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Antibiotic stewardship: Dead bugs do not mutate

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One of the greatest advances in medicine in the last century has been to identify the mechanism of damage and have the tools to intervene in a prompt fashion. The use of fibrinolysis in both acute myocardial infarction (AMI) and stroke has significantly improved patients' outcomes.[1] Time is life, golden hour, and so on are now terms that have saved many lives. In patients with sepsis, the complexity arises; signs and symptoms are often nonspecific, and consequently, early identification is a challenge to overcome as the mortality rates are higher than AMI or stroke. For instance, septic shock is characterized by low blood pressure that does not improve after fluid replacement compared to an anterior AMI where chest pain and electrocardiography changes are manifested.[2]

Antibiotics are one of the most important medical improvements of the past century, allowing us to cure infections that would have frequently been fatal in the past. Antibiotics have transformed modern medicine and saved millions of lives. Making the right choice of antibiotics, particularly for sepsis, is fundamental.[3] Mortality from sepsis has continued to decrease year on year, at least in developed countries, mostly after the introduction of the Surviving Sepsis Campaign (SSC), based on results in different countries and health-care settings. However, sepsis is still one of the leading causes of death worldwide.[4] The number of lives lost every year is underestimated, as 85% of all cases are estimated to occur in resource-poor settings and data from these regions are scarce. Recent high-quality data from middle-income countries suggest that mortality rates, both for sepsis and septic shock, are striking high, ranging from 50% to 70% compared to the 26% found in a recent systematic review based on data from high-income countries.[5]

Evidence-based medicine (EBM) integrates clinical experience and patient values with the best available research information. The implementation of care bundle to empiric antibiotic administered to patients represents the best available evidence to having their infections effectively treated. EBM is the judicious, reasonable, painstaking, and meticulous use of modern, best evidence in making clinical decisions of individual patients. Septic shock is mostly fatal, and the window opportunity to rapidly reduce bacterial load during the shock period to a subcritical threshold is limited. Time/delay-dependent irreversibility of organ injury and irreplaceability of the injured organ are critical determinants of survival. The SSC strongly recommended that empirical broad-spectrum antibiotics should be given within 1 h of sepsis identification to patients with septic shock and also to those with sepsis and without shock.[6] This recommendation has been criticized. One of the main criticisms is the lack of randomized clinical trials to support the use of antibiotics within the first hour in septic patients. However, data from multiple

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observational studies, prospective and retrospective,[7–9] and meta-analysis[10] clearly suggested that early antibiotic administration is associated with improved survival even among patients without shock.[11] A recent publication on mandated care in the USA[12] showed that the completion of the 3-h bundle at 6 h was associated with mortality that was approximately 3 percentage points higher than the mortality associated with completion of the bundle within the first hour. Although some might consider a 3% reduction as a marginal benefit, similar rates of reduction are targets in the cardiology field. Considering an estimated of 1.5 million cases per year in the USA and a mortality rate of 23%, a 3% reduction would mean saving more than 10,000 lives every year.

Another common criticism is that these studies are biased. There are many factors that should be considered when time-to-intervention studies are analyzed that could affect mortality, such as patient complexity (more complex patients may be more diagnostically challenging), time zero for sepsis (hospital arrival time/time of clinical deterioration), accessibility of medical facility, and others. However, although complex patients might have a delay in diagnosis and, consequently, in the administration of antibiotics, complex patients are not necessarily more severely ill ones. From another perspective, sickest patients tend to receive antibiotics earlier, resulting in a bias against the hypothesis of benefit from earlier administration. Statistical adjustment can help reducing the bias. It is also a potential source of bias the inclusion of less severely ill patients throughout a quality improvement initiative because of increased awareness.[13] However, the association between time to antibiotics and mortality is demonstrated considering all individuals, both those included at the baseline period and during the intervention.

There is a lot of concern that early use of antibiotics in patients with suspected sepsis and without shock might lead to antibiotics' overuse, mainly by unskilled young physicians who are afraid of losing the golden hour. A proper assessment of the risk of sepsis is certainly needed, and these borderline patients will probably benefit less from this aggressive intervention than patients with shock. However, the mortality rates for sepsis without shock at presentation are still very high, mainly in resource-poor settings.[14] The risk assessment should take into consideration the baseline mortality rates and the balance between cost and benefit. We have not yet established the potential harm caused by a wrong sepsis diagnosis or by the infusion of a single dose of antibiotics. By contrary, we have sufficient observational data suggesting the hazard of postponing recognition. The concern that overuse will increase resistance is justified. However, a wrong misconception is to blame a physician in front of a potential critically ill patient. Antibiotics, if used appropriately, can be lifesaving, as there is an increasing threat from the rise in antibiotic resistance in many regions of the world.[15] There are many explanations to this problem, including the misuse and overuse of them. Almost three-quarter of antibiotics, in the USA, are given to animals; antibiotic overprescribing is a common problem in primary care, where viruses cause most infections. For human use, general practitioners issue almost 90% of all antibiotic prescriptions, and self-medication with antibiotics is unregulated and available over the counter without a prescription in many parts of the world.[16] There are two major determinants of increase in antibiotic resistance: prolonged courses of antibiotics and subinhibitory and subtherapeutic antibiotic concentrations. Both can promote the selection of pathogen strains due to antibiotic-induced gene expression can increase virulence.

