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Pro/Con Debate

Pro: High dose of therapeutic plasma exchange Mind the gap!

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ABSTRACT

'Mind the gap' is a recorded warning phrase used in the London Tube since 1969. The following article is meant to be a warning of an increasing knowing–doing gap in routine practice of therapeutic plasma exchange (TPE), a treatment method that is used more and more throughout the world. The American Society of Apheresis recommendations, including the most recent ones from 2016, suggest using a TPE volume of 1.0–1.5 times the actual calculated plasma volume of the patient. There are only a few exceptions to that rule, such as the recommnded exchange volume in vasculitis or mushroom poisoning. The published literature suggests that in routine clinical practice in many institutions in several countries the exchanged volume might in fact be lower than recommended by the guidelines. In the following article we argue for a high dose of exchanged plasma volume, yet sketch different scenarios on how this time-averaged high dose can be delivered in various ways depending on the underlying disease, refuting a one-size-fits-all strategy that might facilitate the procedure but may result in 'underpheresis' in many patients. Further, the objectives underlying the use of smaller exchange volumes, especially the gap between the cost of blood products and the reimbursement of TPE are discussed. Lastly, the knowing–guiding gap is described, which can only be overcome by collecting high-quality data and conducting prospective clinical trials in the field of TPE.

'Mind the gap', a recorded phrase first introduced in 1969 in the London Tube, warns passengers entering and leaving the train about the horizontal (and sometimes vertical) spatial gap between the train door and the station platform. But there are more than spatial gaps. In the business world, there are so-called knowing–doing gaps [1], i.e. a gap between what companies know they should do and what they actually do. Based on this definition, there a numerous knowing–doing gaps in the field of medicine as well, ranging from the trigger haemoglobin for blood transfusion to the primary and secondary prophylaxis of cardiovascular disease. In the field of blood purification, a prime example of a knowing–doing gap is the applied exchange volume in therapeutic plasma exchange (TPE).

TPE, which was first described as an extracorporeal blood purification technique >100 years ago [2], preferentially removes pathogenic substances of high molecular weight such as autoantibodies, lipoproteins, cryoglobulins, light chains, endotoxins, circulating immune complexes and cholesterol-containing lipoproteins from plasma [3], making it an indispensable treatment method for an increasing number of diseases [4]. Aside from the removal of various substances, TPE can also replenish missing plasma components such as ADAMTS13, a protease that degrades von Willebrand factor multimers in thrombotic thrombocytopenic purpura (TTP) [5]. According to the 2016 guidelines of the American Society of Apheresis (ASFA), it is the treatment of choice for acute anti-neutrophil cytoplasmic antibody (ANCA)-associated rapid progressive glomerulonephritis, TTP, Guillain–Barré syndrome, Goodpasture syndrome and cardiac allograft rejection [6]. Even not considering very high treatment numbers in special situations like the 2011 German Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome crisis [7], treatment numbers are continuously increasing for transplant-related diseases as well as in neurological patients. Moreover, despite the lack of solid data, TPE is used in the intensive care setting, e.g. for sepsis with multi-organ failure [8], as it removes a plethora of pro-inflammatory cytokines [9].

THE GUIDING–DOING GAP

As in previous versions of the Guidelines on the Use of Therapeutic Apheresis in Clinical Practice, the 2016 ASFA recommendations suggest using a TPE volume of 1.0–1.5 times the individually calculated total plasma volume (TPV) of the patient [6]. There are only a few exceptions to that rule in adult

patients, such as vasculitis, for which an exchange volume of 1.0 times the TPV is recommended, and poisoning, for which an exchange volume of 1–2 times the TPV is suggested [6].

The published literature on TPE, which might be influenced by publication bias, reports a wide range of exchanged plasma volumes, with many reports not even coming close to the suggested 1.0–1.5 times the TPV being exchanged. Almost 30 years ago, an open prospective observational study from 1987 to 1989 in East Germany (1945 procedures in 419 patients) reported an average exchange volume of 2.7 (± 0.78) L or 43 (± 13.9) mL/kg body weight [10]. Today, even tertiary care centres in Germany report exchanging only 0.4–1.0 times the calculated plasma volume [11]. A recent study from India reports an overall exchange volume as low as 2.09 ± 0.91 L [12]. Although, the calculated plasma volume of the patients is not reported by the authors, the TPE dose is likely to be <1.0 × TPV, and will most likely not exceed this by much in a highly publicized clinical trial in TTP patients in which only 3500 mL/TPE were exchanged in patients with a body mass index of 28 kg/m^2 [5]. On the other end of the exchange volume dose spectrum, an ongoing randomized controlled study evaluating the role of plasma exchange in patients with ANCA-associated vasculitis suggests exchanging the plasma volume based on body weight only (60 mL/kg) [13]. Moreover, recently high-volume TPE, defined as a volume equal to 15% of ideal body weight (8–12 L of fresh frozen plasma), improved outcomes in patients with acute liver failure by increasing liver transplant–free survival as compared with the standard care [14].

