Outi Jauhola

HENOCH-SCHÖNLEIN PURPURA IN CHILDREN
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HENOCH-SCHÖNLEIN PURPURA IN CHILDREN

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 12 of the Department of Paediatrics, on 4 May 2012, at 12 noon

UNIVERSITY OF OULU, OULU 2012
Abstract

The aim of this work was to describe the clinical features and clinical course of Henoch-Schönlein purpura (HSP) in a prospective setting, to compare the efficacy of cyclosporine A (CyA) and methylprednisolone (MP) pulses for the treatment of severe HSP nephritis (HSN) and to study the effect of prophylactic prednisone treatment given at disease onset on the long-term outcome.

A total of 223 children with newly diagnosed HSP were followed up prospectively for 6 months. Patients with severe HSN also had extrarenal symptoms more frequently during this time. Protein loss via the intestine was more common than previously described, occurring in 3% of the patients. HSN developed in the early course of the disease. The results suggest that weekly urine dipstick tests are indicated for 2 months after HSP onset and individually for over 6 months in cases of HSN or HSP recurrences. Prednisone did not affect the frequency or timing of the appearance of HSN.

The efficacy of CyA and MP treatments was evaluated in a trial with a mean follow-up time of 6 years involving 24 paediatric patients (11 CyA, 13 MP), 15 of whom were randomized and 9 were treated according to the given protocol without randomization. Oral CyA was not inferior to intravenous MP pulses and proved to be an efficient, safe steroid-sparing treatment for severe HSN. All the CyA-treated patients achieved remission of nephrotic-range proteinuria within 3 months, while remission was achieved more slowly in the MP group and only in 6/13 (46%) with the initial treatment. There was no difference in the renal biopsy findings two years after initiation of the therapy.

The 8-year outcome of HSP was assessed by means of a health questionnaire in 160 (94%) of the 171 former patients in the randomized placebo-controlled prednisone trial and in 138 (81%) with urine analysis and measurement of blood pressure. HSP carried a good prognosis, although skin relapses occurred up to a decade after the initial onset and could be accompanied by late-onset nephritis. Hypertension and/or renal abnormalities were recorded in 13% of the patients, being more frequent in those with an initial occurrence of HSN (OR 4.3, p=0.009, 95% CI 1.4–14.0) and warranting long-term follow-up of HSN patients. Early prednisone treatment did not affect the long-term outcome of HSP and should not be routinely used.

Keywords: corticosteroid treatment, cyclosporine, hematuria, IgA glomerulonephritis, methylprednisolone, prognosis, proteinuria, Schoenlein-Henoch purpura
Tiivistelmä

Väitöskirjan tarkoituksena oli kuvata Henoch-Schönleinin purppuran (HSP) oireita ja taudinkulkua, verrata siklosporiini A:n (CyA) ja metyyliprednisolonipulssihoidon (MP-pulssihoidon) tehoa vaikean HSP-nefriitin (HSN) hoidossa ja selvittää taudin alussa annetun prednisonihoidon vaikutusta pitkäaikaisennusteeeseen.


Varhaisen kortisonihoidon pitkäaikaisvaikutuksia arvioitiin 8 vuotta lumekontrolloidun prednisonihoitotutkimuksen jälkeen, jolloin aiemman tutkimuksen 171 potilaasta 160 (94 %) vastasi terveyskyselyyn ja 138 (81 %) osallistui virtsa-analyysin ja verenpaineen mittauksen sisältäneeseen seurantatutkimukseen. HSP:n ennuste oli lyhyt, vaikka taudin iho-oireet saattoivat uusia jopa 10 vuoden ajan ja taudin uusiutumisen yhteydessä saattoi ilmaantua myöhemmin HSN. Kohonnut verenpaine ja/tai valkuais-/verivirtaisuus todettiin 13 %:lla. Ne olivat yleisempiä potilailla, joilla oli ollut HSN taudin alkuvaiheessa (OR 4.3, p=0.009, 95 % CI 1.4–14.0). Siten HSN-potilaiden pitkäaikaisseuranta on tarpeen. Varhaisella kortisonihoidolla ei ollut vaikutusta taudin ennusteeeseen, minkä vuoksi kortisonia tulee käyttää HSP-potilaiden hoidossa vain harkiten.

Asiasanat: ennuste, hematuria, IgA-nefropatia, kortisonihoito, metyyliprednisoloni, proteinuria, siklosporiini
Acknowledgements

This work was carried at the Department of Paediatrics, University of Oulu, during the years 2004–2012. I am grateful to Professor Mikko Hallman, MD, Head of the Department, and Professor Matti Uhari, MD, for creating an inspiring atmosphere for both scientific and clinical work. I have really appreciated the statistical skills taught to us on Monday mornings. I thank Docent Päivi Tapanainen, MD, Chief Physician at the Department of Paediatrics, for her support in combining clinical work and research in the clinic.

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I wish to thank all the co-authors, Professor Olli Koskimies, MD, Docent Marja Ala-Houhala, MD, Pekka Arikoski, MD, Docent Helena Autio-Harmainen, MD, Tuula Hölttä, MD, Docent Timo Jahnukainen, MD, Docent Jukka Rajantie, MD, and Timo Örmälä, MD, for contributing their expertise to this work. I have enjoyed all the Paediatric Nephrology Meetings and your company through the years. I am grateful to Juha Turtinen, BSc, for his friendly and skilful assistance with the statistics. I thank all of the doctors and nurses in health care centers and university and central hospitals that participated in the trials, and Helena Moilanen, a registered nurse, for helping in organizing the laboratory tests throughout the country. I am grateful to Malcolm Hicks, MA, for his excellent revision of the language of my thesis.

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My parents, Maarit and Raimo, deserve great admiration and thanks for the support and encouragement they have given me throughout my life. My father
gave me my first lessons in paediatrics, and the lessons are still continuing. I also wish to thank my sister Inari, her partner Julius and all the close relatives for their support and friendship. I thank Ville Ojansivu, BSc for help with computers. Special thanks go to my dear friends Eveliina Jakkula, MD, Elina Kilpeläinen, MD, Virpi Koskela-Niska, MD, Elina Koskela, MD and Elise Sarjanoja, MD, for their joyful friendship.

Oulu, March 2012
Outi Jauhola
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ANCA</td>
<td>Antineutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>AST</td>
<td>Antistreptolysin O titre</td>
</tr>
<tr>
<td>C0</td>
<td>Pre-dose concentration</td>
</tr>
<tr>
<td>C2</td>
<td>Concentration 2 hours post dose</td>
</tr>
<tr>
<td>C3/C4</td>
<td>Complement component 3/Complement component 4</td>
</tr>
<tr>
<td>CHCC</td>
<td>Chapel Hill Consensus Conference</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C reactive protein</td>
</tr>
<tr>
<td>CyA</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>Cyst-C</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>EULAR</td>
<td>European League against Rheumatism</td>
</tr>
<tr>
<td>GABS</td>
<td>Group A β-haemolytic streptococcus</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>Hpf</td>
<td>High-power field</td>
</tr>
<tr>
<td>HSP</td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>HSN</td>
<td>Henoch-Schönlein purpura nephritis</td>
</tr>
<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
</tr>
<tr>
<td>IgAN</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>ISKDC</td>
<td>International Study of Kidney Disease in Children</td>
</tr>
<tr>
<td>MMF</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>MP</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>NA</td>
<td>Not available</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>RPGN</td>
<td>Rapidly progressive glomerulonephritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>PRES</td>
<td>Pediatric Rheumatology European Society</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>UP/C</td>
<td>Urine protein/creatinine ratio</td>
</tr>
<tr>
<td>U-Prot</td>
<td>Urine protein</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:


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1 Introduction

Henoch-Schönlein purpura (HSP) is a small vessel vasculitis mediated by immunoglobulin A (IgA)-immune complex depositions. It is the most common vasculitis in childhood, with reported incidences varying from 6.1 to 26.5 per 100 000 (Aalberse et al. 2007, Penny et al. 2010). Its aetiology is not completely understood, but exposures to various antigens such as infective agents, vaccinations and drugs are considered to be possible immunological triggers (Allen et al. 1960, Saulsbury 2002).

