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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Remdesivir and COVID-19

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Remdesivir is safe and moderately effective in the treatment of patients with COVID-19.

SOURCES: Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Preliminary report. *N Engl J Med* 2020 May 22;NEJMoa2007764. doi:10.1056/NEJMoa2007764. [Online ahead of print].
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Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir in Covid-19. *N Engl J Med* 2020;382:10.1056/NEJMc2015312#sa4. [Online ahead of print].
Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *Erratum. Lancet* 2020;395:1694.
Gilead Sciences Inc. Gilead announces results from Phase 3 trial of remdesivir in patients with moderate COVID-19. Press Release. June 1, 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19

Wang and colleagues randomized adults with moderate-to-severe COVID-19 to treatment to receive remdesivir or placebo in a 2:1 ratio. Many patients also received one or more of the following: lopinavir-ritonavir, interferon alfa-2b, and corticosteroids. The median interval from symptom onset to study enrollment was 10-11 days. The study found no statistically significant improvement with the use of remdesivir. However, it was significantly underpowered as a result of premature termination because of an inability to enroll patients as the outbreak came under control in Wuhan (236 of a planned 325 were enrolled), reducing the power to detect a significant difference in their targeted improvement from a planned 80% to 58%. This meant that no

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Infectious Disease [ALERT]

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firm conclusion could be drawn from this study. However, it did suggest that, if remdesivir was effective, its impact would not be huge.

Beigel and colleagues reported the preliminary results of a larger international, multicenter National Institute of Allergy and Infectious Diseases (NIAID)-sponsored trial (ACTT-1) in which adults with severe COVID-19 were randomized (1:1) to up to 10 days of treatment with remdesivir or placebo. Entry requirements included hospitalization, polymerase chain reaction (PCR)-confirmed infection, pulmonary infiltrates on chest radiography, or SpO_2 < 94% on room air or requirement for supplemental oxygen or need for mechanical ventilation. Among the exclusion criteria were pregnancy and creatinine clearance < 30 mL/min. The analysis included 1,059 patients.

Patients were enrolled a median of nine days after symptom onset. The median time to recovery was 11 days (95% confidence interval [CI], 9 to 12 days) in remdesivir recipients and 15 days (95% CI, 13 to 19 days) in those assigned placebo. The calculated rate ratio for recovery was 1.32 (95% CI, 1.12 to 1.55; $P < 0.001$). The median time to recovery was calculated from the day of enrollment to the first day when one of the following occurred: the patient was hospitalized but no longer required oxygen or the patient was not hospitalized either with or without a supplemental oxygen requirement and/or activity limitation.

The day 14 Kaplan-Meier mortality estimates for those receiving remdesivir was 7.1%, while it was 11.9% among placebo recipients, giving a hazard ratio for death of 0.70 (95% CI, 0.47 to 1.04). Remdesivir was well tolerated. Further analysis through day 28 is pending.

In a separate trial, Goldman and colleagues examined whether 10 days of remdesivir administration was superior to five days of therapy in an open-label, randomized trial in 397 hospitalized patients with confirmed infection, radiological evidence of pneumonia, and SpO_2 < 94% on room air. After adjustments for imbalances in illness severity at randomization, there was no overall significant difference in outcomes between the two durations of therapy.

On June 1, 2020, the pharmaceutical sponsor, Gilead, announced the results of a yet unpublished trial in which 584 patients with moderate disease (X-ray evidence of pneumonia and SpO_2 > 94%) were randomized (1:1:1) to standard of care, or to five days or 10 days of remdesivir treatment. They reported that "compared with those who received standard care, patients in the five-day remdesivir group were 65% more likely to show clinical improvement at day 11 (OR [odds ratio] = 1.65; 95% CI, 1.09-2.48). They also determined that patients in the 10-day remdesivir treatment group had increased odds of clinical improvement at day 11 compared to those who received usual care, but the observed increase was not statistically significant (OR = 1.31; 95% CI, 0.88-1.95)."

Finally, Grein and colleagues reported the results of the Gilead remdesivir compassionate use program for patients with severe disease (57% receiving mechanical ventilation) and noted clinical improvement in 36 of 53 (68%). The mortality rate was 13%, with six of 34 (18%) patients receiving invasive ventilation dying, while only one of 19 (5%) not requiring mechanical ventilation died. The drug was well tolerated.

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All of these reports indicate that remdesivir is well tolerated, but only two compared treatment with this drug to placebo, thus allowing an assessment of efficacy. The study by Wang and colleagues failed to find benefit of remdesivir, but the study's power (58%) was severely limited because of its early discontinuation because of a lack of enrollment. Thus, it failed to answer the question of efficacy. The NIAID trial by Beigel and colleagues demonstrated a significant, albeit moderate, benefit of remdesivir relative to placebo in patients with severe disease. While the drug's use hastened time to recovery by approximately 30%, its effect on mortality failed to achieve statistical significance, although it came close, with the upper limit of the 95% confidence interval being 1.04. However, this study was analyzed

before all the data were available, and there will be further word on this trial.

