Challenging the One-Hour Bundle Goal for Sepsis Antibiotics

David A. Talan, MD*; Donald M. Yealy, MD

*Corresponding Author. E-mail: dtalan@ucla.edu.

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In this edition of *Annals*, Spiegel et al[1] address the lack of evidence supporting the 2018 Surviving Sepsis Campaign 1-hour care bundle.[2] That bundle sets septic care targets to occur within 1 hour of emergency department (ED) arrival. Spiegel et al discuss various aspects of the newest Surviving Sepsis Campaign bundle, including resuscitative approaches; we focus on the 1-hour antibiotic target. The basis for this antibiotic delivery goal rests with data supporting the notion that for each hour of delay for a septic patient, the risk of progression to worse forms of sepsis or death increases.

Although antibiotics save lives, this simple axiom of "antibiotics within 1 hour is best" approach oversteps the data. The Surviving Sepsis Campaign guidelines broadly characterize sepsis as a medical emergency, so it follows that the term "delay" is an event that shouldn't happen. Use of this term obscures the nonarbitrary reasons that effective antibiotics often start later; that is, the patients who get them later are different. Confounding the associations that support the notion of harm with any antibiotic delay in individuals with sepsis are coincident populations at risk of poor outcomes, including patients with subtle infection presentations (eg, chronically ill, multiple comorbidities) and those with infections resistant to usual initial antibiotics (eg, long-term care, previous hospitalization and antibiotics). These confounders can lead to the unintended but potentially erroneous assumption that specific time differences have precise effects on outcomes. Furthermore, the general association of treatment time to adverse outcomes may be nonlinear and not exist until many hours after treatment for most septic ED patients.

Kumar et al[3] first noted a potential link between timing of antibiotics and outcomes in a retrospective study of hypotensive septic inpatients. The authors observed approximately 80% survival if septic patients received in vitro–active antibiotics within 1 hour of the onset of hypotension, with a subsequent approximately 8% survival rate decrement with each additional hour to treatment. Although alluring, the treatment effect seems startlingly large, and the data in this 1989 to 2004 cohort may help inform why skepticism exists. Within the same study are footprints suggesting confounding; notably, the paradox of a lower survival rate (52%) among patients who received antibiotics *before* hypotension compared with those who received them within the first few hours of the onset of septic shock. Ascribing a biologic effect to antibiotics for either the improvement or the decreased survival is a problem endemic to observational or natural experiment designs, which are prone to these threats.

More recently, a study by Whiles et al[4] of 3,929 patients with severe sepsis noted an approximately 8% hourly incremental increased risk of progression to septic shock with longer time to antibiotics (Figure). Evidence of confounding again exists, along with the suggestion of a nonlinear relationship in the antibiotic time versus outcome relationship. There was little change in the progression to septic shock rate (ie, worsening) until after 5 hours, and by then, approximately 75% of patients had received antibiotics. That smaller, later-treated patient group—approximately 25% of the cohort—differed from those treated earlier, with higher Charlson comorbidity index scores and additional disease diagnostic codes. This aligns with common practice, in which bedside providers note sepsis is often harder to recognize in patients with comorbid illness and that septic patients with comorbid illness have a worse prognosis in general. A similar approximate 5-hour inflection in the trend of time to antibiotics and mortality existed in 2 larger studies with a combined near 80,000 ED-presenting patients with sepsis.[5,6] Notably, the relationship of time to antibiotics and mortality was highest for patients with septic shock or sepsis with hypotension as opposed to less advanced sepsis. This suggests some safety in allowing time for a more careful diagnostic approach for many patients. Another recent trial that randomized 2,672 patients with suspected