The dominant clinical features are palpable purpura and petechiae, arthritis, abdominal pain and nephritis, but other organs may also occasionally be involved. Most paediatric patients have a self-limited disease, but severe intestinal bleeding or intussusception may cause acute complications (Allen et al. 1960, Katz et al. 1991). In a systematic review of 12 series comprising 1133 children, the renal disease affected one third of the patients, varying from intermittent haematuria and proteinuria to severe nephrotic-nephritic syndrome (Narchi 2005). The long-term prognosis is mainly dependent on the severity of renal involvement (Goldstein et al. 1992, Ronkainen et al. 2002).

There is a lack of evidence-based data on the treatment of HSP. Corticosteroids have been shown to treat the abdominal and joint symptoms efficiently but not to prevent the development of nephritis (Chartapisak et al. 2009). The data on randomized controlled trials (RCTs) regarding early corticosteroid treatment are nevertheless limited to a follow-up time of 12 months. Various regimens and combinations of treatments have been used for severe Henoch-Schönlein nephritis (HSN) in small, uncontrolled patient series (Chartapisak et al. 2009), while only one study has been made in a randomized setting (Tarshish et al. 2004). RCTs are needed to optimize the treatment of severe HSN, which causes high morbidity among patients.

This research was designed to investigate the clinical features of HSP, the efficacy of oral cyclosporine A (CyA) and intravenous methylprednisolone (MP) pulses for the treatment of severe HSN, and the long-term outcome for unselected patients treated with early prednisone or a placebo.
2 Review of the literature

2.1 Historical aspects

In 1801, William Heberden described a 5-year-old boy with macroscopic haematuria, abdominal pain, bloody stools, arthralgia and bloody points over his legs (Heberden 1801). Later, in 1837, Johann Schönlein described the association of purpuric cutaneous lesions with arthralgia (Schönlein 1837), whereupon his former pupil, Eduard Henoch, went on to recognize gastrointestinal (GI) and renal involvement in this syndrome completing the modern definition of the disease (Henoch 1868), which acquired the name Henoch-Schönlein purpura. Since the original description, there has been variation in the terminology, including anaphylactoid purpura, allergic vasculitis, Henoch-Schönlein syndrome, rheumatoid purpura and Schönlein-Henoch purpura (Szer 1994, Garzoni et al. 2009).

2.2 Diagnosis of HSP

In 2008, the European League against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PRES) published a new classification of childhood vasculitides (Ozen et al. 2010). The consensus criteria for the diagnosis of HSP require purpura or petechiae with lower limb predominance in the presence of at least one of the following: diffuse abdominal pain, any biopsy showing predominant IgA deposition, acute arthritis/arthralgia, and renal involvement defined as any haematuria and/or proteinuria (Ozen et al. 2010). These criteria yield a sensitivity of 100% and a specificity of 87% for the diagnosis of HSP (Ozen et al. 2010).

The EULAR and PRES criteria supersede the 1990 American College of Rheumatology (ACR) (Mills et al. 1990) and the 1994 Chapel Hill Consensus Conference (CHCC) (Jennette et al. 1994) criteria for vasculitides, which were both based only on adult data. These criteria have been criticized for their poor sensitivity of 31–65% for HSP and controversialities that might result in the overdiagnosis of HSP, especially in children (Ozen 2005). Both the 1990 ACR and the 1994 CHCC classification criteria were meant for distinguishing HSP from other vasculitides rather than for diagnosing it (Ozen 2005). HSP is a rare disease in adults, with an incidence of 1–2 per 100,000 (Penny et al. 2010), and
the diagnosis is routinely confirmed by means of a skin or kidney biopsy (Davin & Weening 2003, Shrestha et al. 2006, Kawakami 2010).

2.3 Clinical features of HSP

The site, extent and severity of blood vessel involvement in HSP determine the clinical picture for an individual patient (Prais et al. 2007). The dominant clinical features are palpable purpura and petechiae, arthritis and arthralgia, abdominal pain and nephritis. The frequencies of these findings in the largest prospective and retrospective patient series are described in Tables 1 and 2. Other organs such as the brain, lungs and scrotum may also be involved occasionally.

Table 1. Comparative analysis of the main clinical features of Henoch-Schönlein purpura in the largest prospective patient series (I).

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Mean age, range (y)</th>
<th>Boys (%)</th>
<th>Skin symptoms</th>
<th>Joint symptoms</th>
<th>GI symptoms</th>
<th>Renal symptoms</th>
<th>Recurrences</th>
</tr>
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<tbody>
<tr>
<td>Jauhola</td>
<td>Finland</td>
<td>2012</td>
<td>223</td>
<td>7.1</td>
<td>55</td>
<td>100%</td>
<td>90%</td>
<td>57%</td>
<td>46%</td>
<td>25%</td>
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<tr>
<td>Al-Sheyyab</td>
<td>Jordan</td>
<td>1999</td>
<td>48</td>
<td>6.5</td>
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<td>NA</td>
<td>NA</td>
<td>46%</td>
<td>NA</td>
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<tr>
<td>Fretzayas</td>
<td>Greece</td>
<td>2008</td>
<td>74</td>
<td>5.2</td>
<td>55</td>
<td>99%</td>
<td>92%</td>
<td>62%</td>
<td>26%</td>
<td>66%</td>
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<tr>
<td>Huber</td>
<td>Canada</td>
<td>2004</td>
<td>40</td>
<td>NA</td>
<td>NA</td>
<td>100%</td>
<td>95%</td>
<td>98%</td>
<td>NA</td>
<td>15%</td>
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<tr>
<td>Muslu</td>
<td>Turkey</td>
<td>2002</td>
<td>30</td>
<td>9.7</td>
<td>57</td>
<td>100%</td>
<td>83%</td>
<td>27%</td>
<td>43%</td>
<td>NA</td>
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<tr>
<td>Mean Total</td>
<td></td>
<td></td>
<td>415</td>
<td>6.9</td>
<td>53</td>
<td>100%</td>
<td>91%</td>
<td>60%</td>
<td>42%</td>
<td>36%</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td>30–223</td>
<td>1.5–16.7</td>
<td>40–57</td>
<td>99–100%</td>
<td>83–95%</td>
<td>27–88%</td>
<td>26–46%</td>
<td>15–66%</td>
</tr>
</tbody>
</table>

GI: gastrointestinal; NA: not available; y: years.
Table 2. Comparative analysis of the main clinical features of Henoch-Schönlein purpura in the largest retrospective patient series (I).

