Blood Purification

Advances in Chronic Kidney Disease 2007

9th International Conference on Dialysis,
January 24–26, 2007, Austin, Texas

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Preface

The 9th Annual International Conference on Dialysis, Advances in CKD 2007, organized by the Renal Research Institute, New York, with the cooperation of the ISN, ISPD, NKF and RPA, is a well-established meeting in the US which has consistently presented the views of leaders in the field of chronic kidney disease on novel and often provocative scientific and clinical aspects of current interest.

As in previous years, this year's meeting, held in Austin, Texas, January 24–26, has a large international representation (13 of 38 speakers from outside the US), with perhaps more than the usual emphasis on clearly drawn differences of opinion which are best explored in debates. These include challenges to current guidelines on peritoneal dialysis dose (Bargman and Winchester) and also a challenge to guidelines in general (Amerling), how dialysis dose should be best measured (Gotch and Twardowski), and the value of observational research (Daugirdas and Port).

The first part of the meeting, as usual, is devoted to the problems inherent in the management of a dialysis center, including potential problems in providing an adequate dose (Diaz Buxo), finances of the individual facility (de Oreo), impact of government billing rates for erythropoietin use on hemoglobin levels (Ofsthun), and the management of dialysis units in Europe (Gatti).

An important emphasis on diabetes is presented including a key note address on changing the fate of diabetics in the dialysis unit (Broumand) and a discussion of the much anticipated KDOQI guidelines on diabetes (Nelson).

New information on common problems include a review of the importance of dialysate composition (Hoenich), and the difficulties in increasing fistulas and decreasing catheters (Sands). Fresh thoughts on the role of body composition in indicating dialysis outcomes (Kotanko), the problems of an excess or deficiency of vitamin C (Handelman), and the current state of the application of nanotechnology (Fissell) are addressed. The pharmacologic problems of the chronic kidney disease patient is examined (Mueller), and a critical analysis of imaging methods for coronary artery calcification is made (Lembcke).

The frequently neglected role of periodontal disease as a cause of problems in dialysis patients is analyzed (Offenbacher).

Finally, Ronco provides a molecular approach to infection in chronic kidney disease, using detection of bacterial DNA in patients with sepsis.

We owe thanks to Mary Carter, the Research Program Director, and Ingrid Adelsberger in New York who coordinate this impressive conference, as well as Anna Saccardo, Ilaria Balbo and Silvia Fracasso who worked in Vicenza on the final arrangements of the manuscripts. Special thanks to Karger for the usual outstanding quality of the publication.

We hope that attendees enjoy the meeting, and the other readers will enjoy the presentations and contributions in this issue.

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Finances of the Independent Dialysis Facility

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Key Words

Medicare composite rate · Case mix adjustment · Payer mix · Bundled payment

Abstract

Medicare pays 80% of the cost of dialysis treatment and associated medications. Congress directed the Centers for Medicare and Medicaid Services (CMS) to develop both a process of regular and more or less 'automatic' updates of composite rate setting and 'bundling' as much of the laboratory and ancillary medications as possible into the composite rate. In response to this mandate, CMS revised the wage indexing process, added an annual update, and removed the limits on the wage index range. CMS has moved the 'margin' from medication acquisition and administration to an annually revised 'drug add-on' to the composite rate and fixed reimbursement of separately billed medication (ancillary) to the average sales price +6%. CMS is funding a demonstration project on near 100% bundling to be completed by 2008 that will include metrics for automatically increasing the base composite rate.

The independent dialysis facility receives its revenue from the provision of dialysis and related services. Unlike large dialysis organizations, independent dialysis facilities ordinarily do not benefit from the sale of dialysis equipment, artificial dialyzers, or the provision of pharmacy or laboratory services.

While Medicare has paid for dialysis since 1974, in 1983 Medicare simplified the two-method payment system to a single composite rate (CR). Hospital-based dialysis facilities receive USD 4 more than non-hospital-based facilities. The difference was justified based on apparently higher overhead, not patient acuity. Congress establishes the CR. Unlike other Medicare-funded services, there is no required annual update. The CR includes the dialysis procedure (supplies and disposables), routine medications (analgesics, saline, oxygen, heparin, etc.), routine laboratory testing, wages, administration, depreciation, etc. The Medicare Payment Advisory Commission makes recommendations for changes (increases or decreases) to the Centers for Medicare and Medicaid Services (CMS) that are forwarded to Congress. Each change in the CR requires legislation.

From 1983 to 2005, there have been 6 adjustments to the CR (1986 decreased USD 2, 1991 increased USD 1, 2000 increased 1.2%, 2001 increased 2.4%, 2004 increased 1.6%, 2005 increased 1.6%). Despite these net increases,

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when adjusted for inflation, the 2005 CR of USD 128 compared to the original 1974 rate of USD 138 is less than USD 37.

In addition to the CR, providers bill Medicare for the administration of ancillary medications (erythropoietics, iron, vitamin D, antibiotics, etc.). Historically, as the cost of providing the CR services exceeded reimbursement for these services, providers were able to cover their costs by the margin provided through the difference between the acquisition price of the medication and the reimbursement based on 95% of the average wholesale price (AWP).

Since the acquisition price varied based on the buying power (and negotiating skill) of the provider and AWP was 'fixed' for the whole industry, the difference created perverse incentives to choose medications as much for the margin realized as for the medical necessity or benefit among and between specific drugs.

CMS recognized the inadequacy of CR funding but was equally concerned that the inefficiency of the CR policy resulted in 'over' or 'selective' prescription of ancillary medications. To mitigate this effect, CMS decided to reimburse ancillary medications at acquisition price + 6% (ASP+6) and to increase the CR by the difference between reimbursement under 95% AWP and ASP+6. To accomplish this, CMS measures the difference and divides it by the projected number of dialysis treatments. The value is corrected for the increase in the producer price index increase for prescription drugs, the expected increase in the end-stage renal disease (ESRD) population, and the projected growth in the drug utilization per patient.

For the first year of this process, 2006, the calculation led to a USD 18.88 (14.2%) increase in the base CR (USD 130.40). CMS increased the wage-adjusted CR by 14.2%. For 2006, CMS estimated that the growth in prescription drug use per patient would be 0. They estimated that there would be a net increase in the producer price index and incident growth resulting in 4.9% increase in the difference between 95% of AWP and ASP+6. The 4.9% was added to the USD 18.88 (USD 0.93) to a new amount of USD 19.81. The new add-on is 15.2% of the base CR of USD 130.40. For 2007 the wage-adjusted base CR will be increased by 15.2%. As of this writing, CMS has not published the ASP+6 prices for the first quarter of 2007.

The base CR is the national reference against which regional wage indices are applied to a fraction of the base CR. From 1990 through 2005, the wage index was based on metropolitan statistical areas (MSA). It was a blend of the 1980 bureau of labor statistics and the 1986 CMS hospital wage indices. The aggregate index was applied to 40% of the base CR. The range was constrained from 0.9 to 1.3.

Starting in 2006, the wage index was based on core-based statistical areas (CBSA), and applied to 54.7% of the base CR. The upper limit of 1.3 was removed. Since only Congress can increase the total 'cost' of the program to Medicare, any changes beyond the base CR have to be 'budget neutral'. Any increase in an adjusted CR has to have a compensating decrease.

Since the wage indices have not been updated since 1990, the new rates created significant reductions in the wage-adjusted CR to many providers. To mitigate this impact, CMS agreed to phase in the new wage-adjusted CR and constraints on the lower limit of the index over 4 years. While the projected lower limit was to be 0.8 for 2006, budget neutrality allowed for a lower limit of 0.84. For 2007, the blend will be an average of the 2005 wage-adjusted CR (128.35 with 40% adjusted for the MSA wage index) and the 2007 wage-adjusted CR (130.40 with 53.7% adjusted for the 2007 CBSA index update).

Table 1 demonstrates the calculation of the blended wage-adjusted CR. Line 1 shows the base CRs for 2005 based on MSA and 2007 based on CBSA. Line 2 shows the portions and impact of the wage index. Line 4 shows the resulting wage-adjusted CRs. Line 5 shows the effect of the transitional blend, for 2006 it was 3:1 in favor of the MSA rate, for 2007 it is 1:1, or the average of the two rates. Line 6 shows the effect of the 15.2% drug add-on. The wage-adjusted, blended CR with drug add-on is the basis for the next step in CR adjustment, case mix.

Updating the wage component of the CR allowed for the regional variation in the cost of providing service. The next goal is to define the cost of providing service based on patient variables. The Kidney Economic and Cost Center at the University of Michigan analyzed facility cost reports, facility characteristics, and patient characteristics to see how facility level costs vary. This study provides the basis for both the demonstration project on a fully bundled CR and the case mix adjustment in effect since April 2006.

The variables found to explain variation in facility level costs were the size and age of the patient. These relationships were further analyzed in terms of body surface area (BSA) and body mass index (BMI). These are mathematical and statistical relationships that are not necessarily clinically obvious.

The purpose of this adjustment is to distribute the CR funds more effectively. Since only Congress can increase the funds allotted to the program, the case mix adjustments need to be 'budget neutral'. The total impact of

Table 1. Calculation of case mix-adjusted, budget-neutral, wage-indexed, blended composite rate with drug add-on

			MSA 2005			CBSA 2007	
1	Composite rate		128.35			130.40	
			Labor	Other		Labor	Other
2	× labor fraction	0.4	51.34	77.01	0.5371	70.04	60.36
3	× wage index	1.193	61.26		0.9883	69.22	
			77.01			60.36	
4	Wage adjusted CR		138.27			129.58	
5	Blended rate	1:1			133.93		
6	× drug add-on	1.152			154.28		
7	× neutrality	0.9116			140.65		
8	× age factor	1.094			153.87		
9	× BMI factor	1.0			153.87		
10	× BSA factor	1.0292			158.36		

Case mix adjusted for a 75-year-old, 173-cm, 78-kg patient (BMI 26.1 kg/m^2, BSA 1.917 m^2) dialyzed in Cleveland, Ohio.

case mix adjustment would be an increase of about 9%. Before the application of the case mix adjustment, the blended wage-adjusted CR with drug add-on is multiplied by the budget neutrality factor 0.9116. Line 7 of table 1 shows the effect of this adjustment.

Table 2 shows the factors applied due to age. Note that if a patient is under 18 years old and the total factor is 1.62, neither BMI nor BSA are considered. BMI is calculated as weight (kg) divided by height (m) squared (kg/m^2). The normal range is 20–25 kg/m^2. If the BMI is <18.5 kg/m^2, the adjustment factor is 1.112, otherwise the BMI factor is 1.0. For the calculation of BSA the equation is BSA = $kg^{0.425} \cdot cm^{0.725} \cdot 0.007184$, and the $BSA_{factor} = 1.037^{((BSA\ 1.84)/1.0)}$. Note that a 175-cm, 70-kg person has a BSA of 1.84 m^2, and a patient with a BSA of 1.84 m^2 has a factor of 1.0. Figure 1 shows the graphical relationship between BSA and the factor.

Table 1 shows how the case mix adjustment is applied to a single patient. In this example the patient is 75 years old, 173 cm tall, weighing 78 kg (BMI 26.1 kg/m^2, BSA 1.917 m^2), and dialyzing in Cleveland, Ohio. The effect on the CR is to increase the wage-adjusted CR with drug add-on by about USD 4, and the budget-neutral CR by about USD 18.

Table 2. Age adjustment factors for case mix

Age	Factor
<18[1]	1.620
18–44	1.223
45–59	1.055
60–69	1.000
70–79	1.094
≥80	1.174

[1] If a patient is <18 years old, no BSA or BMI adjustment is used. The total case mix adjustment is 1.620.

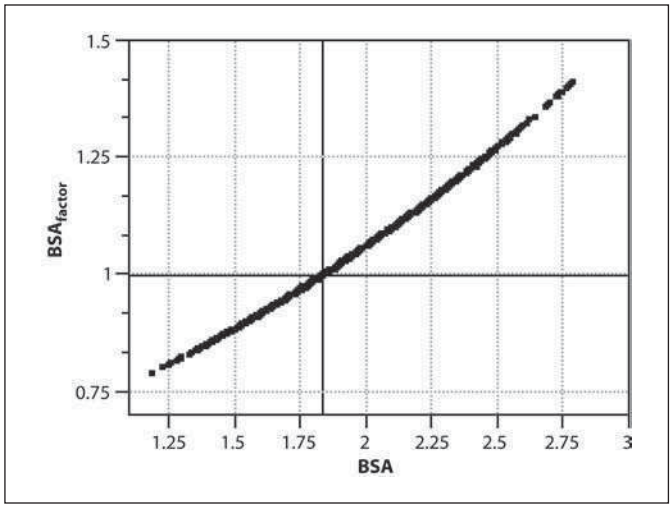

Fig. 1. Relationship between BSA and the BSA_{factor}. The factor of a 1.84 m^2 person is 1. It increases or decreases above and below that surface area.

Table 3. An example of the case mix adjusted (CMA) composite rate would be in a typical mix of patients

	Factor	Average patient value	Factor	Budget-neutral CR	CMA CR
1	Age	63.4	1.091		
2	Height, cm	169.01	–		
3	Weight, kg	80.6	–		
4	BMI, kg/m^2	28.29	1.003		
5	BSA, m^2	1.899	1.1027		
6	CMA	–	1.124	140.65	158.09

The assumption is made that all patients are dialyzed in the same geographic wage area. The factors are averaged from the individual patient values and cannot be calculated from the average value as they are neither linear nor continuous. The final CMA is the product of the factors in lines 1, 4, and 5. The CMA CR is calculated as the product of the budget-neutral CMA (as calculated on line 7 of table 1) and the CMA factor (line 6).

The CMS website (http://www.cms.hhs.gov/PCPricer/01a_ESRDCalculator.asp) has a 'pricer' application that allows the user to calculate the 2007 case mix-adjusted CR for any given patient of known age, height and weight, dialyzing in a known CBSA.

In order to estimate the impact on a panel of patients, it is necessary to calculate the individual case mix adjustments and apply them to the budget-neutral CR then to average the individual CRs.

Table 3 estimates how case mix adjustment might effect a population of patients. In a hypothetical panel of patients with an average age of 63.4 years, average height of 169 cm, average weight of 80.6 kg, the aggregate case mix adjustment would be 1.124 applied to the budget-neutral CR. Since these factors are neither linear nor continuous, the summary factors represent the distribution within the categories rather than the average of the categories. Table 3 shows that BSA represents almost 90% of the total case mix adjustment.

The foregoing discussion is based on Medicare reimbursement. Most dialysis facilities have a mixture of payers ('payer mix'). While Medicare is the preponderant payer, the percentage of Medicare patients varies significantly from facility to facility. The payer mix has an important impact on treatment revenue.

The CR is a reference for dialysis reimbursement, but it is not controlling. Payers are free to negotiate rates for dialysis with providers through various contracts including the CR services and ancillary medications to global bundled contracts for all dialysis, medication and laboratory services.

Table 4 demonstrates the simplest of these variations for 2 hypothetical mixes of payers for the services included in the CR. It assumes that Medicare pays 80% of the blended, wage-adjusted CR with the drug add-on (table 1, line 6), that patients have secondary coverage for the other 20% of the CR, that Medicaid pays 90% of the national, base CR, and that the commercial payer has 'negotiated' a 40% discount from the facility charges of USD 1,000.

Medicaid cannot pay more than the CR, but can and does pay less. Medicaid does not add the 15.2% drug adjustment. It reimburses ancillary medications according to its own fee schedule. Table 4 shows the national base CR but could just as easily use the wage-adjusted rate (blended or otherwise). Facilities can and do set their charges above (4–6 times higher) the CR. Payers negotiate 'discounts' from facility charges or accept charges at some multiple of the CR. Table 4 shows that a shift from an 80% Medicare and 15% Medicaid mix to a 40% Medicare with 0% Medicaid has the effect of increasing the net treatment revenue by 250%.

Total revenue is a sum of the treatment revenue and the ancillary revenue. Ancillary revenue is being programmatically shifted to the treatment revenue by adding a drug factor to the CR. The intention is to make the ancillary revenue essentially equal to the ancillary expense and to reduce the decision for ancillary prescription to solely medical considerations.

The next phase of dialysis reimbursement revision is based on the Congressional directive to CMS to develop a bundled rate based on a 'market basket' of labor and non-labor goods and services included in the ESRD CR.

Table 4. The impact of payer 'mix' on treatment revenue

Payer	Charge	Rate	Payer mix	
			80% Medicare 15% Medicaid 5% commercial	40% Medicare 0% Medicaid 60% commercial
Medicare	154.28	0.8	98.74	49.37
Secondary	154.28	0.2	24.68	12.34
Medicaid	130.40	0.9	17.55	0
Commercial	1,000.00	0.6	30	360.00
Treatment revenue			171.02	421.71
Allowance for bad debt (3%)			–5.13	–12.65
Net treatment revenue			165.89	409.06

Medicare rate is the wage-indexed, blended composite rate with the drug add-on, before adjustment for budget neutrality or case mix. The Medicaid rate is based on the 'base' composite rate without the drug add-on. In this example, Medicaid pays 90% of the base CR.

To that end, a demonstration project is under way to study various models to predict per patient costs based on geographic, facility, and individual patient characteristics. The project is to be completed in 2008.

Along with the ESRD initiative for a self-adjusting, annually updated, bundled payment process is a Medicare-wide initiative to reward providers (facilities and physicians) for performance against nationally agreed upon, evidence-based quality outcome standards. Current proposals put as much as 30% of the CR revenue at risk as a hold-back to fund a pool that would be repaid to providers based on achievement of outcome standards.

Finally, dialysis providers, manufacturers, renal pharmaceutical companies, and various renal professional, trade and patient organizations are cooperating to sponsor legislation submitted to Congress in 2005 (Kidney Care Quality and Improvement Act, HR. 1258; S.635. Text and status of the House and Senate versions of the bill are available at the 'Thomas' website: http://thomas.loc.gov/). The purpose of this legislation is to formalize an increase in the CR, a process of annual updates, and the creation of a council of renal experts to advise Congress and CMS in developing the quality and performance standards.

Suggested Reading

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Dialysis and Nanotechnology: Now, 10 Years, or Never?

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Key Words
Dialysis · Nanotechnology · Renal replacement

Abstract
Nanotechnology, defined as the science of material features between 10^{-9} and 10^{-7} of a meter, has received extensive attention in the popular press as proof-of-concept experiments in the laboratory are published. The inevitable delay between feature articles and clinical endpoints has led to unwarranted skepticism about the applicability of the technology to current medical therapy. The theoretic advantages of micro- and nanometer scale engineering to renal replacement include the manufacture of high-hydraulic permeability membranes with implanted sensing and control structures. Recent data in membrane design and testing is presented, with a review of the challenges remaining in implementation of this technology.

The kidney is unique in that it is the first organ for which long-term ex vivo substitutive therapy has been available and lifesaving. Renal failure prior to the era of hemodialysis and transplantation resulted in certain death, and this outcome of renal failure is still current outside the industrialized world.

In the United States, 452,000 patients were listed as having end-stage renal disease (ESRD) by the 2005 USRDS database, of whom 324,826 were receiving maintenance dialysis [1]. The prevalence of ESRD in the United States is rising at approximately 8%/year [1, 2]. The financial cost of dialysis is immense, estimated at USD 64,614/hemodialysis patient/year and USD 47,384/peritoneal dialysis patient/year. In contrast, transplant patients cost an average of USD 22,142/patient/year [1].

The higher cost of maintenance dialysis when compared with transplantation does not translate into better results; annual mortality for patients listed for transplant and awaiting a kidney is 6.3%, compared with only 3.8% for patients listed for transplant who did receive a kidney. These statistics compare favorably to the 16.7% annual mortality for ESRD patients not listed for transplant [3]. Transplantation, despite its advantages in terms of cost, morbidity, and mortality, is severely limited by the scarcity of donor organs. In 2006, there are over 300,000 patients on dialysis and 72,983 patients on the kidney waiting list. Only 4,096 renal transplants were performed in the first quarter of 2006, based on the Organ Procurement and Transplantation data as of 9 June 2006.

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Defibrillation as a Paradigm for Technology and Healthcare Delivery

Dialytic treatment of ESRD is at an awkward stage of development in the early 21st century. The clinical success of dialysis has led to its broad acceptance as standard of care for ESRD. However, as the ESRD population continues to grow, the dollar cost and morbidity of intermittent in-center hemodialysis has drawn increased attention from physicians and the public and driven exploration of new modes of treatment.

It is instructive to explore the impact of technology on another treatment, defibrillation, whose history remarkably parallels that of dialysis. Today, defibrillation and dialysis remain standard lifesaving treatments. However, in the last decade, the parallel histories of defibrillation and dialysis have diverged. Hemodialysis remains, for the most part, a bedside treatment requiring the patient to report to a treatment center and be assessed by a health care provider. That provider connects the patient to a large machine, which the provider then continuously monitors and adjusts during the course of treatment. In contrast, defibrillation has undergone two quantum leaps enabled solely by advances in technology. First, recognition of a malignant cardiac rhythm is no longer dependent on real-time physician monitoring and diagnosis. Computerized signal-processing algorithms now routinely allow automated rhythm recognition. This permits non-experts and bystanders to correctly identify and treat a malignant heart rhythm using an automated external defibrillator. Second, microelectronics, circuitry and battery technology have allowed the implantation of automated internal cardioverter/defibrillators into high-risk patients, allowing them freedom of movement and independence during monitoring. Purely technological developments in solid-state electronics and signal processing drove two key events in arrhythmia management: healthcare providers were liberated from rote technical tasks (watching a monitor), so they could provide skilled human interaction with patients, and the site of care was relocated from a cardiac monitoring bed in a hospital, which is impractical for all patients at risk of arrhythmia, into the home, the community and eventually the patient's own body.

The success of implantable cardioverter-defibrillators lies in their implementation of the '3Rs' of medical technology: the site of care has been *relocated* from the clinic to the patient's own body; disposables have been *reduced* or eliminated, and treatment *relies* on automated sensing and control structures, rather than human input. Initial steps applying this paradigm to treatment of renal failure are now well known. McFarlane et al. [4] demonstrated the reduced cost of home dialysis while delivering a significantly increased treatment dose. Home dialysis systems have successfully relocated care out of the clinic and into the home, for a select group of patients who are able to administer their own treatments.

The challenge is to broaden access to independent treatment while reducing costs of care. Technology that reduces the need for direct patient control and monitoring of treatment will expand the population of patients willing or able to undertake home therapy. A compact long-life hemofiltration membrane would reduce disposable costs for at-home or in-center dialysis. Nanotechnology and microelectromechanical systems (MEMS) are being applied to renal replacement [5–7]. What follows is a brief overview of the promise and the progress of nanomedicine in ESRD care.

Critical Technologies for Hemodialysis/ Hemofiltration

Membrane Design

Hemodialysis and hemofiltration share a common extracorporeal circuit design: blood is continuously extracted from the patient through a central venous catheter or through a specially constructed vascular access. Occlusive roller pumps applied to the blood tubing pull blood from the patient and push it through a hollow-fiber dialyzer, whence it then returns to the patient via the same vascular access device. Attempts to use the patients own blood pressure (continuous arteriovenous hemofiltration) as the driving force for blood purification have not been widely successful, as the pressure gradients required to extract blood through the catheter, push blood through the dialyzer at high enough pressure to generate ultrafiltrate in clinically useful volumes, and return the blood to the patient far exceed systemic arterial pressure. The hollow-fiber dialyzers themselves are large and impractical to wear or implant, and have limited service lifetimes (<100 h). A dialyzer or hemofiltration membrane with high hydraulic permeability and extended lifetime would be a fundamental improvement in a wearable or even implantable device.

Automated ECF Sensing

The kidney accomplishes at least six vital homeostatic roles on time scales spanning minutes to days [8]. The most critical short-term homeostatic role is clearly con-

trol of extracellular fluid (ECF) volume; should ECF regulation go awry, death from pulmonary edema or cardiovascular collapse may shortly ensue. In dialytic practice today, extracellular volume is estimated by patient weight. A patient's true 'dry weight' is quantitated by removing fluid volume during the dialysis session until the patient experiences symptomatic hypovolemia. Total body weight is in fact only a very crude surrogate for effective intravascular volume, a conceptual quantity encompassing blood volume, cardiac output, and systemic vascular resistance. A significant fraction of the human monitoring in hemodialysis is directed towards ECF volume control. Nurses or technicians weigh the patient, adjust the dialysis machine, and remain vigilant for signs and symptoms of volume overload or cardiovascular collapse. Automated ECF volume sensing is a key technology in automated dialysis.

Nanotechnology and Filtration Membrane Architecture: Pore Geometry and Steric Hindrance

Existing polymer membranes used in dialysis and ultrafiltration have been extensively studied. The pores in such membranes are formed by extrusion and solvent casting techniques. The geometry and surface chemistry of the pores arise from the chemistry of the polymers and the fluid dynamics of the casting process. In general, the hollow-fiber membranes are fairly thick or employ a multilayer scaffold for mechanical support, and have a distribution of pore sizes rather than a regular array of uniform pores. Pores in conventional polymeric membranes tend to be either roughly cylindrical, have a round orifice terminating a larger channel, or have a structure resembling an open-cell sponge. Extensive description of porous structures used in commercial ultrafiltration and microfiltration may be found in [9, 10]. It is not clear that any of these structures provide optimal geometries for membrane filtration for two reasons.

First, a wide dispersion in pore sizes within a membrane leads to imperfect retention of molecules larger than the mean pore size of the membrane. This is remedied in practice by engineering the mean pore size of the membrane to be sufficiently small that negligibly few pores are large enough to allow passage of a solute above the desired molecular weight cutoff of the membrane. This has the undesired effect of reducing the mean pore size in the membrane and thus reducing the hydraulic permeability of the membrane. Engineering narrower pore size distributions ameliorates this dilemma, allowing sharper transitions from passage to retention and maximizing the mean pore size of the membrane [11].

Second, the round shape of conventional pores dictates a fourth-power dependence of hydraulic permeability on pore radius:

$$\frac{Q}{\Delta P} = \frac{\pi r^4}{8 \mu L}$$

where Q denotes volumetric flow, P is hydrostatic pressure, r is the radius of the pore, μ is viscosity, and L is the length of the pore, which may or may not be the same as the thickness of the membrane. A pore that is slit-shaped allows steric hindrance to solute passage dictated by the smallest critical dimension of the pore, while increasing hydraulic permeability by a factor of the long dimension of the pore:

$$\frac{Q}{\Delta P} = \frac{wh^3}{12 \mu L}$$

where w is the long dimension of the slit, h is the thickness of the slit, and L is again the length of the pore. Consequently, it might be predicted that filtration structures with parallel slit-shaped pores might have superior performance when compared to structures with round pores. With that in mind, it is interesting but speculative to note that natural selection has produced filtration structures with elongated, slit-shaped geometries in the kidney, in the beaks of filter-feeding birds such as the flamingo, and in the baleen of filter-feeding whales. Arrays of slit-shaped pores with small dimensions to 5–7 nm have been manufactured and tested as immunoisolation membranes, filters, and substrates for tissue culture [6, 7, 12].

Nanotechnology and Filtration Membrane Architecture

Electrostatic Effects

Many materials have an anionic surface charge at physiologic pH. The net charge density on a microfluidic substrate in contact with an aqueous solution gives rise to an electrical double layer in the aqueous solution. This charge density creates an electric field, drawing oppositely charged ions towards it and driving like-charged ions away from it. This shielding layer is commonly known as the Debye layer or the electrical double layer [13]. For nanometer scale pores, the thickness of the electrical double layer can be the same order of magnitude as the pore size itself, and can contribute to rejection of

charged solutes by the pore even for a theoretical solute of infinitesimal size (and thus no steric hindrance).

Initial Data

Silicon nanopore membranes (SNMs) with 10–100 nm × 45 μm slit pores were designed and fabricated at the Cleveland Clinic Foundation and Case Western Reserve University. Initial hydraulic characterization of these membranes has been completed [6, 7]. Silicon chips bearing 1 × 1 mm arrays of approximately 10^4 slit pores were fabricated via sacrificial layer techniques (fig. 1) [14]. The pore structure is defined by deposition and patterning of a polysilicon film on the silicon wafer. The critical submicron pore dimension is defined by the thickness of a sacrificial SiO_2 layer, which can be grown with unprecedented control to within ±1 nm. The oxide layer is etched away in the final processing step to create the porous polysilicon membrane.

The hydraulic permeability to gas, deionized water, and phosphate-buffered saline (PBS) of these novel membranes was tested in a custom-engineered ultrafiltration cell. Gas flow data were well fitted by transitional flow models, consistent with pore sizes approximating the mean free path of the gas molecule. Liquid flow was almost perfectly predicted by conventional Navier-Stokes predictions (fig. 2).

Rejection of charged proteins in solution by SNMs was examined in the same ultrafiltration cell. Briefly, solutions of three proteins (carbonic anhydrase, 25 kD, bovine serum albumin, 66 kD, and sweet potato amylase, 200 kD) in 1× PBS (150 mM) and 10× PBS (1,500 mM) were subjected to ultrafiltration by SNMs. Even for membranes with pore sizes much larger than the molecular radii of the proteins, some rejection of the proteins by the membrane was observed, but this effect was abrogated in high ionic strength solutions, strongly suggesting an electrostatic barrier to passage (fig. 3). Further definition of steric and electrostatic barriers to passage is an area of active research.

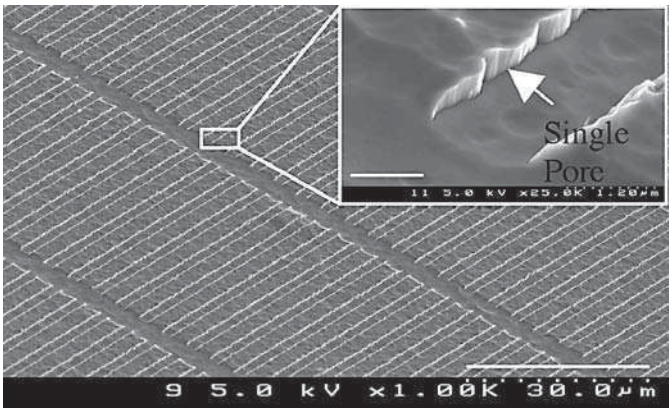

Fig. 1. Scanning electron micrograph of a silicon nanopore membrane. Scale bar = 30 μm. The higher-power inset shows a single pore extending into the plane of the membrane surface. Scale bar = 1 μm.

MEMS and ECF Volume Sensing

Critical to the success of an automated dialysis platform is on-line real-time estimation of ECF volume, a complex engineering problem in its own right. Esophageal Doppler monitoring (EDM), pulmonary-artery catheters, and peripheral waveform analysis all provide measures of central hemodynamic parameters. Bioimpedance and hematocrit monitoring may provide estimates of changes in blood volume. Various volume estimation techniques have been deployed in outpatient maintenance hemodialysis [15]. Blood volume monitors have yielded mixed results in clinical trials. An implanted right ventricular pressure monitor appeared to provide valuable clinical information over and above clinical judgment in a very small series [16].

MEMS has traditionally referred to miniature components integrating sensors, actuators, and electronics [17]. These devices are produced using many of the same microfabrication techniques as those used to manufacture integrated circuits on silicon substrates. This manufacturing strategy enables the mass production of miniature, high performance, mechanical, fluidic, and optical components that can be integrated with electronics at low unit cost.

The telemetric application of MEMS sensor technology to hemodialytic systems has two component requirements: (1) sensing and (2) data transmission. If no internal power source is to be used, external powering of the system becomes a requirement, as well. This can be accomplished via inductive coupling, using radiofrequency transmission from an external source, the charging of a capacitor located on the implanted MEMS chip, and the releasing of the energy to power the MEMS chip and circuit in order to transmit sensed data to an external receiving source. An alternate, and even simpler, scheme is suitable for capacitive MEMS sensors, where changes in the sensing parameter can be translated into capacitance variations of the MEMS sensor. In such cases, the MEMS sensor can be configured into a passive tank circuit that

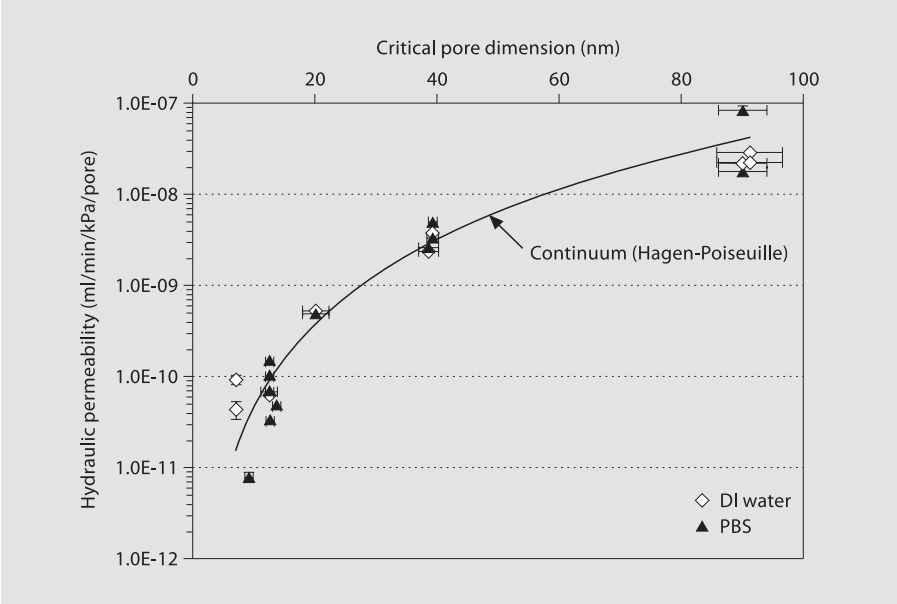

Fig. 2. Hydraulic permeability of silicon nanopore membranes (SNMs). Hydraulic permeability per pore (K_{UF}, y axis) to phosphate-buffered saline (PBS, ▲) and deionized water (DI water, ◇) for SNMs with pores 8–100 nm in small dimension (x axis). Multiply by 1.33×10^9 for ml/min/mm Hg/m^2.

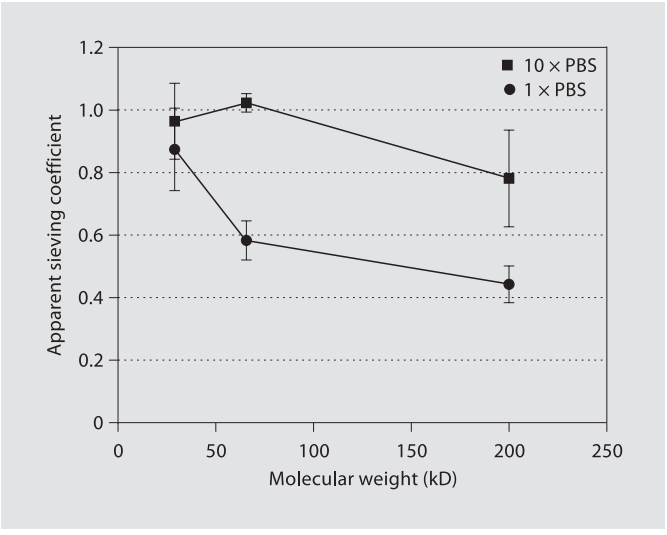

Fig. 3. Rejection of proteins by 42-nm pore. Apparent sieving coefficients for carbonic anhydrase (25 kD), bovine serum albumin (66 kD), and sweet potato amylase (200 kD) in 150 and 1,500 mM PBS. The high-ionic strength solution minimizes electrostatic shielding between the molecule and the much larger pore.

is comprised of the variable capacitor and a fixed inductor. This tank circuit exhibits a characteristic resonant frequency that varies as the capacitance changes. An external probe can be used to detect the resonant frequency of the implanted sensor without the use of any circuit in the implanted chip. Millimeter-scale continuous-reading wireless probes have been demonstrated for use within deep tissues, and could be adapted for continuous monitoring of hemodynamic parameters, permitting closed-loop cardiovascular feedback for autonomous hemofiltration systems [18].

A View to the Future

The two most significant barriers to implementation of this technology to renal replacement are long-term biocompatibility of the materials and strategies for synthetic homeostasis. At present, SNMs are manufactured from silicon and silica, possibly the worst choice of material for blood biocompatibility imaginable. The material choice at present is driven solely by fabrication and prototyping convenience, with little more significance attached to that choice than the choice of balsa wood for

wind-tunnel models of airplanes and cars. Surface modification of silica and alumina with polyethylene glycol has been well demonstrated, as well as dendrimeric polysaccharides and other surfactant polymers [19–23]. These developments give significant optimism that the medium-term (months to years) biocompatibility of nanopore filters will be achievable [24, 25]. More difficult will be replicating the salient features of the pleiotrophic and redundant neuroendocrine control of ECF volume with sensors and a computerized algorithm. Just as research in membrane design informs our understanding of glomerular physiology, efforts to replicate mechanisms of volume homeostasis may illuminate and expand our understanding of hypertension and cardiovascular disease.

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Blood Purification

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The Basic, Quantifiable Parameter of Dialysis Prescription Is Kt/V Urea; Treatment Time Is Determined by the Ultrafiltration Requirement; All Three Parameters Are of Equal Importance

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Key Words
Hemodialysis · Treatment time · Mortality

Abstract
There have only been two randomized controlled trials studying outcome as a function of dose in hemodialysis (HD). The first was the National Cooperative Dialysis Study which showed that adequate dialysis was achieved with spKt/V >1.00. The second study was HEMO which was originally designed to study spKt/V 1.2 compared to spKt/V 1.45. Unfortunately by the time HEMO was started, observational studies (OS) had convinced the nephrology community that the minimum adequate dose of spKt/V was 1.40, so the lower target was increased to 1.4 and the upper target to 1.7. The study showed no difference in outcome, although OS have now demonstrated that outcome improves up to spKt/v 2.00. Analysis of HEMO as treated showed that there is a fundamental flaw in dose-targeted OS in that the optimal dose always, but spuriously, increases as the studied dose increases due to dose-targeting bias. Similar flaws exist in the association of treatment time to outcome.

The rational of intermittent dialysis therapy for end-stage renal disease is intermittent removal of accumulated low molecular weight toxic catabolites of protein (U, H^+, K^+, $_iP$, Ca^{2+}) and Na^+ and H_2O, all of which are normally eliminated by the kidneys. Thus virtually all the solutes targeted for removal with intermittent dialysis therapy are of low molecular weight and cleared by diffusive transport across the dialyzer, except Na^+ and H_2O which are removed by ultrafiltration (Q_f). The only larger molecular weight solute with established uremic toxicity is β_2-microglobin and no established concentration levels have been identified to minimize clinical toxicity.

Dialysis Prescription

The only widely accepted method to quantify the dose of dialysis is the fractional clearance of urea from body water or Kt/V_U, where K is dialyzer urea clearance, t is treatment time and V is the urea distribution volume (KDOQI) which is considered to be a dose surrogate for removal of low molecular weight toxins. There have been two prospectively randomized, controlled trials (RCTs) of dialysis therapy [1, 2] and in both these trials the dialysis dose was tightly controlled with urea kinetic modeling (UKM). In contrast there have been no prospectively RCTs on the effect of treatment time on outcome. Over the years large observational studies (OSs) have not shown a consistent effect of treatment time on mortality until recently two fairly large OSs were report-

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ed which statistically show an association of longer treatment time with lower mortality [3, 4]. However, the validity of OSs, which might be characterized as 'guilt or innocence by association', have recently been seriously questioned [5]. It is important to trace the historical roles that RCTs and OSs have played in understanding the dialysis dose to provide a perspective on the validity of these recent OSs correlating long treatment time with reduced mortality.

The National Cooperative Dialysis Study

Dialysis technology was changing rapidly in the 1960s and 1970s. The inefficient Kiil dialyzers used with 8- to 12-hour treatment times were being replaced by new dialyzers with smaller blood volumes and more reproducible and higher clearances developed through the stimulus of the Artificial Kidney Chronic Uremia Program of the NIH, but there was no agreement on a definition of adequate dialysis. A consensus was reached at the NIH Conference on Adequacy of Dialysis in 1974 that a prospective controlled trial of dialysis was required. The trial subsequently designed and carried out was the National Cooperative Dialysis Study (NCDS) [1] which was guided by UKM [6], and its basic design is shown in figure 1. UKM was used to control blood urea nitrogen (BUN) at 2 nominal levels of 70 ± 10 and 120 ± 10 mg/dl with protein intake (normalized protein catabolic rate or NPCR, g/kg) controlled to $0.80 \leq \text{NPCR} \leq 1.40$. The protocol also called for short and long treatment times for both low and high BUN groups as shown in figure 1. The short treatment times were targeted at 2.5–3.5 h and long treatment times 4.5–5.5 h and the mean times achieved were 3.2 and 4.5 h, so a substantial difference in treatment time was in fact observed.

Clinical outcome in the NCDS for 10 groups of 16 patients each expressed as percent success or failure is plotted in figure 2A [7]. Groups II and IV with high BUN had a 56% incidence of failure while groups I and III with low BUN had 13% failure which was thought to confirm the hypothesis that high BUN resulted in poor outcome. However, there was a 5th group (V) of patients with NPCR <0.80 that had a very high incidence of failure (75%) which was unrelated to BUN [7]. In an attempt to understand group V, the UKM which was used to guide the study was solved for BUN over a wide range of spKt/V and NPCR with results shown in figure 2B. When spKt/V is held constant, BUN is a linear function of NPCR as depicted in figure 2B for $0.4 \leq \text{spKt/V} \leq 2.0$.

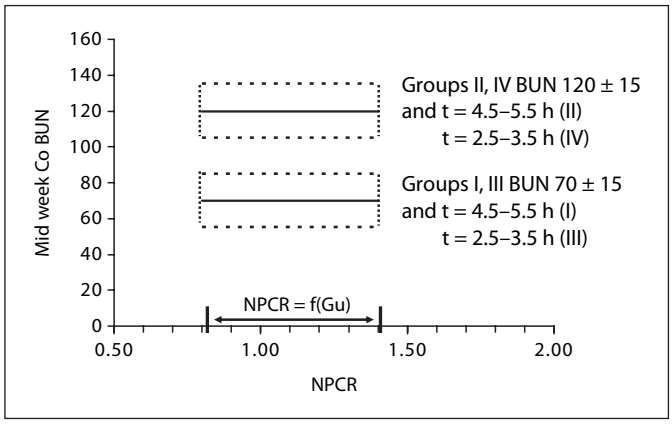

Fig. 1. The design of the NCDS. The protocol called for identical control of pretreatment BUN as a function of NPCR in the low and high BUN groups with short and long treatment times as described. t = Treatment time.

An analysis of NCDS data with the UKM grid in figure 2B is shown in figure 3 where it can be seen that spKt/V ≥1.0 clearly separated the patients in groups II, IV and V with a high failure rate from groups I and III with a low failure rate. The analysis in figure 3 is portrayed in figure 4 as the relative probability of failure as a function of spKt/V. These data were interpreted to show that the mechanism by which dialysis controls uremia can be quantified as the magnitude of dialyzer urea clearance (Kt) normalized to urea distribution (V) or Kt/V. It was concluded that an adequate dose of dialysis was achieved with Kt/V = 1.00 and no improvement was seen with higher doses up to spKt/V 1.40. The step function, outcome, shown in figure 4 represents the two levels of dosing in this prospectively randomized database.

The NCDS Dosing Controversy and HEMO

In addition to the step function in outcome shown in figure 4, continuous linear and exponential functions relating probability of failure to Kt/V could also be written with equivalent p values as described in the mechanistic analysis paper [7]. Subsequently others strongly argued that outcome should be an exponential function as shown in figure 5A because of accumulating OS experiences which indicated continuing improvement in outcome up to spKt/V 1.40 [8]. The HEMO study [2] was subsequently undertaken to evaluate the benefit of higher dialysis doses in a RCT. The HEMO study design

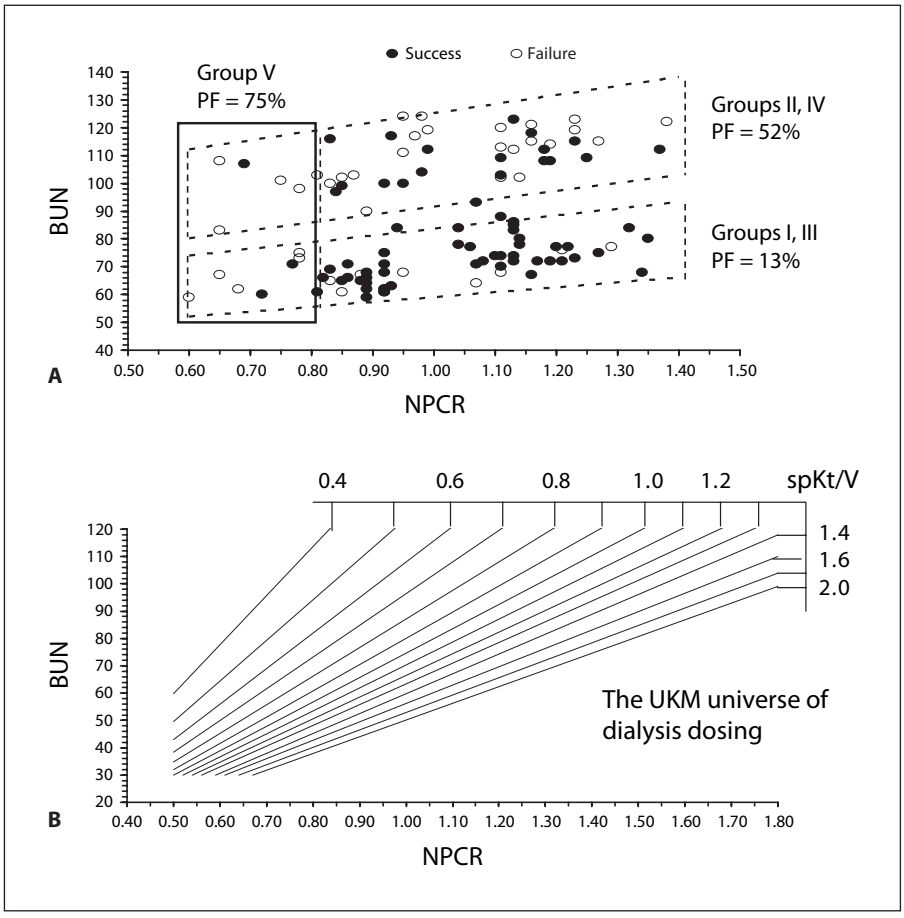

Fig. 2. A Results of NCDS. **B** Solution of urea model. PF = Probability of failure.

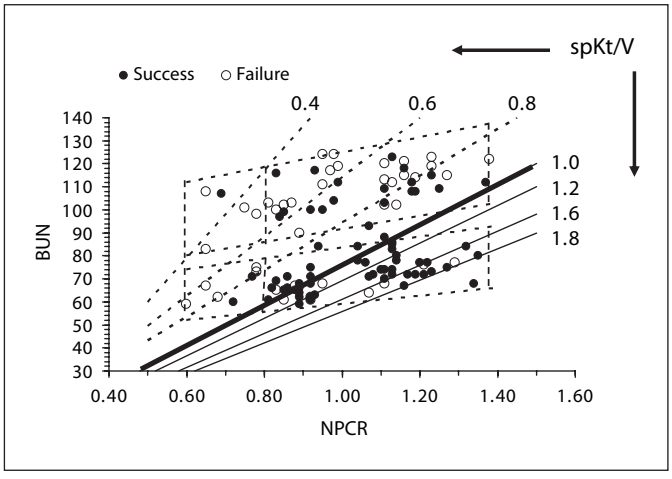

Fig. 3. NCDS outcome results with a superimposed Kt/V grid indicate that outcome failure was virtually eliminated when Kt/V > 0.80 and Kt/V = 1.00 clearly separated all three failure groups (II, IV and V) from those with successful outcome (I and III).

developed in the pilot phase called for a standard arm with spKt/V 1.1–1.2 and a high dose arm spKt/V 1.4–1.5. As shown in figure 5B, this would have overlapped the high dose arm in NCDS and provided an evaluation of dose from the combined RCTs ranging from 0.45 to 1.50.

By the time the pilot phase of HEMO was finished, there was clinical consensus in the nephrology community that OS had shown that the minimum adequate dose was spKt/V = 1.40 and consequently the standard dose arm was moved up to spKt/V = 1.40 as shown in figure 6. The increase of standard arm to 1.40 eliminated any evaluation with HEMO on the validity of the NCDS conclusion spKt/V >1.0 would not improve outcome. Much to the surprise of many, there was no difference in outcome in the standard arm vs. the high dose arm in HEMO, and we still do not know if spKt/V = 1.4 is better therapy than spKt/V = 1.0 since the NCDS remains the only comparative study of dosage in that range.

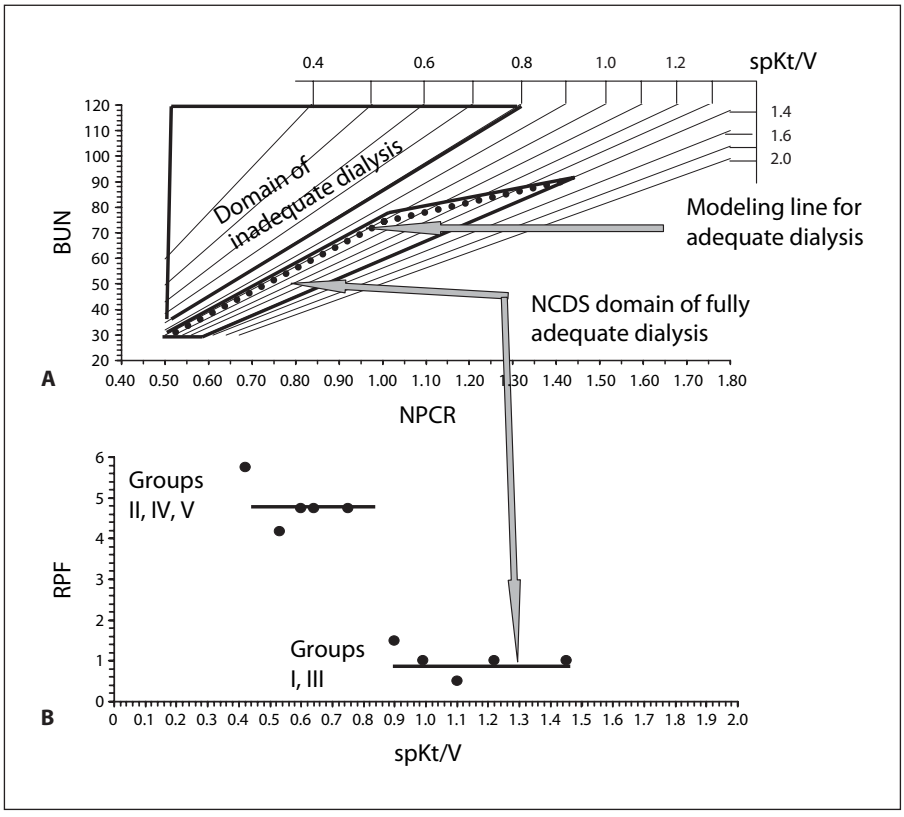

Fig. 4. Results of mechanistic analysis of NCDS outcome.

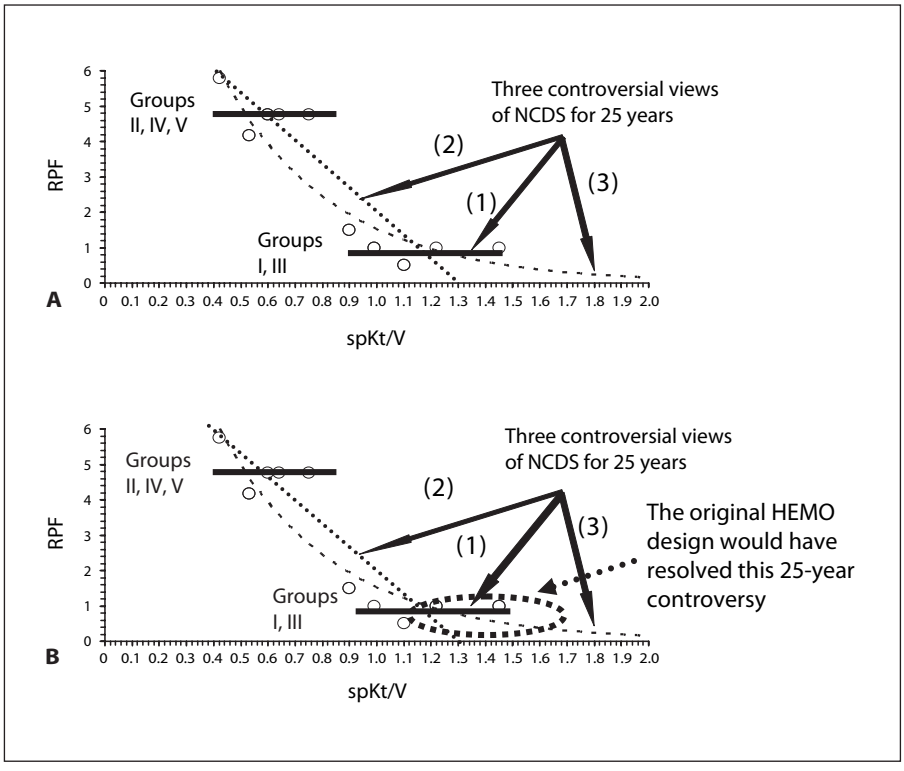

Fig. 5. Three highly controversial views of outcome in NCDS.

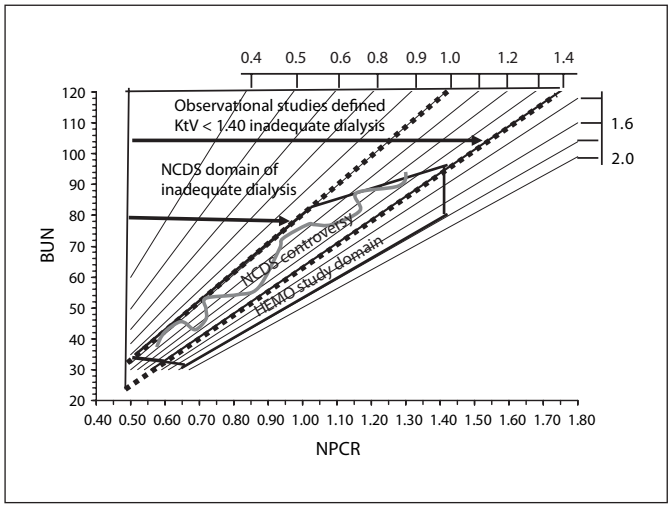

Fig. 6. Observational studies reported during the pilot phase of HEMO were interpreted to show that spKt/V <1.40 was inadequate dialysis. These studies had a profound effect on HEMO and moved the standard therapy area up to spKt/V = 1.4. Consequently the domain of NCDS dosing controversy over 25 years was not even studied.

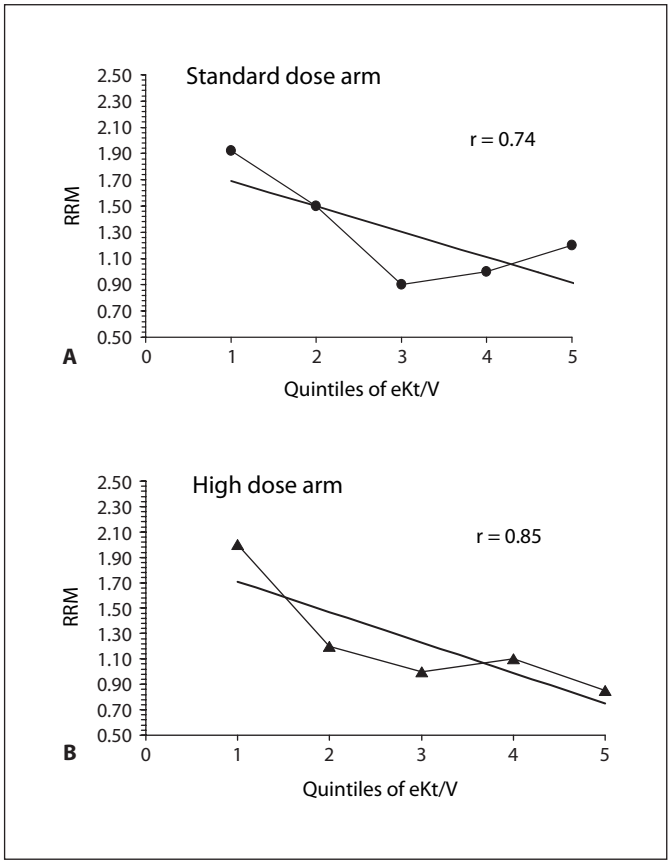

Fig. 7. Observational studies result in ever higher minimum adequate dosage recommendation due to the powerful effect of dose targeting error as illustrated by the HEMO data. It is a self-fulfilling prophecy inherent in the design of observational studies.

Reconciliation of RCT Results with OS Results

Many patients had to have a reduction in dose to fit even the higher spKt/V = 1.40 target for the standard arm of HEMO. This caused concern about inadequate dialysis, especially in patients who did not quite reach the spKt/V goal of 1.40. Consequently the HEMO safety committee instructed the Data Coordinating Center (DCC) to stratify the standard arm by quintiles of Kt/V and monitor outcome over this range in the standard arm [5]. The results of these analyses are shown in figure 7A where a highly significant decrease in RRM was observed as the stratified spKt/V increased in the standard arm. This observation might well have resulted in early termination of the study and a conclusion that the minimum adequate spKt/V is 1.6 if the DCC had not done the same analysis in the high dose arm and found exactly the same relationship. This striking dose targeting bias found in both arms of HEMO reveals a serious flaw in OSs – they are in a sense self-fulfilling prophecies in that the optimal dose found always increases as the dose range studied increases. This is further illustrated in figure 8A where it can be seen that the only domain of inadequate dialysis is spKt/V <1.0 found with NCDS since the 2 HEMO groups showed no difference in outcome. Figure 8B shows the HEMO dose stratification results expressed as approximate values of spKt/V in the two arms. The two arms had equal outcomes, but using OS techniques it would have been spuriously concluded that there was a continuous decrease in mortality over the whole range of dosage despite that fact that very little more solute is being removed as spKt/V increases from 1.0 to 2.0 with thrice weekly dialysis.