The randomized trial by Goldman and colleagues contributed useful information in demonstrating that, overall, there was not a significant benefit of 10 vs. five days of therapy (although there was a hint that 10 days may have been better in patients receiving extracorporeal membrane oxygenation or mechanical ventilation). Remdesivir was well tolerated in all the studies. Finally, the unpublished randomized trial noted earlier is reported to have found a benefit from remdesivir treatment in patients with moderately severe COVID-19. However, the reason for possibly greater benefit from a five-day treatment course relative to 10 days of therapy is puzzling.

Thus, the efficacy and safety of remdesivir in the treatment of COVID-19 patients has been demonstrated. Although the effect was perhaps more modest than one might hope, this nucleotide analog is, at least for now, the (only) treatment of choice for patients with this infection. It also should be kept in mind that earlier initiation of treatment may prove more beneficial — the median intervals from symptom onset in the two placebo-controlled trials were 10 and nine days.

The current formulation of remdesivir must be administered intravenously, and, apparently, there is no plan for an oral formulation for technical reasons. However, Gilead has indicated that they are developing a formulation suitable for inhalation, which will be the subject of future studies. ■

ABSTRACT & COMMENTARY

Macrolides During Pregnancy — Behind the Headlines

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Despite published concerns, there is no good evidence that macrolide use during pregnancy causes birth defects.

SOURCE: Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: Population based cohort study. *BMJ* 2020;368:m331.

The macrolide antibiotics, erythromycin, clarithromycin, and azithromycin, are used commonly during pregnancy. However, safety concerns have been raised.

Thus, Fan and colleagues reviewed data from a large cohort of primary care patients, including, in fact, approximately 7% of people in the United Kingdom. This database is thought to be representative of the diverse population of the United Kingdom. Children born from January 1990 through June 2016 were included if they were registered within six months of birth. Stillborn babies were excluded, as were babies with known genetic syndromes and offspring of mothers who received a "known" teratogen during pregnancy.

Fan and colleagues looked particularly at those mothers who received a prescription for a macrolide between the fifth and final weeks of their gestation. Comparison groups included those who had been treated with penicillin, those who had received a macrolide or a penicillin prescription between 50 and 10 weeks prior to the pregnancy, and siblings of the children included in the study cohort.

The primary outcome measures were malformations and neurodevelopmental disorders (cerebral palsy, epilepsy, attention deficit disorder, and autism spectrum disorder). There were 1,071,379 live births in the database during the study period, and 726,274 had adequate data for inclusion without meeting exclusion criteria. (Most of the excluded subjects were excluded because adequate pre-pregnancy data were not available to complete all aspects of the study.) A total of 621,669 were excluded since they did not receive antibiotics during pregnancy. For comparison, that left 104,605 who had received a macrolide or penicillin, and comparison groups of 82,314 who had received a macrolide or penicillin prior to pregnancy and 53,735 siblings of treated mothers. Of the treated cohort, 24,714 were treated in the first trimester, and 79,891 were treated during subsequent

trimesters. Penicillin antibiotics were given approximately 10 times as often as macrolides.

Major malformations were seen in 27.7 per 1,000 children born to mothers who had received a macrolide in the first trimester and in 17.7 per 1,000 children of the mothers who received a penicillin during the first trimester. Corresponding prevalence rates for the subsequent two trimesters of pregnancy were 19.5 for macrolides and 17.3 for penicillins. Specifically, cardiovascular malformations were seen in 10.6 per 1,000 live births for macrolides vs. 6.6 for penicillins. Genital malformations, such as hypospadias, were reportedly more common with macrolide use than with penicillin use in all trimesters. Based on these data, the authors proposed that, until further data are available, macrolide use in pregnancy be replaced by the use of other antibiotics whenever feasible.

■ COMMENTARY

Fan and colleagues did a rigorous retrospective study to determine whether macrolide use during pregnancy is associated with increased risks for birth defects and neurodevelopmental problems in the children born to macrolide-treated mothers. The study had a large enough population base to be adequately powered to identify relevant risks. The investigators wisely used several different comparison groups to help readers infer risks actually due to macrolide use, as opposed to other coincident pregnancy-related situations. They concluded that: "prescribing macrolide antibiotics during the first trimester of pregnancy was associated with an increased risk of any major malformation," and, "macrolide prescribing in any trimester was associated with an increased risk of genital malformations." Their work has already prompted a published warning about macrolide use during pregnancy in the nursing literature.[1]

If true, these conclusions should prompt "caution" and a decision to use alternative antibiotics "if feasible," as the authors suggested. However, several thought processes cast doubt on the appropriateness of the published conclusions.