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Mean age, range (y)</th>
<th>Boys (%)</th>
<th>Skin symptoms</th>
<th>Joint symptoms</th>
<th>GI symptoms</th>
<th>Renal symptoms</th>
<th>Recurrences</th>
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<tr>
<td>Allen</td>
<td>USA</td>
<td>1960</td>
<td>131</td>
<td>4</td>
<td>64</td>
<td>100%</td>
<td>68%</td>
<td>53%</td>
<td>40%</td>
<td>NA</td>
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<tr>
<td>Balmelli</td>
<td>Switzerland</td>
<td>1996</td>
<td>139</td>
<td>5.4</td>
<td>58</td>
<td>100%</td>
<td>79%</td>
<td>66%</td>
<td>43%</td>
<td>7%</td>
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<tr>
<td>Blanco</td>
<td>Spain</td>
<td>1997</td>
<td>116</td>
<td>6.9</td>
<td>66</td>
<td>100%</td>
<td>80%</td>
<td>64%</td>
<td>25%</td>
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<td>Calvino</td>
<td>Spain</td>
<td>2001</td>
<td>78</td>
<td>NA</td>
<td>46</td>
<td>100%</td>
<td>78%</td>
<td>73%</td>
<td>54%</td>
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<td>Chang</td>
<td>Taiwan</td>
<td>2004</td>
<td>261</td>
<td>6.9</td>
<td>53</td>
<td>100%</td>
<td>43%</td>
<td>58%</td>
<td>20%</td>
<td>NA</td>
</tr>
<tr>
<td>Fischer</td>
<td>Germany</td>
<td>1990</td>
<td>119</td>
<td>6.4</td>
<td>54</td>
<td>100%</td>
<td>76%</td>
<td>76%</td>
<td>54%</td>
<td>NA</td>
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<tr>
<td>Hamdan</td>
<td>Jordan</td>
<td>2008</td>
<td>68</td>
<td>5.9</td>
<td>59</td>
<td>100%</td>
<td>75%</td>
<td>63%</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>Kaku</td>
<td>Japan</td>
<td>1998</td>
<td>194</td>
<td>6.3</td>
<td>50</td>
<td>100%</td>
<td>72%</td>
<td>57%</td>
<td>34%</td>
<td>NA</td>
</tr>
<tr>
<td>Nong</td>
<td>Taiwan</td>
<td>2007</td>
<td>107</td>
<td>6.2</td>
<td>59</td>
<td>95%</td>
<td>47%</td>
<td>72%</td>
<td>28%</td>
<td>NA</td>
</tr>
<tr>
<td>Peru</td>
<td>Turkey</td>
<td>2008</td>
<td>254</td>
<td>8.65</td>
<td>58</td>
<td>100%</td>
<td>66%</td>
<td>56%</td>
<td>36%</td>
<td>NA</td>
</tr>
<tr>
<td>Potts</td>
<td>UK</td>
<td>1987</td>
<td>133</td>
<td>6</td>
<td>60</td>
<td>99%</td>
<td>80%</td>
<td>56%</td>
<td>40%</td>
<td>NA</td>
</tr>
<tr>
<td>Prais</td>
<td>Israel</td>
<td>2007</td>
<td>260</td>
<td>5.7</td>
<td>57</td>
<td>100%</td>
<td>68%</td>
<td>59%</td>
<td>35%</td>
<td>3%</td>
</tr>
<tr>
<td>Rigante</td>
<td>Italy</td>
<td>2005</td>
<td>94</td>
<td>6.3</td>
<td>49</td>
<td>100%</td>
<td>68%</td>
<td>61%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Sano</td>
<td>Japan</td>
<td>2001</td>
<td>134</td>
<td>6.3</td>
<td>53</td>
<td>100%</td>
<td>74%</td>
<td>72%</td>
<td>49%</td>
<td>NA</td>
</tr>
<tr>
<td>Saulsbury</td>
<td>USA</td>
<td>1999</td>
<td>100</td>
<td>5.9</td>
<td>57</td>
<td>100%</td>
<td>82%</td>
<td>63%</td>
<td>40%</td>
<td>33%</td>
</tr>
<tr>
<td>Shin</td>
<td>Korea</td>
<td>2006</td>
<td>206</td>
<td>7.2</td>
<td>55</td>
<td>100%</td>
<td>63%</td>
<td>52%</td>
<td>38%</td>
<td>25%</td>
</tr>
<tr>
<td>Trapani</td>
<td>Italy</td>
<td>2005</td>
<td>150</td>
<td>6.1</td>
<td>63</td>
<td>100%</td>
<td>74%</td>
<td>51%</td>
<td>54%</td>
<td>35%</td>
</tr>
<tr>
<td>Mean</td>
<td>Total</td>
<td></td>
<td>2544</td>
<td>6.4</td>
<td>56</td>
<td>100%</td>
<td>68%</td>
<td>60%</td>
<td>36%</td>
<td>17%</td>
</tr>
</tbody>
</table>

GI gastrointestinal; NA not available; y years.
2.3.1 Skin

The existence of non-thrombocytopenic palpable purpura and/or petechiae is mandatory for a diagnosis of HSP (Ozen et al. 2010). The typical HSP purpura is slightly elevated and palpable (Figure 1) as a result of extravasated blood and fluid combined with inflammation (Kawakami 2010). The rash may resemble a urticarial or erythematous macular-papular rash before developing into palpable purpura. It is typically symmetrically distributed over the extensor surfaces of the lower legs, buttocks and arms. Lesions may also spread to the trunk and face (Saulsbury 1999, McCarthy & Tizard 2010). The purpuric lesions fade over several days, to be replaced by hyperpigmentation that will disappear completely with time (Saulsbury 1999).

Haemorrhagic bullous lesions, which can result in slowly healing ulcers, necrosis and scars (den Boer et al. 2010), are rare in childhood HSP (Saulsbury 1999). This more severe skin manifestation develops if the HSP vasculitis is not limited to the upper layer of the dermis as usual, but is extended to its whole thickness (Ishii et al. 2005).

Fig. 1. The classical HSP palpable purpura, petechiae and oedema of the lower limbs and the atypical cockade purpura involving the face in infantile HSP (Ronkainen et al. 2007). The photos are published with permission from the parents of the patients and the original publisher, the Finnish Medical Society Duodecim.
2.3.2 Joint

Pain, oedema and functional limitation of the joint indicate joint involvement in HSP, which typically affects the lower limb joints and particularly the ankles and knees. The upper extremity joints may also be affected. Periarticular oedema causes functional limitation of the joint, while it is unclear whether HSP can cause synovitis. Although joint involvement can be debilitating, it does not result in permanent deformity (Saulsbury 1999).

2.3.3 Gastrointestinal

Gastrointestinal manifestation of HSP is typically limited to mild colicky periumbilical or epigastric abdominal pain and nausea, but in some cases the abdominal pain can be severely debilitating. Some form of bleeding is common, although massive haemorrhage is rare (Chang et al. 2004, McCarthy & Tizard 2010). Protein-losing enteropathy, pancreatitis and hydrops of the gallbladder are rare features of HSP (McCarthy & Tizard 2010, Nakamura et al. 2010).

The most common gastrointestinal complication of HSP is intussusception, which is typically ileo-ileal, in contrast to idiopathic intussusception due to the intramural haemorrhage and oedema in that part of the intestine (Ebert 2008). Other abdominal complications include appendicitis (Kim et al. 2005, Soyer et al. 2008), bowel obstruction (Potts et al. 1987, Katz et al. 1991) and perforation (Chang et al. 2004).

2.3.4 Renal

The reported incidence of glomerulonephritis varies greatly depending on the definition of the renal disease, the methods of detection and the nature of the patient series (Tables 1 and 2). The most common features of HSN are isolated microscopic haematuria with and without proteinuria, and macroscopic haematuria is also common. Acute nephrotic and/or nephritic syndrome affects approximately one fifth of all children with HSN (Narchi 2005).

2.3.5 Urogenital

The reported incidence of scrotal involvement in HSP varies from 2 to 38%, partly due to the wide range of the definition, varying from skin oedema alone to
severe scrotal pain (Ben-Sira & Laor 2000). The scrotal symptoms are typically mild but may mimic testicular torsion (Soreide 2005). Testicular torsion complicating the HSP vasculitis of the testis is extremely rare, however (Loh & Jalan 1974). There are anecdotal case reports of ureteral stenosis, priapism and penile swelling associated with HSP (Lind et al. 2002, Sandell et al. 2002).

2.3.6 Neurological

Central nervous system involvement in HSP is rare. The most common manifestation is headache, followed by subtle encephalopathy with minimal changes in mental status, labile mood, apathy and hyperactivity. Seizures, intracranial haemorrhage, infarction and peripheral neuropathy have also been documented in case reports (Garzoni et al. 2009). Severe hypertension typically occurring with renal involvement in HSP may also cause neurological symptoms (Garzoni et al. 2009).

2.3.7 Cardio-pulmonary

The presence of severe hypertension without evidence of renal involvement in HSP has been described only in anecdotal case reports (Whyte et al. 1997, Hammami et al. 2009). Cardiac arrhythmias and the involvement of cardiac vessels or myocardium have been reported in a few adult HSP patients (Polizzotto et al. 2006, Lutz et al. 2009). Pulmonary manifestation of HSP is also very rare. Diffuse alveolar haemorrhage is the most common and most severe pulmonary manifestation, and interstitial pneumonia and interstitial fibrosis have also been reported (Tizard & Hamilton-Ayres 2008, Chen et al. 2011).

