

# Understanding Differences

*by* Yasmine mashabi

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## EDITORIAL

### Understanding The Differences Between Apheresis, Plasmapheresis, and Plasma Exchange: The Urgency of Understanding Terminology in Daily Clinical Practice

**Memahami Perbedaan antara Apheresis, Plasmapheresis, dan Pertukaran Plasma: Urgensi Memahami Terminologi dalam Praktek Klinis Sehari-hari**

Yasmine Mashabi<sup>1</sup>, Agnes Tineke Waney Rorong<sup>2</sup>, Fauzan Abdillah<sup>3</sup>, Henie Widowati<sup>4</sup>

<sup>1</sup>Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

<sup>2</sup>Department of Psychiatry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

<sup>3</sup>Department of Ear, Nose, and Throat, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

<sup>4</sup>Department of Internal Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

[yasmine.mashabi@trisakti.ac.id](mailto:yasmine.mashabi@trisakti.ac.id)

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Apheresis is a medical procedure that has evolved significantly since it was first introduced as a manual blood separation method by Abel, Rowntree, and Turner in the early 20th century.<sup>1</sup> The original concept of this therapy originates from ancient practices like bloodletting, which was based on Hippocrates' theory of bodily fluid balance.<sup>2</sup> Today, modern apheresis includes various techniques for separating blood components using advanced equipment, serving both donor needs and the treatment of specific diseases. With technological progress, this procedure has become widely used in fields such as neurology, nephrology, hematology, and immunology.<sup>3</sup> However, as its indications and clinical applications expand, terms like apheresis, plasmapheresis, and plasma exchange are often used interchangeably even by healthcare professionals potentially leading to terminology confusion that could affect clinical decision-making.

This review is necessary, considering the still insufficient and inconsistent understanding of the differences in concepts, mechanisms, and therapeutic purposes of apheresis, plasmapheresis, and plasma exchange, both in clinical practice and in the scientific literature. Some references mention that although apheresis generally refers to the process of separating blood components, plasmapheresis more specifically describes the removal of plasma, and plasma exchange refers to the replacement of patient plasma with substitute fluid.<sup>4</sup> The lack of this conceptual distinction can lead to errors in the selection of procedures, interpretation of scientific evidence, and formulation of therapy guidelines. Therefore, an in-depth study is needed to comprehensively review the historical developments, terminology, and clinical applications of these three terms, aligning understanding and practices in the field while also filling the existing literature gaps.

#### Apheresis

Currently, apheresis is defined as a procedure in which blood is processed and separated into its main components such as red blood cells, white blood cells, platelets, and plasma using a

machine, with the aim of selectively collecting one or more of these components according to clinical indications.<sup>5</sup> Therapeutically, apheresis procedures are used to cure, reduce, or help manage a disease and its symptoms. This procedure is typically performed by collecting whole venous blood from the patient's body, then separating it into cellular and non-cellular components (plasma) or their fractions, and returning the cellular components to the body. Similar to the working principle of kidney dialysis, blood is pumped out of the body through an extracorporeal tubing system into a machine for processing, then returned to the patient after the target components are removed. The goal of apheresis therapy is to reduce the levels of abnormal substances circulating in the blood. Theoretically, if the causative agents of disorders can be identified and selectively removed, then the pathological processes can be controlled, and the patient's clinical condition is expected to improve. According to the American Society for Apheresis (ASFA), the use of apheresis in therapy is based on categories of evidence and levels of recommendation, which are determined by clinical effectiveness.<sup>2</sup> Apheresis includes various types of procedures, depending on the blood component targeted for removal. Some of these include erythrocytapheresis (removal of red blood cells), leukapheresis (removal of white blood cells), plateletapheresis (removal of platelets), plasmapheresis (removal of plasma), and therapeutic plasma exchange (Therapeutic Plasma Exchange/TPE). As the term suggests, plasmapheresis aims to remove plasma from the patient's circulation. Meanwhile, in TPE, the removed plasma is replaced with replacement fluid, such as albumin or donor plasma, as part of a therapeutic strategy to eliminate pathological substances dissolved in the plasma.<sup>6</sup>

### Plasmapheresis

Plasmapheresis is a therapeutic procedure performed extracorporeally with the goal of removing, replacing, or restoring blood plasma and its components.<sup>7</sup> The procedure primarily involves two main methods: centrifugation and filtration through a semi-permeable membrane. Centrifugation separates blood components based on differences in specific gravity, while membrane filtration sorts particles by size. Among healthcare facilities worldwide, the most commonly used plasmapheresis technology is the automated centrifugation system due to its high efficiency and accuracy. Although centrifugation-based technology is more commonly used, in some hospitals especially for patients undergoing hemodialysis plasmapheresis is performed using a membrane separation method. In centrifugation-based plasmapheresis, the separated plasma is discarded, while the red blood cells and replacement fluids, such as donor plasma or colloid solutions, are returned to the patient's body. In contrast, membrane-based plasma separation enables the selective removal of unwanted macromolecules, allowing the filtered plasma to be processed and returned to the patient without the need for replacement fluids. Therapeutic plasmapheresis is used to treat various medical conditions involving toxic or pathogenic substances in the plasma, such as autoantibodies or abnormal immunoglobulins, which can be removed through filtration. This procedure has proven effective in managing several diseases, including Myasthenia Gravis, Thrombotic Thrombocytopenic Purpura (TTP), Guillain-Barré Syndrome, Rheumatoid Arthritis, and Type 1 insulin-dependent Diabetes Mellitus, among others conditions.<sup>8</sup> The American Society for Apheresis (ASFA), through its Apheresis Applications Committee, classifies indications for therapeutic plasmapheresis into four main categories. Category I includes medical conditions where plasmapheresis is recommended as a first-line treatment. Category II involves disorders that can be managed with plasmapheresis as a second-line option, used

