Editorial

Can lactate dehydrogenase (LDH) be used as a marker of severity of pneumonia in patients with renal transplant?

Carlos M. Luna, María M. Perín

Pulmonary Diseases Division, Hospital de Clínicas, Universidad de Buenos Aires, Buenos Aires, Argentina

Correspondence to: Carlos M. Luna, MD, PhD. Pulmonary Diseases Division, Hospital de Clínicas, Universidad de Buenos Aires, Arenales 2557, Piso 1 Dep A, 1425, CABA, Buenos Aires, Argentina. Email: dr.cm.luna@gmail.com.

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The development of immunosuppression during the last decades improved the graft survival but increased the susceptibility to infections after solid organ transplant. Pneumonia is a very frequent infection in patients with renal transplant (1,2), and bacterial etiology remains the most common cause of both, nosocomial, and community acquired pneumonia (CAP), in those patients (3,4). The incidence of pneumonia after kidney transplantation has been estimated to be, between 9% and 18% (5,6). Early after transplant, there is an increased risk of nosocomial pneumonia due mainly to multi-resistant gram-negative bacilli including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and gram-positive cocci, particularly *Staphylococcus aureus* and less frequently *Streptococcus pneumoniae*. Later, particularly during the first 6 months following transplantation, community-acquired bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma*, *Chlamydia* and *Legionella*) are the usual causative organisms, but opportunistic pathogens in relation with the immunosuppression, may appear. Pneumonia occurring in kidney transplant receptors are associated with high morbidity and mortality (4). During the immunosuppression, especially in the late period that occurs after a few years after the transplant, in the context of chronic immunosuppression pneumonia can also be caused by low virulence bacteria that do not produce this disease in the immunocompetent host. The diagnosis of pneumonia due to those opportunistic organisms in these patients usually delays the initiation of an appropriate therapy and results in an increase of morbidity and mortality due to this lung infection (5,6). The radiologic features could be atypical, pulmonary infiltrates could be due to different causes, approximately one-third of those infiltrates in these patients are non-infectious (7,8).

Severe CAP is a common way of presentation in kidney transplant patients and is complicated with higher morbidity and mortality rates, even when there have been important advances in the management of these patients (9-11).

Among the parameters potentially useful as predictors of outcome in renal transplant patients with pneumonia, those related with renal function, the clinical pneumonia scoring systems and the biomarkers should be taken into consideration. Regarding with renal function, low baseline estimated glomerular filtration rate (EGFr) has been found to be associated with mortality following CAP and sepsis, however it has been rarely examined according to clinically meaningful categories of EGFr (12). In relation to the scoring systems Pneumonia Severity Index (PSI) and CURB-65, they were designed to be used to assess severity of pneumonia, in immunocompetent patients those with a score >2 were found to be at a high risk of death. However, in immunosuppressed patients, mortality rate was found to be higher than in those immunocompetent for each of the classes of these scores (area under the curve 0.62 and 0.67 respectively) (13). About biomarkers, they have been proposed as indicators of severity, as a tool to differentiate bacterial from viral infection and to decide to stop the administration of antimicrobials. Different biomarkers,

including C-reactive protein (CRP) and procalcitonin (PCT), are used in the evaluation of the severity of illness and predicting the outcome in CAP (14-18).

The appearance of an acute phase reaction involving cytokines and the occurrence of hepatic metabolic changes are associated with the increased or decreased concentration of acute phase proteins (APPs), associated with function alteration and pathology. The decrease of the concentration of albumin level is considered a negative APP, and has been associated with functional impairment, severity of illness and death in several conditions including pneumonia (19). On the other hand, high CRP and PCT level, have been suggested to be associated with bacterial etiology, severity of illness and death in patients with CAP (20,21).

Kamat *et al*. in a systematic review and meta-analysis found that serum PCT levels do not have sufficient sensitivity or specificity to distinguish bacterial from viral CAP (12). Little is known about the relationship between the presence of the positive APPs CRP and PCT with death from pneumonia in transplant recipients. Savaş Bozbaş *et al.* (22) observed in 86 patients who underwent solid-organ transplant (including 44 with renal transplant), although there was a significant correlation between serum levels of PCT and CRP (r=0.45; P<0.001) and neutrophil count (r=0.24; P=0.025). There was no correlation between mortality and PCT level or CRP level (P>0.05).

Scores and biomarkers have not been used routinely in the evaluation of severity and outcome of CAP in immunocompromised patients and do not necessarily would work in renal transplant patients in the same way as they do in immunocompetent individuals. Having new data capable of clarifying whether the patient has a more serious clinical picture and is at risk of death can improve the management of them (23).

Su *et al*. performed a retrospective study on 77 renal transplant recipients who were admitted with severe CAP, in which the concentration of lactate dehydrogenase (LDH) on day 1 and day 3 were recorded and recorded their 90-day mortality. They found that the LDH level was significantly higher on day 1 in non-survivors and the same happened on day 3. Analyzing the of LDH kinetics from day 1 to day 3, they observed an increase of its concentration in non survivors and a decrease in survivors, and; they confirmed these findings in a multivariate analysis and concluded that they were independently associated with 90-day mortality (24). These findings are in line with a study by Ewig *et al*., who observed near 15 years ago that the increase of serum LDH concentration was useful to determine the severity of disease in lung parenchyma and the inflammation in pneumonia who was associated with a higher mortality (25). Although LDH is a recognized marker of the presence of an infection due to *Pneumocystis jiroveci* in immunocompromised patients including those who received renal transplantation, its incidence has been reduced with prolonged use of prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) (26).

This concept of using LDH concentration as a biomarker of pneumonia in renal transplant recipient was catched by Liu *et al*., who developed a score that they called "expanded-CURB-65 score", defined by using the CURB-65 score factors plus LDH >230 μ/L, albumin <3.5 g/dL and platelet count $<100\times10^9$/L, which proved to be simpler and more effective in 1,640 consecutive hospitalized CAP patients in predicting mortality than the pneumonia severity scores (27).

LDH is a cytoplasmatic enzyme expressed in nearly all types of cells of the body. It is released into blood when cell experiences injury or death caused by ischemia, excess heat or cold, starvation, dehydration, injury, bacterial toxins, drugs and chemical poisonings (28). Su *et al*. demonstrated that serum LDH elevated post renal transplant could be used as a marker of severe pneumonia in transplant patients (24). But it is necessary also to consider that different conditions potentially associated with increased level of LDH, including posttransplant lymphoproliferative disorder, *P. jiroveci* pneumonia, thrombotic microangiopathy-hemolytic uremic syndrome, acute renal infarction or hemolytic anemia from dapsone (alternative to TMP-SMX for prophylaxis against *P. jiroveci*), represent diagnostic and clinical challenges that could be involved in the care of renal transplant patients (29).

LDH have demonstrated in the past that could work as good as CURB-65 and PSI or CRP and PCT or other newer APP and biomarkers to predict the outcome in CAP in general, but also in CAP occurring in patients that underwent kidney transplant. However, LDH is not used to identify the severity of illness in CAP. This seems to be the result of the progress of medicine, but it could also be considered as the result of the perception that the appearance of a newer marker makes the oldest one undesirable or non-functional, although it still works perfectly (known as perceived obsolescence).

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Footnote

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