2.3.8 Clinical course of HSP

Joint and/or abdominal symptoms of HSP precede the rash by up to 14 days in 30–43% of patients, which prevents diagnosis at this stage (Saulsbury 1999, Calvino et al. 2001). Therefore intense abdominal or scrotal pain without purpura may lead to unnecessary laparotomy or orchiectomy (Katz et al. 1991).

The extrarenal symptoms of HSP are reported to be self-limiting within 2 weeks in 83% of patients (Trapani et al. 2005), while almost all patients recover within 6–8 weeks (Saulsbury 1999). Recurrences are common, as shown in Tables 1 and 2, although these episodes are generally milder and of shorter duration than
the primary one (Saulsbury 1999, Trapani et al. 2005). The recurrences generally subside after 4 months (Saulsbury 1999, Prais et al. 2007).

In a systematic review of 12 studies, 91% of those who developed HSN did so within 6 weeks of presentation and 97% within 6 months (Narchi 2005). The nephritis is typically mild and self-limited, but a few children develop persistent kidney disease that can progress to end-stage renal disease (ESRD) (Narchi 2005).

The prognosis for HSP is considered excellent in patients without renal disease, although intestinal bleeding or intussusception may cause acute complications (Allen et al. 1960, Katz et al. 1991). A recent small study made a novel observation of the possible increased risk of functional GI disorders years after recovery from HSP (Saps et al. 2011). The prognosis for HSN is unpredictable, as long-term renal morbidity may manifest even decades after apparent recovery, even in patients with an initially mild disease (Goldstein et al. 1992, Coppo et al. 1997, Ronkainen et al. 2002).

2.4 Influence of age on symptoms

The clinical features of HSP may be atypical at the extremes of age. HSP is rare in infants and young children (Amitai et al. 1993), in whom a purpuric skin rash is typically cockade and involves the face (Fiore et al. 2008), as shown in Figure 1. This is thought to result from a proportionately larger head and its correspondingly large blood supply (Amitai et al. 1993). Subcutaneous oedema of the face and limbs is a prominent feature, while involvement of the joints, GI tract and kidneys is uncommon. The duration of the disease is usually short, recurrences are infrequent and the prognosis is excellent (Allen et al. 1960, Al-Sheyyab et al. 1995). This leads some authors use the term “acute haemorrhagic oedema of infancy” and to suggest that this is a distinct clinicopathological entity from HSP (Saulsbury 1999, Fiore et al. 2008). Many others nevertheless believe that the distinct features of infantile HSP provide another example of the wide clinical spectrum of HSP (Amitai et al. 1993).

The age at disease onset is considered to be an important factor for disease severity and outcome in HSP (Meadow et al. 1972, Garcia-Porrua et al. 2002). It has been reported that the incidence of nephritis and HSP recurrences increases with the age in childhood HSP (Shin et al. 2006a, Alfredo et al. 2007, Hamdan & Barqawi 2008).

In adults, HSP represents a more severe clinical syndrome, with a higher frequency and a more severe form of renal involvement, resulting in renal
insufficiency within a decade in up to 54% of cases (Blanco et al. 1997, Shrestha et al. 2006). In a Finnish cohort, 11% of the adult patients with HSN developed ESRD within 6 years (Rauta et al. 2002).

2.5 Histopathology

Histological analysis of a skin biopsy is the most reliable tool for diagnosing HSP (Davin & Weening 2003), but it is necessary in children only if the diagnosis of HSP is in doubt (Ozen et al. 2010). The skin biopsy should be performed at the edge of a fresh lesion to maximize the chances of finding IgA deposits, which disappear with time due to proteolysis in necrotic lesions and phagocytosis (Davin & Weening 2003). A renal biopsy is indicated when kidney findings are sufficiently severe to consider immunosuppressive treatment, such as heavy proteinuria and decreased glomerular filtration rate (GFR). The clinical severity of HSN does not always parallel the severity of the renal pathological findings, and patients with persistent milder nephritis should also undergo a kidney biopsy (Edström Halling et al. 2005, Zhang et al. 2007).

Histologically, cutaneous HSP is a leukocytoclastic form of vasculitis with vessel wall necrosis and perivascular accumulation of inflammatory cells, mostly polymorphonuclear leukocytes and mononuclear cells, surrounding the capillaries and postcapillary venules of the dermis (Vernier et al. 1961). Immunofluorescence staining reveals the presence of IgA deposits in blood vessels and connective tissue, while immunoglobulin G (IgG), immunoglobulin M (IgM), C3, C4 and alternative complement pathway components are also frequently found (Faille-Kuyper et al. 1976, Davin & Weening 2003). An intestinal biopsy, which is rarely indicated, shows similar leukocytoclastic vasculitis and IgA deposition in the submucosal blood vessels (Ebert 2008).

According to the definition of IgA nephropathies, predominant IgA deposits in a granular and sometimes diffuse pattern in immunofluorescence is required for a diagnosis of HSN. The renal immunohistological findings of HSN are indistinguishable from those typical of IgA nephropathy (IgAN) (Davin et al. 2001). The IgA deposit is typically found in the mesangium, and sometimes in the capillary walls (Niaudet et al. 1993, Davin et al. 2001). The primary finding is mesangial proliferation with hypercellularity. Focal necrosis and segmental capillary collapses may appear. Epithelial crescent formation represents more significant inflammatory damage (McCarthy & Tizard 2010). The histopathological changes involved in HSN are presented in Figure 2.
Fig. 2. Two glomeruli from HSN ISKDC gradus III show mesangial proliferation (thin arrows) and epithelial cell proliferation (thick arrows) with a clear crescent formation in the lower glomerulus. Periodic Acid Schiff-staining. Original magnification x 20 (left). Immunofluorescence staining for IgA shows abundant granular fluorescence in the mesangial and some paramesangial areas. FITC-immunofluorescence staining. Original magnification x 40 (right).

The histological changes visible in HSN are graded according to a classification devised by the International Study for Kidney Disease in Children (ISKDC) (Counahan et al. 1977). Several modifications of this ISKDC classification and semiquantitative grading systems have also been used for analysing kidney histopathology (Niaudet & Habib 1998, Foster et al. 2000, Kawasaki et al. 2003a, Tarshish et al. 2004, Edström Halling et al. 2009). The ISKDC classification and a semiquantitative grading system originally introduced for IgAN are described in Tables 3 and 4.

Table 3. The classification of Henoch-Schönlein purpura nephritis devised by the International Society for Kidney Disease in Children (Counahan et al. 1977).

<table>
<thead>
<tr>
<th>Gradus</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal alterations</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferation</td>
</tr>
<tr>
<td>III</td>
<td>Focal or diffuse proliferation or sclerosis with &lt;50% crescents</td>
</tr>
<tr>
<td>IV</td>
<td>Focal or diffuse mesangial proliferation or sclerosis with 50–75% crescents</td>
</tr>
<tr>
<td>V</td>
<td>Focal or diffuse mesangial proliferation or sclerosis with &gt;75% crescents</td>
</tr>
<tr>
<td>VI</td>
<td>Membranoproliferative-like lesions</td>
</tr>
</tbody>
</table>
Table 4. Histological scoring system for IgA nephropathy (Ronkainen et al. 2006a).

