F, L1014S,

and 1575Y gene mutations. These data suggest that multiple genotypic and metabolic mechanisms for resistance are simultaneously developing in the mosquito population in West Africa, requiring an updated and comprehensive strategy for mosquito vector control. ■

Resistance Erodes Standard Treatment for Pneumonia

SOURCE: Haessler S, Lindenauer PK, Zilberberg MD, et al. Blood cultures versus respiratory cultures: 2 different views of pneumonia. *Clin Infect Dis* 2020;71:1604-1612.

To examine whether current guidelines for the treatment of pneumonia remain appropriate, researchers conducted a large multicenter study of adults with pneumonia admitted to 177 United States hospitals between 2010 and 2015. Patients admitted with a principal diagnosis of pneumonia, respiratory failure, acute respiratory distress syndrome, or sepsis with a secondary diagnosis of pneumonia, and who also had blood and/or respiratory cultures obtained on admission were included in the analysis. A total of 138,561 hospitalizations met criteria, of which about two-thirds were considered community-acquired pneumonia (CAP) (68%) and one-third was deemed healthcare-associated pneumonia (HCAP) (32%).

Blood cultures were obtained on admission in 99% of hospitalizations and respiratory cultures were obtained in 18%. Positive cultures were infrequent: Only 9.3% of all admissions had a positive culture, including 4.6% with a positive respiratory culture alone, 4.3% with a positive blood culture alone, and 0.3% with both positive respiratory and blood cultures. In those able to produce a sputum specimen, respiratory cultures were positive in 28%, and patients with HCAP were more likely than those with CAP to have a positive sputum culture (33% vs. 25.4%, $P < 0.001$). Of all the blood cultures obtained, only 4.7% were positive.

Among those with positive blood cultures alone, *Streptococcus pneumonia* (33%) and *Staphylococcus aureus* (22%) were the most common organisms isolated, followed by *Escherichia coli* (11.8%), *Klebsiella* spp. (4.6%), *Pseudomonas aeruginosa* (3.5%), group B strep (2.7%), *Haemophilus influenzae* (2%), and *Proteus mirabilis* (1.6%). More than one-third of *S. aureus* bacteremias were methicillin-resistant (36%). In contrast, in those with only positive respiratory cultures, *S. aureus* (33.6%) and *Pseudomonas aeruginosa* (17%) were the most common isolates. In those with both positive blood and respiratory cultures, *S. aureus* was more common (44.5%) (41% was methicillin-resistant), followed by *S. pneumoniae* (32%) and *Pseudomonas aeruginosa* (7.7%).

The prevalence of resistance to recommended first-line CAP antibiotics (i.e., ceftriaxone plus azithromycin or a respiratory quinolone) was assessed by organism and by culture site. Two hundred nine patients were excluded because their organisms lacked clear Clinical & Laboratory Standards Institute (CLSI) breakpoints. Overall, 42% of admissions with a positive culture grew an organism resistant to first-line therapy for CAP, including 27% of those with positive blood cultures. Gram-negative organisms isolated in either blood or respiratory cultures were more likely to be resistant to CAP therapy than gram positives (51.8% vs. 35.4%). Patients with only positive respiratory cultures were twice as likely to yield organisms resistant to CAP therapy, but their outcomes were better, suggesting that some of these organisms represented colonizers rather than true pathogens.

Although two-thirds of the patients in this study were considered to have CAP and one-third HCAP, empirical antibiotic therapy administered at the time of admission did not necessarily reflect these designations. For those patients with only positive respiratory, only positive blood, or both positive respiratory and blood cultures, anti-methicillin-resistant *S. aureus* (MRSA) antibiotics were administered to 42%, 48%, and 66% ($P < 0.001$). Similarly, HCAP-guideline antibiotics were administered in 11.8%, 15.7%, and 27%, respectively, and four or more antibiotics were administered in 17.5%, 21%, and 33%, respectively. This suggests that providers were cognizant of the severity of disease at presentation and the risk of MRSA and multidrug-resistant organisms (MDRO) in some patients.

Despite these efforts, patients with both positive blood and sputum cultures generally had more acute and chronic illness, with significantly higher case fatality rates (25%) than those patients with only positive blood (12%) or respiratory cultures (11%); and they had significantly longer lengths of stay.

Predicting the bacterial etiology of pneumonia on presentation to the hospital, when empirical antibiotic therapy must be chosen, is challenging — and the choice depends on many factors, including the acuity of the presentation, chronicity of underlying disease, recent residence in long-term care, and the anticipated flora. Not mentioned in this article is the benefit of "flagging" those patients with recognized MDROs from prior cultures in an electronic computer system,

as well as the use of nares MRSA polymerase chain reaction (PCR) to identify those patients at risk for MRSA pneumonia. These data suggest that CAP therapy may no longer be relevant for many patients with CAP, and the required use of the current CAP bundle with limited antibacterial therapy choices should be re-assessed. ■

Homelessness and COVID-19

SOURCE: Cha S, Henry A, Montgomery MP, et al. Morbidity and mortality among adults experiencing homelessness hospitalized with COVID-19. *J Infect Dis* 2021;224:425-429.

