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EDITORIAL

Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch–Schönlein purpura nephritis

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Introduction

The long-term prognosis of Henoch–Schönlein purpura nephritis (HSPN) depends on the severity of initial clinical symptoms and histological features [1, 2]. The risk of evolution into a chronic kidney disease (CKD) may be as high as 50, 40 and 15 % for the combination of onset with nephrotic and nephritic syndrome, nephrotic syndrome, nephritic syndrome and/or heavy non-nephrotic proteinuria, respectively [1]. The International Study of Kidney Disease in Children (ISKDC) classified the risk of progression on the basis of the histology severity mainly according to the extent of crescent formations. Combining three studies with a follow-up of about 6 years [3–5], Haas [2] demonstrated that 25 % of children biopsied for HSPN had severe outcomes (persistently active renal disease and/or worsened stages of CKD, including end-stage renal failure), in correlation with the ISKDC grades of renal pathology damage. These data indicate that children with HSPN have to be carefully followed, since some cases can have a catastrophic evolution.

However, the therapeutic choice can be challenging because—apart from mild renal clinical symptoms and histological lesions that almost always are associated with good long-term outcome, and the association of nephrotic and nephritic syndrome with high histological grade [1–6] that most frequently leads to CKD—the long-term prognosis cannot predicted with certainty at disease onset. More importantly, there is a paucity of evidence-based (EB) data to guide treatment decisions for HSPN. Doctors are therefore confronted with the dilemma of undertreatment and increased risk of CKD or over-treatment and the risk of unnecessary side effects.

Recently, the Kidney Disease Improving Global Outcome (KDIGO) initiative published guidelines on the treatment of HSPN [7]. In view of the lack of EB data for HSPN treatment and similarities between HSPN and primary immunoglobulin A nephropathy (IgAN), the KDIGO guidelines resorted to data regarding the treatment of the two diseases in similar clinical conditions.

The aims of the present paper are:

1) To analyse to what extent the therapeutic suggestions/recommendations of those guidelines take into account the pathophysiological differences between HSPN and IgAN
2) To examine if the guidelines are consistent with data reported by uncontrolled series from clinical experts of the disease and the current therapeutic attitudes.

KDIGO guidelines for HSPN treatment

The guidelines are as follows [7]:

> 11.1.1: We suggest that children with HSP nephritis and persistent proteinuria, >0.5–1 g/d per 1.73 m^2, are treated with ACE-I or ARBs. (2D)
>
> 11.1.2: We suggest that children with persistent proteinuria, >1 g/d per 1.73 m^2, after a trial of ACE-I or ARBs, and GFR >50 ml/min per 1.73 m^2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see Chapter 10). (2D)

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11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see Recommendation 10.6.3). (2D)
10.6.3.1: Define crescentic IgAN as IgAN with crescents in more than 50 % of glomeruli in the renal biopsy with rapidly progressive renal deterioration (Not Graded)
10.6.3.2: We suggest the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see Chapter 13). (2D).

The guidelines for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis specify that oral prednisone is preceded by three methylprednisolone (MP) pulses with additional plasma exchange (PE), when the plasma creatinine level is >500 μmol/L (recommendation 11.2.1,10.6.3, 13.2.1 and Table 30 of reference [7]). The same guidelines are recommended independently from the patient's age, both for children and adults with HSPN.

Pathophysiological differences between primary IgAN and HSPN

Transposing treatment guidelines prepared for IgAN to HSPN should take into account the different pathophysiological mechanisms underlying these disorders which are in some ways similar, but differ in many relevant features and lead to possible different outcomes.