Effect of Treatment Time on Patient Outcome in the NCDS

A very frequent commentary about the NCDS is that the slightly increased mortality with short treatment time was highly significantly, clinically, falsely interpreted as not significant because p = 0.06, and therefore the nephrology community was misled about the importance

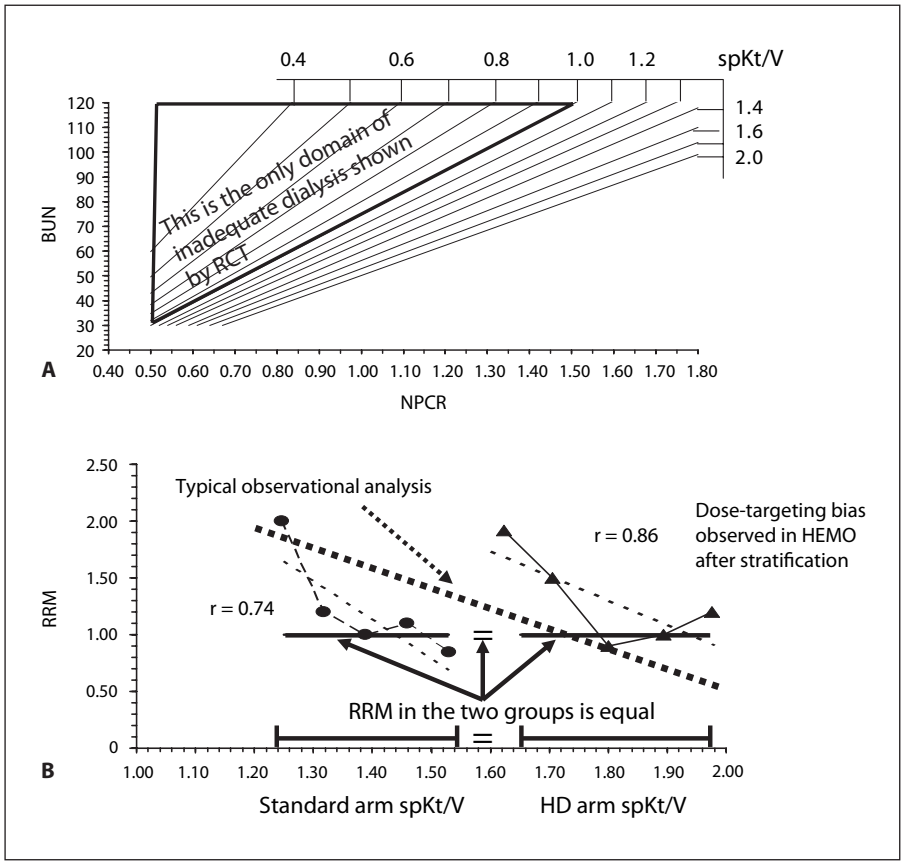

Fig. 8. Reconciliation of observational studies with randomized trials.

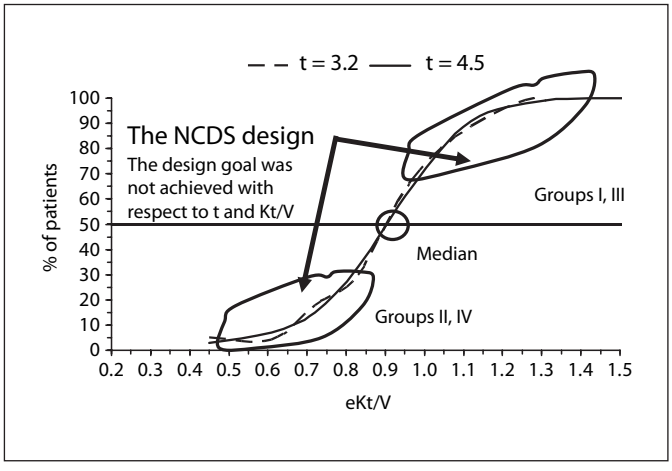

Fig. 9. The NCDS design called for identical distributions of spKt/V at treatment time (t) = 2.5–3.5 and t = 4.5–5.5 h as illustrated here. In this plot values for short t are plotted as virtually identical to those with long t. This part of the design was not achieved.

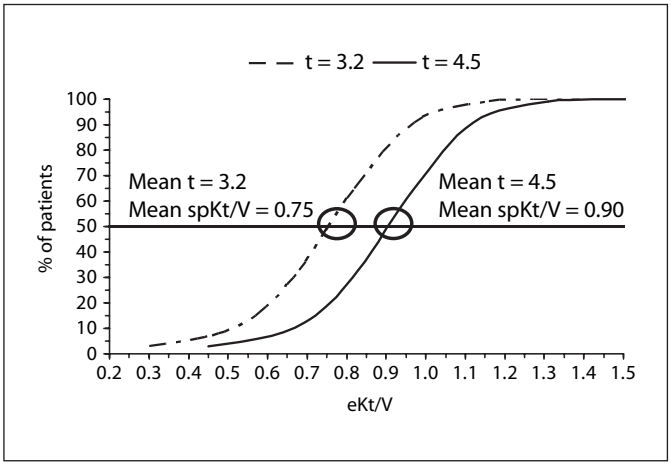

Fig. 10. The NCDS design called for identical distributions of spKt/V at treatment time (t) = 2.5–3.5 and t = 4.5–5.5 h as illustrated in figure 9 and the spKt/V distribution for mean t = 3.2 h was substantially lower than for mean t = 4.5 h. This part of the design was not achieved.

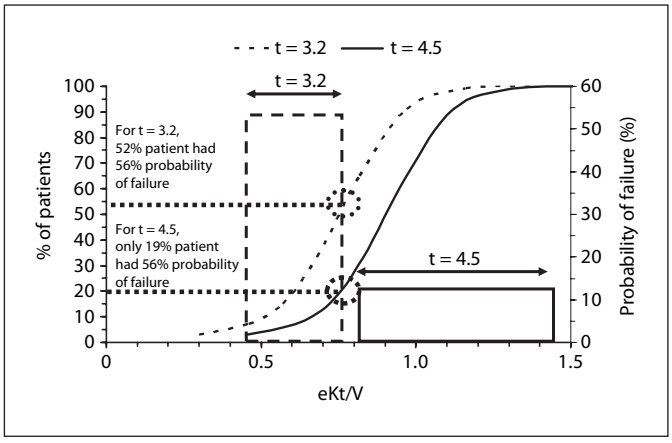

Fig. 11. The marginal p = 0.06 in the NCDS for RRF = f(t) was clearly of no significance because of the highly significant correlation of Kt/V to treatment time.

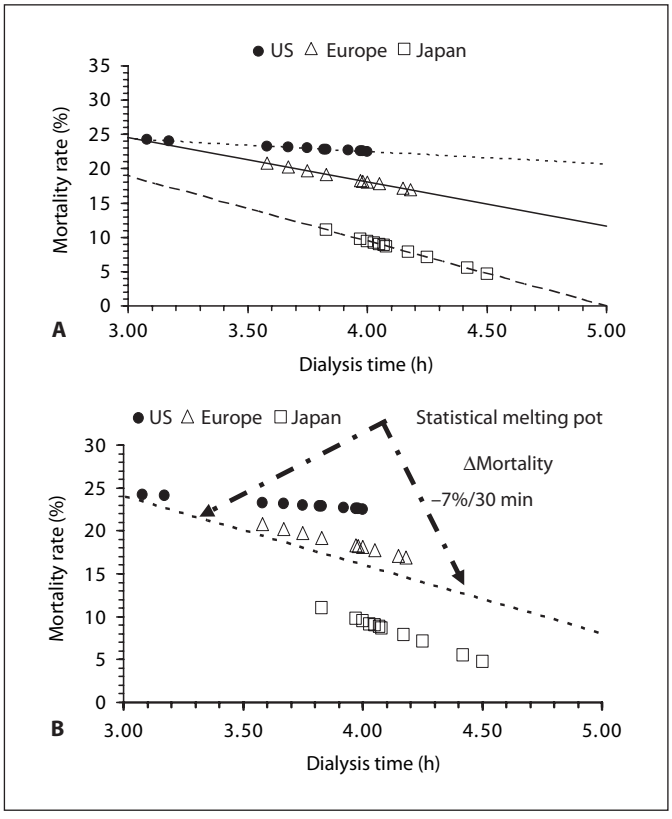

Fig. 12. Mortality rate as function of treatment time in DOPPS data. **A** The regression of mortality rate on treatment time is extremely variable across different geographic regions. These curves are not convincing evidence of a generalizable inverse dependence of mortality on treatment time. **B** The DOPPS data after statistical analysis showed that mortality rate decreases 7%/30-min increase in treatment time.

of treatment time in the dialysis prescription [3, 4, 9, 10]. In fact, the contrary argument might be more reasonable: The marginal effect seen actually may suggest that short time was beneficial in the study because the study design goal of separating Kt/V from treatment time was not achieved and Kt/V was significantly lower in the short time groups compared to long time groups. The study design is schematically illustrated in figure 9 where it can be seen that median spKt/V 0.90 and identical distributions should have been prescribed and delivered in both short and long time groups. The actual distributions are shown in figure 10 where the Kt/V distribution is substantially lower in the short time patients compared to long time patients with median 0.75 vs 0.91. The profound effect of this can be seen in figure 11 where 52% of the short time patients were in the Kt/V region of 56% probability of failure while only 18% of the long time patients fell into the high probability of failure region. It is surprising that there was not a more significant relationship between the probability of failure and treatment time in view of the 5-fold increase in risk of failure in the low Kt/V group. The effect of Kt/V was never tested in the initial analysis of the NCDS [1] but rather a surrogate, tacrolimus urea, which is a very poor substitute for Kt/V since it cannot distinguish the effect of protein catabolic rate.

Effect of Treatment Time on Outcome in the DOPPS Studies

It was recently reported that longer treatment reduced mortality in the DOPPS database for three large geographic areas: US, Europe and Japan [3]. The authors concluded that the data supported the generalized conclusion that mortality rate fell by 7% for each 30-min increase in treatment time. The data reported for each region adjusted for comorbidities are plotted in figure 12A and the statistical conclusion of a 7% decrease in mortality for each 30-min increase in treatment time is shown in figure 12B. It is not reasonable to generalize these data with such striking geographic differences in the effect of treatment time. The effect is almost negligible in the US and quite striking in Japan while mortality is much lower in Japan at all levels of treatment time.

Twardowski [9] has argued that 'short thrice weekly hemodialysis is inadequate regardless of small molecule clearance' and recommends 5- to 8-hour treatment time. Evaluation of this belief with the DOPPS data requires

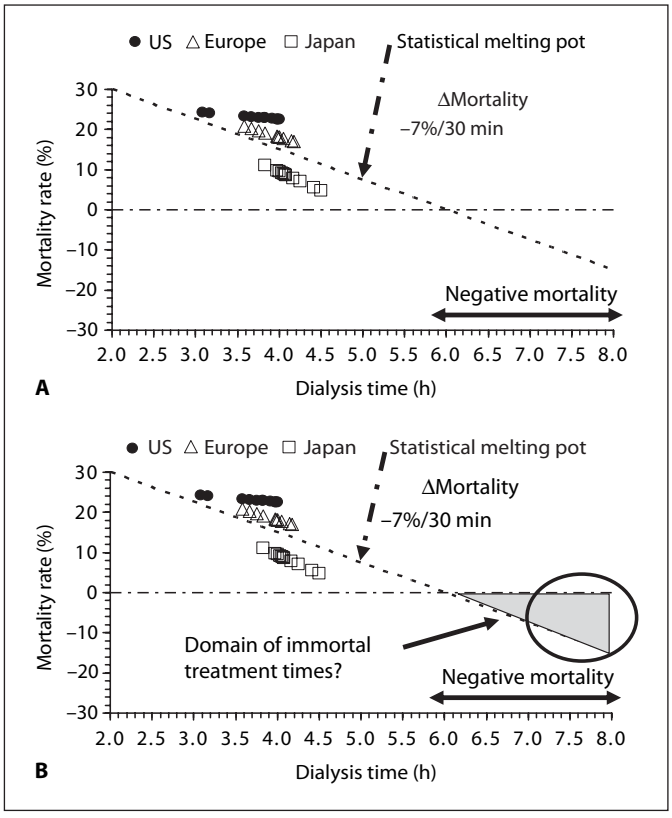

Fig. 13. Extrapolation of DOPPS data to a treatment time of 8 h. **A** Domain of mortality. **B** Domain according to Twardowski [9].

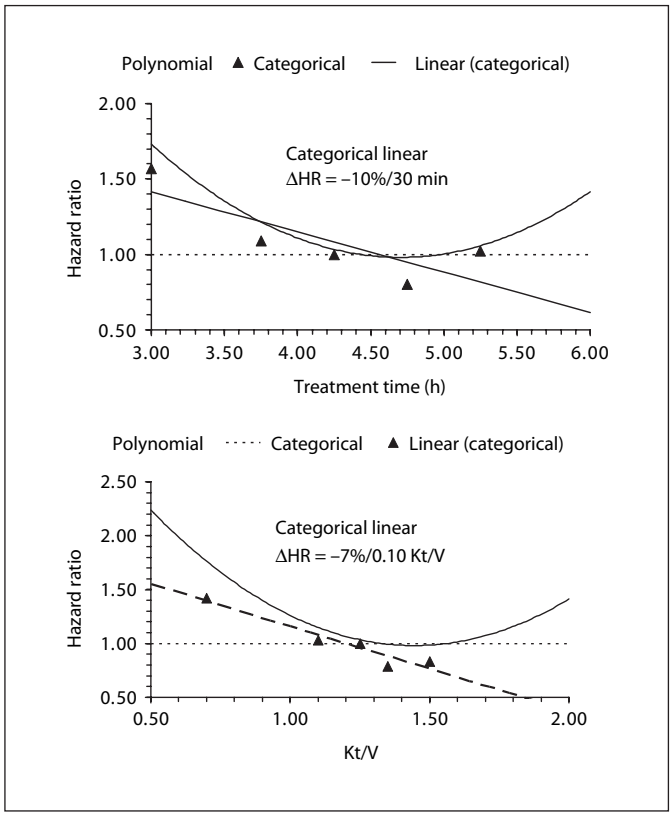

Fig. 14. Results of Australia New Zealand observational study of outcome as function of treatment time and Kt/V. The categorical analyses show the typical tell-tale signs of dose targeting error for both Kt/V and treatment time. The polynomial fit shows U-shaped outcome responses for both parameters. Which is correct and why should there be a U shape?

expansion of the X axis to cover the disputed treatment time range from 2.0 to 8.0 h as shown in figure 13A. Clearly the DOPPS data do not cover such a wide range and, in fact, the mortality rate becomes negative when the DOPPS regression is extended to a treatment time of >5.5 h as shown in figure 13B. Twardowski's [9] belief that 8-hour treatment times are required for adequate clinical outcome might actually be expected to achieve immortality when viewed from a geometric interpretation of DOPPS data outcome.

It was also concluded in the DOPPS paper that slower ultrafiltration rates correlated with lower mortality. This is difficult to understand when in DOPPS II the mean ultrafiltration rare was 9.9 in Japan and 9.8 in the US [3] (table 1).

Association of Hemodialysis Dose and Session Length with Mortality in Australia and New Zealand

This study was reported simultaneously [4] with the DOPPS study. It was an OS using data from the Australia New Zealand Dialysis Registry (ANZDATA). It is of interest to note that 20% of patients in ANZADATA are on home dialysis which is not a generalizable therapy category with external validity in view of the very low frequency of home dialysis in most countries. Further, the dialyzers most often used are low flux which also raises question about the generalizability of the data. Certainly arguments about time and minimum mortality cannot be compared in low flux compared to high flux therapy.

The reported outcome as a function of treatment time and Kt//V in the ANZDATA study are shown in figure 14. The analyses of categorical outcomes follow the typical

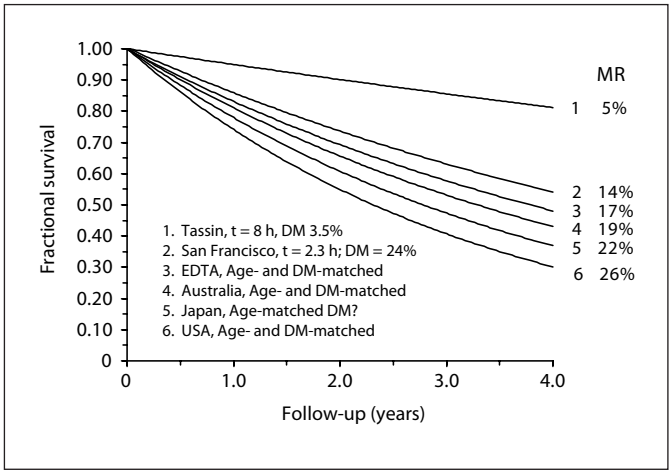

Fig. 15. Mortality rate in hemodialysis patients is dependent on the quality of treatment time not necessarily the quantity of treatment time. From Gotch and Uehlinger [12].

linear response seen with a dose targeting error in OS for both treatment time and Kt/V. The authors also reported a continuous polynomial U-shaped regression which they used to locate an inflection point of minimum mortality in the region of 4–5 h which is contradictory to the categorical analysis.

A Final OS Anecdote

In 1992 when the data from Charra et al. [11] appeared showing very low mortality with long 6- to 8-hour treatment times, we reported the analysis of our 4-year experience in San Francisco with high flux dialysis [12] and UKM. We examined several of the large international databases and matched each database with respect to age and diabetes to our results with the results shown in figure 15. Certainly the unique data from Charra et al. [11] stand out, but the next lowest mortality rate was in San Francisco with by far the shortest mean treatment time of 2.3 h.

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Size Matters: Body Composition and Outcomes in Maintenance Hemodialysis Patients

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Key Words
Hemodialysis · Body composition · Uremic toxins · Epidemiology, reverse

Abstract
In hemodialysis patients a low body mass index (BMI) is correlated with an unfavorable clinical outcome, a phenomenon known as 'reverse epidemiology'. Mechanisms underlying this observation are unclear. We propose the following: uremic toxin generation occurs predominantly in visceral organs and the mass of key uremiogenic viscera (gut, liver) relative to body weight is higher in small people. Consequently, the rate of uremic toxin generation per unit of BMI is higher in patients with a low BMI. Body water, mainly determined by muscle mass, serves as a dilution compartment for uremic toxins. Therefore, the concentration of uremic toxins is higher in small subjects. Uremic toxins are taken up by adipose and muscle tissues, subsequently metabolized and stored. Thus, the larger the ratio of fat and muscle mass to visceral mass, the lower the concentration of uremic toxins and the better the survival. To test this hypothesis, studies on uremic toxin kinetics in relation to body composition are needed.

Introduction

Risk factors, such as hypertension, obesity and hypercholesterolemia, play an important role in the development of cardiovascular disease, not only in the general population but also in chronic kidney disease patients. In contrast to epidemiological data from the general population, in maintenance hemodialysis (MHD) patients low body mass index (BMI, defined as the weight in kilograms divided by height in meters squared) is correlated with an unfavorable clinical outcome, a phenomenon referred to as 'paradoxical' or 'reverse' epidemiology.

A decrease in mortality risk with a higher BMI was reported for the first time in a population of mostly young, non-diabetic patients treated with MHD in France during the 1970s [1]. Subsequently, several investigators found a significant inverse relationship between mortality risk and body size, unaffected by adjustments for comorbidities, in prevalent and incident hemodialysis patients [2–4]. In a retrospective analysis of 10,000 MHD patients from the Dialysis Outcomes and Practice Patterns Study the relative risk for mortality was 0.84 in overweight patients and 0.78 in individuals with obesity as compared with patients in the BMI range of 23–

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24 kg/m^2 [4]. In contrast, in a study based on 116 Japanese MHD patients [5] followed for 12 years, a BMI of >23 kg/m^2 was correlated with a lower survival rate than a BMI of 17.0–18.9 kg/m^2.

Fat loss may be associated with a worse outcome in MHD patients. In a recent study [6] body fat was remeasured (by means of near infrared interactance) in 411 MHD patients after 6 months. After adjustment for demographics and surrogates of muscle mass (MM) and inflammation (i.e., mid-arm muscle circumference, serum creatinine, and proinflammatory cytokines), a fat reduction of ≥1% was associated with a death risk 2 times ($p = 0.004$) that of patients who gained fat (≥1%).

This is surprising because abdominal adiposity has shown associations with inflammation [7] and atherosclerosis [8] in MHD patients, just as in the general population. In particular, visceral adipose tissue (VAT) is associated with the prevalence of carotid atherosclerosis in MHD patients [8]. However, no study in hemodialysis patients has reported on the differential effects of VAT and subcutaneous adipose tissue (SAT) on long-term survival.

Adipose tissue is a heterogeneous multifunctional organ rather than simply a passive storage site for excess energy. Its subcutaneous and visceral compartments present significant differences in morphology, physiology, metabolic activity, and hormonal sensitivity [9]. To date, more than 100 products have been reported to be secreted by adipose tissue [10], including TNF-α, IL-6, IL-8, plasminogen activator inhibitor-1, angiotensin-II, leptin, and adiponectin. Unlike adiponectin, most of these circulating factors are elevated in obese subjects. An increased local production of angiotensin-II contributes to insulin resistance and the metabolic syndrome. Leptin suppresses food intake and is considered a proinflammatory cytokine [11]. It is conceivable that in a given individual the proportion of SAT to VAT may ultimately define the degree of proinflammatory activity of fat.

Using 24-hour urinary creatinine excretion as an indicator of MM, a study in a large cohort of MHD patients showed that the protective effect conferred by a high BMI is limited to those patients with normal or high MM [12]. By design, this study was limited to subjects with residual renal function. Although this study has been criticized on methodological grounds [13, 14], important insights into the interactions of BMI and MM were given.

The complex and poorly understood balance between the negative effects of adipose tissue (i.e. its proinflammatory aspects) and the advantageous influence of an adequate nutritional state may change over time. It was speculated that a high BMI is advantageous in the short term, but not over a longer period of time [15, 16], but the cause(s) of the improved survival in overweight and obese CHD patients remains obscure.

Limitations of Studies to Date

The critical point is that BMI does not differentiate between fat and muscle; BMI and changes in BMI do not exclusively reflect total adipose tissue mass (TATM) or changes in TATM. MM contributes significantly to BMI, and at any given BMI the relative contributions of TATM (and its components, VAT and SAT) and muscle tissue to it may vary substantially between individuals. Consequently, body composition cannot be inferred from BMI data accurately and across the whole spectrum of BMIs. Moreover, to date in hemodialysis patients only limited data on the relative contributions of SAT and VAT to TATM are available [8]. So far, no comprehensive study on body composition (defined in terms of MM, VAT, and SAT) and its relationship to outcomes has been performed in MHD patients. The question of a relationship between visceral mass and outcomes has not been addressed at all. There exists a gap in our understanding of the relationship between BMI and body composition (in terms of fat, MM, and visceral organ mass) and on how the components of body composition relate to outcomes in MHD patients.

Why Does High BMI Confer a Survival Advantage: An Alternative Hypothesis

The reduced survival in MHD patients with a low BMI has recently been explained by a novel hypothesis [7]. Briefly, both in healthy and MHD subjects, visceral organ mass (i.e. high metabolic rate compartment, HMRC) relative to whole body mass ($HMRC_{\%BW}$) is inversely related to weight and urea distribution volume (V). V, as determined by urea kinetic modeling, is closely related to MM (fig. 1), whereas fat mass contributes only marginally. Viscera are the most likely source of uremic toxins, and their mass and metabolic activity may be related to uremic toxin generation. According to this hypothesis the concentration of uremic toxins in V is higher in subjects with a low V (and thus low MM and low BMI), resulting in an under-dialysis in low BMI patients when dosed by Kt/V. Dialysis dose is currently pre-

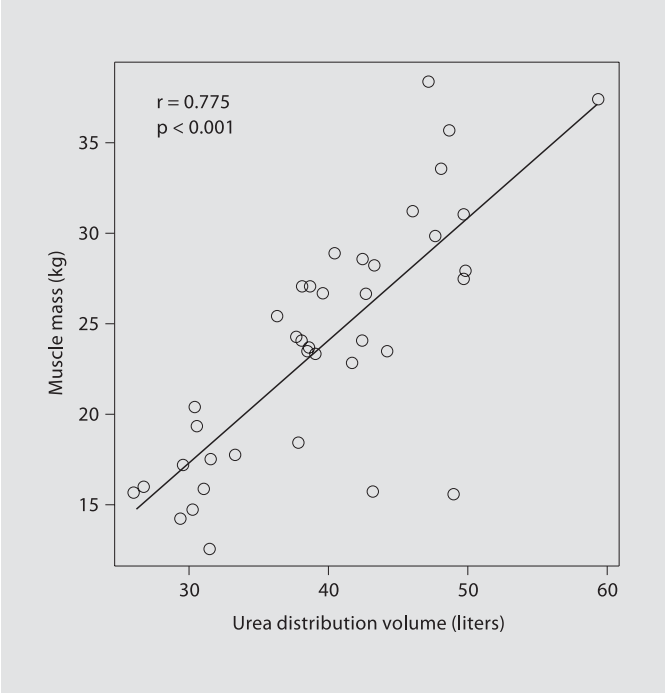

Fig. 1. Muscle mass (estimated by whole body MRI) is positively correlated with urea distribution volume derived from urea kinetic modeling (for details of the methods applied see [17].

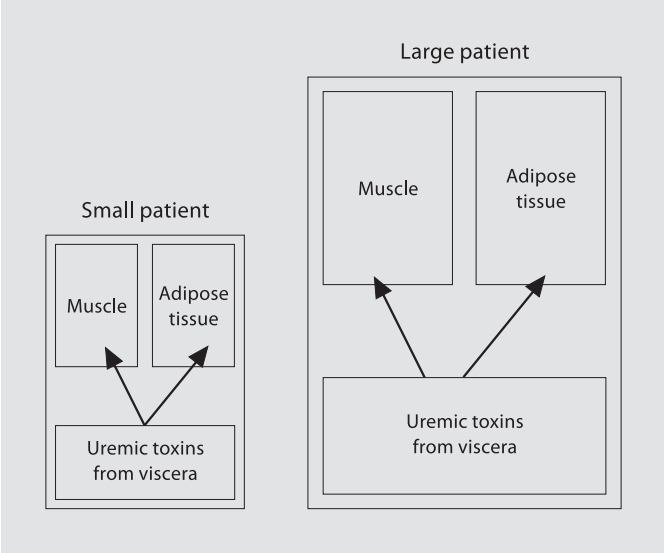

Fig. 2. Uremic toxin generation in the visceral organs and their mass relative to body weight is highest in small people. Consequently, the rate of uremic toxin generation per unit of weight (or BMI) is highest in patients with low body weight (or BMI). Body water, the volume of which is mainly determined by the muscle mass, serves as the dilution compartment of uremic toxins. In addition, uremic toxins (lipophilic >> hydrophilic) are taken up by adipose and muscle tissues and subsequently metabolized and stored. Thus, the larger the ratio of fat and muscle mass to visceral mass, the lower the concentration of uremic toxins.

scribed based on V with the basic assumption that body composition variability is not relevant and the only differences between individuals having different values for V is quantitative and not qualitative. This hypothesis is difficult to test, since visceral mass cannot easily be assessed in a large cohort of MHD patients. Currently with novel high-resolution MRI data becoming available, it will be possible to develop models for the estimation of visceral mass.

In addition to the dilution of uremic toxins in a larger volume in patients with larger body mass (and thus larger V), uremic toxins may be metabolized, detoxificated, and stored in adipose tissues and skeletal muscle. This may be particularly relevant for lipophilic uremic toxins such as p-cresol and pentosidine, which can penetrate the lipid bilayer of cell membranes easily but are poorly removed by hemodialysis [18]. It has recently been shown that the concentration of pentosidine, a lipophilic uremic toxin, is indeed higher in MHD patients with a lower BMI [19]. This concept is summarized in figure 2.

In order to test this hypothesis, detailed studies on uremic toxin kinetics (both hydrophilic and lipophilic) in relation to body composition and dialysis vintage are needed. In these studies, the mass of specific organs (especially liver and gut), subcutaneous and visceral fat and MM have to be measured accurately (e.g. by whole-body MRI). Results from such studies may provide valuable information for tailoring the dialysis dose to the individual patients' needs.

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Impact of the Change in CMS Billing Rules for Erythropoietin on Hemoglobin Outcomes in Dialysis Patients

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Key Words
Anemia · Dialysis · Erythropoietin · Hemoglobin · Medicare

Abstract
On April 1, 2006, new Centers for Medicare and Medicaid Services (CMS) rules for billing erythropoietin (EPO) for dialysis patients went into effect. Two key provisions of the rules were to cap the dose for a single patient at 500,000 IU/month and to mandate a 25% reduction in dose for patients whose latest hemoglobin (HGB) or hematocrit (HCT) in the prior month exceeded 13 g/dl or 39%, respectively. The purpose of this article is to document the effect of the rules change on HGB outcomes in a single large dialysis provider whose computer system was modified to enforce the rules. HGB and EPO doses for 5 months following the implementation were analyzed retrospectively. The most noteworthy observation is that while the rule appears to have reduced the percentage of patients with an HGB of >13 g/dl slightly, it has also increased the percentage of patients with HGB in the medically undesirable range of <11 g/dl.

Background

The Centers for Medicare and Medicaid Services (CMS) issued Change Request 4135, the 'National Monitoring Policy for EPO and Aranesp® for End Stage Renal Disease (ESRD) Patients Treated in Renal Dialysis Facilities' in Transmittal 751 on November 10, 2005. This CMS EPO Monitoring Policy (EMP) took effect on April 1, 2006. Two key provisions of the rules were to cap the dose for a single patient at 500,000 IU/month and to mandate a 25% reduction in dose for patients whose latest hemoglobin (HGB) or hematocrit (HCT) in the prior month exceeded 13 g/dl or 39%, respectively.

This analysis of the effect of the EMP on hemoglobin outcomes is limited to the dialysis facilities which were owned by Fresenius Medical Care North America (FMCNA) prior to the acquisition of Renal Care Group (RCG) in March 2006. RCG facilities were not included because the EMP rules were implemented differently in the RCG information system. In the FMCNA system, the computer system was set up to prevent entry of physician orders or administration of doses which would exceed the 500,000 IU limit. The maximum allowable dose per administration depends on the frequency of the medication order, i.e., 35,000 U 3×/week dosing, 50,000 IU 2×/week dosing, and 100,000 IU 1×/week dosing.

While the EMP policy allows the use of HGB or HCT, for simplicity the remaining discussion will focus on HGB values. The FMCNA recommended anemia management algorithm continues to encourage physicians to modify dose to achieve a target HGB of 11–12 g/dl. However, if a patient's latest HGB in the prior month is >13 g/dl, then the FMCNA computer system requires that the dose in the EPO prescription be reduced by 25%

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on the first of the following month. Approximately 10 days before the end of the month, the system provides a report on which patients require dose changes. Immediately prior to the end of the month, any of those physician orders which have not been reduced by at least 25% are terminated by automatic entry of an end-of-the-month stop date in the order. For patients with an HGB of >13 g/dl, the computer system will not accept a new physician's order for EPO that does not meet the mandatory minimum dose reduction. A validation process run each day makes sure that the administered doses are equal to the ordered doses. After any data entry errors have been corrected, clinical variances must be documented for any remaining discrepancies. Thus, the computer system essentially has enforced the new CMS rules. While minimum and maximum dose limits had previously been used to catch data entry errors for doses which were substantially (typically 3 times) outside the expected range, never before has the FMCNA computer system been used to restrict physician orders.

It should be mentioned that the requirement to change doses effective on the first of the month was a change in clinical practice for the 1,100+ legacy FMCNA facilities. This requirement stemmed from the fact that the fiscal intermediaries who process bills to Medicare could only evaluate dose reductions on a month-to-month basis. Even ignoring the issue of differences in the number of days in consecutive calendar months, if a physician were to reduce the dose per treatment by 25%, from 4,000 to 3,000 U/Rx halfway through the month (on the 7th of 12 treatments in month 1), the apparent dose reduction on a month-to-month basis would be given by:

(Total month 1 dose – total month 2 dose)/total month 1 dose = (42,000 – 36,000)/42,000 = 14.2%

Because this would appear to be less than the required 25% dose reduction, the fiscal intermediary would pay for only 75% of the 36,000 IU billed in month 2, which clearly would be a tremendous financial burden for the dialysis provider. By delaying the dose reduction until the first of the month, the total month 1 dose is 48,000 IU, and the month-to-month dose reduction is exactly 25%. On Friday, August 25, 2006, in Transmittal 1043, CMS released Change Request 5251 which changed the EMP rules effective on October 1, 2006. The change request eliminates the reference to a specific minimum dose reduction of 25%, and requires the provider to indicate whether the dose has been 'reduced and maintained in response to a hematocrit or hemoglobin level'. The same document states: 'Providers are reminded that CMS expects that as the hematocrit approaches 36.0% (hemoglobin 12.0 g/dl), a dosage reduction occurs. Providers are expected to maintain hematocrit levels between 30.0 to 36.0% (hemoglobin 10.0–13.0 g/dl).' As of September 1, 2006, FMCNA is awaiting further clarification and has not changed its implementation of the April version of the EMP rules.

Methods

Hemoglobin results for approximately 95,000 patients per quarter were included in this analysis. Patients were included regardless of modality (HD vs. PD), setting (in-center vs. home), admission status (permanent or transient), or medication use. No patients or laboratory results were excluded. For each time period, intra-patient 3-month averages were determined as the mean of all HGB values in the 3 months. For creation of histograms, the 3-month averages were rounded to the nearest 0.1 g/dl. Intra-patient 1-month HGB averages were also determined. The mean of the patient mean HGB was then calculated for trending.

EPO doses administered in-center are recorded for each dialysis treatment. Intra-patient 1-month averages were determined as the mean of all in-center doses in 1 month. The mean of the patient mean dose was then calculated for trending.

Results

Figure 1 shows the distribution of 3-month average HGB immediately before and after the implementation of the EMP on April 1, 2006. It is not surprising that there is a relatively small difference between the two distributions, given that the lifespan of the red blood cell in dialysis patients averages 64 days [1]. Overall, there was a 0.2% decrease in the percentage of patients with a 3-month average HGB of >13 g/dl. On the other hand, there was a 1.1% increase in the percentage of patients with a 3-month average HGB of <11 g/dl. An HGB of <11 g/dl has previously been shown to be associated with a greater risk of mortality and hospitalization [2, 3].

Figure 2 shows the distribution of the 3-month average HGB 3 months before and 2 months after the rules were changed. Due to the publishing schedule, only 5 months of follow-up could be included. With the longer follow-up time, the percentage of patients with a 3-month average HGB of <11 g/dl increased (2.0% in 5 months), but surprisingly the percentage of patients with a 3-month average HGB of >13 g/dl actually *increased* by 0.7%, rather than decreasing further. Closer inspection reveals that a rise of 1.0% occurred between Q2 2006 and June–August 2006,

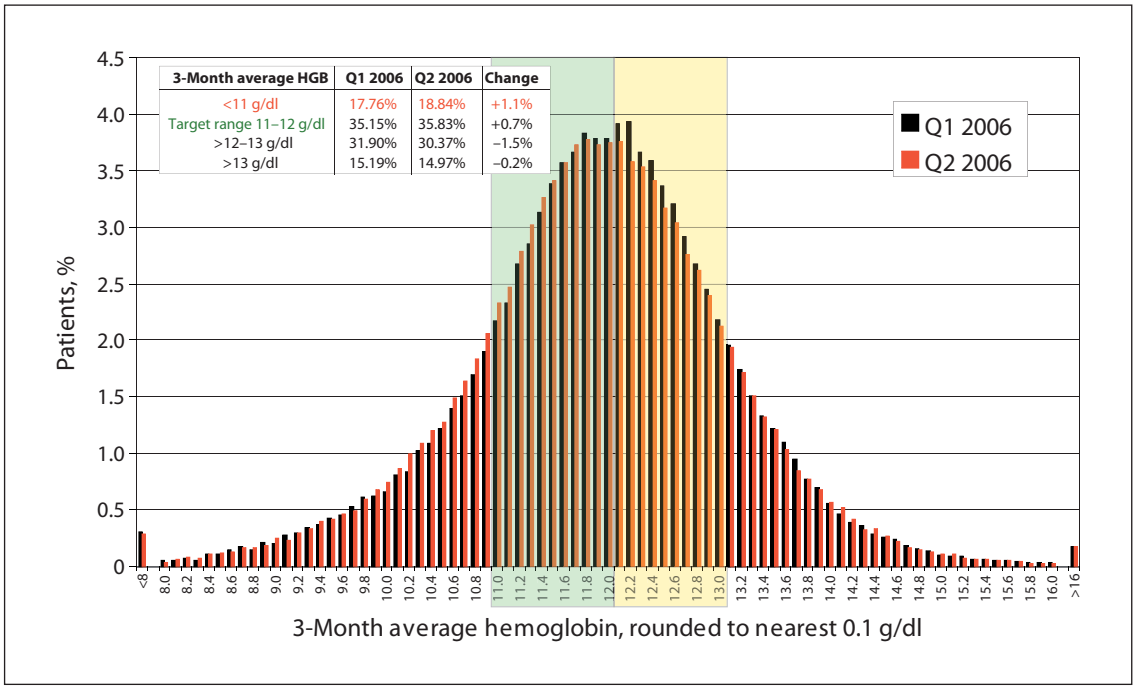

Fig. 1. Distribution of 3-month average hemoglobin immediately before and after implementation of the CMS EPO monitoring policy on April 1, 2006.

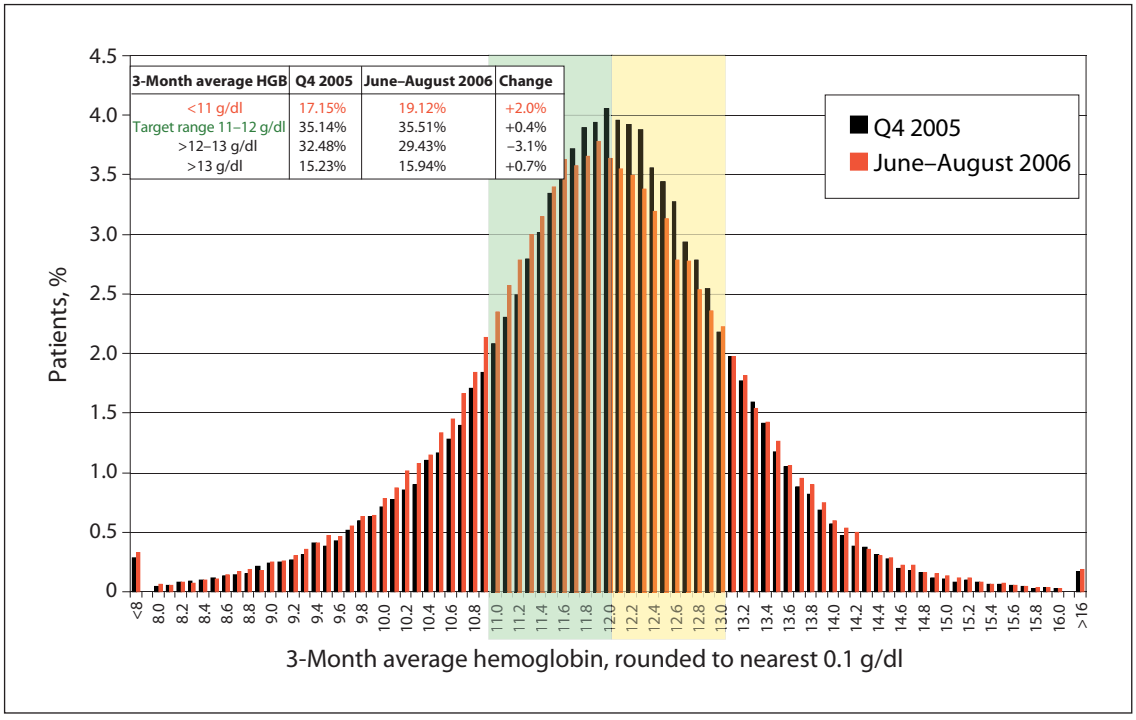

Fig. 2. Distribution of 3-month average hemoglobin 3 months before and 2 months after implementation of the CMS EPO monitoring policy on April 1, 2006.

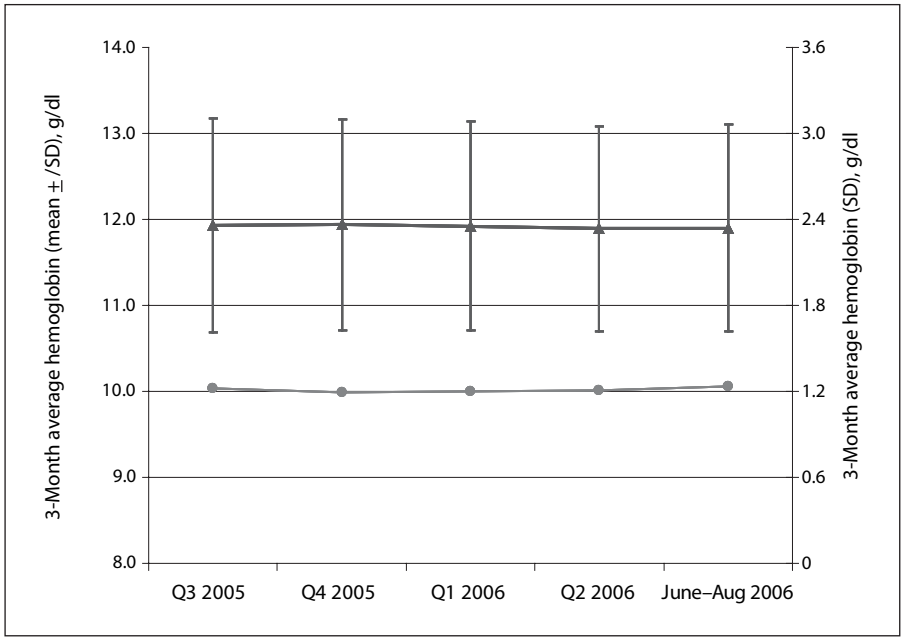

Fig. 3. Trend in 3-month average hemoglobin before and after implementation of the CMS EPO monitoring policy on April 1, 2006. ▲ = Mean ± SD of 3-month average HGB; ● = SD of 3-month average HGB.

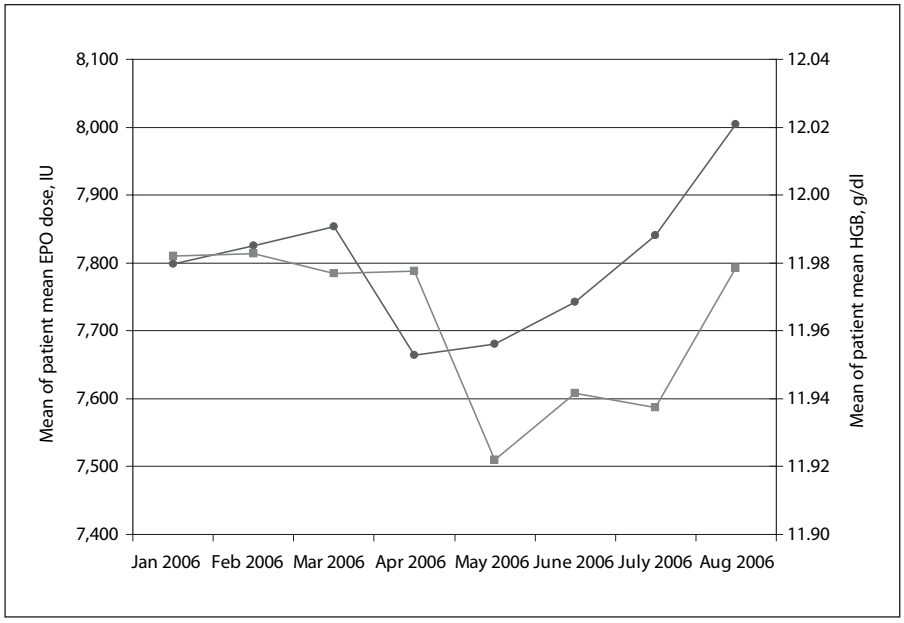

Fig. 4. A transient drop in the monthly mean hemoglobin followed a transient drop in the mean in-center EPO dose after implementation of the CMS EPO monitoring policy on April 1, 2006. ● = Mean in-center EPO dose; ■ = mean HGB.

suggesting that physicians' attempts to counteract falling HGB values resulted in overshooting the target, and reduced the percentage of patients in the two central regions of the bell curve (i.e. 11–13 g/dl) by 2.7% over 5 months.

Figure 3 shows the trend in the 3-month average HGB over a 14-month period. A relatively small drop in mean HGB is noted after April 1, 2006. The standard deviation of the population is shown to be quite stable at 1.2 g/dl, consistent with previous data [4]. If anything, there appears to be a small rise in standard deviation in the latest period shown, suggesting a slight widening of the distribution, the exact opposite of the desired effect.

The immediate impact of the EMP is more clearly seen in figure 4, which shows monthly data for the average in-center EPO dose and the average HGB. An immediate drop in dose is seen in April, while a drop in HGB follows in May 2006. The mean dose begins to rise in May, and continues to rise through August 2006. This suggests that physicians

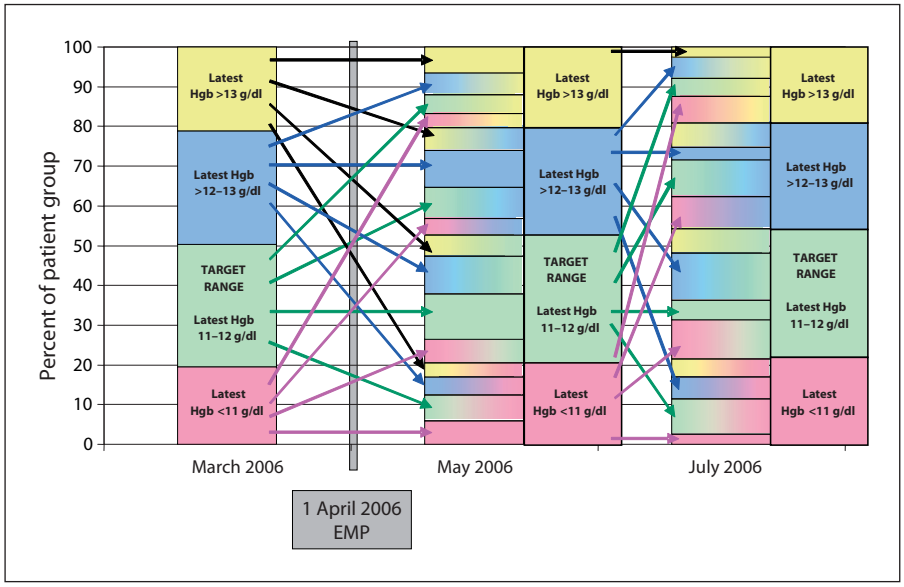

Fig. 5. Movement among hemoglobin categories for 73,002 patients with at least one HGB value in each of three months (March 2006, May 2006, July 2006). The stacked bars containing solid colors represent the percent of patients categorized by their latest HGB in each month: pink for latest HGB <11, green for latest HGB in the target range of 11–12, blue for latest HGB >12–13, and yellow for HGB >13 g/dl. The two-tone bars represent patients who moved from one category to another, with the left-hand color chosen to denote the prior HGB category.

responded to reduced outcomes with higher EPO doses. After a 3-month fall, the monthly mean HGB returns to its March/April level in August 2006. One might expect that the higher dose observed in August 2006 will cycle back down in response to the rebound in HGB values.

One might ask why the company's strict enforcement of the mandatory dose reduction required by the EMP did not substantially reduce the percent of patients with HGB in that range. This can be best understood by examining the movement of patients among HGB categories, as shown in figure 5. This analysis includes 73,002 patients with at least one HGB value in each of three separate months (March 2006, May 2006, and July 2006). The stacked bars containing solid colors represent the percent of patients categorized by their latest HGB in each month: pink for latest HGB <11, green for latest HGB in the target range of 11–12, blue for latest HGB >12–13, and yellow for HGB >13 g/dl. The two-tone bars represent patients who moved from one category to another, with the left-hand color chosen to denote the prior HGB category. While the percent of the subgroup of patients with latest HGB >13 g/dl dropped only slightly (21.1% to 20.2% to 19.2%), only 2.6% of the patients present in all 3 months remained in the HGB >13 group throughout. Further analysis reveals that the majority of these patients received little or no EPO.

In summary, 5 months of follow-up data show that the April 2006 EMP rules appear to have reduced the percentage of patients with a HGB of >13 g/dl slightly, but with the side effect of putting a greater percentage of patients into HGB categories of <11 g/dl. Given the observed intra-patient HGB variability, it is unrealistic to expect that the percentage of patients >13 g/dl will be reduced substantially using current anemia algorithms without increasing the percentage of patients with HGB <11 g/dl. Furthermore, it remains to be seen whether there will be an overall savings in EPO costs for dialysis patients as a result of the EMP. More up-to-date data will be presented at the conference in January 2007.

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Guidelines for Guidelines

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Key Words
Practice guidelines · Health insurers · Conflicts of interest

Abstract
Practice guidelines are proliferating in medicine. In addition to methodological problems that cause guidelines to be outdated rapidly, they are plagued by conflicts of interest. They are largely consensus opinions of panels of experts, most of whom are supported by industry. Professional societies, health insurers, Centers for Medicare and Medicaide Services, and dialysis providers also benefit from guidelines. Little attention is paid to the potential for harm to patients, and to the profession of medicine, from the widespread use of guidelines.

Introduction

On December 14, 1799, the most revered president in US history, George Washington, was assassinated by his physicians! In the 12 h preceding his death, he underwent approximately 2.4 liters of bloodletting, prescribed by his physicians for treatment of what was very likely a bacterial tracheitis. A new procedure, tracheostomy, recently witnessed by one of his junior physicians was considered and rejected by the senior (managing) physician. Rigid adherence to the 'standard of care' killed the father of our country [1].

Guidelines which seek to define the 'standard of care' are proliferating in medicine (see the National Guideline Clearing House, www.guideline.gov). This is a government agency, in partnership with the American Medical Association and the American Association of Health Plans, which currently lists over 1,500 guidelines dealing with all areas of medicine. Why do we need guidelines for guidelines? Any trend this broad and pervasive should be examined closely. As physicians we need to be aware of not only methodological issues but also of the driving forces behind them, and the risk they present to the practice of medicine as we know it.

Problems with Guidelines

Methodological problems with guidelines abound. They have been enumerated elsewhere [2, 3], and we will briefly review them here. Guidelines are pieced together by committees, often referred to as working groups. A defined body of literature is identified. This is reviewed by the group and forms the scientific underpinnings for the guidelines. Time constraints compel establishment of a cutoff date after which no further publications are considered. This necessarily means that many guidelines will be obsolete by the time they are released. At the very least, it ensures that guidelines will be trailing edge. Why should a busy clinician, hoping to provide the benefits of the latest research to his patients, bother looking at guidelines based on research that is over 5 years old at best? It

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is much more time-effective to perform a quick literature search on PubMed, or read a current review on UpToDate.

The Heisenberg uncertainty principle states that we can never know anything with certainty because every act of measurement distorts that which we seek to measure. Nowhere is this more so than in medical experiments, where the placebo groups always seem to do much better than the general population. In many disciplines, particularly nephrology, the database upon which guidelines are based is shaky. There are few randomized, controlled, prospective trials in nephrology, and those that have been published are usually inconclusive. In nephrology, we would literally be unable to practice if we were limited to randomized, controlled trials for guidance. Nephrology guidelines are largely opinion-based. The makeup of the working groups then assumes major importance. We will discuss this more later.

Even randomized, controlled trials are subject to interpretation and opinion. They invariably look at large populations and results may not fit with the specific patient in the physician's practice.

Guidelines remain untested. Have guidelines influenced practice and raised the standard of care? Since 1989, the Agency for Health Care Policy and Research has spent hundreds of millions of dollars to measure 'what works' and to develop clinical guidelines. As of 1994, the agency could not point to a single example of its work affecting clinical practice. In 1996, the agency stopped working on practice guidelines and left that to professional organizations, which have developed more than 1,000. It now concentrates on 'how we can reduce inappropriate variation' [AM News February 24, 2003]. Guidelines will exert a major influence when they become actively implemented as clinical performance measures and when Pay for Performance (P4P) gets underway. This is one of the dangers to medical practice alluded to earlier. Outside parties can only dictate medical practice by adopting *guidelines that we have created* and turning them into mandates via P4P. We are witnessing the evolution from centralized payment for care to centralized prescription of that care! It is already well underway in the United Kingdom [4].

In response to claims for payments (which must be accompanied by diagnosis codes) submitted by us, we have received written questions from insurance companies if special tests recommended in KDOQI guidelines for specific stages of chronic kidney disease had been performed. It is of interest that there are no published studies of hard end-point outcomes of intervention based on the recommended testing. The next stage, of course, is litigation should a practitioner fail to order theses tests. Another reason we need tort reform in America.

Who Benefits from Guidelines?

Have patients benefited from guidelines? We do not know. To the extent they are followed, adoption of certain guidelines may well harm some patients. Bringing patients to the K/DOQI PTH goal of 150–300 pg/ml may be partly responsible for the epidemic of adynamic bone disease. Raising the upper level of hemoglobin from 12 to 13 g/dl may harm some patients, considering that higher levels of hemoglobin have been associated with excess mortality in two prospective studies, both of which were stopped prematurely [5].

If patients are not benefiting from guidelines, who is? I suppose overworked physicians and physician-extenders perceive a benefit from having things laid out in cookbook form; it is a big time saver. This is increasingly important as shrinking Medicare reimbursement has led to higher patient loads and volume of service. But the major beneficiaries are those with large financial stakes: the pharmaceutical industry, professional societies, dialysis companies, insurance companies, Centers for Medicare and Medicaide Services (CMS), and the guideline writers all reap considerable financial benefit from the guideline industry.

Industry heavily underwrites guideline creation, at least in nephrology. Amgen is the principle sponsor of the NKF-K/DOQI guidelines, and as Coyne points out (op. cit.), with potential financial benefits from guidelines for anemia and bone management. There are many other examples. The entire guideline process is tilted towards increasing use of pharmaceuticals since most clinical trials are sponsored drug studies (funded by industry). It is easy to see how guidelines recommending ever-lower blood pressure, cholesterol and glycosylated hemoglobin targets could fuel a major expansion of drug prescribing in these areas.

Professional societies receive millions from industry and government to create guidelines. The AMA, which derives considerable income from the CPT-4 procedure coding systems (that enable payers to control reimbursement) is collaborating with the government to fabricate clinical performance measures that will be used to restrict payments through P4P. Using 'a standard method of delivering or facilitating coordinated care from diagnosis to management, based on the National Kidney

Foundation's KDOQI evidence-based clinical practice guidelines' the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) will award a certificate of excellence for kidney disease management based on fulfillment of certain eligibility criteria. The JCAHO web site states on the certificate award, 'It is the best signal to your community that the quality care you provide is effectively managed to meet the unique and specialized needs of CKD patients. In fact, demonstrating compliance with these national standards and performance measurement expectations may help obtain contracts from employers and purchasers concerned with controlling costs and improving productivity.' Do we really need this? Do we want more scrutiny by more organizations? Of course, on top of this are the subscriber fees for the certificate of excellence.

A byproduct of the K/DOQI guidelines was the addition of 20 million plus 'CKD' patients, many of whom are likely healthy old folks with borderline eGFR. Large dialysis providers benefit from specific guidelines to use intravenous medications during dialysis, particularly vitamin D analogs. These drugs continue to generate profit for dialysis units, in spite of the recent reimbursement changes to reduce incentives to administer drugs during treatment. There is no convincing evidence for the superiority of intravenous over oral therapy with these agents, other than for compliance. Oral D-analogs are used predominantly outside the US, where these incentives do not exist, without apparent detriment.

Insurance companies and CMS both fund, and benefit from, guidelines which they perceive as a way to control payments to providers. Guidelines are mostly authored by academic physicians and other professionals, many of whom derive significant industry support in the form of speaking honoraria, research support, and consulting fees. There may or may not be direct compensation for the work involved with guideline formation, but there are certainly speaking and consulting opportunities that flow from guideline involvement. Conflicts of interest must surely exist, but are usually downplayed. In a 2004 survey of over 200 guidelines from the National Guideline Clearing House, only 90 had details of authors' conflicts of interest, and of these only 31 had none.

Conclusions

Looking at the many problems with guidelines we ask, do we really need them at all? Why are there no guidelines for dentists, veterinarians, or lawyers? These professions have kept control of their destinies by rejecting direct third-party reimbursement, and all the strings that come attached with this. Ultimately, guidelines and P4P become means to bypass the doctor-patient relationship and centrally determine how medical care is delivered. They replace the art of medicine with paint-by-numbers. Guidelines are fatally flawed. They are more likely to do harm than good and should be rejected.

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Diabetes: Changing the Fate of Diabetics in the Dialysis Unit

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Key Words

Diabetes mellitus · End-stage renal disease · Diabetic nephropathy · Renal replacement therapy · Maintenance hemodialysis

Abstract

The prevalence of diabetes mellitus (DM) is very high worldwide. According to the World Health Organization in 2000 the worldwide prevalence of DM was 171,000,000. Diabetic nephropathy is a major vascular complication of DM. If DM is not treated early and adequately, many diabetic patients may reach end-stage renal disease (ESRD) secondary to advanced irreversible diabetic nephropathy. In many countries diabetic nephropathy has become the single most frequent cause of prevalent ESRD patients undergoing maintenance hemodialysis (MHD). In the early era of renal replacement therapy (RRT) by means of intermittent hemodialysis the prognosis of diabetic patients undergoing MHD was extremely poor and disappointing. While the prognosis of patients suffering from diabetic ESRD and maintained by chronic intermittent dialysis has greatly improved, the rehabilitation rate and survival of these patients continue to be worse than those of non-diabetic patients. A preexisting severely compromised cardiovascular condition, vascular access problems, diabetic foot disease, interdialytic weight gain, and intradialytic hypotension explain most of the less favorable outcome. Despite improved techniques and more aggressive medical therapy in recent years, a review of the fate of diabetics in dialysis units since 1972 reveals that these patients have had significant morbidity and mortality. We still have a long way to go in order to achieve more ideal outcomes for our patients. Most of the diabetic ESRD patients are still maintained by MHD, but they can choose other modalities of RRT such as chronic ambulatory peritoneal dialysis (CAPD), kidney and kidney plus pancreas transplantation. The results of different studies and national registries on the mortality and morbidity of ESRD patients being maintained on different modalities of dialysis are conflicting. It can be concluded that the two modalities of dialysis (CAPD and MHD) are almost comparable in terms of survival. The recent suggestions for nocturnal daily hemodialysis, short daily hemodialysis, and an integrative care approach for the management of diabetics with ESRD provides better promise for these patients.

