Ventilator - Associated Pneumonia and The Role of Procalcitonin

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INTRODUCTION

Ventilator – associated pneumonia (VAP) is the most frequent intensive care unit (ICU) nosocomial acquired infection in patients on mechanical ventilation and is associated with prolonged hospital stay and higher ICU mortality. Few data about VAP evolution after institution of appropriate anti microbial therapy. Several studies showed that clinical and biological parameters evolved differently for survivor and non survivor of patients with or without VAP recurrence, but the parameters chosen proved not to be predictive of outcome. The search continues for a reliable prognostic marker that could rapidly (as of the first days of treatment) distinguish patients who will have favorable, as opposed to unfavorable, outcomes. Early identification of patients at high risk of death of VAP recurrence may provide an opportunity to change the treatment strategy to improve outcome. Ventilator associated pneumonia remains important causes of morbidity and mortality despite advances therapy, better supportive care modalities and the use of a wide range of preventive measures. VAP refers to pneumonia that develop more than 48-72 hours after endotracheal intubation. The incidence of VAP is 10-50% in the ICU. Mortality rate is 24-76% and patients in ICU will have 2-10 times higher mortality than patient without pneumonia. Death from VAP is caused by shock, sepsis, respiratory failure and irrational antibiotic treatment.1

PATHOGENESIS

Ventilator associated pneumonia (VAP) is diagnosed when all the following criteria are met:
1. persistent pulmonary infiltrate on chest radiograph
2. temperature > 38° C
3. Leukocytosis > 10,000 m³
4. Purulent tracheal secretions
5. Significant growth (10⁴ cfu/ml) or more quantitative cultures of distal bronchoalveolar lavage fluid sample obtained by fibrooptic bronchoscopy.

Ventilator associated pneumonia (VAP) is caused by various pathogenic bacteria, (polymicrobial) and seldom caused by virus or fungi, in immunocompetent patients. Bacterial infection is caused by gram negative bacteria e.g. P. aeroginosa Escheria coli, Klesibsiella pneumoniaea and Actinobacter species. In the USA, the frequency of gram positive infections e.g. Staphylococcus aureus and especially Methicillin-resitant S. aureus (MRSA) is quite high. Hospital surveillance of nosocomial infection at the University of North Carolina showed the same pattern.

In normal situation, the respiratory tract has a mechanism to protect itself from infection by means of the epiglottis and larynx, cough reflex, tracheobronchial secretion, mucosa cilliar, cell mediated immunity/humoral immunity and phagocytosis system which included macrophages in the alveoli and neutrophils. In intubated patients there are disturbance of the natural barriers between oropharynx and trachea, causing the micro organism to invade the lower respiratory tract leading to infection. The tracheobronchial tree and oropharynx of patients on ventilator often have colonization of gram negative bacteria.

Procalcitonin (ProCT), a protein of 116 amino-acids with a molecular weight of 13 kDa, was discovered 25 years ago as a prohormone of calcitonin produced by C-cells of the thyroid gland and intracellularly cleaved by proteolytic enzymes into the active hormone. Circulating levels of ProCT in healthy subjects are below detection limit. Since 1993 when its elevated level was found in patients with bacterial infection, ProCT became an important protein in the detection and differential diagnostics of inflammatory state. The Production of ProCT during inflammation is linked with

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a bacterial endotoxin and with inflammatory cytokines (TNF, IL-6). ProCT detectable in the plasma during inflammation is not produced in C-cells of the thyroid. The probable site of ProCT production during inflammation is the neuroendocrine cells in the lungs or intestine.

Serum levels of procalcitonin are very low in healthy individuals. Although little is known about the biologic properties of procalcitonin and its origin, procalcitonin levels rise during bacterial infections but not during viral infections or inflammatory reactions of noninfectious origin. Moreover, the procalcitonin levels have been associated with prognosis during sepsis and septic shock. In pulmonary injury and pulmonary infection, the circulating concentrations of procalcitonin in infection, and other calcitonin precursors increase rapidly, probably in response to sepsis-related cytokine release from pulmonary neuroendocrine cells of the bronchial epithelium and/or mononuclear cells. Recently, Duflo and colleagues reported that serum procalcitonin could be used as a complementary diagnostic marker of VAP and, moreover, that its serum level were higher in nonsurvivors than survivors.