THE KNOWING–GUIDING GAP

Why do the ASFA guidelines recommend a fixed dose range for dozens of different diseases? Where does this one-size-fits-all approach come from? This recommendation is mainly based on the removal kinetics of immunoglobulin G (IgG), first described by Kaplan in [15] 18 patients evaluating 102 treatments using a simplified-formula plasma volume {[0.065 × weight (kg)] × (1−haematocrit)} for estimating the effect of TPE on Igs, especially IgG. To recommend a fixed relative volume of TPE seems rather odd given the various substances the treatment aims to remove or replenish. Moreover, the efficacy of the removal/replenishment depends on several factors, such as the volume of distribution of the substance, the synthetic and catabolic rates, as well as the equilibration rate between the compartments [16]. Last but not least, even in diseases where the pathological substance has been identified and can be measured, its degree of removal might not be paralleled in the degree to which the clinical symptoms regress. Evaluating the clinical course of patients with myasthenia gravis up to 3 months after double filtration plasmapheresis, it was found that the acetylcholine receptor antibody levels correlated poorly with neuromuscular symptoms, but the changes in antibody concentration seemed to predict the clinical course [17].

So what is the right dose for TPE? As summarized in Table 1, the right dose will most likely differ from disease to disease and the concept of a time-averaged dose might be more appropriate than a fixed dose at a fixed frequency. If removal of large substances is the aim of TPE, one has to realize that the efficacy of TPE decreases as the total exchanged volume increases, as the removed substances may need hours to days to diffuse from the extravascular to the intravascular compartment. Also, the acuity of the disease might have an impact on treatment intensity and frequency. In the seminal study by Rock *et al.* [18] in patients with thrombotic microangiopathy, the first three treatments exchanged 1.5 times the predicted plasma volume followed by 1.0 times the predicted plasma volume thereafter, resulting in a mean exchanged plasma volume of 21.8 L [18]. This 'hit hard and early' approach, known from antibiotic therapy, might even be more important in disease states like liver failure, where exchange of plasma volume equalling 15% of ideal body weight (8–12 L of fresh frozen plasma) in a single treatment lasting up to 9 hrs improved outcome [14]. These are treatment coordinates that might also be beneficial for treating septic patients (Figure 1). On the other hand, in neurological diseases, like steroid-unresponsive relapse of multiple sclerosis, a treatment cycle over a longer period of time using smaller volumes might be appropriate (Figure 1). Depending on the exchange fluid, the treatment frequency of TPE might be limited by the removal of coagulation factors if only albumin is used as an exchange fluid [11]. Although a detrimental effect of a high dose of TPE has

Table 1. Examples for different TPE doses and frequency depending on the underlying disease

Treatment day	TPE/sepsis	Acute rejection	Desensitization	Myasthenia	GBS	Multiple sclerosis	RPGN
Exchange fluid Treatment day	FFP × TPV	Albumin	Albumin	Albumin	Albumin	Albumin	Albumin
0	1.5	1.5	1	1.2	1	1	1.6
1	1.5	1.5	1	1.2		1	1.6
2	1.5				1		
3	1.2	1.2	1	1.2	1	1	1.6
4	1.2						
5	1	1.2	1.2	1	1	1	1.6
6	1						
7		1.2	1.5	1	1	1	1.6
8	1						
9							1.6
10	1						
11							1.6

GBS, Guillain-Barré syndrome; RPGN, rapidly progressive glomerulonephritis.

