

## Renal protection in IgA nephropathy requires strict blood pressure control

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### Introduction

Primary IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide [1,2]. Although IgAN was considered a benign condition for many years, we now know that many cases eventually progress to end-stage renal failure. According to recent reviews, the actuarial renal survival at 10 years is 80–85% in most studies. Moreover, 30–40% of affected individuals develop end-stage renal failure within 20 years from the apparent onset of the disease [1,2]. Impairment of renal function, severe proteinuria and arterial hypertension are the strongest predictors of an unfavourable outcome. Among histological parameters, proliferative glomerulonephritis with crescents or advanced lesions (glomerulosclerosis and interstitial fibrosis) are the most reliable prognostic markers. Despite considerable progress in our understanding of IgA biology, the aetiology and fundamental pathogenic mechanisms of mesangial IgA deposition have remained unsolved [2]. For this reason, treatment options of IgAN patients currently lack a disease-specific approach.

Furthermore, progression to irreversible renal parenchymal damage follows a final common pathway in most cases of chronic proteinuric nephropathies that is relatively independent of the initial insult. IgAN is no exception in that regard. The risk factors for progression of IgAN are the same as in most other chronic glomerulopathies, including hypertension, proteinuria, smoking and early elevation of serum creatinine. Hypertension is the most well known, the

most frequently examined and probably also the most important of the risk factors for renal disease progression. This commentary will focus on the epidemiology and pathophysiology of hypertension, on the value of 24 h ambulatory blood pressure measurement (ABPM), on target blood pressures and on treatment options for hypertension in chronic IgAN.

### Epidemiology and pathophysiology of hypertension in IgAN

The prevalence of hypertension in adult IgAN lies between 19 and 53% at the time of renal biopsy. Malignant hypertension occurs in 7–15% of patients and is associated with a rapid decline in renal function if not promptly treated. Subias *et al.* emphasized that the incidence of malignant hypertension in adults with IgAN is sometimes underestimated [3]. Renal biopsy in severely hypertensive patients might unmask patients who actually have malignant hypertension secondary to IgAN.

The pathophysiology of hypertension in IgAN patients is uncertain. In early publications, Zucchelli *et al.* [4] found normal levels of total exchangeable sodium. Valvo *et al.* [5], on the other hand, detected expanded total blood volume and plasma volume in both normotensive and hypertensive patients with IgAN. Valvo *et al.* described normal plasma renin activity and high total peripheral resistance in hypertensive patients and suggested that this state of affairs might be related to increased sympathetic nervous system activity. Nevertheless, Zucchelli *et al.* found normal plasma norepinephrine levels in these patients [4]. Boero *et al.* detected an increased erythrocyte  $\text{Na}^+$ – $\text{Li}^+$  counter transport [6]. The authors suggested that counter transport might represent a valuable marker of increased risk to develop hypertension during the course of the disease [6]. Konishi *et al.* recently found sodium sensitivity of blood pressure in patients with IgAN, even when they were normotensive and had normal renal function [7]. There was a close relationship between sodium sensitivity of blood pressure and renal histological damage.

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Components of the 'metabolic syndrome' have been associated with hypertension in IgAN patients. Eioro *et al.* demonstrated that hypertension was highly associated with insulin resistance [8]. Previously, Fliser *et al.* documented that insulin resistance and hyperinsulinaemia were already present early in the course of IgAN [9]. Syrjänen *et al.* found that hypertension and proteinuria were commonly associated with hyperuricaemia and hypertriglyceridaemia [10]. Furthermore, overweight was a significant independent risk factor for the development of arterial hypertension [11].

### Value of 24 h ABPM

There is no general agreement about the clinical utility of ABPM in IgAN patients. Suffice it to say, in patients with chronic renal disease of any cause, ABPM is better than office blood pressure in predicting left ventricular hypertrophy and progression of renal dysfunction. Furthermore, ABPM effectively excludes white coat hypertension and defines diurnal blood pressure variability, compared with casual blood pressure measurements.