Introduction

The prevalence of diabetes mellitus (DM) is very high worldwide. According to the World Health Organization (WHO), in 2000 the worldwide prevalence of DM was 171,000,000. In 2005, the WHO estimated that by 2030 the worldwide prevalence of diabetes will reach 366,000,000 [1]. End-stage renal disease (ESRD) second-

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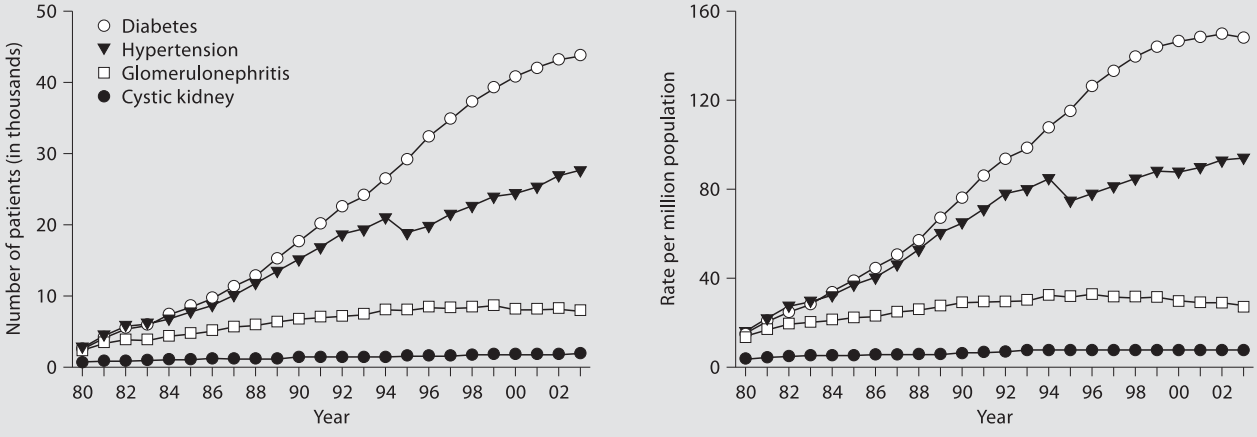

Fig. 1. The incident counts and adjusted incidence rates by primary diagnosis in ESRD patients according to the USRDS.

ary to advanced diabetic nephropathy (DN) requiring renal replacement therapy (RRT) is one of the most serious complications of DM. According to the 2005 United States Renal Data System (USRDS) estimates, the number of patients suffering from DN and ESRD who are admitted to dialysis units is increasing dramatically. The incidence of reported ESRD was 4.3% with type-1 DM and 40.5% with type-2 DM [2]. Figures 1 and 2 reveal the incidence and prevalence of DM in dialysis according to the USRDS. The incidence of patients with DN requiring dialysis is globally significant. 36 and 22% of incident dialysis patients in Germany and Australia, respectively, have ESRD due to DN [3]. This figure is no less in developing countries, for instance in Iran 25.2% of incident dialysis patients are reported to have ESRD as a result of DN [4]. Figure 3 shows the incidence of RRT according to different registries [5]. Indeed it can be claimed that many developed and developing countries are in the midst of an epidemic of ESRD. Part of this epidemic can be explained by the increase in life expectancy that has occurred worldwide in the past two centuries [6]. Currently the effect of general health improvement is more pronounced in developing countries. For example in Iran, a country which is considered to be a medium human development country, the life expectancy at birth increased to 70.1 years in 2002. As a result, the total population has increased from 33.4 million in 1975 to 68.1 million in 2002. In Pakistan which is considered to be a low human development country, the total population in 1975 was 70.3 million, and in 2002, it increased to 149.9 million. These figures for countries with high human development, e.g. Belgium, have changed less dramatically; the population was 9.8 million in 1975 and 10.3 million in 2002. In the USA the population grew from 220.2 million in 1975 to 291.0 million in 2002 [7]. The remarkable population growth which is being observed in developing countries is a welcome consequence of decreased mortality during infancy and young adulthood, better nutrition and the control of infections, and improved education. An unwanted consequence of these improvements has been the emergence of chronic metabolic diseases including ESRD. It can be concluded from this fact that, in the third millennium, the global epidemic of ESRD will be of importance worldwide and more importantly in developing countries. This fact may not be quite evident as the prevalent worldwide ESRD data are reported from patients who are undergoing maintenance hemodialysis (MHD). In developing countries, the number of patients reaching dialysis is dramatically less than the number of patients who die before reaching dialysis. Another major problem in the developing world is the lack of reliable statistics regarding the incidence and prevalence of diseases, morbidity, and mortality.

Even for the developed countries, providing enough funds for management of RRT has not been easy, and certainly for the developing countries, it is a dream. These facts impact the fate of diabetics in the dialysis unit and elsewhere. Indeed it is very hard to improve the fate of any

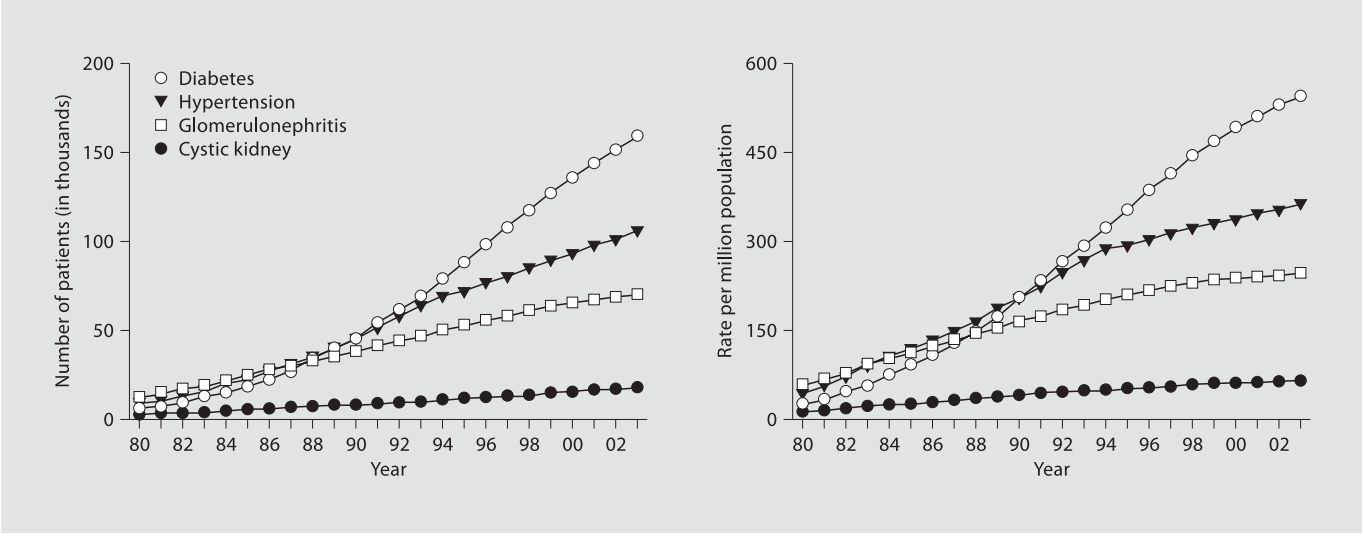

Fig. 2. Prevalent count and adjusted rates by primary disease according to the USRDS 2005 annual data report.

disease in the presence of poverty. Even if newer technology becomes cheaper in the future, the scarcity of funds, wealth and infrastructure in the underdeveloped world will be a barrier to changing the fate of the diabetic patient.

Changing the Fate of Diabetics in the Dialysis Unit

In a symposium on diseases of kidney reported in 1971 Williem J. Kolff was quoted as saying in 1938, 'Gradually the idea grew in me that if we could only remove 20 g of urea and other retention products per day we might relieve this man's nausea and that if we did this from day to day, life might still be possible' [8]. Dunea [8] started his article after this statement and wrote, 'Within three decades dialysis has revolutionized the field of nephrology and opened new vistas in the treatment of uremia. … Yet, dialysis gradually outgrew its difficult beginnings and became established among the great medical achievements of our age.' In this article there is no mention of the diabetic ESRD patient. A year later in 1972, Ghavamian et al. [9] report on 9 patients with renal failure resulting from DN who were treated by hemodialysis. The average duration of diabetes was 21 years and the average duration of nephropathy was 26 months. One patient survived for more than 3 years. The others survived 9, 20, 19, and 13 months, respectively. Overall mortality was 78% at the end of 1 year. All patients had problems with clotting or infection of the bloodstream access routes or both. All had further visual deterioration. Neuropathy was not accelerated. Muscle wasting, hypoproteinemia, and fluid overload were common. Dialysis for such patients may be considered as a palliative measure with little likelihood of long-term survival or improvement in quality of life. Four of their patients were male, 3 female, and the age ranged from 26 to 49 years. The duration of proteinuria was 1–5 years.

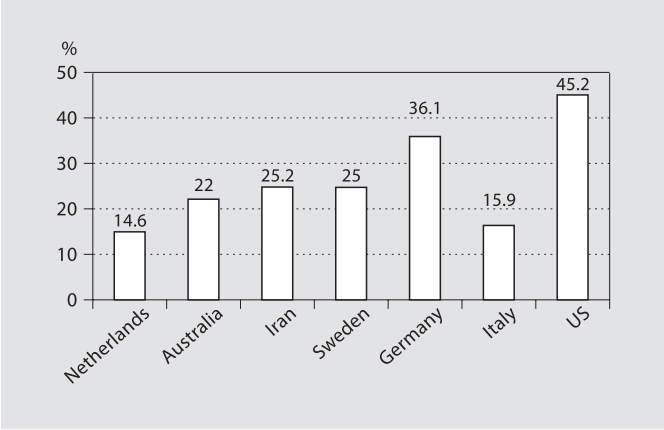

Fig. 3. Year 2000 percentage of incident renal replacement patients with diabetes as the primary diagnosis according to national registries. Modified with kind permission from Prof. Locatelli.

It is evident that the problems facing diabetic ESRD patients are still the same, maybe with less ophthalmologic problems but more atherosclerotic cardiovascular disease (CVD) and congestive heart failure.

This was the fate of a diabetic ESRD patient in a developed country such as the USA in the early 1970s. There is no doubt that in those days there was no hope even for non-diabetic ESRD patients to have access to dialysis treatment even for one day in many countries. Certainly at present we are equipped with much better technology, medications and understanding of the pathophysiology of the disease, but still we have a long way to go in order to achieve more ideal outcomes for diabetic ESRD patients.

The situation for all ESRD patients was the same until the passage of public law 92-603(HR1) which allowed the federal government to fund the treatment of approximately 85–90% of Americans with ESRD.

Approximately 13,000 patients were being treated by intermittent hemodialysis and 200–300 by peritoneal dialysis when the law became effective in July 1973. Additionally, about 2,400 patients/year received kidney transplants. Publicity related to passage of the bill resulted in a large influx of new patients. The potential impact of the law is put into perspective by envisioning 10,000 to 13,000 new patients entering treatment each year [10]. Nevertheless, 9 months after passage of the law, July 1973, many serious difficulties in implementation remained. In his article discussing the major unwanted effects of hemodialysis treatment in all patients, Ginn [10] concluded that major problems remained regarding: (1) nutrition; (2) hypertension; (3) anemia; (4) bone disease in uremia; (5) pericarditis; (6) blood access; (7) hemodialysis equipment, and (8) water treatment in hemodialysis.

Although there is nothing specific related to diabetic ESRD patients from those days, the general status of dialysis and its problems did exist for all ESRD patients. To realize the different status of the early era of dialysis, Ginn [10] stated, 'Dialysis patients often tolerate very low hematocrit values remarkably well, in part because the myocardium becomes conditioned by chronic anemia, and in part because red cell levels of 2,3-diphosphoglycerate (DPG) increases in anemia, especially during androgen therapy. Contrarily, if serum inorganic phosphate is lowered below normal range by dialysis and/or aluminum gels, then 2,3-DPG levels are reduced. Increased levels of 2,3-DPG improve tissue oxygenation by decreasing the affinity of hemoglobin for oxygen. On the other hand, conventional dialysis usually induces a transient combined respiratory and metabolic alkalosis in patients who often are initially mildly acidotic. Acidosis increases oxygen dissociation whereas alkalosis reduces oxygen dissociation. Continued frequent hemodialysis generally benefits but does not eliminate the anemia. Because of increased needs, regular iron supplements should be given. Some patients respond to oral iron administration. Others require intravenous iron, e.g., up to 50 ml of Imferon infused over several hours. Meticulous care in returning all blood from the dialyzer and minimizing the number of laboratory tests are obviously important. Androgens in large doses, such as 400 mg of testosterone enanthate per week, have been found to benefit many patients who still have kidneys, but their effect in anephric patients is unpredictable. Androgenic side effects have not been severe, even in female patients, if preparations are used which minimize such effects. If they do occur, however, they are irreversible.'

These statements are contrary to our understanding today. Anemia is not tolerated by the medical community. Regardless of the benefit of 2,3-DPG no one will accept hyperphosphatemia, and the recommendation is to bring serum phosphate down to normal for many different reasons including secondary hyperparathyroidism which can by itself adversely effect anemia. The use of androgen is not recommended, and finally, currently acidosis is considered very harmful and bicarbonate dialysate is the ideal solution for patients on dialysis.

As can be seen, insight into the etiology of anemia in ESRD has come a long way. While the trade-off hypothesis could in part explain the different approach in the early 1970s in the management of patients undergoing MHD [11], at present we are equipped with a more effective armamentarium in our fight against uremia. We do not have to wait for one organ to be sacrificed for the survival of another organ, such as the bone sacrificing part of its structure and quality, in order for the body to tolerate and decrease the adverse effects of renal failure on organs such as the nervous system. Gradually some skepticism grew about this phenomenon. A decade later Fine [12] wrote: 'A number of physiologic adaptations in chronic uremia serve to palliate the functional loss imposed on the kidneys by progression of the toxic aspects of the disease process. Logically, therapeutic strategies should seek to reinforce the adaptive responses while suppressing or retarding the toxic progression. However, such strategies are not without pitfalls and limitations.'

Although the role of the kidney in erythropoiesis was known for a long time, there was clearly no knowledge about clinical use of erythropoietin in those days [13]. It was not until the results of a combined phase I and II

clinical trial were published that erythropoietin therapy became clinically relevant [14]. Up to that time 25% of 150,000 ESRD patients on dialysis required intermittent red cell transfusions [15]. It is easy to assume that those patients would have developed unwanted events such as blood-borne infections, hepatitis, iron overload, further bone marrow suppression and HLA antigen sensitization.

Considering the above-mentioned facts, one can imagine how much the fate of diabetic patients has been under constant change in the dialysis unit since 1970.

Today diabetes is the most common global cause of chronic kidney disease (CKD), present in one fourth to two thirds of all patients with renal impairment [4, 16]. Anemia is more severe in diabetic ESRD patients and 2–3 times more prevalent in diabetics with CKD and ESRD than in non-diabetics with the same degree of renal impairment [17]. It has recently been recognized that in diabetic patients anemia is seen not only in pre-terminal renal failure, but frequently also in patients with only minor derangement of renal function [18]. A major cause of anemia is an inappropriate response of erythropoietin to anemia. Additional factors are iron deficiency and iatrogenic factors, e.g. ACE inhibitor treatment. Because most of the late complications of diabetes involve ischemic tissue damage, it would intuitively be plausible that treatment with human recombinant erythropoietin should be beneficial to ESRD patients. With regard to the question of the management of anemic patients with DN, there is not sufficient evidence from controlled clinical trials to come up with a satisfactory answer. The question remains whether correction of anemia with erythropoietin treatment is beneficial with respect to diabetic end-organ damage in patients with diabetic ESRD. The new KDOQI anemia guidelines published in May 2006 define anemia as a Hb of <13.5 g/dl for males and <12.0 g/dl for females and a target Hb of ≥11 g/dl with caution when intentionally maintaining Hb at >13 g/dl. For target iron stores, the recommendation is a TSAT of at least 20%, and a lower ferritin limit of 200 ng/ml in HD-CKD and 100 ng/ml in non-HD-CKD [19]. A ferritin level of >500 ng/ml is not recommended. Adjuvant therapy such as L-carnitine and ascorbate are not routinely recommended because of low quality evidence, lack of efficacy, and also safety concerns regarding ascorbate. Androgen use is not recommended as current guidelines reflect serious safety concerns. Evidence for efficacy is low quality.

A hyporesponse to an erythropoiesis-stimulating agent (ESA) and iron therapy can occur. The patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse if the Hb level is persistently <11 g/dl, and if the ESA dose is equivalent to epoetin of >500 IU/kg/week. Factors most commonly associated with persistent failure to achieve target Hb levels for at least 6 months despite ESA therapy include persistent iron deficiency, frequent hospitalization, hospitalization for infection, temporary catheter insertion, permanent catheter insertion, hypoalbuminemia, and elevated C-reactive protein (CRP) levels. Other contributing factors include pancytopenia/aplastic anemia, hemolytic anemia, chronic blood loss, cancer, chemotherapy, or radiotherapy, inflammatory diseases, acquired immune deficiency syndrome, and infection.

Nowadays susceptibility to infection is more common in countries where the dialysis dose is less than the recommended dose of the HEMO study [20]. Financial restrictions and a shortage of manpower and equipment especially in diabetic ESRD patients play a role in the susceptibility to infections. In dialysis units in developed countries, tuberculosis has been reported in immigrants from endemic areas; this is especially more common in DN [21]. Except in patients suffering from HIV and ESRD, more efficient dialysis and as a result better nutrition has decreased the incidence of TB in diabetics in the dialysis unit.

Despite significant improvements in technology and the knowledge of RRT, the morbidity and mortality of ESRD patients remains high. Poor nutrition and protein and calorie intake are major contributing factors for protein-energy malnutrition (PEM). The recommendations for better and healthier nutrition have not changed since the early 1970s. The recommendation was: '… to prevent (or to correct) body protein deficiency, to provide adequate calories … usually 1–1.5 g of high biologic value protein per kg/day' [10]. Although the importance of adequate nutrition and calories has been recognized since the 1970s, for various reasons inadequate nutrition has continued to be a problem. There are many causes of protein calorie malnutrition in maintenance dialysis patients. The three major causes are probably a low nutrient intake, intercurrent or underlying illnesses, and the dialysis procedure itself [22]. In underdeveloped countries, a shortage of equipment and manpower plus the expense result in inadequate dialysis. Sometimes uneducated patients decide to eat less so as to have less waste byproduct of protein. This poor nutrition decreases the blood urea measured, so the patients think their need for dialysis will be less, while it is known that low serum nitrogen levels as a result of PEM are associated with an increased

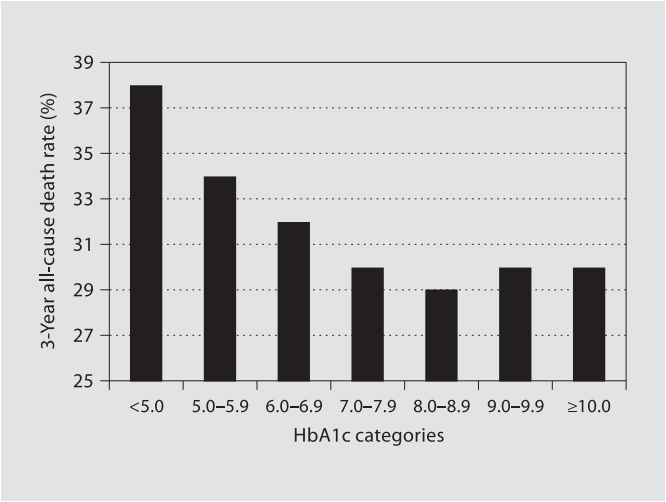

Fig. 4. Raw unadjusted mortality rate.

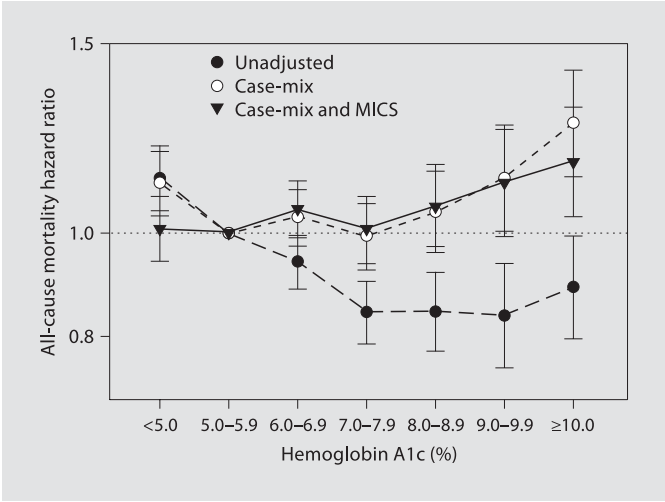

Fig. 5. Mortality rate adjusted for case mix and malnutrition-inflammation complex syndrome (MICS).

mortality in ESRD patients undergoing MHD. Even in developed countries the prescribed dose of dialysis is usually not adequate. The result of inadequate dialysis is loss of appetite and anorexia leading to decreased protein and calorie intake. Diabetic patients appear to be more sensitive than non-diabetics to inadequate dialysis [23]. PEM is a common phenomenon in maintenance dialysis patients and a risk factor for poor quality of life and increased morbidity and mortality, including cardiovascular death in these individuals [24]. To explore the effects of CRP and the normalized protein catabolic rate on serum albumin and creatinine, the laboratory data from 364 hemodialysis patients were analyzed for 6 consecutive months using a multivariate mixed model with conservative biases. The conclusion was that inflammation and dietary protein intake exert statistically significant and clinically meaningful competing effects on serum albumin and creatinine over time. Therapeutically, the model would predict that by increasing the normalized protein catabolic rate from 0.8 to 1.2 g/kg/day, one might expect an increase in albumin of approximately 0.5 g/dl and an increase in creatinine of approximately 4.4 mg/dl over a 6-month period, all else being equal [25]. Atherosclerotic CVD, PEM and the wasting syndrome are common in patients with ESRD and contribute to the increased morbidity and mortality of these patients. Serum albumin, CRP, and interleukin-6 predict malnutrition [26]. In a random sample of 4,025 patients the prevalence of coronary heart disease was 38%. The incidence was significantly more common in diabetic patients (46.4%) than in non-diabetic patients (32.2%). Much of the cardiac pathology is acquired even prior to establishment of end-stage renal failure [27]. In another study about causes of death among patients with ESRD, 84 diabetic and 74 non-diabetics were evaluated by coronary angiography. Triple vessel coronary artery disease was significantly more common among the diabetic subjects (27 vs. 12%, $p = 0.005$) [28].

Glycemic control appears to impact the survival of diabetic ESRD patients. In a study investigating 150 diabetic ESRD patients, it was found that good glycemic control (HgbA1c <7.5%) predicted better survival [29]. In order to determine the optimal target for glycemic control in diabetic dialysis population, the DaVita national dialysis database was analyzed. Of 82,933 patients undergoing MHD in DaVita outpatient clinics over 3 years, 26,187 MHD patients had HbA1c measurements at least once. Raw mortality data revealed that lower HbA1c values were associated with higher all-cause mortality rates (fig. 4); accordingly, unadjusted survival analyses indicated lower death risks in MHD patients with higher HbA1c values. Similar findings were noted with cardiovascular death. However, after adjusting for potential confounders including case-mix, age, gender, race, dialysis vintage and dose, comorbidity, and surrogates of the malnutrition-inflammation complex syndrome (MICS), HgbA1c values of >8% were incrementally associated with higher all-cause and cardiovascular death risk. The authors concluded that the greatest survival was observed with HbA1c of <8% (fig. 5) [30].

Diabetic ESRD patients on dialysis respond to insulin differently. The risk for hypoglycemia increases during hemodialysis sessions. The compensatory homeostatic response to hypoglycemia may increase the risk of abnormal blood pressure regulation. Similarly, if glucose-free dialysates are used, then diabetic patients may become hypoglycemic, as insulin is not removed during dialysis and there may be an inappropriate neuroendocrine response [31].

In a randomized, placebo-controlled, unblinded, cross-over study of 44 hemodialysis patients, 34 patients without diabetes and 10 patients with diabetes were allocated to treatment with and without glucose in the dialysate during two 10-week periods. Blood pressure and blood glucose levels were determined 5–8 times in each dialysis session during both periods. Systolic and diastolic blood pressures decreased with glucose in the dialysate in patients with ESRD, presumably because of insulin-induced vasodilatation in patients without diabetes. Blood glucose level regulation improved in the diabetic subgroup, and blood glucose levels were not greater in patients with diabetes with glucose in the dialysate [32].

The presence of autonomic dysfunction can also impair patients' ability to maintain blood pressure following a large degree of fluid removal by ultrafiltration. The incidence of intradialytic hypotension has been reported to be from 5 to 40% of all the patients on MHD [31]. As dysfunction of the autonomic nervous system is more common in diabetic ESRD patients, intradialytic hypotension is more common in this subgroup of dialysis patients [33]. Activation of the Bezold-Jarisch reflex, which involves decreased sympathetic and increased parasympathetic nervous system activity, may also occur with ultrafiltration, causing sudden intradialytic hypotension [34]. A less common and much more obscure derangement of blood pressure control during hemodialysis in ESRD patients is increases in blood pressure, that is, intradialytic hypertension. This syndrome is multifactorial and the pathogenesis is not clearly understood [35]. Most patients with ESRD on MHD have chronic hypertension. There is no disagreement on the role of hypertension as a risk factor for increased cardiovascular or cerebrovascular events in the general population [36]. Despite the accepted danger of high blood pressure in the general population, there is evidence that in ESRD patients there is a link between low blood pressure and poor survival [37]. This phenomenon has been referred to as reverse epidemiology, and besides hypertension, other known risk factors behave in opposite ways in patients with ESRD as a result of MICS. Components of reversible epidemiology are shown in table 1.

Table 1. Components of reverse epidemiology in dialysis patients

Obesity
Hypercholesterolemia
Hypertension
Homocysteine
Creatinine
Calcium
Potassium
Iron
Advanced glycation end products
Others: leptin, bicarbonate

There are many different intradialytic and interdialytic complications that diabetic ESRD and ESRD patients have, albeit occasionally they are more pronounced in diabetic ESRD patients. Adverse cardiovascular effects of hyperphosphatemia may be more extensive and severe in diabetic ESRD patients because of the unwanted effects of nephropathy on the cardiovascular system prior to the establishment of ESRD.

The well-being of diabetic patients is greatly influenced by diabetic foot disease. In one report, diabetic foot disease resulted in amputation of lower limbs in 14% of ESRD patients [38]. The association of diabetic foot lesions with advanced DN may be explained by the long duration of diabetes, macroangiopathic and neuropathic complications or a combination of both [39].

Another major determinant of the fate of diabetic ESRD patients includes hemodialysis equipment. In the early 1970s approximately 50–55% of patients were being treated by coil dialyzers, some 25–30% by parallel plate units, and about 20% by hollow fiber capillary dialyzers [10]. At present, dialyzers are more biocompatible and efficient with lower capacity facilitating more efficient dialysis in comparison with the past [40].

Patient survival in diabetics on maintenance dialysis is lower than that seen in non-diabetics. As noted in the 2005 USRDS report, approximately 25% of diabetic ESRD patients survived 5 years after the initiation of dialysis [2]. Survival also varies inversely with age, being best in young normotensive patients without any clinical CVD [5]. The USRDS excludes patients who died within the first 90 days of the initiation of dialysis, so the result is of limited value [2]. The situation is comparable in other countries. In Iran, the dialysis outcome was reported for

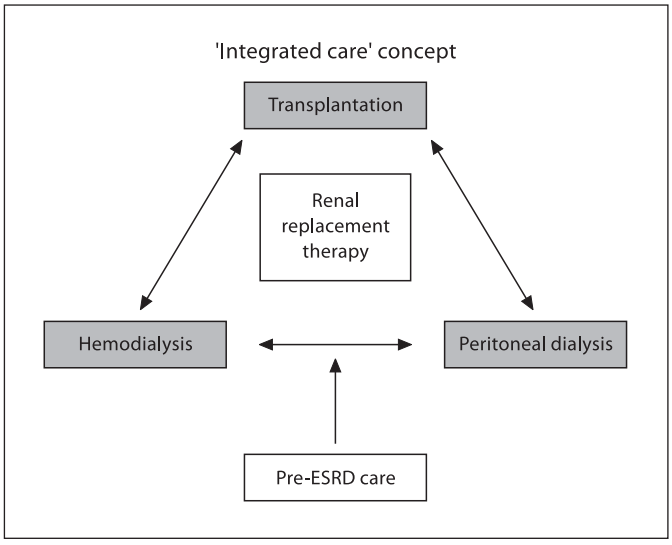

Fig. 6. Different modalities of renal replacement therapy.

Table 2. The integrated care concept

- Patient survival and quality of life are two very important factors in the selection of a dialysis modality
- The majority of studies have compared the two modalities as 'competitors' rather than as 'complementary' techniques
- Since every RRT has a technical 'drop-out', it is very likely that a patient will need several modalities during his lifetime and transfer from one technique to another will often be needed
- Survival studies of patients on RRT should evaluate 'the best therapeutic strategy', i.e. the succession of modalities that:
  - Allows an optimal total survival
  - Utilizes the specific advantages of each modality at any given moment of the patient's life in an optimal way
  - Avoids the drawbacks of each modality as much as possible
- Appropriate statistical statistics should be applied for correct analysis

68 patients with DN and 66 non-diabetics. The mortality was 52.9% in diabetic patients. Survival seems somewhat better because of the selection criteria [41]. The adequacy of dialysis and the decrease in nutritional status may also be contributors to the worse outcome in diabetics. Diabetic patients appear to be more sensitive than non-diabetics to inadequate dialysis prescriptions.

The morbidity associated with insufficient dialysis in diabetics may be mediated through anorexia, leading to decreased caloric and protein intake. Death by withdrawal from dialysis is also more likely to occur in diabetics.

MHD is the most common dialysis modality used worldwide [2]. For many reasons, different modalities may be more ideal for different patients. In a national cohort study of 1,041 patients starting dialysis (274 patients receiving peritoneal dialysis and 767 patients receiving hemodialysis at baseline) it was concluded that the risk of death in patients with ESRD undergoing dialysis depended on dialysis type [42]. It has been suggested that short daily hemodialysis will improve the quality of life, rate of hospitalization and mortality [43]. It has been suggested that home daily nocturnal hemodialysis may have the highest survival for diabetic patients on MHD [44]. Nocturnal hemodialysis offers a high dose of dialysis, improves biochemical parameters and quality of life. Despite the significant losses, in a study of 24 patients under daily nocturnal hemodialysis, protein malnutrition was not seen. Most of the patients were anabolic [45]. Further studies are needed to see how short daily hemodialysis or daily nocturnal hemodialysis affect diabetic ESRD patients.

Finally, it has been suggested that the different modalities of RRT should be complementary and not competitive. For this reason an integrative care approach is necessary for ESRD patients whereby, when appropriate, patients are started on peritoneal dialysis, followed by kidney transplantation whenever possible and transferred timely to hemodialysis when peritoneal dialysis-related problems arise. This approach would perhaps enable us to make use of the entire RRT arsenal (table 2; fig. 6) [46].

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Major Difficulties the US Nephrologist Faces in Providing Adequate Dialysis

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Key Words
Dialysis adequacy · Medical economics

Abstract
Aim: To identify the major difficulties nephrologists in the US face in providing adequate dialysis. ***Methods:*** To identify the perceived obstacles to achieving adequate dialysis in the US, 30 clinical support specialists responsible for nursing education and training were polled. Their responses together with those found in the recent literature were summarized and analyzed. ***Results:*** The obstacles identified fell into the following major categories: (1) economic; (2) personnel shortage; (3) education, and (4) cultural. The principal specific difficulties identified in providing adequate dialysis were the provision of sufficient time and frequency of dialysis, adequate volume control and vascular and peritoneal access. ***Conclusions:*** The obstacles we currently face are serious but can be conquered through better understanding of the problems and education of professionals, patients and payers. The simple improvement in two specific areas, the creation of more native arteriovenous fistulae and growth of home dialysis, are identified as the highest priorities to overcome these obstacles.

Before embarking on identifying the major difficulties the American nephrologist faces in providing adequate dialysis, we must examine the issue of provision of adequacy and clinical outcomes in the US compared to other countries. During the past decade we have observed a heated debate between those justifying the higher mortality rate among US dialysis patients and those explaining the differences in mortality between the US and other industrialized countries based on differences in the practice of dialysis [1, 2]. Table 1 summarizes some of the arguments used in these debates to justify their respective positions. There is no doubt that the statistical analysis is greatly complicated by variables that are difficult to adjust such as race (100% Asians in Japan and a mixture of African-Americans, Hispanics, Native Americans and Caucasians in the US), cultural differences, degree of patient compliance and financial incentives. Nonetheless, the marked differences in survival between the US and other industrialized nations, particularly among older patients, and the obvious differences in dialytic practices deserve our consideration.

Even if there are significant differences in the practice of dialysis between the US and Europe and Japan, are these practices important in determining outcome? In other words, do the significant differences in treatment time and UFRs explain the differences in survival between the US and the rest of the industrialized world? Furthermore, the definition of adequacy remains controversial. Should we measure adequacy with Kt/V, Kt, middle molecule clearances, an index reflecting solute removal and achievement of dry weight, nutritional parameters, inflammation parameters and/or purely clinical observations?

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Table 1. Arguments that justify or criticize the lower US survival for dialysis patients

Justification	Criticism
US has the world's highest treatment rate for incident kidney failure	Inadequate dialysis: faster and short dialysis, high ultrafiltration rate
Universal acceptance for uremia therapy in the US	Japan accepts almost as many diabetics as the US and the mean age of incident patients is higher in Japan
Genetic differences better explain the results elsewhere (Japan)	Older Americans live longer than older Japanese
Less compliant patients in the US	Better training of physicians in dialysis in Japan and Europe
Larger patients in the US	Nursing shortage and limited training in the US
Higher transplantation rate, reducing the pool of more viable patients	

The most recent report from the DOPPS Study shed some light on these issues and especially on the important role of treatment time on patient outcomes [3]. This is pertinent since a significant change in treatment time is to a great extent controlled by the existing infrastructure, reimbursement, personnel availability, patient acceptance and compliance and the general practice culture of the community. Longer treatment time and slower ultrafiltration rate (UFR) have been considered advantageous for hemodialysis (HD) patients for some time. According to the ANZDATA 2004 report, unadjusted patient survival improves for all increments of dialysis time in the range of 12 h/week to more than 18 h/week [4]. Furthermore, the hazard ratio (RR) for death was reduced by 23% when treatment time was increased to 4.5–4.9 h/session as compared to the reference treatment time 4.0–4.4 h/session. In Japan, treatment time longer than 4.5 h was associated with reduced RR death up to approximately 6 h and short dialysis times increased the risk of death over the reference of 4.5 h [5]. The recent DOPPS report showed that Europe and Japan have significantly longer ($p < 0.0001$) average treatment times than the US [3]. Kt/V increased concomitantly with treatment time in all three regions. Treatment time made a greater contribution to delivered Kt/V in Japan than in Europe or the US, where blood flow contributed more to K and treatment time accounted for a very small proportion of total Kt/V (2–3%). Treatment time of >240 min was independently associated with a significantly lower RR mortality (RR = 0.81, $p = 0.0005$). Every 30 min longer dialysis time was associated with a 7% reduction in RR ($p < 0.0001$). A synergistic interaction occurred between Kt/V and treatment time toward mortality reduction ($p = 0.007$). Most importantly, UFR >10 ml/h/kg was associated with higher odds of intradialytic hypotension (OR = 1.30, $p = 0.045$) and a higher mortality risk (RR = 1.09, $p = 0.02$). A longer dialysis time and higher Kt/V were independently, as well as synergistically, associated with lower mortality and rapid UFR was associated with higher mortality risk. In view of the marked differences in treatment time, UFR and all-cause mortality between the US and Europe and Japan, it is pertinent to identify the major difficulties the nephrologist may face in providing adequate dialysis in the US.

To identify the perceived obstacles to achieve adequate dialysis in the US, we contacted 30 clinical support specialists responsible for the nursing education and training for a large dialysis provider in the US. This group of educators is exposed to a medical team caring for more than 125,000 patients. Their responses are summarized in table 2.

Increasing time and frequency of HD should improve adequacy. However, three principal obstacles have been identified that impede its implementation: (1) the complex logistics with the present infrastructure required to increase the frequency and/or time of dialysis sessions; (2) the higher cost mostly associated with the additional personnel time, and (3) resistance from nurses and patients. The obvious solution to this problem would be treatment of a higher proportion of patients at home. The under-utilization of center stations is often quoted as an obstacle to home dialysis referral since there is an economic incentive to fill up in-center vacancies. Furthermore, home therapy requires a minimal number of patients before it becomes financially profitable since there are fixed operational expenses (dedicated training nurses and physical plant) that are independent of revenue [6]. Finally, the present reimbursement methodology provides no direct outcome-based financial incentives. This process may very well change in the future with the in-

Table 2. Obstacles to achieving adequate dialysis in the US

Inability to increase time and frequency of HD
Logistics/infrastructure
Economics
Resistance from nurses and patients
Underutilization of center stations: tendency to fill up in-center before sending patients home
Home therapies require a minimal number of patients to break even: difficulty obtaining support during the growing period
No direct outcomes-based financial incentives
Culture of short dialysis or 'dialysis in the fast lane' despite high cardiovascular comorbidity and inadequate volume control
Noncompliant patients
Signing off treatment early or arriving late
Skipping treatments
Reluctance to use larger and more frequent PD exchanges or longer time on HD
Nursing shortage and high staff turnover
Poor supervision of patient data by nursing supervisors or nephrologists
Lack of adequate education in dialysis
Physicians
Nurses
Patients
Inadequate vascular or peritoneal access
Patient's reluctance to accept venipunctures after experiencing central lines
Frequent hospitalizations due to comorbid conditions independent of end-stage renal disease
Suboptimal treatments during hospitalizations

troduction of global capitation and disease management programs. Disease management is likely to improve end-stage renal disease outcomes and should reward those who offer optimal dialysis by reducing the cost of treating complications [7].

We have evolved into a culture of short and efficient dialysis, perhaps a reflection of the fast-paced, high technology American way and personnel shortage. In an attempt to avoid inadequate dialysis, formal guidelines such as K/DOQI have been formulated and goals of adequacy established. Technological advances have made it possible to attain the goals in an ever shorter time by increasing the surface area and improving the configuration of hemodialyzers, increasing blood and dialysate flows and providing better monitoring devices to prevent intradialytic complications (blood volume monitors and blood temperature monitors). The application of these tools and practices have made it possible to satisfy the adequacy goals in an ever-increasing proportion of patients, but with minimal impact on patient survival [8]. This brings into question the validity of the adequacy goals and has generated interest in other clinical parameters that may be as or more important than solute removal indices. Short, efficient, thrice weekly HD does not leave much room for error. It is also very taxing on large individuals and those with high ultrafiltration requirements. Short and highly efficient dialysis makes noncompliant patients particularly vulnerable. There are a considerable number of patients who sign off treatment early, arrive late for dialysis, entirely skip treatments or try to negotiate shorter dialysis times with the nephrologist. The mere sight of the person responsible for patient transportation often generates a request for stopping treatment. Such practices are rare or entirely unacceptable in most other cultures. Non-adherence with dialysis has been reported to be associated with increasing mortality and hospitalization risk [9]. Other studies have suggested that American dialysis patients are less compliant with therapy than those in other countries [10]. In addition to noncompliance, patients are often reluctant to increase time on HD or use larger and more frequent peritoneal dialysis (PD) exchanges.

There is a serious nursing shortage in the US and a definitely slowing rate of growth in the number of registered nurses. Their current average age exceeds 45 years, with only 9.1% under the age of 30 as compared to 25.1% in 1980 [11]. A random sample of 1,000 members of the American Nephrology Nurses Association confirmed a

similar average age for nephrological nurses and identified that 19% of the nurses were planning to leave their job within the next year [12]. This national nursing shortage compounded by a high staff turnover in dialysis units is a significant obstacle to the implementation of any practices that require additional personnel time. Furthermore, it compromises the quality of nurse training and the supervision of patient data. The high turnover significantly increases the cost of provision of therapy by reducing the productivity of personnel during training, compromises continuity of care and has the potential to increase errors.

The lack of adequate education in dialysis and related disciplines for physicians, nurses and patients is considered to have adverse consequences on achieving adequate dialysis in the US. Nephrology training programs and nursing school curricula generally do not offer sufficient exposure to care for dialysis patients. Mehrotra et al. [13] showed that 29% of US training programs had less than 5 PD patients per fellow and there were wide variations in the amount of time trainees spent caring for HD and PD patients. Most programs offer 3 or fewer months of exposure to outpatient HD and many offered no exposure to PD [14]. The obvious way to correct this educational deficiency is formal restructuring of the training curriculum to include dialysis theory and practice. In the interim, comprehensive core curricula on PD and home HD are available and should be utilized [6]. Similarly, patient education and better understanding of the various therapeutic options is likely to improve compliance with therapy and increase the proportion of patients achieving adequacy goals.

Inadequate vascular or peritoneal access is a frequent and important impediment to achieving adequacy. Adequate blood flow is essential to obtain our small solute clearance goals. High blood flows become more important when dialysis time is short or frequency is low. Similarly, poor peritoneal flow results in higher dialysate transit time or non-dialytic time and could significantly compromise solute clearance. Furthermore, there is overwhelming evidence of an increased risk of death associated with inadequate HD access [15–18]. There is also a clear association between PD catheter placement and the development of exit site and tunnel infections that often lead to peritonitis, catheter loss and technique failure. However, there is no evidence that catheter selection or type of implantation technique affects clinical outcomes.

Dhingra et al. [15] analyzed data from the USRDS and clearly showed that the type of vascular access correlates with mortality risk in the US. The associated RR of death was higher for patients with arteriovenous (AV) grafts and central venous catheters as compared to those with AV fistulae in diabetic and non-diabetic patients. Cause-specific analyses found higher infection-related deaths for catheters and AV grafts compared with AV fistulae among diabetics and to a lesser extent also among non-diabetic patients.

Pastan et al. [16] reported their analysis of a large retrospective cohort to assess the association between risk of death and type of vascular access. The crude mortality from all causes or attributed to infection was significantly higher among patients with grafts and central venous catheters as compared to AV fistulae. The adjusted odds ratios for all-cause and infection-related death among patients dialyzed with a catheter were significantly higher compared to those with AV fistulae. Similarly, Lorenzo et al. [17] showed that unplanned dialysis initiation and temporary catheter use were independently associated with greater mortality rates in incident patients. The combined influence of both variables was associated with greater morbidity and mortality than either variable alone.

Despite the strong evidence supporting the use of a native AF fistula for vascular access and the efforts to promote this practice, the utilization of native AV fistulae remains below the 65% goal of K/DOQI and significantly lower than that of other countries [18–21]. The goal of a prevalent functional AV fistula placement rate of >65% (Guideline 8.1.2.1) is consistent with the Centers for Medicare and Medicaid goal of 65% by 2009. Furthermore, a 70% AV fistula access rate can be achieved even among diabetics and women [22–25].

The Centers for Medicare and Medicaid, in close collaboration with key stakeholders in the renal community, introduced an initiative called Fistula First with the goal of increasing the use of AV fistulae as the primary vascular access in all suitable HD patients [26]. While the present prevalence rate is significantly lower than the K/DOQI Guidelines, Fistula First reported a gratifying increase to 41% average prevalence rate as of January 2006. It is also being recognized that treatment with PD as the initial mode of renal replacement therapy provides an excellent opportunity to create an AV fistula and the time for its maturation.

A related obstacle to achieving adequate dialysis in the US is the patient's reluctance to accept venipunctures after experiencing a central line. Unfortunately, despite the significant recent increase in AV fistula utilization in the US, the number of central venous catheters has also increased significantly [18, 27].

Frequent hospitalizations due to comorbid conditions independent of end-stage renal disease also interfere with the achievement of adequate dialysis. The transfer of a patient from their center or home environment to the hospital often results in delays of transfer of medical records and change in dialysis prescription, downgrading of the dose or frequency of dialysis or even missing the treatment altogether. Compounding this issue, many of these patients are hospitalized for conditions associated with hypercatabolic states that require additional dialysis, but appropriate adjustments are not made, rendering dialysis suboptimal.

In conclusion, the obstacles faced by American nephrologists in providing adequate dialysis are many and serious, but can definitely be overcome. Many of these obstacles are related to the reimbursement system and other economic factors, while others can be easily conquered with better education and the nephrologists taking control of important decisions and practices. Foremost among these are the creation of a native AV fistula with avoidance of central venous catheters and the pursuit of home dialysis. The home alternative is the answer to many of these obstacles and can fit better with the current reimbursement structure.

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What Is Needed to Achieve a Hemoglobin of 11.0–13.0 g/dl in End-Stage Renal Disease

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Key Words
End-stage renal disease · Hemoglobin · Anemia

Abstract
Effective treatment of anemia in end-stage renal disease (ESRD) results in reduced fatigue and improved quality of life. The National Kidney Foundation's 2006 anemia treatment guidelines recommend maintaining hemoglobin (Hb) at >11 g/dl, while noting that there is insufficient evidence to routinely maintain Hb levels ≥13.0 g/dl. Success in achieving Hb levels within these targets requires careful monitoring and adjustments to treatment. In addition, causes for diminished response and refractory anemia must be adequately evaluated. In this article, factors important for achieving Hb 11–13 g/dl in patients with ESRD are reviewed.

Effective treatment of anemia is a vitally important aspect of caring for patients with end-stage renal disease (ESRD) on hemodialysis or peritoneal dialysis (PD). Anemia causes reduced carriage of oxygen to the body's tissues and organs, resulting in symptoms such as fatigue and dyspnea. If untreated, then quality of life is degraded, with restriction of activities and life experience. Since the widespread availability of recombinant human erythropoietin in 1989, the lives of hundreds of thousands of ESRD patients have been improved.

The National Kidney Foundation's (NKF) anemia treatment guidelines, updated in 2006, include an evidence-based guideline recommending that the hemoglobin (Hb) level be >11 g/dl [1]. The level selected reflects the balancing of expected benefit and risk, with benefit defined as improved quality of life. Other potential positive outcomes of treatment, such as reduced mortality risk, have not been demonstrated by randomized controlled trials. A total of 22 published randomized controlled trials were used to determine the target Hb level [1]. The workgroup determined that quality of life improved in an apparently continuous fashion in the range of Hb levels (8–16 g/dl) tested in different studies [2–9].

The NKF guidelines also include the statement, 'In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels ≥13.0 g/dl in ESA-treated patients' [1]. This clinical practice recommendation is based on the finding of possible safety concerns at this and higher levels of Hb. A well-powered study in hemodialysis patients that compared hematocrit targets of 30 ± 3 and 42 ± 3% (Hb levels of approximately 10 and 14 g/dl) was stopped prematurely with a nearly statistically significant increased risk for death in

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the higher hematocrit group [2]. In another study, patients assigned to a Hb target 13.5–14.5 g/dl had an increased incidence of cerebrovascular adverse events [3]. While the results of these studies are not conclusive, the workgroup determined that routine treatment to targets above 13 g/dl could not be recommended. Therefore, the NKF guidelines essentially establish a Hb target range of 11–13 g/dl for patients with ESRD. In the remainder of this article issues will be explored related to achieving Hb levels within this range for individual patients. Success in maintaining a high proportion of patients within the target range is a suitable quality goal for a dialysis unit, network or other aggregated group of units. Issues related to such population-based management, and the related performance improvement techniques will also be discussed.

The primary driver of an achieved Hb level is the effective use of recombinant human erythropoietin (from this point forward the broader term erythropoiesis-stimulating agent (ESA) will be used). Both administration of ESAs and the monitoring of Hb levels are episodic, finite events. This differs from the natural state where oxygen delivery to tissues is constantly sensed, and erythropoietin production is continuous and adjusted as needed to prevent tissue hypoxia [10]. The episodic nature of ESA treatment makes it difficult to maintain a stable Hb level [11]. This was particularly true with the NKF's previous narrower target range of 11–12 g/dl. Lacson et al. [12] found that only 38.4% of hemodialysis patients actually had Hb in the 11–12 g/dl range at a given time. It can be seen that this Hb instability occurs as a result of anemia treatment practices, episodic ESA administration and the narrow target range. When the Hb level rises above target, dialysis unit protocols drive a mechanical reduction or holding of ESA dose that initiates a downwards trajectory of Hb. As the Hb level falls through the 11–12 target range, protocols generally do not call for ESA dose adjustment. It is not until Hb declines to <11 g/dl that most protocols will drive an increased dose of ESA resulting in a change in Hb trajectory. The narrow target range encourages frequent dose changes, and a recurrent cycling of the Hb level [13]. It is hoped that the NKF's 2006 broader target range of 11–13 g/dl will lead to more stable Hb levels.

Ideally, ESA management should be individualized and matched to the specific patient's response characteristics and Hb trend. There is great variability in response to ESAs, some patients respond to dose changes with rapid and robust changes in Hb, others with a gradual, stuttering response. It is clearly a flawed concept that a one-size-fits-all dose-adjustment protocol could possibly result in consistent Hb responses. Nonetheless, in the service of convenience, almost all ESA dose-adjustment protocols lack individualization. Moreover, protocols have no capacity for recognition of trends. Therefore, treatment based on protocols fails to make necessary dose adjustments when Hb is rising or falling through the target range. The ability to recognize trends, to associate them with clinical events that may be driving them, and to determine the appropriate adjustment to ESA dosing requires the input of a clinician. However, anemia treatment and monitoring that relies on the availability of clinicians may suffer from inattention and delayed treatment changes. While protocols are inflexible, and fail to account for patient response characteristics and trends in Hb, their convenience and facility for use by nurses makes them a necessary tool. To the greatest degree possible, however, nephrologists should use their clinical judgment to supplement and occasionally override documented ESA dose adjustments. The ultimate solution to match patient ESA responsiveness, trends in Hb and ensure timely treatment decisions may come from sophisticated computerized dose adjustment software.

Iron treatment is an important component of achieving target Hb levels. Iron deficiency commonly reduces the efficiency of ESA treatment in hemodialysis patients [14]. The NKF 2006 guidelines recommend maintaining serum ferritin above 100 ng/ml for PD patients and 200 ng/ml for patients on hemodialysis. For transferrin saturation, the recommendation is to maintain a level above 20% for all patients with ESRD. Generally, patients on hemodialysis will require treatment with intravenous iron to achieve these target levels. Oral iron has been demonstrated to lack efficacy when used in this patient population [15–17].

There are two widely used, but quite different approaches to intravenous iron treatment in hemodialysis patients. One is to test iron status periodically (usually every 3 months) and to treat with a brief course of intravenous iron if iron test results are below target [18]. The second approach is to anticipate the development of iron deficiency by treating with a regular weekly dose of iron [19, 20]. It is unclear whether either of these two strategies results in superior efficacy as published studies have not fully addressed this issue. However, if a patient requires more than one course of treatment per year with the intermittent approach, then it would be sensible to convert to a weekly dose schedule. Typically 25–62.5 mg/week of iron sucrose or sodium ferric gluconate is effective [1].

For PD, there is far less published literature related to iron management. In contrast to patients on hemodialy-

sis, these individuals experience far less blood loss, and probably have a lower incidence of iron deficiency. Because there have been few published studies of iron management in PD [21, 22], the implications of iron deficiency and the optimal approach to treatment are unclear. Since it is likely that iron deficiency impairs response to ESA treatment in these patients, iron supplementation should be provided to maintain target levels of serum ferritin and transferrin saturation. Oral iron, administered between meals can be given with a daily dose of 200 mg of elemental iron. Intravenous iron is convenient in hemodialysis, since patients have intravenous access established thrice weekly. In PD, administration of intravenous iron is clearly inconvenient, and treatment should be reserved for patients who are refractory to oral iron.

Effective supplementation with iron will help to maintain Hb >11 g/dl. However, with reference to maintaining Hb within the 11–13 g/dl target range, it is important to consider the interplay of iron and ESA treatment. Supplementation with iron to an iron-deficient patient will result in more effective erythropoiesis and increased Hb levels. As Hb rises, iron is transferred from storage tissues to the enlarging erythron. Often, despite recent intravenous iron treatment, this transfer of iron out of storage tissues will result in the redevelopment of iron deficiency [18]. Since Hb has risen, the redevelopment of iron deficiency may occur in parallel with a reduction in ESA dose. Together, the reduced ESA dose and the redevelopment of iron deficiency can cause a late decrease in Hb after intravenous iron treatment. Failure to appreciate the intertwined effects of iron and ESA treatment can induce secondary cycling of Hb levels [13]. The simplest solution is to monitor iron status more frequently after a course of intravenous iron. Once monthly testing would be optimal, and should be continued for 3 months after treatment.

Another key factor that interferes with the ability to achieve stable Hb levels within the 11–13 g/dl target range is the effect of intercurrent illness and hospitalization. The level of Hb may decrease prior to hospitalization and remain depressed for several weeks to months afterwards [23]. Since the response to ESAs may be diminished during the acute illness, blood transfusion should be considered if severe anemia is present. After hospital discharge particular attention should be given to anemia management. The dose of ESA should be increased to a level that will ensure optimal erythropoiesis. Iron status should be checked to assess the effect of hospitalization on iron stores. Frequent blood sampling in the hospital as well as surgical blood loss may contribute to induce severe iron deficiency. Adequate treatment with iron after hospitalization will help to stabilize recovery of anemia. However, if infection is still present then intravenous iron treatment should probably be deferred until after hospitalization.

One type of intercurrent illness, occult infection of old, nonfunctioning arteriovenous grafts, merits particular discussion. Ayus and Sheikh-Hamad [24] have found that such infections are common and may be difficult to diagnose clinically. Nassar et al. [25] found that these infections have a substantial effect of blunting the effectiveness of ESA treatment. Importantly, removal of the infected graft may result in significantly improved Hb levels [25]. The difficulty of these infections is illustrated by a recent patient treated by our research program. The response to the ESA, CERA, declined for 2 months in parallel to a profound increase in the C-reactive protein level. The level of Hb during this period declined from 11.9 to 9.2 g/dl. Concern for the possibility of infection led to careful physical examination, which revealed no source. Ultimately the patient was found to have an occult graft infection. It is useful to note that elevated C-reactive protein levels may be a harbinger of inflammation and occult infection in patients on dialysis [26].

When a patient has Hb that is persistently <11 g/dl, despite an adequate dose of ESA, causes for anemia other than erythropoietin deficiency should be considered. The evaluation should begin with history and physical examination, and review of red cell indices, haptoglobin, vitamin B_{12} and folic acid levels. Careful evaluation for occult infection or other causes of persistent inflammation should be conducted. Fecal occult blood testing should be performed to exclude the possibility of gastrointestinal blood loss. If clinical evaluation does not reveal the cause of refractory anemia then bone marrow examination should be considered.

Maintenance of Hb within the target range involves not only achieving Hb >11 g/dl, but avoiding excessive periods of time with Hb >13 g/dl as well. As discussed above, this is based on studies that have indicated the possibility of harm with intention to treat to higher levels of Hb [2, 3]. Our understanding of the potential harm of higher levels of Hb is rudimentary and inconclusive at present. Further analysis and research are necessary to better understand the scope of the relationship and the underlying biology. At present, the NKF recommendation that there is insufficient evidence to recommend routinely maintaining Hb levels ≥13.0 g/dl seems to be appropriate.

One important aspect of the upper Hb target that has been insufficiently explored is the relationship of volume flux to Hb. Since Hb is measured before dialysis in hemodialysis patients, the level is at least partially diluted and artifactually lower than it would be in the euvolemic state. In some patients this effect may be particularly important. For a patient who gains 5 kg of fluid weight between dialysis treatments, the Hb level is a very poor estimate of actual red cell mass. If this hypothetical patient started dialysis with a Hb of 13 g/dl, at the end of dialysis the Hb level could be greater than 16 g/dl. At such high Hb levels blood viscosity is significantly increased, and vascular injury, thrombosis and access clotting are possible. It would seem prudent, with such wide variation in weight gains with dialysis treatment, that the Hb target should be individualized.

On a population basis, maintenance of a successful anemia treatment program hinges on the appropriate and thoughtful use of data. Mean Hb, ESA dose, and iron parameters should be reviewed on a regular basis. In addition to mean values, it is also valuable to track the percentage of patients with Hb <10, <11, 11–13 and >13 g/dl. Trends over time should be reviewed. In this regard it is helpful to use control limits to differentiate natural variation from true deviations from standards. Benchmarking is important, both national and regional mean values should be used, if available, for comparison. It is important that those involved with any aspect of anemia treatment receive feedback on unit level data. That would include physicians, nurses, administrators and others as appropriate. If individual physician level data are available, then reports with benchmarks should be provided in a confidential manner.

In conclusion, it is recommended that the Hb level be maintained at >11 g/dl for patients with ESRD during ESA therapy. Successful treatment directly benefits the patient through improved quality of life. There is insufficient evidence to recommend routinely maintaining Hb levels at ≥13.0 g/dl. Consistent maintenance of the Hb level within the 11–13 g/dl range requires ongoing Hb monitoring and adjustment to ESA dose. Causes of diminished ESA response should be identified and treated appropriately. To the extent possible, individualization of management has the potential to most fully optimize treatment.

