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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

# Surviving Sepsis 2021 Update

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SYNOPSIS: The Surviving Sepsis Guidelines (last updated in 2016) have just been updated. Some of the important changes include clearer differentiation of sepsis vs. septic shock and, for many recommendations, changing the strength of recommendation and quality of evidence to support many recommendations.

SOURCE: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49:e1063-e1143.

This paper reflects the work of dozens of co-authors from both the Society of Critical Care Medicine and the Infectious Diseases Society of America (IDSA). Some of the important changes from the 2016 Surviving Sepsis Guidelines are detailed in Table 1 of this 81-page paper containing 653 references.[1] These changes include:

1. The quick sepsis related organ failure assessment (qSOFA) score now is recommended as the best sepsis screening tool.
2. Blood lactate measurements now are considered a weak recommendation with low quality of evidence.
3. The previous strong recommendation for giving patients with sepsis initial fluid administration of 30 mL/kg has been downgraded to weak with low quality of evidence.
4. Use of capillary refill time as an adjunctive means of assessment of perfusion has been added as a weak recommendation with low quality of evidence.
5. Administration of antibiotics within one hour of presentation for both possible sepsis and septic shock has been changed to recommending this only for septic shock or sepsis where likelihood of infection is high.
6. Administration of antibiotics within three hours for possible sepsis without shock has been downgraded from a strong to a weak recommendation.
7. A new recommendation for adults with a low likelihood of infection and without shock is that it is now suggested to defer antimicrobials while continuing to monitor the patient closely.

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8. A best practices statement in the 2021 guidelines now states that in adult patients thought to be at high likelihood of harboring methicillin-resistant *Staphylococcus aureus* (MRSA), appropriate antibiotics targeting MRSA should be given rather than the previous recommendation to give broad-spectrum antibiotics.
9. Similarly, for adult patients considered to be at high risk for being infected with fungal pathogens, it now is recommended that empiric antifungal coverage be given, rather than the previous recommendation to cover all possible pathogens.
10. Balanced crystalloids, rather than normal saline, now are recommended for resuscitation.
11. Gelatin is no longer recommended for resuscitation.
12. For adults with septic shock, it is recommended to start vasopressors peripherally rather than waiting for a central line to be placed.
13. The new guidelines state that there is little evidence to support a restrictive vs. liberal fluid infusion strategy after initial fluid resuscitation.
14. For adults with sepsis-induced hypoxemic respiratory failure, it now is suggested to use high-flow nasal oxygen over noninvasive ventilation.
15. For adults with sepsis-induced severe acute respiratory distress syndrome (ARDS), the new guidelines suggest using veno-venous (VV) extracorporeal membrane oxygenation (ECMO) when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use.
16. For adults with septic shock and an ongoing requirement for vasopressor therapy, the 2021 guidelines suggest using intravenous (IV) corticosteroids.

## ■ COMMENTARY

The 2021 revision of the Surviving Sepsis Guidelines are a big improvement over the 2016 version. Readers may remember that many of the recommendations in the 2016 Surviving Sepsis Guidelines were not supported by evidence, yet were made with an often strong recommendation level. This resulted in the IDSA withdrawing its support for the guidelines.[2]

The 2021 guidelines now highlight areas of uncertainty and also clearly differentiate between septic shock (where rapid administration of antibiotics and appropriate fluid resuscitation are critical to survival) vs. "sepsis" without septic shock, where the potential harms of inappropriate antibiotic administration and overly aggressive fluid resuscitation may cause significant harm.[3] Unfortunately, the Centers for Medicare and Medicaid Services SEP-1 quality bundles do not yet reflect the now nuanced and evidence-backed Surviving Sepsis Guidelines. Because many hospital quality improvement programs are tied to SEP-1 bundle compliance, this likely still will cause many patients to receive inappropriate antibiotics, excessive fluid resuscitation, and other inappropriate treatment. Recently IDSA has recommended changes to these SEP-1 quality measures as well.[4] ■

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ABSTRACT & COMMENTARY

# Pediatric Pneumonia — Diagnostic and Therapeutic Stewardship

***By Philip R. Fischer, MD, DTM&H***

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SYNOPSIS: A randomized multicentered trial in the United Kingdom and Ireland shows that children receiving amoxicillin for community-acquired pneumonia do similarly well with lower dose (35-50 mg/kg/day vs. 75-90 mg/kg/day) and shorter duration (three vs. seven days) treatments.

SOURCE: Bielicki JA, Stohr W, Barratt S, et al. Effect of amoxicillin dose and treatment duration on the need for antibiotic re-treatment in children with community-acquired pneumonia: The CAP-IT randomized clinical trial. *JAMA* 2021;326:1713-1724.