As originally published, the paper suggested that the authors' recommendation to restrict the use of macrolide antibiotics during pregnancy was in line with published British guidelines. However, as noted in a correction subsequently published online, those British guidelines actually had merely advised to use macrolides only when the benefit outweighs the risk,[2] similar to guidelines for any medication. The authors concluded that macrolide use "in any trimester" was associated with the risk of malformations. This conclusion runs counter to consideration of plausibility. The malformations evaluated, specifically genital malformations such as hypospadias, result from alterations in fetal development taking place early in pregnancy. Genital structures are already formed before the third trimester,[3] and it is not plausible that a treatment in the third trimester could reverse aspects of formation/development that are completed already. Nonetheless, Fan and colleagues used their data to conclude that second- and third-trimester exposure to macrolides does increase the risk of hypospadias.

In addition, Fan and colleagues reached their "any trimester" conclusions when combining data from each trimester. When there was a strongly significant statistical association during one part of pregnancy, statistical significance ($P < 0.05$) still was present when including data from trimesters during which there was no significant difference. Such was the case with genital malformations, mostly hypospadias, when the researchers found a "significant" P value in one trimester and then combined data from the other trimesters to conclude that the "risk" related to all trimesters.

Statisticians also would remind us that "statistical significance" actually just means that there is more than a 5% chance of a meaningful difference between groups. When 20 different unassociated variables are evaluated, one would expect, statistically, that at least one of those variables would rank in that "$P < 0.05$" significance range. Fan and colleagues made scores of comparisons, without using a Bonferroni or other "correction factor" in testing significance, and found only a very small number that "reached significance." It is possible that the identified risk of 10.6 per 1,000 incidence of cardiac malformations with macrolide use during the first trimester, compared to a 6.6 per 1,000 incidence in penicillin-treated mothers ($P = 0.03$), with a total of 172 incident cases among the whole database, was the result of the "random chance" of finding some variables with low P values when testing scores of factors. Similarly, it is not surprising that an apparently random "risk" was found (with a P value of 0.018) of urinary malformations in siblings of children whose mothers received macrolides vs. penicillin during pregnancy.

Of course, one could wonder if the illness prompting antimicrobial use, rather than the antimicrobial itself, might have triggered the risk of poor fetal outcomes. Wisely, Fan and colleagues provided indication-based data about their findings. In a supplemental table, they showed that macrolide vs. penicillin use for respiratory infections during the first trimester was associated only with a risk of cardiac malformations (95% confidence interval for risk, 1.05-2.51).

However, there was no increased risk specifically for ventricular septal defects, atrial septal defects, or patent ductus arteriosus. Also, there was no difference in risk between these groups for other malformations or other poor neurodevelopmental outcomes.

In fact, the clearly negative findings of this study are valuable. Macrolide use in pregnancy was not associated with any risk of cerebral palsy, autism spectrum disorder, attention deficit hyperactivity disorder, or epilepsy. In a recent meta-analysis, macrolide use during pregnancy had only a "weak association" with any risk of congenital malformations, and that was only with first-trimester exposure and with either gastrointestinal or musculoskeletal malformations.[4] A separate systematic review published last year by Fan and colleagues found hints only of macrolide-related risk of miscarriage, cerebral palsy, epilepsy, and gastrointestinal malformations — but not other malformations, stillbirths, or neonatal deaths.[5]

Interestingly, 25% of the 726,274 children in this study were exposed to prenatal macrolides or penicillins, and an additional 7% were exposed to other antibiotics. Thus, approximately one-third of women received antibiotic treatment during pregnancy. For those for whom an indication for antimicrobial therapy was identified in the medical record, 75% were treated for respiratory infections. One reasonably could wonder if bacterial respiratory infections truly required antimicrobial treatment in such a large proportion of pregnant women. Doubt about all the treatment actually being necessary certainly adds support to the notion that antimicrobials should be used judiciously and only when truly indicated, whether or not specific risks of treatment are identified.

Thus, these new data from Fan and colleagues provide significant reassurance about problems that are likely not due to macrolide use during pregnancy. They do not provide evidence of much significant risk for even cardiac and genital malformations being due to macrolide use. At the same time, these new data do provide good reminders that antimicrobials should be used judiciously during pregnancy. ■

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ABSTRACT & COMMENTARY

Monotherapy of *Pseudomonas aeruginosa* Bacteremia — Which β-Lactam Antibiotic Is Best?

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: No significant difference in the mortality of patients with *Pseudomonas aeruginosa* bacteremia was seen regardless of treatment with a carbapenem, ceftazidime, or piperacillin-tazobactam. However, the emergence of resistance occurred significantly more frequently in those treated with a carbapenem — largely related to imipenem use.

SOURCE: Babich T, Naucler P, Valik JK, et al. Ceftazidime, carbapenems, or piperacillin-tazobactam as single definitive therapy for *Pseudomonas aeruginosa* bloodstream infection: A multisite retrospective study. *Clin Infect Dis* 2020;70:2270-2280.

Babich and colleagues retrospectively evaluated the outcomes of β-lactam monotherapy in 767 adults with monomicrobial *Pseudomonas aeruginosa* bacteremia at 25 centers in nine countries during 2009-2015. Patients treated with carbapenems (meropenem or imipenem), ceftazidime, or piperacillin-tazobactam (PT) were included in the analysis.