ASSAYS FOR PROCALCITONIN MEASUREMENT

Ghillani et al developed a specific assay with a monoclonal antibody directed against residues 96-106 of ProCT as the capture antibody and another directed against residues 70-76 as the tracer which detected only intact ProCT. The sequence 70-76 is part of the katacalcin molecule. To date, only one kit is commercially available (Lumitest ProCT, Brahms Diagnostica, Berlin, Germany). This test is an immunoluminometric assay using a capture antibody directed against residues 96-106 and a tracer antibody directed against the 70-76 sequence. While there are certainly disadvantages in this monopoly, it does have the advantage that the majority of studies of the clinical usefulness of ProCT use the assay and reference material and are thus directly comparable. The assay has a small sample volume requirement of 20 uL serum or plasma. From a practical point of view the following recommendations are suggested:
- Cut-off values for clinical decision-making are essential and must be context-specific.
- Normal values are in general < 0.5 ug/L.

SERUM AND PLASMA PROCALCITONIN IN INFECTION AND INFLAMMATION

The first seeds of interest in the relationship between ProCT and infection came from early studies using assays for calcitonin-like activity. Assicot et al using a specific assay together with an assay were the first who detect calcitonin and N-proCT, in infection. Procalcitonin measurements in the serum of 79 children with suspected infections showed that ProCT alone was raised during septic conditions and burns and that the serum levels related to the severity of microbial invasion. In 21 uninfected children the serum ProCT was < 0-1 ug/L, whereas in 19 patients with severe bacterial infections it was 6-53 ug/L, decreasing rapidly during antibiotic therapy. In local infection and in 18/21 patients with viral infection, serum ProCT was low-between 0-1 and 1,5 ug/L. Among nine severely burned patients the time course of ProCT concentration was closely related to the onset of infectious complications and acute septic episodes. Concentrations of calcitonin were normal in all subjects. This thorough prospective study led to the proposal that serum ProCT could be a new marker for severe generalized infections or sepsis.

PROCALCITONIN AS A MARKER OF INFECTION IN THE INTENSIVE CARE UNIT

Several studies have addressed the issue of which markers best indicate severity of SIRS and the onset of sepsis in the patient in the intensive care unit following major trauma or surgery. It is important to examine the findings in some detail as they differ in case mix and selection.

Oberhoffer studied patients admitted to the intensive care unit and categorized for infection. They found that the ability of infection markers to predict survival was best for serum ProCT (sensitivity 88%, positive predictive value 57%), good for serum CRP (sensitivity 66%, positive predictive value 51%) and poor for leukocyte count and body temperature. Schroder et al examined the relationship of serum levels of TNF, IL-6, CRP and ProCT to survival in patients with septic shock and found that only ProCT and IL-6 showed a difference between survivors and non-survivors; of these, serum ProCT was the most reliable because patients who died demonstrated significantly higher levels than did survivors at any time point.

In a study made by Eduard-Charles, Guerin-Valeria, in 690 patients admitted in Scale/Patis, 290 (42 were ventilated for 48 hours or more, 69 patients/40%) with VAP. These authors found that serum Procalcitonin levels were higher, and persistently high during the clinical course of non survivors.

Studies have shown that ProCT encompasses many of these features: its use significantly improves the sensitivity and specificity of a diagnosis of bacterial sepsis; it is more helpful than C-reactive Protein and...
proinflammatory cytokines indiscriminating between viral and bacterial infections and noninfectious causes of inflammation (including in the acute respiratory distress syndrome) and it is predictive of outcome.5

Clinically apparent infections are sequels of complex and variable interactions between host immune response, microbes, and their toxins. Obviously, the resulting clinical syndrome is far more complex to be reduced to elevated levels of any specific surrogate marker. Accordingly, it cannot be overemphasized that the prognostic accuracy of ProCT and its optimum cutoffs are completely dependent on use of a sensitive assay in an appropriate clinical setting. ProCT is not a substitute for a careful history and physical examination. Yet as a surrogate marker it provides important additional information and calls into question currently used “gold standards” for the clinical diagnosis of bacterial infections, including VAP. Ideally, an ultrasensitive ProCT assay should be reliably-measure, the normal circulating concentrations of this molecule in healthy individuals.6 A rapid assay assures that results can be incorporated into clinical decision making. However, as is the case for all diagnosis tests, a serum ProCT concentration must always be evaluated and be enhanced with appropriate respect for the clinical context.

If in the first day the levels of ProCT ≥ 1 ng/ml the prognosis were not good (odds ratio 12.3) and if the third day serum ProCT ≥ 1.5 ng/ml, the prognosis were worse, and if the seventh day serum level ProCT > 0.5 ng/ml, the prognoses were bad/odds ratio 64.2).

ProCT can be as a guide to anti microbial therapy in patients with lower respiratory infections (Crain et al).

The result of recent investigations suggests that the procalcitonin concentration closely parallels the severity and evolution of infection. Moreover, it seems to be useful as a prognosis marker in VAP and a guide to anti microbial therapy.

**CONCLUSION**

In conclusion, the serum procalcitonin levels may provide an early indication of VAP outcome. Further studies are required to delineate the role of this marker in early risk stratification.

**REFERENCES**