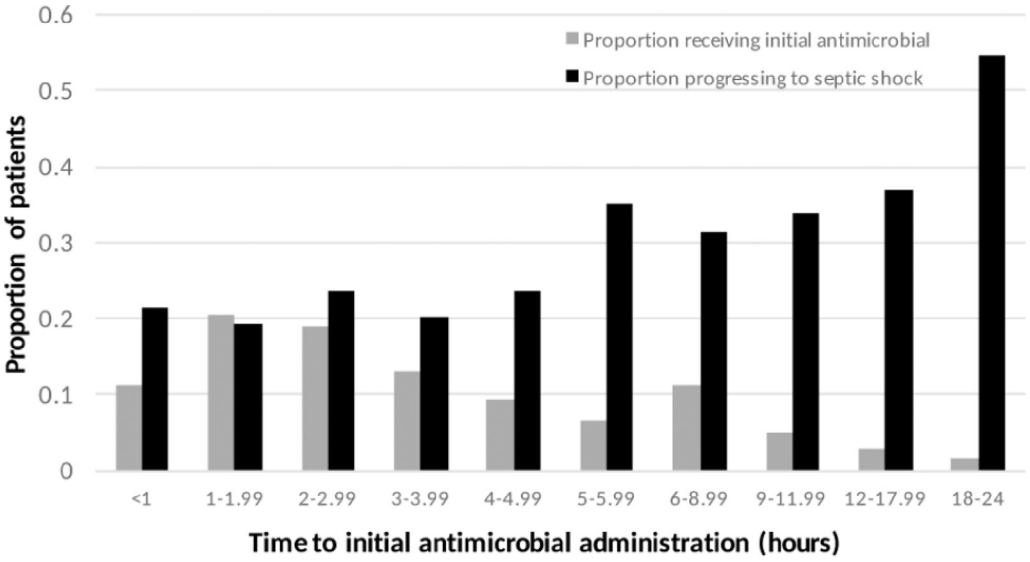

Figure. Progression from severe sepsis to septic shock and time to antibiotics among ED-presenting patients.[4]

sepsis (>95% without shock) to receive antibiotics in ambulances or quickly in an ED did not find that the median 96-minute-earlier administration linked to improved outcomes.[7] These data all underscore that the 1-hour antibiotic target may not be possible or necessarily advantageous for all patients with eventual sepsis diagnoses.

Patients with multidrug-resistant infections tend to have comorbid condtions, which can have bearing both on the timing of effective antibiotic delivery and outcomes, and that difference alone can alter the timing of effective antibiotic delivery. When we studied extended-spectrum β-lactamase–producing infections in ED pyelonephritis patients in 2013 to 2014, three quarters of these patients did not receive an in vitro effective antibiotic initially, only later.[8] Patients at risk of extended-spectrum β-lactamase infections were more often chronically ill and had previous antibiotic exposure, a group at increased risk of a worse outcome.

Promotion of 1-hour broad-spectrum antibiotics for all patients with suspected sepsis has potential unintended negative consequences. To meet this target for all patients who *may* receive a diagnosis of sepsis, early treatment of many who do not ultimately have sepsis will occur, including treatment of patients with some inflammatory response findings or even temporary physiologic changes but who are not septic. The concern mirrors the experiences of an earlier fixed interval for starting antibiotics in patients with suspected community-acquired pneumonia; then, earlier therapy for many with any potential eventual pneumonia diagnoses created widespread misuse with downstream complications, including serious problems, such as more frequent *Clostridioides difficile* infection. Other consequences exist in practice. These include payer and regulatory body penalties (withholding reimbursement or downgrading performance assessments) or tort claims (from not meeting this 1-hour target or from complications from an antibiotic ultimately unneeded). None of these latter occurrences aid patients or those providing care.

Because of the evidence gaps with the antibiotic part of the Surviving Sepsis Campaign bundle, some organized medical societies declined to support the recommendations. The Infectious Diseases Society of America withheld its endorsement of the Surviving Sepsis Campaign 2016 guidelines and the 1-hour bundle, noting that 40% of patients admitted to intensive care for sepsis ultimately do not have that condition, leading to adverse consequences of unnecessary antibiotics.[9] The Infectious Diseases Society of America and others have encouraged gathering more data to confirm the diagnosis and a less rigid time threshold.[10] The American College of Emergency Physicians (ACEP) also did not approve the 2018 Surviving Sepsis Campaign 1-hour bundle and began conversations with Surviving Sepsis Campaign leaders to improve the bundle content and message, sharing concerns similar to those noted by the Infectious Diseases Society of America and in the article by Spiegel et al. We think this reluctance to embrace a 1-hour antibiotic goal is wise; we do not think that antibiotics are unimportant, but the current