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Vitamin C Neglect in Hemodialysis: Sailing between Scylla and Charybdis

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Key Words
Vitamin C · Hemodialysis · Oxalosis, systemic

Abstract
In our efforts to meet the vitamin C requirements of dialysis patients we confront a medical dilemma – do we allow the patient to become depleted of vitamin C, with the accompanying hematological and other consequences (Scylla), or do we provide for adequate tissue levels of vitamin C, which has been thought to carry the risk of oxalosis (Charybdis). Many practitioners are certain that either one outcome (deficiency) or the other (oxalic acid toxicity) is inevitable, and much like Odysseus, no safe course is to be found. The recent accumulating evidence that vitamin C improves the management of anemia in dialysis patients compels us to find a safe passage through this dilemma. The serious vitamin C deficiency seen in many patients may also contribute to poor oral health and chronic fatigue. The evidence for oxalosis from vitamin C supplements stems from hemodialysis as practiced 20 years ago. Investigators using this therapy are not observing systemic oxalosis, and the most current data support the conclusion that vitamin C therapy is safe for dialysis patients. The question will be resolved by controlled trials that address both vitamin C effectiveness and safety.

In the Odyssey, the task set to Odysseus is to sail between the sea monster at Scylla and the whirlpool at Charybdis. In the myth, a course away from one is virtually certain to lead to the other, although the myth opens the possibility that extraordinary seamanship might lead to safe passage. Are we faced with the same delicate balance in providing appropriate levels of vitamin C for dialysis patients?

Limited dietary intake of vitamin C has long been a major issue in dialysis therapy [1]. Most dietary vitamin C is provided by foods such as orange juice, strawberries, and broccoli, which are rich in potassium. Since hyperkalemia is a major risk factor for dialysis morbidity and mortality [2], the renal dietitian often instructs the patient to limit intake of potassium-rich foods [3]. Many of the best sources of vitamin C are excluded by these guidelines, and low dietary vitamin C intake can readily occur. The problem is aggravated by vitamin C losses during dialysis, which may remove several hundred milligrams of vitamin C in a single dialysis treatment [4, 5]. Normal plasma vitamin C levels in the nondialysis population are 30–60 μM [6]. By contrast, plasma vitamin C in dialysis patients is frequently <10 μM [7], and may be as low as 2 μM [Handelman, in preparation]. Vitamin C deficiency may be seen as Scylla, the sea monster that would doom the ship.

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The appropriate response to restricted vitamin C intake from diet is to provide dietary vitamin C supplements. But here we are faced with the specter of Charybdis, the whirlpool. The metabolism of vitamin C includes the formation of oxalic acid, which has limited solubility in human tissues. When the plasma concentration of oxalate exceeds 40 μM, there is at least the possibility of oxalate crystals forming in a variety of tissues, including retina, skin, joints, and cardiac muscle. This syndrome, called primary oxalosis, is often found in children with a metabolic defect that forms excessive oxalate in the liver. Primary oxalosis often leads to early kidney failure and death, and is only treatable by liver transplantation. Prior to the advent of reliable high-flux dialysis therapy, some cases of oxalosis were observed in patients with end-stage renal disease [8, 9]. Following implementation of 3×/week dialysis therapy, with weekly standardized $Kt/V > 2$, oxalate deposits could not be detected in a thorough biochemical analysis of biopsy and autopsy material from hemodialysis patients [10], and no case reports of oxalate deposition have been reported in recent years in dialysis patients as a result of vitamin C supplement use. However, the usual guidance provided in nephrology textbooks and manuals on renal nutrition is to 'limit dietary vitamin C supplements to 60 mg/day, to avoid oxalosis' [11]. For many patients, this dosage has not achieved the normal range of plasma vitamin C, and deficiency is widespread. For many in nephrology, oxalosis (Charybdis) seems the greater peril, and vitamin C deficiency (Scylla) is accepted as unavoidable.

Vitamin C Effects on Erythropoiesis

The management of anemia utilizes much of the resources dedicated to patients on dialysis; hemoglobin, ferritin, transferrin saturation, erythropoietin therapy and the intravenous administration of iron complexes (IV-iron) are reviewed extensively for each patient, with dose adjustments monthly or even at more frequent intervals. Improved vitamin C status may lead to improved anemia management in these patients. The biochemistry of vitamin C and iron are intimately related; at the level of the gastrointestinal tract, vitamin C helps maintain iron as Fe^{2+}, which is more soluble than Fe^{3+} at the alkaline pH of the small intestine, and is more readily absorbed across the intestinal mucosa [12, 13]. However, the iron requirements of dialysis patients are greater than most persons with normal renal function, and several investigations [14, 15] have reported that oral iron supplements have limited ability to meet the iron needs of these patients. The consensus among dialysis clinicians is therefore that IV-iron is obligatory in these patients, although further study may document the beneficial effects of dietary vitamin C on utilization of oral iron.

Vitamin C can affect mobilization of iron from Kupffer cells and other sites in the reticuloendothelial system (RES). When storage iron accumulates beyond the requirement of the body for iron, it may be converted from ferritin to hemosiderin, a form of iron with limited bioavailability, which can accumulate in the bone marrow of dialysis patients [16]. Studies in guinea pigs have shown that vitamin C aids the conversion of hemosiderin iron to ferritin iron [17], which can be exported from the storage cell and carried on transferrin to sites of red blood cell synthesis in the bone marrow. In Bantu siderosis [18], administration of dietary vitamin C supplements led to a significant increase in serum iron, indicating that vitamin C was helping to mobilize stored iron in these patients. During the initial phase of vitamin C therapy in siderotic subjects, there was an accelerated release of urinary oxalic acid [19], consistent with conversion of vitamin C to dehydroascorbate by interaction with stored ferric ion, followed by catabolism of dehydroascorbate to oxalate. Dialysis patients may also accumulate excess iron stores in the gastrointestinal mucosa [20], which could lead to rapid breakdown of vitamin C provided by the diet, and limit the impact of supplemental vitamin C on plasma vitamin C levels.

IV-iron may only be partially utilized for Hb synthesis in dialysis patients. A dose of 1 g iron could theoretically produce 300 g Hb, which should increase Hb to 15 g/dl, from a baseline value of 10 g/dl. But the usual outcome of a standard 1-gram course of IV-iron administered to hemodialysis patients is to increase Hb to only 11 g/dl [14, 21], which indicates that 20% of the iron was available for Hb production. In a 1-year study of chronic kidney disease patients (stage 3 renal failure), a 2.4-gram IV-iron regimen led to 10–20% of the predicted increment of Hb in the bloodstream [22]; the remainder may have gone into long-term storage in the reticuloendothelial system, and accumulation of large deposits of hepatic iron has been documented in hemodialysis patients after prolonged IV-iron therapy [23].

The interactions of vitamin C with intravenous iron complexes provide in vitro evidence for potentially positive actions of vitamin C supplements in hemodialysis patients. These iron complexes contain relatively little 'free' iron, about 1–5% [24], and there is probably limited immediate release of iron to the bloodstream after injec-

tion. The iron complexes are generally taken into the lysosomal apparatus within a few hours [25, 26], and the iron is released following decomposition of the complex within the storage cell [27]. However, at mildly acidic pH (ca. 4–5), which is the pH of the lysosomal vacuole [28], vitamin C can release large amounts of the iron content from the complexes, and as much as 60% of the iron can be solubilized in several hours [Handelman, in preparation]. Improved vitamin C status could assist in utilizing IV-iron after its uptake into the lysosome.

These actions of vitamin C have been exploited in several longitudinal studies that used intravenous vitamin C to improve erythropoiesis and decrease erythropoietin (EPO) requirements in patients with low Hb levels [29–31]. These investigators selected patients who required high-EPO doses and who had elevated ferritin levels, indicative of a state of EPO resistance. Intravenous vitamin C (1,000–3,000 mg/week) was able in many of these patients to reduce EPO requirements and increase blood Hb levels, although negative results have also been reported [32]. Similar effects of high plasma vitamin C were observed in a cross-sectional study of plasma vitamin C and EPO requirements [33].

Do Hemodialysis Patients Also Show Symptoms of Scurvy?

Since dialysis patients can have plasma vitamin C concentrations of $<10\ \mu M$, the occurrence of scurvy is a possible outcome. Dialysis patients often have gingivitis, which is usually diagnosed as periodontal disease [34], but vitamin C deficiency should be considered, since bleeding gums are a major scorbutic symptom. Dialysis patients frequently complain of fatigue; since fatigue is an early symptom of scurvy [35], the role of vitamin C deficiency should be further explored [36]. Scurvy is also associated with increased bone resorption [37], and impaired resistance to infection. Many of the symptoms of scurvy are seen in dialysis patients, and therefore specific diagnosis has been difficult to achieve. To resolve this controversy, a controlled trial of vitamin C supplements in patients with low plasma vitamin C levels is warranted to examine its effect on scurvy-like symptoms.

Finding a Safe Path between Scylla and Charybdis

Multiple factors contribute to vitamin C deficiency in dialysis patients: dietary restriction, losses during dialysis, and fear of oxalosis. This uncertainty is compounded by difficulties in measurement of plasma vitamin C, which is very unstable in the blood sample [38, 39]. Currently, plasma vitamin C is rarely determined. Standardized clinical methods for measuring plasma vitamin C are urgently needed, which would allow measurement of vitamin C to be done as a routine procedure to assess vitamin C status.

The improved Hb response to iron therapy seen in many patients indicates that there is a true Scylla of vitamin C deficiency; is there likewise a true Charybdis of oxalosis in hemodialysis patients? There has been no evidence for at least 10 years that dialysis patients are harmed by increased doses of vitamin C, but this worry persists among nephrologists. Controlled studies of the impact of vitamin C supplements on the occurrence of oxalate deposits are needed, and then perhaps we can show that the whirlpool has vanished with modern dialysis treatment, and practitioners can sail safely on with the use of supplemental vitamin C.

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Haemodialysis Fluid: Composition and Clinical Importance

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Key Words
Dialysis fluid composition · Haemodialysis · Bacterial contamination

Abstract
Dialysis fluid is produced by the blending of treated water with electrolytes at the patients bed side. Its preparation and composition are important elements of treatment optimisation since many of the constituents play a role in patient well-being. Ideally the composition of the dialysis fluid should match that of plasma, but due to differences between patients, as well as the increasing number of elderly patients receiving treatment, have resulted in a move towards individualisation of the electrolyte and buffer composition to patient needs. Such individualisation is facilitated by the availability of technology, however it is not yet possible to individualise minor electrolytes, such as K^+, Ca^{2+} and Mg^{2+}. Early dialysis treatments were frequently accompanied by pyrogen reactions arising from bacterial contamination of the dialysis fluid. Today the focus is on the stimulation of mononuclear cells by bacterial fragments contributing to chronic inflammation associated with long-term haemodialysis therapy, and which has led to suggestions regarding the desirability of using ultra-pure dialysis fluid to prevent or to delay complications associated with their presence.

Introduction

The process of haemodialysis relies upon a diffusive gradient across the membrane contained in the haemodialyser or artificial kidney to facilitate solute and fluid removal from the patient during treatment as well as to normalise electrolyte imbalances. To permit this, whilst blood flows on one side of the membrane or is contained within the hollow fibre, dialysis fluid, a buffered electrolyte solution, flows on the outer side of the membrane or around the hollow fibre. This article focuses on the importance of dialysis fluid composition and the role that this plays on both morbidity and long-term management of patients undergoing regular dialysis treatment.

The Production of Dialysis Fluid

Historically the production of dialysis fluid was by the manual mixing of concentrated electrolyte solution with water in a large tank, which was then heated and pumped to the dialyser [1]. With the advent of single-patient proportioning systems in the late 1960s, the production of the dialysis fluid moved to the patients bedside and whilst this approach remains the most widely used, alternatives such as a central delivery system or systems that incorporate pre-mixed dialysis fluid continue to be used [2].

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Fig. 1. Two different approaches to bicarbonate concentrate used in haemodialysis. **a** The Bi Bag (Fresenius Medical Care). **b** BiCart cartridge (Gambro Renal Products).

Early single-patient proportioning systems used sodium bicarbonate for buffering, but problems arising from the formation of calcium carbonate meant that this approach was abandoned in favour of acetate [3]. Acetate remained the buffer of choice until the early 1980s when, with the increased use of high-efficiency dialysis treatments and the availability of new technology to minimise calcium carbonate formation, bicarbonate re-emerged as the preferred buffer.

The preparation of bicarbonate-buffered dialysis fluid requires the use of two separate concentrates, an acid concentrate containing sodium chloride, calcium chloride, magnesium chloride, potassium chloride, glucose monohydrate and a small amount of organic acid generally in the form of glacial acetic acid, although other acids may also be used (sodium di-acetate, lactic acid or citric acid), and bicarbonate or base concentrate containing powdered or liquid bicarbonate (fig. 1). Systems in current clinical use proportion these at different ratios with the more commonly used ratios being 1:1.225:32.775, 1:1.83:34, and 1:1.72:42.28 (acid concentrate:base concentrate:water). The different proportioning ratios are a consequence of the presence of varying amounts of sodium chloride in the bicarbonate solution, necessitating a corresponding adjustment in the acid concentrate to achieve the final electrolyte concentration.

The dialysis fluid thus produced is heated and degassed before passing to the dialyser. Safety circuits monitor the ionic composition to ensure patient safety and comfort. At the normally used temperatures (36.5–38°C) dialysis produces a marked increase in body temperature and considerable heat accumulation arising from peripheral, and cutaneous vasoconstriction arising from the body's compensation for the ultrafiltration induced decrease in blood volume. This thermal accumulation contributes to treatment-related vascular instability and has led to the development of temperature or thermal balance monitoring and control systems to minimise hypotension [4, 5].

Table 1. Water contaminants known to pose problems to the dialysis patient

Symptom	Related water contaminants
Anaemia	Al, chloramine, nitrate, Pb, Cu, Zn, Si
Bone disease	Al, fluoride, Si
Hypertension	Ca, Mg, Na
Hypotension	Bacteria, endotoxin, nitrate
Acidosis	Low pH, sulphate
Muscle weakness	Ca, Mg
Nausea/vomiting	Bacteria, endotoxin, chloramine, low pH, nitrate, sulphate, Ca, Mg, Cu, Zn
Neurological disturbances	Al, Pb, Ca, Mg

FDA 89-4234 manual on water treatment for hemodialysis.

Table 2. Water and dialysis fluid microbiological contaminant levels in US and European standards

	Water		Dialysate	
	bacteria CFU/ml	endotoxin EU/ml	bacteria CFU/ml	endotoxin EU/ml
AAMI, proposed	200[a]	2[b]	NS	NS
AAMI, current	NS	NS	200	2
EBPG	100	0.25	100	0.25

NS = Not specified. EBPG = ERA-EDTA best practice guidelines.
[a] Action level 50 CFU/ml.
[b] Action level 1 EU/ml.

Water for the Production of Dialysis Fluid

Generally patients undergoing three times weekly dialysis treatments utilise dialysis fluid flow rates of between 500 and 800 ml/min, which corresponds to the use of 120–200 litres of fluid over a 4-hour treatment session. In contrast to the normal population, who not only are exposed to significantly lower volumes of water and in whom the gut offers a high degree of protection from impurities that may be present, dialysis patients are not only exposed to higher volumes of water, but during dialysis only the semi-permeable membrane present in the dialyser separates their blood from the dialysis fluid. Thus many of the permitted contaminants in drinking water have the potential to cause problems in dialysis patients (table 1). To minimise risks from such exposure, standards for water quality such as the AAMI/RD62 in the United States have been developed and implemented. These define the maximum permitted contaminants with compliance linked to reimbursement. The attainment of the required levels in the water used for the preparation of the dialysis fluid is by the additional water treatment, the nature of which is dependent upon the quality of the feed or raw water.

An emergent issue resulting from the removal of chemicals such as chlorine and chloramine, added as part of municipal water treatment to minimise bacterial proliferation, is that treated water is prone to bacterial proliferation unless appropriate disinfection and quality assurance systems are in place. The awareness of the importance of microbiology on patient mortality and morbidity has resulted in a harmonisation of microbiological standards regarding the quantification methods relating to water used in the preparation of dialysis fluid and in the introduction of more stringent limits for specific applications such as haemofiltration and haemodiafiltration which mandate the use of ultra-pure water for the preparation of the dialysis fluid (table 2).

Table 3. Comparative composition of dialysis fluid and plasma

		Dialysis fluid mEq/l	Plasma mEq/l
Electrolytes	Na	136–140	136–145
	Cl	99–110	98–106
	K	0–3.0	3.5–5
	Ca	1.5	2.0–2.6
	Mg	0.5–1.0	0.8–1.2
Buffer	Acetate	2.5–5.0	
	HCO_3	27–39	21–28
Glucose		2.0	0.8–1.2

Dialysis Fluid Composition

The classical approach to dialysis fluid composition was to make the electrolyte composition identical to that of the plasma of a healthy individual (table 3). Today with the availability of technology as well as the awareness of the influence of various components on patient well-being and treatment outcome, considerable individualisation is possible and practiced.

Electrolyte Composition

Sodium

Sodium is the main cation of the extracellular fluid and, during dialysis, is removed from the body by both diffusion and convection. As dialysis evolved, there has been considerable interest in adjusting the sodium levels in the dialysis fluid largely to improve patient tolerance to the dialysis procedure. Sodium levels in the dialysis fluid may be considered as 'hyponatraemic' hypernatraemic' or 'isonatraemic' [6], with current technology, the levels no longer need to be constant throughout treatment [7].

In clinical practice the use of hyponatraemic dialysis fluid (sodium concentration 130–135 mmol/l) has declined and should be avoided as secondary to the loss of sodium by diffusion, there is a decrease in plasma osmolarity resulting in cellular over-hydration which contributes to disequilibrium syndrome (fatigue, 'washed-out' feeling, muscle cramps, headache, neurological symptoms), and intradialytic hypotension. For the majority of patients a hypernatraemic dialysis fluid (sodium concentration 140–145 mmol/l) is used to avoid excessive sodium losses arising from ultrafiltration and to prevent cardiovascular instability during treatment. The use of such sodium levels has drawbacks, namely that it can result in sodium gain, contribute to the development of hypertension, trigger thirst causing a high water intake in the interdialytic interval, which requires the use of high ultrafiltration rates during treatment resulting in hypotensive episodes. The hypotension induced may prevent dry body weight achievement and prompt the dialysis staff to administer hypertonic saline, thereby contributing to the progression of cardiac failure and/or pulmonary oedema.

Isonatraemic dialysis fluid requires the dialysis fluid sodium level to be matched to that of the sodium in plasma water, and the calculation of sodium balance using a mathematical model. Due to practical difficulties this approach has only seen experimental application.

The manipulation of the dialysis fluid sodium concentration or conductivity either alone or in combination with profiling of the fluid removal rate during treatment (to modulate vascular refilling) has been widely applied to improve blood volume preservation, and reduce hypotensive episodes during treatment. Whilst such an approach improves refill from both the intracellular and interstitial spaces to the intravascular compartment, the high dialysis fluid sodium levels used reduce dialytic removal of sodium and can result in a sodium overload [8].

Calcium

The current dialysate calcium level has been arrived at over time in conjunction with the evolution of other aspects of calcium metabolism in this population. In the 1960s, the constituents of the dialysate were arbitrarily determined to best match normal serum levels. Because of impaired calcium absorption with resultant hypocalcaemia, it soon became apparent that higher levels of dialysate calcium could be used to support the serum calcium level. Early studies of parathyroid hormone in the late 1960s showed that these higher dialysate calcium levels of 1.75 mmol/l (3.5 mEq/l) were also associated with lower parathyroid hormone levels.

At this time aluminium-containing compounds were the medication of choice to control phosphate levels, in preference to magnesium- or calcium-containing compounds. With the identification and synthesis of calcitriol, the problems of hypocalcaemia were ameliorated and the need for calcium loading via the dialysate lessened. The traditional high calcium dialysate continued to be widely used to maintain a high normal serum calcium using both dialysate and calcitriol in order to maximise parathyroid hormone suppression.

Today many dialysis patients dialyse with dialysis fluid containing 1.5 mmol/l calcium and some use levels of 1.75 mmol/l [9]. Recently, there has been a trend to lower dialysate calcium concentrations because of the frequent occurrence of hypercalcaemia with the use of calcium-containing phosphate binders. Accordingly the current K/DOQI guidelines recommend an absolute maximum elemental calcium load of 2,000 mg/day, including calcium-containing medication and a maximum dialysate calcium concentration of 1.25 mmol/l to avoid intradialytic calcium loading.

Calcium ions also play a pivotal role in the contractile process of both vascular smooth muscle cells and cardiac myocytes, and dialysis fluid calcium concentrations affect blood pressure [10]. Low dialysate calcium concentrations, however, expose the patient to the risks of negative calcium balance and increase in parathyroid hormone concentration, particularly if patients are non-compliant with the intake of calcium-containing phosphate binders [11, 12].

The choice of dialysis fluid calcium concentrations for patients undergoing haemodialysis remains a matter of considerable debate. Malberti and Ravani [13] concluded that a dialysis fluid calcium level of 1.5 mmol/l seems to be suitable for the majority of patients on haemodialysis or post-dilution on-line haemodiafiltration. However, Sigrist and McIntyre [14] took a more pragmatic approach and suggested that, even with a dialysis fluid level of 1.25 mmol/l, many patients were experiencing calcium overload contributing to the development of vascular calcification. They suggested that an upper dialysate concentration of 1.25 mmol/l may not be ideal for every patient and that dialysis fluid concentrations should be prescribed with reference to plasma calcium levels. With the availability of calcimimetics, which suppress the secretion of parathyroid hormone by sensitising the parathyroid calcium receptor to serum calcium, further adjustments in the dialysis fluid calcium levels are likely.

Potassium

Potassium is the most abundant intracellular cation and a major determinant of intracellular osmolality. Haemodialysis patients are subject to a disturbed potassium homeostasis and are frequently hyperkalaemic.

The removal of potassium during dialysis is via diffusion as the level in dialysis fluid is set lower than in the plasma water. The amount required to be removed during treatment varies between 50 and 100 mmol/l depending on patient dietary compliance, but for stable dialysis patients a dialysate potassium level of 2 mmol/l maintains the plasma levels at <6 mmol/l and avoids post-dialysis hypokalaemia.

Patients with cardiac disease and arrhythmias may require higher potassium levels in the dialysis fluid (3–3.5 mmol/l) and when using such concentrations, plasma levels should be frequently monitored during treatment as a fall in serum potassium is associated with an increased QT dispersion which is associated with severe ventricular arrhythmias and sudden cardiac death. Amelioration of such a dispersion may be helped by potassium profiling [15, 16].

Magnesium

Normal plasma concentrations of magnesium are between 0.8 and 1.2 mmol/l. In dialysis patients levels may be normal increased or even decreased. Low plasma levels have recently been identified as a possible risk factor for haemodialysis headache [17]. Commercially manufactured concentrates contain magnesium concentrations ranging from 0.25 to 0.75 mmol/l. Magnesium-free concentrate is also available. Normalisation of plasma levels can be achieved by the use of magnesium concentrations of 0.25–0.50 mmol/l. Further adjustment of the dialysis fluid levels may be necessary in patients treated with oral magnesium preparations such as OsvaRen (Fresenius Medical Care AG & Co), the recently approved phosphate-binding agent made from a combination of calcium acetate and magnesium carbonate. The use of zero concentrations should be avoided as their use is associated with severe muscle cramps.

Chloride

The majority of the chloride in the body is found in the extracellular compartment where it is the main anion with normal plasma levels between 98 and 106 mmol/l. The chloride concentration of commercially produced dialysis fluids varies between 98 and 112 mmol/l and is governed by electrolytes such as sodium, potassium, calcium and magnesium levels in the dialysis fluid since they are present in the form of chloride salts.

Other Constituents

Glucose

Contemporary dialysis fluids can be either glucose-free or contain glucose up to 200 mg/l. The use of glucose-free dialysis fluid is associated with significant glucose loss during treatment with a risk of hypoglycaemia and should be avoided. A glucose concentration of 100 mg/dl

seems reasonable for the majority of patients, such levels may also be helpful in ameliorating post-dialysis fatigue and headache [18]. Whilst 200 mg/dl should be used for those patients in whom the nutritional value of supplementation is a priority.

Buffer

The kidney is a key organ of hydrogen ion (H^+) handling, and metabolic acidosis is one of the main complications of uraemia. Correction through dialysis occurs through buffer supply, rather than through H^+ clearance. Diffusive influx of buffer into the patient has been used since the beginning of the dialysis era. Historically acetate was used, although acetate is not a buffer as such, but derives its buffering action through metabolism. Technical issues with the production of bicarbonate-buffered dialysis fluid favoured the use of acetate until the 1980s when technical developments preventing the formation of calcium carbonate and the awareness of the problems associated with acetate uptake in high flux and high efficiency dialysis progressively led to the use of bicarbonate as the preferred dialysate buffer. However, it continues to be used in emerging economies due to its lower cost and ability to be used with less complex proportioning systems.

The bicarbonate flux from the dialysis fluid to the patient is determined by the trans-membrane concentration gradient. The usual dialysis fluid concentration is 35 mmol/l, leading to a pre-dialysis concentration of between 22.0 and 23.0 mmol/l [19], a value in agreement with the recommended goal proposed by KDOQI guidelines [20].

The level of dialysis fluid bicarbonate may need to be adjusted if pre-dialysis levels are below 17 mmol/l or above 27 mmol/l since these levels are associated with an increased risk of mortality [21].

Increasingly in Europe dialysis patients are being treated by newer convective therapies such as haemodiafiltration, an extracorporeal technique which utilises a large amount sterile bicarbonate-buffered dialysate as infusion solution to compensate for fluid removal with this technique. For such treatments the bicarbonate concentration in dialysate (and substitution fluid) ranges from 27 to 35 mmol/l.

Microbiological Quality

Febrile reactions were common in the early dialysis procedures. The electrolyte concentrates in use today are manufactured in accordance with internationally recognised standards such as ISO 13958, Concentrates for Haemodialysis and Related Therapies. The acid concentrates do not support bacterial growth, however liquid bicarbonate concentrates have been shown to support bacterial growth and there may be a rapid increase in levels after dilution [22]. High levels in the dialysis fluid lead to pyrogen reactions and fever [23, 24]. Intact bacteria cannot cross the dialyser membrane, however bacterial products such as endotoxins, muramyl di-peptides and exotoxins, potent inducers of cytokines and stimulators of the acute phase response, are able to transfer leading to the stimulation of mononuclear cells and contributing to chronic inflammation associated with long-term haemodialysis therapy. Such transfer is related to the type of dialyser membrane (cellulosic vs. synthetic) and the mode of dialysis (low flux vs. high flux with back filtration).

Enrichment of the Dialysis Fluid

Although dialysis fluid predominantly contains electrolytes, a buffer and glucose, the potential exists for other compounds to be added for specific applications. The first such approach was the addition of urea to the dialysis fluid to minimise dialysis disequilibrium [25] which was also used more recently by Doorenbos et al. [26]. Other compounds that have been added include amino acids to compensate for the loss during dialysis [27, 28], ethanol for the treatment of ethylene glycol or methanol overdose [29]. Gupta et al. [30] used this approach to transport ferric pyrophosphate complexed with sodium citrate into the blood of patients undergoing haemodialysis to replenish their iron stores. An increase in treatment frequency is gaining popularity. Prolonged daily nocturnal dialysis has been shown to result in hypophosphataemia in patients treated with this modality and in this setting the addition of phosphate to the dialysis fluid may prove to be helpful in normalising plasma phosphate levels.

Conclusions

The preparation and composition of dialysis fluid is an important element of treatment optimisation since many of the constituents play a role in patient well-being. Whereas historically the composition of the dialysis fluid was matched to that of plasma in respect of electrolytes, today technology permits individualisation of the major components of dialysis fluid, such as the sodium and bicarbonate, to the patients requirements to improve treat-

ment tolerance, however it is not yet possible to individualise minor electrolytes, such as K^+, Ca^{2+} and Mg^{2+}. Specific compounds may also be added to the fluid for special clinical situations.

Early dialysis treatments were frequently accompanied by pyrogen reactions arising from bacterial contamination of the dialysis fluid. Today the focus is on the stimulation of mononuclear cells by bacterial fragments contributing to chronic inflammation associated with long-term haemodialysis therapy, which has led to suggestions regarding the desirability of using ultra-pure dialysis fluid to prevent or delay complications associated with their presence [31].

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Inflammation and Subclinical Infection in Chronic Kidney Disease: A Molecular Approach

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Chronic kidney disease · Inflammation · Infection, subclinical

Abstract
Inflammation and infection seem to be important causes of morbidity and mortality in chronic kidney disease (CKD) patients; subclinical infections have been proposed as an important cause of inflammatory syndrome, but to date this hypothesis remains speculative. We developed a method for the molecular detection of the presence of bacterial DNA in a population of CKD patients in order to correlate the molecular data with the degree and level of inflammation and to evaluate its usefulness in the diagnosis of subclinical infection. The study was divided into two phases: (1) a population of 81 CKD patients was screened for the prevalence and level of inflammation and the presence of possible infection, and (2) a subgroup of 38 patients, without evident clinical causes of inflammation, underwent complete molecular evaluation for subclinical infection using bacterial DNA primers for sequencing. Additionally, complete analysis was carried out in the blood and dialysate compartments of the hemodialyzers used. The general population showed a certain degree of subclinical inflammation and no difference was found between patients with and without evident causes of inflammation. Hemoculture-negative patients were positive for the presence of bacterial DNA when molecular methods were used. We found a correlation trend between the presence of bacterial DNA and the increase in hs-CRP, IL-6 and oxidative stress (advanced oxidation protein product) levels and a reduction in the mean fluorescence intensity for HLA-DR. Hemodialyzer membranes seem to have properties that stick to bacteria/bacterial DNA and work as concentrators. In fact, patients with negative bacterial DNA in the circulating blood displayed positivity in the blood compartment of the dialyzer. The dialysate was negative for bacterial DNA but the dialysate compartment of the hemodialyzers used was positive in a high percentage. Moreover our data suggest that bacterial DNA can traverse hemodialysis membranes. Molecular methods have been found to be far more sensitive than standard methods in detecting subclinical infection. The presence of bacterial DNA seems to influence the variation in some parameters of inflammation and immunity. Apart from the limitations and pitfalls, the molecular method could be useful to screen for subclinical infection and diagnose subclinical sepsis when the hemoculture is negative. However, the identification of the microorganism implicated must be done with species-specific primers.

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Introduction

Inflammation and infection seem to be important causes of morbidity and mortality in chronic kidney disease (CKD) patients. CKD-associated chronic inflammation has been reported in 30–60% of North American and European dialysis patients. A generalized increase in the inflammatory response in these patients may occur via various mechanisms including decreased clearance of proinflammatory cytokines [1, 2], and overproduction of proinflammatory cytokines caused by an elevated number of circulating monocytes and an enhanced cytokine production per cell [3, 4]. Data suggest that inflammatory biomarkers, such as interleukin-6 (IL-6) and the archetypal acute phase reactant C-reactive protein (CRP), are not only markers but also mediators of atherosclerotic/thrombotic lesions and cardiovascular diseases in man. The expansion of proinflammatory cytokines may be induced by endotoxinemia/bacteremia due to gastrointestinal vascular congestion and loss of permeability [5, 6], increased oxidative and carbonyl stress [7, 8], and increased susceptibility to infections due to uremia, old age, and comorbid conditions [9]. In addition, in patients undergoing maintenance hemodialysis the exposure to bioincompatible tubing and dialysis membranes, the presence of access grafts or intravenous catheters, and poor quality of dialysis water and back-filtration may chronically aggravate the inflammatory processes [10, 11]. To date, the prevalence of the chronic inflammatory syndrome associated with latent infection has not been identified in hemodialysis patients, and whether an infectious agent will ultimately be identified as an important cause of this syndrome remains speculative. A significant proportion of patients who appear to be clinically septic have negative hemocultures (presence of bacteriostatic factors or prior antibiotic treatment) or culture growth is poor: certain human pathogens require special conditions to grow. Successful isolation can be slow, have low sensitivity and in some instances is impossible; organisms may also be sequestered by macrophages or hide in tissue foci so that standard methods fail to detect them. One of the most common microorganisms causing false-negative cultures is *Pseudomonas aeruginosa*.

The presence of pathogens may be identified using molecular methods such as studying a stable part of the genetic code which also allows the identification of the phylogenetic relationship of bacteria; the part of DNA most commonly used for taxonomic purposes is the 16S ribosomal RNA gene (16S rRNA) [12, 13]. This gene can be compared not only among bacteria, but also with the 16S rRNA of archeobacteria and the 18S rRNA gene of eukariotes. Closely related bacterial species often have identical rRNA sequences [14–16] which can be amplified by polymerase chain reaction (PCR) techniques. Highly variable regions within the amplicon permit phylogenetic analysis and, in some cases, may be species-specific. On the basis of the sequence of the amplicon the microorganism can be located in the phylogenetic tree. Since amplification by PCR does not rely on the viability of the microorganisms, this technique can be useful for detecting microorganisms in blood, human body fluids or other sources even in the presence of inhibitors of bacterial growth.

The 16S rRNA gene is 1,550 bp long and consists of highly conserved sequences interspersed with variable sequences. Primers were designed to target a conserved region of bacterial 16S rRNA gene; the forward primer is located at the beginning of the conserved region, while the reverse one is located 540 bp downstream. The sequence of the variable region in between can be used for comparative taxonomy. For most clinical bacterial isolates the initial 500-bp sequence provides adequate differentiation for identification even though sometimes sequencing the entire 1,500-bp gene may be necessary to distinguish particular taxa or strains.

In this study we use molecular techniques (16S rRNA gene amplification and sequencing) to detect the presence of bacterial DNA in whole blood, hemodialyzer compartments and dialysate of chronic hemodialysis patients in order to evaluate their usefulness in subclinical infection detection and biological monitoring procedures.

In a single center population of chronic hemodialysis patients, the aims of the study were: (1) to evaluate the degree of inflammation (inflammation markers); (2) to evaluate the prevalence of subclinical bacterial infection in a subgroup of clinically silent patients using molecular methods; (3) to correlate the molecular methods with standard hemoculture methods; (4) to correlate subclinical infection with the degree of inflammatory abnormalities; (5) to evaluate whether bacterial DNA can be found in the hemodialyzer of bacterial DNA-negative patients, and (6) to evaluate whether bacterial DNA can pass through membranes within the hemodialyzer.

Materials and Methods

Study Design

The study was divided into two phases.

Phase 1 was used for the detection of prevalence and the level of inflammation in the entire dialytic population of the Vicenza hemodialysis center. Blood samples were collected from 81 pa-

tients under sterile conditions immediately after needle insertion but before any intravenous fluid was given (mid-week dialysis session) to measure the inflammatory parameters and make microbiological analyses (standard and molecular).

Phase 2 was used for the molecular evaluation of the presence of bacterial DNA in patients and hemodialyzers. 38 patients (of the original 81) without evident clinical infection or clear causes of inflammation were selected for this study. Whole blood and dialysate were collected during treatment. Blood was collected just after needle insertion and spent dialysate was collected every hour (4 samples of 50 ml). Samples from the blood and dialysate compartments of the dialyzers were collected following treatment and after filter washing, also collecting the last washing solution for control. Patients were excluded if they had apparently active infection or antibiotic administration within 2 weeks, and/or if other sources of inflammation such as periodontal disease, malignancy, autoimmune disease, trauma, infarction, etc., were present.

Controls

In phase 1 the whole blood of 20 healthy blood donors was collected for the inflammation study.

Microbiological study controls in phase 1 were internal controls for amplification (DNA from *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *P. aeruginosa* ATCC 35218, *Candida albicans* ATCC 90028); whole blood of 20 healthy blood donors, and dialysis ultrapure water collected from different points of the treatment plant.

In phase 2 the microbiological study control was performed through simulated use of sterile hemodialyzers and water monitoring. Five unused hemodialyzers were treated in the same way as the patients' hemodialyzers after treatment, and microbiological monitoring of ultrapure water was collected from 6 different points of the water treatment plant.

Inflammatory Markers

The inflammatory markers evaluated have been divided into three categories.

(1) Inflammation Markers Modified in Response to Inflammation. High-sensitivity C-reactive protein (hsCRP): CRP (μmol/l) expresses an enhanced hepatic synthesis of proteins activated by conditions of chronic or repeated immune challenge. Interleukin 6 (IL-6) was measured as ng/l. The cells of the immune system are influenced by the toxic effect of uremia and by different dialytic procedures. Patients on renal replacement therapy are at high risk of infectious complication. It appears that in uremia B-cell function is normal, but there is a defect in T-cell function. During the interdialytic interval, cytokine production from monocytes is normal, even though these cells release large amounts of proinflammatory cytokines such as IL-6. Small bacterial DNA fragments [17] and contaminants such as lipopolysaccharide are able to induce IL-6 in human mononuclear cells. Albumin (g/dl) was measured in patients with inflammation, infection or injury, and the catabolism and transendothelial transport of albumin may be increased while its synthesis is decreased.

(2) Markers of Immune Disregulation. The following parameters were evaluated. Percent monocytes HLA-DR+ was determined by flow cytometric analysis. HLA-DR expression, measured by flow cytometric analysis as medium fluorescence intensity (MFI) DR, may be an important parameter to evaluate the function of immunocompetent cells. A low expression can lead to severe immunodeficiency and has been associated with an increased risk of infection after surgery or trauma. Apoptosis, measured as a percentage of cells after incubation of patient plasma on U937 cells for 96 h, can be correlated to HLA-DR since it is related to defective immunity. Hemodialysis patients show a higher rate of apoptosis compared to healthy people, which is possibly related to retained uremic toxins. U937 in RPMI 1640 medium supplemented with 10% heat inactivated fetal calf serum (FCS), 2 mM L-glutamine, 100 IU/ml penicillin, 100 mg/ml streptomycin were kept in a controlled atmosphere incubator (5% CO_2) at 37°C. 10^6 U937 cells were incubated with patient and donor plasma plus 0.5 ml RPMI solution. Apoptosis was assessed by fluorescence microscopy after 96 h of incubation [18, 19].

(3) Causes of Inflammation (Oxidative Stress). CKD patients undergoing hemodialysis present an imbalance in oxidative equilibrium, characterized by a reduction in oxygen radical scavenger activity and an enhanced production of reactive oxygen species leading to an acute/chronic inflammatory response. As oxidative stress parameters we evaluated advanced oxidation protein products (AOPPs), glutathione (GSH) and reactive carbonyl compounds (RCOs). AOPP is a marker of oxidative stress and is formed by myeloperoxidases and chlorinated oxidants generated by neutrophils. Determination of AOPP was performed by spectrophotometry (absorbance reading 340 nm) and the concentration is expressed as nmol/l of chloramine T equivalents. GSH, measured as μmol/10^6 cell, is the major determinant of the redox status in mammalian cells. It maintains intracellular redox equilibrium and regulates cellular defenses augmented by oxidative stress. Patients with endothelium dysfunction have lower GSH [20]. RCOs are derived by carbohydrates, lipids and amino acids which become the precursors of RCOs in hemodialysis patients. Determination of RCOs was performed by spectrophotometry (absorbance reading 370 nm) using dinitrophenylhydrazine binding and the concentration is expressed as nmol/l of proteins [21].

DNA Extraction from Whole Blood

DNA from 200 μl of heparin-treated whole blood was extracted using a QIAamp DNA mini kit (Qiagen) following the manufacturer's instructions. DNA was digested with proteinase K in an appropriate buffer for 2 h at 56°C to allow optimal cell lysis and binding of the DNA to the QIAamp membrane. DNA was then adsorbed onto the QIAamp silica gel membrane during brief centrifugation. Salt and pH conditions ensured that proteins and other contaminants were not retained on the membrane. DNA bound to the membrane was washed twice in two brief centrifugations using two different buffers which significantly improves the purity of the eluted DNA without affecting DNA binding. Purified DNA was eluted with an elution buffer in a concentrated form and was then suitable for direct PCR use.

DNA Extraction from Dialysate

200 ml of dialysate collected during dialysis was centrifuged at 2,000 rpm for 10 min in order to pellet bacterial cells. The pellet thus obtained was digested overnight in 10 mM Tris-HCl (pH 8.3) and mM KCl 50 with proteinase K to a final concentration of 0.5 μg/μl and Nonidet P-40 at 55°C. The mixture was then boiled for 10 min and centrifuged to remove debris. The supernatant was used as template for amplifications.

DNA Extraction from Dialyzers

25 ml of a mixture containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, proteinase K to a final concentration of 0.5 μg/μl and Nonidet P-40 was injected separately into the blood and the dialysate compartments of the filters. The filters were then incubated at 42°C overnight to allow complete digestion of biofilm if present. Then, in order to avoid the cross-contamination between the solutions in the two compartments, we separately removed the two solutions by gentle drawing them from the arterial and dialysate ports in two sterile tubes. The solutions were boiled for 10 min and centrifuged to remove debris. The supernatant was used as direct template for amplifications. All processes were done under sterile techniques.

DNA Isolation and Extraction from Ultrapure Water

In order to evaluate microbiological quality, 200 ml ultrapure water for dialysis were collected at different points in the treatment water plant (formula 10, loop 1, loop 2, Fresenius, AK 2000 and integra) and filtered in a 0.2-μm Millipore membrane. The membrane was then treated to extract DNA, if present, by means of 10 mM Tris-HCl (pH 8.3) and 50 mM KCl with proteinase K to a final concentration of 0.5 μg/μl and Nonidet P-40 at 55°C overnight. The mixture was then boiled and ready for amplification.

16S rRNA Amplification. It was shown that the phylogenetic relationships of bacteria and, indeed, all life-forms could be determined by comparing a stable part of genetic code [20, 21]. The DNA part now most commonly used for taxonomic purposes for bacteria is the 16S rRNA gene [13]. In this study, the primers used for amplification of 16S rRNA were 355F (5′-CCTACGGGAGGCAGCAG-3′) and 910R (5′-CCCGTCAATTCCTTTGAGTT-3′). 200–1,000 ng of template DNA were used for amplification in a 50-μl reaction mixture with a final concentration of 67 mM Tris HCl (pH 8.8), 16 mM $(NH_4)_2SO_4$, 200 μM dNTPs, 3,5 mM $MgCl_2$, 25 pmol of each primer and 1 U Taq polymerase (GoTaq DNA polymerase, Promega, Madison, Wisc., USA). The temperature scheme used for the amplification was: 95°C for 5 min then 35 cycles of 95°C for 45 min, 53°C for 45 min and 72°C for 45 min and a final extension step of 7 min at 72°C. The amplification products were visualized in 3% Nu:Sieve 3:1 Agarose (Cambrex Bio Science, Rockland, Me., USA) with 5% gel star staining (Cambrex) using standard techniques. All samples were tested at least twice before reporting. To avoid risk of contamination, tissue preparation, PCR amplification and electrophoresis were performed in different rooms. In each assay negative and positive controls were run. The negative control contained all the PCR reagents and sterile bi-distilled water.

Precautions taken to avoid laboratory contamination included: the use of different areas for pre-PCR preparation and sample preparation and managing (post-PCR area); the use of face masks, gloves, caps and glasses, and the use of barrier tips and different pipettes when handling reagents and specimens in the pre- and post-PCR areas. Native Taq polymerase from *Thermophilus aquaticus*, instead of recombinant, was used to avoid the presence of contaminant DNA from commonly found bacteria. A negative and a positive control were included in each run. All procedures were performed after at least 12 h of UV sterilization of the workplace, and amplification of the β-globin gene was performed to evaluate sample degradation or the presence of inhibitors.

Amplification Products Excision from Gel and DNA Sequencing

After electrophoresis, the amplification products, if present, were excised from gel and purified with Wizard SV Gel and PCR Clean-up System (Promega, cat. No. A9282) following the manufacturer's instructions. The products then underwent sequencing reaction on GeneAmp 9700 (PE Biosystems). The ABI Prism BigDye Terminator v1.1 cycle sequencing kit (Applied BioSystems, Foster City, Calif., USA) was used for the sequencing reaction; the primer used was the reverse (910 R) and the final reaction volume was 20 μl. The thermal cycling conditions were 25 cycles of 10 s at 96°C, 5 s at 50°C and 4 min at 60°C. The reaction products were purified with Centri-Sep Columns (Princeton Separation) to remove exceeding DyeDeoxy™ terminators before automated sequencing on ABI PRIMS 310 genetic analyzer (Applied BioSystems). The sequences obtained were examined on the web site http://www.ncbi.nlm.nih.gov/blast.

Hemocultures

A minimum of 10 ml of blood was obtained and immediately inoculated into BacT/Alert Fanh aerobic and anaerobic bottles (BioMerieux, Marcy I'Etoile, France), and the bottles were incubated for ≤7 days. The bottles were then processed in a BacT/Alerth 3D automated blood culture system (BioMerieux). Blood cultures were performed at the time of filter and ultrafiltrate collections and at the beginning of the hemodialysis session.

Results

Phase 1

Inflammatory Markers

The inflammatory markers were evaluated in the whole population (81 patients) and in the same population divided into 2 subgroups: a group in which evident causes of inflammation could be clinically demonstrated (43 patients), and a group with inflammation but no evident causes for it (38 patients). The results are shown in table 1. Comparison of the 43 patients with known causes of inflammation with the 38 patients without causes of inflammation reveals a trend to an increase in IL-6 in the second group. Other parameters are not significant. Thus, the level of inflammatory parameters is not significantly different in the 2 groups, suggesting that a similar level of inflammation may be present. A further consideration is that, in general, the level of inflammatory markers is remarkably low compared to other populations.

Microbiological Parameters

The whole blood from all 81 patients was hemoculture negative, while 11 of 81 (13.58%) patients had positive bacterial DNA in the whole blood. After sequencing 8 had *Pseudomonas* spp. DNA while the last 2 had a strong signal, but no readable sequence. All controls (blood donors

Table 1. Inflammatory markers evaluated in the whole population and in the two subgroups 43 patients with evident causes of inflammation and 38 patients with inflammation but without evident causes

Population	Inflammatory response (markers/cytokine)			Immune disregulation			Causes of inflammation (oxidative stress)		
	HsCRP mg/dl	IL-6 pg/ml	albumin g/dl	AOPP μM	GSH μmol/10^6 cells	RCOs nmol/mg protein	apoptosis plasma on U937 cells at 96 h, %	MFI DR+	monocytes HLA-DR+ %
Total (n = 81)	1.06 ± 1.21	17.56 ± 27.34	3.86 ± 0.43	237.63 ± 136.67	5.04 ± 1.06	1.00 ± 0.56	45.14 ± 0.07	99.2 ± 40.46	96.47 ± 3.83
Evident causes of inflammation (n = 43)	1.11 ± 1.27	11.08 ± 11.44	3.80 ± 0.46	217.05 ± 117.85	4.93 ± 1.08	0.99 ± 0.28	46.77 ± 0.07	91.63 ± 42.16	95.86 ± 3.97
No evident causes of inflammation (n = 38)	0.99 ± 1.16 n.s.	24.73 ± 36.75 p = 0.034	3.93 ± 0.40 n.s.	260.93 ± 153.51 n.s.	5.17 ± 1.03 n.s.	1.00 ± 0.76 n.s.	44.42 ± 0.07 n.s.	107.76 ± 37.14 p = 0.073	97.17 ± 3.59 n.s.

Table 2. Correlation of molecular data obtained in whole blood and inflammatory markers in the whole population (81 patients)

Population	Inflammatory response (markers/cytokine)			Immune dysregulation			Causes of inflammation (oxidative stress)		
	HsCRP mg/dl	IL-6 pg/ml	albumin g/dl	oxidative stress determined by AOPP, μmol/l	oxidative stress determined by GSH μmol/g Hb	carbonyl stress nmol/mg protein	apoptosis plasma on U937 cells at 96 h, %	MFI DR+	monocytes HLA-DR+ %
rDNA+ (n = 11)	0.89	22.41	3.62	257.55	4.75	4.65	43%	75.79	94.4
rDNA– (n = 70)	1.08	16.78	3.9	234.5	5.09	0.92	46%	102.87	96.8

and ultrapure water samples) had negative hemoculture and negative bacterial DNA. Internal controls for amplification were used to standardize the molecular protocol.

Inflammatory Markers vs. Molecular Data in All Patients

Inflammatory markers were compared to the molecular data obtained from whole blood. The statistical correlation was not significant because of the limited number of patients, but a trend can be noticed for an increase in IL-6 and carbonyl stress (RCOs) and a reduction in MFI in bacterial DNA-positive patients when compared with bacterial DNA-negative patients. The results are summarized in table 2.

Phase 2

Molecular Evaluation of Patients with No Evident Causes of Inflammation

The molecular evaluation of the 38 patients (of the original 81) without clinical infection or clear causes of inflammation was performed in whole blood, spent dialysate and hemodialyzers (blood and dialysate compartments). 34 (89.5%) patients were positive in one or more of the collected samples, while only 4 (10.5%) were completely negative. Four of 38 (10.5%) patients had bacterial DNA in whole blood collected after needle insertion prior to any fluid infusion: 2 had *Pseudomonas* spp., and 2 could not be sequenced. Seven of 38 (18.4%) patients had bacterial DNA in spent dialysate collected every hour during treatment: 1 could not be sequenced, and 6 had *Pseudomonas* spp. 19 of 38 (50%) patients had bacterial DNA in the blood compartment of the hemodialyzer: 10 could not be sequenced, and 9 had *Pseudomonas* spp. 23 of 38 (60.5%) patients were positive in the dialysate compartment: 4 could not be sequenced; 15 had *Pseudomonas* spp., and 4 had environmental infections such as *Halomonas* spp., *Proteobacterium* unc. Dividing patients for positivity according to different compartments (blood side considering whole blood and blood compartment, and dialysate side considering spent dialysate and dialysate compartment), the results are as follows: none were only whole blood or spent dialysate positive; 7 patients were only blood compartment positive; 9 patients were only dialysate compartment positive; 2 were whole blood and blood compartment positive; 2 were dialysate compartment and spent dialysate positive, and 14 were positive in more than one sample (different compartments). The results of sequencing are reported in table 3.

Table 3. Molecular evaluation and sequencing in a population with no evident cause of inflammation divided for positivity in one or more different compartments

Positive collection points	Bacterial DNA-positive patients	Sequencing
Whole blood only	0	/
Spent dialysate only	0	/
Blood compartment only	7	*Pseudomonas* spp.
Dialysate compartment only	9	*Pseudomonas* spp., *P. mendocina, Halomonas, Proteobacterium* unc.
Whole blood/blood compartment	2	*Pseudomonas* spp.
Dialysate compartment/dialysate	2	*Pseudomonas* spp., *P. mendocina*
Different compartments (dialysate/blood)	14	Cannot be sequenced
Negative	4	/
Total	38	

All the 3 sterile hemodialyzers (TORA 1 B3, NIPRO 190 E, TERUMO E 18) used as controls were negative both in the blood and dialysate compartments.

Bacterial DNA-positive and -negative patients were compared with inflammation data (table 4). Bacterial DNA-positive patients showed a trend toward an increase in hsCRP, IL-6, AOPP and a decrease in MFI DR+.

No significant results were obtained by comparing the groups divided as in table 4 according to the inflammatory data. But a trend was noticed in the following parameters for bacterial DNA patients when compared with bacterial DNA-negative patients: increases in hs-CRP, IL-6 and AOPP production and a reduction in MFI DR+. These data are indicative of an increase in inflammation (CRP), stimulation of mononuclear cells for proinflammatory cytokine production (IL-6), increase in oxidative stress by AOPP, and a decrease in immune response (MFI DR+) in the bacterial DNA-positive population.

Discussion

The 16S rRNA gene amplification is described as the 'gold standard' in the identification of bacterial 'isolates' as it is robust, reproducible and more accurate and sensitive than the phenotypic testing. It allows detection of even small amounts of bacterial DNA regardless microorganism viability. In our study molecular methods were far more sensitive than standard methods (hemocultures) in detecting the presence of bacterial DNA and presumably subclinical infections in whole blood, but mostly in the hemodialyzer. However, in most cases it was not possible to identify the implicated microorganism due to the inability to isolate single bacterial strains. Actually the hemodialyzer seems to work as a concentrator, allowing the detection of even small amounts of bacterial DNA. Schindler et al. [17] demonstrated that small fragments of bacterial DNA can induce IL-6 in mononuclear cells. In our investigation patients with positive bacterial DNA showed a tendency to increase IL-6 when compared to negative bacterial DNA patients. There was also an increase in oxidative stress by AOPP (almost doubled) and CRP (more than 3 times higher) indexes of inflammation, and a reduction in MFI DR+ indicative of an immunodeficiency status that can be associated with an increased risk of infection. This trend can be observed in the whole population when comparing patients positive for bacterial DNA in whole blood with negative patients, and this becomes more evident within the selected population (patients without clear causes for inflammation) when comparing positive to negative bacterial DNA patients. This might mean that the cause of inflammation in these patients was a subclinical infection which cannot be detected with standard methods.

Apart from the higher sensitivity of the method, in our study some interesting findings emerged. Actually in some cases we were able to detect bacterial DNA in both the blood and dialysate compartments of the hemodialyzer. This findings might have two possible explanations: bacteria can traverse the hemodialyzer membrane, as demonstrated in a recent study by Hansard et al. [22], or bacterial DNA can pass through the membrane. A recent investigation by Schindler et al. [17] demonstrated that small fragments of bacterial DNA can pass from the dialysate compartment to the blood compartment of the hemodialyzer inducing the production of IL-6 in mono-

Table 4. Population with no evident causes of inflammation (38 patients); comparison of inflammatory data and molecular data in bacterial DNA-positive and -negative patients

Population	Inflammatory response (markers/cytokine)			Immune dysregulation			Causes of inflammation (oxidative stress)		
	HsCRP mg/dl	IL-6 pg/ml	albumin g/dl	AOPP μM	GSH μmol/10^6 cells	RCOs nmol/mg protein	apoptosis plasma on U937 cells at 96 h, %	MFIDR+	monocytes HLA-DR+ %
Bacterial DNA+ (34)	1.06	26.41	3.93	273.62	5.17	1.0	45	103.44	97.1
Bacterial DNA– (4)	0.3	10.3	3.87	153.02	5.16	1.03	41	144.36	98.5

No significant differences could be noted but a trend was displayed for HsCRP, IL-6, AOPP, MFI.

nuclear blood cells. High molecular weight bacterial DNA weighs several billion Daltons [23], but its conformational structure is different from proteins and this might influence the migration from one compartment to the other, in whichever direction. Actually we were able to detect fragments higher than 500 bp and this suggests that 'at least' 540 bp long DNA may traverse the membrane. This could happen during dialysis treatment where both the microorganism itself, as proposed by Hansard et al. [22], or its DNA, freed from the bacterial cells, can pass through the membrane.

Moreover, the hemodialyzers have adsorptive and sticky properties to bacteria/bacterial DNA and work as concentrators. This last finding was confirmed by the fact that patients negative on standard hemoculture and molecular detection in whole blood were positive within the blood and dialysate compartments of the hemodialyzer.

Our findings suggest that hemodialyzer membranes may concentrate bacteria/bacterial DNA both in the blood and dialysate compartments and that DNA may traverse the membrane from blood to dialysate. Sometimes a back-filtration process may allow the passage of DNA fragments from dialysate to blood as demonstrated by Schindler et al. [17]. Bacterial DNA differs from vertebrate DNA for the presence, distribution and number of 'CG cores' which are unmethylated in bacteria [24]. This different motif allows the mammalian phagocytic cell to distinguish, recognize and be activated by bacterial DNA inducing the production of several cytokines. This means that bacterial DNA fragments are immunological active, but they need these unmethylated CG motives to activate the innate immune system to recognize invading pathogens using the 'pattern-recognition receptors'. The best characterized receptor is the Toll-like receptor (TLR) which is expressed in a variety of immune system cells. Bacterial DNA fragments bind to a specific TLR (TLR-9) and induce the production of cytokines such as IL-6. The study by Schindler et al. [17] deals with small DNA fragments in clinically used solutions and in dialysate, but they also performed PCR specific for larger fragments of bacterial DNA and were able to detect them. We were able to detect bacterial DNA in the whole blood of the patient prior to dialysis treatment, and for the same patient we were able to find the same DNA in the dialysate compartment. This means that bacterial DNA could come from dialysate, but also from the patient. In both cases the presence of the microorganism itself or its DNA activates the immune system causing the production of proinflammatory cytokines, such as IL-6 and the increase in CRP. The reduced immune system functionality measured by MFI of HLA-DR-positive cells might contribute to the development of infection. The passage of DNA from one side of the hemodialyzer to the other is not a rule and is probably dose-dependent. Actually, in the selected population 16 patients had bacterial DNA only on the dialysate compartment/spent dialysate and it can be argued that in these patients the bacterial origin is environmental (namely *Pseudomonas* spp. or *P. mendocina* or uncultured γ-proteobacterium). Actually the dialysate is one of the potential sources of infection (back-filtration process). Nine patients had bacterial DNA only in the blood compartment/whole blood but not on the dialysate side, and this is suggestive of subclinical infection. 14 patients had bacterial DNA both on the blood and dialysate side but the sequence could not be interpreted because probably more than one microorganism was present and their DNAs were mixed.

This technology, however, has a number of limitations: the higher cost of the instruments required; the need for experienced personnel, and the necessity of careful quality control to prevent laboratory contamination (false-positive results). The presence of multiple microorganisms does not allow sequencing because the dimen-

sions of the amplicon are similar for all bacteria (about 540 bp) and this makes them overlap when run on an electrophoresis gel so that no separation of different bands/microorganisms for sequencing is possible. This means that different strategies must be adopted, such as the use of specific primers for targeted microorganisms, to make a correct identification. Moreover, the exact determination of related species by sequencing of the amplification product leads to unsatisfactory ambiguity in speciation especially when partial sequences are used to match BLASTN sequences. This means that, unless we exactly determine the sequence and consequently the microorganism, we cannot say whether it comes from the patient or from the dialysate, namely the *Pseudomonas* spp. might be *P. aeruginosa* (human) or *P. mendocina* (environmental).

