Procalcitonin Sub-Study

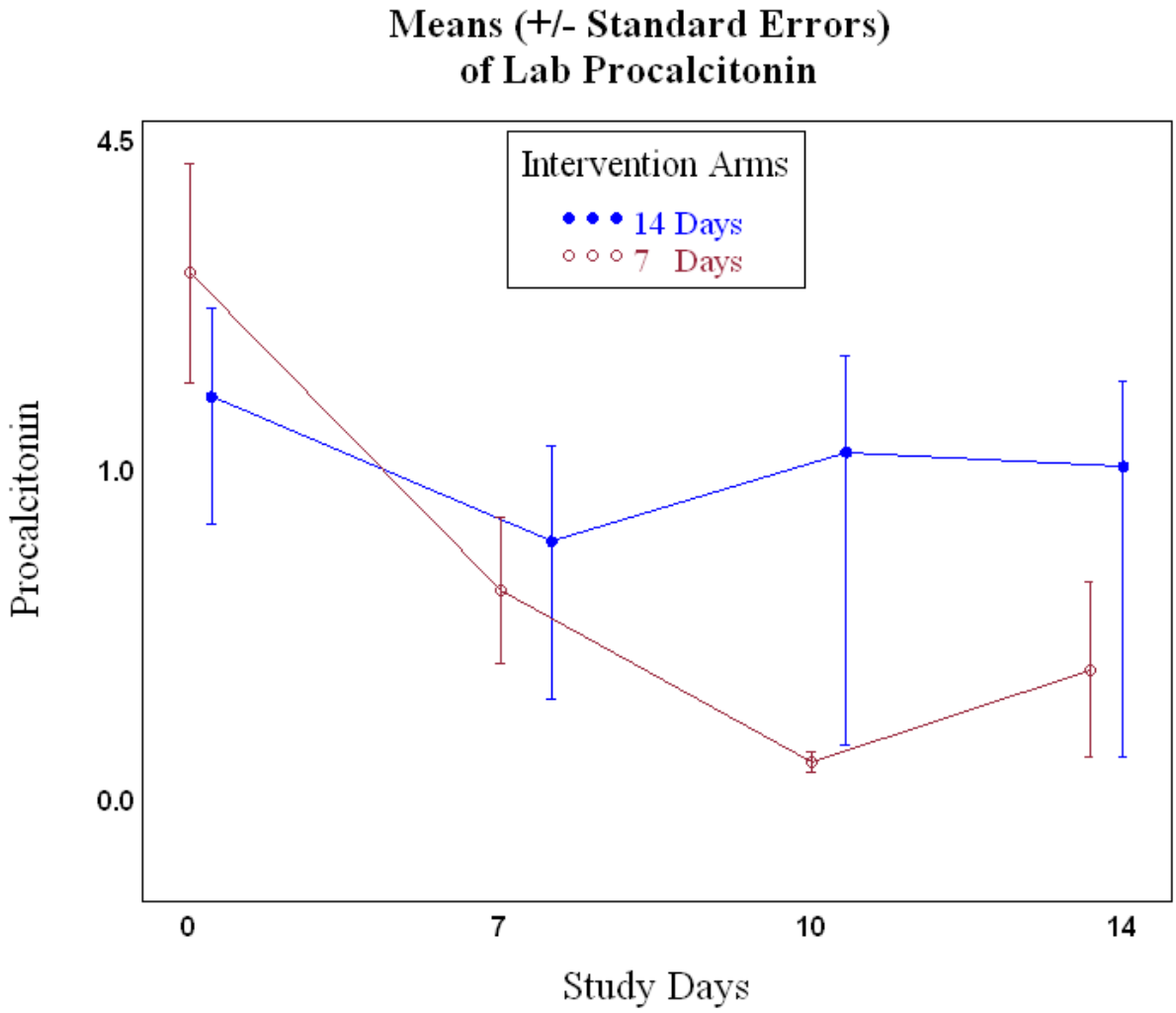
The BALANCE Trial is randomizing patients to fixed shorter (7 days) versus fixed longer (14 days) treatment for bacteremia, rather than assessing an individualized biomarker-guided antibiotic stopping rule.

However, in this procalcitonin (PCT) sub-study we will assess the time profile of PCT measurements among a subset of the first 286 consenting patients enrolled at 3 BALANCE study sites. Blood samples will be drawn on the randomization day and at days 7, 10 and 14 from the index blood culture collection to measure PCT levels. Around 3 ml of whole blood will be drawn from those participants who have signed the optional additional informed consent for blood collection. Samples will be stored in a freezer at -25 ± 6°C at each participating site, and then batched and forwarded to the central study site for measurement at the end of the study period. Analysis will be performed using the Biomerieux MiniVidas assay (Biomerieux, QC, Canada). The results will not be made available to the treating team, because this could unduly influence clinical practice and protocol adherence, and is ethical because none of the participating sites are currently using PCT as part of routine clinical practice. Following study completion, we will compare the decline in procalcitonin levels from day 7 to day 14, among patients randomized to 7 versus 14 days of antibiotic treatment. We hypothesize that the decline in procalcitonin levels will be non-inferior among those patients receiving 7 days of treatment.

The primary statistical analysis will measure the 'difference in differences' between day 7 to 14 procalcitonin levels in the two treatment groups. We will require 286 patients (143 in 7 day arm, 143 in 14 day arm group) to demonstrate that the decline in PCT is non-inferior with shorter course treatment (assuming mean change in PCT of -0.7 in both arms, standard deviation of 3.0, non-inferiority margin 1.0, power 0.8, alpha 0.025). These parameters are derived from our pilot RCT work (data below), as well as prior Canadian Critical Care Trials Group studies of longitudinal PCT levels in critical ill patients with sepsis. (Reynolds *CCM* 2012).

In secondary analyses, we will assess the proportion of patients in each intervention arm with PCT levels below 0.25 - the assay treatment threshold above which antibacterial treatment is recommended. This comparison will be made at the randomization day, day 7, day 10 and day 14.

In the BALANCE pilot RCT, we have already demonstrated the feasibility of this approach among a subset of 13 patients. Among this group, 11 of 13 (85%) consented to this optional additional blood sampling for PCT levels. Processing was successful for 100% of specimens. The means and standard errors of PCT levels at randomization day and days 7,10 and 14 are displayed for each intervention arm below.


Means (+/- Standard Errors)
of Lab Procalcitonin
Intervention Arms
14 Days
7 Days
Procalcitonin
4.5
1.0
0.0
0
7
10
14
Study Days