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PRESCRIPTION

Latest news and updates from the Faculty of Pharmacy, Universiti Teknologi MARA

When illness alters drug handling:

Understanding pharmacokinetic changes to optimise antimicrobial dosing

By Dr. Janattul Ain Jamal

Antimicrobials remain one of the most important drugs in modern medicine, yet their effectiveness depends greatly on how they are handled within the human body. One of the most important considerations is how pathophysiological changes during illness can profoundly reshape antimicrobial pharmacokinetics (PK). Understanding these alterations is essential not only for therapeutic success but also for preventing toxicity, resistance, and treatment failure. Therapeutic drug monitoring (TDM) and pharmacokinetic/pharmacodynamic (PK/PD) principles have become central tools in this effort.

Critical illness represents a unique PK landscape. Conditions such as sepsis, shock, and major trauma alter blood flow, capillary permeability, protein binding, and organ perfusion can lead to significant PK changes, particularly on two important parameters that relate to dosing, the volume of distribution (Vd) and clearance. Mechanical ventilation, vasopressors, and renal replacement therapy (RRT) further add layers of variability.

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My interest in this area began in 2006, when I first worked as an intensive care unit (ICU) pharmacist at a tertiary hospital under the Ministry of Health (MOH). I often struggled to identify the most appropriate dosing adjustment for ICU patients receiving various forms of RRT, and they were 'very sick' with complex infections. It soon became increasingly clear that the 'one-size-fits-all' dosing paradigm did not apply to those patients whose physiology had shifted dramatically due to infection, inflammation, organ dysfunction, or medical interventions. This has sparked an intense curiosity in me to explore how these dynamic pathophysiologic changes during illness can alter drug PK, ultimately shaping the need for individualised dosing.

My first major research endeavour in this area began in 2012 when I embarked on my PhD study. I conducted a prospective PK study on beta lactam antibiotics, focusing on critically ill Malaysian patients receiving continuous RRT (CRRT) (MerPip-RT Study). The study evaluated two modes of antimicrobial administration, intermittent and continuous infusion, and examined their ability to achieve PK/PD targets. Two original research papers have been published from this work in the International Journal of Antimicrobial Agents and the findings have since been widely cited and incorporated into major international guidelines. Among the work I have undertaken, the study I regard as the landmark of my research interest was the discovery that drug clearance during CRRT could be estimated based on the RRT dose (or effluent flow rate). Published in Critical Care Medicine in 2014, this finding has been extensively referenced by ICU clinicians and researchers worldwide and remains a foundational concept for optimising antimicrobial dosing in critically ill patients undergoing various modes of CRRT.

Emerging technologies are reshaping the landscape of antimicrobial PK studies. Tools such as population PK models and Bayesian software offer promising paths toward more precise and personalised dosing. However, in Malaysia, the use of TDM beyond its traditional applications remains limited, largely due to resource constraints in measuring certain antimicrobials, particularly beta-lactams. This is ironic, as beta-lactams are also the most commonly used antibiotics in critically ill patients with sepsis, similar to practices worldwide.

When TDM is not feasible, a strong understanding of the fundamental of drug PK, illness-related pathophysiologic changes, and pathogen characteristics becomes essential for individualised antimicrobial therapy. These gaps, especially in Malaysian practice, highlight the need for continued research and education to improve personalised antimicrobial dosing.

My current research in collaboration with the Faculty of Medicine, UiTM, continues the journey by exploring optimal beta lactams dosing in Malaysian ICU patients. We are also examining patient-specific factors and the potential role of microRNA in guiding dosing strategies for beta lactams, an important step toward precision medicine. This FRGS-funded study (FRGS/1/2024/SKK15/UITM/02/4) is now actively recruiting eligible critically ill patients in the ICU at Hospital Al-Sultan Abdullah (HASA), UiTM.

Ultimately, my work in this area is driven by a simple but profound belief: understanding the patient's physiology is the first step to choosing the right dose. Illness changes the way the body handles drugs, and unless we account for these changes, even the most potent antimicrobial may fail. Bridging the gap between pathophysiology and pharmacokinetics allows us to deliver safer, smarter, and more effective therapy.

About the author:

Dr. Janattul Ain Jamal is a registered pharmacist and Principal Lecturer at the Faculty of Pharmacy, Universiti Teknologi MARA (UiTM). She holds a Bachelor of Pharmacy and a Master of Clinical Pharmacy from Universiti Kebangsaan Malaysia, and a PhD in Medicine from The University of Queensland, Australia.

