A new generation of sepsis therapeutics is in development to promote clearance of microbial pathogens or their mediators and regulate the deleterious elements of the systemic host response in sepsis/septic shock. These investigations are undertaken with the realization that prior efforts to improve outcomes in sepsis have failed either by: (1) failing to account for the intrinsic complexity of sepsis pathophysiology; or (2) assuming that septic patients would respond in a uniform and predictable manner to the experimental therapy. Clearly the definition for sepsis as an infection with systemic inflammatory response syndrome does not define a patient population that consistently and predictably reproduces the same outcome with novel sepsis therapeutics. The current sepsis treatments in clinical development predictably reproduce the same outcome with novel sepsis therapies.

**Abstract:** A new generation of sepsis therapeutics is in development to promote clearance of microbial pathogens or their mediators and regulate the deleterious elements of the systemic host response in sepsis/septic shock. These investigations are undertaken with the realization that prior efforts to improve outcomes in sepsis have failed either by: (1) failing to account for the intrinsic complexity of sepsis pathophysiology; or (2) assuming that septic patients would respond in a uniform and predictable manner to the experimental therapy. Clearly the definition for sepsis as an infection with systemic inflammatory response syndrome does not define a patient population that consistently and predictably reproduces the same outcome with novel sepsis therapeutics. The current sepsis treatments in clinical development predictably reproduce the same outcome with novel sepsis therapies.

**Conclusion:** Novel therapeutics now under clinical evaluation are targeting one of the following: the pathogen or microbial mediators (hemofilters); epithelial barrier support strategies (protease inhibitors, growth factors); endothelial barrier protectors (angiopoietin-1/Tie 2, anti-complement antibodies, thrombomodulin, etc.); immune reconstitution agents (anti PD1 antibody, thymosin–1, GM-CSF), or other targets (gelsolin, pro–protein convertases, HMGB-1 antibodies, and pro-resolving agents). In this era of precision medicine it is now possible to define a responsive patient population to a specific agent with much better accuracy. This biomarker-based strategy is now being put to the test in current clinical trials in sepsis with new therapeutic agents.