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BUFFER SYSTEMS AND BIOCOMPATIBILITY IN PERITONEAL DIALYSIS

Introduction

The field of peritoneal dialysis (PD) is undergoing a rejuvenation process exemplified by advances at multiple levels: patient outcomes, practice enhancement, delivery systems, dialysis solutions, and basic research. The vindication of peritoneal dialysis as a robust method of renal replacement therapy with wide suitability to various patient groups has been amply documented. Patient outcomes show progressive improvements across the globe. The practice of PD has benefited from the formulation of clinical guidelines that help establish care pathways for quality delivery of therapy. While debate still continues on small-solute clearance targets, the overall systematization of care standards is a welcome outcome. Improvements in connectology and greater sophistication in automated delivery systems are significantly helping to reduce complications and enhance the quality of life of patients on PD. Novel dialysis solutions that address previously unmet clinical needs are becoming part of standard practice in Europe, North America, and Asia and making encouraging beginnings in other parts of the world. Finally, basic research in PD is reflecting the dynamism of the age of genomics and proteomics.

The present supplement to *Kidney International* attempts to encapsulate information related to the flourishing of renal science in the field of peritoneal dialysis, with an emphasis on new insights into the role of new dialysis solutions and their importance to buffer systems and membrane biocompatibility. Guo and Mujais open the series with a review of current outcomes of patients on PD in North America, illustrating the remarkable success story of the therapy and its continuing favorable evolution. They document the success of PD both when it is the first renal replacement modality as well as when it is used in patients who have had a vintage therapy with other modalities, such as hemodialysis and transplantation. The enhanced survival of patients on PD is a strong stimulus to considerations of optimization of dialytic care to meet the requirements of long-term success with the therapy.

Mehrotra et al present a detailed and scholarly review of the impact of correction of acid-base balance on the biologic underpinnings of good health. They examine the consequences of failure of correction of uremic metabolic acidosis and the expected benefits of interventions at metabolic and end-organ levels. The state of correction of acid-base balance with standard PD solutions is described by Mujais in a report of the largest series of patients on manual, as well as automated, PD in North America. The success of PD in correcting acidosis in the majority of patients can be contrasted with the lesser success of intermittent therapies. The determinants of acid-base balance are examined in detail with interesting distinctions observed between manual and automated forms of PD. The topic is further developed in the review by Heimburger and Mujais, which details the pathways followed by buffer moieties. They describe the distinct behavior of buffer transport under the distinct conditions of single buffer systems with the limitations of these systems as far as regulatory control and non-physiologic conditions, and illustrate the operational advantages of complementary buffer systems.

The relevance of the introduction of novel solutions for PD is put into perspective by the paper of Williams et al. They describe the insights gleaned from a biopsy registry rich in material from patients on standard lactate-based solutions. Albeit cross-sectional, the large representation of differing patient vintage on the therapy, as well as the well-chosen control populations, allows the authors to delineate a natural history of the peritoneal membrane with traditional solutions. The factors that may have regulated this natural history, as well as the framework for elaboration of future advances in the field of preservation of the peritoneal membrane, are presented by Holmes and Faict. Their paper offers a clear and systematic background for the papers that follow.

Hoff takes this issue to the next level. After offering a scholarly and detailed examination of the elements of biocompatibility of dialysis solutions in general, she delves into an exhaustive review of the in vitro studies that have been performed to evaluate the biocompatibility of a dialysis solution formulated at physiologic levels for pH, bicarbonate, and pCO_2, and the use of a complementary buffer system of bicarbonate/lactate that allows delivery of an adequate buffer mass for replenishment of physiologic stores without exceeding the physiologic concentrations of the prevalent bicarbonate/pCO_2 buffer system.