Conclusions

Bacterial DNA has been detected in the hemodialyzer of hemoculture-negative CKD patients using molecular methods which were found to be far more sensitive than standard methods. The correlation of bacterial DNA presence and inflammatory parameters has shown an increase in CRP, IL-6 and AOPP and a decrease in MFI DR+ cells, an index of the presence of inflammation probably induced by bacterial DNA or bacteria, and decreased immunity. Apart from the number of limitations and problems encountered, the molecular method seems to be useful as a diagnostic tool for screening subclinical infection and diagnosing sepsis when hemoculture is negative. Bacterial identification, however, must be done with species-specific primers. More investigations need to be performed to confirm these results.

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Managing Complexity at Dialysis Service Centers across Europe

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Key Words
Dialysis, quality of treatment · Database, dialysis · Monitoring system · Reimbursement

Abstract
Introduction: Dialysis is probably one of the areas of medicine with more guidelines than any other. Issues such as dialysis dose are dealt with in those guidelines, and minimum values to be reached are defined. A target has to be set and reached by using a data-driven continuous quality improvement (CQI) approach. Data collection must be programmed and structured from the beginning. ***Methods:*** Fresenius started its activities as a dialysis provider in 1996, following the merger of its dialysis business with the leading service provider in the US, National Medical Care. Currently Fresenius Medical Care's European activities involve more than 320 dialysis centers located in 15 countries and treating more than 24,000 patients. Management is based on a bi-dimensional organization where line managers can rely on international functional departments. Under this framework, the CQI techniques are applied in conjunction with benchmarking in a system driven by quality targets. In order to combine clinical governance with management targets, the Balanced ScoreCard system was selected. The Balanced ScoreCard monitors the efficiency of each dialysis center compared to an ideal model, targeting maximum possible efficiency whilst having a unique target for patient outcomes. ***Conclusion:*** A clear definition of targets is fundamental and activities need to be monitored and continuously improved; scientific collection of clinical data is the key.

Introduction

The average age of the dialytic population has increased by about 2 years in the past 3 years. This is due to the fact that, on average, new incident patients are older and the prevalent patients (those already on dialysis) are surviving to a much older age. In addition, there has been an increase in the transplantation rate which normally affects younger patients. The number of diabetic patients has also increased at the same pace, and similarly the incidence of patients with catheters has increased.

This demographic composition boosts the importance of good dialysis to ensure patient well-being and rehabilitation. These increasingly fragile patients complicate the challenge to all caregivers every single day. The importance of having a strong multidisciplinary team to face this new reality is becoming increasingly obvious.

In the vast majority of European countries taking care of all persons requiring medical assistance whilst at the same time respecting the values of human dignity is considered a primary duty of every government.

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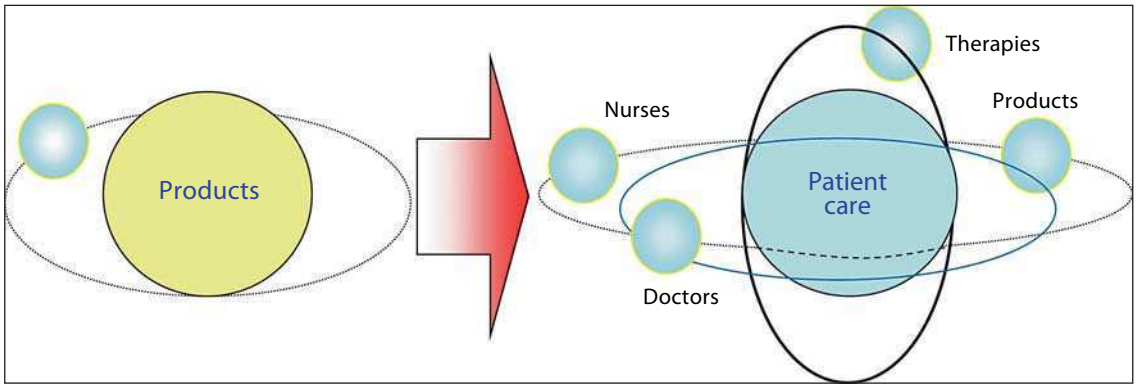

Fig. 1. The change of focus at FME. Internal presentation by Dr. E. Gatti, 1997.

Under this ethical assumption, there is absolutely no contradiction but much more reciprocal support between the strategies aiming to improve patient outcome (mortality and morbidity) and the goals of creating sustainable and continuous value for the shareholders.

This central role of the patient has driven the entire organization of Fresenius Medical Care's network of dialysis centers (fig. 1). With maximum patient outcome as the company mission whilst at the same time viewing the patients as being the company's most valuable asset, Fresenius Medical Care prides itself on applying nothing less than the best and most adequate dialytic strategy.

Hence Fresenius Medical Care's strong move towards high-flux dialysis, online hemodiafiltration, ultrapure dialysate and treatment protocols compliant with state-of-the-art guidelines as proposed by the international scientific community. Knowing that medical treatment has to be more than clinical excellence and taking the patient's quality of life into consideration during and between treatments, Fresenius Medical Care's attention is also constantly addressed to the quality of its dialysis facilities and whenever possible also to any other needs a patient may have: good access to transplantation networks, psychological and nutritional support, as well as support in sociological issues.

This definition of the social role of a company also means the recognition of obligations with respect to two other groups of stakeholders: to employees and the community as a whole.

Fresenius Medical Care embraces the challenge to maximize the benefits for all stakeholders, aware that the pattern of their interactions is very clearly one of a positive and self-reinforcing loop.

Quality Assurance and Continuous Quality Improvement, the Power of Data

Dialysis is probably one of the areas of medicine with more guidelines than any other. The first clinical guideline in the field of dialysis practice was released by the US Renal Physicians Association in 1993 [1], followed by the Dialysis Outcome Quality Initiative (DOQI) Guidelines of the National Kidney Foundation in 1998 [2–6]. Later on, several European scientific societies, such as the EDTA [7], British Renal Association [8], and the Società Italiana di Nefrologia [9], prepared their own guidelines following the American example but adapting them to European or local conditions. The availability of guidelines is only the first step in quality assurance and implementing guidelines is just one part of the whole quality assurance management system. Quality assurance can be defined [10] as 'all those planned and systematic actions necessary to provide adequate confidence that a product or service will meet performance requirements'.

Important issues such as dialysis dose (equilibrated Kt/V) are dealt with in those guidelines defining minimum values to be reached, but very often the percentage of patients that should reach that standard (e.g. 80% of patients with more than 1.20 of equilibrated Kt/V) is not included. Then, a target has to be set, and since it should be feasible to reach this target, it is usually defined in a stepwise fashion, i.e. using a continuous quality improvement approach. Accordingly, at each stage of the continuous quality improvement cycle (Plan-Do-Check-Act), projects for improvement are initiated, results evaluated and, if the final product is better than the previous cycle (i.e. increased proportion of patients reaching the goal), the new options are integrated into the standard process.

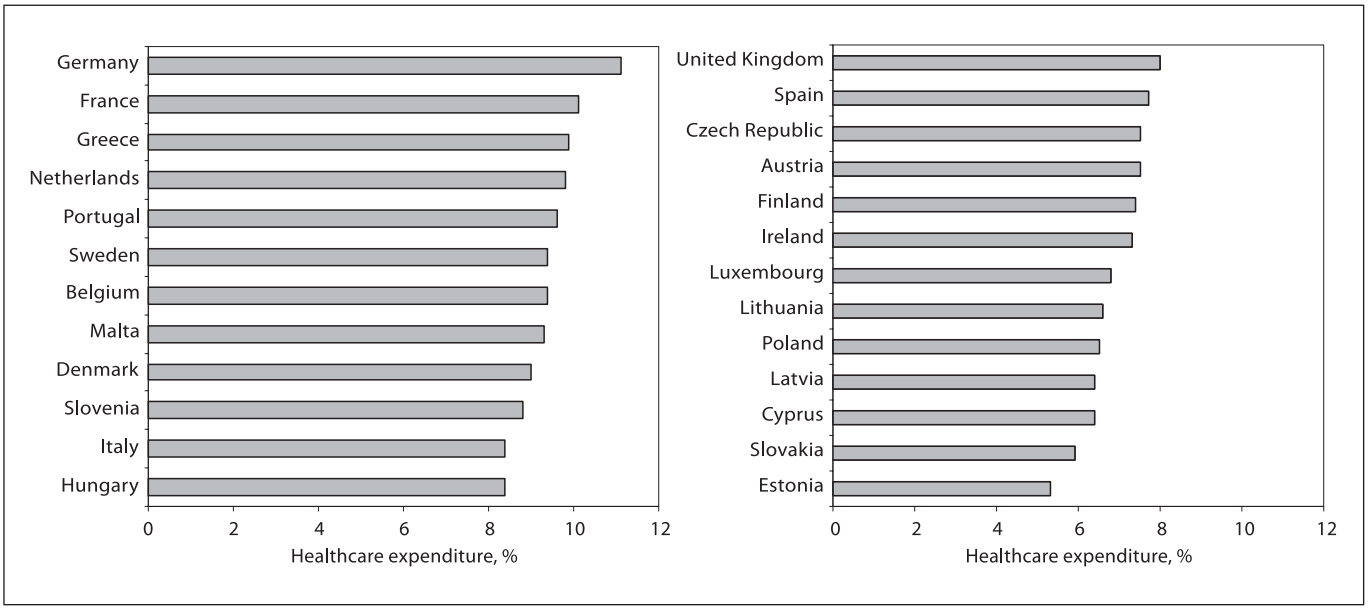

Fig. 2. Healthcare expenditure in percent of the GDP of the European Union (WHO).

From this description, it is clear that quality assurance and continuous quality improvement are data driven. Opinions and perceptions, even if from skilled physicians, have no place in this approach. Therefore, the other important component of such a system is a clinical database containing all the information required to be able to operate the system.

The fast development of sophisticated hardware and software over the past years has eliminated the potential problem of storing large amounts of clinical information, allowing dialysis providers to collect as many parameters as they find necessary. This fact bears the risk of assuming that all data are equally important and therefore, given the technological conditions, all data must be collected and monitored. If we follow this assumption, we would lose the challenge of using data to continuously provide dialysis patients with an appropriate quality of care, due to the lack of a well-defined structure for data acquisition. Thus, behind any data management system for dialysis patients, a strategy is needed: the purpose must be clearly stated; the list of variables required must be established, and the structure of the database must be as logical as possible following the normal processes adopted in the dialysis centers.

There are many different categories of data that can be collected in dialysis (all available parameters, from the dialysis machine, comorbid conditions, outcome data) but there must be a reason for the data collection. Data collection must be programmed and structured from the beginning by the dialysis service provider. Without appropriate structure and data codification no benefit will be achieved for patients (identification of problems) or service providers (system efficiency improvement), especially in such a complex environment as Europe consisting of many countries with all their differences, starting from languages to laws and regulations.

Complexity of Europe

Economics, Regulations and Framework for a Dialysis Service Provider

Geographical Europe is composed of more than 40 countries with large economic, demographic and political differences.

The gross domestic product (GDP) per capita ranges from less than USD 5,000 in some eastern European countries to more than USD 40,000 in some wealthier western European ones [11]. The population demographics of the 800 million European inhabitants is also highly diverse from country to country. Average life expectancy is about 71 years for the male and 79 years for the female population in the whole of Europe, but if we look at eastern Europe alone, life expectancy is on average more than 5 years lower [12].

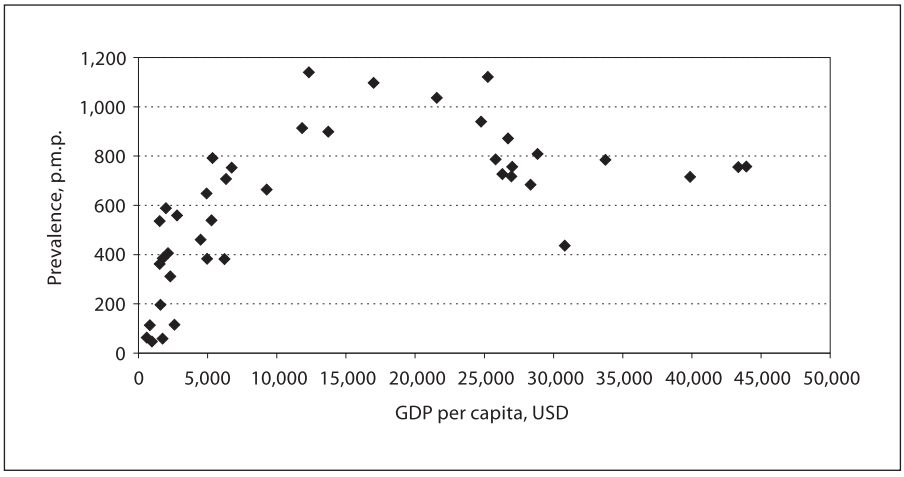

Fig. 3. Prevalence of ESRD versus economic welfare in 42 European countries.

Both population demographics and economic strength are factors that highly influence the structure and amount of funding of the countries' healthcare systems. Healthcare expenditure as a percentage of GDP among the European countries varies from less than 4% to around 12% [13]. In the European Union alone, healthcare expenditure as a percentage of GDP varies from around 5% in Estonia to more than 11% in Germany showing the considerable difference in the financial resources dedicated to healthcare within the region (fig. 2).

In the field of renal disease the comparison of the national economic strength (GDP) and the prevalence of end-stage renal disease (ESRD) patients suggests that economic factors may impose restrictions on treatments in European countries where the GDP per capita is below a limiting value (around USD 10,000) [14]. No correlation between economic strength and ESRD prevalence exists when the GDP per capita exceeds the USD 10,000 threshold (fig. 3).

Among European countries, healthcare systems are funded either through taxation (the Beveridge model) or through premium-finance, mandatory social insurance (Bismarck model) [15]. The different structures of funding have certain implications regarding the organization of the provision of healthcare services. In countries in which the system is funded by taxation the presence of private healthcare providers is in general lower than in those countries where the funding system is based on social security payments. This is somehow confirmed in the dialysis field (fig. 4).

With the exception of Portugal, in all countries where the system is funded through taxes the presence of private dialysis providers does not exceed 23% of all treated dialysis patients. In 75% of the countries analyzed above in which the system is funded though social insurance payments, the presence of private providers is between 19% (i.e. Austria) and 78% (i.e. Hungary).

The presence of private dialysis providers is steadily growing in the region. In the year 2000 the percentage of European hemodialysis (HD) patients treated by private providers was around 32%. In the year 2005 this was 39%. Of this 39%, around 37% was being treated by private chains (e.g. Fresenius Medical Care, Gambro, Baxter, B. Braun, Euromedic, Générale de Santé), and the remaining 63% was being treated in private doctor centers.

Despite the average increase in the presence of private dialysis providers in Europe, local regulations in some European countries still limit or do not permit the provision of private dialysis services at all. In countries like Belgium, Denmark, Finland and Luxembourg the dialysis provider system is only public. Private providers have no access to reimbursement for dialysis services. In other countries (e.g. Austria, Greece, Italy, Portugal, Slovenia, Sweden, the Netherlands and Turkey) private dialysis service is limited to some HD modalities while peritoneal dialysis modalities are not offered (fig. 5).

In some European countries (e.g. Spain, Italy) regional authorities can also define additional regional regulations concerning the type of therapies that private dialysis providers may offer and the level of reimbursement. In any case, dialysis services are always regulated and controlled by the healthcare authorities, and the strict regulations on the opening and functioning of a dialysis facility are not homogeneous between the various European countries.

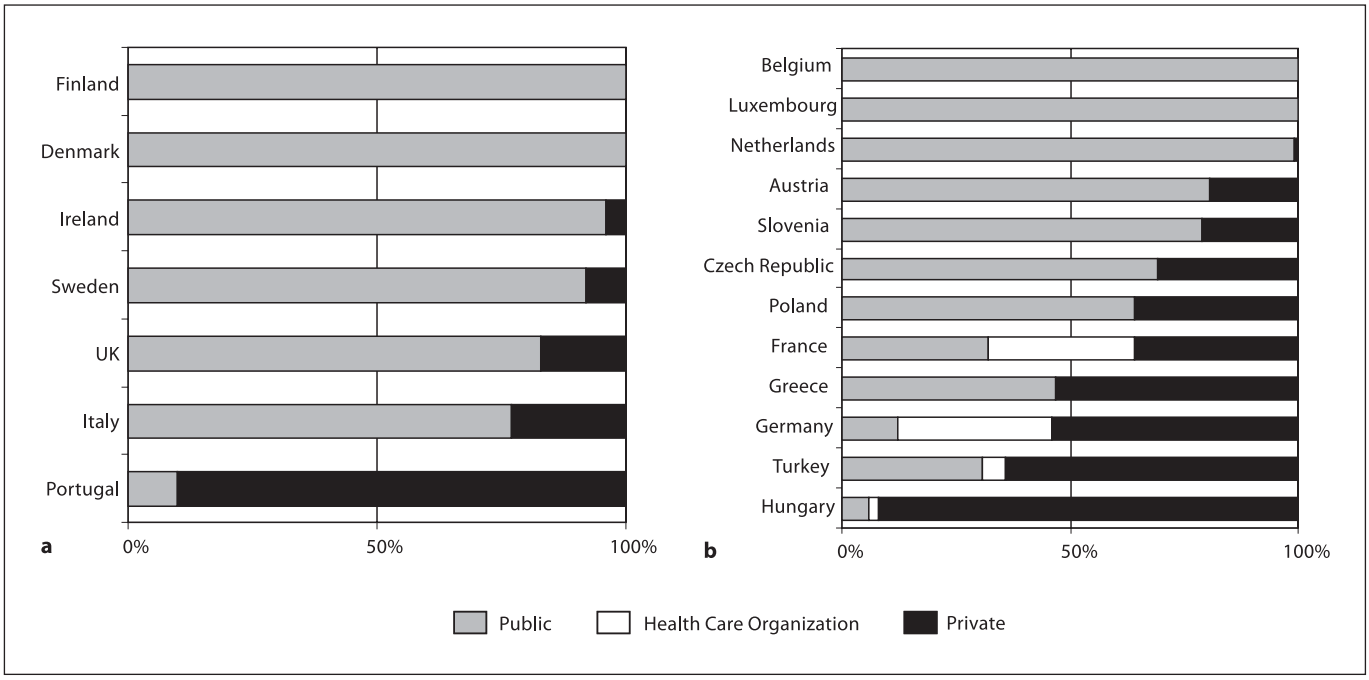

Fig. 4. Relation between type of funding and dialysis providers' ownership. Providers presence is measured as the number of patients treated (year 2005). **a** National taxes (Beveridge system). Reimbursement structure is based mainly on global budgets and fee-for-service. The provider structure is mainly public. **b** Social Security payments (Bismarck system). Reimbursement structure is based mainly on fee-for-service and a flat rate. Private providers play a significant role.

In Spain and the UK private providers can only operate thanks to multi-year contracts assigned via tender by public hospitals or healthcare authorities which 'outsource' the complete dialysis service. In many other countries collaborations or agreements with public hospitals are necessary to maintain the clinical continuity, thereby ensuring the high level of quality a stand-alone unit cannot, in some cases, ensure.

Reimbursement Variability: Different Structures in Line with Risk Allocation

The reimbursement system can be defined as the system that establishes who has the right to receive reimbursement for dialysis services (eligibility), how this reimbursement has to be given (reimbursement modality) and the amount of the reimbursement in monetary terms (reimbursement rate). It was explained previously that different regulations exist within Europe concerning who is eligible for dialysis reimbursement, and that access to reimbursement for private dialysis providers is still limited or not permitted at all in many countries.

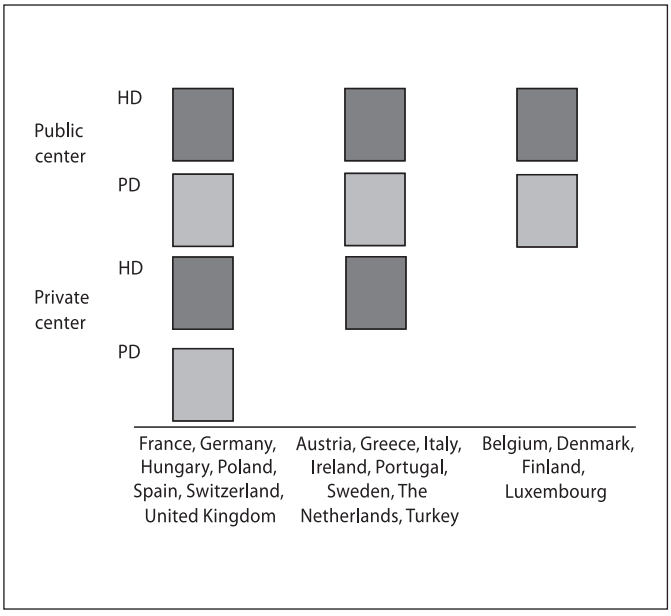

Fig. 5. Access to dialysis reimbursement for private and public providers in selected European countries. In many countries, private providers still have limited or no access to reimbursement.

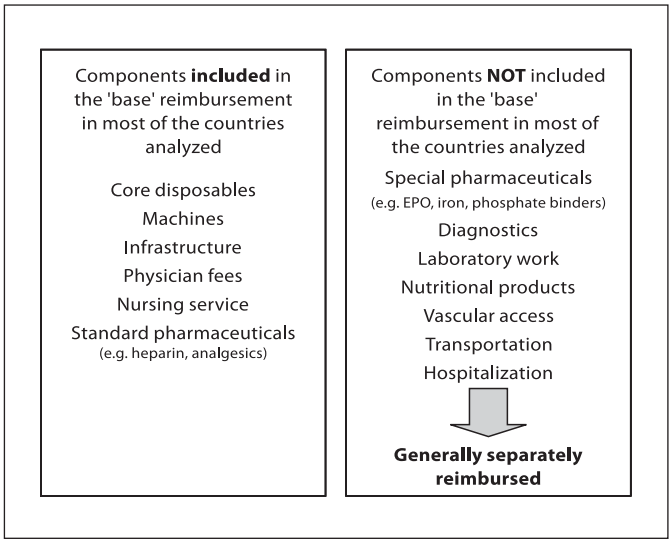

Fig. 6. Product and service cost factors generally included or excluded from the reimbursement rate in selected European countries. Countries analyzed: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Portugal, Spain, Slovenia, Sweden, and Turkey.

Looking at the dialysis reimbursement modalities, again the picture is not homogeneous among European countries [16]. There are three main types of reimbursement modalities in Europe [16]: budget transfer, 'fee for service' and flat rate. In some cases, the reimbursement modality varies within the same country depending on the type of provider (public or private).

Budget transfer is a reimbursement modality used mainly for public providers in most of the countries where the funding is based on taxation and in some of the countries where it is based on social security (e.g. Spain, Czech Republic).

'Fee for service' is the most common reimbursement modality for private providers in all countries (an exception is, for example, Hungary where reimbursement to private providers is based on budget) and for the public providers in countries where the funding system is based on social security payments.

Germany is particular in that it is the only country in Europe in which the reimbursement modality is a flat weekly rate independent of both the type of provider and the type of dialysis therapy provided.

The larger variety of situations comes when analyzing the reimbursement rates in the different European countries. The rates may vary as a function of various factors: (1) the number and types of products and services included; (2) the type of dialysis modality, e.g., HD, ambulatory peritoneal dialysis, continuous ambulatory peritoneal dialysis, hemodiafiltration (HDF), hemofiltration, online HDF; (3) the kind of provider, i.e. public, private, nonprofit organization, and (4) the place of the treatment, e.g. a dialysis center, a limited care center, at home. Even within the same country there are often several reimbursement rates, each of them corresponding to different combinations of these factors.

Any comparison of rates between different countries is very complex and the combination of the factors to which the rate refers is almost never the same because the cost elements covered by the reimbursement rates are considerably different and regulated in different ways from country to country (labor costs, utilities, infrastructure and drug prices).

Reimbursement rates for standard HD treatments in private clinics can vary by more than 100% within Europe. A lot of this variability can of course be explained by country-specific regulations and cost factors (e.g. labor, utilities), but a lot also comes from the number and type of products and services included in the rate. As an example, in some countries (e.g., Poland, Romania and Slovenia), erythropoietin, which can represent a significant part of the cost of the treatment, is included in the reimbursement rate for private providers, while in other countries it is reimbursed separately. The same can apply, for example, to patient transportation or to physician's fees. Figure 6 shows which product and service elements are generally included in the reimbursement rate and which are generally reimbursed separately in a selected group of European countries.

The general structure of the reimbursement and the combination of the factors that determine the reimbursement rate determine the way the dialysis provider operates in different countries, thereby determining a variety of business models involving various levels of risk. For example erythropoietin, its inclusion in dialysis reimbursement is a clear allocation of the financial risk of anemia management to the dialysis service provider. The higher the number of products and services included in the reimbursement the higher the number and level of economical risks that the provider has to undertake (fig. 7).

Dialysis Centers: Categories Responding to Patients' or Payers' Needs?

Dialysis patients can be treated in three main types of locations: the dialysis center offering full medical and

nursing assistance (either in a hospital setting or in dialysis clinics); the limited care center offering limited medical and/or nursing assistance, and the home environment (main location of treatment for peritoneal dialysis patients).

In 2005, of the 340,000 European dialysis patients about 36,000 were treated at home (94% of them with peritoneal dialysis therapies and 6% with home HD therapy), around 17,000 were treated in limited care centers (of this figure more than 15,000 are in France and Italy), and the remaining 288,000 were treated in dialysis centers with full assistance.

The offer of HD service locations is, once again, not homogeneous in Europe. Country regulations sometimes limit the offer to centers with full medical and nursing assistance (e.g. Czech Republic, Greece, Slovenia, Turkey). In Spain home HD is allowed but limited care centers are not permitted as the full time presence of a nephrologist is required by law. In 2005, eight European countries were treating patients in limited care centers while home HD was practiced in almost 20 countries.

France is the European country in which the largest variety of treatment locations is possible. Patients can be treated in five different types of location: the dialysis center, the 'unités de dialyse médicalisée', the 'unités d'autodialyse assistée', the 'unités d'autodialyse simple', and the patient's home. The dialysis centers are normally placed in hospital structures and must have the possibility to supply hospitalization services. In dialysis centers full medical and nursing assistance is assured. The 'unités de dialyse médicalisée' must work under the supervision of a team of nephrologists but the presence of a nephrologist during the dialysis session is not compulsory. The 'unités d'autodialyse simple or assistée' only assure the presence of nursing personnel during the dialysis session and are operated with special low patient/machine ratios.

Different Environments, One Commitment: The Best Dialysis according to the Resources Available

Within Europe dialysis is unanimously recognized as a life-saving treatment for patients suffering from ESRD. In the European Union access to therapy is in most cases assured for patients requiring it and, in general, the costs of dialysis therapy are fully covered by country healthcare systems with no or extremely low patient participation in payments.

Despite the variety of reimbursement systems, regulations and organization of service provisions between the different countries, a high and uniform level of quality

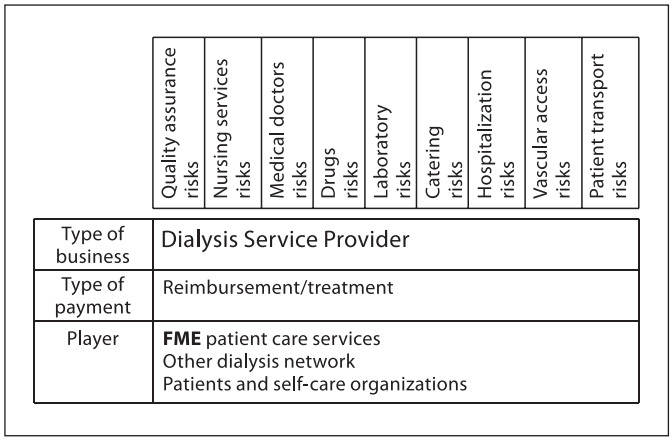

Fig. 7. Business-related risks for dialysis providers.

care must be assured and delivered by a dialysis provider operating across all these different economic, political and legal environments [15, 17].

Respecting international outcome guidelines, the strict monitoring of the activities in all countries to assure compliance with these guidelines, and the provision of as comparable as possible treatments for all patients are simultaneously the aim and the challenge of any dialysis service provider operating in Europe.

Characteristics of Fresenius Medical Care's European Network

Countries, Patients and Centers of Fresenius Medical Care's European Network

Fresenius started its activities as a dialysis provider at the end of 1996 following the merger of its dialysis business with the leading service provider in the US, the National Medical Care (Boston, Mass., USA). The creation of Fresenius Medical Care in Europe (FME) started from the original group of National Medical Care clinics in Portugal and Spain, and then FME decided to develop a European network in order to become a global player. Through strategic acquisitions, the construction of de novo clinics, privatizations and participation in public tenders, FME was able to build a network currently (end of August 2006) involving more than 320 clinics located in 15 countries and treating more than 24,000 patients, which corresponds to 9–10% of all HD patients in those countries (fig. 8).

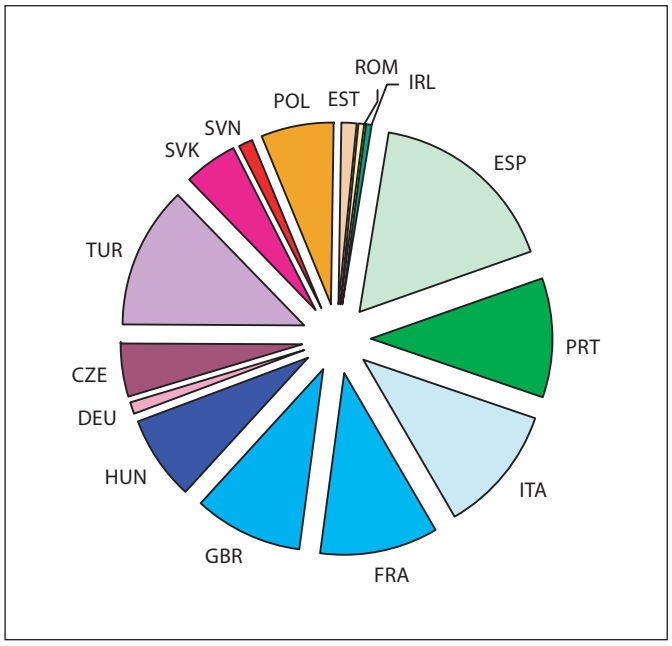

Fig. 8. Distribution of FME centers across Europe.

Support Organization and Central Departments

The management of the network is realized thanks to a bidimensional organization in which line managers can rely on some international functional departments. From the clinical point of view, the department Clinical Management Europe (CME) is responsible for the coordination of specific activities in the whole European region. CME has several responsibilities, from clinical governance to technical coordination as well as the allocation of training resources. It works with local reference people, including a Country Medical Director and persons responsible for nursing and data quality in each country organization. CME provides the consolidation and assessment of the clinical data collected and channels clinical studies and publications.

Other functions directly involved in the provision of dialysis services are: (1) Innovation and Technology Dialysis Care which supports and coordinates the construction of new facilities and the implementation of new technical solutions, whilst experiences derived from millions of treatments per year are analyzed and channeled to Research and Development; (2) Water Technology and Fluid Management Department; (3) Quality, Environmental and Regulatory Management which is responsible for the implementation of the Integrated Management System (IMS, see below), and (4) Nursing Care Management for the improvement of dialysis practices and procedures.

It has to be stressed that FME only expands its dialysis network in those countries where a subsidiary is already present to ensure a minimum standard of organization already exists.

Clinical and Organizational Monitoring

IMS: Working with Guidelines (EBPG) and SOPs

Orientation towards quality and continual improvement is a fundamental principle within Fresenius Medical Care and a key element of management policy for all business sectors. Within the Patient Care Business Unit, FME aims to set and achieve higher standards of dialysis care supported by both internal, corporate requirements as well as external standards. FME's overall approach to quality assurance is based on the principles of continuous quality improvement (CQI) as presented in the 1990 Institute of Medicine report 'Medicare: a strategy for quality assurance' [17]. CQI is a theory; it is not a structure for an effective dialysis quality assurance program. In order to manage the practical implementation of these varying requirements the concept of an IMS was selected.

With such a system it is possible to manage major internal process-related requirements, e.g. reporting in the clinical database, and simultaneously to fulfill the requirements of ISO standards and legal obligations. Two standards in particular are in focus, ISO 9001:2000 for the Quality Management System and ISO 14001:2004 for the Environmental Management System. In addition risk management is an essential part of the IMS.

Under this framework, the CQI techniques are applied in conjunction with (mainly) internal and (where possible) external benchmarking in a system driven by quality targets. Benchmarking is obviously data driven and therefore, in the late 1990s a project was initiated to create a clinical database aimed to support quality assurance in FME dialysis centers located in Europe.

Benchmarking and Monitoring Systems, the Role of EuCliD® 5, the Complete Therapy Information System

The description of the first version of the database, named EuCliD® (European Clinical Database), has already been published [18]. Right from the outset EuCliD® was structured to follow a logical information flow. During the last years the software has been updated and a new project based on an enlarged scope has been initiated. The new project was aimed not only to support quality assurance, but also to facilitate the day-to-day work of the

clinical staff. Additionally, a major focus on patient safety aspects was included in the design input document.

The result, EuCliD® 5, is a multilingual and fully codified software using, as far as possible, international standard coding tables (ICD10 [19], ISCED [20], ISCO-88 [21] etc.). EuCliD® 5 collects and handles sensitive medical patient data, and ensures the confidentiality of these data [22]. EuCliD® 5 has been approved by the respective national or regional authorities prior to data entry and the initiation of data transfer. Of course, the transfer of private patient data out of the dialysis center is not permitted.

In summary the system collects and works on the following data.

Patients: (a) admission (main demographics, anamnesis, comorbids, laboratory tests, treatment prescription, etc.); (b) complete clinical follow-up including dialysis treatment (each session is recorded with all vital parameters collected with a direct interface from the dialysis machine); (c) pharmacological therapy, specialists' examinations, blood transfusions, carpal tunnel syndrome surgery, parathyroidectomy, etc.; (d) laboratory tests with automatic calculation of some variables (including dialysis dose); (e) movements (holidays, transfers to other units); (f) key indicators of clinical outcome (morbidity with cause of hospitalization, mortality and cause of mortality), and (g) other specific local needs (pharmacovigilance).

Dialysis unit: Personnel, facility installations (stations, water treatment, dialysis machines), resource planning (installations, purchasing, patient sessions).

From the technical point of view, EuCliD® 5 is a web application which can be easily run with a browser without the need of any ad hoc installation on the local client. EuCliD® 5 relies on the Microsoft.NET framework, in particular the programming language used is C#, the database engine is Microsoft SQL Server 2000 and the reporting engine is Microsoft Reporting Services. To facilitate data collection related to the individual dialysis session a 'smart client' has been developed to work on a pocket PC which is WIFI-connected to the network. EuCliD® 5 has been interfaced with a Dialysis Management system, allowing the automatic import of data generated by the dialysis machine itself. In addition, different software interfaces for importing laboratoy data have been developed.

Microsoft.NET framework allows only restricted access to information stored in the database. Sensitive information is encrypted at database level using the Advanced Encryption Standard (AES) which is an encryption standard of the US government. The Secure Socket Layer is used as a transmission protocol which due to its cryptographic characteristics is able to provide secure communications.

All sensitive patient information is stored in a database encrypted according to the AES standard.

Every night, all non-sensitive information is consolidated on a central database, permitting analysis of updated information on the following working day.

Coming back to the CQI process, the targets should only be defined once the database is working and collecting high quality data, and a monitoring/reporting system based on clinical indicators derived from evidence-based clinical guidelines is in place. This allows the completion of the components in order to activate clinical governance. The discussion of the clinical targets is realized by a specific council, including the country medical directors. These targets consider quality and safety aspects. Under the quality domain, patient satisfaction [23], markers of quality of treatment, and markers related to outcome and also treatment options are included.

According to European Best Practice Guidelines [24], high-flux HD and convective treatments are considered the top therapeutic options for the treatment of ESRD patients, but the increasingly high costs of these treatment options remain the main limitation, and only by redesigning the process by which care is delivered will it be possible to improve the quality of care and finally even reduce overall healthcare expenditure. This is the main reason justifying the introduction of the Balanced ScoreCard (below). It is the only integrated approach which simultaneously considers all the different domains related to dialysis practice.

The Balanced ScoreCard: Following the Mission of Patient Care from Different Perspectives

In order to combine clinical governance with management targets, it is necessary to select a methodology which allows clear definition of goals and gives clear messages to all associates and stakeholders.

Every country has its own specific legal requirements regarding dialysis. Fresenius Medical Care therefore decided to adapt the Balanced ScoreCard [25] methodology, which reconciles and tracks the strategic direction of the organization at any level (enterprise-wide, country-wide, single unit, etc.) using interconnected perspectives, objectives and key performance indicators (KPIs).

Therefore, the ScoreCard system was selected to monitor the efficiency of each dialysis center compared to an

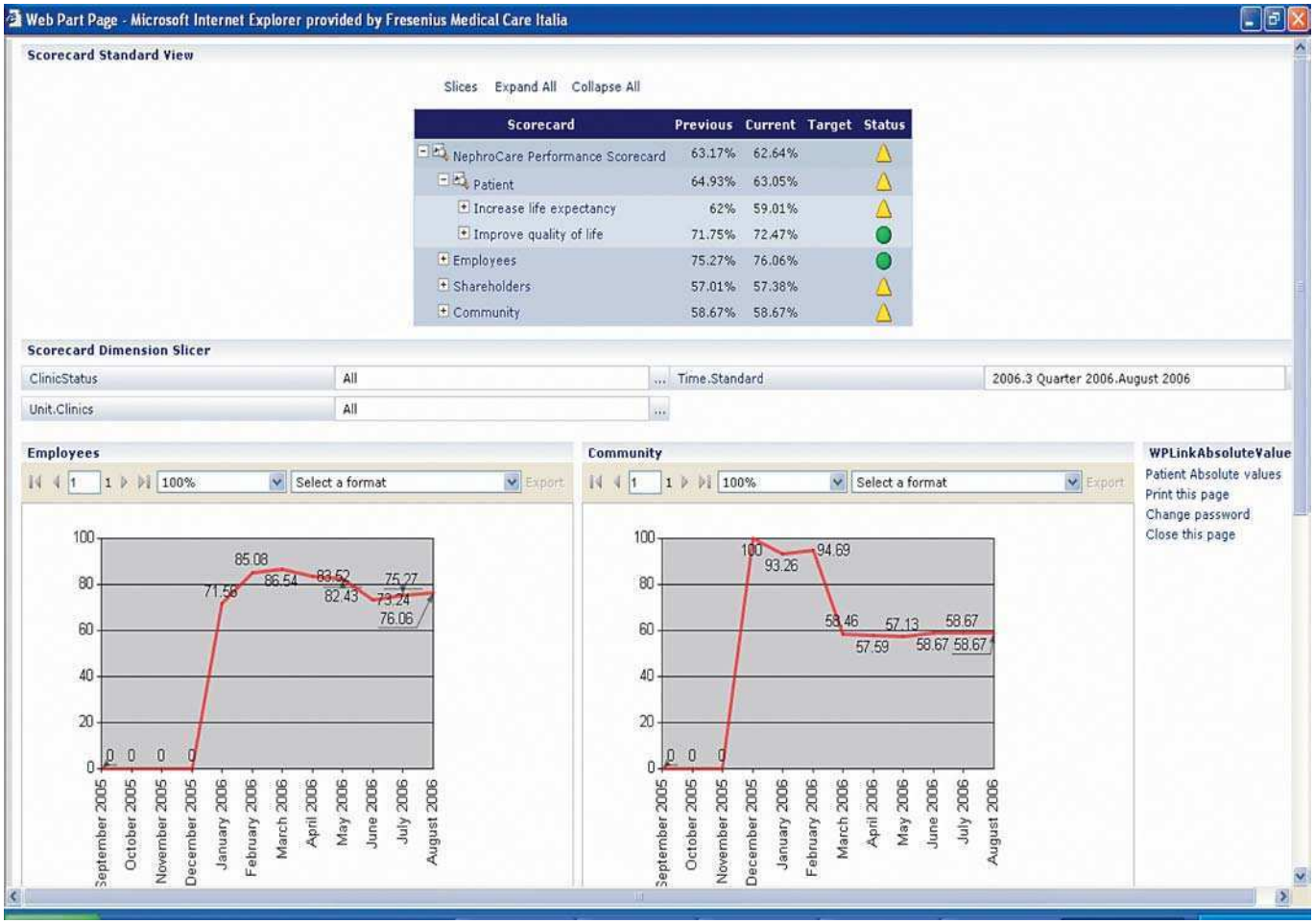

Fig. 9. NephroCare ScoreCard: simulation of two perspectives in a newly integrated clinic.

ideal model, based on local requirements and targeting maximum possible efficiency whilst having a unique target for patient outcomes as described in the European Best Practice Guidelines.

The ScoreCard is also used to align the different country organizations around the same quality indicators. These indicators require the allocation of a responsible person, the creation of a project, a follow-up system, and a reward in case of success (fig. 9).

The structure of the ScoreCard, with its perspectives, objectives and key performance indicators is based on the Quality Policy of Fresenius Medical Care. It acknowledges the company's responsibilities for its patients, employees, shareholders and communities (the 4 perspectives) and to justify these responsibilities it expresses Fresenius Medical Care's commitment to specific quality objectives.

The patient perspective is the most important part of the ScoreCard and therefore has the highest weight. The two objectives within this perspective are to increase life expectancy and to improve the quality of life of patients treated within FME's network of dialysis centers. The selected KPIs focus on good clinical outcomes as well as on patient safety and satisfaction and their targets are based on the European Best Practice Guidelines and the consensus of FME's Country Medical Representative Committee.

The objectives of the employees perspective and the shareholders perspective are to maintain qualified personnel and promote their professional development on the one hand, and to promote the continuous development of the company, thus obtaining attractive returns for the shareholders on the other hand. Therefore the selected KPIs focus on functioning personnel management

and on well-established management processes and financial controls.

The community perspective has as objectives the justification of FME's various social responsibilities, compliance with all legal requirements and safety standards and FME's contribution to the preservation of the environment. The focus of the selected KPIs is quite wide, ranging from minimizing accidents to employees, to the upholding of ISO certifications and the establishment of processes to save water, electricity and waste.

Managing Complexity

The Importance of Best Practice Transfer across the Borders: Setting Core Elements and Driving Local Adaptations

As pointed out, while different country settings impose different combinations of services and require adaptation to local practices, international clinical outcome guidelines determine the same level of quality care to be delivered. The challenge today is to give the right answer to satisfy the expectations of payers and to achieve the same level of good dialysis outcome that all patients deserve.

In order to successfully manage the different country environments, and in response to the same quality expectations, FME has leveraged the differences, transforming them into strengths which form the backbone for the management of the network [26].

This integrated approach and its development, together with a common set of tools (first and foremost EuCliD® 5 and the ScoreCard) have been rolled out under the umbrella of the NephroCare® Excellence (NCXL) framework. NCXL is a step further towards higher harmonization and quality standards. It defines a structured platform of services for a first-class service provider network.

This standardization, and the way it is built and communicated, is not meant to make the world flat, on the contrary it drives resources on the important issue: managing specific and variable aspects of treating an individual dialysis patient. The NCXL framework system provides solutions to standard problems, so the organization can promptly react to deviations and, as applicable, can redefine the platform.

Variability as the Strength of the Network

In order to transform variability into strength and long-term value creation any organization should align resources to common targets, eliminate possible conflicts between functions or business units, focus on specific (variable) problem areas and, finally, create transparent behavior.

Fresenius Medical Care has followed this strategy, working in the following three steps.

The first step is to define and share 'core' values and technologies on a 'meta-national' basis. Consensus on the 'core' elements was the result of a long process involving FME as a manufacturer of dialysis products, with good relations to the medical community and research centers. The same entrepreneurial spirit [27] was then transmitted to FME's approach to managing its dialysis center network and this together with the experience inherent in the newly acquired clinic network shaped the 'core' elements.

In Europe, where no existing network was acquired, the central functions (in particular quality assurance and clinical management) started to reshape the knowledge of single dialysis centers as they joined the organization. Immediately projects and developments of a common management system were born trans-nationally, and Fresenius Medical Care's strategy of knowledge sharing and cooperation was a real asset that fuelled the creation of the various elements of the IMS.

In adopting the NXCL tools the development of those systems required a knowledge collection from around the globe, an engineering effort and strong management support both centrally and locally. Thus it was the network of dialysis centers itself which created, developed and reworked the 'core' values and tools which, through interaction with the central functions, were automatically accepted, implemented and improved at local level.

The second step was to mobilize the dispersed knowledge and to create a knowledge-based environment among associates both at center level and throughout the Fresenius Medical Care Network, whilst fully integrated with the external care environment.

A clear example of this is the new EuCliD® 5: developed in Italy, personalized and improved in Portugal, imported in Romania, re-adapted in France. The programming is not based on the prerequisites of one country alone. The legal requirements are specific to each local situation, but the background platform, the workflow safety and the query system are the same.

Clinical governance and managerial entrepreneurship (supported by EuCliD® 5 and the ScoreCard, respectively) have in this way created a common framework and playground: this standardization of language and knowledge has made the focus on patient outcome targets much clearer, for managers and physicians alike.

The last step is to become operational and get started on the local adaptation. This phase is supported by local players who assume responsibility and set specific and relevant targets.

Normally three barriers, deeply rooted in organizational design, structures and corporate beliefs, make it difficult to break free of geography even when a company recognizes the threats of global dispersion of knowledge [28]: (1) the primacy of the home base, while dispersed knowledge needs dispersed 'sensors'; (2) the idea of 'weight equals voice', while nice ideas from small units must be heard, and (3) the assumption that local adaptation is important only locally, while it is in fact an opportunity for learning.

NCXL is about getting operational again at the local level and about bringing the core elements and tools to the local reality. It has to be done everywhere and in a consistent way. The three barriers have not been encountered so far within the culture of FME.

Where Are the Differences between the Different Solution Approaches of Dialysis Networks?

In Europe there are some important national champions, like the German 'Kuratorium für Dialyse und Nierentransplantation e.V.(KfH)' and the French 'Générale de Santé' or the newly established Euromedic, but alongside FME there are only two other private vertically integrated networks, with transnational operations: Gambro Healthcare and B. Braun's Avitum.

Almost all of these organizations have established CQI programs, certified ISO processes, and medical guidelines integrated in their management systems.

While the ingredients of FME's management system correspond to those of the other organizations, and while the patient population and external obligations are the same for all, FME has a very distinctive approach, and the results achieved come from a few very important differences.

(1) A strong commitment towards the patient, anticipating the rules or reimbursement systems in the implementation of the newest technologies and therapies. This happened, for example, in Portugal in the late 1990s when FME decided to stop reuse without being awarded with additional resources. It happened again with the almost generalized adoption of high-flux dialyzers and it is happening today with the commitment to switch to online HDF for all patients.

(2) The unique possibility, for physicians with EuCliD® 5, to immediately intervene and guide the prescription, thanks to having real online clinical data.

(3) The scientific contribution of the FME network to the evaluation and improvement of therapies and the production of dialysis devices. The combined force of the FME network of nephrologists and EuCliD® 5 producing peer-reviewed and prize-awarded publications.

(4) Finally, the multidisciplinary team approach to care is the only one able to cope with the multifaceted needs of a HD patient.

Conclusions

Quite often difficult undertakings require simple solution approaches. A clear definition of targets is fundamental: the patient deserves the best possible dialysis treatment to optimize outcome and quality of life. Winning models need to be monitored and continuously improved; scientific collection of clinical data is the key.

The second step is the consistent multiplication of common elements to dedicate maximum resources to the target achievement and to the challenges coming from the variety and differences of the environment.

Medical and nursing care have to be wholly dedicated to patients in a genuine team approach that reinforces the learning process of all people involved and of the same system. From this viewpoint variety and complexity are strengths.

The consequences of the recognition of obligations with respect to shareholders and community are finally an efficient allocation of resources that will positively affect, in a self-reinforcing loop, the possibility to improve the treatment of patients, respecting the dignity and the personal development of all human beings involved.

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Treatment Time and Ultrafiltration Rate Are More Important in Dialysis Prescription than Small Molecule Clearance

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Key Words

Dialysis duration · Ultrafiltration · Sodium profiling · Hypotension, intradialytic · Hypertension · Kt/V_{urea} · Lag phenomenon

Abstract

Chronic hemodialysis sessions, as developed in Seattle in the 1960s, were long procedures with minimal intra- and interdialytic symptoms. Over the next three decades, dialysis duration was shorten to 4, 3, even 2 h in thrice weekly schedules. This method spread rapidly, particularly in the United States, after the National Cooperative Dialysis Study suggested that the time of dialysis is of minor importance as long as urea clearance multiplied by dialysis time and scaled to total body water (Kt/V_{urea}) equals 0.95–1.0. This number was later increased to 1.3, but the assumption that hemodialysis time is of minimal importance remained unchanged. However, Kt/V_{urea} measures only the removal of low molecular weight substances and does not consider the removal of larger molecules. Nor does it correlate with the other important function of hemodialysis, namely ultrafiltration. Rapid ultrafiltration is associated with cramps, nausea, vomiting, headache, fatigue, hypotensive episodes during dialysis, and hangover after dialysis; patients remain fluid overloaded with subsequent poor blood pressure control leading to left ventricular hypertrophy, diastolic dysfunction, and high cardiovascular mortality. Kt/V_{urea} should be abandoned as a measure of dialysis quality. The formula suggests that it is possible to decrease t as long as K is proportionately increased, but this is not true. Time of dialysis should be adjusted in such a way that patients would not suffer from symptoms related to rapid ultrafiltration, would not have other uremic symptoms and most patients would have blood pressure controlled without antihypertensive drugs.

The evolution of hemodialysis duration and various measures of dialysis adequacy has recently been reviewed [1–3]. This article will provide a synopsis of these reviews, updated with recent Dialysis Outcomes and Practice Patterns Study (DOPPS) data, strengthening the notion that longer hemodialysis duration and slower ultrafiltration is associated with reduced mortality and better treatment tolerance of hemodialysis patients [4]. A short discussion of volume-dependent hypertension and the 'lag phenomenon' will be also included.

Evolution of Dialysis Duration

In the early 1960s chronic hemodialyses were long procedures, usually 20–40 h/week on standard Kiil dialyzers in-center [5] or 8–10 h three times weekly at home [6]. The first trials of shorter dialysis duration were at-

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tempted in the late 1960s. Schupak and Merrill [7] indicated that shorter dialysis sessions (total duration of 12–16 h/week with the use of coil dialyzers) achieved biochemical control similar to that achieved on Kiil dialyzers with longer dialysis durations.

The tendency to shorten dialysis duration continued in the 1970s. The major incentive was the need of more intensive utilization of dialysis centers because the number of candidates for chronic dialysis markedly exceeded the availability of treatment facilities [8, 9]. In the late 1970s, an increasing number of centers in Europe and in the US followed this trend. Short dialysis had a tremendous appeal to the patients once they were told that the results were not worse than those with long dialysis.

Justification for Short Dialysis

Three factors were necessary for the widespread acceptance of short dialysis: economic incentives, technical feasibility, and medical/scientific justification [10]. Economic incentives were demonstrated by early proponents of short dialysis. In the meantime, very efficient dialyzers had been designed and their values demonstrated in short-term studies [11, 12]. Nevertheless, short-term studies would not be sufficient for the widespread use of short dialysis. Some scientific support and a mathematical formula were needed to define an adequate dose of dialysis and justify short treatment duration.

Square Meter-Hour Hypothesis and Dialysis Index

The first such formula was developed in the early 1970s. Uremic peripheral neuropathy was a common complication of hemodialysis and very resistant to treatment. This complication was not dependent on urea and creatinine concentrations, but was rare with 24–27 h weekly hemodialysis on standard Kiil dialyzers and in patients on peritoneal dialysis. Based on these observations, Babb et al. [13] first proposed the idea that toxins responsible for neuropathy might be in the molecular weight range of 2,000–5,000 Daltons. They originated the term 'middle molecules' (MMs) and calculated that their clearance is the product of the overall mass transfer coefficient and the membrane area. This hypothesis led to the 'square meter-hour hypothesis', which implied that by doubling the surface area of a hemodialyzer the time of dialysis could be halved for equivalent MM removal [13–15]. This was an important step in the justification of high efficiency, short time dialysis. Ultimately 'a dialysis index', the first quantitative description of adequacy of dialysis, was developed [15]. The formula takes into consideration residual renal function, which was omitted in formulas developed later.

Urea Kinetics

In the late 1970s and early 1980s, short dialysis received support from a new measure of dialysis adequacy based on urea kinetics. Gotch and Sargent [16] recommended that the minimum dose of dialysis (dialyzer urea clearance, treatment time and frequency) should be sufficient to result in mean predialysis blood urea nitrogen (BUN) values of 80 mg/dl in patients with documented protein intakes of at least 1.0 g/kg/day. It is worth noting that, unlike the MM clearance, the urea clearance is significantly influenced by blood and dialysate flow rates, because urea molecules diffuse rapidly through the membrane and from red blood cells to the plasma. Therefore, to maintain a high concentration gradient of urea between blood and dialysate, high blood and dialysis solution flow rates are required. The National Institutes of Health (NIH) sponsored the National Cooperative Dialysis Study (NCDS) to establish the objective, quantitative criteria for the adequate dose of dialysis [17]. Urea kinetics coupled with the monitoring of nutrition was chosen as the criterion of dialysis dose [18]. It was accepted that the single measure of dialysis dose should be Kt/V_{urea}: the amount of urea clearance (K) multiplied by time (t) and divided by urea distribution volume (V). Morbidity was used to judge the quality of dialysis. Patients with high BUNs and short hemodialysis durations were hospitalized more often compared to the group with high BUN but longer dialysis; however, this was statistically insignificant and in the final recommendations, the length of dialysis was considered as only marginally important [19]. It is amazing that the length of dialysis was rejected as an important factor on the basis that p was <0.06 instead of the sacrosanct 0.05. It was forgotten that absence of evidence is not evidence of absence. However, it was recommended that 'short dialysis should be prescribed with caution in patients who are likely to suffer cardiovascular complications' [20]. In later analysis of the NCDS, Gotch and Sargent [21] concluded that 'normalized protein catabolic rate over 1.0 g/kg/day and Kt/V_{urea} over 1.0 per treatment in hemodialysis is of no apparent clinical value with the cellulosic dialyzers in thrice-weekly treatment schedule'.

The results of this study spurred other studies to demonstrate that dialysis time could be halved by doubling blood flow and dialyzer surface area [22, 23]. Although clearances of small molecular substances did not differ

significantly, the tolerance of dialysis was worse and hypotensive episodes were more frequent with shorter dialysis sessions particularly in patients without residual urine output [24]. It is worth mentioning that early studies indicating benefits of short dialysis were carried out in patients starting chronic hemodialysis and *eo ipso* with substantial residual urine output. In the NCDS study, residual renal function was not taken into account, but most patients were of short dialysis vintage, so it is likely that their residual renal function was significant.

Problems with Short Dialysis (Small t)

Early Reports

In the first paper on shorter dialysis duration, Schupak and Merrill [7] reported a markedly higher rate of hypertension problems than in the early reports with longer dialysis [5, 6]. The French Dialysis Registry reported a gradual decrease in hemodialysis duration during the 1970s and a higher rate of hypotensive episodes [25]. In 1983, the European Dialysis and Transplant Association reported 'the proportion of deaths in the Federal Republic of Germany was twice as high in short dialysis' [26].

An early warning that a short duration of dialysis was associated with multiple problems related to water and sodium retention came in the report by Sellars et al. [27]. Exchangeable sodium was significantly increased with short dialysis, and more patients required antihypertensive drugs. Another warning came from Germany in the report by Wizemann and Kramer [28] in 1987. They did not observe any significant differences in serum biochemistry between short (2.5 h) and long dialysis (4 h), except for serum phosphate, which was lower during longer dialysis. However, weight gains were higher, blood pressure control was worse, and hypotensive episodes were markedly more frequent with shorter dialysis [28].

High Mortality

In the US, the relative mortality risk was about 20% higher in patients receiving a dialysis duration of <3.5 h compared to those with treatment for >3.5 h [29, 30]. The annual mortality in US patients has increased from 10 to 25% over the last three decades, but has remained stable at around 10% in Japan [31]. During the period 1982–1987, hemodialysis mortality in the US was found to be 22% higher than in Europe and 40% higher than in Japan [32] and the duration of dialysis was 23.5% shorter in the USA than in Europe and 40% shorter than in Japan [33]. The experience in Tassin, France, clearly indicates that longer dialysis (8 h thrice weekly) than is usual in the US improves patient survival [34]. When comparing the survival of US patients to those dialyzed in Tassin, it is in the older age group that the difference is particularly pronounced. While the risk of death is two times higher in the US in the patients younger than 45 years, it is 12 times higher in patients older than 65 years [34, 35]. This finding is thus similar to the Japan-US comparison, where the relative risk of death in the US also markedly increases with the age of the patients [32].

The results from the Japanese dialysis registry [36, 37] showed that shorter dialysis increases death rates. In Europe, Valderrábano [38] reported a lower gross mortality rate in patients who were dialyzed for more than 12 h/week as compared to those dialyzed for ≤12 h/week; the difference in mortality was particularly considerable in patients over 65 years old.

A recent DOPPS [4] showed reduced mortality with longer treatment time. Statistical adjustments were made for patient demographics, comorbidities, dose of dialysis (Kt/V), and body size. Every 30 min longer on hemodialysis was associated with a 7% reduced relative risk of mortality. The association was present in USA, Europe, and Japan, but was most pronounced in Japan. A synergistic interaction occurred between Kt/V and treatment time ($p = 0.007$) toward a mortality reduction. An ultrafiltration rate of >10 ml/h/kg was associated with 9% increased mortality risk.

