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Bacterial Coinfection in COVID-19 and Influenza Pneumonia

The crucial question at the time a patient is hospitalized for pneumonia is whether the infection is bacterial and, therefore, whether an antibiotic should be administered. Availability of highly sensitive PCR technology to identify a respiratory virus tells us whether a viral infection (most of which are as yet untreatable) is present but does not answer the question of whether a patient has bacterial coinfection (1).

In this issue of the *Journal*, the European Multicenter Comparative Clinical Trial by Rouzé and colleagues (pp. 546–556) retrospectively compares the frequency of bacterial coinfection in patients requiring ICU care for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza virus (2). The subject is of great interest as well as of practical importance. Pfeiffer discovered *Haemophilus influenzae* during an influenza outbreak in 1892, and by 1918, *Haemophilus*, *Streptococcus pneumoniae*, and *S. pyogenes* were well recognized as prominent bacterial coinfecting organisms in influenza. Morens and colleagues (3) restudied all available evidence in persons who died of influenza in the 1918–1919 pandemic, reporting evidence of secondary bacterial infection in "virtually all" patients. *Staphylococcus aureus* was added as an important coinfecting organism in the influenza epidemic of 1958 (3).

These findings have led physicians to use empiric antibiotics in patients admitted to the hospital for influenza. They have led me to redouble my efforts to determine the presence or absence of a bacterial coinfection, an approach I greatly prefer to empiricism. Influenza has widespread effects on bacterial clearance, adherence, and invasion (4, 5) and may or may not be unique among respiratory viruses in its association with bacterial coinfection—the question addressed in the study by Rouze and colleagues. One cannot be certain whether influenza is more highly associated or just more intensively studied than, for example, respiratory syncytial virus pneumonia.

When the SARS-CoV-2 pandemic began, the role of bacterial coinfection was undetermined. Patients were dreadfully ill, and physicians and ICU staff were dreadfully stressed. Antibiotics were used liberally, perhaps excessively (6), based in part on recommendations of the surviving sepsis campaign, which, it should be noted, was not endorsed by the Infectious Diseases Society of America (7).

Studies of bacterial coinfection in coronavirus disease (COVID-19) have reported a broad range of results (8–10). Their methods need to be examined carefully to understand the discrepancies, and the results need to be contextualized. For example, in one multicenter cohort study of 48,902 patients hospitalized for COVID-19 (8), microbiologic studies were done in 8,649 (17%), of which 1,107 (13% of those with microbiologic studies, 2% of the total number of patients) yielded positive cultures for a recognized pathogen. Only 318 (0.7% of the total) were obtained within 2 days of admission. No wonder the authors concluded that, "microbiologically confirmed bacterial infections are rare."

In contrast, a meta-analysis of 7,107 patients hospitalized with COVID-19 identified bacterial coinfection in 4.9% on admission and 16.0% on admission to an ICU (10). Although much higher than the former study (and still subject to all the same problems of numerator and denominator), these seemingly low proportions need to be considered in the context of the documentation of bacterial infection in community-acquired pneumonia (CAP), most of which we regard as (and treat for) bacterial infection. The CDC's prospective study of community-acquired pneumonia in adults identified a bacterial cause in only 17% of CAP (11). My identically designed but smaller and more

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rigorously controlled single-center study (12) found a bacterial cause in 30% of cases, a substantially greater yield. Subsequently, with meticulous quantitative microbiology and attention to the role of normal respiratory flora, I demonstrated a bacterial cause in 75% and a microbiologic cause in 95% of patients with CAP who were selected based on their ability to provide a high-quality sputum within 16 hours of admission (13). Twenty percent of all patients had documented bacterial and viral coinfection; thus, the finding of a respiratory virus by PCR does not mean that antibiotics need not be given. The generalizability of small studies is always open to question, and they will not provide sufficient numbers to compare bacterial coinfection with specific viral etiologies as done by Rouze and colleagues, but a potential flaw of large studies is that appropriate bacteriologic studies may simply not be done. Knowing how difficult it is to obtain valid specimens from patients admitted for pneumonia, I believe that the absence of microbiologic studies explains very low yields.

In the paper by Rouze and colleagues, 36 European ICUs retrospectively reviewed bacteriologic results in 10–20 consecutive patients with either COVID-19 or influenza who had been admitted to an ICU <48 hours previously and required mechanical ventilation. The goal was to identify bacterial coinfection as determined using standard culture-dependent methods, which is, in my opinion, an advantage over studies that use PCR of nasal secretions to identify bacterial coinfection (1). Thirty-four percent of patients with influenza versus only 10% of patients with COVID-19 had an identified bacterial pathogen. Although ICU admissions bias results toward more serious illness, respiratory specimens in intubated patients can be obtained in every case. Studies of COVID-19 and influenza were not contemporaneous, and the reader needs to presume that the rate of obtaining respiratory secretions for culture was similar in both periods. We also do not know in how many patients such cultures were done or the frequency or duration of prior antibiotic administration. In other words, the true rate of bacterial infection in both viral infections might be greater.

Nonetheless, I regard this as a very good study. The results are reliable and readily interpretable. There is no apparent bias toward one or the other virus, although the cases were not contemporaneous and practice patterns may have changed with the onset of COVID-19. The results show that bacterial coinfection is far less frequent in SARS-CoV-2 than in influenza pneumonia.

How should these findings affect our practice? First, they should remind us that obtaining respiratory secretions in any patient hospitalized for pneumonia should be a high priority for proper practice of intensive care. By policy, a respiratory sample should be sent when any patient with a pulmonary infiltrate is intubated for respiratory support. Once empiric antibiotics are given, a clock starts ticking, and after 16–18 hours the value of a negative culture falls off rapidly (14).