1) In HSPN, especially in children, the glomerular lesions in initial biopsies are often severe, showing signs of acute glomerular inflammation with leukocyte influx and resident glomerular cell proliferation, frequent tuft necrosis and crescent formations. These active lesions can be found as well in IgAN, if renal biopsy is performed during gross hematuria or phases of rapid progression, but in most cases of IgAN they are rather uncommon [8, 9]. The typical frequent presence of crescents in HSPN strongly influenced the ISKDC classification, which grades the severity in HSPN mainly according to the percentage of glomeruli with crescents [2]. In some series, most patients with HSPN present with 20–30 % crescentic glomeruli [for a review: 9], while in IgAN crescents are detected in 5–10 % of renal biopsies, generally occupying only a part of the capsule parietal wall [9]. This difference with IgAN may result from more intense subendothelial deposition of IgA circulating complexes (IgACC) in HSPN [for a review: 6, 8].
2) Another difference with IgAN is the high frequency of endocapillary proliferation and inflammatory cell infiltration by polynuclear neutrophils in HSPN [for a review: 6, 8, 9].
3) Nephritic and nephrotic syndromes are more frequent in HSPN, reflecting the acute pathophysiological mechanism and acute disease onset of HSPN [8].
4) HSPN is often an acute disease and cannot be assimilated to IgAN. HSPN is more benign in children who frequently undergo a complete remission, while in adults the disease is more frequently progressive with the classical features of a chronic renal disease, being in these cases more similar to primary IgAN [for a review: 8].

Both diseases result from the glomerular deposition of IgACC, hence the pathophysiological mechanisms of HSPN and IgAN present with relevant differences that might result in a different response to the same treatment. Remission and healing after an acute onset are more common in HSPN than in IgAN. CKD in HSPN is likely to result from scars and hyperfiltration secondary to acute inflammatory episodes, whereas the major mechanism leading to CKD in IgAN is dependent upon a more chronic, indolent and continuous process of mesangial proliferation and matrix accumulation with possible exacerbations—such as during infectious episodes—finally leading to glomerulosclerosis [6, 8].

Several observations emphasize the crucial effect of the acute onset of HSPN in determining scars leading to CKD, including:

1) The relationship between the severity of initial clinical and histological signs and the long-term prognosis [1–5];
2) The correlation between chronicity score and time elapsed between clinical onset of kidney involvement and renal biopsy [10];
3) The possible rapid evolution of crescentic glomerular lesions to complete glomerulosclerosis [11];
4) A worse evolution when treatment is delayed even shortly [12–15];
5) CKD developing years after apparent complete resolution [1, 12].

Those observations emphasize the importance of treating initial episodes adequately, without delay, considering that HSPN belongs to the vasculitis class of renal diseases in which a timely diagnosis and prompt treatment is of paramount importance in determining the final outcome.

Comment on the use of angiotensin converting enzyme inhibitor or angiotensin receptor blockers

Following the KDIGO guidelines [7], a patient with nephrotic syndrome-associated proteinuria persistently at >1 g/day/1.73-m^2, <50 % of glomeruli with crescents and a glomerular filtration rate (GFR) of >50 ml/min/1.73 m^2 will first receive a course of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARBs) (recommendation

11.1.2). According to the mode of action of those drugs [reduction of the intracapillary pressure and inhibition of the stimulation of mesangial cells (MC) induced by binding of angiotensin to specific MC receptors], proteinuria and MC proliferation may be reduced, but the endocapillary inflammatory component and the crescents are not expected to improve. The efficacy of this strategy in moderately severe HSPN patients (proteinuria with albuminemia of >2.5 g/dl, normal GFR and a I–III histological grade) is suggested in one retrospective study by the normalization of proteinuria and stabile normal GFR at last follow-up after 3–4 years [16]. However, following this guideline may delay a potentially more effective treatment and increase the risk of CKD progression in patients with ISKDC grade III who present a relevant percentage of crescentic glomeruli (although <50 %) and/or a massive inflammatory leucocyte infiltration and/or necrotic lesions. Unfortunately, these lesions, if not healed, leave sclerotic irreversible scars.

In conclusion, this KDIGO recommendation seems to be appropriate for chronic cases lacking acute inflammation and necrotizing and crescentic lesions, in which MC activation and/or hyperfiltration are the leading pathogenetical mechanisms for damage progression. However, when proteinuria is the expression of a mostly acute inflammatory glomerular disease, delaying a more effective anti-inflammatory treatment for months may be dangerous with respect to the final outcome.

