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LESS IS MORE IN INTENSIVE CARE

Biomarkers in the ICU: less is more? Not sure

Pedro Póvoa[1,2,3*], Jorge I. F. Salluh[4,5] and Thiago Lisboa[6,7,8]

Why do we use biomarkers?

In the twenty-first century, there is still no gold-standard test to diagnose infection [1] and it relies on a combination of unspecific systemic signs, signs of organ involvement, and microbiologic documentation [2]. Since these clinical signs lack accuracy and microbiologic results are unavailable early in clinical course, antibiotics are frequently prescribed without a definite diagnosis of infection [3]. These limitations led clinicians to search for biomarkers that could be used as surrogate markers of infection [4, 5]. From the hundreds of biomarkers that were studied, only two, C-reactive protein (CRP) and procalcitonin (PCT), are present in our daily practice. Despite frequent, routine use is not backed by undisputable evidence.

What are the questions that biomarkers can answer?

The clinical usefulness of biomarkers can be divided into prognostic and predictive. In infection and sepsis, the vast majority of the available biomarkers have been evaluated to assess prognosis [4]. But the clinical usefulness of a biomarker that only determines the risk of poor outcomes remains limited [4, 6].

To define whether a patient that looks septic is indeed infected [7], we need predictive biomarkers that may improve our process of triage, diagnosis, risk stratification, and assessment of response to antibiotics [8]. Unfortunately, studies on these are scarce and the idea of a perfect biomarker remains elusive. The ideal predictive biomarker should present very low or undetectable levels if the patient is not infected, its concentration should rise ideally before clinical signs of infection, and its levels should anticipate clinical course of infection either decreasing if the patient improves or remain elevated if the infection is not resolving [6, 9].

Are biomarkers potentially harmful?

We are in an era of a huge development of new diagnostic technologies [10]. In infection and sepsis, the next dilemma will be to know the usefulness of each of these new biomarkers/technologies as well as their role in infection management. The next big question is whether in the near future we will decide to treat an infection just on the basis of the surrogate biomarker. In critically ill patients, most biomarkers do not allow identifying clear cut-off values and significant overlap is present. So, although central tendency measures such as mean may differ, no definite point or level is available to unequivocally discriminate between two different pathologic statuses most of the time. Ideally, only after identification of a cut-off that is accurate and reproducible to identify the pathologic status, should we be confident to run trials in which biomarker alone will drive specific interventions.

How many biomarkers do we need?

Let us consider the use of panels of biomarkers. There are several examples of studies assessing the best possible combination of biomarkers in the diagnosis of infection. Probably, the most complete started with an exploratory phase where the authors assessed > 150 biomarkers; then, a total of nine were selected. And a combination of the best three, related to inflammation, coagulation, and renal injury, gave the best diagnostic accuracy, with an area under the curve (AUC) of 0.8, using a complex equation to determine the so-called sepsis score [11].

But is it necessary and feasible in clinical practice to perform such a complex and expensive approach? In the CAPTAIN study, the authors evaluated the diagnostic accuracy of 29 biomarkers, 10 whole blood RNAs, and 14 leukocyte surface markers and they found that no isolated biomarker nor any combination performed better than CRP alone (AUC = 0.73) [12].

*Correspondence: povoap@netcabo.pt
[3] Unidade de Cuidados Intensivos Polivalente, Hospital de São Francisco Xavier, CHLO, Estrada Do Forte Do Alto Do Duque, 1449-005 Lisbon, Portugal
Full author information is available at the end of the article