Intradialytic Hypotension and Duration of Dialysis

Intradialytic hypotension (IDH) occurs in 25–50% of short, thrice weekly hemodialysis treatments in the US. The detrimental effect of IDH is being increasingly recognized as an important factor in the increased relative risk of death due to acute coronary syndrome, and arrhythmias [39–41]. Dialysis hypotension occurs because a large volume of blood water and solutes are removed over a short period, exceeding the plasma-refilling rate and the reduction of venous capacity [42, 43]. Short dialysis is associated with high-speed ultrafiltration and rapid removal of small molecules, thus swiftly depleting plasma volume. In a study by Ronco et al. [44] ultrafiltration rates of 0.3, 0.4, 0.5, and 0.6 ml/min/kg were associated with approximate rates for IDH of 8, 15, 26, and 60%, respectively. In addition to an increased mortality with rapid ultrafiltration, a recent DOPPS [4] also showed markedly higher odds of IDH episodes in patients with an ultrafiltration rate of >10 ml/h/kg.

Stratagems to Reduce IDH without Prolonging Dialysis Duration

Although the K/DOQI Guidelines [45] and others [39, 42, 43] admit that to avoid IDH the ultrafiltration rate should not exceed the refilling rate, there is no stress on the lengthening of dialysis sessions, the simplest way to avoid the problem. Instead, multiple maneuvers have been applied to increase the plasma-refilling rate and decrease venous capacity such as: isolated ultrafiltration [46], high dialysate osmolality [24, 47], dialysate bicarbonate instead of acetate [48, 49], lowered dialysate temperature [50], and higher dialysate ionized calcium [51]. Rapid lowering of serum potassium during dialysis and high dialysate magnesium were also considered as factors augmenting hypotensive episodes [43]. Finally, predialysis withdrawal of blood pressure medications and/or use of blood pressure-rising drugs, such as ephedrine, fludrocortisone, caffeine, and midodrine have been recommended [52].

The most popular recent method of preventing IDH was ultrafiltration and sodium profiling. Although a multitude of approaches has been tried [53], the most common was application of a high ultrafiltration rate and high sodium concentration at the beginning of dialysis with a gradual or stepwise decrease in dialysate sodium concentrations and ultrafiltration rates throughout the dialysis session [54]. Whereas short-term studies showed improvement in the incidence of hypotensive episodes, a careful study of sodium balance showed that improvement was related to a positive sodium balance, leading to chronic volume overload, hypertension, myocardial hypertrophy, and increased cardiovascular mortality [55, 56].

Hypertension in Hemodialysis Patients

Hypertension occurs in 90% of patients starting hemodialysis and persists in 70–90% of hemodialysis patients in the US [57]. In the large, multicenter Hemodialysis (HEMO) Study, more than 70% of patients were hypertensive by JNC VI guidelines, and almost 75% required antihypertensive medications [58]. This is contrary to the situation in the late 1960s, when strict control of true dry body weight was practiced and the majority of patients did not require antihypertensive agents [59]. There is a consensus that most patients on dialysis have volume-dependent hypertension. Only a small proportion of patients have vasoconstrictive hypertension requiring bilateral nephrectomy in the past [59] or blood pressure medications at present. The problem is how to achieve normovolemia and control blood pressure without medications.

Blood Pressure Control by Dietary Measures and Low Dialysate Sodium

The possibility of controlling blood pressure in a renoprival state by drastic reduction in dietary salt intake was first shown by Kempner [60, 61] in the 1940s. It was subsequently shown that the beneficial effect of the 'rice diet' on hypertension was related to the lowering of plasma volume and extracellular fluid space [62]. In the 1960s it was considered as mandatory to restrict dietary salt intake in hemodialysis patients to control blood pressure. This restriction was combined with long dialysis sessions and relatively low dialysate sodium. The achievement of blood pressure control was very gradual. It was not surprising for the hemodialysis pioneers as this phenomenon was already observed by Kempner [60, 61] in the 1940s. In the first patient on a 'rice diet' containing less than 500 mg of salt, blood pressure was lowered gradually from 230/145 to 135/90 mm Hg in 8 weeks [60]. Even achievement of dry body weight does not lead immediately to controlling blood pressure because the relationship between extracellular volume status and blood pressure is not simple and linear, but complex because of a lag of several weeks between the normalization of the time-averaged extracellular volume and the decrease in blood pressure ('lag phenomenon') [63]. The exact pathomechanism of the lag phenomenon is not clear. It is likely that this may be caused by the retention of circulating factors, such as asymmetric dimethyl-L-arginine, a potent inhibitor of nitric oxide synthesis and Na^+,K^+-ATPase inhibitors that may remain elevated because of a large volume of distribution and ineffective removal [64]. Elevated sodium may remain in the arterial smooth muscles and be responsible for vasoconstriction. It may take several weeks of normovolemia for the intracellular sodium to escape. Regardless of the mechanism, the normalization of blood pressure by volume control is tricky, requires patience and a good understanding of the problem [56, 63, 64]. Several groups have tried to lower extracellular volume and blood pressure without lengthening dialysis duration by dietary measures and low dialysate sodium [65]. In 8 patients Krautzig et al. [66] tried a regime of gradual lowering of the dialysate sodium concentration from 140 to 135 mEq/l at a rate of 1 mEq/l every 3–4 weeks and restricting dietary salt intake while maintaining dialysis duration of 4–5 h/session. It is worth stressing that dialysis duration was longer that practiced in the US.

The authors reported lowering blood pressure in these patients with a possibility of stopping blood pressure medications in 4 patients and only a moderate increase in the frequency of cramps during dialysis. The control of extracellular volume by a low sodium diet without prolongation of dialysis duration and low dialysate sodium is difficult; it increases intradialytic symptoms and requires a very strict adherence to an unpalatable diet.

Blood Pressure Control and Duration of Dialysis

Hypertension is less frequent in Europe and Japan where dialysis time is longer. The lowest mortality related to cardiovascular causes is reported from the Centre de Rein artificial, Tassin, France [56], where long duration hemodialysis is practiced. Long-term mortality in this center is lower in patients with lower mean blood pressures. In addition, gentle ultrafiltration and proper estimation of dry body weight allows the achievement of good blood pressure control in the majority of patients [56]. Hypotension, in patients dialyzed thrice weekly for 8 h, is a strong indicator that the patient weight dropped below the true dry body weight [56]. With rapid ultrafiltration, hypotension is dependent mostly on hypovolemia, which occurs long before the dry body weight is achieved. In spite of clear evidence that short dialysis is associated with poor blood pressure control, the blame is commonly put on suboptimal drug therapy, excessive interdialytic weight gains ('patient noncompliance'), and the practice of withholding antihypertensive medications before dialysis [67].

With long-duration hemodialysis sessions, blood pressure could be controlled without antihypertensive therapy in 90–95% of patients [56, 68]. These patients have volume-dependent hypertension. The remaining 5–10% of patients has 'refractory' hypertension, treated with bilateral nephrectomy in the past, but nowadays these patients respond to antihypertensive therapy with converting enzyme inhibitors [69]. The originator of chronic dialysis is Belding H. Scribner, who practiced long-duration dialysis sessions in the 1960s, and in recent years advocated forcefully departure from short dialysis and better attention to volume management for blood pressure control [63, 70–72]. Other groups also advocate longer dialysis sessions for better blood pressure control [73–75]. A recent randomized crossover study of long (6–8 h) dialysis thrice weekly at home and short (3.5–4.5 h) thrice weekly in the dialysis center showed much better control of blood pressure and a reduction in hypotensive episodes with longer dialysis sessions [76]. Even moderate prolongation of dialysis sessions from 253 ± 15 to 273 ± 25 min together with strict control of sodium balance over 3–4 months allowed control of blood pressure in 10 of 16 patients with 'dialysis-resistant' hypertension [77].

The K/DOQI guidelines do not recommend the duration of dialysis as an independent measure of dialysis adequacy. After discussing all arguments for and against the importance of dialysis duration, the work group could not reach a consensus on this subject and did not include it in the final recommendations [45]. Some work group members felt strongly that the time of dialysis should not fall below 2.5 h, but a duration of dialysis of >4 h was not recommended [45]. However, I see no good explanation for why duration of dialysis is dismissed as unimportant.

Problems with High Small Solute Clearances (Large K)

Blood Flow and Efficiency of Dialysis

Short dialysis with fixed Kt/V_{urea} leads to maximization of dialysis efficiency by using higher efficiency dialyzers and high blood and dialysate flows; however, the influence of blood flow on the efficiency of dialysis is markedly lower than dialysis time. Removal of MMs (including phosphorus) is only slightly dependent on blood and dialysate flows [13], so compensating shortened dialysis time by increasing blood flow is not effective. This is not only related to the slow diffusion of these molecules through the membrane, but also to multicompartmental behavior, i.e., slow diffusion from the extravascular space to the plasma [78]. This process may be compared to the poor 'plasma-refilling rate' of water and sodium in high ultrafiltration rate hemodialysis. It is worth realizing that even for removal of small molecules, an increased time of dialysis is more effective than increased blood and dialysate flows, because $spKt/V_{urea}$ (single pool) is directly proportional to dialysis time, but K is exponentially, not linearly, proportional to blood and dialysate flows.

High Blood Flow Rates and Retrofiltration

The introduction of ultra-short dialysis treatments with high blood flow and high flux dialyzers brought other unexpected, undesirable effects, namely back filtration or retrofiltration of dialysate to the blood compartment [79, 80]. Ronco [81] explained that back filtration (retrofiltration) is particularly pronounced with long dialyzer and the high flows of blood and dialysate. The consequence of bacterial product delivery from the dialysate to the blood stream is an acute phase reaction with

consequent chronic inflammation, protein-energy malnutrition, and accelerated arteriosclerosis constituting the well-described malnutrition-inflammation-arteriosclerosis syndrome [82, 83].

High Blood Flow Rates and Blood Access Problems

According to the DOPPS, in the US the mean dialysis duration of 213 min is the lowest of the seven nations participating in the study and the prescribed blood flow rate of 401 ml/min is the highest [84]. The requirement of high blood flow increases demand on blood access. There are major differences in blood access use between Europe and the US in both genders, in all age groups, and in patients with and without diabetes. In addition, survival of arteriovenous fistulas is better in Europe than in the US [85]. It is my strong suspicion that the differences are related, at least in part, to the differences in required blood flow. For instance, primary arteriovenous wrist fistulae providing blood flows of 300 ml/min may be considered adequate in Europe where the mean prescribed flow is 300 ml/min, but are considered inadequate in the US where the prescribed blood flow is over 400 ml/min [86]. Such fistulae are abandoned and other blood accesses are created instead in the US. Even fistulae providing blood flows of 350 ml/min are in jeopardy because of repeated attempts to achieve higher blood flows using tourniquets and other maneuvers. With these attempts, the intima of the fistula is damaged by suction of the inflow needle, and the survival of the fistula is shortened. Finally, hypotensive episodes suddenly reduce fistula blood flow and predispose to clotting. If intravenous catheters are used as blood accesses, large catheter lumens are required to achieve high blood flows. The large diameter catheter fits the vein too tightly and predisposes to damage of the vein wall, vein thrombosis and stenosis [87]. Thus, the requirement of very high blood flow may be a contributing factor to poor blood access results in the US.

Advantages of Long Dialysis (Large T)

From the above discussion, the advantages of long dialysis to the patients are obvious: better tolerance of dialysis, better control of blood pressure, better removal of MMs, better rehabilitation, and longer survival. The average ratio of patients to dialysis personnel is 3–4 to 1 in the US. Because of better tolerance of dialysis with fewer hypotensive episodes, the same ratio in Tassin is 6 to 1 [56]. Thus, the financial disadvantage of longer dialysis may be blunted by a reduced staff requirement. Long dialysis sessions may be performed at home without increased cost to the providers.

Kt/V_{urea} Should Be Abandoned as a Measure of Dialysis Quality

The acceptance of this index was based on insufficient data and their false interpretation. In the NCDS study the tendency toward lower morbidity with longer dialysis duration was rejected as statistically insignificant because p was 0.06 instead of 0.05 (sic!). However, the power of this study was low because of an insufficient number of patients, short study duration (52 weeks) and disregard of residual renal function, which must have been substantial as many patients were of short vintage. It is worth repeating that the absence of evidence is not the evidence of absence. Combining dialyzer urea clearance (K), dialysis duration (t) and urea distribution volume (V) in one formula and accepting this formula as a measure of dialysis adequacy has brought disastrous consequences. The formula suggests that it is possible to decrease t as long as K is proportionately increased, but this is not true. For instance, increasing dialyzer urea clearance (K) may compensate for shorter dialysis time (t) regarding urea removal, but it cannot compensate for the dialysis tolerance depending on the rate of ultrafiltration, nor has it reflected removal of bigger molecules. A very small urea distribution volume (V) will provide large Kt/V_{urea} in malnourished patients, even if their dialysis duration is short and dialyzer clearances are low. One can imagine that following only Kt/V_{urea}, patients loosing appetite, poorly nourished, may maintain this index of dialysis adequacy continuously loosing weight and urea distribution volume (V) until their demise. The Kt/V formula is misleading and should be abandoned as a measure of dialysis quality. Would any aircraft pilot use an altimeter showing the wrong altitude?

Clinical Assessment of Dialysis Quality

One may ask what index of dialysis adequacy should be used instead of Kt/V_{urea}. It is tempting to give a simple formula, easy to implement and easy for bureaucrats to control. If such a formula were really developed, nephrologists would not be needed in dialysis centers – computer programs and dialysis technicians would suffice. I do not believe that such a formula will be developed any time soon as dialysis is a very complex procedure. The use of rigid, quantitative guidelines (e.g., $spKt/V_{urea}$ of 1.3 per dialysis) assumes that all patients behave identically in

response to therapeutic maneuvers, like the mean of the group, but this is not true [88]. Medicine is still an art, not exclusively science; the individual approach assumes that there are differences among patients which require adjustment of the dialysis prescription for each patient based on clinical symptoms and signs. It is better to use clinical judgment instead of misleading formulae.

During the early years of chronic hemodialysis, the definition of adequate dialysis was based on the two essential goals of dialysis: eradication of signs and symptoms of uremia, and rehabilitation [5]. In the early 1970s, the definitions were based on a mixture of resolution of clinical symptoms and laboratory data [68, 89, 90]. This approach of assessing adequacy is subjective, requires very careful monitoring of patients, and is time-consuming, but it is relevant for the individual patient. In this context I would like to cite Ronco's [91] formula for a general approach to dialysis, MDt/P, where MD is the doctor and t/P is the time spent with the patient.

In the 1970s it was considered obvious that an absence of uremic symptoms predicted low morbidity and mortality. Does it hold true in the 2000s? The DOPPS found a strong association between lower scores for the three major components of health-related quality of life and higher risk of death and hospitalizations in hemodialysis patients [92]. In another DOPPS report, physical functioning was better in Japan and Europe than in the US, where there is the highest mortality. Particularly striking was the high percent of comorbidities related to hypervolemia, such as hypertension, congestive heart failure, and dyspnea in patients dialyzed in the US, where the duration of dialysis is the shortest [93].

Conclusions

Kt/V_{urea} is a poor measure of dialysis quality because it combines three unrelated variables into one formula. These variables influence the clinical status of the patient independent of each other. It is impossible to compensate short dialysis duration (t) with the increased clearances of small molecular substances (K), because the tolerance of ultrafiltration depends on the plasma-refilling rate, which has nothing in common with urea clearances. Clinical assessment is the best criterion of dialysis quality. Longer dialysis provides better tolerance of ultrafiltration, less frequent intradialytic hypotensive episodes, better control of blood pressure, and lower mortality.

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Increasing AV Fistulae and Decreasing Dialysis Catheters: Two Aspects of Improving Patient Outcomes

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Key Words

Dialysis access · Vascular access · Hemodialysis · Arteriovenous fistula · Polytetrafluoroethylene graft · Dialysis catheter · Central venous catheter · Dialysis access complications · Arteriovenous graft

Abstract

Maximizing arteriovenous (AV) fistula prevalence and minimizing catheter use have become the dominant issues in hemodialysis vascular access management and offer the promise of improved patient outcomes with decreased overall expenditures. Recent efforts have increased AV fistula prevalence in the US to 42.9% with regional rates as high as 59.5% and with complementary declines in AV grafts. This should decrease access procedures but may not fully realize the potential reductions in mortality and cost possible if combined with catheter reduction. Successful catheter reduction requires similar approaches to those utilized in the Fistula First Program. Educating patients, the use of clearly defined protocols and updating payment systems to include chronic kidney disease care are crucial to continued progress. Expansion of the Fistula First Program to include a focus on decreasing catheter prevalence and complications should be considered as a requirement in the push toward the breakthrough targets of 66% AV fistula prevalence.

Introduction

Maximizing arteriovenous (AV) fistula prevalence and minimizing catheter use have become the dominant issues in hemodialysis vascular access management. AV fistulae are the preferred choice of hemodialysis access because they last longer, require less maintenance and result in a lower mortality than AV grafts or central venous dialysis catheters. In contrast, dialysis catheters adversely impact patient outcomes and significantly increase patient morbidity and mortality [1, 2]. Over the past 10 years there has been a significant change in our understanding and approach to vascular access. With the initiation and publication of the Dialysis Outcomes Quality Initiative (DOQI) in 1997 [3], an organized approach to vascular access management, from creation to maintenance and repair, has become the global standard. This has been facilitated by advances in medical technology, information systems, process and outcomes measurement and the movement toward a systems-based approach to care delivery. The impetus for change began with the realization of the profound impact of vascular access failure on patients, payers and providers. An epidemic of AV graft thrombosis, emergent hospitalization, and multiple access procedures in the late 1980s and early 1990s led to efforts to identify AV grafts at high thrombosis risk. New imaging technologies (ultrasound, angi-

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ography) identified the stenoses causing access dysfunction and percutaneous therapies made elective and emergent outpatient interventions (angioplasty and thrombectomy) practical and more readily available. The DOQI guidelines for vascular access marked a crucial step in improving care [3]. For the first time, a comprehensive series of expectations and evidence-based guidelines became available. In conjunction with local, corporate and end-stage renal disease (ESRD) network quality improvement programs, this process facilitated the deployment and use of best practices across the US. The US Renal Data System (USRDS) data [4] and international comparisons from the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that the large regional and international differences in AV fistula prevalence and clinical outcomes were largely unexplained by patient demographics and case mix [5, 6]. The growing realization that access thrombosis is primarily related to polytetrafluoroethylene (PTFE) grafts, that AV fistulae placement is possible in the majority of patients and that superior European patient outcomes are linked to high AV fistula prevalence led to local fistula creation efforts [7–10]. In 2003, the Centers for Medicare and Medicaid Services (CMS) initiated the Fistula First project. Fistula First is an innovative collaboration between CMS, the ESRD networks, the Institute for Healthcare Improvement and the renal community with the stated goal of increasing AV fistula prevalence nationally. Following the successful attainment of 40% AV fistula prevalence (initial Kidney Disease Outcomes Quality Initiative, K/DOQI goal); Fistula First was designated as a national breakthrough initiative with the new goal of increasing AV fistula prevalence to 66% by 2009 [11].

Increasing AV Fistulae

The pathways to increased AV fistula prevalence are now clearly delineated in the K/DOQI recommendations and Fistula First change concepts [11, 12]. Patients should be referred for evaluation for access placement approximately 6 months before dialysis initiation. Arterial and venous mapping, typically by ultrasound is performed to identify appropriate vessels for AV fistula creation [13]. This provides visualization of arteries and veins including the approximately 50% of vessels that are not apparent on physical examination. To minimize early AV fistula failure, arteries should be $\geq$2 mm in diameter, without dampening of the waveform and without a significant pressure differential between the arms. Veins should be $\geq$2.5 mm in diameter, have continuity with the deep venous system and have no evidence of segmental stenosis [8]. An AV fistula is then surgically created in the most appropriate site. These sites may be in the forearm, upper arm, or require transposition of deep vessels in the upper or lower arm to more superficial locations. The fistula should be examined approximately 4 weeks after creation and referred for imaging and correction of identified lesions if not maturing by 6 weeks. Blood flow and vessel diameter increase rapidly following AV fistula creation with no significant change noted after 1 month [14]. Most non-maturing fistula have identifiable lesions that can be corrected by percutaneous techniques. In a series of 100 AV fistulae with early failure, 78% had a venous stenosis, 38% anastomotic stenosis and 46% accessory veins that were preventing adequate maturation. After treatment, 92% became usable for hemodialysis and 84% remained functional at 3 months, 72% at 6 months and 68% at 12 months [15]. Even a thrombosed AV can generally be salvaged. With the advent of percutaneous techniques often including thrombolytics, initial success rates of 78–94% with a 6-month unassisted patency of up to 67% have been reported. This is a significant improvement over previous surgical thrombectomy and has allowed continued fistula use after the development of stenosis or thrombosis [16].

Decreasing Catheter Risk

Dialysis catheters play an important role in the provision of hemodialysis because they can provide immediate access for emergent dialysis and alternatives for patients with inadequate vasculature or medical conditions that preclude alternative access. Ideally catheters function as a short-term bridge to AV fistula or AV graft placement. Unfortunately, catheter use is often prolonged even when not medically necessary. In 2004, 63% of patients maintained on hemodialysis for <0.5 years, 36% on dialysis 0.5–0.9 years and 26% of patients on hemodialysis for 1–1.9 years were dialyzed via a catheter [17]. This occurred despite the fact that over two thirds of catheter patients have adequate vessels for alternative access placement [18] and that catheter patients have almost double the mortality risk of AV fistula or AV graft patients [1, 2].

The standard approach to decrease catheter complications is alternative access placement. Patients who change from a catheter to an alternative access benefit from a 52–60% reduction in their mortality risk (RR = 0.40 case-

mix adjustment, 0.48 baseline covariates adjustment, RR = 0.41 baseline covariates and follow-up adjustment) [19]. One recent report demonstrated that a systematic program of education and mapping followed by AV fistula creation successfully converted 57.9% (70/121, intention to treat) of all catheter patients and 81.4% (70/81) of patients who agreed to venous mapping to a functioning alternative access [18]. An alternative approach is to make catheters safer by decreasing the bacteremia risk. In one report, mortality decreased by 76% and hospitalization for catheter-related bacteremia decreased by 63% with the routine application of an antiseptic/antimicrobial solution (polysporin) at the catheter exit site [20]. Similar reductions in bacteremia have been reported with the use of muperacin ointment. Antimicrobial catheter lock solutions which decrease or prevent the formation of biofilm are also effective. Studies using citrate, taurolidine, gentamycin/heparin, gentamycin/EDTA have reported up to 76–93% reductions in catheter-related bacteremia [21]. Many of these solutions require further research or are not routinely available in the US. However, few facilities have tested or utilized these approaches even when available.

Successes, Challenges and Opportunities

The combination of national and regional vascular access initiatives supported by new medical technologies has successfully increased national AV fistula prevalence from 26% in December 1998 to 33% in December 2002 and 42.9% in June 2006. Regionally, AV fistula rates range from 37.1% in Virginia and Maryland (ESRD network 5) to 59.5% in the Pacific Northwest (ESRD network 16) [11, 17]. During the same period, catheter use has increase from 19% in December 1998 to 27% in December 2002 and remained at 27% in December 2004 [17]. Although programs to increase fistula prevalence do not necessarily increase catheter use, they can unless combined with concerted catheter reduction efforts. Currently, there is no routine coverage for chronic kidney disease (CKD) care and few CKD programs. These programs increase permanent access placement and decrease catheter use surrounding dialysis initiation. In the US, most patients require placement of a central venous catheter for dialysis initiation. Even in regions that have high AV fistula placement rates it often takes a prolonged period of time before the fistula is placed after dialysis initiation. Patients are frequently discharged with plans for referral to a surgeon for AV fistula placement at a later date. Once patients enter an outpatient dialysis unit they are often reluctant to proceed with AV fistula or AV graft placement. Fear of needles, disfigurement, body image, increased length of time for post-dialysis hemostasis, illusions about the availability of transplant and depression, all present potential obstacles to fistula placement. In addition, the advent of ESRD and dialysis initiation frequently places patients and families under severe financial stress. Co-pay requirements may present a significant barrier to further procedures or hospitalization, especially in patients with commercial coverage. Payment restrictions can be a disincentive for providers. In some Medicaid programs, additional payment for access placement is unavailable during the initial admission for dialysis initiation [22]. Following fistula placement, approximately one third of patients will need a secondary procedure to allow proper maturation [15]. During this time patients are dialyzed with cuffed catheters with the attendant increased risk of infection, sepsis and potential death. Changing medical technology may also present new opportunities and challenges. If catheter flush solutions, exit site treatments or new impregnated catheters that prevent bacteremia are proven and become available; catheters may become a more viable alternative. Similarly, medications that prevent thrombosis and the development of pseudo-intimal hyperplasia could lead to a resurgence of PTFE grafts. These rapid technologic changes are difficult to predict and assimilate in guidelines, regulations, payment systems and quality improvement programs.

Conclusions

AV fistula creation coupled with systematic catheter reduction offers the promise of improved patient outcomes with decreased overall expenditures. The success in increasing AV fistula prevalence in the US to 42.9% in June 2006 with regional rates as high as 59.5% is evidence of a significant change in practice patterns. Educating patients, the use of clearly defined protocols and updating payment systems to include CKD care are crucial to continued progress. Current data demonstrate that these increases in AV fistula prevalence have occurred in conjunction with decreased graft use. Although it is still too early to define the clinical and cost impacts, this should decrease access procedures but may not fully realize the potential reductions in mortality and cost possible if combined with catheter reduction. Successful catheter reduction requires sustained efforts with similar requirements (education, mapping and referral) and barriers (fi-

nancial, process and clinical) as the current Fistula First program. Expansion of the Fistula First program to include a 'Catheter Out' initiative with the focus on decreasing catheter prevalence and complications should be considered as requirement in the push toward the breakthrough targets of 66% AV fistula prevalence. Pay-for-performance should include a combination of increasing AV fistula and decreasing catheter prevalence. In summary, the issue is not 'Fistula First' or 'Catheter Out'; both are possible and absolutely necessary.

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The 2006 K/DOQI Guidelines for Peritoneal Dialysis Adequacy Are Not Adequate

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Key Words
K/DOQI guidelines 2006 · Peritoneal dialysis

Abstract
The 2006 National Kidney Foundation K/DOQI guidelines have lowered the peritoneal dialysis adequacy standard of Kt/V_{urea} from 2.1 to 1.7 in anuric patients, largely based on the patient survival results of 2 clinical trials in Mexico and Hong Kong. It is our contention that the guidelines may be misleading since they have chosen to ignore the bias in these trials and have ignored the adverse outcomes in control groups in the trials on which the guidelines are based, as well as the body size of the subjects in these trials. Body size has changed in the US and Canada over the last few decades and there are similar changes worldwide. We suggest that the minimum targets for peritoneal dialysis be reinstituted at the previous standard Kt/V_{urea} of 2.0.

Introduction

Until recently, the accepted National Kidney Foundation (NKF) K/DOQI guidelines for peritoneal dialysis (PD) adequacy was set to a weekly Kt/V_{urea} of 2.1. Data from the Canada-USA (CANUSA) study largely influenced the prior higher Kt/V_{urea}. The revised NKF K/DOQI guidelines for PD adequacy lowered the Kt/V_{urea} from 2.0 to 1.7. This reduction in Kt/V_{urea} is largely based on two randomized trials. The ADEMEX trial, which took place in Mexico, randomized incident and prevalent patients into 2 groups with 2 levels of PD prescription. The study did not find a difference in survival outcome between the groups suggesting no added survival benefit for greater small-molecule peritoneal clearance. A second randomized trial in Hong Kong compared 3 levels of total Kt/V_{urea} in new patients with reduced residual kidney function and also found no difference in survival.

According to recent USRDS data in 2003, there were over 11,281 patients receiving continuous ambulatory PD (CAPD) and 14,544 receiving continuous PD. CAPD and continuous PD accounted for over 3.5 and 4.5% of all patients on renal replacement therapy, respectively. The majority of patients receiving PD were between the ages of 45–64 years accounting for 43%, followed by patients between the ages of 20–44 years (23%). Whites, Blacks and Asians accounted for roughly 65, 26 and 6% of all patients on PD, respectively.

The odds of having a body mass index (BMI) above 30 has increased in incident end-stage renal disease patients.

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White patients experienced 82% higher odds of having a BMI of >30 in 2002–2004 compared to 1996–1998. For Blacks the odds doubled.

Differences in body weight, morphology and morphometry must be considered in the interpretation of measures of adequacy in PD. The K/DOQI recommendations for adequate delivery of dialysis include weekly creatinine clearance normalized to a body surface area (BSA) of 1.73 m^2 as well as weekly Kt/V, with clearance normalized to body volume.

With Kt/V, the V represents the volume of distribution (in liters) of urea. Volume of distribution (Vd) of urea for calculating Kt/V is determined by anthropomorphic estimations of total body water using either the Watson or Hume-Weyers methods (for adults, by sex) or the Mellits-Cheek method (for children, by sex). All of the estimating formulae for total body water are based on measurements of an individual patient's height and weight. As the formulae for BMI and BSA also depend solely on height and weight, patients with larger BMIs will in turn have larger total body water (and V) as well as BSA. How this increase in V and BSA correlates with peritoneal surface area is uncertain.

Critique of K/DOQI

In the ADEMEX study [1] prevalent patients were the majority in the randomized groups (58%) and presumably were survivors of previous treatment and therefore more robust, as well as representing a disproportionate number of low and low average transporters. In regard to the latter we can partially judge the equivalence of the dialysis adequacy and transport test used with the peritoneal equilibration test to define transport characteristics. Deaths attributable to congestive heart failure, ischemic heart disease, stroke, peritonitis and infections were also higher in the control group. This is despite the fact that heart disease was an exclusion criterion. Comparison to the CANUSA study, which was the basis of the previous DOQI standard of 2.0, revealed that age, body weight, and BSA were all lower. Interestingly, obese PD subjects have a poorer survival than those of lesser weight [2]. The only study to compare thinner to obese PD subjects demonstrated that nutrition and small solute clearance were identical – but both groups had Kt/V of 2.0 [3]! In the editorial accompanying the paper Churchill [4] stressed the need for validation and review by learned bodies.

In the Hong Kong study [5] the number of subjects was smaller but did randomize about 100 subjects to each of 3 groups with Kt/V of 1.5–1.7, 1.7–2.0 and >2.1. All patients had a renal Kt/V <1.0. The 2-year survival was similar in all groups whether analyzed according to Kt/V or Kt. However, in the lowest Kt/V group the erythropoietin requirement was greatest, the largest number of patients (30) withdrew, dialysis was inadequate, and ultrafiltration was poorer than in any other group. The BMI was even lower than in the ADEMEX study (table 1). Hospitalization days were not different between the groups.

Table 1

Study	BMI
ADEMEX (1998–2001)	25.5
Hong Kong (1996–1999)	22
CANUSA (1990–1992)	24.6
USA (2002)	28
Canada (1999)	25.5

Churchill [6] has posited that the lack of effect of increased Kt/V on mortality in both of these studies may be due to increased intraperitoneal pressure (as published by the senior author of the ADEMEX study) and exposure to more glucose (and advanced glycation end-products) as exchange frequency fell and exchange volume increased.

Discussion

The gold standard until the 2006 K/DOQI guidelines were adopted was based on the CANUSA study [7], which clearly showed a difference in mortality between different delivered Kt/V values, a 0.1 unit of Kt/V increase conferring a 5% advantageous RR of survival. Interestingly the CANUSA study had a higher death rate in US patients compared to Canadians, and the former had a higher BSA. Peritoneal Kt/V was 1.5 in Americans and 1.7 in Canadians (the renal Kt/V was not different between the 2 groups). Could the difference in Kt/V explain the different mortality rates? We think so, since there were clear separations at all time points on the Cox proportional hazard survival graphs. Since there were more African-Americans in the American than Canadian patient population (African-America hemodialysis patients have a higher survival rate than white subjects), we are even more convinced that the lower Kt/V in the US patient group was responsible for lower survival. It has been said that we should revisit the middle molecule theory to ex-

plain the lack of higher Kt/V_{urea} contributing to survival in the ADEMEX and Hong Kong studies – however, markers of middle molecules were not published in the reports. β_2-Microglobulin was associated with increased hospitalization days, as was lower Kt/V, in the CANUSA study lending some credence to the middle molecule hypothesis, but β_2-microglobulin is also higher in poorly dialyzed subjects. Reanalysis of the CANUSA data revealed that a 5-liters/week increment in residual glomerular filtration rate could explain all the benefits of the increased dialysis dose [8]. However, it does not explain the differences between the 2 countries.

The background mortality in a country's general population is reflected in its dialysis population – a DOPPS study demonstrated substantial differences in US, European and Japanese mortality dialysis patients (in descending order as reflected in the general populations) [9]. Could the background mortality and body size have any influence on the lack of demonstrated advantage of a higher Kt/V. It is interesting to speculate that it might.

The number of patients being treated with CAPD has fallen in recent years – was this due to the inability to achieve the old DOQI standard, and have the new K/DOQI guidelines promulgated an achievable standard?

We think that the new K/DOQI guidelines are not applicable to North American populations.

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Usefulness of a Molecular Strategy for the Detection of Bacterial DNA in Patients with Severe Sepsis Undergoing Continuous Renal Replacement Therapy

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Key Words
Sepsis · Renal failure, acute · Continuous renal replacement therapy · DNA, bacterial · Ultrafiltrate

Abstract
Introduction: Sepsis is a major cause of morbidity and mortality in critically ill patients. Sepsis is associated with cell necrosis and apoptosis. Circulating plasma levels of DNA have been found in conditions associated with cell death, including sepsis, pregnancy, stroke, myocardial infarction and trauma. Plasma DNA can also derive from bacteria. We have recently implemented a method to detect bacterial DNA and, in the present study, we validated this technique comparing it to standard blood culture in terms of diagnostic efficacy. ***Methods:*** We examined a cohort of 9 critically ill patients with a diagnosis of severe sepsis and acute renal failure requiring continuous renal replacement therapy (CRRT). We analyzed bacterial DNA in blood, hemofilters, and ultrafiltrate (UF) by polymerase chain reaction amplification of 16S rRNA gene sequence analysis. Standard blood cultures were performed for all patients. ***Results:*** The blood cultures from 2 of the 9 (22%) patients were positive. However, bacterial DNA was identified in the blood of 6 patients (67%), including the 2 septic patients with positive blood cultures. In 9 (100%) patients bacterial DNA was found on the filter blood side, whereas in 7 (78%) subjects it was found in the dialysate compartment of the hemofilters. Bacterial DNA was never detected in the UF. ***Conclusions:*** Using the 16S rRNA gene, the detection of bacterial DNA in blood and adsorbed within the filter could be a useful screening tool in clinically septic, blood culture-negative patients undergoing CRRT. However, the identification of the etiologic agent is not feasible with this technique because specific primers for the defined bacteria must be used to further identify the suspected pathogenic organisms.

Introduction

Sepsis is the leading cause of morbidity and mortality in critically ill patients worldwide [1]. Rapid and accurate microbiological data, especially from blood culture, prevent inadequate antimicrobial treatment, which has been reported as the most important independent predictor of hospital mortality in intensive care unit (ICU) patients [2, 3]. Unfortunately, blood culture provides high speci-

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ficity but low sensitivity. It has long been known that more than two thirds of clinically suspected sepsis patients have negative blood cultures [4, 5]. Consequently it is necessary to identify the infectious pathogens as soon as the clinical picture of sepsis is seen, especially when conventional blood culture has been negative.

Little is known about plasma circulating DNA, but baseline low levels are present in healthy subjects [6, 7]. DNA probably enters the circulation following cell death (necrosis or apoptosis). Furthermore, the clearance mechanism of circulating DNA is poorly understood, although the liver and the kidneys play a major role for its removal [7]. Plasma DNA also has a bacterial origin in septic patients. Molecular methods have been developed for the detection and identification of bacterial DNA, which exploits the characteristics of the bacterial 16S rRNA gene: this gene consists of highly conserved regions and mixes together highly variable regions, which allow phylogenetic analysis.

The present study aimed to: (1) make a comparison between standard blood culture and 16S rRNA gene sequence analysis in order to validate the usefulness of molecular methods for biological diagnosis in septic patients, and (2) determine whether bacterial DNA is adsorbed within the hemofilter, and if it can pass through the hemofilter and be present in ultrafiltrate (UF) of patients with severe sepsis undergoing continuous renal replacement therapy (CRRT).

Materials and Methods

Study Subjects and DNA Extraction

Nine critically ill patients with acute renal failure (ARF) requiring CRRT were included in the prospective observational cohort study. For all subjects a diagnosis of 'severe sepsis' was made according to the criteria of Bone et al. [8] including (1) at least 2 systemic inflammatory response syndrome (SIRS) criteria; (2) confirmed or suspected infection, and (3) multiple organ dysfunction syndrome. The study protocol was approved by the hospital ethics committee.

All septic patients were treated following the guidelines for severe sepsis and septic shock [9]. Broad-spectrum antibiotics were given to all patients. The clinical characteristics and antibiotic prescriptions are given in table 1. Blood cultures, and blood samples/filters/UF collection for bacterial DNA detection were performed when severe sepsis was diagnosed.

For each subject at least 3 samples for blood culture were obtained from different sites by peripheral venipuncture. In case of suspected catheter-related sepsis, 1–2 blood samples for culture were drawn from the catheter. A minimum of 10 ml of blood was obtained and immediately inoculated into BacT/Alert Fanh aerobic and anaerobic bottles (bioMerieux, Marcy l'Etoile, France), and the bottles were incubated for ≤7 days. The bottles were then processed in a BacT/Alerth 3D automated blood culture system (bioMerieux) [10].

After blood samples had been drawn, DNA from 0.2 ml of heparin-treated whole blood was extracted by means of a commercial DNA extraction kit (QiAmp DNA Minikit, Quiagen Science, Valencia, Calif., USA) according to the manufacturer's instructions. Briefly, DNA was digested with proteinase K and an appropriate buffer for 2 h at 56°C to allow optimal lysis and binding of the DNA to the QiAamp membrane. DNA was adsorbed onto the QiAamp silica gel membrane by centrifugation. Salt and pH conditions ensured that proteins and other contaminants were not retained on the membrane. In order to wash DNA that was adsorbed into the membrane, two different buffers were utilized which significantly improved the purity of the eluted DNA without affecting DNA binding. Purified DNA was then eluted with a buffer in a concentrated form and was suitable for direct polymerase chain reaction (PCR) use.

At the end of a 24-hour CRRT session 200 ml of UF was collected and centrifuged at 2,000 rpm for 10 min in order to pellet bacterial cells if present. After centrifugation, the pellets obtained were digested overnight in a lysis buffer containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, and proteinase K to a final concentration of 0.5 μg/μl and Nonidet P-40 (Roche Applied Science, Mannheim, Germany) at 55°C. The mixture was then boiled for 10 min and centrifuged to remove debris. The supernatant was used as a template for amplifications. Direct precipitation of DNA with sodium acetate 3M and cold absolute ethanol (–20°C) and subsequent water dilution were also performed to evaluate the presence of DNA in solution. Both samples were analyzed for the presence of bacterial DNA.

Filters. 25 ml of a mixture containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, proteinase K to a final concentration of 0.5 μg/μl and Nonidet P-40 was injected into the blood compartment and the dialysate compartment of the filters. The filters were then incubated at 37°C overnight to allow complete digestion of biofilm if presented. Then, in order to avoid cross-contamination between the solutions in the two compartments, we separately removed the two solutions by gentle drawing from the arterial and dialysate ports and collected the fluid in two sterile tubes. The solutions were boiled for 10 min and centrifuged to remove debris. The supernatant was used as a direct template for amplifications. All processes were done under sterile techniques.

rRNA 16S PCR Amplification and DNA Sequencing

It was shown that the phylogenetic relationships of bacteria, and indeed all life-forms, can be determined by comparing a stable part of the genetic code [11, 12]. The DNA part now most commonly used for taxonomic purposes for bacteria is the 16S rRNA gene [13]. In this study, the primers used for amplification of 16S rRNA were 355F (5′-CCTACGGGAGGCAGCAG-3′) and 910R (5′-CCCGTCAATTCCTTTGAGTT-3′): these primers detect a 540-bp region of the 16S rRNA gene. Template DNA was used for amplification in a 50-μl reaction mixture at a final concentration of 67 mm Tris-HCl (pH 8.8), 16 mM $(NH_4)_2SO_4$, 200 μM dNTPs, 3.5 mM $MgCl_2$, 25 pmol of each primer and 1 U Taq polymerase (Eurobio, Courtaboeuf, France). The temperature scheme used for the amplification was: preheating at 95°C for 5 min followed by 35 cycles of 95°C for 45 s, 53°C for 45 s, 72°C for 45 s, and a final extension step of 72°C for 7 min. The amplification products were run through 3% Nu:Sieve 3:1 Agarose (Cambrex BioScience,

Table 1. Clinical characteristics of the patients studied

	Subjects				
	1	2	3A	3B	4
Age, years/gender	69/M	60/M	51/F	51/F	52/M
Diagnosis on ICU admission	perforated ileum, peritonitis	catheter-related sepsis	catheter-related sepsis	after catheter-related sepsis (3 weeks)	acalculous cholecystitis, sepsis
Comorbidities	ESRD on CAPD	ESRD, DM, HT	ESRD, DM, HT	ESRD, DM, HT	coronary artery disease, CHF
Antibiotics used	tazocin, metronidazole, fluonazole	oxacillin, gentamycin	tazocin	nil	tazocin, ceftazidime, amikacin, fluconazole
Type of RRT	CVVH	IHD	IHD	IHD	CVVH
Hemofilter	AV 1000 S (Fresenius)	F10 HPS (Fresenius)	F10 HPS (Fresenius)	F10 HPS (Fresenius)	Diafilter D30 (Minntec)
Membrane type	polysulfone	polysulfone	polysulfone	polysulfone	polysulfone
Surface area, m^2	1.8	2.4	2.4	2.4	0.7
Kuf, ml/h/mm Hg/m^2	52	18	18	18	48
	Subjects				
	5	6	7	8	9
Age, years/gender	56/F	45/M	37/M	79/M	46/F
Diagnosis on ICU admission	bowel ischemia, sepsis	broncopneumonia, septic shock	sepsis? acute rejection?	colon cancer, septic shock after colectomy	sepsis (unknown source)
Comorbidities	CA colon, after colectomy	leukemia, leukopenia, thrombocytopenia	kidney transplant, graft failure (renal vein of transplant kidney and iliac vein thrombosis)	DM	kidney transplant, acute graft rejection
Antibiotics used	amikacin, astreonam, metronidazole	linezolid, tazocin, clarithromycin	ceftriaxone	ciprofloxacin, metronidazole, tazocin	levoflocaxin, tazocin, fluconazone
Type of RRT	CVVH	CVVH	IHD	CVVH	CVVH
Hemofilter	Diafilter D30 (Minntec)	Diafilter D30 (Minntec)	NC 2085 (Bellco)	AV 600 S (Fresenius)	Diafilter D30 (Minntec)
Membrane type	polysulfone	polysulfone	synthetically modified cellulose	polysulfone	polysulfone
Surface area, m^2	0.7	0.7	1.8	1.4	0.7
Kuf, ml/h/mm Hg/m^2	48	48	7.5	40	48

ESRD = End-stage renal disease; DM = diabetes mellitus; HT = hypertension; CHF = congestive heart failure; CA = cancer; RRT = renal replacement therapy; CVVH = continuous veno-venous hemofiltration; IHD = intermittent hemodialysis.

Rockland, Me., USA) with 5% gel star staining (Cambrex Bio Science) using standard techniques. All samples were tested at least twice before reporting. In order to avoid risk of contamination, tissue preparation, PCR amplification and electrophoresis were performed in different rooms. In each assay a negative and a positive control were run. The negative control contained all the PCR reagents and sterile bi-distilled water.

After electrophoresis of the amplification products, if present, the PCR products were excised from gel and purified with Wizard SV Gel and PCR Clean-up System (Promega Corp., Madison, Wisc., USA) according to the manufacturer's instructions. The products then underwent sequencing reactions on GeneAmp 9700 (PE Applied Biosystems, Foster City, Calif., USA). A BigDye Terminator v1.1 Cycle sequencing kit (Applied BioSystems) was utilized for the sequencing reaction. The primer used as the template was the reverse one (910R) and the final reaction volume was 20 μl. The thermal cycling conditions were 25 cycles of 96°C for 10 s, then at 50°C for 5 s and at 60°C for 4 min. The reaction products were purified with Centri-Sep 8 Columns (Princeton Separation, Adelphia, N.J., USA) to remove unincorporated dye terminators, and the sequence was determined using capillary electrophoresis (ABI PRISM 310 Genetic Analyzer, Applied BioSystems). The generated DNA sequences were then compared with a database library on the GenBank web site (http://www.ncbi.nlm.nih.gov/blast).

Prescription of Renal Replacement Therapy Techniques

Continuous veno-venous hemofiltration (CVVH) was started in each case when a 'failure' level was denoted using the RIFLE criteria. RIFLE is an acronym indicating: Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function, and End-stage kidney disease [14]. Thus, criteria were a threefold increase in the creatinine level with respect to baseline, or a creatinine concentration of >4 mg/dl, or oligo-

Table 2. Microbiologic results

	Subjects				
	1	2	3A	3B	4
Blood culture (no. of sets)[a]	negative (3)	*Staphylococcus aureaus* (2/3)	*Pseudomonas aeruginosa* (3/3)	negative (3)	negative (5)
Other cultures (site)	–	–	–	–	*P. aeruginosa* (bile, abdominal drainage, BAL, tracheal aspiration)
Bacterial DNA detected[b]					
Blood	negative	non-sequentiable	*Pseudomonas* spp.	negative	non-sequentiable
Filter					
Blood compartment	negative	non-sequentiable	*Pseudomonas* spp.	non-sequentiable	non-sequentiable
Dialysate compartment	negative	uncultured bacteria	*Pseudomonas* spp.	uncultured proteobacterium	*Pseudomonas* spp.
Ultrafiltrate	negative	negative	negative	negative	negative
	Subjects				
	5	6	7	8	9
Blood cultures (no. of sets)[a]	negative (7)	negative (3)	negative (3)	negative (3)	negative (4)
Other cultures (site)	*Streptococcus agalactia* gr. B (tracheal aspiration)	negative (tracheal aspiration)	negative (urine)	negative (BAL)	negative (urine, BAL)
Bacterial DNA detected[b]					
Blood	negative	negative	non-sequentiable	*Pseudomonas* spp.	*Candida albicans*
Filter					
Blood compartment	non-sequentiable	non-sequentiable	non-sequentiable	*Pseudomonas* spp.	*Candida albicans*
Dialysate compartment	non-sequentiable	negative	negative	*Pseudomonas* spp.	*Candida albicans*
Ultrafiltrate	negative	negative	negative	negative	negative

BAL = Bronchoalveolar lavage.
[a] Each set consists of one aerobic and one anaerobic bottle.
[b] Bacterial DNA was detected by bacterial 16S rRNA gene sequence analysis.

anuria lasting for 24 h. 1.8 m^2 polyethersulfone high-flux hemofilters were utilized. A bicarbonate-based solution was used as replacement fluid. Blood access was established with 13-french double-lumen hemodialysis catheters. The blood flow rate was 150–180 ml/min and an ultrafiltration flow rate of 35 ml/kg/h was used in the pre-dilution mode. Prescription was performed with the help of a calculator recently described by our group [15]. In the absence of contraindications, low dose (250–500 U/h) prefilter unfractionated heparin was infused to prevent filter clotting. According to hospital policy, we changed the hemofilter after 24 h of uninterrupted CVVH treatment. Two milliliters of blood and 200 ml of UF were withdrawn from the arterial and effluent ports, respectively, immediately before changing the filters. Then the hemofilters were cleaned with 200 ml of sterile normal saline and removed and the arterial, venous and dialysate ports were closed with sterile taps. All of these processes were done under sterile conditions. Blood was collected into refrigerated tubes containing solid heparin, and UF was collected into four 50-ml sterile tubes.

Statistical Analysis

The χ^2 test was performed in order to compare if molecular techniques differed in detecting or not detecting the presence of the bacteria with respect to standard blood culture. A p value of <0.05 was considered statistically significant.

Results

CVVH was well tolerated by all patients. The blood cultures of 2 of 9 (22%) patients were positive. However, bacterial DNA was identified in the blood of 6 patients (67%; p = 0.06), including the 2 septic patients with positive blood cultures. In 9 (100%; p = 0.01) patients bacterial DNA was found on the filter blood side, whereas in 7 (78%; p = 0.03) subjects bacterial DNA was found in the dialysate compartment of the hemofilters. Bacterial DNA was never detected in the UF.

Detailed results are given in table 2. Briefly, in a positive blood culture patient with catheter-related sepsis from *Staphylococcus aureus* (subject 2), multiple species of bacterial DNA were found in the blood and trapped in the filter, and reported as 'non-sequentiable'. *Pseudomonas* DNA was found in the blood and filter of another positive control patient (subject 3A), which matched the organism yielded from blood culture. Of interest, after 3 weeks of appropriate therapy in this patient (subject 3B), when the organism could not be detected by blood culture and bacterial DNA in blood, bacterial DNA still remained and was trapped in the blood compartment of the hemofilter. Even though repeated blood cultures of subjects 4–9 had been negative, bacterial DNA was recovered from hemofilters used in CRRT by bacterial 16S rRNA gene sequence analysis. Bacterial DNA was identified only in the blood of subjects 4 and 7–9, but not in subjects 5 and 6. However, this diagnostic method yielded a single organism in 2 patients (subjects 8 and 9), and multiple organisms in other patients (reported as non-sequentiable).

Discussion

Sepsis is the tenth most common cause of death in the US [1]. Blood culture and other microbiological cultures represent the standard methods the clinician has to confirm the presence of the pathogen responsible for the septic picture and to start adequate antimicrobial and other adjuvant therapies. Unfortunately the failure rate of these tests remains high. There are valid reasons why bacterial strains that cause clinical sepsis are not recovered by routine blood culture. For example, prior antibiotic treatment may render them nonviable. A second reason is that the organisms may be genuinely hard to grow or require special conditions for growth. Some sources of sepsis may produce transient bacteremia. Organisms may be sequestered in tissue foci, in resident macrophage, in the capillary bed with few being released in the circulation. Under such circumstances, the identification of bacterial DNA in blood and hemofilter by 16S rRNA gene analysis may facilitate bacterial DNA recovery from the clinically septic patients with negative blood cultures. Recent studies have shown that the automated blood culture systems failed to detect symptomatic bacteremia in critically ill patients with a reported incidence of 3–6% [16–18], and of these, *Pseudomonas aeruginosa* is the most common organism causing false-negative cultures [16, 17].

ARF requiring RRT is a common finding during severe sepsis in the ICU. These patients are particularly prone to severe infections and still little is known about the possibility of an extracorporeal clearance of pathogenic agents [19].

The aim of our study was to evaluate the feasibility of 16S rRNA gene analysis in the systemic blood, filter and UF of critically ill septic patients treated by CRRT. In the present study, in a cohort of 9 critically ill patients with a diagnosis of severe sepsis and ARF, the technique described showed satisfactory results in terms of the presence or absence of the microorganism, even when standard blood culture was negative. Despite continued evidence of septic shock, repeated blood cultures of only 2 patients (22%) were positive. However, bacterial DNA was identified from the blood of 6 patients (67%), as well as the 2 septic patients with documented positive blood cultures. Interestingly, in all patients bacterial DNA was found on the filter blood side, even when the DNA test in the blood was negative. These findings suggest that hemofilters might work as concentrators: synthetic membranes used during RRT at the ultrafiltration rates constantly adsorb proteins within their hollow fibers. The thickness of this protein layer at the blood-membrane interface progressively increases, resulting in a potential deposit of bacteria or bacterial DNA beneath this protein gel. In case of an undetectable amount of bacteria and bacterial DNA from blood, this amount may be detected within the 'concentrating' hemofilter. Finally, bacterial DNA was detected in the dialysate compartment of the hemofilters in 78% of subjects. Bacterial DNA weighs several billion Daltons [20] and thus it does not traverse a standard RRT filter with a cutoff of 50 kD. Fragmented bacterial DNA, whose size is less than the hemofilter pores, might cross the membrane and be present in the dialysate compartment. Also, these bacterial DNA fragments must include the 540-bp conserved region of the bacterial 16S rRNA gene detected by the primers for the PCR amplification. In light of these results, a potential role of hemofilters might be speculated in clearing the bacterial circulating DNA by adsorption from the bloodstream. The clinical impact of this clearance was not evaluated in the present study. However, bacterial DNA was not found in the centrifuged and precipitated UF. A recent study by Hansard et al. [21] demonstrated that pathogenic bacteria can be recovered by the culture of UF in clinically septic, blood culture-negative patients. On the contrary, in our patients we could not recover bacterial DNA in the UF of CVVH using DNA detection with the molecular technique. This was confirmed even in septic

patients with positive blood culture (subjects 2 and 3A). The explanations for the incongruity between the detection of bacterial DNA in the UF and dialysate compartment may be: (1) bacterial DNA in the UF is highly diluted and undetectable even by centrifugation or precipitation, and (2) hemofilters have adsorptive properties to bacteria/bacterial DNA on both sides of the membrane.

This technology has a number of limitations. First, this method needs personnel experienced in molecular biology and must be performed under careful quality control to prevent false-positive results. Sequencing analysis is more expensive than the traditional identification methods and in most cases is not useful because of the co-presence of more then one microorganism. A different strategy is imposed if there is a situation in which mixed culture is likely, such as in critically ill patients admitted to the ICU for a long duration where superinfection is often found. In this case, it is impossible to interpret and compare the sequencing results with a standard database and the results will be reported as 'unsequentiable'. The 16S rRNA amplification can however be used as a rapid and very sensitive screening test of positive versus negative samples, while specific primers for defined bacteria must be used to further identify the suspected pathogenic organisms. Furthermore, this method detects bacterial DNA or the fragmentation of bacterial DNA, which may remain in the body despite the absence of viable microorganisms (as demonstrated in subject 3B). Therefore, the diagnostic result of the test should be interpreted simultaneously with the clinical presentation of the patient.

Conclusion

In summary, the use of PCR amplification and sequencing of the 16S rRNA gene in the detection of pathogenic bacteria trapped in the hemofilter of patients undergoing RRT is an alternative tool for microbiological screening in blood culture-negative septic patients. Polyethersulfone high-flux hemofilters adsorb bacterial DNA within their fibers and, potentially, clear these substances from the bloodstream.

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The New KDOQI™ Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and CKD

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Key Words
Chronic kidney disease · Diabetes · Guidelines, KDOQI

Abstract
Background/Aims: The National Kidney Foundation (NKF) recently published new guidelines and clinical practice recommendations for the diagnosis and management of patients with diabetes and chronic kidney disease (CKD). ***Methods:*** Guidelines were developed using an evidence-based approach. When sufficient evidence was lacking, recommendations were developed that reflect expert opinion. ***Results:*** Guidelines describe the process for screening and diagnosis of kidney disease in the setting of diabetes and the management of hyperglycemia, hypertension, dyslipidemia, and nutrition. Recommendations describe the management of albuminuria in the normotensive diabetic patient and the potential value of albuminuria as a marker of treatment efficacy; the impact of diabetes and CKD in special populations; the importance of behavioral self-management; and the value of intensive multifaceted intervention in these high risk patients. ***Conclusions:*** The new guidelines and recommendations update and extend the scope of the NKF's Kidney Disease Outcomes Quality Initiative (KDOQI™).

Nearly 21 million persons in the US have diabetes. About 5–10% of them have type 1 diabetes, which develops as a consequence of the body's failure to produce insulin. Most others have type 2 diabetes, which develops because of the body's failure to properly use the insulin it produces. Projections on the future burden of diabetes suggest that the prevalence will increase 165% between 2000 and 2050, with the greatest increases in the population over 75 years old and among African-Americans [1]. Children are also increasingly affected by diabetes. Most of the increase in the prevalence of diabetes in children and adults is attributable to the alarming rise in obesity.

Diabetes is the leading cause of chronic kidney disease (CKD) in the US, with microalbuminuria found in 43% and macroalbuminuria in 8% of those with a history of diabetes [2]. Moreover, diabetes accounts for 45% of prevalent kidney failure, up from 18% in 1980 [3]. Substantial under-diagnosis of both diabetes and CKD leads to lost opportunities for prevention, and inadequate or inappropriate care of patients with diabetes and CKD may contribute to disease progression.

A similar report was recently published in Nephrology News and Issues (Nelson RG, Tuttle KR: NFK releases new KDOQI guidelines for diabetes and CKD. Nephrol News Issues 2006;20:29.

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Table 1. Work group membership

K/DOQI™ advisors	
Adeera Levin, MD	Michael Rocco, MD
Work group	
Pablo Aschner, MD, MSc	Robert G. Nelson, MD, PhD (Co-Chair)
George L. Bakris, MD	Mary Ann Sevick, ScD, RN
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S. Michael Mauer, MD	Tom Hostetter, MD
Mark E. Molitch, MD	Marc A. Pfeffer, MD, PhD
Andrew Narva, MD	
Evidence review team	
Ethan Balk, MD, MPH	Gowri Raman, MD
Joseph Lau, MD	Katrin Uhlig, MD

Table 2. Staging of chronic kidney disease

Stage	Description	GFR
1	Kidney damage with normal or ↑ GFR	≥90 (with CKD risk factors)
2	Kidney damage with mild or ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR = Glomerular filtration rate; CKD = chronic kidney disease.
Adapted with permission from the National Kidney Foundation [2].

The new Kidney Disease Outcomes Quality Initiative (KDOQI™) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and CKD were developed by the National Kidney Foundation (NKF) to improve outcomes in patients with diabetes and CKD by providing strategies for the diagnosis and management of CKD in the setting of diabetes. The guidelines will be published in 2007 as a supplement to the *American Journal of Kidney Diseases* [4]. Since this review was submitted prior to publication of the guidelines and recommendations, some portions may differ slightly from the published report.

The work group that developed the guidelines and recommendations consisted of individuals with expertise in nephrology, diabetology and endocrinology, pharmacology, social work, nursing and nutrition. They were assisted by an evidence review team with expertise in systematic review of the medical literature. The members of these groups are listed in table 1. Evidence for clinical practice guidelines was derived from a systematic summary of the available scientific literature. When sufficient evidence was lacking, clinical practice recommendations were developed that reflect expert opinion.