Of the 767 patients, 134 (17.5%) died from any cause within 30 days. The all-cause 30-day mortality did not differ significantly by treatment group: 37/213 (17.4%) for ceftazidime, 42/210 (20%) for carbapenems, and 55/344 (16%) for PT. Multivariate analyses of the entire cohort, as well as a propensity score-adjusted cohort of 542 patients, identified several significant risk factors, including functional capacity, being bedridden at baseline, high Charlson comorbidity index, higher sequential organ failure assessment (SOFA) score, and others. Having the urinary tract as the source of bacteremia was protective, while the choice of β-lactam for definitive monotherapy was not significantly associated with mortality.

There was no significant difference between treatment groups in secondary outcomes, including seven-day mortality and clinical or microbiological failure. The latter was defined as persistence or re-isolation of the same bacteria/phenotype (as determined by the antibiotic susceptibility profile if bacteria were not identified) in blood 48 hours or more after definitive treatment initiation and within 30 days of index infection. Microbiological failure occurred in 11.2%, 15.7%, and 11.4% of those treated with ceftazidime, carbapenems, and PT, respectively. There also was no significant difference in adverse events.

Despite the finding that there was not a significant difference in microbiological outcomes by treatment type, carbapenem use was associated with a significantly greater incidence of the emergence of resistance to any antipseudomonal. This largely was associated with imipenem rather than meropenem, occurring in 17.5% of carbapenem recipients overall, but in 12 of 44 (27.3%) of those who received imipenem and 24/162 (14.8%) of meropenem recipients. Resistance occurred in 12.4% of those given ceftazidime and 8.4% of those treated with PT (P = 0.007).

■ COMMENTARY

Although there are published exceptions, a number of retrospective studies have failed to demonstrate that combination therapy is superior to monotherapy in the treatment of *P. aeruginosa* bacteremia. Thus, now it is generally recommended that patients with monomicrobial *P. aeruginosa* bacteremia be treated with a single active β-lactam antibiotic. The study reviewed here asks the next logical question — which β-lactam antibiotic? This large, multicenter, international trial found no difference in mortality or in a number of secondary outcomes in a comparison of treatment with carbapenems, ceftazidime, or PT.

The emergence of resistance to carbapenems has been a matter of concern. Thus, a systematic review found an increased risk of the emergence of resistance in patients with *Pseudomonas* pneumonia who were treated with imipenem compared to various other agents.[1] However, in a separate retrospective comparison of 88 patients with ventilator-associated pneumonia due to *P. aeruginosa*, investigators found no significant difference in such emergence in patients treated with imipenem, meropenem, or doripenem.[2]

Babich and colleagues found a greater incidence of the emergence of resistance to any antipseudomonal antibiotic in association with carbapenem treatment compared to treatment with ceftazidime or PT. They concluded that the latter two agents are preferred. However, the observed increased risk of resistance clearly was associated with imipenem use, not meropenem use. Also clouding the interpretation of the results is the fact that the investigators did not specify the antibiotics to which resistance emerged. ■

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ABSTRACT & COMMENTARY

Contact Isolation Is Not Better than Standard Precautions for Decreasing Acquisition of ESBL-Producing Enterobacterales

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

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

SYNOPSIS: In a multicenter, cluster-randomized crossover trial, researchers compared standard precautions vs. contact isolation for preventing acquisition of ESBL-producing Enterobacterales (ESBL-E) in non-intensive care unit settings. Contact isolation did not decrease the number of hospital-acquired ESBL-E cases, which questions the value of the practice.

SOURCE: Maechler F, Schwab F, Hansen S, et al. Contact isolation versus standard precautions to decrease acquisition of extended-spectrum β-lactamase-producing Enterobacterales in non-critical care wards: A cluster-randomised crossover trial. *Lancet Infect Dis* 2020;20:575-584.

Healthcare facility-acquired infections increase morbidity, mortality, and healthcare costs. They also can hurt the reputation of healthcare institutions. Numerous guidelines and regulatory agencies have recommended contact isolation for antimicrobial-resistant bacteria, including extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E). Maechler et al sought to determine whether contact isolation had any benefit over standard precautions to prevent the transmission of ESBL-E in patients not in intensive care units (ICUs).

The study was conducted in four European countries: Germany, the Netherlands, Spain, and Switzerland. It was a cluster-randomized crossover trial that included adult patients admitted to general hospital wards. Medical, surgical, or combined medical-surgical wards were randomized to continue with standard precautions alone or to implement contact isolation for 12 months, followed by a one-month washout period, then 12 months of the alternative strategy. Researchers obtained rectal swabs for ESBL-E for enrolled patients on admission, once a week thereafter, and on discharge. Investigators collected ward-level data, including protocol adherence, hand hygiene compliance, and antibiotic consumption. The primary outcome was the incidence density of colonization or infection with ESBL-E, defined as the acquisition rate per 1,000 patient-days at risk at the ward level among patients with a length of stay of more than one week. Acquisition of ESBL-E carriage was defined as recovery of ESBL-E isolates from clinical or surveillance cultures after hospital day 3 following an initial negative culture.