Bielicki and colleagues realized that preschool-age children often present for medical care with symptoms and findings suggestive of an infectious illness. Further, they realized that 10% to 40% of European pediatric emergency department visits with concern for infection prompt antibiotic use, with pneumonia being common. In research studies, about one-third of children with community-acquired pneumonia have a bacterial etiology of the illness, and neither blood tests nor chest radiographs can determine definitively whether a particular respiratory infection is due to bacteria or to viruses.

Meanwhile, for children with presumed pneumonia, short courses (three to five days) typically are recommended in low-resource and middle-resource countries, while longer treatment courses are used in high-resource nations. Amoxicillin generally is accepted to be good first-line treatment.

Desiring good evidence regarding adequate dosing and duration of amoxicillin therapy for pediatric community-acquired pneumonia, Bielicki and colleagues organized a randomized controlled trial involving 29 hospitals (one in Ireland, the rest in the United Kingdom). Low (35-50 mg/kg/day) and high (75-90 mg/kg/day) dose amoxicillin and short (three days) and longer (seven days) durations of treatment were compared. The primary outcome was the need for additional antibiotics (for presumed persistent or recurrent pneumonia) within the subsequent four weeks.

Study subjects were children of at least 6 months of age who were dismissed from emergency or observation or inpatient units with antibiotics for community-acquired pneumonia. The diagnosis was based on cough and fever (either measured as being of at least 38°C or reported as fever by parents) and labored breathing or focal chest findings. Children with underlying chronic illness or complicated pneumonia were not included in the study. Study subjects were randomized to low dose vs. high dose and to short duration vs. long duration treatment. Outcomes were followed by symptom diaries, phone calls, and a 28-day follow-up visit.

The median age of participants was 2.5 years. The four groups (low dose — short treatment, low dose — long treatment, high dose — short treatment, and high dose — long treatment) had similar baseline findings. Overall, 95% of participants had previously received routine immunizations. The median temperature at presentation was 38.1°C, the median oxygen saturation was 96%, and 60% of subjects had retractions. The median respiratory rate was 38 breaths per minute, and two-thirds of children were deemed to be tachypneic based on age-related normal rates. More than two-thirds of children had rales on ausculatory exam.

During the two years of the study (2017-2019), 814 children were randomized and had useful data collected. Study groups were similar in that 9.5% of children "required" additional antibiotics for respiratory infection during the four weeks after starting the study course of amoxicillin. This outcome was not statistically different whether the children received high vs. low and long vs. short amoxicillin treatment courses.

Cough persisted slightly longer (12 vs. 10 days) in the short duration treatment group. Clinical outcomes were otherwise similar between groups. Adverse outcomes (including rash and thrush) were similar between treatment groups. The investigators also performed pharyngeal cultures for pneumococcus before and after the study; pneumococcal carriage

and pneumococcal susceptibility to penicillin did not vary between treatment groups.

The authors concluded that, in their study population, lower dose and shorter duration amoxicillin treatments were noninferior to higher dose and longer duration treatments. They acknowledged that they could not definitively determine which children had bacterial vs. viral illnesses, and they did include some children with asthma who also had evidence of community-acquired pneumonia.

## ■ COMMENTARY

Antibiotics save many lives, but antimicrobial stewardship also can save medical expenses, prevent adverse reactions, and preempt public health problems. The new report from Bielicki and colleagues provides good evidence that shorter, lower-dose treatment with amoxicillin is noninferior to longer, higher-dose (conventional) treatment. These data provide good support for using less (in both dose and duration) antibiotic to treat children with pneumonia. Even though adverse events (mostly rash and oral thrush) did not differ based on treatment regimen, and subsequent pneumococcal resistance did not seem to develop, each study group had similar rates of successful recovery. Shorter, lower dose amoxicillin courses seem like a reasonable next step in efforts to reduce antibiotic use among children with pneumonia.

But, did these children truly have bacterial pneumonia? They met accepted criteria, but very few of them had high fever or hypoxia. Tachypnea was common, but young children with bronchiolitis and other viral respiratory infections easily can have tachypnea as well. Abnormal ausculatory findings were common, but those, too, are not very specific for bacterial disease. It is not unreasonable to think that most of these children (but not necessarily the children with complicated pneumonia who were excluded from this study) would have recovered similarly well with no antibiotic use.

The methods section of the paper claims this was a "placebo-controlled" trial, but there was not actually an untreated placebo group in the study. Rather, each subject received some amoxicillin, and it was just the dose and duration that varied. The authors rightly noted that two-thirds of children sick enough to be hospitalized with community acquired pneumonia actually have viral illnesses, and it is likely that at least two-thirds of the children in the current study (most of whom were not sick enough to be hospitalized) had viral illnesses that required no antibiotic treatment — and also decreased the recognition of a difference in outcomes with differing doses and durations of amoxicillin treatment in children who actually had bacterial illnesses.

