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Procalcitonin as a biomarker for infection and sepsis: Yet again

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Biomarkers may be characterized as diagnostic, distinguishing between two states (say, infected or non-infected); prognostic, informing of a likely outcome (say, mortality); or predictive, if a treatment effect is differential between biomarker positivity and negativity [1]. One of the most discussed biomarkers in the infectious diseases and critical care literature is procalcitonin [2-4], a polypeptide that serves as the precursor for calcitonin in thyroid gland C cells and is released in response to microbial toxins and pro-inflammatory mediators [5]. Procalcitonin qualifies as both a diagnostic (an infection or sepsis marker) and predictive (a guide to antimicrobial therapy) biomarker. This being said, procalcitonin biomarker performance has been subjected to a large number of meta-analyses [6-20], suggesting a degree of disquiet regarding the actual level of evidence for procalcitonin utility.

We first summarize certain key parameters of procalcitonin performance as a diagnostic biomarker in 6 meta-analyses, conducted between the years of 2004-2015; author sub-group analyses are not considered (Table 1) [11,14,16-19]. Where reported, heterogeneity was a marked feature, even when restricted to a more circumscribed population of the "critically ill"; the components of heterogeneity presumably reflecting such factors as different procalcitonin assays and threshold levels, patient subgroups, endpoint prevalence, primary study inclusions and exclusions, and study quality / bias [5]. Analytic methods reflected year of publication, with the earlier studies [16-19] using the linear regression model of Moses et al, as opposed to the mixed-effects bivariate approach of the two more recent studies [11,14]; a point of importance for Wacker and co-authors [14]. Overall, the diagnostic performance could at best be described as modest, a point conceded by some of the authors [11, 16, 18] and reiterated by Afshari and Harbath [22], commenting upon the somewhat fulsome conclusions of Wacker *et al.* [14]. The former noted that the sensitivity of 77% corresponded to 23% of patients not receiving adequate therapy and a specificity of 79% corresponded to 21% being unnecessarily treated (Table 1); similarly, a positive likelihood ratio of 3.67 and a negative likelihood ratio of 0.29, being small and containing no information, were "… of little use for guiding initial treatment decisions", especially in the critically ill with a high pre-test sepsis probability [22]. As diagnostic meta-analyses have had a history of poor reporting [23] compared with meta-analyses reporting treatment effects of randomized controlled trials, the attendant vigorous correspondence [22, 24-29] to some of the above meta-analyses is perhaps not surprising.

One outstanding feature of these diagnostic meta-analyses was the variable cut-point procalcitonin thresholds used in the primary studies. Again in a response to the meta-analysis of Wacker *et al.* [14], Ruecker and Schumacher [28] suggested, in agreement with a preliminary observation by Wacker et al, that "investigators of the primary studies seemed to select cutoffs such that they maximised the sum of sensitivity and specificity". They further elaborated an analysis that modelled the assumption that the investigators of the primary studies selected their cutoff such that it maximised a weighted sum of sensitivity (Se) and specificity (Sp): $\lambda.\mathrm{Se} + (1-\lambda).\mathrm{Sp}$; λ (between 0 and 1) was the weight the study investigators attributed to the sensitivity and a λ of 0·5 attributed equal weights to sensitivity and specificity, equivalent to maximisation of the Youden index. The estimate of λ was 0.491, quite close to 0.5, supporting their initial hypothesis. Estimates of pooled sensitivity and specificity were 0.72 and 0.73, even less that those estimates subjected to critique by Afshari and Harbath [22]. In a more recent study Steinhauser et al [30] proposed to model the distribution functions of the underlying biomarker by applying a linear mixed effects model, accounting for a cross-study heterogeneity and dependence (or correlation) of sensitivity and specificity. That is, an attempt was made to utilize all of the available information. Again accessing data from the meta-analysis of Wacker *et al.* [14], 54 data points in total for 26 different values of the procalcitonin thresholds were obtained, yielding a model sensitivity of 0.71 (0.63; 0.78) and a specificity of 0.81 (0.74; 0.86], similar to the previous estimates of Ruecker and Schumacher [28]. The estimated optimal threshold for procalcitonin in this analysis was 1.2 ng/ml. Such an approach to the problem of multiple diagnostic thresholds appears to be a most promising initiative and has been implemented in at least one independent study [31].

Given that procalcitonin as a diagnostic biomarker for sepsis / infection has consistently failed to achieve sensitivities and specificities above 80% (Table 1), it may be surprising that its use has been incorporated into a number of randomized controlled trials as an antibiotic stewardship guide. How are we to understand this? As with any biological variable, single measurements will be subject to random variability and measurement error, potentially generating regression dilution bias and regression to the mean, and repeated measurement would be, prima facie, preferable [32]. Thus algorithms incorporating time-dependent (daily or otherwise) procalcitonin assays have been incorporated into decision-making with respect to anti-biotic prescription [33].

