**Selecting the Most Appropriate Intervention to Study: Fixed Duration Therapy versus Individualized Durations Based on Clinical or Biomarker Based Stopping Rules**

Ideally antibiotic treatment duration should be individualized, and patients should be treated until their infection has clinically resolved (and likely not longer). Unfortunately, a randomized controlled trial based on a clinical stopping rule is not feasible in ICU patients, because there are no specific markers of persistent infection. Fever, for example, is common in ICU, and in only half of cases represents infection. Hemodynamic instability (with vasopressor dependence), respiratory failure (with mechanical ventilation dependence) and multi organ failure can be triggered by infection, but persist long after the offending pathogen and focus have been sterilized. The difficulty in diagnosing infection in ICU and monitoring clinical response to treatment, has generated considerable interest in the use of novel biomarkers to guide antibiotic treatment duration. One biomarker, procalcitonin, has been used successfully to reduce average treatment durations in sepsis. However, only a minority of these patients were bacteremic. Moreover, more than half of patients randomized to the procalcitonin group, were not given algorithm-guided treatment, because the attending physician believed a biomarker-informed duration was inappropriate. Complex clinical rules or potentially inaccessible or expensive biomarkers are unlikely to be used in most Canadian ICUs, impairing the translation of these study findings. Biomarker-based antibiotic duration of therapy is even less feasible for most of the world's population in middle-income or least developed countries.

Instead, we favour a randomized trial of fixed shorter versus longer duration antibiotic therapy, guided by our preliminary studies, as the most easily transferrable result to immediately inform clinical practice. This approach has been successful in 23 randomized controlled trials of infectious diseases that are potentially complicated by bacteremia, including 13 trials of pneumonia, 6 of pyelonephritis, 3 of intra-abdominal infection, and 1 of skin and soft tissue infection. Most notably, a trial in ventilator-associated pneumonia has altered the standard of care for this infection to shorter duration therapy (8 days). However, appreciating the future promise of individual patient focused biomarkers to further nuance treatment decisions, in our procalcitonin substudy we will evaluate how well procalcitonin would have corroborated the decision to stop at 7 days in the shorter duration treatment arm (proportion of patients with procalcitonin levels <0.25 in each arm), and we will also confirm that reductions in procalcitonin levels from day 7 to 14 will be non-inferior in those receiving 7 versus 14 days of antibiotics. Data from the main BALANCE trial, and this procalcitonin sub-study, will provide synergistic information to inform treatment duration for critically ill patients with bacteremia.