Csiky *et al.* evaluated the role of ABPM in predicting the progression of IgAN in 126 patients followed for 36 months [12]. They found an increase in serum creatinine in the eight normotensive non-dippers, but no increase in the 28 normotensive dippers. They also observed an increase in serum creatinine in the 10 patients with 'white coat hypertension', although this increase was less marked than that in the 52 hypertensive patients. The authors concluded that real hypertension, 'white coat hypertension' and lack of circadian rhythm may accelerate IgAN progression.

Two additional studies emphasized the association between ABPM values and early target organ damage in IgAN. Stefanski *et al.* [13] examined 20 normotensive patients with normal renal function and compared them with age-, gender- and body mass index-matched healthy controls. They found that the median 24 h, daytime and nocturnal blood pressure values were significantly higher in the patients than in matched controls. Furthermore, ventricular wall thickness and ventricular septal thickness of the patients were significantly greater than those of matched controls. In addition, they found left ventricular diastolic dysfunction in some of the patients. Szelestei *et al.* [14] examining 12 normotensive and 38 hypertensive IgAN patients found a significantly higher left ventricular mass index and left ventricular diastolic dysfunction in the hypertensive patients. In the hypertensive patients, both the increased left ventricular wall thickness and deterioration in diastolic function were significantly related to night time blood pressure and diurnal index values. However, there was no relationship to daytime blood pressure.

### Target blood pressure

There is no randomized controlled trial evidence devoted specifically to IgAN about target blood pressure required to preserve renal morphology and function. For this reason, we accept the National Kidney Foundation task force recommendations for renoprotection where target blood pressure depends on the severity of proteinuria before treatment. If proteinuria is <1 g/day, the blood pressure should be maintained at <135/85 mmHg, equivalent to a mean blood pressure of 99 mmHg. If proteinuria is >1 g/day, blood pressure should be <125/75 mmHg, equivalent to a mean of 92 mmHg [15]. The antiproteinuric effect of antihypertensive treatment predicts renoprotection. Therefore, the therapy should be titrated not only on blood pressure values, but also on reduction of proteinuria [16]. The target which appears to yield a maximum benefit of proteinuria reduction is <500 mg/day [16,17].

Evidence for the importance of a low-normal target blood pressure in the prevention of chronic IgAN progression was provided by several studies. Kanno *et al.* showed that during a 3 year follow-up, the achievement of a low normal blood pressure (129/70 compared with 136/76 mmHg) minimizes progression, with a mean proteinuria of 1 g/day without additional immunosuppressive treatment [18]. Osawa *et al.* analysed the blood pressure levels at the time of renal biopsy and histological alterations in 332 IgAN patients [19]. Patients with optimal blood pressure ( $\leq 120/80$  mmHg) had minimal histological damage with respect to mesangial proliferation and vessel changes, compared with patients with higher blood pressure. The authors concluded that optimal blood pressure control prevented histological damage in IgAN [19].

### Treatment directed at the renin-angiotensin-aldosterone system (RAAS)

The onset of progressive renal insufficiency is prevented and predicted by the development of proteinuria and hypertension in IgAN. For this reason, until we can target the fundamental pathogenic mechanisms of mesangial IgA deposition to prevent and control IgA-initiated glomerular injury, we should focus on antihypertensive and antiproteinuric therapy. Of note, components of the metabolic syndrome, such as increased insulin resistance, hypertriglyceridaemia and overweight, were detected in a number of studies, in support of the viewpoint that non-immunological mechanisms are probably associated with the progression of IgAN as well. There is no evidence that steroid therapy is superior to optimal supportive care. The latter should be based mainly on RAAS blockade. However, the most perfect study comparing steroid treatment with supportive therapy was initiated >10 years ago before presently accepted blood pressure targets were widely accepted and before

titration of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blocking agents (ARBs) to reduce proteinuria effectively was recommended [20]. Meanwhile, we should therefore consider treating our proteinuric IgAN patients on the basis of recently recommended multiple risk factor intervention strategies for nephroprotection [17,21,22]. The best accepted main elements (with level 1 and some with level 2 evidence) of this strategy are: (i) aggressive blood pressure control starting with an ACEI and/or an ARB using maximum recommended doses if tolerated to reach target levels for hypertension and for proteinuria; (ii) control of blood lipid concentrations with statins; (iii) restriction of salt and protein intake; (iv) smoking cessation; and (v) loss of excess body weight with diet and increased physical activity.

