# Elucidating the Role of Selected microRNAs in Attaining Optimal Pharmacokinetic and Pharmacodynamic (PK/PD) Profiles of Beta-lactam Antibiotics in Critically ill Patients with Sepsis

By: Dr. Janattul Ain Jamal

Sepsis and septic shock remain among the leading causes of intensive care unit (ICU) mortality worldwide. Despite advancements in intensive care, mortality rates for sepsis hover around 30–50%, with septic shock cases seeing rates as high as 87% [1–5]. A major cornerstone of sepsis management is timely administration of effective antibiotics, particularly the beta-lactams, valued for their broad-spectrum activity and safety profile.

However, critically ill patients often present with altered pharmacokinetics (PK) and pharmacodynamics (PD), which complicates antibiotic dosing. Factors such as capillary leak syndrome, fluid resuscitation, organ dysfunction, and renal replacement therapies can significantly affect drug distribution and clearance [6–9]. This leads to suboptimal antibiotic exposure, risking treatment failure, resistance, or toxicity. Beta-lactams, as time-dependent antibiotics, require plasma concentrations to stay above the pathogen's minimum inhibitory concentration (MIC) for a defined percentage of the dosing interval to achieve effective bacterial killing [10]. Traditionally, dosing has been guided by data from non-critically ill populations, limiting its applicability in the ICU.

More recently, research is exploring novel ways to individualise therapy. Among these, microRNAs (miRNAs), the small non-coding ribonucleic acid (RNA) molecules that regulate gene expression, are gaining attention for their potential to influence drug metabolism and treatment outcomes [11–13]. MiRNAs regulate a vast number of protein-coding genes, including those involved in drug absorption, distribution, metabolism, and excretion (ADME). Emerging evidence suggests that individual variations in miRNA expression, shaped by genetics, disease states, or environmental exposures, could contribute to interindividual variability in antibiotic efficacy and safety [14,15]. Several miRNAs have been linked to the expression of enzymes and transporters that modulate beta-lactam kinetics, offering a promising avenue for more precise, miRNA-guided dosing strategies [16–19].

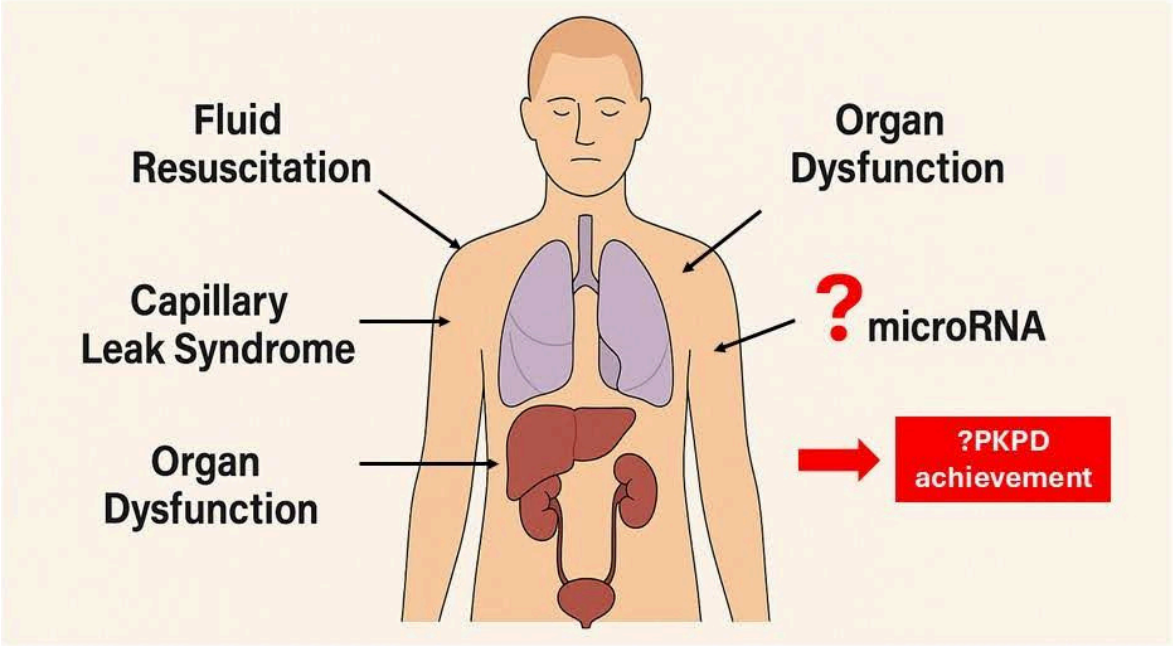


Figure 1: The potential interplay between pathophysiologic changes during critical illness and microRNA that could identify the successful of antibiotic pharmacokinetic and pharmacodynamic achievement in critically ill patients

This three-year project aims to elucidate the expression of miRNAs that could play a role in defining the pharmacokinetic/pharmacodynamic (PK/PD) profiles of two key beta-lactam antibiotics during critical illness, meropenem and piperacillin/tazobactam. The study is structured into three main phases, integrating clinical recruitment, drug concentration measurement, PK/PD modelling, and miRNA expression analysis.

A total of 120 adult ICU patients from four Malaysian hospitals will be enrolled. Blood samples will be taken at predefined intervals within a dosing cycle to determine plasma antibiotic levels, while additional samples will be collected for miRNA profiling. Plasma concentrations will be quantified using high-performance liquid chromatography (HPLC), while miRNA expression will be validated using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Phase 1 focuses on data collection and population-based pharmacokinetic modelling. Phase 2 will examine dose-exposure relationships to evaluate if standard dosing achieves target PK/PD parameters. In Phase 3, the expression of selected miRNAs will be correlated with antibiotic exposure levels, aiming to identify miRNA-based predictors of treatment response.

Data will be analysed using pharmacometric modelling approach, and findings will inform a personalised beta-lactam dosing framework, importantly tailored to the Malaysian ICU population. This framework could eventually be developed into a local clinical dosing tool. The project will also train a PhD student in advanced PK/PD methods and pharmacogenomics, contributing to local research capacity in precision medicine. As we move toward precision medicine, elucidating the role of selected miRNAs may enhance our ability to predict, monitor, and optimise beta-lactam therapy in septic ICU patients. Such innovations could not only improve outcomes but also mitigate the development of antimicrobial resistance in this high-risk population.

## TEAM MEMBERS


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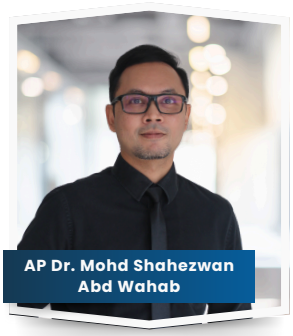
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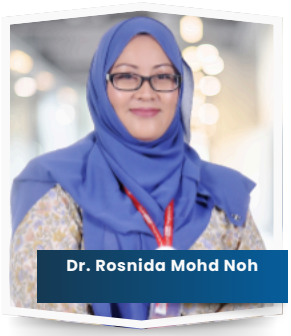
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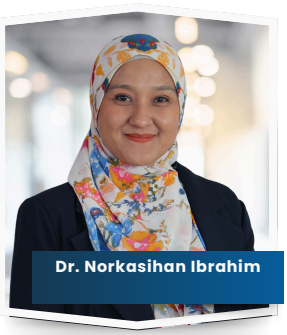
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