A needed step in our continued efforts of antimicrobial stewardship would be to better determine which children with cough, reported fever, and rapid/difficult breathing actually have bacterial illnesses. Bielicki and colleagues rightly acknowledged the difficulty of making an etiologic diagnosis of bacterial pneumonia, since blood tests and radiographs are fairly nonspecific.

Procalcitonin is a precursor to the hormone calcitonin and usually is produced in the thyroid. However, in the presence of inflammatory cytokines, procalcitonin is produced in a variety of bodily tissues — especially in response to bacterial infections.[1] As noted by Bielicki and colleagues, procalcitonin is not specific enough to diagnose bacterial illness.

Even though an elevated procalcitonin level lacks adequate specificity and sensitivity to accurately make a diagnosis of bacterial pneumonia, a low level is highly suggestive of a non-bacterial cause of pneumonia.[2] For children hospitalized with community-acquired pneumonia, low procalcitonin levels are significantly associated with a non-bacterial source of the illness. Thus, a low procalcitonin level might be used to conclude that antimicrobial treatment is not needed in a child who otherwise seems to have pneumonia.[3] Clinical pathways incorporating procalcitonin levels can be effective tools in deciding which children with lower respiratory infection can forego antibiotic treatment.[4]

Similarly, procalcitonin levels are not very helpful in diagnosing cystitis but might be useful in diagnosing pyelonephritis.[5] For meningitis, procalcitonin levels also can be helpful in affirming diagnostic suspicion.[6]

Bielicki and colleagues remind us that children with lower respiratory tract infections often can be treated successfully with less antibiotic exposure than currently is common. Better yet, for the future, will be to determine which children can recover safely without any antibiotic treatment. ■

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ABSTRACT & COMMENTARY

# Melioidosis in the United States

***By Stan Deresinski, MD, FACP***

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SYNOPSIS: Four cases of melioidosis in four states occurred and at least one was traced to a contaminated commercial aromatherapy product.

SOURCE: CDC Health Network. Source identified and case definition established: Multistate investigation of non-travel associated *Burkholderia pseudomallei* infections (melioidosis) in four patients: Georgia, Kansas, Minnesota, and Texas – 2021. https://emergency.cdc.gov/han/2021/han00456.asp?ACSTrackingID=USCDC_511-DM69519&ACSTrackingLabel=HAN%20454%20-%20General%20Public&deliveryName=USCDC_511-DM69519

Between March and late July 2021, cases of melioidosis were detected in Georgia, Kansas, Minnesota, and Texas. Two of the four people with the infections, including a child, died. The first case, which occurred in Kansas in March, was fatal, as was the fourth case, which was diagnosed post-mortem in Georgia in July. None of the patients had traveled outside the continental United States.

Genetic analysis indicated that the isolates of *Burkholderia pseudomallei* causing the infections appeared identical. Initially, large numbers of specimens recovered from several patient households were evaluated, but the source of the infection was not found. This led to a second investigation that included types of specimens not tested previously. Polymerase chain reaction (PCR) testing of a bottle of an aromatherapy product in the home of the July Georgia victim who died identified the presence of *B. pseudomallei* — a Tier 1 select agent. Genetic testing confirmed its relatedness to the clinical isolates.

## ■ COMMENTARY

The implicated aromatherapy product, Better Homes and Gardens Lavender and Chamomile Essential Oil Infused Aromatherapy Room Spray with Gemstones, was manufactured in India and sold by Walmart at 55 stores as well as online. A recall that includes five other scents of the spray has been issued for 3,900 bottles that had been sold.

There is nothing distinctive about the presentation of melioidosis, so the diagnosis requires laboratory confirmation. If suspected, the laboratory should be notified because of the risk of infection associated with exposure. Another important laboratory issue is the fact that laboratory testing using automated identification algorithms, such as VITEK-2 and MALDI-TOF, may fail to identify the organism correctly. In fact, the Texas case in the cluster reviewed here was misidentified as *Burkholderia thailandensis* by MALDI-TOF. The Centers for Disease Control and Prevention states: "Consider re-evaluating patients with isolates identified on automated systems as *Burkholderia* spp. (specifically *B. cepacia* and *B. thailandensis*), *Chromobacterium violaceum*, *Ochrobactrum anthropi*; and, possibly, *Pseudomonas* spp., *Acinetobacter* spp., and *Aeromonas* spp."

[There is nothing distinctive about the presentation of melioidosis, so the diagnosis requires laboratory confirmation.]