Dr. Ain has more than 20 years of experience as a clinical pharmacist within the MOH, with extensive practice in the ICU and antimicrobial stewardship (AMS). During her service in MOH, she has also served as Chairperson for the Clinical Pharmacy Working Committee (Critical Care Subspecialty) and the Clinical Pharmacy Working Committee (Antibiotic Subspecialty), Pharmaceutical Services Programme, MOH. Her research interests centre on antimicrobial dosing optimisation in critical illness. She has led and contributed to numerous national and international studies, with her work published in high-impact journals such as Critical Care Medicine, Clinical Infectious Diseases, and the International Journal of Antimicrobial Agents.

Dr. Ain is currently serving as a member of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) panel developing an international guideline on antimicrobial dosing in patients with and without RRT. She was also recently appointed as one of the interviewer panels for the Malaysian Advanced Clinical Pharmacy Programme (MyACPP) training (AMS), under the Pharmaceutical Services Programme, MOH. Dr. Ain is currently an active member of the Elderly Medication and Safety (EMAS), Research Interest Group, Faculty of Pharmacy, UiTM.

Questions:

1. Explain the difference between pharmacokinetics (PK) and pharmacodynamics (PD) in drug therapy.

Answer:

- Pharmacokinetics (PK) is the study of how the body affects a drug, including its absorption, distribution, metabolism, and excretion (ADME). It describes the concentration of drug in the body over time.
- Pharmacodynamics (PD) is the study of how the drug affects the body, including its mechanism of action, therapeutic effect, and side effects. It relates drug concentration to the pharmacological response.

2. How can critical illness alter the pharmacokinetics (PK) of drugs, and what are the underlying physiological changes responsible?

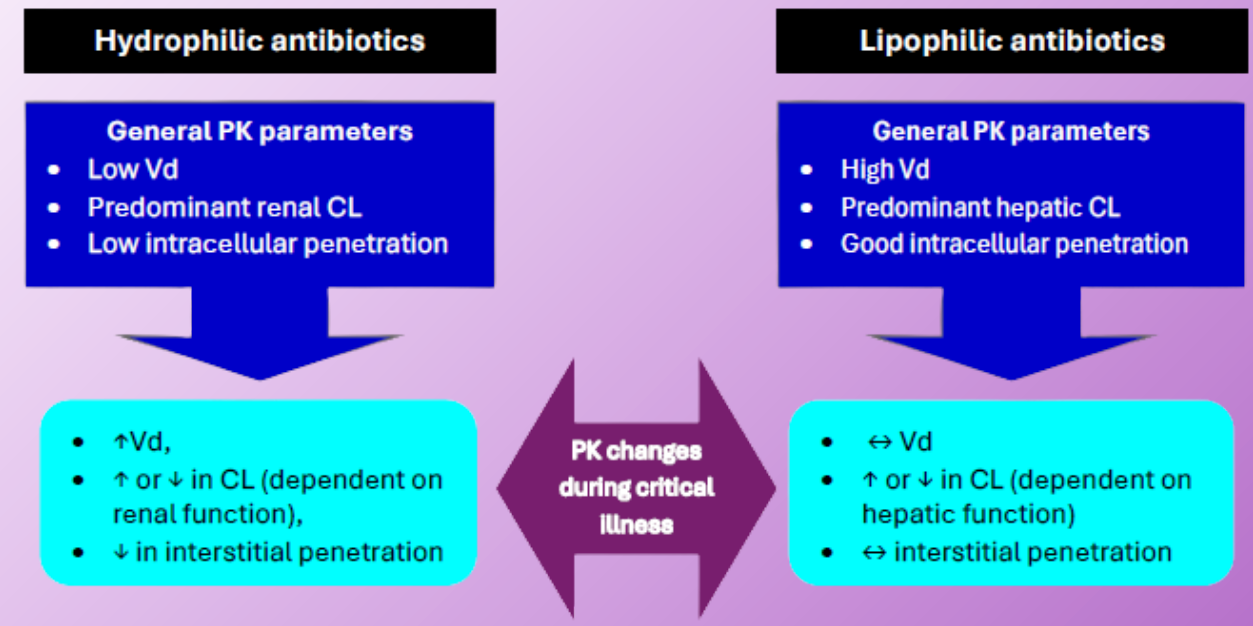
Answer:

- Absorption: Gastrointestinal hypoperfusion or oedema may reduce oral drug absorption.
- Distribution: Increased capillary permeability, fluid resuscitation, and hypoalbuminemia can increase the volume of distribution for hydrophilic drugs and alter protein binding for highly protein-bound drugs.
- Metabolism: Hepatic metabolism may be impaired due to reduced liver perfusion or organ dysfunction.
- Excretion: Acute kidney injury or altered renal perfusion can reduce clearance of renally-excreted drugs.

