Pseudomonas aeruginosa Virulence, Antimicrobial Resistance and Persistence

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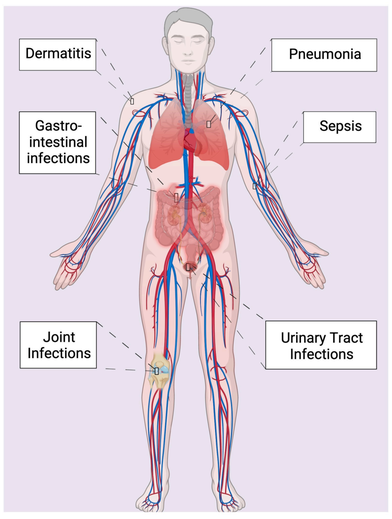
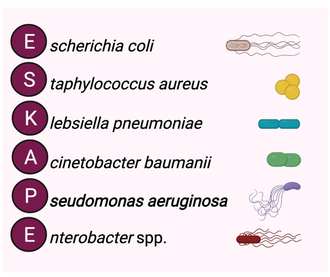
INTRODUCTION

Background

P. aeruginosa is a Gram-negative rod-shaped bacterium with a large genome and high metabolic versatility. This opportunistic pathogen accounts for high morbidity and mortality in cystic fibrosis patients, and represents the second most common cause of hospital-acquired pneumonia.



It can colonize multiple areas inside the human body, and it is part of the ESKAPE pathogen list due to its virulent properties.



P. aeruginosa can cause two types of infections:
A) Acute: high pathogenesis, inflammation and virulence factor production.
B) Chronic antibiotic resistance, immune evasion, biofilm formation and recalcitrance.

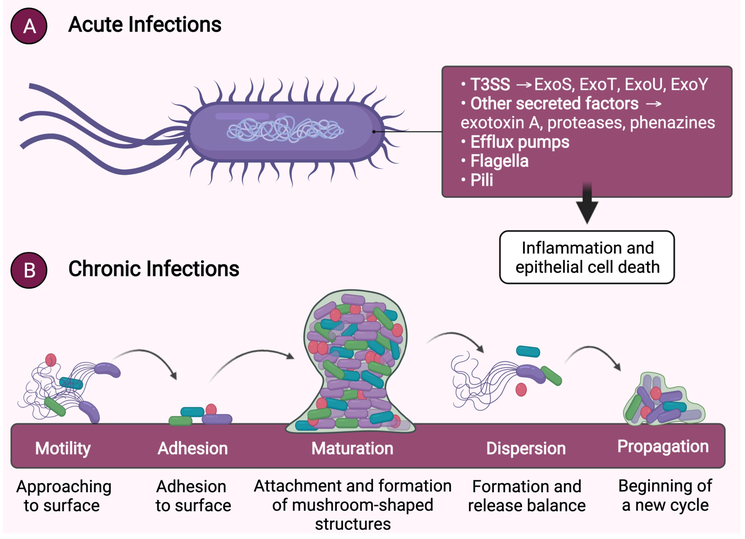
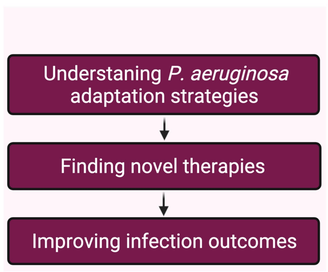


Figure 1: (A) Secretion of exotoxins and other virulence factors through secretion systems leads to epithelial cell death and local inflammation, while flagella and pili help bacteria adhere to biotic and abiotic surfaces. **(B)** Schematization of the biofilm formation process.

Purpose

The aim of this review is to outline the fundamental mechanisms that operate virulence, persistence and resistance to antimicrobial drugs in *P. aeruginosa*.



METHODS

1) Extensive bibliographic research.
2) Supplementary data addition from the UniProt database, epidemiologic reports and unpublished internship reports.
3) Figure shaping in BioRender to summarize the central concepts of the review.