Acquisition of melioidosis in the United States in the absence of foreign travel is very rare, but one case was reported recently in a 56-year-old woman in whom the infection was traced to her freshwater aquarium.[1] ■

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ABSTRACT & COMMENTARY

# Fluvoxamine Reduces the Risk for Hospitalization from COVID-19

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

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SYNOPSIS: A randomized, placebo-controlled clinical trial found fluvoxamine (100 mg twice a day for 10 days) reduced the risk for hospitalization among high-risk outpatients diagnosed with COVID-19.

SOURCE: Reis G, Dos Santos Moreira-Silva EA, Medeiros Silva DC, et al. Effect of early treatment with fluvoxamine on the risk of emergency care and hospitalisation among patients with COVID-19: The TOGETHER randomized, platform clinical trial. *Lancet Glob Health* 2021; Oct. 27;S2214-109X(21)00448-4. [Online ahead of print].

Despite the widespread availability of COVID-19 vaccines, effective treatments that prevent or delay the progression of COVID-19 illness are urgently needed. Ideally, novel therapies should be oral, inexpensive, widely available, and have a low risk of adverse events. There is some evidence that fluvoxamine, an oral selective serotonin reuptake inhibitor used to treat depression, may reduce the risk for hospitalization due to COVID-19.[1] Reis and colleagues, therefore, sought to determine the efficacy of fluvoxamine vs. placebo in preventing hospitalization among outpatients with an early diagnosis of COVID-19.

The study was a randomized, platform, placebo-controlled clinical trial conducted in 11 cities in Brazil. Patients included in the study were at least 18 years of age and presented to an outpatient care setting with an acute illness consistent with COVID-19. They must have had symptoms that started within seven days of the screening date or had a positive rapid test for SARS-CoV-2 antigen performed at the time of screening, or a positive SARS-CoV-2 diagnostic test within seven days of symptom onset. Patients also needed to have at least one additional criterion that put them at high risk for hospitalization, including diabetes mellitus, hypertension, cardiovascular disease, symptomatic lung disease, tobacco abuse, obesity, organ transplant recipient, chronic kidney disease (stage IV or on dialysis), immunosuppression or use of corticosteroid therapy equivalent to at least 10 mg of prednisone per day, history of malignancy in the preceding five years or actively undergoing cancer treatment, or being unvaccinated.

Patients were randomized 1:1 to receive either fluvoxamine 100 mg orally twice a day for 10 days or placebo. An electrocardiogram (ECG) was conducted at baseline for all participants. The primary endpoint was medical admission to a hospital for COVID-19 within 28 days of randomization.

There were 1,497 patients enrolled in the study, of which 741 were randomized to fluvoxamine and 756 to placebo. The median age was 50 years (range, 18-102 years) and 862 (58%) were female. The two groups were well balanced in terms of age, body mass index, and comorbidities. Hospitalization occurred in 79 of 741 (11%) of fluvoxamine recipients vs. 119 of 756 (16%) for those who received placebo; relative risk (RR), 0.68; 95% Bayesian credible interval (95% BCI): 0.52-0.88. Seventeen deaths occurred in the fluvoxamine group and 25 deaths occurred in the placebo group in the primary intention-to-treat analysis (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.36-1.27; $P = 0.24$). The number needed to treat was 20. Fluvoxamine was well tolerated and there were no significant differences in adverse events between those who received fluvoxamine vs. placebo.

## ■ COMMENTARY

The currently available treatments for COVID-19 (i.e., monoclonal antibodies and remdesivir) are given intravenously, so having an effective oral agent would be a game changer. Indeed, the oral direct-acting antiviral molnupiravir has generated considerable interest after it was shown to reduce the risk for hospitalization by 50% in those with early COVID-19.[2] Reports indicate that a novel protease inhibitor, paxlovide, may have 89% efficacy — bringing it to a level similar to that seen with monoclonal antibody therapy. However, other oral options remain an important goal. Since being approved by the Food and Drug Administration (FDA) in 1997, fluvoxamine has had a good safety record and generally is well tolerated. There now is growing evidence, as shown by the study from Reis et al and others, that fluvoxamine is an effective,

safe, and relatively inexpensive treatment option for outpatients with mild COVID-19.The mechanism of action against SARS-CoV-2 is not well understood and needs further investigation. It may be due to anti-inflammatory properties, such as reducing platelet aggregation, decreasing mast cell degranulation, interfering with endolysosomal viral trafficking, regulating inositol-requiring enzyme 1α-driven inflammation, and increasing melatonin levels.[3] Thus, there are likely to be other drugs used in clinical practice that can be similarly repurposed against COVID-19 that are waiting to be discovered.