There were 11,368 patients screened twice and, therefore, included in the per-protocol analysis. The incidence density of ESBL-E acquisition was 6.0 events per 1,000 patient-days at risk (95% confidence interval [CI], 5.4-6.7) for contact isolation vs. 6.1 events per 1,000 patient-days at risk (95% CI, 5.5-6.7) for standard precautions (P = 0.971). A multivariable analysis adjusted for length of stay, percentage of patients screened, and prevalence in first screening cultures found an incidence rate ratio of 0.99 (95% CI, 0.8-1.22; P = 0.917) for contact isolation vs. standard precautions. Antibiotic consumption at the ward level did not differ between intervention protocols. Moreover, there was no difference in acquisition of ESBL-producing *E. coli* (which made up 73% of cases) and *K. pneumonia* between contact isolation and standard precautions. Healthcare worker compliance with hand hygiene and glove and gown use was similar between the intervention periods.

■ COMMENTARY

The concern that patients harboring ESBL-E might contaminate the hospital environment, potentially exposing immunocompromised patients, has been a controversial issue during the past decade. It is well-known that contact isolation requires extra effort and resources, along with potential negative effects on patient satisfaction and safety. Indeed, the need to conserve personal protective equipment (PPE) is particularly salient in light of the COVID-19 pandemic. The study by Maechler et al provides convincing evidence that contact isolation does not reduce acquisition of ESBL-E in general wards compared to standard precautions. This observation makes sense from a molecular epidemiological perspective, since a recent study that used whole-genome sequencing found ESBL-producing *E. coli* have a low transmission frequency.[1]

The study has a couple of limitations. First, it was conducted in general hospital wards, so the findings might not be applicable to the ICU setting. However, the known difficulties with contact isolation still would be present, while potential benefits remain uncertain. Second, the delay in laboratory turnaround time in reporting ESBL-E positive samples (median four days, range three to five days) led to delays in implementing contact isolation. Third, the surveillance screening may have missed some of the ESBL-E carriers. This would have resulted in patients being misclassified as having ward-acquired ESBL-E later in their stay. Fourth, it is conceivable that healthcare workers taking care of ESBL-E positive patients assigned to standard precautions may have treated them differently than other patients without ESBL-E. Finally, evidence suggests that patient-to-patient transmission is not the main pathway for the spread of ESBL-E. Instead, acquisitions outside the hospital or selection pressure (i.e., antibiotic use) are more likely to be the major routes of ESBL-E transmission.

Is this study the nail in the coffin for contact isolation to prevent ESBL-E transmission? It appears so, at least for patients on general hospital wards. Further

investigation of preventing ESBL-E transmission in ICUs with contact isolation using a similar study design seems warranted. But this study should result in changes to future infection prevention guidelines and current hospital policies. ■

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ABSTRACT & COMMENTARY

IDSA Sepsis Committee and SEP-1 Quality Measures

By Dean L. Winslow, MD, FACP, FIDSA, FPIDS

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SYNOPSIS: The IDSA Sepsis Committee proposes that The Centers for Medicare & Medicaid Services' Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) should be applied only to septic shock, not sepsis without shock.

SOURCE: Rhee C, Chiotos K, Cosgrove SE, et al. Infectious Diseases Society of America Position Paper: Recommended revisions to the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) sepsis quality measure. *Clin infect Dis* 2020; May 6. doi: 10.1093/cid/ciaa059. [Online ahead of print].

The Infectious Diseases Society of America (IDSA) Sepsis Committee's position statement included the following concerns:

1. The National Severe Sepsis and Septic Shock Early Management Bundle's (SEP-1) requirement to immediately administer antibiotic therapy for all patients with possible sepsis risks, increasing excessive and unwarranted antibiotic administration.
2. SEP-1 conflates the urgency of antibiotic administration for sepsis and septic shock.
3. Bundle studies supporting SEP-1 are at high risk for bias and likely overestimate benefits.
4. The definition for time zero is complex, subjective, and not evidence-based.
5. Mandating lactate measurements for all patients with possible sepsis is inappropriate.

IDSA recommends the following changes to SEP-1:

1. Sepsis without shock should be removed from SEP-1.
2. Obtaining blood cultures before administering antibiotics should remain part of SEP-1.
3. The interval from septic shock time zero to initiation of broad-spectrum antibacterial therapy should be one hour or less.
4. SEP-1 should require hospitals to report time intervals.
5. Lactate measurements should be removed from SEP-1.