<table>
<thead>
<tr>
<th>Index</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity index (max. 7)</strong></td>
<td></td>
</tr>
<tr>
<td>Cellular crescents</td>
<td>0–3*</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>0–3*</td>
</tr>
<tr>
<td>Tubular dilatation</td>
<td>0–1</td>
</tr>
<tr>
<td><strong>Chronicity index (max. 16)</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrous crescents</td>
<td>0–3*</td>
</tr>
<tr>
<td>Adhesions</td>
<td>0–3*</td>
</tr>
<tr>
<td>Segmental sclerosis</td>
<td>0–2**</td>
</tr>
<tr>
<td>Global sclerosis</td>
<td>0–3*</td>
</tr>
<tr>
<td>Tubular damage</td>
<td>0–1</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>0–1</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>0–1</td>
</tr>
<tr>
<td>Interstitial inflammation</td>
<td>0–1</td>
</tr>
<tr>
<td>Vascular sclerosis</td>
<td>0–1</td>
</tr>
<tr>
<td><strong>Tubulointerstitial index (max. 5)</strong></td>
<td></td>
</tr>
<tr>
<td>Tubular dilatation</td>
<td>0–1</td>
</tr>
<tr>
<td>Tubular damage</td>
<td>0–1</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>0–1</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>0–1</td>
</tr>
<tr>
<td>Interstitial inflammation</td>
<td>0–1</td>
</tr>
</tbody>
</table>

Total biopsy score (max. 28): activity index + chronicity index + tubulointerstitial index.

* 0=0% of glomerules affected; 1=up to 5% of glomerules affected; 2=5–10% glomerules affected; 3=over 10% of glomerules affected.

** 0=0% of glomerules affected; 1=up to 5% of glomerules affected; 2=over 5% of glomerules affect.

2.6 Epidemiology

Henoch-Schönlein purpura is the most common form of small vessel vasculitis in children, with reported annual incidences varying from 6.1 per 100 000 in Dutch children (Aalberse et al. 2007), based on electronic questionnaires sent to paediatricians, to 20.3–26.5 per 100 000 in Scotland, based on a review of hospital discharge diagnoses (Penny et al. 2010). The discrepancy is at least partly related to the study methods and diagnostic criteria used. The incidence rates have been reported to be lower in children of black race (Gardner-Medwin et al. 2002). The annual incidence of nephrotic-range HSN in children under 15 years of age in Finland is reported to be 2 per million (Ronkainen et al. 2003a).
Henoch-Schönlein purpura can affect all age groups but is most common in children between 4 and 6 years of age (Gardner-Medwin et al. 2002, Yang et al. 2005, Aalberse et al. 2007). It is a rare disease in adults with an incidence of 1.1–1.8 per 100 000 (Penny et al. 2010). A slight male preponderance in its occurrence has been suggested (Gardner-Medwin et al. 2002), but this is not generally evident (Tables 1 and 2).

2.7 Aetiology

Although the exact aetiology of HSP is unknown, exposure to various infective pathogens, drugs, vaccines, food allergens and insect bites may be possible immunological triggers (Allen et al. 1960, Saulsbury 1999). An upper respiratory tract infection (URTI) preceding presentation with HSP by some days or weeks has been reported in up to 50% of cases (Saulsbury 1999, Gonzalez et al. 2009) and the occurrence of HSP in children particularly in the autumn and winter months (Saulsbury 1999, Trapani et al. 2005, Yang et al. 2005, Fretzayas et al. 2008) suggests an infectious aetiology. Preceding infections are less frequent in adults, where drugs and toxins may be the primary predisposing factors for HSP (Gonzalez et al. 2009).

Case reports have implicated a wide variety of microbial pathogens in the aetiology of HSP, most recently the pandemic H1N1 virus and the vaccine against it (Urso et al. 2011, Watanabe 2011). A local month-by-month temporal association between hospitalization for group A β-haemolytic streptococcus (GABS), *Staphylococcus aureus*, and parainfluenza virus and hospitalization for HSP has been demonstrated (Weiss et al. 2010b), but there have been only a few studies comparing the incidences of a specific infection in HSP patients and controls. These include studies showing positive serum antibody titres for GABS (Al-Sheyyab et al. 1999) and *Bartonella henselae* (Ayoub et al. 2002) more frequently in HSP patients than in controls. The incidence of increased parvovirus B19 antibodies did not differ between HSP patients and controls (Ferguson et al. 1996). HSP has been shown not to have any tendency to cluster or to vary from one year to another in large epidemiological studies, suggesting that the disease is not caused by a single, contagious agent (Nielsen 1988). It is therefore likely that genetically controlled host responses determine whether or not an individual develops HSP in response to infectious triggers (Brogan 2007).

A cohort study of almost 50 000 adolescent and young adults who had received meningococcal vaccine is virtually the only one proving that there is no
association between a suggested trigger and the occurrence of HSP, demonstrating that a large sample size is needed to test an association for a rare event (Goodman et al. 2010).

2.8 Pathogenesis

Henoch-Schönlein purpura is known to be an IgA-complex-mediated disease, although its pathogenesis is not clearly understood (Lau et al. 2010). IgA is the main immunoglobulin directed against viral and bacterial antigens in the mucosal immune system, and IgA complexes are formed and deposited in the skin, bowel and kidney glomeruli, triggering a localized inflammatory response. Increased serum concentrations of IgA have been described in over half of the patients with HSP (Saulsbury 1999, Calvino et al. 2001, Fretzayas et al. 2008). High serum IgA alone, however, does not predispose patients to HSP, as it rarely affects patients with IgA myeloma (Zickerman et al. 2000).

There are two subclasses of IgA, IgA1 and IgA2, of which only IgA1 is involved in the pathogenesis of HSP. This contains a hinge region with multiple O-linked glycosylation sites, aberrant glycosylation of which has been demonstrated in HSP and HSN (Saulsbury 1997, Allen et al. 1998, Lau et al. 2007). Longitudinal studies to determine whether the IgA1 glycosylation defects persist following resolution of the clinical symptoms would be needed to reveal whether defective glycosylation of IgA1 is a cause or a consequence of the disease (Saulsbury 2010).

The aberrantly glycosylated IgA1 is not cleared by the liver sufficiently well and is prone to aggregate into macromolecular complexes. These accumulate in the circulation, become deposited on the walls of the small blood vessels and provoke inflammatory lesions by the alternative and lectin pathways of complement and direct cell activation (Novak et al. 2002, Kawakami 2010, Lau et al. 2010). Leukocytoclastic vasculitis then develops, resulting in small blood vessel necrosis. This allows extravasation of blood and fluid into the surrounding tissue, resulting in organ-specific symptoms that depend on the location of immune complex deposition (Kawakami 2010).

All HSP patients have circulating IgA1 immune complexes of small molecular mass, but only patients with HSN also have large-molecular-mass circulating immune complexes containing IgA1 and IgG (Lau et al. 2010). The complexes containing IgA1 are excreted in elevated amounts in the urine in
patients with HSN and may provide a specific marker for the activity of the disease (Julian et al. 2007).

Tumor necrosis factor-α (TNF-α), a cytokine produced by macrophages and T cells during an immune response, may also be associated with HSP vasculitis, as a high level of TNF-α is found in tissue and plasma in the acute phase of HSP (Besbas et al. 1997). TNF-α triggers an antigenic reaction in endothelial cells, which causes an increased affinity for binding to IgA and results in vascular inflammation. The specific antigens remain to be determined, however (Gonzalez et al. 2009). The level of endothelins is also significantly higher in the acute phase of HSP, but the significance remains to be determined (Muslu et al. 2002, Gonzalez et al. 2009).

2.9 Genetic aspects

The reported familial cases of HSP (Zhang et al. 2008), the high (2.7%) incidence of HSP in patients with autosomal recessive familial Mediterranean fever (Tunca et al. 2005) and the increased risk of HSP recurrence in living related-donor transplants (Han et al. 2010) support a genetic predisposition for HSP, but efforts to identify a gene that causes HSP have failed (Saulsbury 2010). Several human leukocyte antigen (HLA) types, HLA-DRB1*01, HLA-DRB1*11 and HLA-DRB1*14, are reported to be associated with susceptibility to HSP, and HLA-B35 is associated with an increased risk of HSN but not an overall risk of HSP (Saulsbury 2010).

A number of attempts have been made to identify genetic polymorphisms that may be associated with the development of HSP/HSN or with its severity. Many of these assessed cytokines or cell adhesion molecules involved in the modulation of inflammatory responses and endothelial cell activation. Polymorphism of interleukin 1β, for example, has been associated with the severity of HSN and its renal sequelae (Amoli et al. 2004), while polymorphisms of the ACE gene and angiotensinogen gene (Özkaya et al. 2006) may influence the risk of developing HSP and HSN, respectively. These studies were performed on relatively small numbers of patients, however, and therefore lack the power to be definitive or applicable to all racial groups (Brogan 2007).