The target patient population for this clinical practice guideline is those with CKD stages 1–5, including dialysis and transplant patients (table 2). The emphasis of the guideline, however, is on stages 1–4, since the evidence in stage 5 is either lacking or addressed in other NKF-KDOQI™ guidelines. Consideration is given to the diagnosis, impact, and management of diabetes and CKD in children, adults, the elderly, pregnant women, and in different racial and ethnic groups. The intended readers are practitioners who manage patients with diabetes and CKD, including, but not limited to, primary care providers, nephrologists, diabetologists and endocrinologists, cardiologists, nurse practitioners and physician's assistants, nurses, dietitians, and diabetes educators.

The guidelines describe the process for screening and diagnosis of kidney disease in the setting of diabetes and the management of diabetes and CKD, including the management of hyperglycemia and general diabetes care, hypertension, dyslipidemia, and nutrition. Special topics such as the management of albuminuria in the normotensive diabetic patient and the potential value of albuminuria as a marker of treatment efficacy; the impact of diabetes and CKD in special populations, including minorities and pregnant women; the importance of behavioral self-management, and the value of intensive multifaceted intervention in these high risk patients are also addressed as recommendations.

The new guidelines update and extend the scope of the NKF-KDOQI™ Clinical Practice Guidelines that presently offer strategies to identify CKD [2] and manage hypertension [5], dyslipidemia [6], bone disease [7], anemia [8], nutrition [9], and cardiovascular disease [10] in patients with CKD.

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Coronary Artery Calcifications: A Critical Assessment of Imaging Techniques

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Key Words

Coronary artery · Calcification, coronary artery · Imaging, coronary artery · Calcium scoring, coronary · Computed tomography, electron beam · Multi-slice spiral computed tomography

Abstract

The presence of coronary artery calcifications is a distinct marker of atherosclerosis and the severity of calcifications is claimed to reflect a patient's individual plaque burden. Calcium deposits can be detected non-invasively by cardiac computed tomography (CT). This enables detection of coronary artery disease in a subclinical stage, description of the extent of the disease and risk estimation of future cardiovascular events. However, calcium quantification may also be used to monitor atherosclerotic disease, for example in the context of an intensified medical treatment. For years, electron-beam CT has been considered the gold-standard for calcium scoring. However, multi-slice spiral CT has recently captured the market and seems to achieve better measuring results with regard to the accuracy and reproducibility of calcium scores because of its superior image quality. For an optimal comparability of different CT techniques the calcium load should now be reported as absolute calcium mass rather than the traditional scoring methods.

Introduction

The ability of selected imaging techniques, such as computed tomography (CT), to detect and quantify coronary artery calcifications as a marker of the presence and severity of coronary atherosclerosis has created a growing clinical interest in these applications. This article discusses the clinical importance of coronary artery calcifications, reviews the potential indications for coronary artery calcium scoring and describes the different imaging and reporting methods with special emphasis on electron beam CT (EBCT) and multi-slice spiral CT (MSCT). In addition, the implications of coronary calcium measurements in patients suffering from chronic renal failure will be mentioned.

Significance of Coronary Artery Calcium Measurements

Calcium deposits in the coronary arteries are a highly sensitive marker of underlying coronary atherosclerotic disease. The amount of coronary artery calcium is claimed to reflect the patient's individual coronary artery plaque burden and is considered to be associated with the likelihood of future cardiac events [1–3]. Thus, measurements of coronary artery calcium are generally used for clinical

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risk stratification and individual lifestyle modification [1]. However, a probably more important role of coronary artery calcium measurements may be the evaluation of the response of atherosclerotic plaque burden to medical treatment, for example in patients receiving lipid-lowering drugs or in hemodialysis patients receiving phosphate binders.

Especially patients with chronic renal failure suffer from a significantly increased cardiovascular morbidity and mortality due to accelerated atherosclerotic disease [4]. Renal failure patients have more advanced stages of atherosclerosis when compared to patient with normal renal function. Remarkably, type VII lesions according to the Stary classification, i.e. calcified coronary artery plaques, are found significantly more frequently in renal failure patients. However, it has to be noted that the relationship between coronary artery calcification and coronary artery stenosis is complex and that calcification and luminal obstruction are two different features of coronary atherosclerotic disease [5]. Whereas the absence of calcifications in the coronary arteries makes significant stenosis very unlikely [6–9], even advanced atherosclerotic lesions with heavy calcifications do not necessarily cause significant luminal obstruction. Calcium deposits are frequent elements of ruptured plaques causing significant stenosis, but calcium deposits can also be found in stable, non-obstructing plaques [3]. Although the likelihood of an occlusive coronary artery increases with the amount of calcium, there is no one-to-one relationship. Therefore a calcification does not unavoidably predict luminal obstruction and the sites of coronary artery calcifications do not correlate with the sites of significant coronary artery stenoses [5, 6, 9]. Thus, it remains controversial whether coronary artery calcium scoring is useful for the individual prediction of an adverse coronary event in each individual, for example in a patient with chronic renal failure, an increased calcified coronary artery plaque burden but absence of any other evidence for ischemic heart disease.

Imaging Methods for the Assessment of Coronary Artery Calcifications

In the past numerous imaging modalities have been used to demonstrate coronary calcification, for example fluoroscopy, intravascular ultrasound, EBCT, single-slice CT and MSCT [9].

For a long time fluoroscopy has been used to assess coronary calcifications. However, the capability of fluoroscopy to detect small calcium deposits is poor. Usually only highly calcified, larger atherosclerotic lesions are detectable with fluoroscopy. In addition, fluoroscopy may suffer from an impaired accuracy and considerable interstudy variability depending on the patient's individual imaging conditions as well as the training and experience of the examiner [9].

Intravascular ultrasound is a clinically important tool for the assessment of the coronary atherosclerotic lesion including characterization of atherosclerotic plaque composition and visualization of calcifications [9]. However, intravascular ultrasound is invasive, quite expensive and visualizes only an incomplete portion of the entire coronary artery tree. Intravascular ultrasound is therefore not a suitable imaging technique for screening purposes or for repeated follow-up examinations.

Cardiac CT is extremely sensitive in the detection and quite accurate in the quantification of coronary artery calcifications [9]. In addition, cardiac CT is a noninvasive and quick method that is easy to perform. Thus, cardiac CT is currently regarded as the standard-of-care for the detection and quantification of coronary artery calcifications although the radiation exposure of this technique must be taken into account. However, there was recently a controversial debate about the most suitable cardiac CT imaging technique for coronary artery calcium scoring. The arguments advanced in discussing the pros and cons of the potential techniques pertain to temporal resolution, spatial resolution, image noise, radiation exposure, availability and reference values (see below) [10].

On rare occasions, also other imaging techniques, such as chest radiography, echocardiography and magnetic resonance imaging have been used to detect coronary artery calcifications, but all these methods have no clinical value due to the various imaging restrictions and very low diagnostic accuracy [9].

Cardiac CT for the Assessment of Coronary Calcifications – Technical Principles

EBCT has been very well validated in several experimental and clinical studies and has been extensively used in the past for coronary artery calcium scoring. EBCT was therefore considered the reference method (so-called 'gold-standard') for coronary artery calcium scoring against which all new methods must be judged. The heart of the EBCT scanner is a stationary electron gun that runs at a constant tube current of 625 mA and a tube voltage of 130 kV. The EBCT unit generates an electron beam

that is deflected towards and focused onto one of four target tungsten rings (210°). The emanating radiation fan meets one of two detector rings (216°) on the opposite side. The invariable tube current yields a fixed mAs product that cannot be adapted to the individual patient's body constitution. For coronary artery imaging the so-called ECG-triggered 'single-slice mode' is used, which utilizes 100 ms sweeps along one of the four target rings and acquires a stepwise volumetric data set by moving the patient incrementally along the z axis. Using a standard EBCT scanning protocol, a stack of 40 contiguous slices with a thickness of 3.0 mm is acquired with prospective ECG triggering in diastole.

MSCT is characterized by multiple detector rows that are concurrently targeted by the rotating X-ray tube which allows simultaneous acquisition of multiple axial slices. The first generation of MSCT scanners with 4 detector rows was introduced into clinical practice in the late 1990s. Nowadays MSCT scanners with up to 64 detector rows are in widespread use.

MSCT scanning allows an alternative approach to ECG-synchronized data acquisition, the so-called retrospective ECG gating. For retrospective gating a spiral MSCT scan is performed while the patient's ECG is simultaneously recorded. MSCT data and ECG are synchronized afterwards and images are created at a particular time point within the RR interval. This technique allows retrospective reconstruction of images at any phase of the cardiac cycle. Retrospective ECG gating involves irradiation throughout the entire cardiac cycle and requires a slow table feed for data oversampling to ensure complete phase-consistent coverage of the heart.

The accuracy of coronary artery calcium scoring crucially depends on the occurrence of motion artifacts. To prevent significant motion artifacts a high temporal resolution, namely a short acquisition time and the selection of the optimal phase within the cardiac cycle, is of utmost importance. EBCT achieves a short acquisition time of 100 ms for coronary artery calcium scanning by its technical design that does not involve rotating mechanical components. In contrast, MSCT reaches an acquisition time of only 115–250 ms depending on the scanners maximum gantry speed (330–500 ms/rotation) if a conventional half-scan image reconstruction technique is used. However, the temporal resolution can theoretically be increased by using so-called multi-cycle reconstruction algorithms which combine the raw data required for half-scan image reconstruction not from a single rotation within one cardiac cycle but instead collect data from multiple partial rotations over several cardiac cycles to create images. The factor by which this algorithm improves temporal resolution is equal to the number of cardiac cycles used. Selection of the optimal phase within the cardiac cycle is also needed to minimize motion artifacts. In general, reports in the literature suggest that the optimal cardiac phase for coronary artery imaging is a time window during early diastole (at 40–50% of the RR interval) and another during late diastole (at 80% of the RR interval). However, it is difficult to predict the most suitable time window for an individual examination. Moreover, it has to be noted that each coronary artery has its own optimal time window and that the length and position of the window change with the heart rate. Thus, choosing the optimal cardiac phase by using retrospective ECG gating (where any number of data sets at any time point within the RR interval can be reconstructed afterwards) allows a more effective minimization of motion artifacts when compared with prospective ECG triggering (where the time point within the RR interval has to be selected beforehand).

Spatial resolution and image noise is a crucial parameter for visualization of the coronary arteries and the detection of small calcium deposits. An EBCT standard protocol typically acquires a stack of contiguous slices with a thickness of 3 mm, whereas MSCT now allows acquisition of overlapping slices with a thickness of less than 1 mm. Despite a thinner slice thickness, MSCT scans have a lower image noise and thus a more favorable signal-to-noise ratio compared with EBCT. High image noise levels in EBCT may prevent the detection of small calcium deposits (false-negative result) or may lead to a considerable overestimation of the calcium burden (false-positive result) [11]. Here, the fact that the mAs product of the electron beam scanner cannot be changed by selecting a different tube current is clearly a disadvantage since the scanner operates at a constant tube current and voltage.

Consequently data in the literature demonstrated that MSCT achieves calcium scoring results with at least similar or superior accuracy and reproducibility than EBCT [12–18].

Methods to Quantify Coronary Artery Calcifications in Cardiac CT

Three different ways are commonly used to describe the amount of coronary artery calcium: calculation of the Agatston score, calculation of a volume score and calculation of absolute calcium mass.

The traditional way to describe the calcified coronary artery plaque burden was established by Agatston et al. [19] in 1990. This score is determined by multiplying the area of a calcified coronary artery plaque by a density cofactor chosen on the basis of the peak attenuation of the lesion. The total Agatston score is then calculated as a sum score of all lesions identified within the entire coronary artery tree.

A calcium volume score is simply calculated as the number of voxels of all calcified plaques multiplied by the volume of one voxel. However, it must be noted that a volume score does not necessarily stand for the real volume of coronary artery calcifications, because the definition of calcium is threshold dependent [18].

The absolute calcium mass is as a uniform measure of calcified coronary artery plaque burden that is calculated by multiplying the volume of every calcified plaque with its density value followed by multiplying the sum of all measurements with a scanner- and scan protocol-specific calibration factor. Using the absolute calcium mass instead of the Agatston score or the volume score improves inter-study reproducibility and therefore guarantees a better comparability of calcium measurements even if the data sets are obtained from different scanner types and/or different scan protocols [1, 18].

Non-Contrast-Enhanced versus Contrast-Enhanced CT Studies

Non-contrast-enhanced CT studies provide information about the presence of coronary atherosclerosis and the extent of coronary atherosclerotic plaque burden but does not enable assessment of the vessel lumen, namely the direct visualization of significant coronary artery stenoses. Thus, an attempt was recently made both to measure the coronary artery calcium load and to detect coronary artery stenoses in contrast-enhanced CT studies. Although the great majority of calcified atherosclerotic plaques are still visible on contrast-enhanced CT studies, intravascular contrast material may simulate vascular calcification which may impair the accuracy of calcium scoring results and may hide small calcium deposits [20]. In addition, the potential nephrotoxicity of intravascular contrast media could not be ignored because this may be particularly harmful in patients with compromised renal function. Thus, for the assessment of coronary artery calcifications the use of a non-contrast-enhanced CT study protocol is strongly recommended.

Radiation Dose in CT Studies

In general, all indications for CT examinations must be established with caution due to the use of ionized radiation. For calcium scoring the effective radiation dose of standard CT scan protocols is about 1 mSv in EBCT and between 1 and 6 mSv in MSCT [21–23]. For comparison the average dose of the natural annual background radiation is approximately 3 mSv. However, several attempts have been made to further reduce the CT radiation dose. As an example, the use of specific low-dose CT scanning protocols with reduced mAs und kV settings and the so-called tube current modulation technique may substantially reduce the patient's radiation dose in MSCT without losing the reliability of coronary artery calcium measurements [22–26].

Conclusion

MSCT is now the accepted standard of care and has displaced EBCT in the detection and quantification of coronary artery calcifications. MSCT has an improved image quality, which is characterized by higher detail resolution and lower image noise levels than EBCT. In addition, MSCT offers the chance for retrospective data selection using ECG-gating to avoid motion artifacts. However, limited temporal resolution of current MSCT techniques seems still to be a certain restriction for the accuracy and reproducibility of coronary calcium measurements. Quantification of coronary calcifications should be reported as absolute calcium mass for better comparison of measuring results between the different scanner types and scan protocols. If available, strategies for reducing the radiation dose, such as tube current modulation techniques, are recommended.

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Practical Approaches to Management of Hyperphosphatemia: Can We Improve the Current Situation?

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Key Words
Hyperphosphatemia, management · Phosphorus balance · Hemodiafiltration

Abstract
Despite advanced technology and regular and efficient dialysis treatment, the prevalence of hyperphosphatemia still is unacceptably high. Nevertheless, a neutral phosphorus balance level can generally be achieved by optimization of dialysis prescription in combination with individualized dietary and medical strategies. Besides increasing the fraction of inorganic phosphate (iP) removed by convection through the application of hemodiafiltration, extension of daily or weekly treatment time is the most promising way to neutralize phosphorus balance. Dietary phosphate restriction, the second corner stone of phosphate management, bears the risk of development of protein malnutrition. Phosphate binders (PBs) effectively reduce intestinal iP absorption, but are mostly dosed inadequately in relation to meal phosphorus content. Phosphate management may be substantially improved by enabling patients to self-adjust the PB dose to individual meal phosphate content, similar to self-adjusting insulin dose to carbohydrate intake by diabetics. A recently developed Phosphate Education Program (PEP) provides simple training tools to instruct patients to eye-estimate meal phosphorus content based on newly defined phosphorus units instead of milligrams. PEP is the first approach applying the concept of patient empowerment in the management of hyperphosphatemia in dialysis patients.

Introduction

Cardiovascular mortality is excessively high in the dialysis population worldwide and disturbances in calcium and phosphate metabolism have been identified as important and modifiable risk factors for this patient population [1–3]. The adjusted mortality risk increases by 20–40% with extreme rises in inorganic phosphate (iP; up to 4.2 mmol/l) with similar effects reported for a calcium-phosphorus product of >5.9 $mmol^2/l^2$ [3]. An increased calcium-phosphorus product in conjunction with normal or high calcium levels is associated with hydroxyapatite formation in blood vessels, myocardium and heart valves resulting in structural dysfunction. In recognition of these fatal consequences of abnormal calcium and phosphate metabolism, international guidelines have been published urging for normalization of phosphate levels in chronic kidney disease (CKD) patients. Recommendations include target serum phosphate levels of

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<4.6 mg/dl for CKD stages 3 and 4 and between 3.5 and 5.5 mg/dl for those with CKD stage 5 [4]. However, despite advances in dialysis technology and regular and efficient dialysis treatment, the goal of normalization of serum phosphate levels is rarely achieved by extracorporeal therapy and the prevalence of hyperphosphatemia remains unacceptably highly. Data from the international Dialysis Outcome and Practice Pattern Study (DOPPS) suggest that fewer than 50% of patients meet the target value for serum phosphate and that currently only 5% of all dialysis patients achieve all 4 of the K/DOQI goals for mineral metabolism [5].

Should this be interpreted as a discouragement to continue to thrive for the achievement of normalization of phosphate levels and to accept the increased phosphate levels in the majority of our patients? This article will analyze the limitations of current treatment strategies and offers solutions to overcome these limitations in the practical management of hyperphosphatemia.

The Goal: Achieving Neutral Phosphate Balance

Neutral phosphorus balance is achieved when total body phosphorus generation (G_{iP}) is balanced by total body phosphorus elimination (J_{iP}). Whole body iP generation is dependent on (i) intestinal iP and protein absorption and (ii) the amount of iP released from or deposited in endogenous tissues, such as bone. Phosphate binders (PBs) are used to decrease G_{iP} by effectively lowering intestinal phosphorus absorption. In the face of lacking renal function, iP elimination in dialysis patients is almost completely dependent on dialytic iP removal. It is therefore clear that a neutral phosphorus balance can only be achieved when the total amount of iP, which has either been intestinally absorbed or released from endogenous tissues during the interdialytic phase, is completely removed by dialysis. Since phosphate removal during dialysis is limited, as delineated below, the only way to achieve neutral balance with current treatment strategies is to lower G_{iP} to a minimum by optimizing the effects of PBs and inhibiting or preventing the release of phosphorus from endogenous tissues. The difference between iP generation and total iP removal is the quantity potentially deposited in tissues. In hemodialysis (HD) patients overall iP mass balance can be described as follows:

$$\Delta Tc_{iP} = G_{iP} - Jd_{iP} \quad \text{(eq. 1)}$$

with:

$$G_{iP} = (F_{iP} - Jb_{iP}) \times Z_{iP} + (R_{iP} - D_{iP}) \quad \text{(eq. 2)}$$

where: ΔTc_{iP} = phosphate accumulation in tissue compartments; G_{iP} = phosphorus generation; Jd_{iP} = dialyzer phosphorus removal; F_{iP} = phosphorus content of ingested food; Jb_{iP} = phosphorus removal by PBs; Z_{iP} = intestinal phosphorus absorption rate; R_{iP} = phosphorus release from endogenous tissues, and D_{iP} = phosphorus deposition in endogenous tissues.

What Are the Current Limitations of HD Phosphorus Elimination?

Inorganic phosphorous acts like a small molecular weight toxin with a distribution volume equal to total body water. However, the kinetics of intradialytic phosphate removal differ significantly from classical urea kinetics. While blood urea nitrogen continuously declines during HD and, following a short rebound period immediately after termination of HD, steadily increases during the interdialytic interval, serum iP levels, after an initial relatively steep decline during the first 2–2.5 h, reach a plateau without a further decline during the second half of HD. Moreover, after termination of HD plasma iP rapidly rebounds to nearly predialysis levels [6, 7]. The intradialytic iP plateau predictably occurs when plasma iP baseline levels drop to about 40% of predialysis values. Since dialyzer phosphate clearance does not change during this time, these findings suggest that a substantial fraction of iP removal occurs from the intracellular space and that the transfer rate from the intracellular compartment to the plasma completely balances phosphate removal rate across the dialyzer [8].

For various reasons the average iP removal during a standard conventional 4-hour HD treatment is limited to about 700–900 mg:

(1) Dialyzer iP clearances are much higher from water and plasma than from whole blood. Unlike urea, iP is not freely diffusible across cellular membranes and thus, blood cells act like a barrier for iP diffusion, increasing the diffusion resistance for iP at the dialyzer blood side. Accordingly, intradialytic iP clearance is inversely correlated with hematocrit [9], and decreases in response to an increase in hematocrit during ultrafiltration.

(2) Membrane surface area is an important determinant of iP clearance and should be maximized in order to improve phosphate removal [10]. Limitations are set by the availability of dialyzers with larger membrane surface area.

(3) An increase in blood flow rate (Qb) to >300 ml/min has only limited effects on phosphate removal [11],

whereas raising dialysate flow rate (Qd) is associated with a small, but significant (10%) increase in phosphorus clearance [9].

(4) Limiting treatment time to 4–5 h is the major barrier to better phosphate management. Treatment time is the most important factor governing phosphate elimination and extending treatment time increases iP mass removal even when urea-Kt/V is not changed [12]. The fact that blood iP levels reach a plateau during dialysis favors longer treatment times since, in contrast to urea, a stable concentration gradient across the dialyzer membrane is maintained throughout the second treatment phase, thereby sustaining iP mass removal. It is therefore evident that iP removal benefits much more from extended treatment times than urea removal.

(5) Phosphate removal from peripheral tissues depends on tissue, especially muscle perfusion, which may be reduced due to hypotension or peripheral atherosclerotic vascular disease. Physical activity before or during HD increases iP mass removal by 6–9% [12].

Overcoming the Limitations of HD Phosphorus Elimination

Besides adding a substantial fraction of convective iP removal to the conventional HD treatment, extending daily or weekly treatment time seems to be the most promising way to neutral phosphorus balance. Hemodiafiltration has been demonstrated to enhance phosphate removal by 30–40% up to 1,200 mg/treatment and, on the long-run, to reduce the predialysis plasma iP concentration [13, 14]. Increased intradialytic iP removal has been reported to be associated with a faster and steeper phosphate rebound, which is explained by a stronger stimulation of iP mobilization from endogenous tissues. However, even the removal of 1,200 mg iP/HD is not sufficient to balance an average G_{iP} of 4–5,000 mg iP/week.

Increasing dialysis frequency to 5 or 6 times/week has been reported to be associated with better phosphate control. Several non-randomized studies in small patient cohorts demonstrated significantly improved iP control with daily nocturnal HD (5–6 × 8 h), in some cases even without the use of PBs [15, 16]. Normalization of iP with concomitant reduction or complete withdrawal of PB medication was achieved with 6 × 3 h short daily HD [17], but not with shorter weekly treatment time (6 × 2–2.5 h) [18, 19]. Daily hemodiafiltration may be an attractive alternative offering the combination of short treatment times with increased dialytic iP removal [20].

What Are the Current Limitations of Dietary Phosphorus Restriction?

Hyperphosphatemia would not be a problem without dietary phosphorus ingestion and vascular calcification would most likely be less of a problem. However, although dietary phosphorus restriction is always listed as a corner stone of phosphate management, it is rarely performed successfully in clinical practice for various reasons.

(1) Patients need excessive dietary advice and teaching to be able to restrict phosphorus intake while maintaining an adequate protein/calorie intake. In healthy individuals the average dietary phosphorus intake ranges from 1,000 in females to 1,800 mg/day in males.

(2) Since dietary phosphorus ingestion is closely related to protein intake, phosphorus restriction bears the risk of developing protein malnutrition. For dialysis patients a protein intake of 1.0–1.2 g/kgbody weight/day and maximum phosphorus intake of 1,000 mg/day has been recommended, but a much lower mean dietary intake has been reported with 53.7 ± 28.6 g for protein and 903 ± 468 mg/day for phosphorus [21]. Achieving adequate dietary protein intake will, in most cases, be associated with higher phosphorus intake.

(3) Available tables and booklets listing phosphorus and protein content of food components are cumbersome and time-consuming to use. Even beverages available in the US vary substantially in their iP content [22].

(4) Phosphorus-containing additives in unknown amounts are frequently used for food preservation. It has been estimated that phosphorous intake from additives may amount to 1,000 mg/day [23]. Phosphorus additives are absorbed almost 100% into the circulation. Manufacturers are not required to list the phosphorous content on food labels, thus making it difficult for patients to identify those high-phosphorus foods.

What Are the Current Limitations of PB Therapy?

Patient incompliance with PB prescription is assumed to be a major reason for hyperphosphatemia including inadequate timing of PB intake in relation to the meal, completely neglecting PB intake and taking less than the prescribed amount.

Fixed PB dosing regimens, such as 2 PB pills with each meal, are another problem. This strategy does not take into account the normal day-to-day variations in meal phosphorus content. Our own observations show that dietary iP intake for breakfast, lunch and dinner may vary

between 100 and 800 mg iP, and even snacks, which are in many cases not covered by PB medication, may contribute up to 400 mg to daily total iP intake. According to these observations only 30% of meals are covered with an adequate PB dose, with the majority of meals being under-dosed.

Potential short- and long-term side effects, such as hypercalcemia, may limit the total amount of PBs prescribed per day and, finally, economic reasons may affect PB therapy in many countries where budget restrictions for drug prescriptions have been implemented.

Overcoming the Limitations of Dietary Phosphate Restriction and PB Therapy

From a general viewpoint, it can be stated that it should always be possible to reduce intestinal iP absorption to a level which can be balanced by dialysis phosphorus elimination. That neutral phosphorus balance can be achieved with the combined efforts of today's treatment options has been demonstrated by various studies on the efficacy of PBs. In the treat-to-goal study normophosphatemia was achieved within a couple of weeks after study initiation [24]. The 'secret' of this success lies in repeated and intensive patient counseling and stepwise adjustments of PB dosage to serum phosphate levels. In the treat-to-goal study sevelamer-treated subjects ingested an average of 8 tablets (800 mg), while calcium acetate-treated subjects ingested an average dose of seven tablets (667 mg)/day. In both study groups normalization of phosphate levels (5.1 $\pm$ 1.2 and 5.1 $\pm$ 1.4 mg/dl, respectively) was achieved. The more intense patient care in a study setting may also have contributed to the successful lowering of phosphate levels.

In order to adequately lower intestinal phosphorus absorption, PB dose ideally should be adjusted to the meal phosphorus content on a meal-to-meal basis, similar to adjusting the insulin dose to a meal carbohydrate content in the treatment of diabetes. A new concept (Phosphate Education Program, PEP) has recently been developed which allows patients to self-adjust the PB dose to the phosphorus content of each individual meal. This can only be successfully achieved when assessment of the phosphorus content of a meal is quick and simple without involving multi-page food tables, booklets or even computers. The innovative concept is based on the introduction of the phosphorus unit (PU) which indicates the food phosphorous content, with 1 PU assigned per 100 mg of phosphorous per serving size. Since food components belonging to the same food group (e.g. meat, sea food, vegetables, etc.) tend to have similar phosphorus content, just one PU value can be assigned to whole food groups. For example, any fish filet (serving size 150 g) = 4 PU, and any meat (serving size 150 g) = 3 PU.

The new concept bears the advantage that patients do not have to memorize the phosphorus content of each individual food component, but only the PU value for a limited number of food groups. After eye-estimating the PU content of a meal, the patient self-adjusts the PB dose according to a PB/PU ratio prescribed by the nephrologist. After introducing the PEP concept to the patient, the PB/PU ratio is titrated to the patient's individual needs by repeatedly measuring predialysis serum phosphate levels and re-adjusting the PB/PU ratio until phosphate targets have been achieved. This new concept moves away from strict dietary phosphorus restriction towards a more adequate dosing of PBs. It allows patients to maintain an adequate dietary protein intake with a more liberal diet while at the same time reducing the risk of developing hyperphosphatemia. Diet-related hyperphosphatemia can be prevented by adequate PB dosing. PEP (www.pep-ernaehrungsprogramm.de) is the first approach applying the concept of patient empowerment in the management of hyperphosphatemia in dialysis patients.

Conclusions

Although the prevalence of hyperphosphatemia is still high, it should not be viewed as an indication that it is impossible to achieve the goals set for management of mineral and bone metabolism. Current treatment options including dialysis, dietary phosphorus restriction and the use of PBs can be combined to achieve normalization of phosphate levels.

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Antibodies to Periodontal Organisms Are Associated with Decreased Kidney Function

The Dental Atherosclerosis Risk in Communities Study

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Key Words
Atherosclerosis, dental · Periodontal disease · Kidney disease · Serum antibody · Oral pathogens

Abstract
Background/Aims: Increasing evidence suggests that clinical signs of periodontal disease are independently associated with renal impairment. However, no studies have examined the possible linkage of kidney disease with serum antibody to oral pathogens. ***Methods:*** The periodontal disease status was assessed in an older community-dwelling population (Dental Atherosclerosis Risk in Communities) to include: clinical measurements; oral biofilm microbial composition by DNA checkerboard, and serum antibody immunoglobulin-γ (IgG) titers to specific bacteria by immunocheckerboard. Baseline characteristics were used to compute estimated glomerular filtration rate defining eGFR <60 ml/min/1.73 m^2 as impaired renal function in 103 of 5,032 subjects. Levels of serum IgG to specific oral bacteria were categorized by quartiles (comparing upper vs. lower three) as high titer and GFR <60 as the dependent variable in logistic regression models, adjusting for multiple comparisons (Hotelling T^2) and traditional risk factors including age, race, smoking, diabetes, hypertension, body mass, waist-to-hip ratio, serum triglycerides, HDL, and LDL cholesterol. ***Results:*** High levels of serum IgG to selected periodontal pathogens including *Porphyromonas gingivalis, Treponema denticola* and *Aggregobacter actinomycetemcomitans* were associated with an increased odds for GFR <60 ml/min/1.73 m^2, adjusted odds ratio ranging from 1.6 to 1.8 and $p < 0.05$. ***Conclusions:*** Elevated IgG to periodontal pathogens is significantly associated with impaired kidney function, independent of traditional risk factors. Prospective studies are necessary to confirm these findings.

Introduction

Over the last decade, periodontitis, a chronic bacterial infection of the oral cavity, has emerged as a novel risk factor for cardiovascular disease (CVD). Biofilms in the oral cavity on soft and hard tissues contain greater than 10^{10} organisms, many of which are pathogenic in that they can evade local host defenses to elicit local inflammation, as well as gain access to the circulation to induce systemic inflammation. Within the local periodontal tissues, monocytes and other immune cells recognize lipopolysaccharides in the bacterial cell wall and other toll-

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like receptor agonists and secrete various inflammatory mediators, including prostaglandin E_2 (PGE_2), interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNFα) [1, 2]. The effects of systemic dissemination of these bacteria results in hepatic activation of the acute phase response with increases in C-reactive protein (CRP) and IL-6 [2–4]. Furthermore, oral organisms are capable of invading the endothelial lining of the major elastic arteries [5] and have both nucleotide signals and viable bacteria within atheromatous plaques [6, 7]. Consequently, these bacteria in combination with inflammatory cytokines and acute phase reactants are believed to contribute to an acceleration of systemic atherosclerosis [8–10], and the development of clinical CVD. Indeed, several studies, cross-sectional [11, 12], case-control [13–16], and longitudinal [17–22], have demonstrated an association between the clinical signs of periodontitis and atherosclerotic cardiovascular disease. A smaller number of reports did not show a significant association [19, 23, 24].

Recently, studies have shown that systemic antibody to specific oral pathogens has even stronger associations with cardiovascular risk for events other than clinical signs of disease [25–29]. (This result has been suggested to perhaps reflect the fact that the elevated titers reflect a greater systemic exposure to these pathogens, which is not necessarily related to traditional signs of local periodontal disease.)

Chronic kidney disease (CKD) shares many risk factors with CVD. We had previously postulated that periodontitis may be associated with CKD, and demonstrated this association in two independent population-based surveys [30, 31], and a cohort of patients with end-stage kidney disease [32–34]. These studies used traditional measures of periodontal disease, including a historical definition such as the extent of bone loss around the teeth, but did not consider microbial etiology. Yet the link between periodontal disease and CKD may be more likely attributable to concomitant infection and inflammation that is not readily measured by the clinical evaluation of periodontal disease. In the present study we explored the relationship between serum antibodies to periodontal pathogens and renal insufficiency. We examined the association of serum Immunoglobulin-G (IgG) antibody titers to a specific panel of periodontal bacteria in the Dental Atherosclerosis Risk in Communities population to examine whether increased titers were associated with reduced kidney function.

Methods

Study Population

The population for this study was drawn from the Atherosclerosis Risk in Communities (ARIC) Study. A detailed description of the design and objectives of the ARIC study has been published elsewhere [35]. Briefly, ARIC is a prospective community-based study on the etiology and natural history of preclinical and clinical atherosclerotic disease. Participants were selected by probability sampling of eligible individuals aged 45–64 years from 4 US communities: Forsyth County, N.C.; Jackson, Miss.; suburban Minneapolis, Minn., and Washington County, Md.

ARIC study participants were evaluated with clinical examinations and laboratory studies starting in 1987, and then at 3-year intervals. During each visit numerous demographic, medical, and laboratory variables were recorded for the study participants. The dental component of the ARIC Study (D-ARIC) was performed on a subgroup of the ARIC cohort at visit 4 (1996–1998). Details of the D-ARIC study have been described in a previous publication [36].

Measurements

The D-ARIC consisted of an oral examination, collection of gingival crevicular fluid, oral plaque and serum, and interviews.

Clinical measures included probing pocket depth (PD) and gingival recession on 6 sites for all teeth. The clinical attachment level (AL) was calculated from the sum of pocket depth and gingival recession scores. The examinations were conducted by research dental hygienists who were trained and calibrated initially and at 1-year intervals during the study against a standard examiner. Interclass correlations were calculated at each calibration session and were >0.85 for each examiner. Weighted kappa scores were above 80% and considered to be excellent.

Levels of serum antibody titers to specific organisms were determined using methods recently described by Beck et al. [36]. For these analyses IgG levels to eight periodontal pathogens were determined in nanograms per milliliter. Levels of organism were expressed as counts using known microbial standards. Serum IgG levels were determined using immunocheckerboard arrays using 17 organisms as whole-cell antigens. We analyzed the levels of IgG to 17 organisms within each serum sample including the Red and Orange complex of bacteria (containing 3 and 5 species, respectively) as those pathogens originally designated as clusters by Socransky and colleagues [37] (Red complex organisms: *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia*; Orange complex organisms: *Campylobacter rectus, Prevotella intermedia, Fusobacterium nucleatum, Micromonas micros, Prevotella nigrescens*, and other bacteria: *Aggregobacter actinomycetemcomitans, Selenomonas noxia, Eikenella corrodens, Capnocytophaga ocracea, Vieonella parvula, Streptococcus sanguis, Streptococcus intermedius, Streptococcus oralis* and *Actinobacillus viscosus*). Bacterial specific titers are expressed as nanograms per milliliter IgG using protein A-bound IgG as an internal standard. The total, red and orange complex titers were computed as sums of concentrations. For the purposes of this analysis an elevated titer was considered as the upper quartile and compared to the bottom three quartiles as reference.

The levels of eight periodontitis-related species (*P. gingivalis*, *P. intermedia*, *P. nigrescens*, *T. forsythia*, *T. denticola*, *C. rectus*, *F. nucleatum*, *A. actinomycetemcomitans)* were determined by a

modification of the checkerboard DNA-DNA hybridization method [38]. In brief, subgingival plaque samples are obtained with the help of periodontal curettes and placed in individual prelabeled bar-coded tubes containing 0.1 ml TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.5) and 0.1 ml of 1 M NaOH. Samples are stored at –80°C until assay. The sample DNA was denatured through boiling for 5 min and neutralized using 0.8 ml 5 M ammonium acetate. The DNA was placed into the slots of a Minislot device and thereby deposited as 'lanes' onto a Roche Diagnostics nylon membrane. The DNA was then fixed to the membrane by exposure to ultraviolet light. Pooled DNA of known bacterial numbers (10^5 and 10^6 CFU/ml) for each one of the microorganisms included in the analysis were deposited with the patient's samples. Digoxigenin-labeled whole genomic DNA probes were prepared for each of the reference strains using a random primer technique. For these analyses the level of all 8 organisms was summed to provide a total biofilm count for each subject.

The serum creatinine concentration was determined by the modified kinetic Jaffe method and was used to estimate renal function. Estimated glomerular filtration rate (eGFR) was obtained using the abbreviated Modification of Diet in Renal Disease (MDRD) formula [39]:

$$\text{eGFR (ml/min/1.73 m}^2) = 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}.$$

Age, gender, and race, all based on self-report, were recorded by the ARIC field-site interviewer. Weight was determined with the participant wearing only an under-garment and expressed in kilograms. Body mass index (BMI) was calculated as the ratio of weight in kilograms to standing height in meters squared. Smoking status included 5 levels: current heavy, current light, former heavy, former light, and never. The presence of hypertension was defined as a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or self-reported use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose of ≥126 mg/dl, (200 mg/dl if non-fasting), or self-reported treatment for or a history of diabetes mellitus. Education level was defined as a categorical variable, with either <12 years of schooling or ≥12 years of schooling. High sensitivity CRP (hs-CRP), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined as reported previously [40].

Statistical Analysis

In order to focus on individuals likely to have clinically significant CKD, the primary outcome was defined as the presence of a low GFR (GFR <60 ml/min/1.73 m^2, or stage III CKD). Multivariable cross-sectional modeling using binary logistic regression was used to calculate the odds ratio for low estimated GFR by the level of IgG. For the purposes of this analysis elevated titer was considered as the upper quartile and compared to the lower three quartiles as reference because preliminary analysis of the relationships between these two continuous variables indicated that the relationship was not linear and that there was a threshold effect involving the highest quartile.

Baseline characteristics of GFR groups were compared using χ^2 for categorical variables and t test for continuous variables. These bivariate unadjusted comparisons were considered statistically significant with a p value of <0.05. Mean eGFR group differences for extent of plaque scores of >1, total biofilm counts and extent of interproximal attachment loss of 3 or more mm (AL3+mm, % of sites) were tested for significance by t test.

The association of elevated IgG titers and low GFR was assessed using adjusted logistic regression models. In order to account for multiple comparisons for 17 different IgG titers, a Hotelling T^2 test was performed to show an overall significant effect at $p < 0.05$. Significant differences for each organism titer were then evaluated independently by dichotomizing at the upper quartile. Both minimally and fully adjusted models were developed to adjust for traditional risk factors of periodontal disease and CKD. The minimally adjusted model used demographic and center variables. The fully adjusted model included the variables in the minimally adjusted model, and smoking status, diabetes mellitus, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, education, and BMI.

All statistical analyses were performed using SAS 9.1 (SAS Statistical Package; SAS Institute, Cary, N.C., USA).

Results

The bivariate associations between subject characteristics for individuals with a eGFR of ≥60 ml/min/1.73 m^2 (n = 4928) and low eGFR (n = 103) appear in table 1. In this sample of 5,032 subjects, 76.0% had an eGFR of ≥90, 22.0% between 60–89, and 2.0% at <60. Subjects with impaired eGFR were more likely to have a smoking history, be diabetic, hypertensive and have lower education. Those with a low eGFR were significantly older, had higher BMI and a nonsignificant trend for higher waist-to-hip ratio. Subjects with a low eGFR tended to have higher levels of hs-CRP and LDL that were not statistically significant. However, individuals with low eGFR had statistically higher triglyceride and lower HDL levels.

The periodontal status and oral biofilm bacterial burden by eGFR status are shown in figure 1. The extent of clinical AL+3mm is a measure of the cumulative history of periodontal disease for each subject. Those with a eGFR ≥60 have a mean extent AL3+mm of 22.8% (SE = 0.32) and subjects with a GFR of <60 have significantly (p = 0.005) more periodontal disease with a mean extent AL3+mm of 28.5% (SE = 2.28). Subjects with a eGFR of <60 also had a nonsignificant trend to having greater plaque biofilm levels as assessed clinically by mean extent plaque scores of <1, as compared to a GFR of ≥60 (41.3 ± 0.55 vs. 45.8 ± 3.71, mean ± SE, respectively). Similarly, there were trends for higher total biofilm bacterial counts among subjects with impaired GFR as determined by DNA checkerboard analyses, but there were no statistically significant differences between groups, due to the high variability in bacterial counts (p = 0.47).

Table 1. Demographic and medical characteristics by category of GFR (average values for continuous variables with standard deviation (SD) and frequencies for categorical variables)

Variable	eGFR ≥60 (n = 4,929)	Low eGFR <60 (n = 103)	p value
Race/center			
Jackson	671 (98.5%)	10 (1.5%)	
North Carolina Blacks	109 (96.5%)	4 (3.5%)	
North Carolina Whites	1,313 (97.8%)	30 (2.2%)	
Washington County	1,338 (97.8%)	30 (2.2%)	
Minnesota	1,499 (98.1%)	29 (1.9%)	<0.57
Gender			
Female	2,738 (97.9%)	60 (2.1%)	
Male	2,191 (98.1%)	43 (1.9%)	<0.58
Smoking status			
Never	2,322 (97.7%)	54 (2.3%)	
Former light	1,039 (98.8%)	13 (1.2%)	
Former heavy	818 (97.0%)	25 (3.0%)	
Current light	115 (99.1%)	1 (0.9%)	
Current heavy	453 (99.3%)	3 (0.7%)	<0.01
Diabetes mellitus			
Yes	652 (96.2%)	26 (3.8%)	
No	4,265 (98.3%)	76 (1.8%)	<0.0003
Hypertension			
Yes	2,072 (96.3%)	80 (3.7%)	
No	2,840 (99.2%)	22 (0.8%)	<0.0001
Education			
Low	622 (96.4%)	23 (3.8%)	
Medium	2,161 (98.1%)	43 (2.0%)	
High	2,142 (98.3%)	37 (1.7%)	<0.01
Age, years	62.1 (5.6)	66.5 (5.3)	<0.0001
BMI, kg/m^2	28.5 (5.6%)	30.2 (5.3)	<0.01
Waist-to-hip ratio	0.94 (0.07)	0.96 (0.07)	<0.06
C-reactive protein, mg/dl	6.5 (11.8)	8.5 (13.9)	<0.15
Triglycerides, mg/dl	143.1 (82.3)	183.8 (100.5)	<0.0001
HDL cholesterol, mg/dl	50.7 (16.7)	46.6 (16.1)	<0.01
LDL cholesterol, mg/dl	121.8 (32.5)	125.1 (40.6)	<0.40

BMI = Body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

The serum antibody response to specific organisms shows a marked increase among individuals with eGFR <60 (table 2). There is no elevation in the total IgG titer adjusted for age, race/center and gender when comparing eGFR-normal to eGFR-impaired subjects. Thus, the total IgG titer to the pathogens and commensal organisms is not statistically different. However, when using the Hotelling T^2 test, which corrects for multiple testing, there are overall differences in specific titers as related to renal function. There are specific IgG elevations among individuals with eGFR <60 in both minimally adjusted (age, race/center and gender), and in fully adjusted models (age, race/center and gender, as well as education, diabetes, hypertension, HDL, LDL, triglycerides and BMI). Of particular note is the increased titer (Q4) of *P. gingivalis* associated with 1.6-fold greater risk for impaired eGFR. This is a dominant periodontal pathogen with invasive properties. A second dominant periodontal pathogen (as a member of the Red biofilm complex) that has elevated titers is *T. denticola*. Significant titers are present in fully adjusted models for *S. noxia, A. actinomycetemcomitans* and *V. parvula*. There is no association of increased titers of organisms of the Orange complex which would be associated with early or milder forms of periodontal disease. The increase in specific titers to pathogenic and invasive organisms within the oral bio-

Table 2. Minimally and fully adjusted logistic regression models for each bacteria-specific IgG titer and low GFR (<60) by upper quartile of IgG

Type of IgG antibody	Minimally adjusted model[1]	Fully adjusted model[2]
Total biofilm IgG	1.2 (0.8–1.9)	1.2 (0.8–2.0)
P. gingivalis	1.5 (0.9–2.3)	1.6 (>1.0–2.6)
T. forsythia	0.9 (0.6–1.5)	0.9 (0.6–1.5)
T. denticola	1.6 (1.1–2.4)	1.8 (1.2–2.8)
Total red biofilm IgG	1.0 (0.7–1.6)	1.2 (0.8–2.0)
P. intermedia	1.1 (0.7–1.8)	1.3 (0.8–2.1)
C. rectus	1.4 (0.9–2.2)	1.5 (<1.0–2.4)
M. micros	1.3 (0.9–2.0)	1.4 (0.9–2.2)
P. nigrescens	0.8 (0.5–1.2)	0.9 (0.5–1.4)
F. nucleatum	1.2 (0.8–1.9)	1.2 (0.8–1.9)
Orange biofilm IgG	1.0 (0.6–1.6)	1.1 (0.7–1.8)
S. noxia	1.6 (>1.0–2.4)	1.7 (1.1–2.6)
A. actinomycetemcomitans	1.7 (1.1–2.6)	1.7 (1.1–2.7)
E. corrodens	1.5 (<1.0–2.2)	1.5 (0.9–2.3)
C. ocracea	1.3 (0.8–2.0)	1.4 (0.9–2.2)
V. parvula	1.5 (>1.0–2.3)	1.6 (>1.0–2.5)
S. sangis	1.5 (<1.0–2.3)	1.7 (1.1–2.7)
S. intermedius	1.2 (0.7–1.8)	1.1 (0.7–1.8)
S. oralis	1.5 (0.9–2.2)	1.4 (0.9–2.3)
A. viscosis	0.9 (0.6–1.5)	0.9 (0.6–1.5)
Other biofilm IgG	1.3 (0.8–2.0)	1.2 (0.8–2.0)

The values are odds ratios with 95% confidence intervals.
[1] Minimally adjusted for race/center, age, gender.
[2] Fully adjusted for race/center, age, gender, education, diabetes, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, BMI.

film is consistent with the concept that the more severe periodontal disease seen in renal functionally impaired subjects is associated with a greater systemic dissemination and challenge to these oral pathogens.

Discussion

We have observed a significant association between antibodies to certain periodontal disease organisms and reduced kidney function in a contemporary group of middle-aged individuals. Individuals with high titer antibodies to *P. gingivalis*, *T. denticola*, *S. noxia*, *A. actinomycetemcomitans*, and *V. parvula* were more likely to have reduced renal function, compared to individuals with low titer antibodies to these same organisms. Associations in the fully adjusted models were not attenuated compared to the minimally adjusted models and they remained significant. Furthermore, the point estimates for most to the antibodies tested were >1.0 and the overall Hotelling T^2 test was significant.

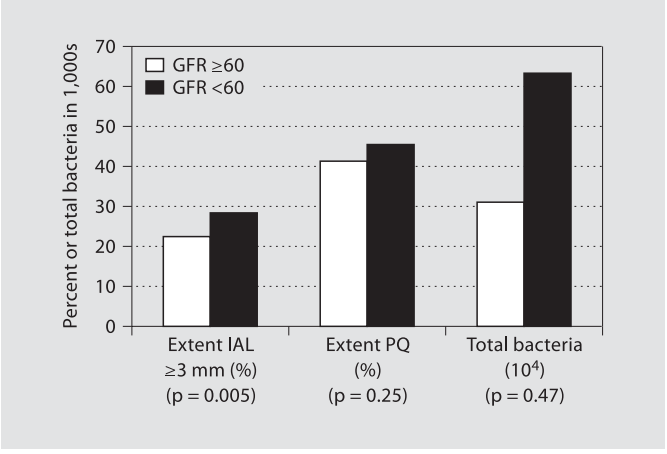

Fig. 1. The extent of periodontal disease and total bacterial load are shown by GFR status. The periodontal mean extent of interproximal attachment loss (IAL) of 3 or more millimeters is significantly worse among those with GFR <60. The mean extent plaque score >1 (Extent PQ) represents a clinical assessment. The total bacterial counts ($\times 10^4$) were determined by whole-chromosomal DNA probes as described in text. p values are shown for unadjusted t tests.

Of note, there is no association of increased titers of organisms of the orange complex, which would be associated with early or milder forms of periodontal disease. The increase in specific titers to pathogenic and invasive organisms within the oral biofilm is consistent in that the more severe periodontal disease seen in renal functionally impaired subjects is associated with a greater systemic dissemination and challenge by these oral pathogens.

Our exploratory analyses, based on an a priori knowledge of shared risk factors for CKD and CVD, are preliminary in nature. Yet, it adds to the growing body of literature that suggests a link between periodontal disease with other systemic diseases involving vascular and renal pathology, including previous studies of historical periodontal disease and CKD [30–34]. Cross-sectional analyses prevent us from establishing the temporality of the association between the elevated serum IgG level to oral pathogens and renal impairment. Furthermore, we readily acknowledge that we cannot rule out that the association could be due to residual confounding by both known and hereunto unidentified factors associated with periodontal disease, renal insufficiency, socioeconomic status, and/or access to medical care.

Periodontitis is a painless, destructive chronic infection of the gums, ligaments, and bone supporting the teeth. The space created by the loss of supporting bone and attachment along with the down growth of the epithelium serving to wall-off and reject the tooth, creates an ulcerated periodontal pocket which serves as an anaerobic site for bacteria-host interaction and systemic microbial exposure. The number of bacteria range from 1×10^3 in healthy shallow crevices to more than 1×10^8 in a single periodontal pocket [41].

Both a localized and systemic inflammatory response arises from the growth and dissemination of these bacterial species. At the level of the gingivocrevicular space, inflammatory cytokines are secreted by activated monocytes and other cells. Systemically, increased serum antibody to these organisms within the biofilm represents a breakdown in the barrier function of the periodontal tissues and a systemic challenge and dissemination of the organisms leading to vascular and hepatic activation.

The bacterial antigens and/or antibodies may induce a maladaptive host response. Numerous cytokines accelerate atherogenesis, thrombus formation, and platelet aggregation [42, 43]. Additionally, thromboxane has potent vasoconstrictive properties [44] and, speculatively, chronic production of this substance may lead to a chronic decrease in renal blood flow. Another bacterial antigen, heat shock protein (hsp), GroEl 60, shares many similarities to human hsp60. Human hsp60, produced in response to endothelial damage, has been postulated to promote atheroma formation [45]. Atherogenesis of the large and medium-sized renal arteries and arterioles may then lead to ischemia [46], glomerulosclerosis [47], and severe renal insufficiency [48].

Antibodies to *P. gingivalis*, a prominent periodontal pathogen, can be harvested from atheromas at autopsy [49–51] in humans, as can viable bacteria [7]. Animal models have demonstrated that bacterial seeding with strains of *P. gingivalis* accelerates the formation of aortic and coronary atherosclerotic plaques in pigs [52] and aortic lesions in mice [53].

Periodontal pathogens may also cause direct cellular damage to the nephron unit, or to its vasculature. Individuals with significant periodontitis have chronic and recurrent episodes of low-level bacteremia. The bacteria may be filtered out of the blood at the glomerulus, where these organisms or their products may invade the capillary endothelium or mesangial cells/matrix. While the direct cellular invasion by periodontal pathogens has yet to be shown in kidney tissue, *P. gingivalis*, a major periodontal pathogen, has been demonstrated to invade coronary and aortic endothelial cells [5, 6]. Invasion of glomerular mesangial cells has been demonstrated by other pathogens, namely viruses such as the human immunodeficiency virus, cytomegalovirus, and parvovirus.

Our study had some important limitations. There were a large number of individuals who declined dental evaluation, were deemed to have medical contraindications to the examination, or did not have values for CRP. It is quite possible that these individuals had a greater proportion of risk factors for kidney disease and other comorbidities. This may have decreased the power to detect a significant association. Furthermore, the absolute numbers of individuals with low GFR was small. Finally, the analysis was cross-sectional in nature preventing any formal hypothesis testing.

In summary, we have demonstrated a cross-sectional association of antibodies to various periodontal organisms and reduced GFR. Prospective analyses are needed to help determine the exact relationship of periodontal disease and kidney disease, yet these findings may spur further investigation of novel risk factors for renal disease, an important step towards reducing the projected burden of end-stage renal disease.

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Selected Pharmacokinetic Issues in Patients with Chronic Kidney Disease

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Key Words
Pharmacotherapy · Chronic kidney disease · Pharmacokinetics

Abstract
Pharmacotherapy plays an important role in the care of a chronic kidney disease (CKD) patient but delivering this therapy can be challenging. Besides alterations in the pharmacokinetic parameters of absorption, distribution, metabolism and elimination, the average CKD patient must take multiple medications each day. The likelihood of an adverse drug reaction increases with each medication added to these patients' daily regimen. In this article we discuss selected pharmacokinetic issues unique to CKD patients.

Introduction

Anyone caring for patients with chronic kidney disease (CKD) is aware of the extent to which pharmacotherapy is involved in the lives of these patients. Recently, it was reported that hemodialysis patients in one large dialysis system were prescribed a median of 12 different medications at any given time point [1]. This number of medications per patient has not changed in over a decade [2]. As pharmacists who work with CKD patients, we find that drug-related issues are foremost on the minds of these patients. Often these issues extend beyond the medications prescribed by their caregivers and go to over-the-counter medications and alternative or complementary therapies that they are taking without the knowledge of their caregivers.

Substantial morbidity and mortality have been associated with 'medication misadventures' in American patients [3], and it is likely that this is magnified in CKD patients. The concept of 'drug-related problems' has been put forward to characterize the myriad of issues that can occur with pharmacotherapy in patients with CKD [2]. A pooled analysis of published reports of medication use in hemodialysis patients found an average of 4.3 medication-related problems in each patient [4]. The most commonly identified medication-related problems in this analysis were inappropriate laboratory monitoring for drug therapy (23.5% of medication-related problems) and incorrect doses of prescribed medications (subtherapeutic dosage 11.2% and overdosage 9.2% of medication-related problems) [4]. Clearly, knowledge of the pharmacokinetic changes in CKD is essential for prescribers and caregivers.

Pharmacokinetic Changes in CKD

Patients with CKD have alterations in all of the pharmacokinetic parameters; absorption, distribution, metabolism and elimination (ADME). These ADME

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changes have been well detailed [5] and must be considered by the clinician before instituting drug therapy. ADME changes in the CKD patient can result in changes in the disposition of a drug and its pharmacologic effect. In this article we address many issues surrounding pharmacotherapy and monitoring in the CKD patient and propose practical approaches to selected drug-dosing dilemmas.

Absorption

The absorption of drug and nutritional supplements can be reduced or slowed in the CKD patient due to delayed gastric emptying. Given that diabetes mellitus is a common cause of CKD, diabetic gastroparesis is a frequent comorbidity. Delayed gastric emptying will alter the absorption profile of orally administered drugs. The absorption of many drugs is affected by gastric pH. Gastric acidity is reduced in predialysis CKD patients compared to controls [6]. Gastric acidity is further mitigated by the ubiquitous use of phosphate-binding antacids by CKD patients. A practical clinical example in which there is an absorption alteration in CKD patients is when furosemide is prescribed in a predialysis CKD patient and a blunted effect is observed. Patients with CKD do not have a particularly high bioavailability of furosemide [7]. Similarly, oral ferrous sulfate is frequently prescribed to CKD patients in combination with erythropoietic agents. Oral ferrous sulfate is poorly absorbed in an alkaline gastric environment, especially when administered concomitantly with oral antacids like calcium carbonate [8]. Further, oral ferrous sulfate frequently causes gastrointestinal pain. Unfortunately, when these patients complain to pharmacists and clinicians about their iron-induced gastrointestinal pain, they are frequently told to take the iron simultaneously with food or milk. This maneuver may well reduce the gastrointestinal pain, but probably it reduces the actual iron absorption to almost nothing because elements in food and milk bind to iron and food and milk raise gastric pH.

A cornerstone of the treatment of CKD patients is the use of phosphate-binding agents. Aluminum is rarely used any more, but calcium, magnesium, and lanthanum-based agents all pose the possibility of chelation of drugs as well as the intended gastrointestinal phosphorus. Tetracycline chelation to antacids is well known to clinicians, but tetracycline is not used often in the CKD patient population. Of more importance to caregivers of CKD patients is the well-described drug interaction of fluoroquinolones (e.g. ciprofloxacin, levofloxacin, ofloxacin, etc.) and metal-based phosphate-binding antacids. In a study by our research group, oral ciprofloxacin bioavailability was reduced by 51% when given simultaneously with four 667-mg calcium acetate tablets [9]. It is not only that there is a reduction in the percent of the fluoroquinolone absorbed that is a problem. The pharmacodynamics of fluoroquinolones suggest that they are more effective when high peak serum concentrations are achieved. This drug interaction also slows the rate of fluoroquinolone absorption, possibly reducing their efficacy. We have witnessed oral fluoroquinolone treatment failures that are ascribed to this drug interaction.

It is not only the metal-based phosphate-binding antacids that may cause changes in absorption. Oral ciprofloxacin's bioavailability is also reduced by nearly half when co-administered with seven 403-mg sevelamer hydrochloride capsules [9]. The typically prescribed remedy to mitigate this interaction is to space the fluoroquinolone and any phosphate-binding agent by at least 3 h.

Another underappreciated drug interaction related to absorption in CKD patients is between prescribed nutritional products and prescribed medications. Malnutrition is the harbinger of poor therapeutic outcome in CKD patients and very precise nutritional guidelines have been established to determine when to administer nutritional supplementation to CKD patients [10]. Often this means using commercially available enteral feeding products, some of which have been especially developed for patients with CKD. However, again using fluoroquinolones as an example, it should be noted that these products contain substantial calcium, magnesium and other elements that can cause significant alterations in bioavailability. For example, our research group found that one can of an enteral feeding product drunk at the same time as an oral fluoroquinolone was ingested, reduced the absorption of ciprofloxacin by an average of 28% and reduced ofloxacin absorption by an average of 10% [11]. Interestingly, gatifloxacin was found to have almost no change in absorption when administered with an enteral feeding product given via nasogastric tube [12].

Distribution

The volume of distribution (Vd) for patients with renal failure can be altered due to volume overload, decreased protein binding, hypoalbuminemia or alterations in tissue binding. The nephrology community is well ac-

quainted with hypervolemic CKD patients. For hydrophilic drugs that have a relatively small Vd, dose adjustment may be necessary in the hypervolemic patient. The most pertinent example of this situation is when an extremely fluid-overloaded patient requires an aminoglycoside. Typically the Vd of aminoglycosides is ~0.25 liters/kg and this distribution is mainly to lean body mass rather than adipose tissues. A CKD patient who is extremely volume overloaded (>110% of 'dry' weight) may require dose adjustment to achieve satisfactory serum concentrations.

