Commentary

Procalcitonin in liver transplant patients - yet another stone turned

Jens-Ulrik Jensen[1,2] and Jens D Lundgren[2,3]

From the Procalcitonin And Survival Study (PASS)
[1]Department of Clinical Microbiology 445, Copenhagen University Hospital, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark
[2]Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, The Panum Institute/Building 21.1, Blegdamsvej 3B, DK-2200, Copenhagen N, Denmark
[3]Centre for Viral Diseases/KMA, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

Corresponding author: Jens-Ulrik Jensen, koordinator@pass-studiet.dk

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See related research by Zazula *et al*., http://ccforum.com/content/11/6/R131

Abstract

Liver transplantation has been reported to initiate increases in procalcitonin levels, in the absence of bacterial infection. The results of a study investigating the course of procalcitonin levels over several days after liver transplantation in noninfected patients were recently reported in *Critical Care*. This study shows that procalcitonin levels increase only transiently, immediately after surgery, and thereafter they rapidly decrease. This new information gives us hope that procalcitonin can be used as a marker of bacterial infection in these patients. Further studies of patients undergoing liver transplantation with and without bacterial infection are needed.

Recently in *Critical Care,* Zazula and colleagues [1] reported a study in which they conducted daily measurement of the biomarker procalcitonin in patients undergoing liver transplantation and resection. The findings provide novel clinical and molecular information on this biomarker.

In patients with severe organ impairment and in critically ill patients, bacterial infection is both common and among the most feared complications, because these infections are associated with a high rate of mortality that increases if they are left untreated [2,3]. Among the various outcome parameters identified to date in patients with septic shock, time to administration of appropriate antimicrobial treatment has been documented to be the factor most predictive of outcome, with survival probability dropping from 83% to 8% with an antibiotic delay of 24 hours. It is a tragic reality that timely diagnosis, monitoring and hence treatment of bacterial infection is frequently not possible in these unconscious, heavily medicated, immunocompromised patients, in whom there is an ongoing inflammatory response caused by multiple factors other than bacterial infection [4].

For these reasons, transplant specialists have long sought a reliable biomarker to assist them in identifying the right treatment at the right time. Procalcitonin has been suggested to be a useful biomarker for this purpose, because it exhibits a favourable kinetic profile as compared with, for instance, C-reactive protein and leucocyte count. It has been also proposed to be more specific for bacterial infection than established markers [5,6]. However, the findings of many studies call into question these proposed advantages of procalcitonin as compared with conventional markers; these were summarized by Tang and coworkers [7]. Some investigators have found that procalcitonin exhibits high sensitivity and specificity in identifying patients with sepsis, especially in populations in which the sepsis syndrome is most often caused by bacterial infection (for example, intensive care unit patients) [6]. Other investigators were unable to reproduce these findings, especially in populations in which the sepsis syndrome is frequently not caused by bacterial infection (for instance, patients presenting at emergency departments) [8].

The difference in performance of procalcitonin reported in these clinical investigations may be accounted for by the 'gold standard' problem and by differences between dynamic and static measurements. Assessment of the clinical value of a biomarker requires that the gold standard be accurate. Sepsis does not necessarily reflect ongoing bacterial infection; many patients with sepsis satisfy two criteria for systemic inflammatory response syndrome, together with 'a suspicion of infection', without actually being infected with bacteria. This mainly affects the sensitivity of the marker. Regarding the second cause of discrepant findings in studies of procalcitonin, namely the difference between dynamic and

static approaches to measurement, many clinical conditions (mainly those that influence function of the gut) result in transient increases in plasma procalcitonin level, possibly resulting from translocation of bacterial products from the gut lumen to the blood. An initial measurement of procalcitonin immediately after surgery and during a hypotensive period (and other circumstances) uniformly shows elevation, even if a bacterial infection is not established [9]. The logical consequence of this is that if a strategy involving a solitary initial measurement is selected, then this will often result in 'false positive' procalcitonin results. This factor mainly affects the specificity of the marker.

Casuistic reports have indicated that procalcitonin is high after liver transplantation in patients without evidence of ongoing invasive bacterial infection, and that this may lead to diagnostic misinterpretation [10].

Zazula and colleagues [1] reported an alternative and interesting approach, based on current knowledge on transient procalcitonin increases after surgery. Specifically, they measured this biomarker for several consecutive days after liver transplantation and resection. The findings of the study are interesting for two reasons. First, as in major abdominal surgery, procalcitonin levels increase transiently for about 24 hours after liver transplant and thereafter they decrease rapidly if no bacterial infection is present. This adds some useful clinical information regarding the time interval over which procalcitonin measurements should be taken in this patient population to distinguish between nonspecific elevations and elevations caused by ongoing bacterial infection (specifically, several consecutive measurements are needed). Second, the level of this transient increase is highly dependent on the type of immunomodulatory therapy the patient is receiving, which gives insight into the physiology and pathophysiology of the procalcitonin polypeptide. Zazula and colleagues provide some relevant interpretation of the findings, extrapolating from the fact that the polyclonal antithymocyte globulin is produced by immunizing rabbits with the human Jurkat T-cell line. As explained in the report, one of the molecules expressed by this cell line is intercellular adhesion molecule-1 (CD54), which is involved in ischaemia-related inflammation, and treatment with polyclonal anti-thymocyte globulin can thereby potentially mimic ischaemia-related inflammation. This is especially interesting because severe human organ ischaemia causes procalcitonin level to increase, sometimes to high levels, and this could represent an alternative explanation for the procalcitonin increases observed after prolonged hypotension.

Where do these observations lead us? An important follow-up study would be to quantify the extent to which consecutive determinations of procalcitonin plasma levels actually alert the physician to the presence of ongoing invasive bacterial infections soon after this infection is established. Even more importantly, does access to procalcitonin levels provide an opportunity to intervene with antibacterial therapy at an earlier time point in the course of the bacterial infection and to employ other routinely available clinical and laboratory-based assessments, thereby improving prognosis? Introduction of routine use of novel biomarkers should be based on demonstration of a benefit when they are applied to a target patient population; hence, it is critical that these questions be addressed before procalcitonin is introduced as a screening tool in patients undergoing liver transplantation. It is hoped that the results of ongoing randomized trials of procalcitonin-guided antibacterial treatment of critically ill patients, powered to assess whether daily procalcitonin measurements can improve survival rates, will inform this discussion.

Competing interests

J-UJ has received travel reimbursements for congress visits from BRAHMS AG; the authors declare that they have no other competing interests.

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