Angiotensin II (AT II) is a multifunctional factor that is important in regulating renal haemodynamics and glomerular permselectivity [23]. Independently of these effects, AT II modulates several mesangial and tubular functions acting as a growth factor and involving the profibrogenic cytokine networks of platelet-derived growth factor (PDGF) and transforming growth factor- $\beta$  (TGF- $\beta$ ). The AT II-induced mesangial cell contraction with efferent arteriolar vasoconstriction initiates glomerular hypertension and hyperfiltration that eventually lead to glomerulosclerosis. The locally produced cytokines and growth factors lead to increased extracellular matrix formation, glomerular and tubular inflammation and, finally, renal fibrosis. The RAAS could also be a local factor involved in the progression of chronic renal failure in IgAN [24]. Overexpression of AT II, its receptors, increased mesangial expression of RAAS mRNAs and intraglomerular hyperactivity of AT II were detected in the renal biopsies of IgAN patients. Furthermore, a direct stimulatory action of polymeric IgA from patients with IgAN on the release of renin and AT II from mesangial cells was demonstrated.

The alterations in glomerular haemodynamics induced by local AT II overproduction would also activate the RAAS. This process might be particularly enhanced in IgAN, where contraction of mesangial cells represents an early step in the pathogenesis of the renal damage. Furthermore, IgA macromolecules deposit in the mesangium, inducing mesangial cell proliferation and sclerosis in IgAN. For these reasons, the actions of AT II upon mesangial cells overlap those of macromolecular IgA. Therefore, patients with IgAN may be more susceptible to the effects of AT II than patients with other glomerulopathies.

Numerous reports devoted to IgAN and other forms of chronic renal disease show that inhibition of the RAAS provides a notable advantage. ACEIs and ARBs can delay the progression of renal damage. This beneficial influence is closely related not only to the known antihypertensive effect but also to the antiproteinuric actions of these drugs [25,26]. The antihypertensive studies in IgAN targeting patients with/without hypertension and/or proteinuria [18,27–35] are summarized in Table 1. Comparing

the studies with one another is difficult because of the different clinical characteristics and different treatment protocols. In most studies, ACEIs and/or ARBs significantly decreased proteinuria. However, even this effect was mild in most studies.

In earlier studies, some benefits of ACEIs were observed in terms of decreasing the decline in renal function [27,33]. In a recent randomized, controlled study with a long follow-up but with relatively few patients, enalapril significantly reduced the rate of renal function loss compared with other antihypertensive agents [29]. In contrast, in two controlled studies, a variety of ACEIs moderately lowered proteinuria without improving renal function [28,34]. In one of the studies, ACEIs reduced proteinuria even in normotensive patients with IgAN [28]. In a retrospective analysis, Cattran *et al.* observed that the maximal benefit in retarding progression in patients with proteinuria  $>3$  g/day and the beneficial effect on progression significantly correlated with the extent to which proteinuria decreased in response to treatment [27].

Four studies with ARBs targeted only proteinuria in patients with IgAN [30–32,35]. ARBs were as effective as ACEIs in reducing proteinuria, but more effective than other antihypertensive agents. Russo *et al.* compared different doses of enalapril with different doses of losartan and detected a significant reduction in proteinuria at all interventions [31]. Combining enalapril with losartan was more effective for proteinuria reduction. However, the study design did not permit an analysis of the effect of RAAS blockade on the progression of IgAN. In the recent COOPERATE study, where 131 of 301 patients had IgAN, the combination of an ACEI and ARB offered superior renoprotection over either an ACEI or ARB alone in non-nephrotic proteinuric renal diseases [36].

## Conclusion

ACEIs and/or ARBs are effective in reducing proteinuria in IgAN. There is some evidence that the compounds reduce disease progression. The effectiveness of the drugs in reducing progression appears to be related to their antiproteinuric effect rather than solely to their blood pressure-lowering effect. Most of the studies summarized in Table 1 were designed and initiated before presently accepted blood pressure targets were widely accepted and before titration of ACEIs and ARBs to reduce proteinuria effectively was recommended. The majority of the immunosuppression studies in IgAN patients had problems in that they provided incomplete data on blood pressure targets, the use of ACEIs and/or ARBs was not optimal and little information was given on the dosage of these drugs. Thus, it is improbable that benefits of immunosuppressive drugs independent of blood pressure-lowering effects can be effectively shown. In our opinion, strict blood pressure control will remain one of the cornerstones in the treatment of IgAN.