Comment on the use of steroids

In those patients not showing protein remission after treatment with ACE-I or ARBs and for whom the proteinuria remains at >1 g/day with kidney function not extremely deteriorated (GFR >50 ml/min/1.73 m^2), KDIGO guideline 11.1.2 (which also concerns patients with nephrotic syndrome with <50 % crescentic glomeruli) suggests a 6-month course of oral prednisone on the basis of randomized control trials (RCTs) showing a benefit in reducing proteinuria and maintaining GFR in adults with IgAN. The only RCTs performed in HSP with oral prednisone were aimed at testing its possible role in the prevention of nephritis [17, 18], and the results were negative [17–19]. To date, no placebo-controlled RCT on oral prednisone alone or methylprednisolone (MP) pulses associated with oral prednisone in established HSPN has been performed. However, there are also no reports proving the benefit of oral prednisone alone in HSPN, whereas several older publications suggested the lack of efficacy of this treatment [5, 20–22]. Because of the latter, the use of prednisone alone has been abandoned in favour of MP pulses followed by oral prednisone—in the most severe cases used in association with immunosuppressive drugs. However, what response to oral steroids should be expected in HSPN patients with nephrotic syndrome, 40 % of crescentic glomeruli, extended leucocyte infiltration, necrotic lesions and a slightly reduced GFR after months of no response to angiotensin inhibitors?

The use of MP pulses is not clearly suggested in the KDIGO guidelines except in cases of HSPN with >50 % glomeruli with crescents and nephrotic syndrome or deteriorating renal function, with referral to the guidelines of ANCA-associated nephritis (guideline 13.2.1); this is due to the rapid anti-inflammatory effect of MP pulses, as mentioned in the rationale of this guideline. The higher efficacy of high doses of steroids to treat crescents is sustained by experimental results. In a rat model of crescentic glomerulonephritis, the maximal therapeutic effect is obtained with 30 mg/kg intravenous (IV) MP [23].

In summary, we suggest that clinicians should not be prone to use oral prednisone alone in cases of grade III with extensive inflammatory lesions for the following reasons: (1) the risk of evolution to CKD even in ISKDC classification grade III [2]; (2) a better effect of MP pulses associated with oral prednisone compared with oral prednisone alone in the case of glomerular inflammation; (3) the negative reports on the beneficial effects of prednisone alone in retrospective case series [5, 20–22]; (4) a possible beneficial effect of MP pulses followed by prednisone suggested in a prospective case series compared to a historical series of the same centre [15] and in the control arm of one RCT [24]; (5) the beneficial effect of MP pulses suggested in multiple drug schemas [25–30].

Comment on the use of immunosuppressive drugs

As there is a very low quality of evidence for the benefits of immunosuppressive agents in HSPN, the KDIGO guidelines do not recommend the use of immunosuppressive drugs with the exception of cyclophosphamide (CPH) in the case of crescentic glomerulonephritis (crescents in >50 % of the glomeruli) with nephrotic syndrome or rapid degradation of GFR (recommendation 11.2.1). The latter recommendation is based on high-quality evidence for the benefits of corticosteroids and CPH which dramatically improve the short- and long-term outcomes of ANCA vasculitis, as mentioned in the rationale for this guideline [31]. It seems therefore paradoxical that immunosuppressive drugs may not be useful in lower grades of inflammatory glomerular lesions when other treatments have failed. Indeed, the study of Pillebout et al. [24] in adults and of Tarshich et al. [32] in children failed to show any advantage of CPH in combination with prednisone and MP on prednisone and MP pulses [24] or of CPH alone versus placebo [32]. However, some possible biases might explain the lack of beneficial effects of CPH in the latter studies. In the study of Tarshish et al. [32], CPH was used alone whereas the efficacy of CPH in ANCA-associated

glomerulonephritis was observed when CPH was associated with prednisone [31]. In the RCT of Pillebout et al. [24], the small number of patients with at least ISKDC grade III (<30 %) might have been insufficient to evaluate the efficacy of CPH in patients with extra-capillary proliferation and result in a significant difference with the control group that received the same steroid treatment (MP pulses followed by oral prednisone). By contrast, the results of one non-randomized prospective trial and several retrospective studies suggest the efficacy of immunosuppressive drugs in association with steroid protocols including MP pulses in severe cases of HSPN [26–30].