The accumulation of RCTs over time obviously limits a definitive answer to the utility of procalcitonin as a predictive biomarker. We

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Table 1. Meta-analysis of Prolactin measurement in the years of 2004-20015

Study	Simon	Uzzan	Tang	Jones	Wacker	Hoeber
Year	2004	2006	2007	2007	2013	2015
Endpoint	Infection	Sepsis	Sepsis	Bacteraemia	Sepsis	Bacteraemia
Population	hospitalised	ICU & trauma	critically ill	ambulatory	critically ill	hospitalized
Analytic method	regression model	regression model	regression model	regression model	bivariate model	bivariate model
Prevalence (%)			31, 88	4, 54	34, 88	
Parameters						
Total n		3943	2097	2008	3244	16514
Pct cut-off (ng/mL)		0.6, 5	2, 20	0.5-2	1.1 (0.5, 2.0)	0.5
I^2 (%: 95%CI)			52.6	64	96 (94, 99)	86
(S)ROC (95%CI)			0.79 (0.73, 0.83)	0.84 (0.75, 0.90)	0.85 (0.81, 0.88)	0.79
Sens (%: 95%CI)	88 (80, 93)	42, 97	71 (67, 76)	76 (66,84)	77 (72, 81)	76 (72, 80)
Spec (%: 95%CI)	81 (67, 90)	48, 100	71 (67, 76)	70 (60, 79)	79 (74, 84)	69 (64, 72)
+LR	3.58 (2.99, 4.28)		3.03 (2.51, 3.65)		3.67	
-LR	0.18 (0.15, 0.23)		0.43 (0.37, 0.48)		0.29	
ORd (95%CI)		15.7 (9.1, 27.1)	7.79 (5.86, 10.35)	9.96 (5.72, 17.02)		

Pct: procalcitonin; (S)ROC: (Summary) Receiver Operator Characteristic Curve; Sens: sensitivity; Spec: specitivity; +LR: positive likelihood ratio; -LR: negative likelihood ratio; Ord: diagnostic odds ratio; CI: confidence interval

present snapshots at the publication juncture of two reviews; by Pavoa and Sullah in 2012 and Andrioli and co-workers in 2017 [6,34]. The former reviewers cited 7 randomized controlled trials (2007 to 2011) assessing the role of procalcitonin-guided antibiotic stewardship in adult critically ill patients. Despite repeated association of this stewardship with a decrease in the duration of antibiotic therapy, the authors identified several trial limitations; high rate of patient exclusion and algorithm overruling, long duration of antibiotic therapy in the control group, disregarding of the effect of renal failure on procalcitonin level, and possible higher mortality and higher late organ failure in the procalcitonin arm. They concluded that the role of procalcitonin-guided antibiotic stewardship was "uncertain" [34]. Andrioli et al identified 10 trials with 1215 participants (search date to July 2015) and were more forthright in their conclusions: "Up-to-date evidence of very low to moderate quality, with insufficient sample power per outcome, does not clearly support the use of procalcitonin-guided antimicrobial therapy to minimize mortality, mechanical ventilation, clinical severity, reinfection or duration of antimicrobial therapy of patients with septic conditions" [6]. However the authors reported a second search in October 2016 and identified 3 further trials (not included in their analysis) with a total of 2695 participants; two multi-site and one single-centre [35-37]. It is not the purpose of this paper to conduct yet another meta-analysis of the use of procalcitonin; a simple search conducted using Web of Science™ on June 26th with the terms "procalcitonin" and "meta-analysis" identified 191 hits. We suffice to summarize the results of the two multi-site trials. Bloos *et al.* recruited 1089 patients with severe sepsis or septic shock and found no mortality effect of procalcitonin-guided antimicrobial therapy, but a reduction of antibiotic exposure by 4.5%, with no influence on resource utilization. They concluded that "The application of a procalcitonin-guided algorithm needs further evaluation" [35]. De Jong et al [36] enrolled 1546 critically ill patients with assumed or proven infection and found an unexpected 5.4% (p=0.01) 28-day mortality reduction and a decrease in both antibiotic consumption and treatment duration with procalcitonin-guided antimicrobial therapy. Of interest, the mean per patient saving in antibiotic costs of €34 (with an average of 7 procalcitonin measurements per patient) had a break-even cost for procalcitonin of less than €4 per measurement. At the hospital of the authors of this paper the cost per measurement is €38. Again, adherence to the antibiotic stopping rules was variable (40-50%) in both studies.

Where do we stand? A single procalcitonin measurement in, say, the emergency department or intensive care unit of a hospital would not appear to be of benefit in guiding decision making for diagnosis and therapy of infection/sepsis. The benefits or otherwise of procalcitonin-guided antimicrobial therapy are still uncertain and would appear to depend upon the cost and medical structure of each jurisdiction.

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