The study by Reis et al was well-designed and is the largest randomized clinical trial to date to investigate the effect of fluvoxamine against COVID-19. However, there are a few limitations and unanswered questions worth mentioning. First, it is uncertain whether fluvoxamine will have the same efficacy against other strains of COVID-19, such as the Delta variant. Second, whether fluvoxamine can help those already hospitalized (e.g., prevent intensive care unit admission) is uncertain. Third, the study was conducted in one geographic area with a relatively homogeneous population, so the results might not be applicable to other regions and should be considered preliminary. Fourth, it is not known whether fluvoxamine is beneficial for vaccinated patients. Finally, the follow-up duration was relatively short and did not measure the effect of fluvoxamine on persistent symptoms (i.e., long COVID) or late deterioration.

The findings in this study are interesting and further support a role for fluvoxamine in the treatment of early COVID-19 in outpatients. Given the prevalence of vaccine hesitancy, an inexpensive oral drug that prevents hospitalizations, especially in the unvaccinated, could have important economic and public health benefits. ■


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ABSTRACT & COMMENTARY

# An Outbreak of Injection Site *Mycobacterium porcinum* Infections After Vaccination in the Workplace


***By Stan Deresinski, MD, FACP***

*Clinical Professor of Medicine, Stanford University*



SYNOPSIS: Vaccine (non-COVID-19) contamination as a result of improper handling led to injection site infections due to *Mycobacterium porcinum*, a rapid growing non-tuberculous mycobacterium present in the environment.


SOURCE: Blau EF, Flinchum A, Gaub KL, et al. *Mycobacterium porcinum* skin and soft tissue infections after vaccinations — Indiana, Kentucky, and Ohio, September 2018–February 2019. *MMWR Morb Mortal Wkly Rep* 2021;70:1472-1477.

*Erratum*: Vol. 70, No. 42. *MMWR Morb Mortal Wkly Rep* 2021;70:1560.

The Kentucky Department for Public Health (KDPH) received notification on Dec. 4, 2018, from a local health department that it had evaluated three patients with skin abscesses at the site of receipt of vaccination at their workplace and provided by "company A." The vaccines administered included influenza; hepatitis A; pneumococcal; or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap). On learning that company A had received similar reports but had not, in turn, reported them to the Vaccine Adverse Event Reporting System (VAERS) or the local health department, the company was ordered to cease vaccine administration and to sequester remaining vaccines and supplies. Two days later, notifications were sent to five counties in which the company had been performing vaccinations. KDPH also notified seven businesses initially identified by company A as sites where they were vaccinating, but KDPH subsequently identified an additional 17 sites that company A had failed to report to them. Eventually, the investigation involved a total of 24 businesses in Kentucky, Indiana, and

Ohio that had contracted with company A to vaccinate their employees and 101 employees meeting the case definition of a vaccine site reaction within 150 days.

The median time to onset of these events after vaccination was 14 days (range 0-126 days). The most frequently reported findings were nodules, erythema, and pain, each occurring in > 84% of cases, with drainage in 57.4%. Thirty clinical specimens sent to public health laboratories yielded *Mycobacterium porcinum* on culture. Pulsed field gel electrophoresis performed at the Centers for Disease Control and Prevention (CDC) indicated these comprised two closely related clusters, with only a single band difference.

■ COMMENTARY

*M. porcinum* is a "rapid grower" of the *Mycobacterium fortuitum* group. Like other organisms of this group, it is present in the environment. Although rarely identified as a cause of human infection, it previously was reported to cause an outbreak of infection in 24 inpatients over five years as a consequence of contamination of the water supply of a Galveston, TX, hospital.[1]

A 2004 report indicates that clinical isolates were susceptible to ciprofloxacin, sulfamethoxazole, and linezolid, and susceptible or intermediate to cefoxitin, clarithromycin, imipenem, and amikacin.[2]

In the vaccine-related outbreak of skin and soft tissue infections reported by the CDC, the epidemiological, microbiological, and molecular findings indicated single source contamination, which most likely occurred during syringe preparation. The investigation identified multiple problems, including improper vaccine storage, handling, and administration, together with lack of training and professional oversight of the involved non-medical personnel. This outbreak was completely preventable, but the breadth and depth of the breakdown in the process described in this report is astounding. ■

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ABSTRACT & COMMENTARY

# Missing the Diagnosis of Congenital Syphilis


***By Stan Deresinski, MD, FACP***

*Clinical Professor of Medicine, Stanford University*



SYNOPSIS: The diagnosis of congenital syphilis was delayed until the post-neonatal period in 2.2% of infants born in the United States 2014-2018.


