



## PROJECT

**Supervisor:**

Marco Ripa

**Title:**

Exploring virulence factors, antimicrobial resistance, and biofilm-forming abilities of *Stenotrophomonas maltophilia*: impact on clinical characteristics and outcomes

**Curriculum:**

Clinical and Experimental Medicine

Link to the personal page of the University  
or relevant hospital site website:

<https://www.unisr.it/docenti/r/ripa-marco>

### Description of the Project (max 3,000 characters including spaces)

#### **Background/gap of knowledge**

*Stenotrophomonas maltophilia* (Sm) has emerged as a relevant pathogen, especially in immunocompromised hosts. Although not inherently highly virulent[1], morbidity and mortality associated with Sm infections in these hosts may be relevant[2]. Furthermore, resistance to first-line treatment such as trimethoprim/sulfamethoxazole (TMP/SMX) or levofloxacin is not infrequent[3], and the optimal treatment strategy has not been clearly defined even for multi-susceptible strains[4]. Further complicating this scenario is the difficulty in distinguishing respiratory tract colonization versus infection[8]. From a microbiological standpoint, Sm harbors several virulence factors that enhance its pathogenicity. One of the primary factors is biofilm formation, which occurs on both abiotic surfaces and host tissues, complicating infection control[9–15].

#### **Rationale and hypothesis**

The purpose of this study is to describe the characteristics and outcomes of patients with Sm bloodstream and respiratory tract infections. Special emphasis will be placed on microbiological aspects such as antimicrobial resistance, biofilm formation, and the presence of specific virulence factors. The hypothesis driving this study is that certain genetic and phenotypic traits of Sm strains, including their biofilm-forming capabilities, are linked to more severe clinical outcomes, antimicrobial resistance profiles, and poor treatment responses in affected patients.

#### **Objectives and specific aims**

The primary aim of the study is to characterize the microbiological and genotypic aspects of Sm bloodstream and respiratory tract infections, and to assess the clinical outcomes in these patients.

The secondary aims are:

- To evaluate the impact of antimicrobial treatment choice on outcomes, with a focus on the molecular basis of resistance in Sm strains;
- To evaluate trends in antimicrobial susceptibility over time, investigating how Sm genetic resistance mechanisms evolve;
- To describe the predictive factors of in-hospital mortality in patients with Sm infections, considering both clinical and microbiological data.

Exploratory aims are:

- To investigate the correlation between specific Sm virulence factors, such as biofilm production and antimicrobial resistance, with clinical outcomes;



- To examine the genetic determinants of biofilm formation and antimicrobial resistance in Sm strains, and how these factors influence infection severity and patient prognosis

**Expected outcomes**

The results obtained by this study could provide valuable insights the molecular characteristics of Sm, particularly virulence factors, biofilm formation properties and antimicrobial resistance profiles, enhancing our ability to predict clinical outcomes and optimize treatment strategies. Additionally, identifying the factors associated with Sm colonization and infection in the respiratory tract will aid in distinguishing between infection and colonization, improving diagnostic accuracy.

**Skills that the student should acquire** (max. 600 characters including spaces):

The PhD student will be expected to acquire a comprehensive skill set spanning clinical and molecular microbiology.

The student will:

- develop proficiency in molecular biology techniques, particularly DNA isolation, quantification, and preparation for sequencing
- build competence in performing whole genome sequencing, using both short- and long-read platforms
- optimize and perform in vitro biofilm assays, including both static and dynamic models
- gain advanced data analysis capabilities
- develop the necessary skills for scientific communication and academic publishing.

