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EDITORIAL

Another piece to add to the puzzle of procalcitonin in renal dysfunction

Otra pieza para el rompecabezas de la procalcitonina en la disfunción renal

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Procalcitonin is a ubiquitous polypeptide which is rapidly released in the presence of bacterial toxins and proinflammatory mediators (IL-1B, TNF-α, and IL-6).[1] In recent years, many researchers have established its relevance for the diagnosis of moderate-to-severe bacterial infections, especially of the respiratory tract.[2,3] In viral infections, however, procalcitonin elevation can be blocked by concomitantly released cytokines (e.g. interferon), and this interaction facilitates differential diagnosis between bacterial and viral infections.[4] Furthermore, since PCT levels decrease with ongoing resolution of infection, repeated evaluation of this biomarker over time might indicate when to stop unnecessary antimicrobial treatment, thus preventing adverse effects on patients, and also decreasing antimicrobial pressure on the high-resistant microorganisms which grow in the complex ICU environment.[5] A recent metaanalysis determined that procalcitonin guidance of antimicrobial treatment in suspected/confirmed sepsis was safe, and resulted in a significant decrease in antibiotic treatment duration, with no impact on mortality or on ICU length-of-stay.[6]

A particular clinical situation is pneumonia produced by influenza viruses requiring ICU admission. Up to one third of these severely affected patients might have concurrent lung bacterial infection, as described during the 2009 pandemia.[7] Theoretically, PCT might aid to discard coinfection and discontinue redundant antimicrobials. Nevertheless, the concomitant development of acute renal dysfunction/failure occurs in 17% of patients with severe influenza[7] might produce increased procalcitonin levels due to decreased elimination, making interpretation difficult.

In this issue of Medicina Intensiva,[8] Rodriguez et al. analyze procalcitonin levels in 663 patients admitted to 148 ICUs in Spain with influenza infection and acute kidney failure (AKI), defined by an elevation in creatinine of 1.60–2.50 mg/dL (AKI I) and 2.51–3.99 mg/dL (AKI II). They excluded more severe forms of kidney failure. In this study, patients had bacterial lung infection on admission carefully discarded after an intensive screening protocol; therefore, any elevation in procalcitonin would be only ascribable to renal dysfunction. The researchers sought to characterize the relationship between procalcitonin and creatinine and procalcitonin and urea (creatinine clearance was not available). Had any of those relations been linear, creatinine elevations might predict the increases in procalcitonin levels exclusively due to renal dysfunction or failure; any further increase might be produced by bacterial coinfection, thus permitting rapid diagnosis and treatment.

Unfortunately, the correlations between procalcitonin and creatinine were weak, even adjusted for other relevant covariates which might act as surrogates of widespread

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inflammation, such as elevations of APACHE II or white blood cell count. Indeed the metabolism of procalcitonin is poorly understood; it is synthetized in the leukocytes, especially in mononuclear cells and in other tissues in response to microbial toxins and certain proinflammatory mediators (e.g., IL-1B, TNF-α, and IL-6),[1] but the mechanisms of elimination still remain to be elucidated. Conversely, other researchers reported a parallel increase of procalcitonin with renal deteriorating function; they also measured procalcitonin in mononuclear cells and detected an elevation in absence of infection which, they speculated, might serve as a marker of low-grade inflammation in advanced kidney disease.[9]

Notwithstanding this, there are other possible explanations to the authors' negative findings: only half of the patients of the entire cohort had procalcitonin measured; and the number of patients with renal dysfunction/failure included might have been insufficient to detect a significant association between renal dysfunction and procalcitonin, since only less than 10% of patients experienced AKI stages I-II.

It is also likely that patients actually had bacterial coinfections which went undetected; sepsis and septic shock are frequently associated with negative cultures. And, last but not least, the real correlation might be between procalcitonin and glomerular filtration rate, which was not estimated by any method; it is known that serum creatinine might not reflect the true renal function in the critically ill.[10]

What is the main message of this study? It might well be that procalcitonin dynamics in renal compromise is complex and poorly understood, and that there might be other mechanisms of elimination, given that the authors found higher values of procalcitonin than those predicted by their equation when progressing from AKI I to AKI II. While renal dysfunction/failure is a state of increased inflammation, the study of Rodriguez et al. point to different mediators other than creatinine and urea to explain increased procalcitonin levels in their patients. And, more importantly, the authors give a word of caution to clinicians about interpreting high procalcitonin levels in the setting of renal dysfunction/failure: they should not give up searching for its most common cause, which is bacterial infection.

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