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The Timing of Early Antibiotics and Hospital Mortality in Sepsis: Playing Devil's Advocate

To the Editor:

In this issue of the *Journal*, Liu and colleagues have reported that hourly delays in antibiotic administration were associated with increased odds of hospital mortality even among patients receiving antibiotics within 6 hours (1) [pp. 856–863]. The overarching theme and implication of these findings is that clinicians should strive to deliver antibiotics to patients presenting to the emergency department (ED) with presumed sepsis as expeditiously as possible to improve survival (1). We applaud the authors' intentions of providing additional evidence that prompt administration of appropriate antimicrobial therapy in sepsis is lifesaving, but making this conclusion without following the outcomes of those patients without sepsis who received prompt, but unnecessary, antimicrobial therapy, leads to potentially skewed and biased assumptions (1–5). In fact, the authors make mention of this in their introduction when they list the potential harms of timely antibiotic administration (i.e., receipt of antibiotics unnecessarily culminating in adverse patient and community consequences, decreased attention to other diseases and patient-specific needs), but overlook this important fact when discussing their results and conclusions (1). The intent of this letter is to highlight the ramifications that neglecting to include those nonseptic patients who needlessly received antibiotics conceivably had on the researchers' results, while urging the investigators to reevaluate their findings in light of this potential bias.

The authors discuss their approach, which led to the 35,000 patients with sepsis who were included in their retrospective analysis, which included incorporating patients admitted with sepsis-specific *International Classification of Diseases* codes who received antibiotics within 6 hours of ED registration time (1). However, the authors neglect to include, and fail to mention, the exclusion of those patients who received prompt antibiotics who were later found not to be septic (i.e., presumably those with systemic inflammatory response syndrome resulting from noninfectious causes or viral infections) (1). It is these patients who received antibiotics unnecessarily, and their direct and indirect downstream health consequences of receiving unneeded antibiotics, that have significant potential to bias the authors' conclusion that prompt antibiotic administration improves survival in patients with sepsis. A more accurate conclusion given the study's methodology might be: for those patients presenting to the ED who received antibiotics within 6 hours and were admitted with a sepsis-specific diagnosis, rapid administration of antibiotics was associated with less odds of mortality.

It is safe to assume that a significant fraction of those nonseptic patients who received antibiotics unnecessarily had poorer outcomes and possibly higher mortality than if they never received antibiotics in the first place (6, 7). To list the potential ways inappropriate and unnecessary antibiotic administration can cause harm is beyond the scope of this letter, but suffice it to say there are many (6, 7).

Overall, we commend the authors for aspiring to demonstrate that antibiotics administered as quickly as possible in patients presenting to the ED with a systemic inflammatory response may improve sepsis survival, but making this conclusion without incorporating the potential harms of delivering unneeded antibiotics to nonseptic patients can lead to potentially inaccurate interpretations. Thus, despite these most recent findings, it remains imperative that clinicians weigh the benefits of prompt antibiotic administration with antibiotic stewardship. ■

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Reply

From the Authors:

Economists have long recognized the importance of externalities: the "spillover" benefits and harms that result from specific actions that are unaccounted for in the cost of the activity itself. In 1920, Arthur Pigou described an example of a negative externality as the sparks emanating from a train traversing railway tracks that ignite surrounding fields and forests (1). When unaccounted for in the train ticket price, the resulting loss of crops or timber, "innocent bystanders" of train travel, become costs borne solely by the landowner. To redress this problem, Ronald Coase suggested that an efficient solution could be achieved through bargaining if the affected parties had access to perfect information about the benefits and harms of the activity (2). With this information, they could agree on appropriate compensation. Short of this, governing bodies could enact Pigovian taxes (named after Pigou) to properly remunerate each party. In either case, the key criterion for a solution is the availability of information about an activity's benefits and harms. Unfortunately, this criterion is rarely met in real-world economics.

Similarly, when it comes to modern antibiotic prescribing practice, we lack adequate information. Even in the relatively narrow question of antibiotic timing among patients hospitalized for acute infection, numerous studies have shown mixed results regarding the importance of earlier antibiotics, resulting in controversy (3). We thus restricted our current study to address this question using highly granular data in a large and contemporary cohort (4) [this issue, pp. 856–863]. However, we did this acknowledging that many other important questions, particularly about the negative externalities of antibiotic timing and use, remain.

For example, as we suggested in our study and Dr. Chertoff and Dr. Ataya have reiterated, what are the innocent bystander costs of prioritizing early antibiotics, either for patients who ultimately do not have infection or even for other patients being treated by the same teams? Recent data highlight the bystander risks associated with being in proximity to another patient requiring urgent intervention (5). On a larger scale, how do we best reconcile outpatient recommendations, which increasingly focus on limiting the use of inappropriate antibiotics, with inpatient recommendations, which increasingly focus on earlier identification and treatment? Further, how do we understand the effect of health system–level antibiotic usage patterns against the background of rising antibiotic resistance threats resulting from medical, agricultural, and husbandry practices (6)?

We urgently need additional studies that inform our decisions about best antibiotic prescribing practices, particularly by allowing us to balance the individual and societal costs and benefits of differing practices. In addition to traditional outcomes studies, we will need ecological studies that look beyond the hospital setting, as well as cost-benefit analyses that enable a longer-term and societal perspective. Randomized clinical trials may play a role when patients present with uncertain diagnoses and less severe organ dysfunction. Novel diagnostic tools allowing us to distinguish bacterial and viral infections may offer even more efficient solutions for tailoring antibiotic use. Over time, these approaches will contribute the critical information we need to answer antibiotic use questions focused less on "who?" and "when?" and increasingly on "for what gain?" and "at what cost?" ■

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