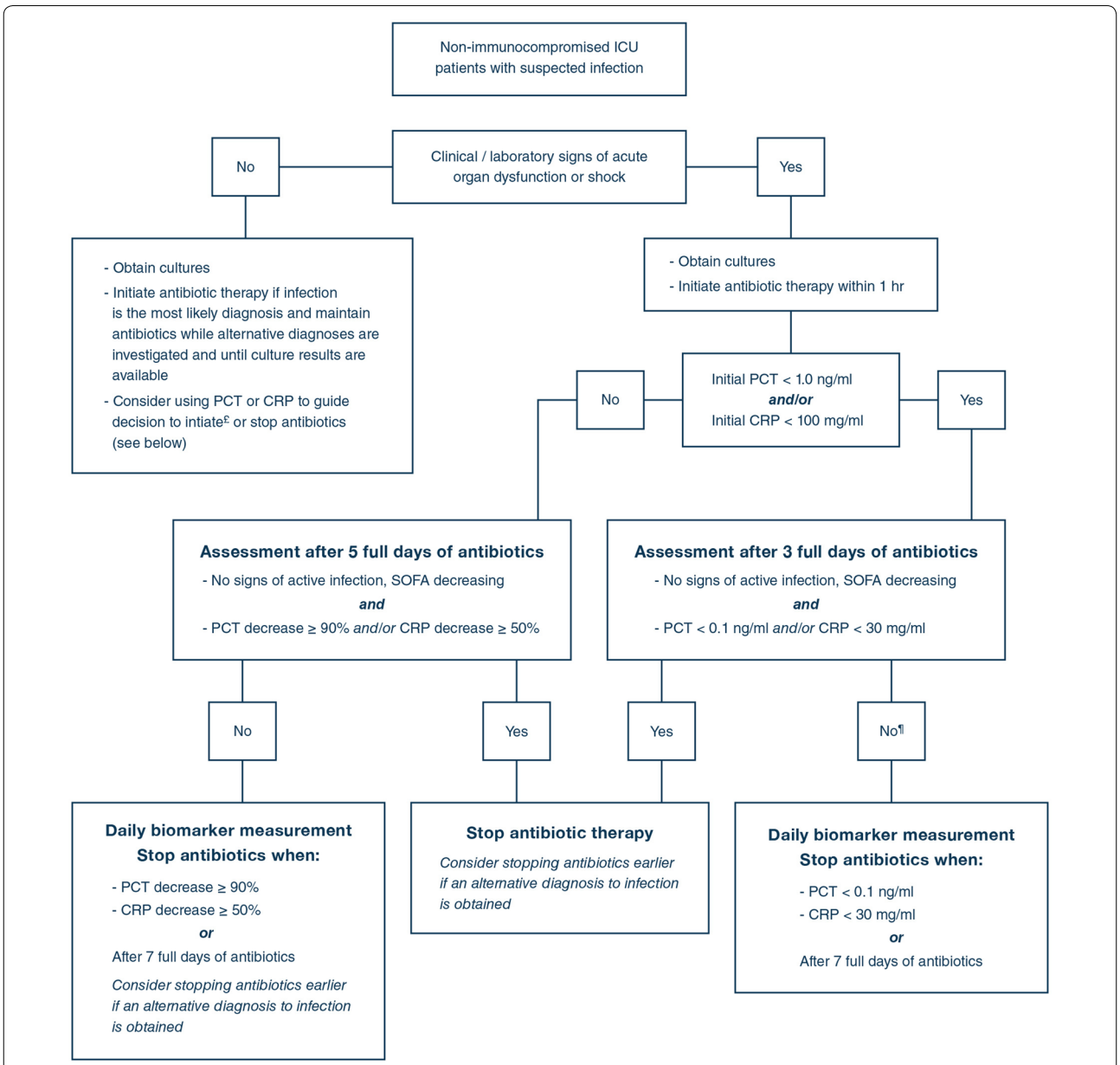

Fig. 1 Use of biomarker to guide antimicrobial therapy in critically ill patients. This flowchart does not apply to immune-compromised patients (e.g., febrile neutropenia) or to patients with infections requiring long-term antibiotic therapy (e.g., infectious endocarditis, cerebral abscess, bacteremia due to Staphylococcus aureus). **£** Initiating antibiotics for all critically ill patients with suspected infection is probably the safest decision, regardless of the levels of laboratory biomarkers. However, this decision must be reassessed daily. PCT and CRP are proposed as additional tools to diagnose infection, and different cut-off levels have been proposed in the literature. **¶** Consider stopping antibiotics before day 7 in patients with no proven infection (e.g., negative cultures) regardless of the levels of CRP or PCT. SOFA, Sequential Organ Failure Assessment [13]

As a result, our current proposal is to use one biomarker, ideally using serial determinations [13, 14].

Do we need new trials of biomarker-guided antibiotic therapy?

Although antibiotics are excellent drugs, they are also associated with several well-known side effects such as emergence of multidrug resistant pathogens, impact on microbiota, toxicity, and increased costs. Biomarker-guided antibiotic therapy is emerged as an attractive tool to determine its duration. PCT is by far the most studied biomarker in several randomized controlled trials (RCT) and meta-analysis, altogether showing significant decreases in duration of antibiotic therapy without any

significant negative impact on prognosis [1, 4]. However, in these RCT the duration of therapy in control groups is systematically above the recommendations based on the best current evidence [14]. In a recent meta-analysis, the decreased duration of antibiotic therapy with PCT-guided algorithms was primarily observed in RCT with high protocol overruling and with algorithms combining PCT and CRP [15]. Even though clinicians typically have a low adherence to general protocols, namely fixed antibiotic duration, biomarkers could provide additional evidence and confidence to discontinue antibiotics earlier.

When and how to use biomarkers?

With machine learning (ML) and other techniques becoming ubiquitous, medicine waits for the application of the "perfect" algorithm potentially moving clinical reasoning and clinical judgment into the background. We are spending more time looking at the computer screen than looking at the patient. This over reliance in the test results is quite dangerous since the ideal biomarker has not yet been discovered. When to use biomarkers? Whenever we need additional information at the bedside, namely in two situations: to help clinicians in the decision to stop antibiotics but using a double-trigger strategy combining biomarker-guided therapy and fixed duration based on the best available evidence [8, 13] (Fig. 1) and also in the early identification of infected patients that are not improving.