SOURCE: Kimball A, Bowen VB, Miele K, et al. Congenital syphilis diagnosed beyond the neonatal period in the United States: 2014-2018. *Pediatrics* 2021;148:e2020049080.

Kimball and colleagues evaluated the extent of the problem of failure of diagnosis of congenital syphilis (CS) during the neonatal period — i.e., during the first 28 days of life. They examined the National Notifiable Diseases Surveillance System to identify cases of this reportable disease throughout the United States among infants born 2014-2018, a period of time when the annual number of all cases of CS increased by 183% from 462 to 1,306. Of the total of 3,834 cases reported during that time, 84 (2.2%) were first diagnosed after the neonatal period, and 67 (including one twin set) born in the United States were symptomatic, while two were asymptomatic, and inadequate information was available for the remainder.

The median age at the time of diagnosis was 67 days, with the diagnosis first made after 3 months of age in 21 (31%) and after 6 months of age in four (6%). The median titer of the serum non-treponemal antibody tests was 1:256 (range 1:1-1:2,048). Two-thirds had physical findings consistent with CS, with the most frequently identified being skin rash, snuffles, and hepatosplenomegaly.

Long bone abnormalities were present in 38 (69%) of those with X-ray examination. Fifty infants underwent cerebrospinal fluid (CSF) examination venereal disease research laboratory (VDRL) testing, and the test was reactive in 18 (36%), while the protein concentration and/or white blood cell count was elevated in 22

(50%) of those tested. A 10-day course of parenterally administered penicillin was given to 61 (91%).

Fifty-five (83%) of the 66 mothers had had at least one prenatal care visit. Sixteen (24%) had primary or secondary syphilis and 25% had early latent infection, while 31 (47%) had late infection or infection of unknown duration. Sixteen (24%) seroconverted during pregnancy, with four of these conversions first detected after delivery. The diagnosis of maternal syphilis was often late, having been made, e.g., more than three days after delivery in 28 (42%) — with 15 of these only being made after the diagnosis in the infant. Three mothers received treatment for syphilis < 30 days prior to delivery.

## ■ COMMENTARY

There has been a disturbing increase in the incidence of CS in the United States since 2012. The Centers for Disease Control and Prevention (CDC) indicates that major reasons include missed opportunities, including a failure to provide adequate treatment despite time diagnosis, inadequate prenatal care, and lack of recommended testing, as well as late seroconversion during pregnancy and failed therapy of the mother. As pointed out by Kimball et al, this represents a failure of public health and healthcare systems as well as clinicians. The cases of late diagnosis reviewed here (along with 245 stillbirths) are "ultimate failures."

The CDC recommends routine serological screening at the first prenatal visit and repeat testing at 28 weeks gestation and at delivery for those deemed at risk. Relying on assessment of risk has been reported to be inadequate and, as a consequence, some states recommend repeat testing for all. The CDC states, "No mother or newborn infant should leave the hospital without maternal serologic status having been documented at least once during pregnancy." All neonates born to mothers with a serological diagnosis of syphilis should have a VDRL or rapid plasma reagin (RPR) test performed on serum (not from cord blood, which may contain passively transferred antibody). Those with positive tests should undergo intense examination (including CSF examination) for manifestations of central nervous system syphilis. Confirmed cases should receive 10 days of parenterally administered penicillin.

The experience reviewed here demonstrates the need for pediatricians to be alert to the potential for CS in post-neonatal infants with consistent clinical manifestations. ■

### REFERENCE

1. Centers for Disease Control and Prevention. Sexually Transmitted Infections Treatment Guidelines, 2021. Congenital Syphilis. https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm

Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## Risk of COVID-19 During Air Travel

SOURCE: Hu M, Wang J, Lin H, et al. Risk of SARS-CoV-2 transmission among air passengers in China. *Clin Infect Dis* 2021 Sept 21; ciab836.doi: 10.1093/cid/ciab836. [Online ahead of print].

Everyone wants to travel for the holidays — and there has been lots of conversation about the risk of COVID-19 transmission during air travel. Some have argued that the type of airplane might make a difference. Most, but not all, commercial jet liners are equipped with high efficiency particulate air (HEPA) filters, and about 40% of the cabin air is recirculated through this HEPA system, which can filter 99.97% of dust, pollen, bacteria, viruses, and any other airborne particles with a size of 0.3 microns or greater. Another 60% of the air is piped into the plane while cruising. Most commercial air flights completely recycle the air within the cabin every three minutes, with about 20 air exchanges per hour.