The present state of the art and relevant results are divided into three blocks addressing virulence, persistence, and resistance.

Review's figures

RELEVANT RESULTS

Virulence

Virulence factor production is crucial for this bacterium's infective potential. This is deduced from the fact that mutants defective in their production or regulation present reduced pathogenicity.
Quorum sensing (QS) systems are fully engaged in the genetic regulation of their production.

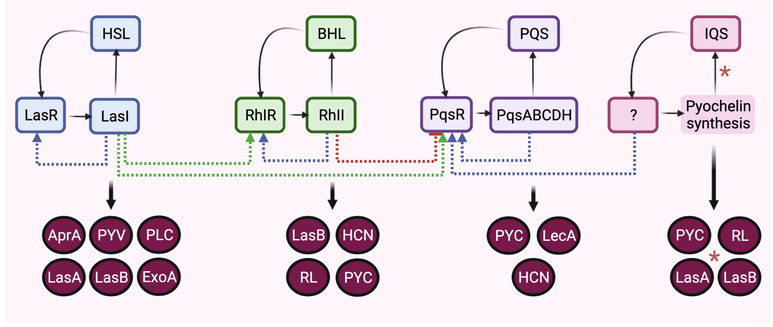


Figure 2: Regulation of virulence factor production via QS. Asterisks indicate steps of the signalling patways that remain unascertained.

Secretion systems like the injectisome (T3SS) and the pseudopilus (T2SS) are crucial for the externalization of most QS autoinducers, as well as tissue-damaging exoenzymes, pigments, and iron acquisition systems.

Virulence factors

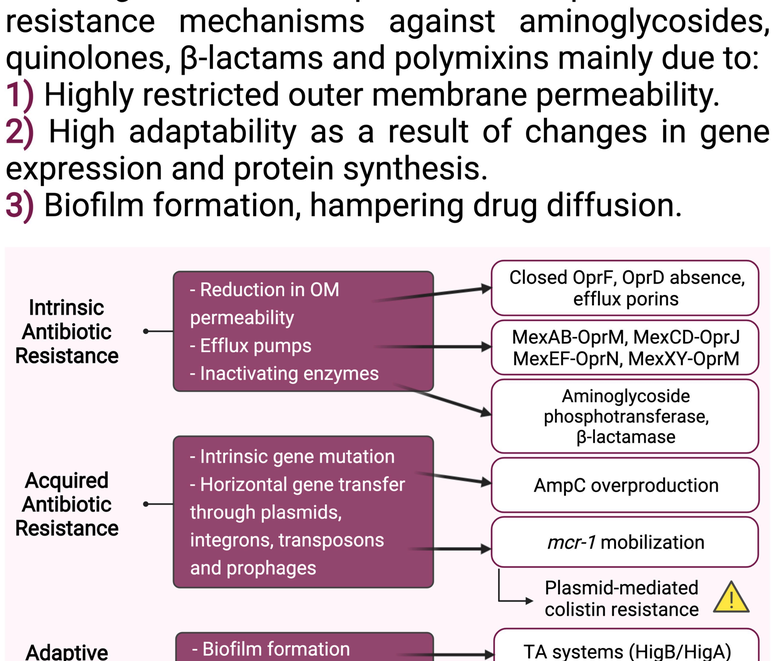


Figure 3: Representation of *P. aeruginosa* during an acute infection. Red dots depict exotoxins, which trigger a proinflammatory response.

Antimicrobial resistance

P. aeruginosa strains possess multiple antibiotic resistance mechanisms against aminoglycosides, quinolones, β-lactams and polymixins mainly due to:
1) Highly restricted outer membrane permeability.
2) High adaptability as a result of changes in gene expression and protein synthesis.
3) Biofilm formation, hampering drug diffusion.

Figure 4: Schematic summary and examples of the major antibiotic resistance mechanisms in *P. aeruginosa*. Special alertness should be applied to plasmid-mediated colistin resistance.