The paper by ter Wee et al then offers a survey of the explorations of biocompatibility in experimental animal models of PD, expounding on the advantages and limitations of such work and offering exciting glimpses of the promises of new solutions. The clinical counterpart of this work is found in the paper by Mackenzie et al. These authors offer the results of the creative

approach that allows the application of sophisticated analytical probing of relevant clinical material and illustrate the value of studying peritoneal cells ex vivo, and soluble cell markers, as windows into the health and behavior of resident and transient cells in the peritoneal space. The results of this approach, which illustrate the benefits of physiologic solutions with complementary buffer systems, are also presented. An original contribution by Skoufos et al showcases the biocompatibility of a variant of a complementary bicarbonate/lactate buffer solution with a lower total buffer mass. The value that two complementary physiologic solutions with differing total buffer mass, but with physiologic levels of the major extracellular buffer system (bicarbonate/pCO_2, pH), lies in is the ability to titrate buffer delivery to the particular needs of individual patients.

The following two papers describe the clinical experience with the complementary bicarbonate/lactate buffer system solution in patients on continuous ambulatory peritoneal dialysis (CAPD) and ambulatory peritoneal dialysis (APD). Pecoits-Filho et al review the results of studies in CAPD and show the benefits of the solution as it pertains to correction of metabolic acidosis, elimination of pain on infusion, and overall positive impact on peritoneal membrane health. Dratwa et al present the original findings of the use of the complementary buffer solution in patients on APD. They reproduce in this population the same benefits as in patients on CAPD and further demonstrate the value of two buffer concentrates in meeting the clinical needs of different patients.

The optimization of buffer composition is not the only advance in peritoneal dialysis solutions composition. The use of alternate osmotic agents helps expand the impact of dialysis solutions on patient health. The use of amino acids as osmotic agents offers the advantage of replacing peritoneal losses of proteins and amino acids, contributing to the nutritional intake of patients with a non-carbohydrate source of calories, and offering a solution with excellent biocompatibility. The replacement of glucose with icodextrin offers a dramatic clinical enhancement of ultrafiltration for the long dwell, and reduces the glucose exposure of the peritoneum. The use of this solution has been associated with major salutary developments, such as regression of left ventricular hypertrophy, better fluid volume control, reduction in blood sugar deviations, and attenuation of hyperlipidemia. An approach that combines the benefits of solutions with alternate osmotic agents and solutions with optimal buffer composition is intuitively obvious. Vardhan et al develop this theme by first reviewing the advantages of the individual solutions and then by illustrating the synergism of their combined use in offering discrete and quantifiable clinical benefits and a low-glucose dialytic regimen.

In the final contribution to this supplement, Pecoits-Filho et al present a visionary description of the full potential value of enhancing the composition of dialysis solutions. They develop the concept that the impact of solution biocompatibility goes beyond the peritoneal membrane and affects systemic functions significantly. Drawing on recent explorations in the areas of systemic inflammation, oxidative stress, and ingestive behavior, among others, they offer the unifying concept of global biocompatibility that encompasses the regional and systemic effects of dialysis solutions.

The contributions in this supplement make it clear that the present status of peritoneal dialysis contains the seeds of a bright future, as well as indications of the path to follow in future innovation. To be able to care for increasing numbers of patients with peritoneal dialysis requires that a policy of iterative innovation be pursued consistently and with vigor at all levels, and we hope that this supplement illustrates the results of such an approach. The publication of this supplement to *Kidney International* was made possible by an unrestricted educational grant from Baxter Healthcare Corporation. The authors wish to acknowledge the support of Ms. Rona McGreevy, Ms. Rosalie Villano, and Ms. Mary Zentz.

NOTE ON THE COVER ART

John William Waterhouse (1849–1917) was an English painter whose art belongs to the school of Victorian Romanticism. Close to the Pre-Raphaelites in his themes, he focused on subjects from the Corpus of Western writings, drawing his inspiration from Homer, Shakespeare, European legends, and the history of Christian martyrs. His works carry such titles as *Hylas and the Nymphs, Ophelia, St Cecilia, St Eulalia, La belle dame sans merci, The Lady of Shalot, Ulysses and the Sirens,* and a few of Circe, among others. The painting reproduced on the cover of this supplement is titled *The Danaïdes*, a work painted in 1903 and currently in a private collection.

OLOF HEIMBURGER, CLIFFORD HOLMES, and SALIM MUJAIS
Division of Renal Medicine, Department of Clinical Sciences, Karolinska Institutet; Huddinge University Hospital, Stockholm, Sweden; and Renal Division, Baxter Healthcare Corporation, McGaw Park, Illinois