■ COMMENTARY

There is no question that modern management of sepsis and septic shock has improved outcomes over the past two decades. The major recommendations that came from the important papers on sepsis management and early goal-directed therapy (and have withstood the test of time) emphasized timely administration of antibiotics and adequate volume resuscitation in conjunction with the use of vasopressors and general supportive care. The Society of Critical Care Medicine has taken the lead on developing specific standards in the context of The Surviving Sepsis Campaign. Although members of the IDSA participate on the committee along with pulmonary and critical care medicine specialists, some irreconcilable differences arose during the 2017 revision, prompting IDSA to publish its concerns.[1]

An important concern that many infectious disease specialists have is that these guidelines are codified as bundles tied to national reporting of hospitals' quality measures (and reimbursement). Because of the nonspecific nature of "sepsis," many patients' non-bacterial infections and noninfectious illnesses often trigger the sepsis bundles. Unfortunately, adherence to these quality measures is not optional, and clinicians feel obligated to follow these guidelines to avoid being "dinged."

A classic case I cared for exemplified many of the problems of rigid adherence to sepsis bundles. The patient was a 90-year-old woman with hypertension and heart failure with preserved ejection fraction who had been confirmed to have influenza A the day before by polymerase chain reaction (PCR) and had been started on oseltamivir. However, she developed wheezing and was transported from a skilled nursing facility to the emergency department. She was mildly febrile and tachycardic, and her blood pressure was 190/100 mmHg. She was wheezing and had bibasilar crackles. Her chest X-ray was suggestive of heart failure, but without evidence of pneumonia. Her white blood cell count was elevated. An intravenous line (IV) was started and she was given albuterol by nebulizer.

Because the constellation of findings triggered "the sepsis bundle," she had a blood lactate drawn (which was now elevated because of the inhaled beta agonists she had just received). Even though bacterial sepsis was unlikely, she was slammed with IV vancomycin + piperacillin/tazobactam and given 2.1 liters of IV normal saline. By the time my inpatient team and I came down to the ED to admit her, she was in florid pulmonary edema, and we needed to give her IV furosemide and she required bilevel positive airway pressure (BiPAP) for a few hours. We also stopped her antibiotics.

When I gently chastised the house staff, they said that they agreed this treatment was inappropriate, but they did not want to get "dinged" if they did not follow the bundle. IDSA's position paper is published to help persuade The Centers for Medicare & Medicaid Services to make appropriate modifications to SEP-1 so that the helpful aspects of the bundle are preserved but we do not hurt patients with inappropriate treatment. ■

REFERENCE

1. IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) Position Statement: Why IDSA did not endorse the Surviving Sepsis Campaign Guidelines. *Clin Infect Dis* 2018;66:1631-1635.

ABSTRACT & COMMENTARY

Ceftriaxone-Resistant *Salmonella* Typhi in the United States Associated with Travel to or from Pakistan and Iraq

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Typhoid fever resulting from antibiotic-resistant strains is being imported from Pakistan and Iraq.

SOURCE: François Watkins LK, Winstead A, Appiah GD, et al. Update on extensively drug-resistant *Salmonella* serotype Typhi infections among travelers to or from Pakistan and report of ceftriaxone-resistant *Salmonella* serotype Typhi infections among travelers to Iraq — United States, 2018-2019. *MMWR Morb Mortal Wkly Rep* 2020;69:618-622.

In November 2016, infections due to extensively drug-resistant (XDR) *Salmonella enterica* serotype Typhi emerged in Hyderabad, Pakistan, with rapid spread to the megalopolis of Karachi, where the population is approaching 15 million. XDR Typhi is defined by the presence of resistance to ceftriaxone, ampicillin, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole. The Centers for Disease Control and Prevention (CDC) subsequently initiated enhanced surveillance for ceftriaxone-resistant *Salmonella* Typhi in the United States in March 2018.

The CDC identified 30 (31%) XDR infections among 96 Typhi infections in U.S. travelers to or from Pakistan from Jan. 1, 2016, to Aug. 31, 2019. The patients ranged in age from 1 to 41 years (median 11.5 years). The majority had visited Sindh province (which contains Hyderabad and Karachi), but 40% had visited only Punjab province. Among the 24 patients for whom the information was available, none had received typhoid vaccination within the previous five years.

During surveillance, in November 2018 the CDC identified a ceftriaxone-resistant Typhi isolate with a distinctly different antimicrobial susceptibility pattern. Although it was resistant to ceftriaxone, ampicillin, and nalidixic acid, it had intermediate susceptibility

to ciprofloxacin and remained fully susceptible to other tested antibiotics, including chloramphenicol and trimethoprim-sulfamethoxazole. The CDC subsequently identified nine additional isolates with similar susceptibility patterns. None of the 10 patients (eight from the United States and two from the United Kingdom) had traveled to Pakistan, but eight of them had traveled to Iraq and one had traveled to Iran. One infant had not traveled, but her asymptomatic father had traveled to Iraq. Of the six patients for whom the information was available, none had received typhoid vaccination prior to travel.

Whole genome sequencing determined that these latter isolates, three of which were tested, were genetically distinct from those associated with travel to Pakistan. Although ceftriaxone resistance to both strains was caused by $bla_{\text{CTX-M-15}}$ carried by an IncY plasmid, the plasmids were not closely related. All Typhi resistant to ceftriaxone in the United States retained susceptibility to both azithromycin and meropenem.