These authors examined risk factors and outcomes for homeless adults admitted to an acute care hospital with COVID-19. Using the COVID-NET population-based surveillance system for acute care hospitalizations in 10 different states, plus the Influenza Hospital Surveillance Project for four additional states, data on laboratory-confirmed COVID-19 hospitalizations were collected. Among nearly 29,000 hospitalizations, only 8,728 cases had sufficient documentation regarding housing at the time of admission. Of these, 199 were homeless adults. The median age was 53 years, and 84% were Black, Latino, or other non-Hispanic other race/ethnicity. Most of the patients (83%) had at least one significant health condition, 32% had diabetes, and 24% were considered obese; tobacco use (46%) and alcohol abuse (34%) were common; and 8% had mental health issues.

A majority (54%) of these homeless patients were hospitalized for > 4 days, 17% were admitted to the intensive care unit (ICU), and 11% required mechanical ventilation. Six patients died (3%), five of whom were 50 years of age or older. As has been observed previously, disease severity was associated with increasing age.

Despite the anticipated poor outcomes, I was surprised that this homeless cohort did as well as they did. Mortality for COVID-19 cases admitted to the hospital early on during the pandemic was reportedly as high as 12% to 18%. A large 2020 study of 11,210 COVID-19 admissions to 92 acute care hospitals across 12 states (many of which were included in this homeless study) found an all-cause mortality of 20.3%, and 31.8% required mechanical ventilation.[1]

More recent data suggest that hospital mortality from COVID-19 may have improved. In a large 2021 study of 192,550 adult hospitalizations with COVID-19 at 555 acute care hospitals in the United States, 13.6% of adults died during the index hospitalization and another 3% were transitioned to hospice care.[2] Since February 2020, our community hospital in Mountain View, CA, has provided care for 1,000 COVID-19 patients, with an overall mortality of 9.3%. One-fourth of admissions required ICU care and one-fourth of those died. That the homeless cohort in this study had much better outcomes than any of these data suggests they may have been admitted for other complicating health reasons or perhaps for psychosocial concerns.

[Persons who are homeless, especially those who reside in camps or shelters, are at increased risk for COVID-19.]

The COVID-19 pandemic has heightened the need for better care and planning for homeless persons. Persons who are homeless, especially those who reside in camps or shelters, are at increased risk for COVID-19 infection; their hygiene, dentition, and general health suffer as the result of their homelessness, and their poor health belies their years, putting them at risk for more severe COVID-19. It also makes COVID-19 discharge planning a challenge; thankfully, our Public Health Department has invested in several "COVID hotels" with private rooms, hot showers, and meals as needed.

A first step would be screening for homeless status on admission to any acute care hospital. Only 30% of admissions identified in this study had adequate documentation of housing. In January 2019, California Senate Bill 1152 was created, requiring acute care hospitals to screen for homelessness on admission and to offer appropriate vaccinations, such as hepatitis A and influenza, as well as screening for appropriate infectious diseases, such as human immunodeficiency virus, hepatitis B, and tuberculosis. Originally intended to halt an outbreak of hepatitis A in the homeless populations in several California counties, this extra screening step in care for homeless persons is helping to solve many problems, including the administration of COVID-19 vaccination to this vulnerable population. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding malaria prevention efforts?

a. They are on hold pending better vaccines.

b. They involve mosquito bite avoidance measures as well as medication and vaccination.

c. They are 95% effective with currently available vaccines.

d. They routinely involve monoclonal antibodies against blood schizonts.

2. Which of the following is correct regarding shedding of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant gram-negative bacilli (MDR-GNB) by colonized patients?

a. MDR-GNB and MRSA are shed with equal frequency.

b. MRSA is shed with greater frequency than MDR-GNB.

c. MDR-GNB is shed with greater frequency than MRSA.

d. Neither MRSA nor MDR-GNB are shed.

3. Which of the following is correct regarding the results of administration of the adjuvanted recombinant varicella-zoster vaccine (Shingrix) 5.1 to 7.1 years post-vaccination?

a. Its protective efficacy fell within the range of 25% to 50%.

b. Its protective efficacy fell within the range of 50% to 75%.

c. Its protective efficacy fell within the range of 75% to 95%.

d. Its protective efficacy fell within the range of 95% to 99%.

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.