alongside standard therapies. Category III covers conditions where scientific evidence supporting the benefits of plasmapheresis is limited, so the decision to use it should be individualized based on the patient's clinical status. Meanwhile, Category IV pertains to disorders for which scientific evidence suggests that plasmapheresis is ineffective or potentially harmful; however, this procedure may still be considered on a case-by-case basis, with ethical considerations and approval from relevant institutional ethics committees taken into account committee.<sup>7</sup>

### Plasma exchange

Therapeutic Plasma Exchange (TPE), also known as plasmapheresis, is an extracorporeal blood purification method designed to remove large molecular weight substances from the bloodstream. Substances that can be removed through this procedure include pathogenic autoimmune antibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxins, and cholesterol-containing lipoproteins.<sup>9-11</sup> Although the terms plasma exchange and plasmapheresis are often used interchangeably, they are technically different procedures. Plasma exchange involves the removal of plasma from the blood circulation and its replacement with specific fluids, such as albumin or donor plasma. In contrast, plasmapheresis only includes the process of removing plasma without fluid replacement. The application of the plasma exchange concept as a therapeutic treatment was first performed on humans in 1959. One significant achievement in the history of this procedure is Michael Rubinstein's success in using plasmapheresis to treat immune disorders, as evidenced by his saving the life of a teenage boy suffering from thrombotic thrombocytopenic purpura (TTP) at Cedars of Lebanon Hospital in Los Angeles. Therapeutic Plasma Exchange (TPE) is an invasive therapeutic procedure that separates plasma from the cellular elements of blood. Through this process, pathogenic antibodies and other large molecules can be eliminated, while the removed plasma is replaced with human albumin and/or fresh frozen plasma (FFP). This method was first developed in the early 20th century. Over time, significant improvements have been made in the implementation techniques of TPE, including enhanced patient safety and expanded clinical indications. In addition, selective techniques have now been applied, enabling the targeted removal of specific proteins while minimizing the loss of important proteins, such as fibrinogen, during standard procedures. This innovation contributes to the increased effectiveness of therapy and overall patient safety.<sup>10</sup>

According to the guidelines issued by the American Society for Apheresis (ASFA), the indications for the use of Therapeutic Plasma Exchange (TPE) are divided into four main categories. Category I includes conditions where TPE is recommended as a first-line treatment, such as myasthenia gravis, Guillain-Barré Syndrome (GBS), and thrombotic thrombocytopenic purpura (TTP). Category II covers diseases where TPE may be used either as a standalone therapy or alongside other treatments, such as cold agglutinin disease, kidney transplant with ABO incompatibility, multiple sclerosis, and systemic lupus erythematosus (SLE). Category III includes conditions where the effectiveness of TPE has not been convincingly proven, but the decision to perform the procedure can be left to the clinical judgment of the physician. Meanwhile, Category IV includes diseases for which the available scientific literature indicates that TPE is ineffective or potentially even harmful, such as in inclusion body myositis and lupus nephritis.<sup>12</sup>

### Clinical Implications of Terminology Errors

The misuse of the term plasmapheresis to refer to plasma exchange is still commonly encountered, both in medical records, clinical orders, and scientific journals. This can have serious consequences, including incorrect indications, the use of a milder procedure in cases that should receive TPE. Safety risks include not performing electrolyte or coagulation monitoring during procedures that require close supervision. Administrative errors where BPJS or insurance claims may be denied due to differences in action codes, and clinical education errors, where students and residents who do not understand the differences from the beginning will carry this confusion into their practice. Recommendations and the urgency of terminology education, where healthcare institutions need to update clinical SOPs and coding procedures based on international references (ASFA). Continuous training for doctors, nurses, and medical documentation personnel, as well as collaboration with clinical pathology and blood transfusion services, is crucial in ensuring that procedures are carried out according to indications. Scientific literature, national guidelines, and medical Education curricula need to emphasize terminology clarification from the ground up.

A clear understanding of apheresis, plasmapheresis, and plasma exchange is crucial in modern medicine. Precise terminology not only improves treatment effectiveness but also enhances patient safety, system efficiency, and clear communication among healthcare professionals. It is essential for the medical community and the world to focus on accuracy in medical terminology because each word influences clinical decisions that can greatly affect lives.

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