Recently, an RCT comparing 1 year of cyclosporine (CyA) to 4 months of prednisone preceded by three MP pulses has shown that CyA gave a 100 % resolution of nephrotic-range proteinuria and a 100 % renal survival rate without additional therapy after a mean follow-up of 6 years. This study shows that treatment of HSPN with CyA is efficacious, safe and not inferior to that of MP pulses and prednisone [33]. As shown by Faul et al. [34], the anti-proteinuric effect of CyA results from stabilization of the actin cytoskeleton in the kidney podocytes rather than from other mechanisms [34].

Therefore, the suggestion of the KDIGO guidelines not to add immunosuppressive drugs to steroids in patients with <50 % crescentic glomeruli even in presence of nephrotic syndrome and/or deterioration of GFR is in contrast with the expert opinion and at risk of not being followed.

Comment on PE

Following the guidelines, PE should be used only in case of rapidly progressive crescentic GN when plasma creatinine is above 500 μmol/L (recommendations 11.2.1 and 10.6.3). This recommendation is based on a multicentre controlled trial on ANCA-associated vasculitis with crescentic glomerulonephritis [35]. This trial showed a significantly higher rate of renal function recovery when patients with the above plasma creatinine values received seven PE sessions compared with those who received three MP pulses in addition to CPH and oral prednisone followed by azathioprine [35]. However, PE is not recommended in cases of ANCA-associated crescentic glomerulonephritis with moderate increases in plasma creatinine values only because no adequate RCT has yet been performed. In HSPN, PE alone has been used with success in two series of pediatric patients [13, 14] presenting with acute renal function impairment, heavy proteinuria or nephrotic syndrome and a histological grade of ≥III [14] or equal to V [13]. At last review, after 4 [14] and 10 years [13], 13 of 14 [14] and six of nine patients [13], respectively, had a normal GFR and complete or almost complete resolution of other renal symptoms. Two patients with ISKDC histological grade V (2/9; 22 %) [13] and one with grade IIIb (1/14; 7 %) [14] had reached end-stage renal disease (ESRD), which is less than in large historical series [1, 2]. However, it must be noted that those three patients were not treated immediately but with a delay exceeding 1 month after the initiation of symptoms. A recent series of 11 adult patients with severe HSPN also reported excellent long-term results using PE associated with steroids [36]. These results suggest that PE should be added at an earlier stage of GFR deterioration in crescentic glomerulonephritis to minimize the risk of CKD.

Conclusions

The difficulty in trying to standardize the treatment for HSPN on the basis of EB data already existing for similar glomerular entities is due to the general clinical course of this disease, which shows neither a slow progression to ESRD (like the majority of patients with primary IgA nephropathy) nor acute and rapidly loss of glomerular filtration (like anti-glomerular basement membrane or ANCA-associated glomerulonephritis). HSPN actually belongs to the group of vasculitides whose major target is the endothelium, which renders the damage acute and rapidly vanishing or results in remodelling, leading to resolution with healing or fibrosis with scars and chronic damage. HSPN progresses mainly by poussées of acute glomerular damage, which might be subclinical and result in recovery with repair or trigger crescent formation, which in turn can regress or proceed to a definitive urinary space obstruction. On the contrary, primary IgAN is mostly a mesangial disease, with a rather slow production of glomerular sclerosis and interstitial fibrosis. However, the renal features of HSPN and primary IgAN are to a great extent similar, and the vasculitic lesions found in the renal biopsy of patients with HSPN are in general mild in comparison to those of ANCA-associated glomerular diseases.

The well-recognized histological similarity between the two diseases has convinced most adult nephrologists that they represent an entity which can benefit from common therapeutic recommendations. The results seem to reassure the clinicians since they finally can find EB-associated recommendations for a protean disease like HSPN. This is the case for recently published KDIGO recommendations.

Expert opinion raises some doubts and aims at advising clinicians about the pitfalls in following indications, which do not consider the extreme variability and unpredictability of the clinical course of HSPN. It is always advisable to interpret the guidelines in the light of real everyday cases.