■ COMMENTARY

The authors pointed out that no ceftriaxone-resistant *Salmonella* Typhi had ever been isolated within the United States prior to 2018. The 33 cases associated with travel to or from Pakistan are the consequence of the ongoing outbreak of XDR Typhi in that country. As of August 2019, there had been approximately 10,000 cases reported in Sindh province. This resulted in the administration of a novel conjugate typhoid vaccine to 9.4 million children in November 2019. While that effort was implemented in Sindh province, the fact that eight of the 33 cases occurred in relation to or from to areas of Pakistan outside that province is an indication that the outbreak has spread.

In addition to this problem, the identification of a genetically different ceftriaxone-resistant strain of Typhi in association with travel to Iraq (and in one case, Iran) raises further concern. Ceftriaxone resistance in this and the Pakistan-related strain was due to an extended-spectrum β-lactamase carried on a mobile plasmid — making spread of this resistance more likely.

An important lesson: None of the individuals in this report for whom the information was available had undergone vaccination in the years prior to travel. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Let's Not Shake on This

SOURCE: Pinto-Herrera NC, Jones LD, Ha W, et al. Transfer of methicillin-resistant *Staphylococcus aureus* by fist bump versus handshake. *Infect Control Hosp Epidemiol* 2020 May 27;1-3. [Online ahead of print].

Not only am I missing the smiles and facial greetings of recognition as I walk down the corridors of the hospital but, in the COVID era, the basic handshake also has been "masked." The origin of the handshake is thought to extend back to the 5th century B.C. in Greece to show you had laid down your weapons as a gesture of peace. As the *National Post* once wrote, "The handshake is one of the highest forms of symbolic currency with the power to unite, divide, seal deals, and broker peace. … It is also a 'universal norm of reciprocity' and its rejection sends a powerful message." Not to mention the "laying on of hands" that usually conveys healing and reassurance. And yet, face-to-face with a new patient and her husband in "reality clinic" (vs. virtual clinic), I realized that, not only could they not see half of my face, nor I theirs, but was I supposed to shake their hands? Apparently not. Later in the morning, one elderly couple was wearing gloves — do you shake gloved hands? My usual currencies of communication with patients had been mucked with.

I have never really thought about a handshake as a hazard, although we touch patients all the time, and hands are a leading source of transmission of micro-organisms in the hospital. My hand was now perceived as a threat.

These authors examined the risk of transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) with a standard handshake, with and without 2 mL of alcohol hand sanitizer, as well as the exchange of bacteria from a "fist bump" and something called a "cruise tap" (when the first knuckle of each hand is tapped). The fist bump has been proposed as a way to extend a hand in greeting while minimizing skin-to-skin contact.

A convenience sample of 50 patients with known MRSA colonization was selected — and the recipient wore a sterile glove, which was then directly

imprinted onto BBL CHROMagar with cefoxitin. Remarkably, a similar frequency of MRSA transfer was observed with the traditional handshake and the fist bump (22% vs. 16%, respectively). However, the risk of transfer was less frequent with the cruise tap (8%). Transfer of MRSA to a gloved hand was significantly reduced by the preemptive use of hand sanitizer (6%).

The 50 patients included 20 residents of long-term care facilities (49%); 31 (62%) had limited mobility, and 25 (50%) had parenteral catheters or indwelling urinary catheters. Only three (6%) reported regular use of hand sanitizer.

The Tricky Business of Treating Early Cocci

SOURCE: Galgiani JN, Blari JE, Ampel NM, Thompson GR. Treatment for early, uncomplicated coccidioidomycosis: What is success? *Clin Infect Dis* 2020;70:2008-2012.

No one disputes the need for treatment of coccidioidomycosis with more severe manifestations of infection (such as progressive necrotizing pulmonary infection or evidence of lymphatic or hematologic spread). Most clinicians offer antifungal therapy to people with early pulmonary infection and compromised cellular immunity, even before more severe manifestations occur. But throughout my career in infectious disease, there still are no good data on the treatment of newly diagnosed symptomatic pulmonary infection in immune competent people.

It is well-recognized that, before the availability of the azoles, a good number of such infections would resolve on their own, without specific antifungal therapy. But since the introduction of the azoles, experts remain divided on the risks and benefits of treatment for early symptomatic pulmonary cocci infection. Some experts advocate that the benefits of fluconazole therapy outweigh the risks, and all such patients should receive treatment, if only to prevent subsequent complications in a few. Others advocate for an individualized approach, based on features of more severe infection. And others argue that early initiation of treatment in otherwise healthy people may blunt the immune system response to infection, and perhaps even increase the risk for later complications.

Certainly, as one stuck in the middle of these arguments, it often is difficult to decide on the duration of treatment in patients with more troubling and persistent symptoms, and the occurrence of late-onset dissemination in some raises questions. Current Infectious Diseases Society of America guidelines recommend (at most) three to six months of fluconazole 400 mg daily, and treatment can be successfully stopped in those whose pulmonary process has resolved, with no evidence of dissemination.