The argument that antibiotics should be withheld in patients without shock until diagnosis is completed and sepsis is confirmed is not sounded. As we know, a 60–90 min window in AMI and stroke is sufficient to perform clinical history, tomography, laboratory exam, and thrombolysis or percutaneous coronary intervention. Although the diagnosis can be challenging, 1 h should be enough to assess a patient suspicious of sepsis to obtain a clinical history and exams, such as image, hemogram, biochemical tests, and molecular assays including procalcitonin and C-reactive protein (CRP), if needed.[17] This should allow the best clinical judgment and decision. Although in intensive care unit patients, the differential diagnosis might increase the difficulty for proper diagnosis, in the emergency department (ED) and wards, the spectrum for differential diagnosis is narrow. Moreover, giving the first dose of antibiotics does not mean we should stop diagnosing our patients. Antibiotics can be withdrawn if further investigation rolls out sepsis. Whether a single dose of antibiotics will increase resistance rates is an improbable and unproved issue. Enhancing our antibiotics' stewardship training is key. Physicians should not be encouraged to treat first and think later. On the other hand, encourage physicians not to give antibiotics to patients with a reasonable suspicion of sepsis as it can have dramatic consequences. We should encourage physicians to "think fast and treat faster".

We, however, advocate for judicious use of antibiotics as with other drugs. In general, in medicine when something is not indicated, it is usually contraindicated. Care bundles, which are a collection of high-impact EBM interventions, have been shown to be an effective way to ensure the effective and consistent delivery of high-quality medical care. Firstly, "start smart", which outlines the decisions and actions that should be taken when considering whether or not to start antibiotics, and "then focus", which outlines the requirement for daily review of antibiotic therapy.[18]

A misinterpretation of the aforementioned is just to start antibiotics without a deep insight in definitive diagnosis of the disease. Doctors have to provide the best care possible applying a "*primum non nocere*" principle, while respecting the nonmaleficence, autonomy, and justice of the attending physician, especially in potential critically ill conditions.

Start smart is the most important part in the bundle, as if a patient is not being treated, the outcome is disastrous. It is particularly relevant in current days because of higher predisposition to sepsis due to comorbidities, repeated and prolonged hospital admissions that are prone to opportunistic infections, impaired innate and adaptive immunity, frailty, and longer expectancy of life. Delay inadequate antibiotic therapy has repeatedly the strongest predictor of survival in septic patients. Reports from different authors around the globe have shown a common denominator that not providing adequate antibiotics kills patients. The timing is a matter of consideration, and recommendations are mainly based on observational studies and some retrospective cohorts. A recent study aimed to determine the benefit of pre-hospital antibiotic administration in patients with suspicion of sepsis. This study failed to demonstrate the benefit of early antibiotic use, but brings an important consideration to the "*nonbelievers*" in prompt antibiotic use, as sepsis was considered on the clinical appearance and initial status of patients in the ambulance. This is not very different to what happens in many EDs. The main concern in current clinical practice is that we are still using the same tools that we had 20 years ago and despite an improvement in care, the mortality for sepsis remains unacceptably high.[19,20]

In summary, sepsis occurs because a pathogen replicates and if untreated, the bacterial (or fungal) load increases exponentially over time. The mechanisms of organ damage involve the release of numerous subproducts from the pathogen with antigenic properties that increases the toxic burden induced by the infection. Unfortunately, lack of recognition and antibiotic administration will not delay tissue injury or multiorgan failure.[8,21] Septic shock has a very narrow window and can only be tolerated for a limited period before generalized organ damage occurs. So, we advocate prompt treatment using the most effective tools for sepsis – antibiotics. Starting right antibiotics does not drive downstream responses of forgetting to continue for medical diagnosis. Let us keep up the fight for sepsis and always remember dead bugs do not mutate.

Conflict of Interest

No conflict of interest for any of the authors regarding the content of the manuscript.

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