**Table 1.** Synopsis of antihypertensive treatment studies in IgAN

Author and type of study	Main clinical characteristics and follow-up period	Treatment design and treatment groups	Definition of high BP	Target BP	Achieved BP	Outcome parameters	Major findings
Cattran <i>et al.</i> [27]. Retrospective study	Scr 1.3–1.8 mg/dl. With/without hypertension. Uprot $\geq 1$ g/day. $\geq 3$ months (mean 29 months)	ACEI or other antihypertensives. $n = 27$ with hypertension: ACEI (in 14 pts combination with other antihypertensives); $n = 55$ with hypertension: other antihypertensive medication; $n = 33$ without hypertension: no medication	DBP $> 95$ mmHg	DBP $< 90$ mmHg	Target BP not achieved in 16% of ACEI and 11% of other medication group	Renal survival (variable outcome parameters). Uprot	Significant reduction of renal function loss and Uprot in patients receiving ACEI
Maschio <i>et al.</i> [28]. Placebo controlled, cross-over study	Normal renal function. Normal BP. Uprot 1.0–2.5 g/day. 12 months	ACEI or placebo. $n = 39$ : fosinopril (20 mg/day) and placebo in two 4 month sequences. Mild restriction in sodium intake ( $< 150$ mEq/day)	$> 140/90$ mmHg		MAP: 90.4 mmHg (fosinopril group) 92.4 mmHg (placebo group)	Uprot	No change in renal function. Mild significant reduction in Uprot
Praga <i>et al.</i> [29]. RCT	Scr $\leq 1.5$ mg/dl. With/without hypertension. Uprot 1.7–2.0 g/day. 78 months (enalapril); 74 months (other antihypertensives)	ACEI or other antihypertensives. $n = 23$ : enalapril (5–40 mg/day); $n = 21$ : other antihypertensives. Low salt diet for hypertensives	$> 140/90$ mmHg	$\leq 140/90$ mmHg		Renal survival (two outcome parameters). Uprot	Significant reduction of rate of renal function loss and Uprot in patients receiving ACEI
Perico <i>et al.</i> [30]. Randomized double blind study	Scr 0.9–2.4 mg/dl. With/without hypertension. Uprot 0.5–4.0 g/day. 28 days	ACEI or ARB. $n = 11$ : enalapril (20 mg/day); $n = 9$ : irbesartan (100 mg/day) plus indomethacin ( $2 \times 75$ mg/day) for three more days			124/69 mmHg (enalapril group); 142/82 mmHg (irbesartan group)	Uprot	Significantly lower BP and age already at baseline in enalapril group. Significant reduction of Uprot (potentiated by indometacin) in both groups
Russo <i>et al.</i> [31]. RCT	Normal renal function. Normal blood pressure. Uprot 1–3 g/24 h 36 weeks	ACEI or ARB or ACEI plus ARB. $n = 10$ : enalapril (10 mg for 4 weeks, 20 mg for another 4 weeks); losartan (50 mg for 4 weeks, 100 mg for another 4 weeks); combination (10 mg + 50 mg for 4 weeks, 20 mg + 100 mg for another 4 weeks)	$> 140/90$ mmHg	$< 140/90$ mmHg	121/68 mmHg (ABPM)	Uprot	Significant reduction in proteinuria (correlate with BP reduction) in all groups. Combination has additive antiproteinuric effect