This helpful article from Dr. Galgiani, a renowned expert on cocci infection, provides some guidance to clinicians struggling with treatment decisions in patients with early symptomatic cocci infection. It is important to distinguish (confidently) between signs and symptoms of ongoing fungal replication and progressive infection vs. common side effects observed in many patients and manifestations of a host immunologic response.

Evidence of ongoing fungal replication or dissemination, which warrants continued treatment, includes progression of pulmonary lesions and cavitation, cutaneous ulceration, subcutaneous abscess formation, lytic bone involvement, active joint infection as manifested by joint effusion and synovitis, and abnormal cerebrospinal fluid (CSF) parameters consistent with meningitis. Histopathologic evidence of continued inflammation, neutrophilic infiltrate, and/or eosinophils and tissue destruction should be taken as evidence of active infection. Beyond these more obvious severe manifestations of infection, Dr. Galgiani adds that extension of azole therapy > 6 months may be considered in other, more unusual circumstances, such as more extensive infiltrate, a pulmonary lesion adjacent to a major blood vessel, new-onset hemoptysis near the end of treatment, or possibly for a frail, elderly patient who is slow to respond to treatment.

In contrast, manifestations of immunologic response, likely secondary to immune complex deposition, such as arthralgias and other rheumatologic signs (e.g., erythema nodosum, elevation in sedimentation rate) commonly occur during the course of infection. Although they may be severe, and even disabling, they are not markers of worsening infection and do not warrant an extension of therapy. The peak onset of arthralgias is ~20 weeks after initial infection. They typically involve the lower extremities, or occasionally the wrists, in a symmetric fashion, but do not lead to synovitis or joint destruction. Similarly, persistent fatigue, malaise, and headache (without evidence of abnormal CSF) are observed commonly in cocci infections, and are not to be attributed to worsening infection.

Finally, to make matters even more confusing, while quantitative complement fixation antibodies can

help to guide therapy, rising titers can be observed in a subset of patients either during successful therapy or months or years later, and by themselves do not necessarily mean the patient is failing therapy or relapsing. Similarly, many patients continue to have detectable titers at the completion of successful therapy, so waiting for an undetectable titer, or even a stable serofast one, is not a requirement for stopping treatment.

On-Site Rapid Detection of Bacteriuria

SOURCE: Michael I, Kim D, Gulenko O, et al. A fidget spinner for the point-of-care diagnosis of urinary tract infection. *Nat Biomed Eng* 2020 May 18. doi: 10.1038/s41551-020-0557-2. [Online ahead of print].

These authors engineered a diagnostic fidget spinner for the rapid detection of bacteriuria in a small 1 mL sample of undiluted urine, which can be used on site and does not require electricity. This clever device is basically a hand-held centrifuge, which concentrates pathogens by > 100-fold with only 12 manual spins of the device. The team incorporated a colorimetric assay, with gradual changes in an orange coloration, to allow for semi-quantitative assessment of bacterial load (1,000 to > 100,000 colony forming units per mL).

The spinner assessment of bacterial load was validated in 39 patients with clinical symptoms of urinary tract infection, and was compared with culturing (which generally takes two to three days for final results). The authors also demonstrated the same colorimetric technique could be used for a down-and-dirty bacterial susceptibility assessment. By adding ciprofloxacin or cefazolin to the sample, if the bacterial colony counts diminished, they inferred that the bacteria present were susceptible. ■

CME QUESTIONS

1. Which of the following is correct regarding remdesivir therapy for patients with COVID-19?

a. It is poorly tolerated.

b. In an adequately powered study, it was associated with more rapid clinical improvement relative to placebo in patients with severe disease.

c. Ten days of therapy was shown to be superior to five days of therapy.

d. Based on already published data, its use is associated with a statistically significant reduction in mortality.

2. Which of the following is true regarding macrolide use in pregnancy?

a. It is strongly associated with epilepsy in exposed newborns.

b. It is associated with gastrointestinal malformations in exposed newborns.

c. It should be considered judiciously, as for any other antimicrobial agent.

d. It is contraindicated.

3. In the study by Babich and colleagues, which of the following is correct regarding treatment of patients with bloodstream infection caused by *Pseudomonas aeruginosa*?

a. Carbapenem use was associated with an increased risk of emergence of new resistance to antipseudomonal antibiotics.

b. Ceftazidime treatment was associated with significantly greater mortality than was treatment with a carbapenem.

c. Ceftazidime treatment was associated with significantly greater mortality than was treatment with cefepime.

d. Carbapenem treatment was associated with significantly greater mortality than was treatment with either ceftazidime or cefepime.

4. Which of the following is among the changes to SEP-1 quality measures recommended by the Infectious Diseases Society of America Sepsis Committee?

a. Greater emphasis should be placed on guideline adherence in patients with sepsis without shock than in those with shock.

b. The interval from septic shock time zero to initiation of broad-spectrum empiric antibiotic therapy should be three hours or less.

c. Continue current reporting of time intervals to initiation of antibiotic therapy.

d. Lactate measurements should be eliminated.

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