Procalcitonin and antibiotic use: imperfect, yet effective

The overwhelming burden of acute respiratory infections is undeniable. An estimated 2·74 million people died of lower respiratory tract infections in 2015 worldwide.[1] Despite being commonly caused by viruses, antibiotics are often used to treat these diseases. In the USA, around 40 million outpatients received antibiotics for respiratory infections in 2007–09.[2,3]

In adults, it is extremely challenging for physicians to differentiate between bacterial and viral respiratory tract infections, as well as exacerbations of other chronic respiratory diseases, because of the overlap of clinical findings and abnormalities seen in ancillary tests. This difficulty in differentiation unequivocally leads to antibiotic overuse in this population of patients.

In the literature it is reported that the appearance of resistant bacterial strains is driven not only by antibiotic use per se, but also by prolonged duration of treatment.[4,5] By contrast with other diseases such as systemic hypertension, in which clinical management can be personalised according to patient needs, the treatment of bacterial infections still follows a one-size-fits-all model. This approach is used because traditional diagnostic methods are not able to identify in real-time the moment when infections have been eradicated and antibiotics are no longer needed.[6] To overcome this limitation, the use of procalcitonin has been proposed.

Procalcitonin is a prehormone that seems to act as a mediator in inflammatory processes.[7] Despite not being perfectly specific for bacterial stimuli, procalcitonin concentrations rise and fall in a pattern most consistent with infection and its subsequent resolution, and are positively associated with the severity of the infectious process.[8] Several randomised controlled trials (RCTs) have successfully shown that procalcitonin-guided treatment algorithms reduce antibiotic use for acute respiratory tract infections in adults.[9] However, questions regarding the safety of procalcitonin-guided treatment remain.

The meta-analysis by Philipp Schuetz and colleagues,[10] published in *The Lancet Infectious Diseases*, confirms the aforementioned results of individual RCTs while showing that the use of procalcitonin algorithms was not associated with antibiotic treatment failure or increased mortality.[10] In fact, the risk of 30-day mortality was significantly lower in the procalcitonin-guided group than in control patients (286 [9%] deaths in 3336 procalcitonin-guided patients *vs* 336 [10%] in 3372 controls; adjusted odds ratio [OR] 0·83 [95% CI 0·70–0·99], p=0·037), which could be explained by a reduction in antibiotic-related side-effects, including *Clostridium difficile* colitis. Having included 26 RCTs and used individual patient data from 6708 participants, this study is well positioned to shed much needed light onto the safety of procalcitonin-guided antibiotic use for patients with acute respiratory tract infections in different settings.

Nevertheless, important challenges still remain regarding the widespread use of procalcitonin to tailor antibiotic treatments. The different procalcitonin cutoff concentrations used in RCTs lead to uncertainty regarding their respective safety and create confusion for hospitals aiming to implement a local programme. Moreover, procalcitonin algorithms that are solely based on biomarker concentrations can be very challenging for clinicians to follow. This problem is especially true when the algorithm recommends the non-initiation of antibiotics in severely ill patients with suspected bacterial infection, for whom a delay in starting treatment is associated with increased mortality risk.[11,12] Studies show that disease severity prompts physicians not only to use antibiotics, but also to extend treatment duration.[13,14] The fear that early stopping of antibiotics might lead to resistance-conferring mutations in bacteria causing an infection is also a challenge. Although selection of mutated infecting strains is a well described pathway to resistance, antibiotic treatments more frequently drive bacterial resistance by causing so-called collateral damage to the host's normal microbial flora, resulting in the selection of resistant commensal strains.[15,16] Finally, evidence regarding the effectiveness and safety of using procalcitonin to tailor antibiotic use in paediatric and neonatal patients is still scarce.

The use of procalcitonin-guided treatment in adult patients with acute respiratory tract infections

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effectively reduces antibiotic consumption without being associated with an increased risk of treatment failure or mortality. Therefore, will procalcitonin solve the antibiotic overuse problem in this patient population? No, it will not. Although procalcitonin provides important information about a potential bacterial cause and the resolution of bacterial processes, the clinical reasoning behind antibiotic-related decisions is also strongly influenced by patient and disease characteristics, such as severity, and physicians' previous experiences, which can easily override any algorithm recommendation.[14] Nevertheless, we should not be looking for perfection when dealing with antibiotic overuse, but for strategies that can mitigate the global bacterial resistance problem. Thus, if procalcitonin can safely decrease unnecessary antibiotic use in different settings, even if imperfectly, it is already worthwhile.

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