Song <i>et al.</i> [32]. Randomized cross-over study	Creat. clear. 25–75 ml/min. Well-controlled BP with ACEI (ramipril). Uprot $\geq 1$ g/24 h. 33 weeks	ACEI plus ARB (two different renal diseases). $n = 14$ : IgAN; $n = 18$ : type-2 DNP. Candesartan (4–8 mg/day) to ramipril (5–7.5 mg/day) vs placebo to ramipril (5–7.5 mg/day) in both groups. Moderate salt restriction		$<130/80$ mmHg	MAP 91–93 mmHg (IgAN); 91–92 mmHg (DNP)	Uprot	Significant mild reduction in proteinuria in IgAN (independent of BP change). No reduction in proteinuria in DNP
Rekola <i>et al.</i> [33]. Retrospective study	Creat. clear >40 ml/min. Hypertension. Uprot 1.8–2.0 g/24 h. 1.7 year (ACEI); 3.1 year ( $\beta$ -blocking agent)	ACEI or $\beta$ -blocking agents. $n = 22$ : enalapril; $n = 34$ : $\beta$ -blocking agents	$\geq 140/90$ mmHg	$<140/90$ mmHg	MAP 100 mmHg (enalapril); 102 mmHg ( $\beta$ -blocking agent)	Renal survival	Significantly slower reduction of GFR on enalapril
Bannister <i>et al.</i> [34]. RCT	Creat. clear. 30–90 ml/min. Hypertension. Uprot: $\leq 6$ g/24 h. 12 months	ACEI or CCB. $n = 13$ : enalapril; $n = 10$ : nifedipin. Low salt diet			MAP 102 mmHg (enalapril); 106 mmHg (nifedipin)	Renal survival. Uprot	No significant difference between the two groups in GFR reduction. Proteinuria reduction ( $\geq 25\%$ ) in 7/13 enalapril-treated and in 1/10 nifedipin- treated patients
Kanno <i>et al.</i> [18]. Non-randomized controlled trial	Scr 1.0–1.1 mg/dl. Hypertension. Uprot: 0.9–1.0 g/24 h. 3 years	ACEI plus CCB (two different BP targets). $n = 26$ : benazepril (2.5–10 mg) plus amlodipine (2.5–10 mg); $n = 23$ : benazepril (2.5–10 mg) plus amlodipine (2.5–10 mg). Salt restriction (6 g/day)	$<150/90$ mmHg	In moderate treatment group $\leq 140/85$ mmHg; in intensive treatment group $\leq 130/70$ mmHg	In moderate treatment group 136/76 mmHg; in intensive treatment group 129/70 mmHg	Renal survival	Significant decrease of GFR in moderate treatment group. Stabilization of GFR in intensive treatment group. No change of Uprot in the two groups
Park <i>et al.</i> [35]. RCT	Scr $<3.0$ mg/dl. Hypertension. Uprot 2.1–2.3 g/day. 12 weeks	ARB or CCB. $n = 20$ : losartan (50 mg); $n = 16$ : amlodipine (5 mg) plus other antihypertensives (except ACEI, ARB and CCB) if needed in both groups		$\leq 125/75$ mmHg	113/77 mmHg (losartan); 114/77 mmHg (amlodipine)	Uprot	Losartan significantly reduced Uprot (from 2.3 to 1.2 g/day), no change of Uprot in amlodipine group

Scr = serum creatinine; ACEI = angiotensin-converting enzyme inhibitors; BP = blood pressure; RCT = randomized controlled trial; Creat. clear = creatinine-clearance; ARB = angiotensin receptor-blocking agents; MAP = mean arterial pressure; Uprot = proteinuria; CCB = calcium channel-blocking agents.

A specific role of RAAS blockade in the prevention of IgAN progression is suggested by the 131 IgAN patient subgroup participating in the COOPERATE study [36]. Similar evidence will hopefully be provided by two large-scale studies that are currently underway in Europe. Furthermore, the usefulness of a multiple risk factor intervention strategy for nephroprotection should be justified by randomized controlled trials in IgAN patients. There is always a place for more and better information.

