

Procalcitonin: a possible marker of invasive fungal infection in high risk patients?

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The incidence of invasive fungal infections (IFIs) in critically ill patients has constantly increased over recent decades, but their diagnosis still presents problems: conventional diagnostic (microscopic examination, fungal cultures) is sometimes insensitive, some procedures (e.g. tissue biopsy) require an aggressive approach not compatible with the critical condition of the patients, so the diagnosis is often based on clinical suspicion or is made too late. Additional markers have been proposed in early diagnosis (mannan, galactomannan, 1 \rightarrow 3-beta-D-glucan antigen tests, specific antibodies or DNA fungal detection) but some of these still require further evaluation [1-5]. Recently, the role of procalcitonin (PCT) as a surrogate marker of fungal infections has been examined. Its quantitative evaluation is considered a valid biological marker in different bacterial diseases [6-8] and it may distinguish bacteremia from non-infectious inflammatory conditions [9]. Regarding fungal infection, literature data are still few and controversial: some authors have reported that serum PCT values are lower during fungal infection than in bacterial infection [10-12].

With the aim of evaluating the diagnostic usefulness of PCT in critically ill patients, we checked for the presence of PCT, compared to *Candida* mannan (CM), 1 \rightarrow 3-beta-D-glucan (BDG) and galactomannan (GM) antigens, in three different groups of patients, all with proven/probable IFIs already diagnosed. Overall 20 subjects were investigated for serum PCT and circulating antigens at the same time of mycoses diagnosis: 8 neutropenic haematologic adult patients (HAE: 7 suffering from acute myelogenous leukemia and 1 from acute lymphoblastic leukemia), 6 preterm infants hospitalized in Neonatal Intensive Care Unit (NICU: 4 very low birth weight and 2 extremely low birth weight) and 6 patients admitted to the Intensive Care Unit (ICU: 4 previously exposed to abdominal surgical procedures and 2 to poly-trauma).

PCT values ranging from 0.5 to 1.0 ng/ml were considered moderately elevated, values > 1.0 ng/ml highly elevated. Regarding circulating antigens, samples were judged positive when levels of BDG were \geq 80 pg/ml, CM \geq 0.5 ng/ml, and GM when Index value was \geq 0.5.

Our study has two main limitations: first, the small size of examined cases, because unsupported by statistical evaluation, might have hidden some differences between different groups with fungal disease; second, our analysis was carried out in selected patients, excluding the cases of documented bacterial sepsis, in order to avoid other causes of a PCT increase.

In 8 HAE patients with fungal disease (5 pulmonary aspergillosis and 3 *Candida* blood stream infection (BSI), 2 by *Candida krusei* and 1 by *Candida parapsilosis*), PCT value remained always very low (< 0.5 ng/ml); BDG and galactomannan tests were positive in patients with pulmonary aspergillosis, while the patients with *Candida parapsilosis*/*Candida krusei* BSIs resulted negative for mannan and positive for the BDG test.

Among 6 NICU patients with BSIs caused by *Candida albicans* or *Candida parapsilosis* (3 cases respectively), PCT values were slightly increased in 4 cases (range 0.55-1.27 ng/ml); one patient showed very high values (17.1 ng/ml) but a severe bacterial BSI was confirmed at the same time; while the PCT values resulted always < 0.5 ng/ml for another patient. In all 6 neonates with *Candida* BSI, the BDG test resulted positive at diagnosis, while the CM antigen resulted > 0.5 ng/ml only in 3 patients with *Candida albicans* infection.

Among 6 ICU patients (5 with *Candida albicans* BSI and 1 with pulmonary aspergillosis), PCT values were very low (range 0.05-0.33 ng/ml) in the BSI patients; BDG and CM antigen were always positive. In contrast, the patient with aspergillosis showed a higher PCT value (1.91 ng/ml) and was BDG/GM positive.

Although it is known that PCT is also synthesized to some extent by leukocytes [13], some studies have shown that PCT may be an infection marker in neutropenic patients [14-16]. Our data highlight low PCT levels in neutropenic haematologic patients, so its value might be underestimated.

In different adult patients, Petrikos et al. [10] found PCT values lower in the early phase of IFIs. Besides, they report that the evaluation of mannan antigen in parallel may help to discriminate between invasive fungal and bacterial infections, especially in the case of *Candida albicans* infection. Also Di Stefano [11] observed that PCT values are lower during fungal than in bacterial infection in preterm infants. Our data suggest that low or slightly increased PCT levels (HAE and NICU patients with *Candida* BSIs respectively), evaluated in tandem with circulating antigens (CM, GM, and BDG), could help to indicate fungal infection and expand the laboratory research.

In surgical patients with clinical signs of sepsis and risk factors for fungal infections, Martini et al. [12] consider a PCT value less than 2 ng/ml as cut-off point to distinguish between sepsis due to *Candida* infection and sepsis of bacterial origin. In surgical patients with candidemia we found very low PCT levels (from 0.05 to 0.33 ng/

ml) and higher values only in the patient suffering from aspergillosis (1.91 ng/ml).

In conclusion, our study suggests that PCT valuation in the serum of onco-haematologic or surgical patients, in contrast to circulating antigens, is not essential to diagnose a deep mycosis. The role of PCT in serum of critically ill patients depends on the population examined and its clinical setting. In fact, its valuation could be useful in premature infants being characterized by

insufficiently specific symptoms. PCT values from 0.5 to 1 ng/ml could focus the suspicion of an infectious process other than the bacterial sepsis and lead us to assess fungal circulating antigens to consider a fungal sepsis. Based on this observation, other studies on larger numbers of cases (especially in NICU patients) are warranted to analyze the predictive value of PCT in fungal diseases.

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