Further situations in which biomarkers can help us include improving phenotyping of clinical syndromes, with promises to enrich RCT entry criteria and move on personalized precision medicine direction, and as an additional feature in ML models improving our ability to predict response to therapy and outcomes.

So, how to use biomarkers? We recommend using serial determinations rather than single measurements since these are more informative and should always be considered along with a dynamic evaluation of the clinical picture. Taking into consideration that the ideal biomarker is not yet available, we have to use cautiously these results. And finally, biomarkers should **NEVER** be used as a stand-alone test, but always in conjunction with a complete clinical evaluation and with a perfect knowledge of the biology, interferences, strengths, and limitations of the biomarker.

Author details
[1] NOVA Medical School, CHRC, New University of Lisbon, Lisbon, Portugal. [2] Center for Clinical Epidemiology and Research Unit of Clinical Epidemiology, OUH Odense University Hospital, Odense, Denmark. [3] Unidade de Cuidados Intensivos Polivalente, Hospital de São Francisco Xavier, CHLO, Estrada Do Forte Do Alto Do Duque, 1449-005 Lisbon, Portugal. [4] D'Or Institute for Reasearch and Education, Rio de Janeiro, Brazil. [5] PostGraduation Program, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [6] Programa de Pos Graduacao Em Clencias Pneumologicas, Hospital de Clinicas, Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil. [7] Universidade LaSalle, Canoas, Brazil. [8] Research Institute, Hospital Do Coração, São Paulo, Brazil.

Compliance with ethical standards

Conflicts of interest
The authors declare no conflicts of interest related to this topic.

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References

1. Póvoa P, Salluh JIF (2012) Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. Ann Intensive Care 2:32. https://doi.org/10.1186/2110-5820-2-32
2. Vincent JL, Mercan D (2000) Dear sirs, what is your PCT? Intensive Care Med 26:1170–1171. https://doi.org/10.1007/s001340000605
3. Klein Klouwenberg PMC, Cremer OL, van Vught LA et al (2015) Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care 19:1–8. https://doi.org/10.1186/s13054-015-1035-1
4. Nora D, Salluh J, Martin-Loeches I, Póvoa P (2017) Biomarker-guided antibiotic therapy—strengths and limitations. Ann Transl Med 5:208–208. https://doi.org/10.21037/atm.2017.04.04
5. Póvoa P, Coelho L, Bos LD (2019) biomarkers in pulmonary infections. Clin Pulm Med 26:118–125. https://doi.org/10.1097/CPM.0000000000000322
6. Póvoa P (2008) Serum markers in community-acquired pneumonia and ventilator-associated pneumonia. Curr Opin Infect Dis 21:157–162. https://doi.org/10.1097/QCO.0b013e3282f47c32
7. Vincent JL (1997) Dear SIRS, I'm sorry to say that I don't like you. Crit Care Med 25:372–374. https://doi.org/10.1097/00003246-199702000-00029
8. Salluh JIF, Souza-Dantas VC, Póvoa P (2017) The current status of biomarkers for the diagnosis of nosocomial pneumonias. Curr Opin Crit Care 23:391–397. https://doi.org/10.1097/MCC.0000000000000442
9. Marshall JC, Vincent JL, Fink MP et al (2003) Measures, markers, and mediators: toward a staging system for clinical sepsis. A report of the fifth Toronto sepsis roundtable, Toronto, Ontario, Canada, October 25–26, 2000. Crit Care Med 31:1560–1567. https://doi.org/10.1097/01.CCM.0000065186.67848.3A
10. Poole S, Kidd SP, Saeed K (2018) A review of novel technologies and techniques associated with identification of bloodstream infection etiologies and rapid antimicrobial genotypic and quantitative phenotypic determination. Expert Rev Mol Diagn 18:543–555. https://doi.org/10.1080/14737159.2018.1480369
11. Shapiro NI, Trzeciak S, Hollander JE et al (2009) A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med 37:96–104. https://doi.org/10.1097/CCM.0b013e318192fd9d
12. Parlato M, Philippart F, Rouquette A et al (2018) Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study. Intensive Care Med 44:1061–1070. https://doi.org/10.1007/s00134-018-5228-3
13. Salluh JIF, Nobre V, Povoa P (2014) Using procalcitonin to guide antimicrobial duration in sepsis: asking the same questions will not bring different answers. Crit Care 18:1–3. https://doi.org/10.1186/cc13870
14. Lisboa T, Salluh J, Povoa P (2018) Do we need new trials of procalcitonin-guided antibiotic therapy? Crit Care 22:17. https://doi.org/10.1186/s13054-018-1948-6
15. Pepper DJ, Sun J, Rhee C et al (2019) Procalcitonin-guided antibiotic discontinuation and mortality in critically Ill adults: a systematic review and meta-analysis. Chest 155:1109–1118. https://doi.org/10.1016/j.chest.2018.12.029