SUJET DE THESE ED 652 2026

Sujet de thèse

Informations sur l'équipe	
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Informations sur le sujet	
Titre du sujet	Development of an *in vitro* model mimicking lung environment for studying bacterial interactions to better predict ventilator-associated pneumonia
Mots clés	Ventilator-associated pneumonia, respiratory microbiota, *Staphylococcus aureus*, bacterial coculture, *in vitro* model
Présentation du projet doctoral	Ventilator-associated pneumonia (VAP) remains the most common healthcare-associated infection and the first cause of antibiotic prescription in intensive care units (ICU) [1]. It affects 10 to 25% of patients who require mechanical ventilation (MV) for more than 48 hours [2]. Colonization of the respiratory tract is a recognized risk factor [3], but it is not systematically associated with the onset of VAP. *Staphylococcus aureus* is a major pathogen, accounting for nearly a quarter of VAP cases in Western Europe [4]. However, many patients colonized with *S. aureus* never develop VAP, suggesting a potential protective role of the respiratory microbiota. Several studies exploring respiratory microbiota have detected a decreased proportion in some taxa (such as *Corynebacterium, Rothia* or *Bifidobacterium*) during MV [5]. These taxa appear to play a protective role in other lung diseases against the adhesion of pathogens to lung cells [6] and towards inflammation [7], however their role in VAP has not yet been explored. In addition, in cohorts of MV patients who did not receive antibiotics and who developed early *S. aureus* VAP, our unit showed an increase in the proportion of certain anaerobic bacteria (mainly *Prevotella*) a few days before VAP onset [8]. Several hypotheses point to an important role for these anaerobic bacteria in the metabolism of respiratory mucus. Anaerobic bacteria of the phylum Bacteroidetes (which includes *Prevotella*) possess an enzymatic arsenal that enables them to break down mucus, which is the sole source of nutrients for bacteria in the respiratory tract [9]. The overall objective of the thesis is to show a protective or deleterious effect of some taxa of the respiratory tract microbiota on the development of early *S. aureus* VAP and to develop a quantitative PCR-based tool targeting those bacteria to better identify patients at high and low risk of VAP development.

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	The first part of the thesis will aim to develop a coculture model to evaluate the role of specific species of the respiratory microbiota on *S. aureus* growth. *Ex vivo* coculture in liquid sputum medium and in a lung-on-chip model will be developed. Using this organoid model, analyses of the lung microbiota evolution and metabolic pathways that either facilitate or block *S. aureus* growth (having therefore a deleterious or protective effect on the development of VAP) will also be investigated through the complementary assessment of bacterial transcriptomic, human mucus and metabolite composition over time. Ultimately, specific PCR targeting the bacteria of interest will be developed using digital droplet PCR (ddPCR). We will evaluate the diagnostic performance of the ddPCR in a collection of endotracheal aspirates of MV patients and determine its sensitivity/specificity to detect patients at high and low risk of VAP.
Références bibliographiques	**1.** Nguile-Makao M et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med. 2010. **2.** American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005. **3.** Paling FP *et al. Staphylococcus aureus* colonization at ICU admission as a risk factor for developing *S. aureus* ICU pneumonia. Clin Microbiol Infect. 2017. **4.** Sader HS *et al.* Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from respiratory samples of patients hospitalized with pneumonia in Western Europe, Eastern Europe and the USA: results from the SENTRY Antimicrobial Surveillance Program (2016–19). JAC Antimicrob Resist, 2021. **5.** Sumner JT *et al.* Transitions in lung microbiota landscape associate with distinct patterns of pneumonia progression. Cell Host & Microbe; 2025 **6.** Tamkin E *et al.* Airway *Corynebacterium* interfere with *Streptococcus pneumoniae* and *Staphylococcus aureus* infection and express secreted factors selectively targeting each pathogen. Infect Immun. 2025. **7.** Rigauts C *et al. Rothia mucilaginosa* is an anti-inflammatory bacterium in the respiratory tract of patients with chronic lung disease. Eur Respir J. 2022. **8.** Meyer S *et al.* Could daily changes in respiratory microbiota help predicting early *Staphylococcus aureus* ventilator-associated pneumonia? Intensive Care Med Exp. 2023. **9.** Glover JS, Ticer TD, Engevik MA. Characterizing the mucin-degrading capacity of the human gut microbiota. Sci Rep. 2022.
Financement doctoral	*Thèse sujet libre*
Informations sur le candidat	
Profil et compétences recherchées	Expertise in fundamental bacteriology: bacterial culture (growth curve, coculture…), molecular biology (PCR, qPCR, ddPCR, NGS…) Good level of English