It has been shown recently that children with HSN and IgAN have raised levels of aberrant galactosylated IgA1 in their serum, and that these children frequently have a parent with a similar serum profile, highlighting the importance of genetic factors in determining the constitution of serum IgA1 (Kiryluk et al. 2007).
2011). The results, however, suggest that aberrant glycosylation of IgA1 is not enough to cause HSN or IgAN. It is likely that other environmental or inherited risk factors are required to produce overt disease (Kiryluk et al. 2011).

2.10 Laboratory findings

The diagnosis of HSP is based on clinical symptoms and findings. The purpose of laboratory evaluation is to exclude other diseases and to identify HSP-related complications. An elevated serum IgA level is a non-specific finding, but argues for HPS rather than any other leukocytoclastic vasculitis. There is no correlation between the serum IgA level and the clinical features of HSP (McCarthy & Tizard 2010), and only a small number of patients with HSP exhibit slight ANCA positivity (Brogan et al. 2010).

Thrombocytopenia and clotting disorders must be excluded, and further examinations, e.g. of antineutrophil cytoplasmic antibodies (ANCA), C3, C4 and immunoglobulins, are warranted if the diagnosis is in doubt (McCarthy & Tizard 2010).

A full blood count may show anaemia or leukocytosis, and the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) may be elevated due to a preceding infection. A throat culture, antistreptolysin O titre (AST), and streptodornase antibodies may confirm a preceding streptococcal infection. The need for further tests to identify other infectious agents depends on the clinical features of the patient (McCarthy & Tizard 2010).

Urinary protein and erythrocytes should be monitored frequently, as HSN might develop during the later course of the disease. In the case of HSN, serum creatinine (Scr), urea and cystatin C (Cyst-C) may be increased and glomerular filtration decreased (Narchi 2005). Low serum albumin may be related to renal or GI disease. In the case of decreased serum albumin without proteinuria, fecal α1-antitrypsin will confirm protein-losing enteropathy (Nakamura et al. 2010). An occult fecal blood test will reveal GI bleeding associated with HSP.

The activity of plasma factor XIII, a fibrin-stabilizing factor, has been reported to be decreased in up to 70% of HSP patients, particularly in those with severe GI symptoms (Kamitsuji et al. 1987, Kaku et al. 1998, Sano et al. 2002). Factor XIII has been suggested as a helpful marker for the diagnosis of HSP even before the onset of purpura (Kaneko et al. 2004). Further studies on factor XIII are needed, however.
2.11 Imaging

Imaging is not needed for the diagnosis of HSP, but might be required in the case of possible complications. Renal ultrasound might demonstrate increased echogenity in the kidneys (Swischuk 2004) but it is usually performed only in the case of severe HSN.

Ultrasound is the initial screening method for patients with intense abdominal pain, since intussusception related to HSP typically is confined to the small bowel and cannot be detected or treated by contrast enema (Chang et al. 2004). In fact, contrast enema has been considered contraindicated in HSP by some authors, since the underlying vasculitis may increase the risk of bowel perforation (Potts et al. 1987, Saulsbury 1999, Chang et al. 2004). Ultrasound may detect perforation of the bowel (Chang et al. 2004), but an abdominal X-ray, computed tomography, or magnetic resonance imaging of the abdomen is sometimes needed. Gastrointestinal endoscopy may be needed to evaluate GI bleeding. The endoscopic findings of HSP include gastritis, duodenitis, ulcerations, submucosal haemorrhage and purpura (Esaki et al. 2002, Ebert 2008).

The sonographic findings in the scrotum related to HSP are considered to be sufficiently characteristic to allow distinction from torsion in most cases (Ben-Sira & Laor 2000).

In HSP-related cerebral involvement, as in other cerebral forms of vasculitis, neuroimaging will characteristically disclose ischaemic lesions, which may be secondary to vessel wall proliferation, with resultant luminal obliteration, thrombotic occlusion, or haemorrhages (Garzoni et al. 2009).

2.12 Differential diagnosis

The diagnosis of HSP is usually obvious, on account of the characteristic palpable purpura and petechiae, but other conditions should be considered in the case of atypical clinical features (Tizard & Hamilton-Ayres 2008). It is especially important to rule out ANCA-positive vasculitides, since these carry a much worse prognosis than HSP and require early aggressive therapy (Koutkia et al. 2001).

Diseases with purpura

Thrombocytopenia and clotting disorders have to be excluded as causes of purpura and petechiae. Sepsis, particularly meningococcal septicaemia, may
cause purpura-like lesions, but the diagnosis of septicaemia is generally clinically obvious (Tizard & Hamilton-Ayres 2008). Drug eruptions, urticaria and erythema multiforme may mimic the skin manifestation of HSP (McCarthy & Tizard 2010). The diagnosis of HSP, however, requires skin lesions at the typical site and the fulfillment of at least one subsidiary criterion (Ozen et al. 2010). In the case of doubt, the diagnosis of HSP should be confirmed with a skin or renal biopsy.

Hypersensivity vasculitis, cutaneous leukocytoclastic angiitis and HSP share the common features of leukocytoclastic vasculitis of the small vessels with prominent skin involvement, but differ in the frequency and type of involvement of other organs (Szer 1994, Tizard & Hamilton-Ayres 2008). Also several other forms of vasculitis, such as polyarteritis nodosa, Wegener’s granulomatosis, microscopic polyangiitis and vascular inflammation secondary to a connective tissue disorder such as systemic lupus erythematosus (SLE), can have a similar clinical presentation to HSP. Immunological serological parameters are useful in the differentiation of some of these conditions. Antinuclear and double-stranded DNA antibodies will rule out SLE and ANCA will rule out the ANCA-positive vasculitides, including Wegener’s granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome (Brogan et al. 2010).

Chronic Epstein-Barr virus infection has been reported to mimic HSP with palpable purpura, haematuria, abdominal pain and arthritis in three paediatric patients. These patients also presented with fever, anaemia, lymphadenopathy, splenomegaly and hepatomegaly, however (Guissa et al. 2010).

Diseases with IgA deposits

Predominant IgA deposits seen in a skin or renal biopsy are pathognomonic for HSP. However in addition to HSN, glomerular mesangial deposits of IgA can be observed in SLE-related nephritis, which can usually be recognized easily from its clinical and serological features and the presence of mesangial immunoglobulins of the full house type (IgG, IgM, IgA) together with both C3 and C1q in the glomeruli (Wen & Chen 2010). Similar immunohistological findings to those present in HSN have been observed in the kidneys of patients with autoimmune, liver and secretory diseases such as dermatitis herpetiformis, liver cirrhosis, coeliac disease or Crohn’s disease (Davin et al. 2001).

HSN and IgAN cannot be distinguished on the basis of a kidney biopsy. These conditions are considered to be related diseases, since both involve identical pathological and biological abnormalities (Davin et al. 2001) and have
been reported to occur in identical twins after adenovirus infection (Meadow & Scott 1985). There are also reports of the development of HSP years after the diagnosis of IgAN (Chishiki et al. 2010).

2.13 Risk factors for HSN

The frequently reported risk factors for developing HSN include age over 4–10 years at onset, persistent purpura for over 1 month, severe GI symptoms and HSP recurrences (Fischer et al. 1990, Kaku et al. 1998, Sano et al. 2002, Rigante et al. 2005, Shin et al. 2006a, Alfredo et al. 2007, de Almeida et al. 2007). Decreased factor XIII activity has also been associated with an increased risk of HSN (Kaku et al. 1998, Sano et al. 2002).

A correlation between an URTI preceding HSP and an increased incidence of HSN has been reported in one study (Gonzalez-Gay et al. 2004), but this association has not been confirmed by others. Patients with HSN have been reported to have a tendency of more frequent previous GABS infections than those without nephritis (Al-Sheyyab et al. 1999). The presence of group A streptococcal antigen in the glomeruli of children with HSN suggests that a previous streptococcal infection might have a role in the pathogenesis of HSN in some patients (Masuda et al. 2003).

