being superior to plasma infusion in inducing disease remission and preventing recurrence.[4] Plasma exchange might have the additional benefit of removing either mutant proteins in patients with genetic abnormalities or anti-CFH antibodies in acquired forms of HUS, factors that antagonize the function of normal proteins.

> ...the response to treatment in TTP and HUS is dependent on the underlying cause of the disease

Rare forms of HUS are caused by mutation of a transmembrane protein, membrane cofactor protein (MCP). Plasma therapy is not expected to be beneficial in patients with this form of HUS: 80–90% of such patients undergo remission whether or not they are treated with plasma.[6,7] Data on the effect of plasma therapy in patients with gain-of-function mutations in complement factors C3 and CFB are too scanty to draw any firm conclusions.

Plasma therapy has proven efficacy in specific forms of aHUS, which makes the design of controlled clinical trials with a placebo arm unethical; such trials would deny patients in the placebo group a life-saving therapy. However, careful analysis of retrospective clinical data on a large series of patients could help to clarify the effect of specific complement abnormalities on the efficacy of plasma therapy and might help to establish the optimum modality and frequency of treatment.

To conclude, the response to treatment in TTP and HUS is dependent on the underlying cause of the disease. A meta-analysis of data derived from populations of patients with profoundly different diseases (caused by infection, or by acquired or genetic defects in either plasma or membrane proteins) is worthless and could potentially mislead physicians. If a clinician who has superficially read this meta-analysis leaves one child untreated, that alone might lead us to question the value of Michael *et al.*'s publication. Although the authors mentioned the limitations of their study, that might not be enough. The message conveyed might have such a negative effect on clinical practice that we wonder whether it should have been published at all.

Patients with genetic abnormalities in ADAMTS13 or circulating complement regulatory proteins benefit from both plasma infusion and plasma exchange. Steroids or rituximab combined with plasma exchange might lead to effective and long-lasting clearance of anti-ADAMTS13 or anti-CFH antibodies in patients with acquired defects. Guidelines[1] recommend starting plasma therapy as early as possible, within 24 h of presentation. Supportive therapy alone and waiting before considering plasma therapy is the best strategy in patients with Stx-HUS, and also probably in cases of aHUS associated with MCP mutations, as both of these forms seem to have a high rate of spontaneous remission.

Clinical trials of specific complement inhibitors or anti-von Willebrand factor antibodies currently in development should carefully consider TTP and HUS as heterogeneous diseases. Accurate screening for acquired and genetic abnormalities is mandatory in selection of patients for clinical trials and for tailoring of future treatments to specific defects.

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HYPERTENSION

The message of World Kidney Day 2009

George L. Bakris and Eberhard Ritz, on behalf of the World Kidney Day Steering Committee

World Kidney Day 2009 was celebrated last month in more than 100 countries, and aimed to raise awareness that the symbiotic relationship between hypertension and kidney disease should be prevented.

The kidney is both a cause and a victim of hypertension. High blood pressure is a key contributor to the deterioration of kidney function, and kidney disease is a common and underappreciated cause of resistant hypertension.[1] Treatment of hypertension has, therefore, become the most important intervention in the management of chronic kidney disease (CKD). For this reason, the recent World Kidney Day on 12 March

2009 emphasized the role of hypertension in renal disease.[2]

Hypertension is a global problem, and the situation is projected to get worse. The world's population is getting older and aging is the most common risk factor for hypertension and diabetes, as well as for CKD. Nearly one billion people worldwide have high blood pressure (>140/90 mmHg), and that number is expected to increase to 1.56 billion by 2025.[3] Over the same period, the prevalence of hypertension is predicted to increase by 24% in developed countries and by 80% in developing regions such as Africa and Latin America.[3]

The US National Kidney Foundation's Kidney Early Evaluation Program (KEEP) is a screening program for individuals at high risk of kidney disease.[4] In the period 1999–2006, the prevalence of hypertension in the KEEP cohort was 43.4%; similar figures have been reported from many Western countries.[4] The rates of hypertension were highest in individuals who were 60 years or older (68–80% versus 25% in those aged 20–39 years) and in non-Hispanic black individuals (53% versus 43% in white people and 34% in Mexican Americans). Furthermore, hypertension was more common in individuals with a high BMI (60% in those with BMI ≥35 kg/m^2 versus 32% in those with BMI ≤23 kg/m^2). Slightly more than half of adults with hypertension were aware of their disease during the period 1999–2004; fewer than half were taking antihypertensive medications; and less than two-thirds had achieved control of hypertension with drugs.[4] This trend in poor blood pressure control is observed worldwide.

The rate of hypertension control is substantially reduced in patients with CKD, particularly those with diabetes.[1,4] The rates of prevalence (86.2%), awareness (80.2%), and treatment (70.0%) of hypertension were high in patients with CKD from the KEEP cohort; however, the rate of blood pressure control was low (13.2%).[4] Male sex, non-Hispanic black ethnicity, and a BMI of 30 kg/m^2 or more were inversely related to the likelihood of blood pressure control. The proportion of patients with hypertension increased with advancing stages of CKD.

On the basis of all the available data, a consensus has been reached that systolic rather than diastolic blood pressure is most closely linked with cardiovascular events and progression of kidney disease. Against this background, a relevant observation is that elevated systolic blood pressure accounted for the majority of patients with inadequate control in the KEEP study.[4] According to guidelines published by the major kidney societies, systolic blood pressure should be lowered to less than 130 mmHg in patients with CKD. Office-measured blood pressure might be inferior to ambulatory blood pressure as a predictor of CKD progression or cardiovascular events.[5] This issue is particularly relevant in CKD because affected patients tend to have elevated night-time blood pressure (that is, little or no nocturnal dip occurs in blood pressure) and their central (aortic) blood pressure tends to be higher than their peripheral (brachial) blood pressure.[5,6] In patients with diabetes, guidelines recommend that blood pressure targets lower than 130 mmHg might provide further benefit, but prospective trials have thus far failed to confirm the epidemiological observations on which those guidelines are based.

