Online Supplement Table S1: Future research ideas

SUBJECT	IDEAS
Diagnosis	1. Assessment of the impact of qualitative proximal versus qualitative distal sampling on prognosis and broad-spectrum antibiotic-free survival in VAP 2. The study should involve equal proportions of ICUs that routinely use one or the other method and should follow careful guidelines for initiating treatment and de-escalation. Treatment of CNS should be discouraged in both groups. Appropriate therapy in both groups should be chosen by an external physician. 3. Assessment of the impact of new molecular techniques for microbiological diagnosis of VAP, early adequate therapy and antimicrobial stewardship 4. When new diagnostic methods become available, should the samples tested be tracheal aspirates or BAL? Can these types of method help us to reduce antibiotic use, or should they only be used with a negative intent, i.e. to narrow the choice if a pathogen is absent, but not always to broaden it if a pathogen is present?
Empirical and targeted antibiotic treatments	1. In patients with HAP/VAP should PK/PD-optimized therapy be used to improve bacterial killing and outcomes? 2. Should we use aerosolized antibiotics as an adjunctive therapy to systemic antibiotics for treating patients infected with very difficult-to-treat microorganisms, such as XDR/PDR Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae? 3. Should we use a regimen combining at least two antibiotics throughout the duration of treatment (and not for only 3-5 days) to treat patients infected with very difficult-to-treat microorganisms, such as XDR/PDR Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae? 4. In patients with HAP/VAP, should antimicrobial therapy be de-escalated once culture results are available in order to avoid the emergence of drug-resistant microorganisms? 5. In patients with HAP/VAP infected with ESBL-producing Enterobacteriaceae, should we systematically use a carbapenem throughout the entire duration of treatment? 6. Is a 4-5 day antibiotic regimen used according to PK/PD characteristics as effective as a 7-8 days regimen in terms of VAP outcome (response, mortality, recurrence)? Does it reduce superinfection and the emergence of MDR microorganisms (VAP caused by Pseudomonas and *Acinetobacter* would be excluded)? 7. Is a 7-8 day antibiotic regimen non-inferior to a 10-14 days antibiotic regimen for *Pseudomonas* and *Acinetobacter* VAP that shows signs of quick response?

	8. Does a fall in procalcitonin at day 7-8 of therapy for MDR/XDR pathogens predict the safety of discontinuing antibiotics? Is a falling PCT level superior to serial clinical exam or scores such as CPIS for determining the safety of antibiotic discontinuation at 7-8 days for MDR/XDR pathogens? 9. Is 7-8 days of appropriate antibiotic therapy sufficient for MDR/XDR pneumonia in immunocompromised patients? Can falling PCT levels predict which immunocompromised patients with MDR/XDR pneumonia can be treated with 7-8 days of therapy? 10. If PCT is not falling at 72-96 hours, how frequently will repeated lower respiratory cultures detect persistence of the original infection and the development of antibiotic-resistant infection?
Prevention	1. What is the most cost-effective antibiotic approach for the prevention of VAP? Is it SOD, SDD, aerosolized antibiotics, or short-course parenteral therapy? 2. Can the short-term administration of aerosolized antibiotics to high-risk ventilated patients reduce the occurrence of VAP and other complications? 3. What is the role of non-traditional agents such as the use of monoclonal antibodies, vaccines, antimicrobial peptides and immunomodulators for the prevention of VAP and other ICU-acquired infections? 4. The clinical effectiveness of SOD and SDD in settings with high rates of antibiotic-resistant bacteria should be established. 5. The potential effect of chlorhexidine use on mortality and its determinants should be studied. 6. The benefits of chlorhexidine use in relation to dose, regimes and formulations should be established.