The perks of prognostic biomarkers: A paradigm switch in the triage of sick febrile patients

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Fever is indisputably one of the most common symptoms triggering the quest for health care provision, globally, but particularly so in low and middle-income countries (LMIC), where infectious diseases remain highly prevalent, and where fever is a well-known cause of premature mortality. The epidemiology of fever is highly variable, with a myriad of different potential etiologies, and heavily dependent on a variety of parameters, including among others, the age of the individual affected, the presence of concomitant conditions, the geographical distribution and circulation of different pathogens, and the implementation of different control measures destined to decrease the risk of certain diseases[1].

In outpatient clinics throughout the world, clinicians visiting sick febrile patients are faced with two diagnostic dilemmas that are at the basis of their management decisions: 1) Is this fever caused by a pathogen that requires antibiotic treatment? and 2) Is this patient at risk of progressing to a life-threatening disease? In high-income countries, the answer to both questions can partially be provided by thorough diagnostic investigations that may be able to identify the underlying cause, and stratify the risk and guide management. In LMIC, however, access to the health system is much more limited, diagnostic tools remain scarce, and management decisions -by definition more subjective- may have much more profound implications. Thus, identifying mechanisms which could help frontline clinicians in these settings reliably answer those two questions could significantly improve their diagnostic and therapeutic approach, and as a result, the well-being and survival probabilities of their patients.

The answer to the first question presupposes that fever arises as the direct response of the human host to the infection caused by a single pathogen, and that as a result, identifying that microorganism will determine a binary decision that can be summarized as follows: a) Bacterial: antibiotics required; b) Non-bacterial: no antibiotics required. However, in the last years, increasing evidence has arisen to counteract the oversimplification of such an approach. First, the assumption that all outpatient infections of presumed bacterial origin require the use of antibiotics is not necessarily true, as many of them can be managed in a conservative manner[2, 3]. Second, large multicenter studies thoroughly investigating the underlying etiology of fever, or other major syndromes often involving fever (diarrhea, respiratory distress, etc.) have

evidenced the paucity of pure single-pathogen infections, pointing instead towards a not uncommon scenario of mixed infections[4-6]. This is typical for instance in the field of pneumonia, whereby respiratory viruses and bacteria have often been described to act synergistically in the clinical syndrome they can both individually cause[7]. Similarly, among pediatric *P. falciparum* malaria cases, secondary bacterial infections can frequently be detected, often triggering a more severe presentation and a poorer prognosis[8]. Additionally, clinical management algorithms based on the identification of signs and symptoms associated with determined conditions and/or the risk of severity and treatment recommendations resulting from them, have been designed to prime sensitivity over specificity, and as a result, tend to overdiagnose antibiotic-requiring conditions, leading to an exaggerated prescription of these drugs. While this approach is generally considered acceptable, due to the fact that it has shown (particularly in children) to contribute to improved survival[9], it does entail obvious deleterious consequences in relation to antimicrobial misuse and resistance, a major global health concern in the 21st century.

In recent times, research on diagnostic biomarkers, one of the most active fields in diagnostic medicine, has focused on identifying proteins (mostly host-response ones) capable of distinguishing between bacterial and viral infections, and therefore, indicative of the need to provide or withdraw antibiotics. This search of such “diagnostic holy grail” has been hampered by the poor reliability of most of the candidate biomarkers, their variation in performance in the light of co-existing conditions (such as for instance malaria, or HIV infection)[10], or the wide variability of their results in relation to the severity and magnitude of the infection. Although some of these proteins have been widely adopted in emergency rooms of Western hospitals for the rapid assessment of patients, a robust and reliably performing biomarker that could be universally used for this purpose among all age groups and in all settings, is far from a reality. This has paved the way to the investigation of prognostic (as opposed to “diagnostic”) biomarkers, i.e those that could reliably stratify risk of adverse outcomes, independently of the infecting agent, and of the clinical features at presentation.