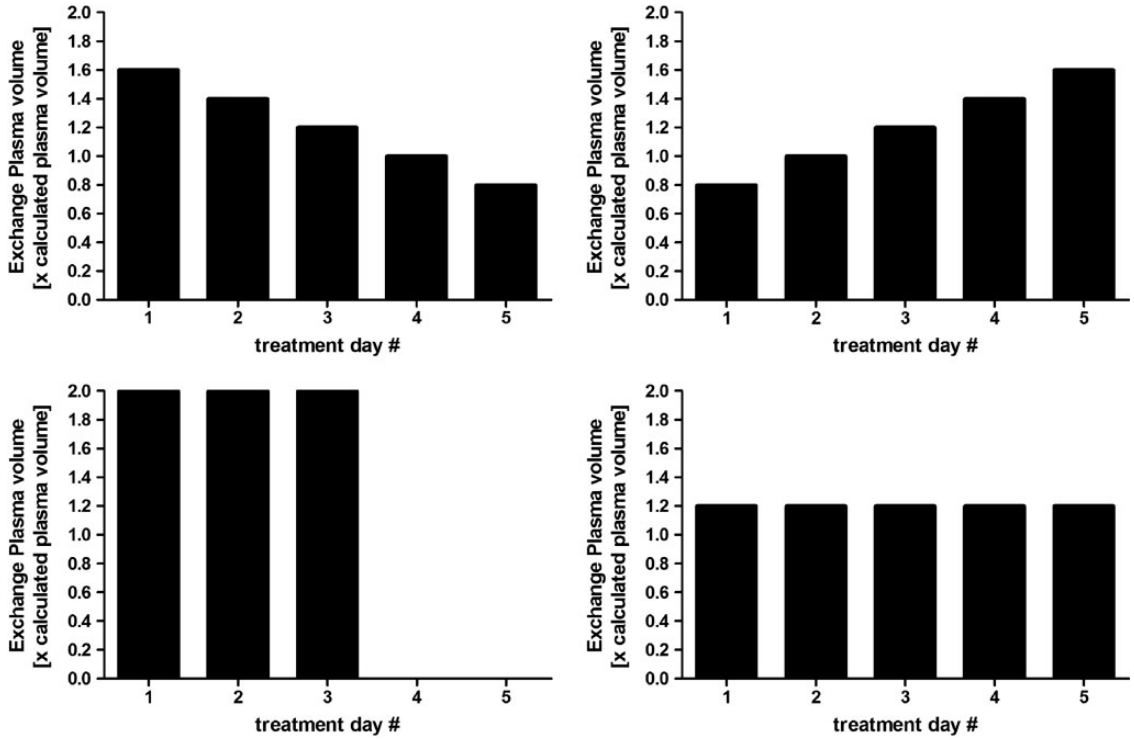

FIGURE 1: Time-averaged plasma exchange volume of 6 times TPV delivered in four different ways: decremental TPE (TTP), incremental TPE (desensitization), high-volume TPE (sepsis, liver failure) and equal dose TPE (GBS).

not been described, one has to realize that TPE also removes drugs that are aimed at treating the underlying diseases, such as rituximab [19] or caplacizumab [5].

REIMBURSEMENT–TREATMENT COST GAP

One prevailing reason for a fixed (low) exchange volume that is not tailored to the actual individually calculated plasma volume of the patient is an economic one. In Germany, the reimbursement for TPE is a fixed payment that includes labour and material (machine, tubing, filter) as well as the blood products (fresh frozen plasma or albumin). The reimbursement rate is not sufficient to cover all the blood product costs in a 100-kg patient with a haematocrit of 30%, let alone enough to cover the expenses for the procedure (labour, machine and disposables). Given the economic pressure of rising costs for blood products, several groups throughout the world tried to use Hydroxyethyl-starch solutions (HES) or HES – albumin solutions as replacement fluid to reduce the cost for TPE [20, 21]. After the European Medicines Agency revoked permission of HES due to untoward medical effects, this does not seem to be a prudent approach.

OUTLOOK

In the same year the recorded 'mind the gap' could be heard in the London Tube, Donald and Doris Fisher opened the first GAP store in San Francisco, CA, USA. They filled the gap in the market for those who had a difficult time finding jeans that fit, as one size does not fit all. Today, a wide variety of styles and sizes allows everyone to find perfectly fitted jeans. We suggest that variations to the theme of high-dose TPE might improve patient-centred outcome parameters. It's time to fill the gap of knowledge in TPE that will allow tailoring the dose to the severity of the disease and the individual plasma volume of the patient—after all, one size does not fit all and we should certainly 'mind the gap'.

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Opponent's comments

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MIND THE TPE VOLUME AND WE INDEED DO

Drs Hafer and Kielstein argue against a one-size-fits-all strategy for the volume of plasma exchange. While the concept is reasonable and in line with a very conservative evidence-based medicine approach, a few points raised by their nicely written article deserve further elaboration.

First, the ASFA guidelines do not recommend a fixed dose range. In fact, the ASFA guidelines recommend exceptions to the most common 'rule' of 1.0–1.5 times the actual calculated plasma volume of the patient in quite a few different disease entities. Furthermore, vasculitis recommendations are similar and not an exception to this rule as the pro view authors report.

Second, the most recent ASFA recommendations address different TPE exchange volumes based on existing literature. Thus we do agree with the authors that the published literature on TPE reports a wide variety of exchanged plasma volumes, with many reports citing different volumes than the commonly suggested 1.0–1.5 times TPV. As such, the exchanged volumes recommended for diseases that are included in the ASFA guidelines is based on the published literature.

The authors complain about the reimbursement problems in Germany, and they should continue to press health authorities to close the gap between actual and reimbursed TPE expenses. As the cost of blood products used for substitution fluids during TPE is increasing every year, many patients, especially in undeveloped countries, cannot be properly treated.

The international apheresis societies should support such initiatives against insufficient reimbursement and promote randomized controlled trials that could provide needed evidence on correct exchanged plasma volume. Unfortunately, the overall experience and evidence is incomplete rather than inconsistent, and more research is necessary to advance our understanding of plasma exchange and what is the correct volume to exchange. Nonetheless, until new results become available, maybe it is too early to suggest high-volume exchange across the board.