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## References

1. D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. *Am J Kidney Dis* 2000; 36: 227–237
2. Floege J, Feehally J. IgA nephropathy: recent developments. *J Am Soc Nephrol* 2000; 11: 2395–2403
3. Subias R, Botey A, Darnell A *et al.* Malignant or accelerated hypertension in IgA nephropathy. *Clin Nephrol* 1987; 27: 1–7
4. Zucchelli P, Zuccala A, Mancini E. Hypertension in primary glomerulonephritis without renal insufficiency. *Nephrol Dial Transplant* 1989; 4: 605–610.
5. Valvo E, Gammara L, Bedogna V *et al.* Hypertension in primary immunoglobulin A nephropathy (Berger's disease): hemodynamic alterations and mechanisms. *Nephron* 1987; 45: 219–223
6. Boero R, Degli Esposti E, Fabbri A *et al.* Increased sodium–lithium countertransport activity in red cells of IgA nephropathy patients. *Kidney Int* 1991; 40: 1118–1122
7. Konishi Y, Okada N, Okamura M *et al.* Sodium sensitivity of blood pressure appearing before hypertension and related to histological damage in immunoglobulin A nephropathy. *Hypertension* 2001; 38: 81–85
8. Eiro M, Katoh T, Sakuma Y *et al.* Insulin resistance highly associates with hypertension in IgA nephropathy. *Clin Nephrol* 2003; 59: 71–78
9. Fliser D, Pacini G, Engelleiter R *et al.* Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int* 1998; 53: 1343–1347
10. Syrjänen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrol Dial Transplant* 2000; 15: 34–42
11. Bonnet F, Deprele C, Sassolas A *et al.* Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 2001; 37: 720–727
12. Csiky B, Kovács T, Wagner L *et al.* Ambulatory blood pressure monitoring and progression in patients with IgA nephropathy. *Nephrol Dial Transplant* 1999; 14: 86–90
13. Stefanski A, Schmidt KG, Waldherr R *et al.* Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. *Kidney Int* 1996; 50: 1321–1326
14. Szelestei T, Kovács T, Barta J *et al.* Circadian blood pressure changes and cardiac abnormalities in IgA nephropathy. *Am J Nephrol* 1999; 19: 546–551
15. K/DOQI. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 2002; 39 [Suppl 1]: S1–S266
16. Kocks MJA, De Zeeuw D, Navis GJ. Optimal blood pressure control and antihypertensive regimens in hypertensive renal disease: the potential of exploring the mechanisms of response. *Curr Opin Nephrol Hypertens* 2002; 11: 135–140
17. Ruggenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal disease. *Lancet* 2001; 357: 1601–1608
18. Kanno Y, Okada H, Saruta T *et al.* Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: a 3-year follow-up. *Clin Nephrol* 2000; 54: 360–365
19. Osawa Y, Narita I, Imai N *et al.* Determination of optimal blood pressure for patients with IgA nephropathy based on renal histology. *Hypertens Res* 2001; 24: 89–92
20. Pozzi C, Andrulli S, Del Vecchio L *et al.* Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol* 2004; 15: 157–163
21. Hebert LA, Wilmer WA, Falkenhain ME *et al.* Renoprotection: one or many therapies? *Kidney Int* 2001; 59: 1211–1226
22. Wilmer WA, Rovin BH, Hebert CJ *et al.* Management of glomerular proteinuria: a commentary. *J Am Soc Nephrol* 2003; 14: 3217–3232
23. Wolf G. Molecular mechanism of angiotensin II in the kidney: emerging role in the progression of renal disease: beyond haemodynamics. *Nephrol Dial Transplant* 1998; 13: 1131–1142
24. Coppo R, Amore A, Hogg R *et al.* Idiopathic nephropathy with IgA deposits. *Pediatr Nephrol* 2000; 15: 139–150
25. Laville M, Alamartine E. Treatment options for IgA nephropathy in adults: a proposal for evidence-based strategy. *Nephrol Dial Transplant* 2004; 19: 1947–1951
26. Reddan DN and Owen WF. IgA nephropathy and inhibitors of the renin angiotensin system. Is reduction in proteinuria adequate proof of efficacy? *Am J Kidney Dis* 2001; 38: 182–185
27. Cattran CD, Greenwood C, Ritchie S. Long-term benefits of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: a comparison to patients receiving treatment with other antihypertensive agents and to patients receiving no therapy. *Am J Kidney Dis* 1994; 23: 247–254
28. Maschio A, Cagnoli L, Claroni F *et al.* ACE inhibition reduces proteinuria in normotensive patients with IgA nephropathy: a multicentre, randomized, placebo-controlled study. *Nephrol Dial Transplant* 1994; 9: 265–269
29. Praga M, Gutiérrez E, González E *et al.* Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol* 2003; 14: 1578–1583
30. Perico N, Remuzzi A, Sangalli F *et al.* The antiproteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. *J Am Soc Nephrol* 1998; 9: 2308–2317
31. Russo D, Minutolo R, Pisani A *et al.* Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. *Am J Kidney Dis* 2001; 38: 18–25
32. Song JH, Lee SW, Suh JH *et al.* The effects of dual blockade of the renin–angiotensin system on urinary protein and transforming growth factor- $\beta$  excretion in 2 groups of patients with IgA and diabetic nephropathy. *Clin Nephrol* 2003; 60: 318–326
33. Rekola S, Bergstrand A, Bucht H. Deterioration rate in hypertensive IgA nephropathy: comparison of a converting enzyme inhibitor and  $\beta$ -blocking agents. *Nephron* 1991; 59: 57–60
34. Bannister KM, Weaver A, Clarkson AR *et al.* Effect of angiotensin-converting enzyme and calcium channel inhibitor on progression of IgA nephropathy. *Contrib Nephrol* 1995; 111: 184–193