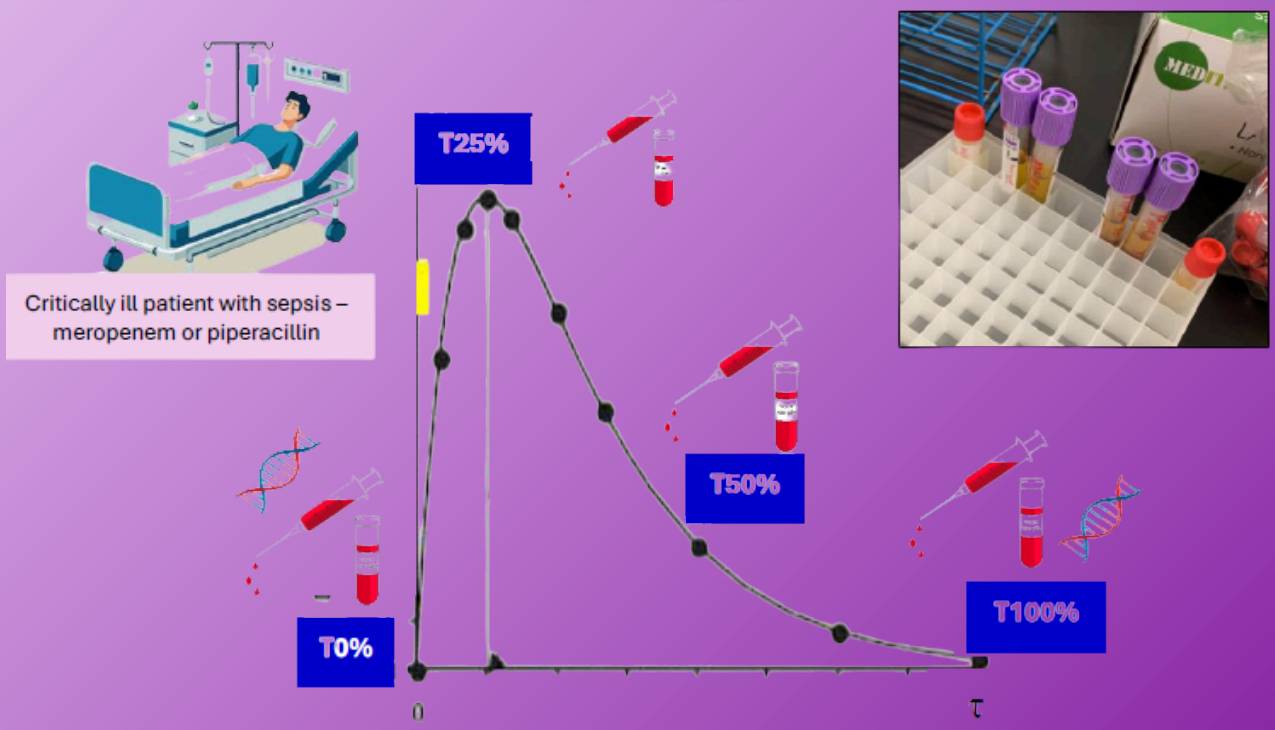
3. A drug has a half-life of 4 hours. Describe how the half-life affects the dosing frequency and plasma concentration of the drug.

Answer:

- The half-life determines how long the drug stays in the body and how frequently it should be administered to maintain effective plasma levels.
- For a drug with a 4-hour half-life, it will lose half of its concentration every 4 hours. To maintain therapeutic levels, the drug may need to be given every 4–8 hours depending on its therapeutic window.
- Half-life also affects time to reach steady-state (usually 4–5 half-lives) and the rate at which drug levels decline after stopping therapy.



The expected changes in PK parameters during critical illness [adapted from Jamal et al., 2012. Curr Op Crit Care 18(5): 460-471]



FRGS 2024: Elucidating the role of selected microRNAs in attaining optimal PKPD profiles of beta-lactam antibiotics in critically ill patients with sepsis (1 August 2024 - 31 July 2027) (on-going recruitment at Hospital Al-Sultan Abdullah (HASA), UiTM)