Children with the same presentation can experience either complete disappearance of urinary signs or rapid or late progression in spite of an apparent remission. Hence the first consideration may be that not only baseline data are needed, but a close observation over days or weeks and, if clinical remission is not attained, the observation must be prolonged

as for other chronic glomerular diseases, such as IgAN. The crucial point is that HSPN can be arrested and reversed when adequately treated in an early stage. This is an opinion, but which is shared by many pediatric nephrologists and corroborated by the observation that patients treated with delay have a higher risk of CKD [10, 13, 14, 37, 38].

Several authors [15, 37, 38] have tried to establish the need for aggressive treatment on the basis of the number of crescentic glomeruli, which represent the hallmark of severe and potentially progressive HSPN: crescents can be produced in poussées of activity, disappear mostly after treatment; however, in mild cases they also occur spontaneously or progress to glomerular obsolescence.

Pathologists have tried to assess the severity of HSPN on the basis of percentage, extension and quality of crescents; however, the severity of a "crescentic" HSPN is difficult to establish since the timing of renal biopsy introduces a great variability. The time elapsed from the initiation of the acute damage and the renal biopsy is crucial [10], and a case could be defined as mildly crescentic glomerulonephritis if renal biopsy is performed early, but after a few days the same case can show >50 % crescentic glomeruli. The repetition of biopsies is mandatory in the case of symptom aggravation or in the case of lack of improvement under therapy. The delay and frequency of biopsy repetition is dependent upon the severity of the symptomatology and histology, on the evolution of the disease and on response to treatment [10]. It is now obvious that the ISKDC classification that grades severity according to the amount of crescents only has become obsolete and should be replaced by a new detailed histological classification similar to that recently published for IgAN [39]. This latter classification takes into account not only the crescents but also the following parameters that have been shown to be independent predictors of renal functional decline and/or response to therapy: mesangial hypercellularity, endocapillary hypercellularity, segmental and global glomerulosclerosis, arterio- and arteriolosclerosis, interstitial inflammation and tubular atrophy/interstitial fibrosis.

Because of sample error possibility and because frequent repetition of kidney biopsy is limited by the invasivity of this procedure, other parameters of disease activity should be tested in prospective studies (urinary excretion of podocytes, urinary and circulating C5b-9 [for a review: 6].

The chance of more EB data becoming available in the short term is small since clinical trials are difficult to set up due to the small number of patients and because the unpredictability of outcome renders the distinction of subgroups according to severity very hazardous. Clinical trials should be set up in the framework of a large international multicentre collaboration to recruit a sufficient number of patients and to accelerate the acquisition of information necessary to provide optimal and largely accepted treatments for patients with HSPN [6]. In the meantime, guidelines should realistically consider the present common practice derived from experts' consensus.

Expert opinion is unanimous about the risk of undertreating children with HSPN, which was very common practice in the past, since most first-level clinical centres, familiar with easily recovering mild HSPN, referred children with progressive HSPN too late to high-care centres. The analysis of data from different registries shows that the percentage of ESRD due to HSPN has declined considerably during recent decades [40, 41]. This is in favour of the benefit of the more aggressive treatments used and reported in the literature during the last 20 years. In conclusion, although the KDIGO initiative produces important data for the improvement of patient treatment, the principle of applying EB data obtained in one clinical entity to formulate guidelines for an another similar but not identical disease might result in pitfalls. Indeed, in the case discussed here, clinicians following the KDIGO guidelines on the treatment of HSPN face the risk of delaying the initiation of effective treatment and increasing the risk of CKD over the long term [12–15].

Treatment protocols including MP pulses, immunosuppressive drugs and PE are generally used at a lower threshold of risk of long-term CKD than in the KDIGO guidelines. This combined with the fact that those guidelines suggested for adults and children with HSPN are only based on RCTs performed in adults with IgAN and not with HSPN and that IgAN is a disease whose pathophysiology is different despite similarities, the hope of obtaining adequate EB information from the existing RCTs is very low. Consequently, it should be expected that pediatric nephrologists would be reluctant to follow those guidelines for fear of undertreatment. The fact that guidelines are used as the reference of good clinical practice in case of lawsuits will further complicate decision-making.

Platforms of experts should be created at the level of International Societies in order to set up prospective studies to validate the KDIGO guidelines, to propose and organized prospective studies on new biomarkers of disease activity and to design RCTs.

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