To assess the risk of COVID-19 transmission during air travel, before mask requirements and other precautionary measures, these authors examined domestic flights leaving Wuhan, China, from Jan. 4 through Jan. 22, 2020, the day before the lockdown. An index case was defined as a confirmed diagnosis of COVID-19 infection following air travel, plus symptom onset within 14 days of departure and within two days of travel, and had the earliest date of symptom onset if one or more cases within three rows of seats. Secondary COVID-19 cases were defined as symptom onset within two to 14 days of travel.

The risk of transmission during actual air flight is hard to estimate, since people may have exposures en

route to the airport, within the terminal, or during exit from the plane, not to mention that many people may travel with friends, family, or coworkers, with additional risk for exposure at home or at work. In an attempt to manage these varying risks, the authors calculated both the upper and lower estimates of secondary attack rates. The upper bound was calculated assuming no work/family relationship between the case, and then they recalculated the lower bound by assuming the person seated next to an index cases was related, and excluded this individual from the estimates.

In all, 5,797 people took 177 domestic flights from Wuhan. A total of 209 travelers were confirmed with COVID-19 infection within two weeks of travel, of which 175 were considered index cases. There were 34 secondary cases, with a median of 4.0 days from departure to symptom onset. The upper bound's secondary attack rate was 0.6% and the lower bound's secondary attack rate was 0.33%. Each index cases resulted in 0.19 to 0.10 secondary infections, respectively (this is pre-mask requirement and pre-vaccination).

However, seat proximity and flight duration were significant factors in the risk of transmission. Seats immediately adjacent to a case had a 9.2% attack rate, with a relative risk of 27.8 compared with other seats on the airplane. The middle seat had the highest attack rate (0.7%) compared with the window and aisle seats (0.6%), most likely because middle seats have twice the chance of sitting next to someone with COVID-19 infection. The upper bound's attack rate was 0.7% for flights less than two hours to 1.2% for flights of 2 to 3.3 hours, whereas the lower bound's estimates of transmission for the same durations were 0% and 0.4%. No difference was observed between Airbus and Boeing jet liners.

The risk of COVID-19 transmission during air travel from Wuhan, China, before the lockdown in January 2020 was small (0% to 0.9%), depending on the duration of the flight, unless a passenger happened to sit next to an index case, in which case the risk ballooned to 9.2%. Face mask requirements and higher vaccination rates in air travelers will further reduce these estimates. Just make sure you do not sit next to someone with COVID. ■

## Symptoms Post-COVID: Loss of Taste in One in Seven

SOURCE: Nehme M, Braillard O, Chappuis F, et al. Prevalence of symptoms more than seven months after diagnosis of symptomatic COVID-19 in an outpatient setting. *Ann Intern Med* 2021;174:1252-1260.

Persistent complaints of physical and mental debility are common in people who have been infected with COVID-19, and some patients may take months to return to work. These authors examined self-reported symptoms at 30-45 days and seven to nine months following diagnosis in a group of relatively healthy, younger adults (18 years of age or older), followed in a COVID ambulatory care clinic in Switzerland. Because COVID-19 patients were not followed in the usual ambulatory care setting, Switzerland's Geneva General Hospital established CoviCare clinics, originally established to follow positive patients every two days by telephone during the first 10 days of their illness. They were contacted again for a telephone interview and were sent an online questionnaire at days 30-45 and at seven to nine months.

A total of 629 individuals participated in the prospective survey, of which 410 completed seven to nine months of follow-up. The mean age was 42.1 years, 61% were female, and 70.7% had no

underlying risk factors. Twenty-five percent were healthcare workers. Most of the patients (96%) were symptomatic at baseline, and the majority reported their symptoms as mild to moderate. Despite being relatively younger and healthier, 40 participants were hospitalized during follow-up. Of the 311 patients who participated at all three time points, 37% reported symptom resolution at days 30-45 and 56% reported symptom resolution by months 7 to 9.

In all, 39% of participants reported residual symptoms at months 7 to 9, including, in descending order of frequency, fatigue (20.7%), loss of taste and/or smell (16.8%), dyspnea (11.7%), and headache (10%). Persisting mental symptoms included difficulty concentrating (5.9%), insomnia (5.7%), and memory loss (5.6%). Women were more likely than men to have persistent symptoms (43.2% vs. 31.1%) at months 7 to 9, and increasing age was associated with a greater frequency of residual symptoms.

When arguing in favor of COVID-19 vaccination, I have stressed that COVID-19 is not just an acute infection but a real disease, with prolonged symptoms for months in four of 10 people infected, even in people who are relatively young and healthy. I mention several people who now are effectively disabled and cannot work or support their families. But what impresses people the most is that one in seven may lose the sense of taste or smell — and it is not just loss of taste or smell, but food actually may taste bad. Can you imagine going through the rest of your life without enjoying food? Try this when counseling people regarding vaccination! ■

## Effectiveness of Cloth and Surgical Masks Against SARS-CoV-2

SOURCE: Adenaiye OO, Lai J, Bueno de Mesquita PJ, et al. Infectious SARS-CoV-2 in exhaled aerosols and efficacy of masks during early mild infection. *Clin Infect Dis* 2021; Sept 14:ciab797. [Online ahead of print].