> ...aging is the most common risk factor for hypertension and diabetes...

Underdiagnosis and undertreatment of CKD is a worldwide problem, and can be attributed partly to low awareness of CKD. Between 1999 and 2006, less than 5% of people in the US with an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2 and proteinuria were aware of having CKD; of those with CKD stage 3, awareness was only 7.5%; for stage 4, awareness was less than 50%.[7] Awareness rates among individuals with CKD stages 3 or 4 were higher if comorbid diagnoses of diabetes and hypertension were present, but even then remained low (20% and 12%, respectively).

> The key to successful prevention of CKD is screening for predisposing comorbidities

The lack of awareness among physicians of risk factors for CKD is also disturbing. In one survey, more than one-third of primary-care physicians in the US were not aware that family history was a risk factor for CKD, while almost one-quarter did not perceive African American ethnicity as a CKD risk factor; by contrast, nearly all perceived diabetes (95%) and hypertension (97%) as risk factors for this disease.[8] Even more problematic was the fact that although diabetes and hypertension were acknowledged as CKD risk factors, the rates of control of blood pressure and blood glucose achieved among those treated for these conditions (that is, the proportion of patients whose levels reached guideline goals) sadly remained well below 50%. Moreover, even awareness of these risk factors does not ensure adequate treatment, for reasons that can relate to the behavior of the patient, the provider or both.

Many consensus panels have been convened over the past decade to consider ways to achieve improved blood pressure control and outcomes in CKD.[9,10] The key is to focus on public awareness and screening as well as programs to educate both patients and physicians. Data from KEEP show that blood pressure values are most likely to reach the goals set once a patient is aware they have kidney disease.[11] Data from Bolivia indicate that once kidney disease is diagnosed, interventions to reduce CKD risk factors such as hypertension are more likely to be instituted.[9] Programs to address the issues of awareness and education, similar to KEEP, have started around the world.

The International Society of Nephrology and the International Federation of Kidney Foundations have an ambitious long-term, worldwide goal: every individual should know his or her blood pressure values, particularly if he or she has diabetes. Additionally, everyone should be aware that prompt treatment is necessary once blood pressure values are no longer in the normal range. Societies

should strongly encourage public health authorities to raise public awareness of CKD and should promote moves to reduce the risk of developing hypertension. Such governmental public health initiatives are exemplified by campaigns in countries such as the UK, Finland and Japan to reduce dietary salt intake and by the introduction of mandatory labeling of sodium content on foods in the US. These initiatives have proven highly successful in reducing rates of cardiovascular mortality and morbidity.

As the world's population ages, the consequent escalation in the prevalence of hypertension and diabetes will lead to further increases in the rates of CKD. This trend will continue to place an undue economic burden on society given the costs of programs to treat end-stage renal disease. In 2005, the US spent $32 billion on such programs. These facts mandate that measures be put forth to ensure timely prevention and detection of CKD and to slow the progression of this disease. The key to successful prevention of CKD is screening for predisposing comorbidities such as hypertension and diabetes, and aggressive treatment of these conditions to guideline goals.

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TRANSPLANTATION

Neural networks for predicting graft survival

Bruce Kaplan and Jesse Schold

Predicting outcomes of renal transplant recipients using standard statistical techniques is difficult. Novel approaches such as the use of artificial neural networks might improve the precision and accuracy in this area of medicine in which numerous and complex events contribute to outcomes.

Despite the contributions of numerous observational studies of kidney transplantation over the past few decades, prediction of outcomes for individual patients remains more difficult than prediction of outcomes following other medical interventions.[1,2] However, a recent article by Akl *et al.* challenges the notion that outcomes for this population cannot be predicted accurately.[3] The authors found that artificial neural networks had a high predictive value for graft survival and greater predictive accuracy than traditionally used nomograms.

The study included 1,900 patients who received a living donor kidney transplant at a single center within a 20-year period. An artificial neural network and a statistically derived nomogram were constructed to predict 5-year graft survival based on demographic, clinical and pharmaceutical data. An external validation data set was used, and the primary results for the artificial neural network indicated a concordance index of 0.88 for the outcome of 5-year graft loss. Moreover, the artificial neural network model was more accurate and sensitive than the nomogram, which had a concordance index of 0.72 with external validation. The high predictive accuracy of the neural network for the conventionally most recognized end point in transplantation is significantly higher than that found by past researchers in the field.[1,4] Furthermore, its improved predictive accuracy over nomograms challenges previous literature that indicated that these techniques were similarly accurate.[5,6]

Many rational explanations exist for the relatively low predictive capability of statistical models in renal transplantation. The complex nature of the immune response, the heterogeneous population and the many comorbidities found in renal transplant patients all probably contribute to the inability to predict outcomes as fundamental as graft and patient survival. Moreover, compared with populations in which predictive models have been used more routinely (for example, in oncology, radiology, cardiology or trauma), the kidney transplant recipient population has a relatively low short-term mortality and graft loss rate. Therefore, the primary outcome events of interest in transplantation often occur long after the initial factors that are used to make predictions. As predictive models often have reduced predictive power for less frequent events, this problem cannot easily be remedied by

Practice points

- Predicting outcomes in renal transplantation is complex
- Techniques such as artificial neural networks might improve the accuracy of predictions for a single patient, but findings should be interpreted with caution and validated over time