Second, microscopic examination of a Gram-stained specimen can be available within minutes. There is a strong tendency to wait 24–48 hours for results of culture and susceptibility to deescalate antibiotics. I have written for many years on the value of examining Gram-stained sputum (14) and finally documented, in a careful prospective study, the remarkable sensitivity and specificity of such examination in a high-quality sample (13). Pulmonary secretions from patients with viral pneumonia may be purulent and may contain as many white blood cells per milliliter as secretions from patients with bacterial pneumonia, but, absent large numbers of bacteria on microscopic examination, bacterial infection is simply not present; a telephone call to the microbiology laboratory might be very helpful in this regard.

Finally, if physicians remain skeptical about these microscopic observations, they still can discontinue antibiotics if cultures do not yield a pathogen, but proper reading of the Gram stain remains important in light of our recent finding (13) that so-called normal respiratory flora may cause up to 20% of CAP.

In summary, documentation of a viral infection does not, by itself, enable withholding of antibiotics because bacterial coinfection is common, albeit more so in influenza than in COVID-19. Efforts to rule in or out a bacterial etiology enables more focused care and limits excessive antibiotic use. ■

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Identifying Survivors of Sepsis at Risk for Adverse Cardiovascular Outcomes

For many years, infections have been recognized as precipitants of incident cardiovascular disease (1). Several epidemiologic studies have reported higher long-term risk of heart failure, myocardial infarction, stroke, coronary revascularization, and atrial fibrillation after viral illness, pneumonia, and sepsis (2–5). The mechanisms underlying the increased risk of cardiovascular disease after sepsis remain incompletely understood, and point-of-care approaches to identify high-risk patients who may benefit from targeted interventions are appealing and much needed.

In this issue of the *Journal*, Garcia and colleagues (pp. 557–565) analyzed the association between serum troponin levels and 1-year cardiovascular events in a multicenter cohort of 14,046 adult survivors of sepsis hospitalization who had no prior cardiovascular diagnosis (6). Patients were categorized into three tertiles based on peak troponin levels measured within the first 14 days of hospital admission, and their association with a composite cardiovascular outcome of atherosclerotic cardiovascular disease (defined as acute myocardial infarction, ischemic stroke, or coronary revascularization), acute heart failure, and atrial fibrillation was assessed. Among the 14,046 patients included in the primary analysis, 6,403 (45.6%) had an elevated troponin level. In unadjusted and multivariable analysis, elevated troponin levels were associated with a "dose-dependent" risk increase in incident cardiovascular events that ranged from 1.37-fold (95% confidence interval, 1.2–1.55) for the lowest tertile to 1.77-fold (95% confidence interval, 1.56–2.00) in the highest tertile. These findings remained robust across multiple sensitivity analyses that included using only patients without missing data (i.e., complete cases), using different imputation strategies for missing data, using troponin as a continuous variable instead of *a priori* defined tertiles, and exclusion of cardiovascular events that occurred during hospitalization. In addition, the authors used eValues to assess the potential effect of unmeasured confounders (7). For example, the eValue for the association of peak troponin in the highest tertile and 1-year cardiovascular events was 2.94, indicating that residual confounding could explain the observed association only if there existed an unmeasured covariate with a relative risk association of at least 2.94.

Numerous previous studies have demonstrated an increased risk of cardiovascular events in survivors of sepsis (2–5). However, many of these studies, particularly those using administrative data, were limited in their ability to identify preexisting cardiovascular disease. We commend Garcia and colleagues on their efforts to identify patients with preexisting cardiovascular disease. They leveraged the advantages of a large integrated healthcare system and performed a 5-year look back using outpatient and inpatient records to identify presepsis comorbidities in addition to 3 months of medication data to identify current use of antihypertensives, statins, and antiplatelet drugs. The data sources used to identify preexisting chronic disease and length of the look-back period are indeed important, as shorter look back periods and use of single data sources (e.g., inpatient or outpatient data) underestimate the prevalence of chronic health conditions and consequently overestimate the hazard of incident cardiovascular disease (8, 9). This is particularly relevant for atrial fibrillation, which is often missed even during periods of intensive monitoring (10).

One common critique of composite outcomes, which are more commonly used in cardiovascular clinical trials than not, is that individual components are often unreasonably combined, inconsistently defined, and inadequately reported, which makes their interpretation challenging (11, 12). In the current study, Garcia and colleagues used a composite endpoint of atherosclerotic cardiovascular disease, acute heart failure, and atrial fibrillation diagnosis. Of the 2,012 (14.3%) patients who experienced the outcome, more than two-thirds (1,425 or 70.8%) had a new diagnosis of atrial fibrillation, and among the complete case subgroup, 27.2% (2,164/7,965) had an episode of atrial fibrillation during hospitalization. New onset atrial fibrillation is the most common arrhythmia encountered in ICUs and particularly prevalent among patients with sepsis (10, 13). It is associated with increased length of stay and hospital death (14), but its significance for long-term mortality and implications for subsequent treatment are debated (15), perhaps because many view "this type" of atrial fibrillation as a distinct and reversible manifestation of critical illness with unique predisposing factors (16). Because persistent inflammation and immunosuppression are common among survivors of sepsis (17), cardiovascular outcomes such as atrial fibrillation should be studied in this context, and this approach may broaden the number of candidate treatment strategies beyond anticoagulation and rhythm control (18).

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