data do not support the current proposed target. Sepsis mortality rates were much higher in the preantibiotic era, and it is logical to associate antibiotic use and timing effect outcomes. However, we suspect that poorer outcome rates will not increase immediately without 1-hour antibiotic therapy for many patients with sepsis, even if true for some subgroups. Phenotyping sepsis forms and then matching these to rigorous designs examining antibiotic deployment will be a key way to elucidate this relationship and allow sensible, quality care. Emerging molecular infectious agent diagnostic testing will also allow more rapid and accurately-targeted treatment.

In accordance with these observations, we think some rational priorities for sepsis performance improvement emerge. First, these investigations support targeting patients with septic shock or sepsis with hypotension for early administration of broad-spectrum antibiotics while providing other critical resuscitation. Second, among patients without shock, use a more deliberate approach to diagnosis, with special attention to consider sepsis in at-risk groups (immunocompromised or with comorbid illnesses) who don't have clear sepsis findings. Look hard for sepsis and do so frequently; infection is a common reason chronically ill patients deteriorate, and they are often unable to provide detailed history and may not manifest fever, the most immediately available hallmark of infection. Absence of fever is associated with increased sepsis-related mortality and longer time to antibiotics.[11]

We also think choosing the best antibiotic agent(s) is important; be aware of risk factors for more challenging pathogens when selecting initial empiric treatment. Patients exposed to hospital and long-term care environments and those treated with antibiotics within the last few months may not be adeqautely treated with the common empiric agents, such as ceftriaxone, a fluoroquinolone, or piperacillin-tazobactam. One of the best predictors of current infection with a multidrug-resistant pathogen is having had one previously.[7] Check the electronic medical record before prescribing empiric antibiotics. The goal is not just to start any antibiotic soon; it is to start the right ones early.

Most of the time, the ED care team gets it right; they look early and often, and they intervene when they recognize sepsis. Seek to be prompt, but do not pay homage to a set interval. Obviously septic patients allow straightforward care decisions; for many others, taking a slightly longer time to administer antibiotics while gaining more insight is likely the safest approach overall by improving diagnostic accuracy plus antibiotic decisionmaking. The 2018 Surviving Sepsis Campaign 1-hour care bundle threshold—notably, the expectation to initiate antibiotics for all patients with eventual sepsis diagnoses within this interval—is simplistic and not currently supported as the optimal approach. It is time to take a more informed approach to administration of empiric antibiotics for patients with suspected sepsis in the ED.

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Author affiliations: From the Departments of Emergency Medicine and Medicine, Division of Infectious Diseases, Olive View–UCLA Medical Center, Sylmar, CA, and The David Geffen School of Medicine at UCLA (Talan); and the Department of Emergency Medicine, University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, PA (Yealy).

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(continued from p. 333)

DIAGNOSIS:

Paraneoplastic dermatomyositis associated with colon adenocarcinoma and hepatitis B. Dermatomyositis is an uncommon autoimmune connective tissue disease that combines myopathy and distinctive cutaneous manifestations.[1] Patients usually present with progressive symmetric weakness of proximal limbs, associated with skin changes. Highly diagnostic lesions of dermatomyositis include heliotrope rash, Gottron's papules, and Gottron's sign.[2,3] Other typical findings are holster sign, erythematous rash on the chest (V sign) and on the back of the neck and shoulders (shawl sign), and dilatated and tortuous capillary loops of the nail folds, associated with thickening and roughness of the cuticles.[1,4] These signs may alert clinicians to the presence of dermatomyositis and allow early diagnosis and treatment.

Author affiliations: From the Dermatology Division, Department of Medical Clinics, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil (Filho); and the Department of Surgery (Brito) and Department of Radiology and Medical Imaging (Queiroz, Mello, Valentin), Hospital São Francisco, Ribeirão Preto, São Paulo, Brazil.

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