Newer variants of SARS-CoV-2 are generally believed to be more transmissible. So how well do regular cloth or surgical masks work against the newer variants? These authors examined the efficacy of usual cloth masks and surgical masks in 49 non-vaccinated COVID-19-positive college students, who provided blood, saliva, mid-turbinate, and fomite (phone mouthpiece) specimens, and 30-minute breath samples with and without masks. Participants were asked to speak loudly and sing into a Gesundheit-II breath sampler for 30 minutes. Samples were collected on two or more visits at least two days apart within 0-12 days of a positive test or onset of symptoms. Participants were tested without a mask, with a surgical mask, and with the cloth mask they brought with them to the testing. Viral ribonucleic acid (RNA) was quantified, and cultures were performed on VERO cell media.

In unmasked participants, viral RNA was found in 31% of coarse droplets (> 5 µm) and 45% of fine aerosols (≤ 5 µm), as well as 65% of fomite samples from the telephone mouthpiece. The amount of viral RNA detected in coarse and fine aerosols was reduced by 77% and 48%, respectively, when wearing either a cloth or surgical mask; no significant difference was observed between different mask types. Quantitative RNA in mid-turbinate swabs (but not saliva) was strongly associated with the amount of virus observed in aerosols. Interestingly, virus could be cultured in 68% of mid-turbinate specimens, 32% of salivary specimens, but only 3% of the fine aerosol samples in persons wearing a mask, and none of the fine aerosol samples from persons not wearing a mask. In addition, none of the fomite samples were culture-positive.

[Ordinary cloth and surgical face masks provide a moderate reduction in the exhaled virus in 30-minute breath samples in COVID-19-infected, unvaccinated persons.]

Four of the individuals were found to have the newer alpha variant virus, whereas the others were infected with earlier strains. Viral shedding was significantly greater in these four individuals (18-fold greater). When adjusted for cough and mask wearing, viral RNA was 100-fold greater in coarse aerosols and 73-fold greater in fine aerosols, suggesting that newer strains are indeed more transmissible.

Ordinary cloth and surgical face masks provide a moderate reduction in the exhaled virus in 30-minute breath samples in COVID-19-infected, unvaccinated persons, although newer more transmissible variants were more likely to generate aerosols with greater amounts of viral RNA. Samples in this study were obtained from students who were speaking loudly and singing into a breath sampler for an extended period of time, which likely increased the risk of finding detectable RNA, but probably more closely mimics the real world, e.g., sitting around a dinner table or chatting at a bar. ■

## CME INSTRUCTIONS

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## CME QUESTIONS

**1. Which of the following is true regarding an elevated procalcitonin?**

a. It is helpful in diagnosing bacterial pneumonia in children.

b. It rules out viral pneumonia in a febrile, coughing, tachypneic child.

c. It might be relevant in the evaluation of pediatric pyelonephritis and meningitis.

d. It results primarily from cytokine-induced stimulation of pulmonary tissues.

**2. Which of the following is correct regarding the known putative mechanism of action of fluvoxamine against SARS-CoV-2, the etiologic agent of COVID-19?**

a. It acts as a protease inhibitor.

b. It acts as a chain terminator.

c. It causes multiple mutations in viral nucleic acid.

d. It is unknown.

**3. Which of the following is correct regarding the newly updated Surviving Sepsis recommendations for 2021?**

a. It now is acceptable to defer antimicrobial initiation and to observe in non-shock patients with a low likelihood of infection.

b. Blood lactate measurement now is considered a strong recommendation based on high-quality evidence.

c. Antibiotic administration must be initiated within one hour of presentation in patients with non-severe sepsis or septic shock.

d. Corticosteroid administration is contraindicated in all patients with sepsis or septic shock.

**4. Which statement is correct regarding melioidosis?**

a. While cases have been diagnosed in the United States, none have ever been acquired locally.

b. It is caused by *Burkholderia cepacia*.

c. It poses a potential risk to laboratory personnel, who should be warned that its presence is suspected.

d. The etiologic agent is readily identified by all test systems using automated identification algorithms.

**5. Which statement is correct regarding *Mycobacterium porcinum*?**

a. It is a member of the *Mycobacterium avium*/intracellulare group.

b. It is present in the environment.

c. Its recovery from a patient always indicates colonization.

d. It always is non-pathogenic.

## 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.