RELEVANT RESULTS

Persistence

Biofilm formation is an evident hallmark of bacterial persistence. These complex aggregates of bacteria provide them with protection and nutrients, and allow cell-to-cell communication.
The motility to sessility switch is mediated by QS systems, cdGMP and two component systems.

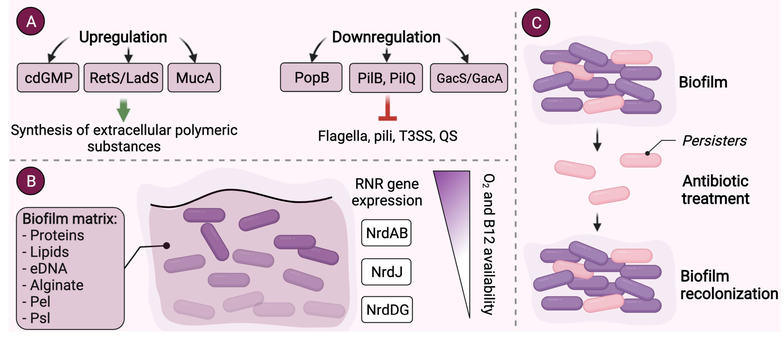


Figure 5: (A) Predominant changes in gene expression leading to biofilm formation. **(B)** Composition of the biofilm matrix and differential ribonucleotide reductase gene expression according to the O_2 and B12 gradients. **(C)** Recolonization process led by persisters.

This bacterium's pathogenesis in patients with cystic fibrosis is a clear exemplification of *in vivo* biofilm formation and chronic infection establishment under pro-oxidant conditions, as depicted below.

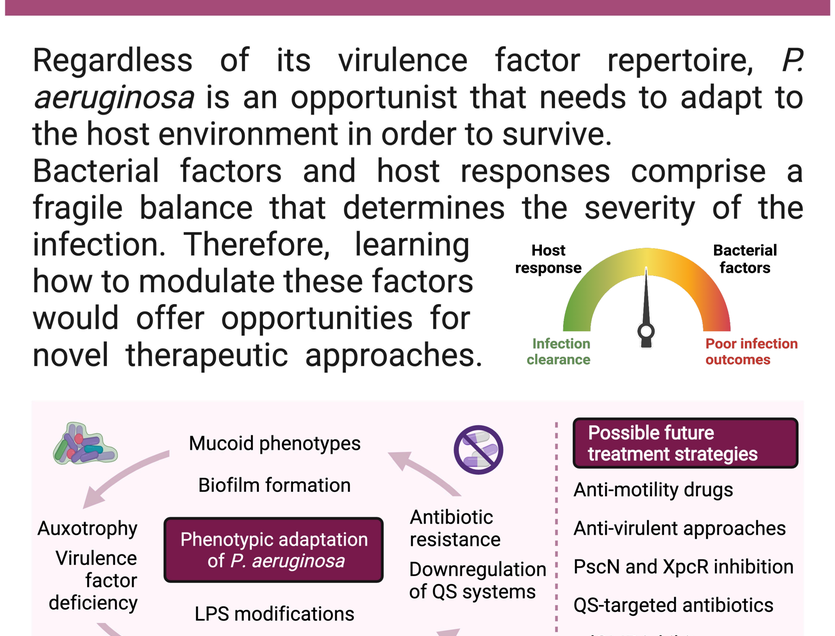


Figure 6: Representation of *P. aeruginosa* during a chronic infection. The hypermutability phenomenon leads to high phenotypic diversity.

CONCLUSIONS

Regardless of its virulence factor repertoire, *P. aeruginosa* is an opportunist that needs to adapt to the host environment in order to survive.
Bacterial factors and host responses comprise a fragile balance that determines the severity of the infection. Therefore, learning how to modulate these factors would offer opportunities for novel therapeutic approaches.

Figure 7: Schematic summary of the main phenotypic adaptations of *P. aeruginosa* upon the establishment of a chronic infection and possible future treatment strategies to improve patient prognosis.

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Full bibliography

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