35. Park HC, Xu ZG, Choi S *et al.* Effect of losartan and amlodipine on proteinuria and transforming growth factor- $\beta$ 1 in patients with IgA nephropathy. *Nephrol Dial Transplant* 2003; 18: 1115–1121
36. Nakao N, Yoshimura A, Morita H *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet*, 2003; 361: 117–124

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## Peritonitis: limiting the damage

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Reducing the morbidity associated with peritonitis is one of the major challenges to improve outcomes for patients on peritoneal dialysis (PD). In the short-term, during the actual episode, patients suffer pain, risk of hospitalization and social inconvenience, with extra and often numerous hospital visits. In one series, peritonitis accounted for 25% of hospital admissions for patients on PD [1]. In the long term, peritonitis is a major cause of patients transferring to haemodialysis, accounting for 13–54% of technique failure in long-term continuous ambulatory peritoneal dialysis (CAPD) patients [2] and 43% of patients on automated peritoneal dialysis (APD) [3]. Even in patients who recover from the initial episode, peritonitis causes other long-term sequelae, such as changes in membrane permeability and sclerosing peritonitis, which eventually contribute to technique failure.

Severe or repeated episodes of peritonitis are particularly damaging to the peritoneal membrane. Davies *et al.* [4] showed that in the short term, single episodes had no significant effect on membrane permeability or ultrafiltration, while recurrences or clusters of infection caused an increase in membrane permeability and reductions in ultrafiltration. Interestingly, these changes were more marked with higher cumulative dialysate leukocyte counts, independently of the infecting organisms. Longitudinal studies have not shown that these effects on membrane transport persist for the long term (over years) [4,5]. However, such studies are difficult to interpret. Patients with severe peritonitis will probably not be included either

because of poor ultrafiltration, or because of another episode of peritonitis. There is one study, though, that does suggest a subtle long-term ultrafiltration dysfunction after a single episode of peritonitis [6]. *In vitro* evidence shows that there are pathways from acute inflammation to longer term fibrosis and angiogenesis in the peritoneum that would explain the association between peritonitis and ultrafiltration dysfunction [7].

Sclerosing peritonitis is a rare but devastating complication in patients on PD. Mortality is high, with rates of 37.5% being reported [8]. Although sclerosing peritonitis is a complication predominantly of long-term PD, with most cases occurring after 5 years [8], peritonitis is also an important predisposing factor. A recent large multicentre study from Japan showed that 30% of patients with early-onset sclerosing peritonitis (before 10 years) was associated with peritonitis, though this was not true with onset after 10 years on PD. The Australian data also suggest that around a third of cases are directly associated with an episode of peritonitis [9].

Minimizing the impact of peritonitis in the patient on PD will have a considerable effect on their experience of PD and will also extend their time span on this modality. Several strategies are required to achieve this as shown in Box 1.

### Reducing the incidence of peritonitis

Peritonitis rates vary from centre to centre and are largely determined by patient selection, quality of patient training and social factors. Despite early reports when patients were carefully selected for APD, there is no consistent difference between peritonitis rates for CAPD and APD. There have been some advances. Regular use of mupirocin at the exit site

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