**References** (max. 15)

- [1] Looney WJ, Narita M, Mühlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. *Lancet Infect Dis* 2009;9:312–23.
- [2] Huang C, Lin L, Kuo S. Risk factors for mortality in *Stenotrophomonas maltophilia* bacteremia – a meta-analysis. *Infect Dis (Lond)* 2024;56:335–47.
- [3] Bostanghadiri N, Sholeh M, Navidifar T, Dadgar-Zankbar L, Elahi Z, van Belkum A, et al. Global mapping of antibiotic resistance rates among clinical isolates of *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. *Ann Clin Microbiol Antimicrob* 2024;23. <https://doi.org/10.1186/s12941-024-00685-4>.
- [4] Wang C-H, Lin J-C, Lin H-A, Chang F-Y, Wang N-C, Chiu S-K, et al. Comparisons between patients with trimethoprim–sulfamethoxazole-susceptible and trimethoprim–sulfamethoxazole-resistant *Stenotrophomonas maltophilia* monomicrobial bacteremia: A 10-year retrospective study. *J Microbiol Immunol Infect* 2016;49:378–86.
- [5] Sarzynski SH, Warner S, Sun J, Matsouaka R, Dekker JP, Babiker A, et al. Trimethoprim-sulfamethoxazole versus levofloxacin for *Stenotrophomonas maltophilia* infections: A retrospective comparative effectiveness study of electronic health records from 154 US hospitals. *Open Forum Infect Dis* 2022;9. <https://doi.org/10.1093/ofid/ofab644>.



- [6] Ko J-H, Kang C-I, Cornejo-Juárez P, Yeh K-M, Wang C-H, Cho SY, et al. Fluoroquinolones versus trimethoprim-sulfamethoxazole for the treatment of *Stenotrophomonas maltophilia* infections: a systematic review and meta-analysis. *Clin Microbiol Infect* 2019;25:546–54.
- [7] Shah MD, Coe KE, El Boghdadly Z, Wardlow LC, Dela-Pena JC, Stevenson KB, et al. Efficacy of combination therapy versus monotherapy in the treatment of *Stenotrophomonas maltophilia* pneumonia. *J Antimicrob Chemother* 2019;74:2055–9.
- [8] Pathmanathan A. Significance of positive *Stenotrophomonas maltophilia* culture in acute respiratory tract infection. *Eur Respir J* 2005;25:911–4.
- [9] Ryan RP, An S-Q, Allan JH, McCarthy Y, Dow JM. The DSF family of cell-cell signals: An expanding class of bacterial virulence regulators. *PLoS Pathog* 2015;11:e1004986.
- [10] An S-Q, Tang J-L. Diffusible signal factor signaling regulates multiple functions in the opportunistic pathogen *Stenotrophomonas maltophilia*. *BMC Res Notes* 2018;11:569.
- [11] Alcaraz E, García C, Friedman L, de Rossi BP. The rpf/DSF signalling system of *Stenotrophomonas maltophilia* positively regulates biofilm formation, production of virulence-associated factors and  $\beta$ -lactamase induction. *FEMS Microbiol Lett* 2019;366. <https://doi.org/10.1093/femsle/fnz069>.
- [12] Flores-Treviño S, Bocanegra-Ibarias P, Camacho-Ortiz A, Morfín-Otero R, Salazar-Sesatty HA, Garza-González E. *Stenotrophomonas maltophilia* biofilm: its role in infectious diseases. *Expert Rev Anti Infect Ther* 2019;17:877–93.
- [13] de Oliveira-Garcia D, Dall'Agnol M, Rosales M, Azzuz ACGS, Alcántara N, Martinez MB, et al. Fimbriae and adherence of *Stenotrophomonas maltophilia* to epithelial cells and to abiotic surfaces. *Cell Microbiol* 2003;5:625–36.
- [14] Ryan RP, Monchy S, Cardinale M, Taghavi S, Crossman L, Avison MB, et al. The versatility and adaptation of bacteria from the genus *Stenotrophomonas*. *Nat Rev Microbiol* 2009;7:514–25
- [15] Yin C, Yang W, Meng J, Lv Y, Wang J, Huang B. Co-infection of *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* in hospitalised pneumonia patients has a synergic and significant impact on clinical outcomes. *Eur J Clin Microbiol Infect Dis* 2017;36:2231–5.