2.14 Treatment of HSP

In most cases HSP is mild and self-limiting, requiring only symptomatic treatment. Bed rest and analgesics may be necessary for those with acute arthralgia or abdominal pain. Intravenous fluids may be required in cases of severe abdominal pain and vomiting (McCarthy & Tizard 2010). Acetaminophen is preferred, while non-steroidal anti-inflammatory drugs should be avoided especially in patients with GI and renal manifestations (Ebert 2008).

The skin manifestations of HSP rarely need treatment, but there are reports of the successful use of corticosteroids, particularly with bullous lesions. Steroid-sparing agents such as dapsone or colchicine have also been used, but bullous lesions may also heal spontaneously (den Boer et al. 2010).

In the initial enthusiasm for corticosteroids that started in the 1950’s it was soon noticed that they can reduce morbidity associated with abdominal pain (Allen et al. 1960). A meta-analysis of the role of corticosteroids in the treatment of HSP identified 3 randomized and 12 observational studies involving 1309
patients in all who were treated with early corticosteroids or supportive care. The corticosteroids reduced the mean time to resolution of the abdominal pain, and also recurrence rates and the frequency of intussusception, although the differences were not significant (Weiss et al. 2007). In a RCT prednisone was shown to reduce the severity and duration of both abdominal and joint symptoms and to hasten the resolution of mild nephritis (Ronkainen et al. 2006b). A large retrospective study showed that the early use of corticosteroids is associated with a reduced need for abdominal imaging, endoscopy and surgery in hospitalized children with HSP (Weiss et al. 2010a).

The data on other treatments provided for HSP are very limited. In a small controlled trial intravenous administration of factor XIII concentrate led to a notable improvement in the symptoms after 3 days (Fukui et al. 1989), and several case studies report a dramatic improvement in severe GI, pulmonary, or cerebral symptoms after plasma exchange (Davin 2011). There are also anecdotal reports of the successful use of methotrexate (Rettig & Cron 2003), mycophenolate mofetil (MMF) (Nikibakhsh et al. 2010), rituximab (Donnithorne et al. 2009) and intravenous immunoglobulin (Heldrich et al. 1993) for treating severe extrarenal manifestations of HSP.

2.15 Prevention of HSN

Five RCTs involving 789 paediatric patients have evaluated the efficacy of early prednisone treatment in preventing the development of nephritis (Mollica et al. 1992, Islek et al. 1999, Huber et al. 2004, Ronkainen et al. 2006b, Dudley et al. 2007). For two of these only preliminary results have been published as abstracts (Islek et al. 1999, Dudley et al. 2007). Two trials reported a benefit obtained from prednisone, but both of them had a high risk of bias due to inadequate or unclear allocation concealment and no placebo group (Mollica et al. 1992, Islek et al. 1999). A recent Cochrane meta-analysis concluded that prednisone did not affect the risk of renal involvement developing or persisting at 1, 3, 6 and 12 months and that the overall quality level of evidence received from the RCTs was moderate (Chartapisak et al. 2009). It is therefore becoming clear that prophylactic corticosteroids do not prevent the development of HSN.

A different conclusion was reached in a systematic review of 15 studies which suggested that early treatment with glucocorticoids lowered the likelihood of developing persistent renal disease (Weiss et al. 2007). The majority of the studies reviewed were retrospective and non-randomized, however, and therefore
vulnerable to bias. Two other systematic reviews shared the conclusion with the Cochrane meta-analysis in that the existing evidence does not support short-course prednisone at presentation with HSP for preventing persistent renal disease (Bogdanovic 2009, Zaffanello & Fanos 2009).

In addition to corticosteroids, efforts have been made to prevent HSN with medication that reduces blood clotting, in two small trials published only as abstracts. Dipyridamole or aspirin provided no benefit in preventing nephritis (Yoshimoto et al. 1987), while heparin seemed to reduce the risk of HSN (Yanyan et al. 2001). The potential side effects of heparin include severe bleeding, however, and therefore such treatment is not justified for unselected HSP patients with a good overall prognosis (Chartapisak et al. 2009).

2.16 Treatment of HSN

Henoch-Schönlein purpura nephritis is typically mild and self-limited. In the case of heavy proteinuria, reduced GFR or persistent milder nephritis, a kidney biopsy is warranted. However, therapeutic decisions should not be based solely on biopsy findings, as a biopsy performed too early might not detect the severity of the developing kidney damage (Ronkainen et al. 2002, Ronkainen et al. 2003a). Additionally, the HSN lesions might be under-represented or over-represented in the small fragment of renal tissue obtained (Davin 2011).

Several authors have recently reviewed the literature relating to the treatment of severe HSN and concluded that the data are very scarce (Bogdanovic 2009, Chartapisak et al. 2009, Zaffanello & Fanos 2009). The only published RCT evaluated the efficiency of cyclophosphamide treatment for severe HSN (Tarshish et al. 2004), while a number of case reports and retrospective studies with relatively short follow-up periods have reported better outcomes than expected with various treatments that suppress the immune system or prevent blood clotting. These studies were uncontrolled, however, and involved small numbers of patients with variable selection criteria and pretreatment periods. In addition, there was concern over a reporting bias that favoured good results. The possibility of a spontaneous recovery from HSN makes the role of the treatment in observational reports still less decisive (Bogdanovic 2009, Chartapisak et al. 2009, Zaffanello & Fanos 2009).

It was first suggested by Niaudet & Habib (1998) that immunosuppressive treatment with MP pulses should be started in the early course of the disease,
before the crescents become fibrous. This probably also applies to all other forms of treatment (Tanaka et al. 2003, Ronkainen et al. 2003a).

**Angiotensin-converting enzyme inhibitors**

Angiotensin-converting enzyme inhibitors (ACEI) have been shown to effectively decrease proteinuria and slow progression of renal impairment in IgAN among both normotensive and hypertensive patients (Coppo et al. 2007). No studies have been carried out on patients with HSN, however. Given the similarities in pathology between these two conditions, ACE inhibition should be considered for the treatment of persistent proteinuria and as a first-line therapy for hypertension in patients with HSP as well (McCarthy & Tizard 2010).

**Immunosuppressive treatment**

Corticosteroids have been most widely used for the treatment of severe HSN, often in combination with other treatments (Bogdanovic 2009). Niaudet & Habib (1998) suggested an improved outcome for severe HSN with MP pulses followed by prednisone in a prospective uncontrolled study, and a favourable role for an initial high dosage of corticosteroids combined with other treatments such as urokinase, mizoribine and tiptrygium has been reported in several uncontrolled studies (Kawasaki et al. 2003a, Deng et al. 2010, Kawasaki et al. 2011).

In addition to corticosteroids, a variety of immunosuppressive drugs have been administered to patients with severe nephritis. The results of treating HSN with cyclophosphamide are not promising, since a RCT showed no difference in the outcome between the use of cyclophosphamide or supportive treatment alone (Tarshish et al. 2004). Another RCT performed on adults with severe renal or visceral manifestation of HSP showed no difference in the outcome for patients treated with corticosteroids with or without cyclophosphamide (Pillebout et al. 2010). Similarly, the effects of treatment with corticosteroids and ACEI with or without cyclophosphamide did not differ in paediatric patients with HSN or IgAN in a retrospective study with a follow-up of 10 years (Edström Halling et al. 2009). Another retrospective study, however, suggested that treatment with cyclophosphamide, MP and urokinase pulses, warfarin and dipyridamole might be more efficient than a combination therapy of this kind without cyclophosphamide (Kawasaki et al. 2004a).
Retrospective studies have demonstrated the efficiency of CyA alone (Ronkainen et al. 2003b, Park et al. 2011) or with corticosteroids (Shin et al. 2005a, Shin et al. 2005c), both for achieving stable remission and for reducing histological changes in severe HSN with nephrotic-range proteinuria. CyA treatment has also been reported to be efficient in patients who have not responded to various immunosuppressants before its initiation (Ronkainen et al. 2003b, Park et al. 2011). Some patients, however, have developed CyA dependence (Ronkainen et al. 2003b, Park et al. 2011).