Muscle wasting, commonly seen in CKD patients may also reduce the Vd of hydrophilic drugs. Obesity will have different effects on Vd. Patients with a body mass index (BMI; kg/m^2) of 40 or greater are considered to be severely obese. Obesity has been linked to an increased risk of renal failure [13]. The presence of obesity in a CKD patient presents a challenge to the clinician developing a drug regimen. On the one hand, the larger patient may require larger doses than a smaller person. However, the amount of dosage increase is dependent on whether the drug in question is water- or fat-soluble. Water-soluble medication doses may need to be increased in very large patients; because these drugs do not distribute well into adipose tissue, the relative increase in dose is not necessarily linearly related to the weight of the patient. Many attempts to determine optimal dose adjustment parameters have been developed [14]. Published dosing guidelines for obese patients exist [15, 16] but they do not incorporate the concept of kidney disease in these guidelines. It is unclear whether application of these obesity dosing guidelines to renal disease dosing guidelines will lead to appropriate drug regimens in obese CKD patients.

Another factor influencing the Vd of drugs in CKD patients is plasma protein binding. The most striking example of this phenomenon is the disposition of phenytoin in CKD patients. Phenytoin is ~90% protein-bound (primarily to albumin) in patients with normal renal function, and has a Vd of 0.6–0.7 liters/kg. In patients with kidney failure, the protein binding of phenytoin is less than that of a normal subject. Part of this may be due to the hypoalbuminemia seen in many patients with CKD. It has been postulated that the albumin molecule itself has a different conformation in renal failure and that change affects protein binding [17]. Further, the presence of retained unspecified uremic molecules compete with phenytoin to bind to albumin, further reducing phenytoin binding [18]. There is a take-home message for the practicing nephrologist with respect to phenytoin therapy in CKD patients. Phenytoin serum concentration monitoring in CKD patients should be conducted using unbound (free) phenytoin values. These unbound values already account for any alteration in protein binding, and the 'therapeutic range' of unbound phenytoin is the same as that for patients with normal renal function. If unbound values are not available from your laboratory, then know that for any reported total serum phenytoin concentration, the amount of drug that is unbound is higher than that seen in normals. Consequently, the total serum phenytoin 'therapeutic range' is *lower* than what it is for patients with normal renal function. A total serum phenytoin concentration in a hypoalbuminemic dialysis patient might be 'therapeutic' when the value is only 5 mg/l (the therapeutic range in normals is typically 10–20 mg/l). These same patients may exhibit phenytoin toxicity even when their total serum phenytoin concentration is as low as 10–12 mg/l.

Digoxin is another drug that has been reported to have a lower volume of distribution in CKD patients than in subjects with normal renal function [19]. Consequently, calls for a reduction in digoxin loading dose have been made for years [20]. However, this long-standing belief has been called into question. The unusually high digoxin observed after administration of digoxin in CKD patients may have been caused by a laboratory artifact. Many have reported that a 'digoxin-like immunoreactive substance' appears in CKD patients [21] that falsely elevates certain nonspecific digoxin assays that were used more than a decade ago. Contemporary assays do not appear to be affected by this substance. Consequently, optimal dosing of digoxin in this population is unknown. Nonetheless, caution is warranted. CKD patients do seem to exhibit increased sensitivity to digoxin effects, possibly due to the electrolyte disturbances seen in CKD patients.

Metabolism

As kidney function declines so does the kidneys ability to metabolize drugs. The brush border of the kidney is responsible for the metabolism of many drugs, and this also declines as glomerular filtration rate (GFR) declines. Non-renal metabolism of drugs in patients with CKD is a fascinating area of research. Retention of unspecified retained uremic molecules may affect hepatic enzyme activity [22]. These enzymatic changes may result in increased or decreased hepatic metabolism [23]. Indeed, even the dialysis procedure itself has been found

Table 1. Selected drugs to avoid or use with caution in CKD patients

Drug	Common use	Normal dose	Adjusted dose for CKD	Reason for caution	Toxicities
Codeine	analgesic opioid	15–60 mg every 4 h	reduce dose 25–50%	active metabolite eliminated by kidneys	apnea, seizure, hypotension
Meperidine	analgesic opioid	1–1.5 mg/kg every 3–4 h	reduce dose 25–50%	retained metabolite normeperidine lowers seizure threshold	CNS depression, respiratory depression, seizure
Midazolam	anesthetic benzodiazepine hypnotic	dose varies by route and indication	reduce dose by 50%	active metabolite	apnea, sedation, drowsiness
Morphine	analgesic opioid	Dose varies by route and indication	reduce dose by 50%	active metabolite eliminated by kidneys	CNS depression, respiratory depression
Procainamide	anti-arrhythmic	sustained release 500 mg – 1 g every 6 h	extend dosing interval	active NAPA metabolite accumulation	Sinus bradycardia, sinus node arrest, Q-T interval prolongation
Propoxyphene	analgesic opioid	65 mg every 3–4 h or 100 mg every 4 h	avoid: CrCl <10 ml/min	active metabolite eliminated by kidneys	cardiotoxic metabolite
Silver sulfadiazine	antibacterial 1% cream	1/16th inch to affected site	use with caution/avoid prolonged use	absorption following prolonged treatment	leukopenia crystalluria

Sources: Thompson Micromedex Healthcare [28] and Bennett et al. [29].

to affect drug metabolic pathways in patients. Changes in metabolism for stage-5 CKD patients on dialysis have recently been reported. The removal of uremic mediators [24] by hemodialysis improves CYP3A4 metabolism acutely as has been seen by the administration of telithromycin. Stage-5 CKD patients on dialysis administered telithromycin after dialysis have a higher rate of clearance than patients with a creatinine clearance of 11–40 ml/min.

Elimination

In stage-5 CKD patients, the primary route of drug elimination is often the dialysis procedure itself. However, in predialysis CKD patients, dosage adjustments are usually required for renally eliminated drugs. Nearly every marketed drug has had the renal adjustment calculated based on a Cockroft-Gault-derived estimate of creatinine clearance. However, the modification of diet in renal disease (MDRD) equation [25] is now considered a better estimate of GFR. Indeed many institutions have begun routinely calculating the MDRD GFR estimate when laboratory results are reported. It is possible that a dose based on MDRD GFR estimates might be different from Cockroft-Gault-derived doses, however, a clinical study comparing dosing regimens and patient outcomes based on these two techniques has yet to be conducted. In general the MDRD and Cockroft-Gault equations should result in similar dosage recommendations [26].

Another important drug elimination consideration in CKD patients is the accumulation of renally eliminated drug metabolites (table 1). Many drugs have metabolites that have pharmacologic activity. Some of these metabolites are also active drugs with similar activity in their own right (morphine, codeine). Some retained metabolites in CKD have therapeutic activity that differs from the parent compound (procainamide/n-acetylprocainamide). More common are the toxic metabolites that accumulate in CKD that contraindicate the use of the parent compound at all (meperidine, propoxyphene).

Drug Dosing

In any patient in whom a rapid therapeutic response is needed, a loading dose must often be administered. As described earlier, selected drugs have altered Vd in CKD patients and consequently the loading dose must be modified from loading doses used in patients with normal renal function. Phenytoin and digoxin could be examples of when the loading dose used should be smaller than what might be used in non-CKD patients. In CKD patients, the maintenance dose regimens of many drugs are modified by extending the dosing interval since drug clearance is usually delayed in these patients. Extending the interval will extend the time for a drug to reach steady state (3–5 half lives) and may delay achieving therapeutic goals.

Typically, the dose of a renally eliminated drug is reduced and/or the dosing interval extended in patients with CKD. Whether one technique or the other is used depends on the pharmacodynamics of the drug. Drugs that require maintenance of a serum concentration over the dosing interval should be administered as often, but with reduced doses. Drugs for which specific peak serum concentrations must be achieved will be dosed with an extended interval.

Comprehensive drug dosing guidelines are available to the clinician to determine which technique should be used. However the accuracy of these dosing guidelines has recently been called into question. Vidal et al. [27] compared the renal drug dosing recommendations of four commonly used published references. They found a surprising amount of disagreement between the four references. For example each drug-dosing recommendation had a different description of renal impairment with little agreement among categories. The authors also found several instances in which one recommendation stated a drug required no dosage adjustment but another stated that the same drug was contraindicated in renal impairment.

Conclusion

Clinicians caring for patients with CKD face many challenges. The CKD patient population can average 12 different medications or more per day which may need to be taken multiple times per day, as well as alterations in their individual pharmacokinetics. Consensus is needed among drug-dosing recommendations as well as a further understanding of potential 'drug misadventures' specific to the CKD patient to improve patient care.

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A Kinetic Model of Calcium Mass Balance during Dialysis Therapy

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Key Words
Dialysis · Calcium mass balance, kinetic model · Extracellular fluid

Abstract
A kinetic model of Ca mass balance during dialysis has been developed. It is a single-compartment, variable-volume model to compute Ca mass balance during dialysis in its volume of distribution, the extracellular fluid. The model was used to analyze literature data which were suitable for the assessment of Ca mass balance over the course of dialysis. The modeled analyses predicted the serial plasma Ca concentrations very well. The mass balance analyses revealed a pool of rapidly diffusible Ca beyond the extracellular fluid distribution volume where Ca could be mobilized ($M+_{Ca}$) or sequestered ($M-_{Ca}$) very rapidly at rate equal but opposite in sign to dialyzer flux and thus effectively maintain near constant plasma Ca in the face of dialyzer Ca concentration gradients. This pool is likely the large pool of diffusible (miscible) Ca in connective tissue and on bone surfaces. Analysis of net Ca flux during dialysis with Cdi_{Ca} = 2.50 mEq/l suggests that 80% of patients are in positive Ca balance during dialysis. Further studies are required to verify the model and to develop a model of interdialytic Ca mass balance.

Ca Kinetics in Dialysis Therapy

The primary purposes of Ca kinetic modeling during dialysis are: (1) to quantitatively assess Ca mass balance during dialysis with current therapy; (2) to determine the feasibility of predicting Ca mass balance from key dialysis prescription parameters so that it can be prospectively prescribed and controlled in dialysis therapy, and (3) to minimize accumulation and inhibit vascular calcification and mortality. There are no reported studies that we are aware of attempting to develop a model to analyze Ca mass balance during dialysis. A review of this subject in PubMed for the past 30+ years indicated the most complete balance data were contained in a paper by Hou et al. [1] published in the American Journal of Kidney Disease in 1991. They reported mean serial blood levels and total net dialysate flux every 30 min in 6 patients on three different concentrations of Cdi_{Ca} – 3.50, 2.50 and 1.50 mEq/l. These mass balance data are extremely useful but the authors did not attempt to formulate a model for kinetic analysis of the data. Ca mass balance measurements were reported by Nolph et al. [2] in 1974 for continuous ambulatory peritoneal dialysis (CAPD) with Cdi_{Ca} = 0. The Nolph data were combined with the Hou data to provide data sets covering a very wide range of Ca dialysance for purposes of initial model development. Two other useful

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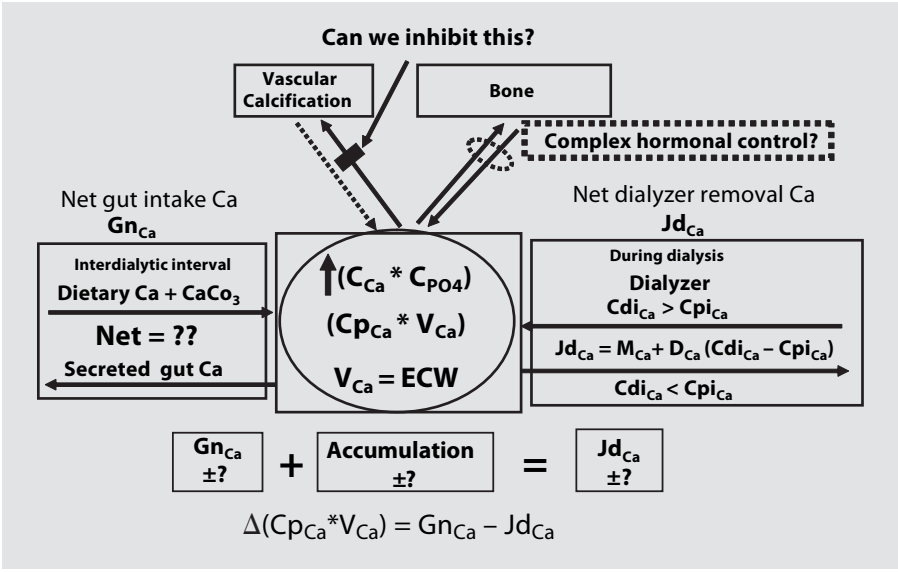

Fig. 1. Ca mass balance in dialysis therapy is undefined. Can we inhibit vascular calcification by minimizing Ca accumulation?

data sets were found [3, 4] and used for the development of the model described below. Several other reports of mass balance in the literature were found but most reporting measurements of ionized Ca ($C_{Ca^{2+}}$) which, as will be shown below, do not yield reproducible mass balance calculations. The initial formulation of a Ca mass balance model reported here was evaluated by the feasibility of closing mass balance on reported data [1–4].

Ca Mass Balance over the Complete Dialysis Cycle

Ca mass balance (accumulation in the body) will be determined by the net intake of Ca minus the removal of Ca as schematically depicted in figure 1. The volume of distribution for ionized Ca ($V_{Ca^{2+}}$) is defined as being anatomically equal to the extracellular fluid volume (V_{ECW}). The ultrafiltrate during dialysis is considered uniformly removed from V_{Ca}, a well-mixed pool of ionized, diffusible Ca^{2+}. There is virtually no quantitative understanding of the magnitudes of intake, removal and accumulation with current dialysis therapy. We hope that we can learn to predict and control mass balance and the risk of Ca accumulation in the vascular system through use of kinetic modeling of Ca in dialysis therapy.

The Hou data reviewed here reported only total plasma Ca as mM (see Appendix) which is commonly the case with clinical data since ion-selective Ca electrodes are still not widely used. Consequently the interrelationships between the various units of the Ca concentration must be discussed. The total plasma Ca (C_{CaT}) is the sum of approximately equal moieties C_{CaB} and $C_{Ca^{2+}}$ expressed as mass units, mM or mg/dl. Thus C_{CaT} reported in mM can be taken as equal to the ionized, diffusible fraction, $C_{Ca^{2+}}$ mEq/l. This is very useful since C_{CaT} expressed as mM provides a numerical value for $C_{Ca^{2+}}$ mEq/l, assuming the protein-binding ratio remains constant which has been assumed in the analyses developed below, and provides more realistic estimates of mass balance than calculations based on measurements of ionized Ca by ISE as will also be shown below.

Ca Flux across the Dialyzer

It is anticipated that we can describe Ca mass balance across the dialyzer as follows: the mechanism of transport of ionized Ca out of the blood compartment (Jb_{Ca}) is dialysance (D_{Ca}) which is defined as:

$$Jb_{Ca} = D_{Ca}(Cpi_{Ca} - Cdi_{Ca}) + Cbi_{Ca}*Q_f \quad (1)$$

for simplification the valence number is dropped but all flux equations assume ionized or diffusible Ca.

From mass balance across the blood compartment we can write:

$$Jb_{Ca} = (Cpi_{Ca} - Cpo_{Ca}) *Qe + Cpo_{Ca}*(Q_f) \quad (2)$$

Combine equations 1 and 2 to define dialysance as:

$$D_{Ca} = [Jb_{Ca} - Cpo_{Ca}*Qf]/(Cpi_{Ca} - Cpo_{Ca}) \quad (3)$$

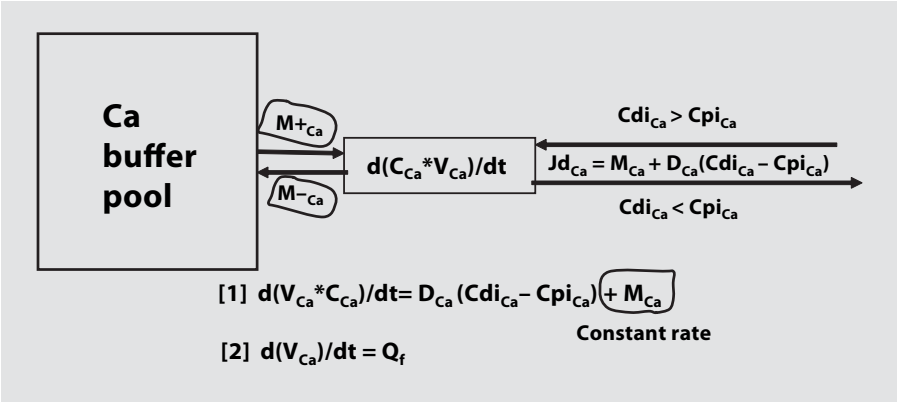

Fig. 2. Ca modeling equations must contain a term for rapid mobilization and sequestration of Ca during dialysis with a concentration gradient for Ca between plasma and dialysate.

From mass balance across the dialysate compartment we can write:

$$Jd_{Ca} = (Cdo_{Ca} - Cdi_{Ca})Q_{di} + Cdo_{Ca}*Q_f \quad (4)$$

Since $Jp_{Ca} = Jd_{Ca}$, combine equations 3 and 4 to calculate Q_e:

$$Q_e = [(Cdo_{Ca} - Cdi_{Ca})*Qdi_{Ca} + Cdo_{Ca}(Q_f) - Cbi_{Ca}(Q_f)]/[Cpi_{Ca} - Cdi_{Ca}] \quad (5)$$

It is very likely that Q_e, which is the effective blood diffusion volume flow rate, is equal to the plasma water flow rate but will require verification with in vivo data to solve equation 5. Note that all concentrations are expressed as the aqueous concentration of ionized Ca in the blood and dialysate compartments.

The Ca Model and Ca Buffer Pool

The model is again depicted in figure 2 where another compartment, termed a Ca 'buffer pool', is shown. This buffer pool is defined as a source of very rapid Ca mobilization ($M+_{Ca}$) into extracellular fluid (ECW) or sequestration ($M-_{Ca}$) beyond ECW during dialysis when there is a concentration gradient between plasma and dialysate. As shown quantitatively below, such a Ca pool rapidly buffering changes in plasma concentration was found to be required mathematically to close mass balance of clinical data with the model. It must be emphasized that only the intradialytic portion of the dialysis cycle is considered in the following and no attempt has been made here to close mass balance over the complete cycle which will include accumulation or depletion during the interdialytic phase of the cycle. Good estimates of Ca^{2+} balance between dialyses will be required to optimize prescription writing.

Mass balance of Ca^{2+} during a dialysis treatment is defined as change in Ca content of the single well-mixed Ca distribution volume, $\Delta(Cp_{Ca^{2+}})*(V_{Ca^{2+}}) + M_{Ca}$ during dialysis as shown in figure 2. Thus we can write:

$$d(V_{Ca^{2+}}*Cp_{Ca^{2+}})/dt = D_{Ca^{2+}}(1 - Q_f/Q_e)*Cdi_{Ca^{2+}} - D_{Ca^{2+}}((1 - Q_f/Q_e) + Q_f)*Cpi_{Ca^{2+}} + M_{Ca} \quad (6)$$

$$dV_{Ca^{2+}}/dt = - Q_f \quad (7)$$

where Q_f is the ultrafiltration rate during dialysis. Solution of equations 6 and 7 over one dialysis for the end dialysis concentration results in:

$$Cpt_{Ca^{2+}} = Cdi_{Ca^{2+}} - (Cdi_{Ca^{2+}} - Cpo_{Ca^{2+}})*((Vt_{Ca^{2+}}/Vo_{Ca^{2+}})\wedge D_{Ca^{2+}}(1/Q_f - 1/Q_e)) + M_{Ca}/D_{Ca^{2+}}(1 - Q_f/Q_e)*(1 - ((Vt_{Ca^{2+}}/Vo_{Ca^{2+}})\wedge D_{Ca^{2+}}(1/Q_f - 1/Q_e))) \quad (8)$$

where Cpi_{Ca} = end dialysis plasma Ca, Cdi_{Ca} = dialysate inlet Ca, Cpo_{Ca} = predialysis Ca, Vt_{Ca} and Vo_{Ca} are V_{Ca} post- and pre-dialysis, Q_f is the ultrafiltration rate and Q_e is the effective blood flow rate equal to plasma volume flow rate; and the term M_{Ca} represents sequestration ($M-_{Ca}$) or mobilization of Ca^{2+} ($M+_{Ca}$) into $V_{Ca^{2+}}$ from the Ca_{BP} induced during dialysis as discussed above.

A direct analytic solution for M_{Ca} can be obtained from simple rearrangement of equation 8 to give:

$$M_{Ca} = \frac{Cp_{t-} - Cdi + (Cdi - Cpo)*\left((V_t/V_o)\wedge D_{Ca}(1/Q_f - 1/Q_e)\right)\left(D_{Ca}(1 - Q_f/Q_e)\right)}{1 - (V_t/V_o)\wedge\left(D_{Ca}(1/Q_f - 1/Q_e)\right)} \quad (9)$$

If serial values are available for Cpi_{Ca}, Cdi_{Ca}, V_{Ca} and Q_d, mass balance can be evaluated from calculated serial values for change in content of Ca^{2+} in its distribution volume plus mobilization of Ca, i.e., $\Delta(Cpi_{Ca}*Vt_{Ca}) + (M_{Ca}*t)$ and compared to serial measurements of dialysate content, $(Cdi_{Ca} - Cdo_{Ca})*Q_dT$. In this way the inter-

nal consistency of plasma and dialysate concentrations and the validity of the kinetic model can be evaluated from the mass balance: if we are accounting for all Ca^{2+} removed from the body it should equal that recovered in dialysate, i.e.:

$$\Delta(Cpi_{Ca}*V_{Ca}) - M_{Ca}*t = (Cdi_{Ca} - Cdo_{Ca})*QdT \quad (10)$$

recalling that the M_{Ca} is negative if Ca^{2+} is sequestered in and positive if it is removed from the Ca_{BP} so that mass balance in the body is change in body content minus total M_{Ca}.

If only serial plasma concentrations are available, total Ca removal from only its distribution volume can be calculated from:

$$JpT_{Ca} = \Delta(Cpi_{Ca}*V_{Ca}) \quad (11)$$

over the total dialysis.

Use of the Model to Calculate Ca Mass Balance in Reported Clinical Studies

The model was used to analyze four reported clinical studies [1–4]. The analyses consisted of fitting calculated plasma concentrations to the reported values with the model and the calculation of mass balance as described above and comparing to that reported for dialysate. The serial $V_{Ca^{2+}}$ was estimated as 1/3 of total body water (TBW) considered to average 33 liters. If weight loss was given this was used as total Q_f and if not (usually the case) it was assumed to be 2 liters. Discussions of the individual data set analyses follow.

The Hou Study

This is the most complete data set available [1]. Nine equally spaced serial values for Cpi_{Ca} were measured over 4-hour dialyses in 6 patients with three different $Cdi_{Ca^{2+}}$ and mean values were reported. Total dialysate was collected during each sequential interval to measure total dialysate removal of Ca. These identical measurements were made using three different levels of Cdi_{Ca}: 3.50, 2.50 and 1.50 mEq/l. Body water and Q_f were not given, so average V = 33 liters and Q_{fT} = 2.0 liters were assumed for the calculations. The Ca dialysance (D_{Ca}) was calculated for each sequential intradialytic interval from the reported mean rate of Jd_{Ca} measured during the interval divided by the Cdi_{Ca} minus mean Cpi_{Ca} during the interval in accordance with:

$$D_{Ca} = Jd_{CaT}/(Cdi_{Ca} - Cpi_{Ca}) \quad (12)$$

recalling that all dialysate Ca is considered ionized and the total Ca concentration in plasma (Cpi_{CaT}) expressed in mM is considered numerically equal to Cpi_{Ca} expressed in mEq/l. Serial values of Cp_{Ca} were calculated with equation 9 and also with M_{Ca} = 0.

The serial measured and model calculated Cpi_{Ca} and Cdi_{Ca} values are plotted for the Hou data in figure 3. The calculated values agree very closely with values observed with all three dialysate concentrations when M_{Ca} is adjusted with equation 9. The powerful effect of $M-_{Ca}$ can also be seen. The values for Cpi_{Ca} have nearly reached equilibrium with Cdi_{Ca} when M_{Ca} = 0 in the calculations. Note that although there is some change in $Cp_{Ca^{2+}}$, the plasma concentration is far from equilibrium with $Cdi_{Ca^{2+}}$ after 4 h of dialysis with substantial positive and negative Ca concentration gradients. The Ca buffer pool was very effective to minimize change in Cpi_{Ca}. The properties of this pool will be discussed further below.

Koo et al.: Studies of Ca-Free Dialysate for Hypercalcemia

Koo et al. [3] reported Cp_{CaT} with Cdi_{Ca} = 0 values in 7 studies of 6 patients with hypercalcemia and renal failure due to malignancies. They reported Cpi_{CaT} values predialysis, at 1 h of dialysis and postdialysis, and Kt/V_U. V_{Ca} was estimated as 11 liters and D_{Ca} was estimated to be 50 ml/min in these studies from reported dialyzers and Q_b. A representative plot of one of these studies is shown in figure 4. Note that the modeled values correlate closely with measured values and $M+_{Ca}$ is consistently positive showing substantial mobilization of Ca to support the serum Ca with a strongly negative blood to dialysate concentration gradient and minimize the fall in Cpi_{Ca}.

Mass Balance

Equation 10 was used to examine mass balance serially during the course of the dialyses reported by Hou et al. [1] with results given in figure 5. There was a nearly perfect correlation between the sum of change in Ca content of V_{Ca} and the sum of M_{Ca} and $Jd_{Ca^{2+}}$ indicating closure of mass balance.

In 1971 Nolph et al. [2] reported very complete Ca mass balance data during four 24- to 48-hour CAPD treatments with exchanges hourly to treat hypercalcemia due to vitamin D intoxication in a patient with end-stage renal disease. They reported both $D_{Ca^{2+}}$ and D_{CaT} from measurements of both C_{CaT} and $C_{Ca^{2+}}$ in total dialysate and in plasma during the course of dialyses. Thus Ca re-

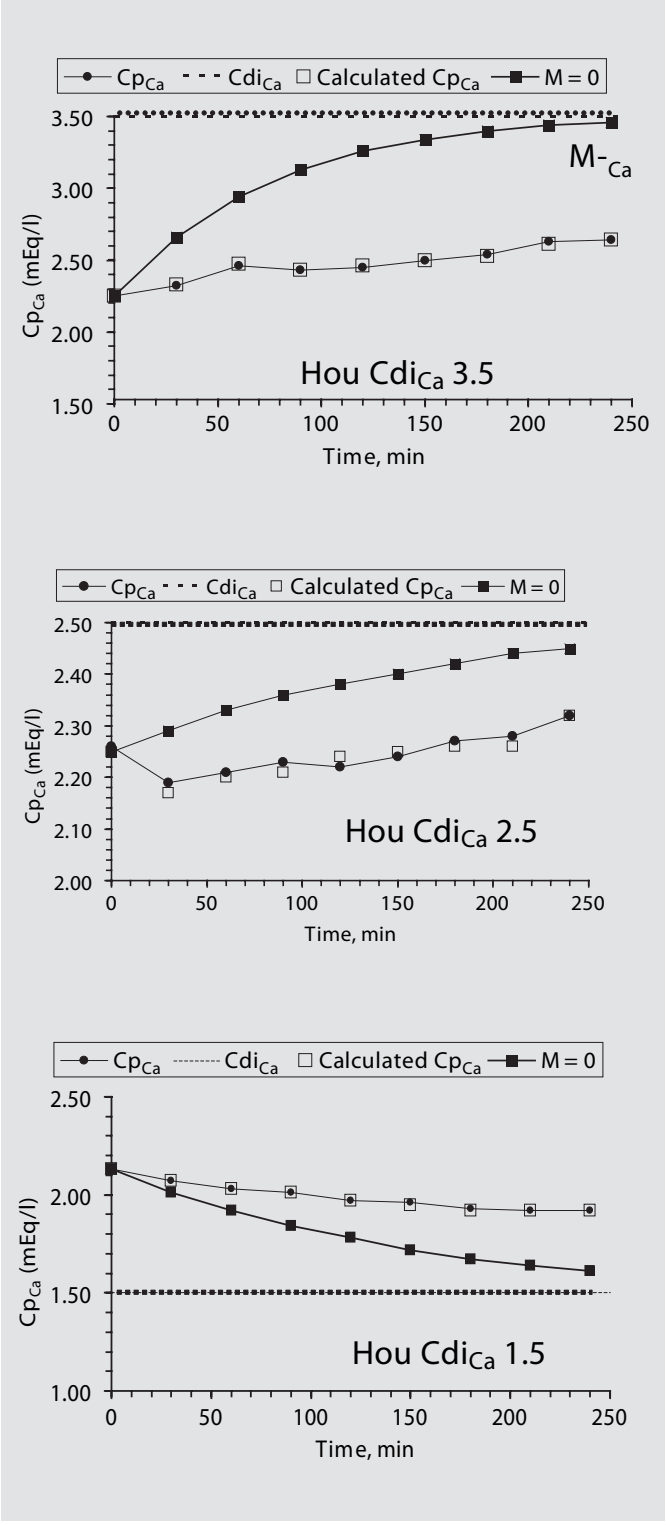

Fig. 3. Plasma Ca profiles calculated from the data of Hou et al. [1] with and without fitting values for M_{Ca}.

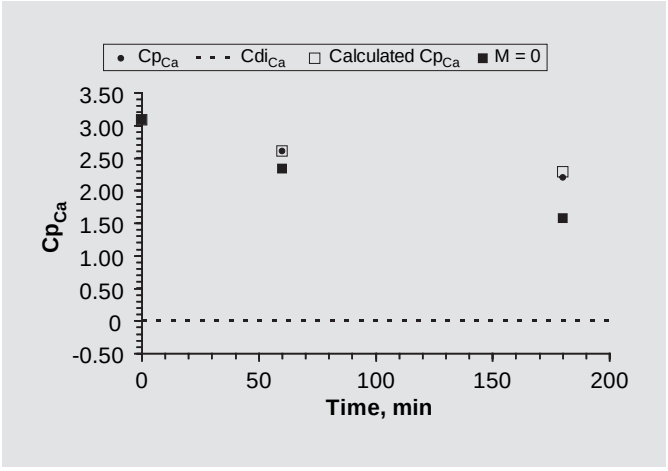

Fig. 4. A representative plasma Ca profile in a hypercalcemic patient dialyzed for 3 h with $Cdi_{Ca} = 0$. Note that due to mobilization of Ca from the buffer pool, plasma Ca remained in normal range despite a large Ca gradient from blood to dialysate.

moval from V_{Ca} and recovery in dialysate could be calculated with both sets of measurement and directly compared for validity to predict mass balance. Analysis of their C_{CaT} data with the Ca kinetic model is shown in figure 6 combined with the Hou data. Excellent agreement between the calculated removal from the body and measured recovery in dialysate can be seen over a total flux range from –1,500 to nearly +1,000 mg and D_{Ca} 5–172 ml/min during these treatments. The Nolph data were also analyzed with the Ca model using the $C_{Ca^{2+}}$ measurements and these results are discussed below.

Analysis of Reported Ionized Ca Mass Balance

Although measurement of ionized Ca by direct potentiometry should theoretically be the best measure of diffusible Ca, analysis of reported data with mass balance criteria indicate that is not true. This was evaluated in data reported by Argiles et al. [4] and the Nolph data with results shown in figure 7. Note that mass balance could not be closed with the $C_{Ca^{2+}}$ data. We interpret this to reflect the greater inherent variability in ISE measurements compared to colorimetric-based measurements of total Ca and simple estimation that 50% is ionized.

Ca Buffer Pool

The plots in figures 3 and 4 quantify the powerful effects of sequestration ($M-_{Ca}$) and mobilization ($M+_{Ca}$) on resisting increases and decreases in $Cp_{Ca^{2+}}$ with positive and negative dialysate to blood concentration gradients,

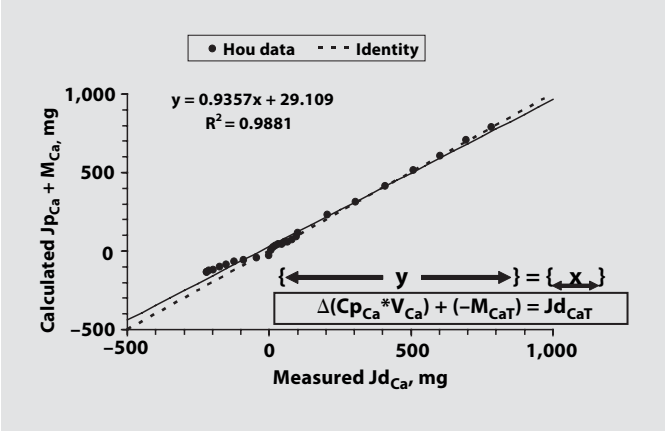

Fig. 5. Comparison of measured dialysate Ca removed to that calculated from the kinetic model ($\Delta Cp^*V_{Ca} + M_{Ca^{2+}}$). There is nearly perfect correlation over a wide range. Certainly this is in part due to linkage of clearance calculated from the plasma and dialysate Ca values but the amount removed by $\Delta Cp^*V_{Ca} + M_{Ca^{2+}}$ is calculated from the kinetic model. As shown below similar analyses with ionized Ca data do not result in closure of mass balance.

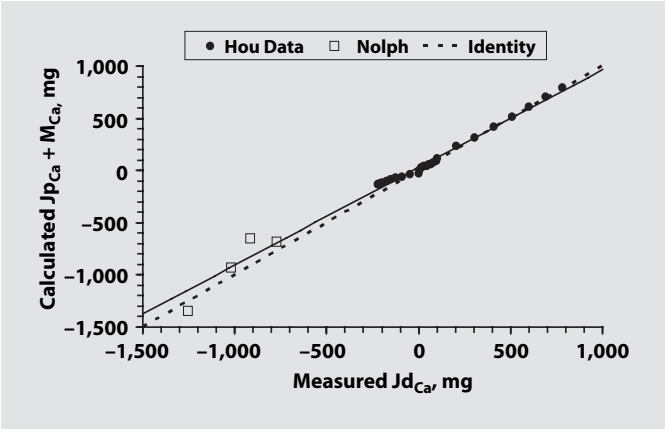

Fig. 6. Mass balance calculated from the CAPD data of Nolph et al. [2] also agrees well with that measured in dialysate. Thus mass balance agreement was shown with the model over a range of D_{Ca} 6–172 ml/min and Ca flux +700 to –1,400 mg.

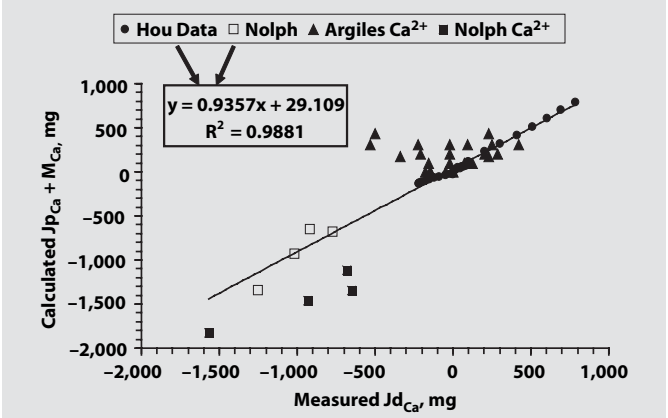

Fig. 7. Comparison of mass balance calculated from the data of Hou et al [1] and Nolph et al. [2] using estimated Ca^{2+} with the data of Argiles et al. [4] and Nolph et al. [2] using measured Ca^{2+} values. Mass balance is much more reliably determined with estimated Ca^{2+} values compared to measured Ca^{2+} values.

respectively. This relationship might be a useful tool for physiologic studies. What controls M_{Ca}? Can PTH operate that rapidly? Can the M_{Ca} response to dialysis provide some estimate of Ca depletion or overload? These are interesting considerations that might be pursued with the model but the first question is what the properties of this pool are.

The magnitudes of M_{Ca} observed in the Hou data over time are shown in figure 8. Note that M_{Ca} was constant throughout the course of these 240-min dialyses which would be expected if M_{Ca} represents a response which maintains the Cpi_{Ca} constant when exposed to a dialyzer concentration gradient.

It is also important to note that the magnitude of M_{Ca} is inversely proportional to the gradient and the sign of M_{Ca} is opposite the sign of the gradient reflecting mobilization of Ca from the buffer pool with a negative gradient and sequestration of Ca with a positive gradient. The magnitude of M_{Ca} compared to the change in Ca content of V_{Ca} is depicted in figure 9 for the Hou data with Cdi_{Ca} 3.50. Sequestration ($M-_{Ca}$) accounted for 98% of the total accumulation of Ca with a concentration gradient of +1.25 mEq/l and there was virtually no change in Cpi_{Ca}. These relationships lead directly to the hypothesis shown in figure 10 where M_{Ca} is postulated to be a linear function of the driving force.

Miscible Ca Pool

The relationships in figures 4, 5 and 8–10 clearly show a powerful mechanism operating to stabilize Cpi_{Ca} during dialysis with a Ca concentration gradient across the dialyzer. Figure 11 is a diagram of Ca distribution in the body derived from isotope dilution [5]. What is striking, and may be highly relevant to the mechanism underlying M_{Ca}, is that V_{Ca} has been found to be in rapid diffusion equilibrium with a much larger pool of Ca in the periosteum and exchangeable bone surface Ca. This pool would

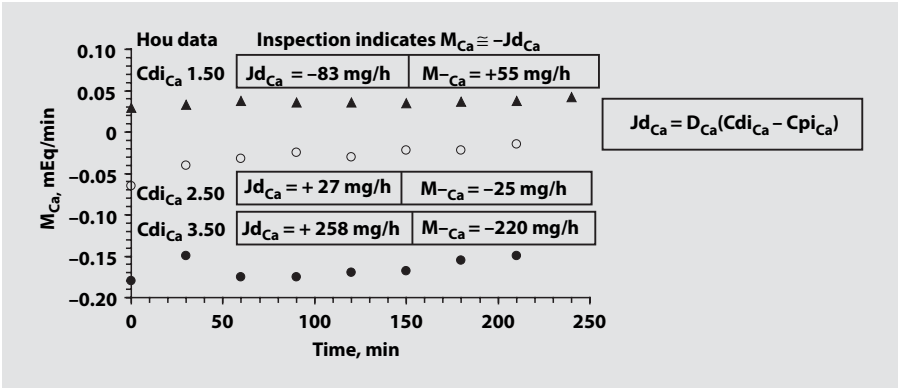

Fig. 8. Mobilization ($M+_{Ca}$) and Sequestration of Ca ($M-_{Ca}$) in the buffer pool. (1) The rate of M_{Ca} is constant during dialysis. (2) It is directly proportional to dialyzer flux, Jd, but opposite in sign. (3) The total net flux of Ca may be predictable from Cpi and prescribed D_{Ca}, Cdi_{Ca} and td. (4) It is important to note that these relationships predicting mass balance will be linearly dependent on $D_{Ca}(Cdi_{Ca} - Cpi_{Ca})$ and treatment time rather than the usual exponential relationship.

have the effect of greatly increasing the effective V_{Ca} by 8-fold and could readily explain the rapid rates of M_{Ca} seen in the above analyses. Thus the acute control of Cpi_{Ca} during dialysis may be wholly or in part a passive process of diffusion equilibrium rather than a hormonal response. Further studies are required to clarify this.

Generalized Solution of the Ca Model

As developed above, kinetic estimation of Ca mass balance over the course of a dialysis would require values for V_{Ca}, D_{Ca}, Cdi_{Ca}, Cpo_{Ca} and M_{Ca}. A value for V_{Ca} can be readily estimated from V_u and, with an appropriate in vivo data base we should be able to reliably calculate D_{Ca} from values for in vivo KoA_{Ca}, Q_b, Q_d and Q_f. Since the threat to $Cpi_{Ca^{2+}}$ during dialysis is the driving force for Ca flux, $D_{Ca}*(Cdi_{Ca} - Cpi_{Ca^{2+}})$, it might be anticipated that M_{Ca} is a well-defined function of this driving force, i.e., that it is dependent on the combined driving force variables. The relationship of M_{Ca} to $D_{Ca}*(Cdi_{Ca} - Cpi_{Ca^{2+}})$ was examined using the data developed from the literature. The sequential steps in model formation can be viewed in figures 12 and 13. Figure 12A shows all the serial M_{Ca} values calculated from each data set plotted as a function of the inlet concentration gradient and D_{Ca} for each data set indicated for each group. What is missing here is an axis to express the effect of D_{Ca}. From the behavior of M_{Ca} described in figure 8 M_{Ca} would be expected to be a linear function of $(Cdi_{Ca} - Cpi_{Ca})$ with the slope related directly to D_{Ca} and a zero intercept when $(Cdi_{Ca} - Cpi_{Ca}) = 0$ (except for convective flux). Figure 12B shows the linear regression for each data set with the regression coefficients with the curves forced through 0.

The slopes were then regressed on D_{Ca} and the modeling equation shown in figure 12 derived and shown to be:

$$M_{Ca} = -0.01 + (-0.0008*D_{Ca} - 0.001)*(Cdi_{Ca} - Cpi_{Ca}) \quad (13)$$

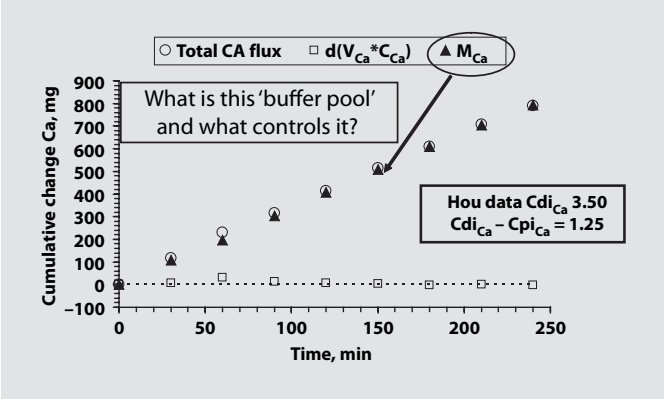

Fig. 9. The importance of the Ca buffer pool in sequestration of positive Ca balance with high Cdi_{Ca}. The net change in the Ca content of extracellular fluid was virtually zero. More than 99% of the positive Ca balance was sequestered in the Ca buffer pool.

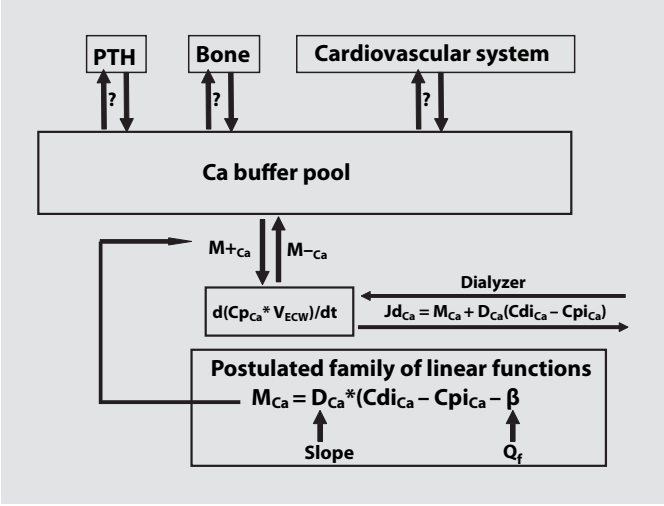

Fig. 10. M_{Ca} appears to be a linear function of the driving force for Ca flux across the dialyzer.

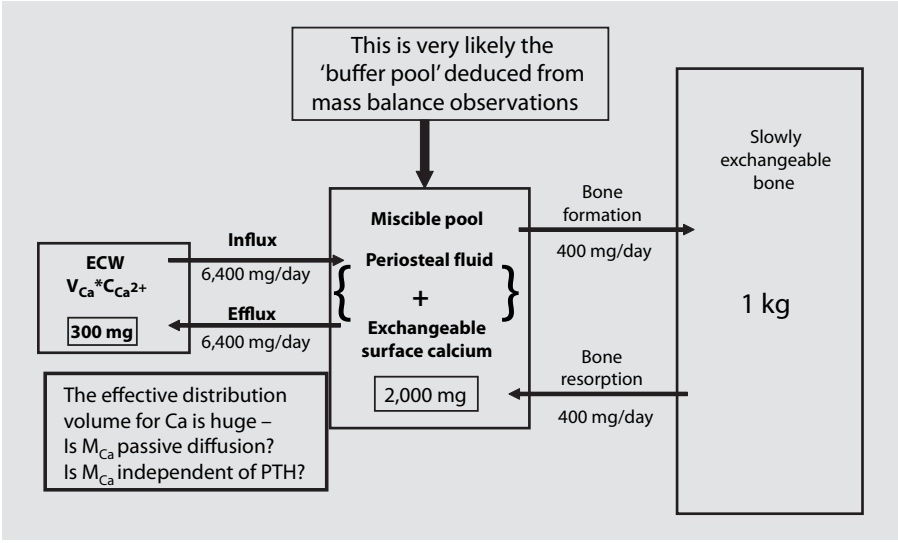

Fig. 11. The miscible pool of Ca is very likely the 'Ca buffer pool'.

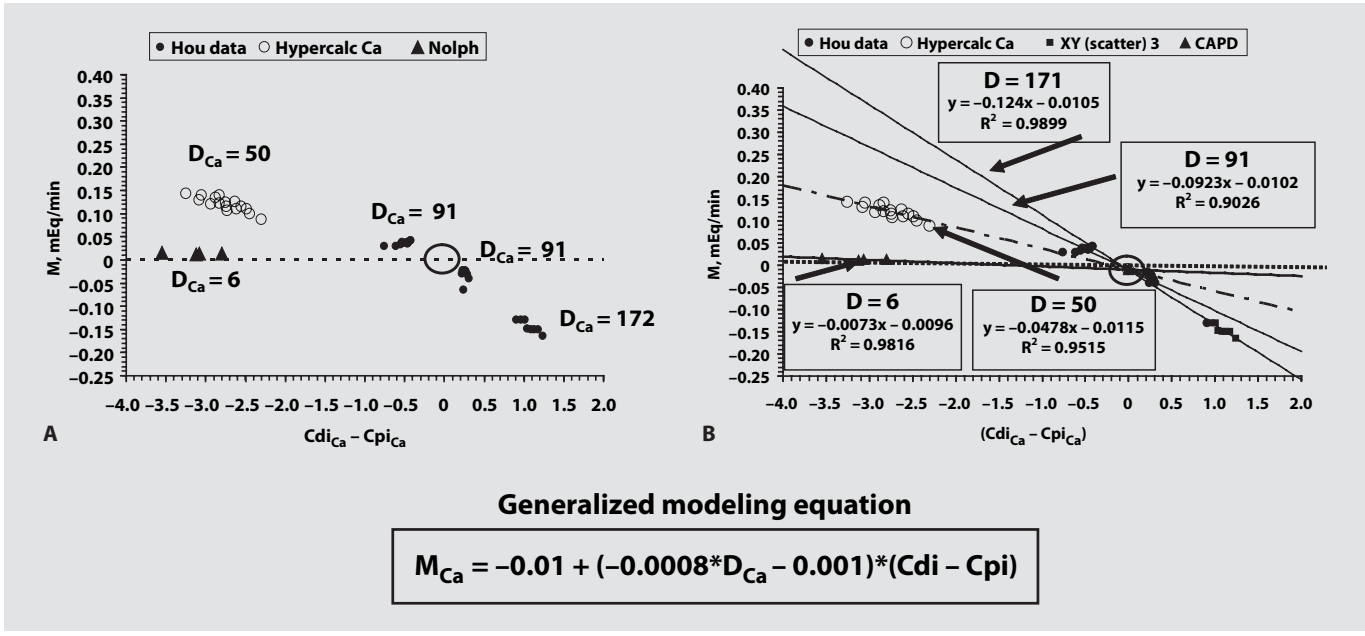

Fig. 12. A The five data sets used to develop the model are shown where serial calculated M_{Ca} is plotted as a function of the inlet Ca gradient and D_{Ca} for each data set is shown. **B** Linear regression for each data set forced through zero. These slopes were regressed on D_{Ca} and the final generalized modeling equation derived as a function of D_{Ca} and $Cdi_{Ca} - Cpi_{Ca}$ is shown above.

Figure 13 graphically depicts the generalized modeling equation solved over a range of $-1.00 \leq (C_{di}Ca - C_{pi}Ca) \leq 1.00$ and D_{Ca} ranging from 6 to 200 ml/min. Note that high rates of sequestration or mobilization of Ca are predicted over this range with highly efficient dialyzers.

Modeled Estimates of the Distribution of Ca Balance during Dialysis of FMC Patients with Currently Prescribed $Cdi_{Ca^{2+}}$

The frequency distribution of Cp_{CaT} observed in the FMC patient population (~65,000 patients) is shown in figure 14A along with distribution in normal subjects and

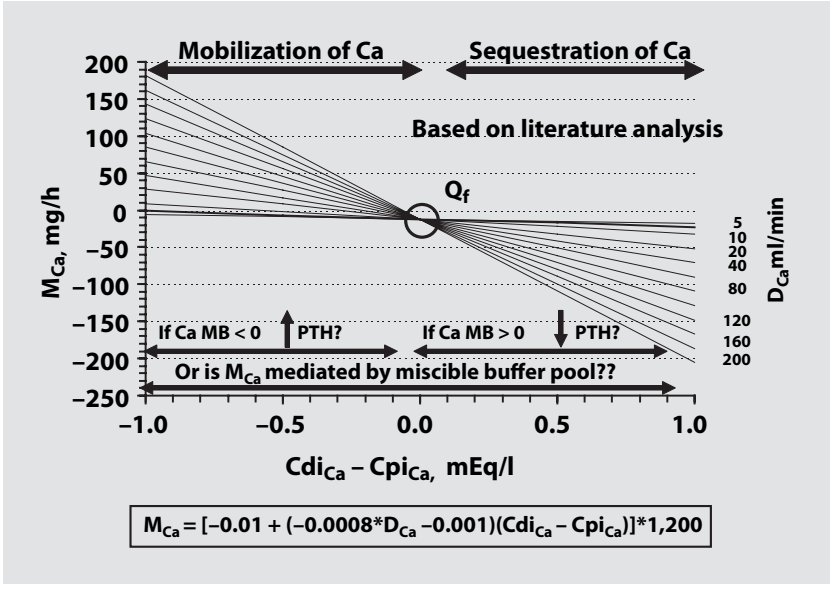

Fig. 13. The rate of mobilization (M) of Ca from the buffer pool modeled as a function of dialyzer inlet Ca gradient and Ca dialysance and expressed as mg/h. Note that substantial mobilization rates are predicted with relatively small gradients. How are mobilization and sequestration internally mediated in the body and how do they relate to vascular calcification?

the typically prescribed Cdi_{Ca} 2.50 mEq/l. These data are quite striking, and simple inspection of the plot suggests that we must be routinely diffusing a substantial quantity of Ca into nearly all of the FMC patients using a standard dialysate Cdi_{Ca} 2.50 mEq/l. Net Ca flux was calculated from the Ca distribution assuming D_{Ca} 150 ml/min and t = 3.5 h with results shown in figure 14B. These calculations indicate that 80% of the patients are in positive Ca balance up to 400 mg during dialysis. There needs to be further evaluation of the appropriateness of nearly universal positive Ca balance during dialysis based on reliable estimates of interdialytic Ca balance as developed below.

Discussion

These preliminary analyses suggest that it may be possible to reliably model and predict Ca balance during dialysis. It must be emphasized, however, that the model must be validated in patients with appropriate in vivo studies of mass balance measurements which are guided by the model.

It will also be essential to obtain measurements of interdialytic Ca balance as a function of dietary and binder Ca intake which will require metabolic ward studies.

The model suggests that we are at present routinely loading Ca during dialysis in most patients, which, with or without use of $CaCO_3$ binders, would appear to be inappropriate management of Ca/P balance in these pa-

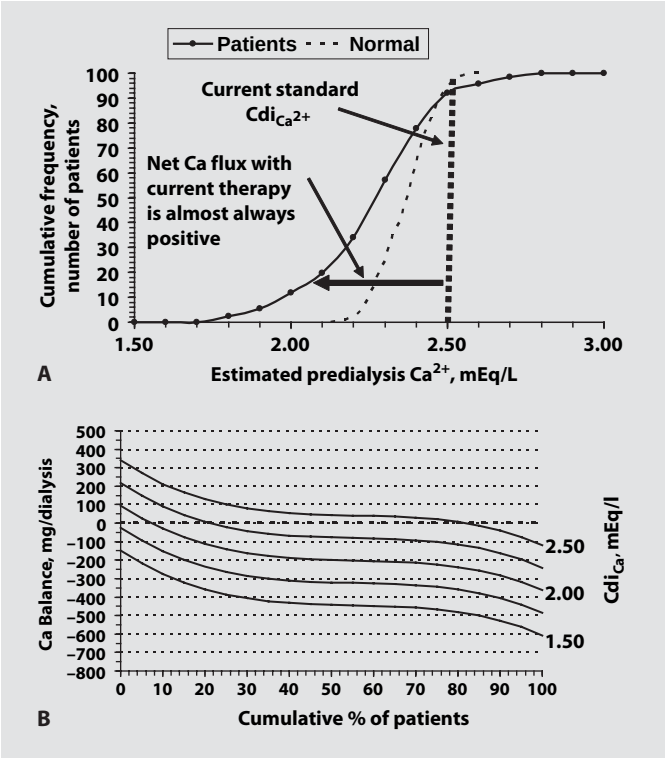

Fig. 14. A Frequency distribution of calculated Cp_{Ca} in FMC patients compared to normal subjects and the current standard Cdi_{Ca}. Simple inspection of the data indicates that there is substantial uptake of Ca from the dialysate during dialysis in virtually all patients. Is this optimal therapy? **B** Modeled Ca balance during dialysis calculated as a function of $Cdi_{Ca^{2+}}$ and the frequency distribution of $Cop_{Ca^{2+}}$ in FMC patients. Note that Ca balance is positive in nearly all patients when Cdi_{Ca} = 2.5 mEq/l. What should Ca balance be? There are no clinical guidelines at this time because there are no overall mass balance data.

tients. It does not intuitively make sense that we should be providing positive Ca balance during dialysis to essentially all our patients [5]. It would seem likely that with widespread use of vitamin D analogues and normal to high dietary protein intakes there may be a substantial amount of Ca absorption from diet and binders which would logically mandate negative Ca balance during dialysis for optimal management of mineral metabolism in these patients. There is a high rate of vascular calcification which may to a considerable extent be due simply to mismanagement of Ca and P balance with chronic overloads of both Ca and P [5]. As noted above, the Ca loading is directly proportional to treatment time so that the use of longer treatment time to increase PO_4 removal will also result in increased Ca loading with current therapy unless there is appropriate adjustment of Cdi_{Ca}. Substantial improvement in clinical outcome might result from the validation of the model and its clinical use to control mass balance in dialysis therapy. The model could also possibly provide a novel experimental tool to evaluate the effects of acute quantified levels of net positive and negative Ca balance on PTH for example. It can be used to remove substantial amounts of Ca with $Cdi_{Ca^{2+}}$.

We will proceed with in vitro studies already underway with aqueous solutions of bovine plasma and bovine whole blood to characterize dialysance of Ca with the FMC low- and high-flux dialyzers. Once we have these numbers we plan to promptly start in vivo studies with the model at RRI. Initial protocols have been written for these studies.

Current Conclusions with Regard to Ca Modeling

(1) A model of Ca balance during dialysis has been developed from review of polished data.

(2) Further In vitro and in vivo studies will be required to acquire a data base for KoA_{Ca} in low-flux and high-flux dialyzer and Q_eCa which can be used to reliably calculate in vivo D_{Ca} from dialyzer KoA_{Ca}, Q_b and D_e form in vivo mass balance studies.

(3) In vivo mass balance studies at RRI will be required to validate the model over appropriate ranges of D_{Ca} and $(Cdi_{Ca} - Cpi_{Ca})$.

(4) Interdialytic Ca mass balance studies will be required to assess mass balance over the complete dialysis cycle and optimization of Ca balance during dialysis.

(5) When the model is fully validated it should be possible to reliably prescribe and analyze Ca mass balance during dialysis.

Appendix

It is implicit in the following that all units of mass, flow and time are compatible, i.e., mass/ml, ml/min or mass/l, liter/min.

Ca	calcium, either bound or ionized	Jp	rate of solute flux in plasma water across the blood compartment of the dialyzer
Ca_{BP}	a mathematically defined pool from which Ca can be mobilized or sequestered during dialysis with a dialysate to blood concentration gradient	K	clearance defined as $D(1 - Q_f/Q_e)(Cpi + Q_f)$
D	dialysance which is defined, if $Q_f = 0$, for any solute in accordance with either $D = Jp/(Cdi - Cpi)$ or $D = Jd/(Cdi - Cpi)$	MB	mass balance
		Q	volumetric flow rate
		Q_e	the fraction of Q_{bw} from which solute is removed by diffusion across the dialyzer
DPI	dietary protein intake	Qpi, Qpo	plasma water inlet and outlet flow rates
Cdi, Cdo	solute concentration in inlet and outlet dialysate streams	Qdi, Qdo	dialysate inlet and outlet flow rates
		Q_f	ultrafiltration rate
Cpi, Cpo	solute concentration in dialyzer inlet and outlet plasma water; Cpo and Cpt refer to concentrations at the beginning and end of dialysis or in some instances to the beginning and end of intervals during dialysis	Qp	plasma water flow rate
		t	time
		T	total time or total amount
		V_{ECW}	extracellular fluid volume
		V_{Ca}	ionized Ca distribution volume
Jb	rate of solute flux in the blood compartment	Vo and Vt	predialysis and end dialysis volumes or in some instances at the beginning and end of defined intervals during dialysis
Jd	rate of solute flux across the dialysate compartment		

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