In this issue of the Clinical Infectious Diseases journal, Melissa Richard-Greenblatt and colleagues assessed, among a series of 507 febrile adult Tanzanian patients (age range 23-49 years) which included 32 deaths, the prognostic ability of a panel of 11 host-response biomarkers of endothelial activation and immune dysfunction, previously hypothesized to be adequate and "etiology-agnostic" predictors of disease severity and mortality, when measured at clinical presentation [11]. They also assessed procalcitonin (PCT) and C-reactive protein (CRP), two well-known acute phase proteins routinely used in emergency departments for risk-stratification and management decisions in high-income countries, and a variety of widely utilized clinical severity scores, including qSOFA (quick Sepsis Related Organ Failure Assessment), SOFA (a modified version of it adjusted to LMIC settings), SIRS (Systemic Inflammatory Response Syndrome) clinical criteria, and the Glasgow Coma Scale (GCS). Of all markers assessed, STREM-1 (soluble triggering receptor expressed on myeloid cells-1, a protein member of a family of cell surface receptors, functioning as modulators of the inflammatory response in sepsis) seemed to have the best prognostic accuracy (AUROC 0.87, 95% CI 0.81-0.92) for predicting day 28 mortality, clearly outperforming the two reference markers (PCT and CRP), and superior or similar to some validated clinical scoring systems on their own. Interestingly, the addition of STREM-1 to those scoring systems seemed to further enhance their prognostic accuracy. Importantly, STREM-1 retained its prognostic abilities irrespective of the underlying etiology (viral vs. bacterial), a finding that further supports the theory that pathways in which this biomarker is elevated are common to a variety of different infectious pathogens and can therefore be truly considered a harbinger of life-threatening disease.

The implications of this study are notable. First, these results substantiate previous work describing the prognostic performance of specific host biomarkers of the endothelial activation and immune dysfunction pathways in sick children and adults, further corroborating their predictive importance not only for specific diseases (such as malaria[12], or sepsis[13, 14] for instance), but also for the much wider "fever syndrome"[15]. Second, these results highlight the importance of advocating for a triaging strategy that focusses on

risk-stratification, rather than on pathogen-family identification. Indeed, detecting those patients who do not necessarily appear severely ill but do have an objective measurement that is highly suggestive of an adverse outcome certainly provides more actionable information than just identifying whether the underlying etiology requires antimicrobials or not, particularly at the peripheral health system level, where a wrong decision can have profound implications in the likelihood of survival. Finally, the clear identification of one or more markers consistently associated with severity progression, sets a standard upon which designing new point of care (POC) tests based on their measurement in plasma, so as to assist clinicians in their assessment and decision-making processes. Such POC tests should be, ideally, deployable at the peripheral health system level, electricity-independent, rapid (providing results within minutes), qualitative of semi-quantitative (i.e suggesting two or three possible scenarios, such as “No risk”, “Moderate risk” or “high risk”), stable and providing reproducible results, and of sufficient low-cost so as to be implemented at a large scale, particularly in those settings where other diagnostic tools are scarce. The addition of such prognostic tools to already existing clinical algorithms could enhance those already in place, while providing an objective measurement upon which basing critical management decisions.

Conceptually, such triaging tools could also be utilized in other clinical scenarios, where important management decisions need to take place, such as for example when deciding transfer of patients to a higher-level facility, when planning a switch from a parenteral treatment to an oral one, or at the moment of discharge, when anticipating the post-discharge mortality risk is not always easy, constituting a new paradigm shift in terms of outcome prediction. In this respect, and before any further development in this area, it would appear important to design a comprehensive clinical development plan consisting on a series of well-designed prospective randomized control trials, using biomarker levels on arrival as the key element in which to base therapeutic and management decisions, with disease severity and mortality as endpoints. This will teach us whether their real-life utilization does have the same impact that the exciting and promising results of this study anticipates.

I declare no competing interests.

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