Small retrospective studies have suggested that patients treated with azathioprine and corticosteroids may have a better outcome than those treated with corticosteroids alone (Foster et al. 2000, Shin et al. 2005b). It is likely, however, that the historical controls used by Foster et al. (2000) included patients with more severe disease (Bogdanovic 2009). There are only anecdotal reports on the treatment of HSN with the new immunosuppressant MMF, which has been employed in cases of several other vasculitides (Nikibakhsh et al. 2010).

Removal of IgA1 and IgA1 complexes

The favourable role of plasmapheresis may be due to the removal of circulating complexes and inflammatory and procoagulatory substances (Kawasaki et al. 2004b, Davin 2011). Controlled studies on its efficacy are lacking, however. Plasmapheresis combined with immunosuppressive treatment has been used for rapidly progressive glomerulonephritis (RPGN) in a few retrospective studies (Schärer et al. 1999, Kawasaki et al. 2004b). In two studies plasma exchange was used as the only treatment in a total of 23 paediatric patients with severe HSN, and good response was reported, comparable to that achieved with immunosuppressive drug treatment. The authors emphasized that early treatment was important for achieving success. Three patients had progressed to ESRD after 4–10 years, however (Hattori et al. 1999, Shenoy et al. 2007).

Other therapies

Medications that prevent blood clotting, such as warfarin, dipyridamol and acetylsalicylic acid, have been used along with immunosuppressive agents by several authors, because of the suggested role of fibrin in the pathogenesis of crescents (Chartapisak et al. 2009). There are no reliable data on these forms of
treatment, however, and it is possible that they may cause bleeding complications (Davin 2011).

Since HSP is often triggered by an infection, the removal of any source of chronic bacterial infection is thought to be beneficial in the treatment of HSN (Davin 2011). Clinical remission of HSN after tonsillectomy has been mentioned in several case reports and in a patient series of 16 children (Inoue et al. 2007), although most of these patients also received immunosuppressive medication.

Rituximab, a therapeutic monoclonal antibody against the surface antigen CD20 expressed by B cells, has been introduced recently in case reports as a new therapeutic option for HSP skin, GI and renal manifestations (Donnithorne et al. 2009, Pillebout et al. 2011).

2.17 Long-term prognosis for HSN

Prognostic factors

Until the 1980s, HSN was considered to be mostly a disease with spontaneous recovery. Awareness increased after the publication of the first long-term follow-up studies, as reviewed by Davin (2011). When Meadow et al. (1972) reviewed the outcome for 62 patients, a poor prognosis was associated with the presence of nephritic and nephrotic features, a high proportion of crescents in the renal biopsy and an age at onset over 6 years. These findings have been later confirmed by others, as discussed below. The prognosis is unpredictable, however, as chronic kidney disease (CKD) can occur even after complete healing and normalization of the urinary sediment and even minimal urinary abnormalities can lead to CKD after decades (Goldstein et al. 1992, Coppo et al. 1997, Ronkainen et al. 2002).

Most of the reports describing the outcome for patients with HSN demonstrate a correlation between disease severity at onset and eventual outcome (Goldstein et al. 1992, Niaudet et al. 1993, Schärer et al. 1999, Ronkainen et al. 2002, Kawasaki et al. 2003b, Narchi 2005). In the systematic review of Narchi (2005) that included 1133 children with HSP, 1.6% of those who had isolated haematuria or non-nephrotic proteinuria on presentation developed long-term renal function impairment, compared with 19.5% of those with nephritic or nephrotic presentations.

It has been suggested in several studies that the prognosis for HSN is correlated with the degree of renal pathology, defined as the presence of crescents.
(Counahan et al. 1977, Yoshikawa et al. 1981, Niaudet et al. 1993, Schärer et al. 1999, Kawasaki et al. 2003b, Tarshish et al. 2004). When the results of three studies were combined (Counahan et al. 1977, Yoshikawa et al. 1981, Schärer et al. 1999), the incidence of severe complications, including active renal disease, CKD or ESRD, after a mean follow-up of 6 years was 0%, 15%, 15%, 35%, 70%, and 66% for ISKDC grades I, II, III, IV, V, and VI, respectively (Davin 2011).

The most recent studies nevertheless suggest that clinical findings and renal histology at presentation do not predict the renal outcome in children with HSN (Narchi 2005, Butani & Morgenstern 2007, Mir et al. 2007, Edström Halling et al. 2009, Soylemezoglu et al. 2009, Wakaki et al. 2011, Xia et al. 2011). This may be due to the effect of immunosuppressive treatment being received only by those with more severe clinical and histological features at presentation (Soylemezoglu et al. 2009, Davin 2011). There is therefore a need for a new histological classification for the histopathological evaluation of HSN (Working Group of the International IgANephropathy Network and the Renal Pathology Society 2009, Davin 2011). It has been suggested that the outcome could be predicted by histological findings other than crescents, such as the extension of deposits, macrophage infiltration, interstitial inflammation and tubulointerstitial changes (Foster et al. 2000, Soylemezoglu et al. 2009, Edström Halling et al. 2010).

In several studies no relation was found between age at presentation and outcome, even though the children presenting with more severe HSN at onset tended to be older than those whose symptoms were less serious (Allen et al. 1960, Counahan et al. 1977, Ronkainen et al. 2002, Ronkainen et al. 2003a, Coppo et al. 2006). Other suggested predictors of a poor outcome include decreased factor XIII activity at onset (Kawasaki et al. 2003b) and persisting proteinuria (Coppo et al. 2006, Shenoy et al. 2007, Edström Halling et al. 2010, Wakaki et al. 2011).

The risk of end-stage renal disease

Although the period from the diagnosis of HSP to the onset of ESRD may last several decades, ESRD can also develop early as a consequence of RPGN. As concluded in a recent review of the literature (Bogdanovic 2009), it could be estimated that 1–2% of all HSN patients from unselected series will ultimately develop CKD, as defined by persistent hypertension, proteinuria or decreased GFR (Koskimies et al. 1981, Stewart et al. 1988, Narchi 2005). This is in contrast to children with HSN followed up at tertiary centres, in whom the risk of
progression to CKD or ESRD is 5–18% at 5 years, 10–20% at 10 years and 20–32% at 20 years (Goldstein et al. 1992, Coppo et al. 1997, Schärer et al. 1999, Butani & Morgenstern 2007). The results obtained with a Finnish cohort were similar, as 35% of the patients with initial severe HSN had renal impairment a mean of 24 years after disease onset compared with 7% of those with mild or no nephritis (Ronkainen et al. 2002).

HSN has been reported in the past to account for 5–15% of all cases entering ESRD in childhood (Meadow 1978, Bunchman et al. 1988). On the other hand, recent data show that HSN accounts for only 1.5% of children requiring renal replacement therapy in the United Kingdom (Lewis et al. 2006), possibly suggesting that more aggressive treatment may have had a beneficial impact on the outcome (Davin 2011).

**HSP after renal transplantation**

Henoch-Schönlein purpura nephritis may recur in a transplanted kidney, ranging from an isolated mesangial IgA deposit observed in a kidney biopsy to full-blown glomerulonephritis with or without extrarenal manifestations (Saulsbury 1999). In a retrospective cohort of 339 patients who had received a renal transplant on account of HSN, the graft survival rate over 10 years was 59%. The cause of the graft loss was HSN recurrence in 14% of the cases (Samuel et al. 2011).

In a study based on 3 cohorts with 51 patients, the HSN recurrence rate in the transplanted kidney was 29% (Han et al. 2010), living related-donor transplants being associated with a higher risk of recurrence than unrelated-donor transplants. The graft survival rate of HSN transplants was not inferior to that of transplants performed on account of IgAN or other causes (Han et al. 2010).

**Pregnancy after childhood HSP**

Long-term follow-up studies show that women with a history of HSP during childhood have an increased risk of complications during pregnancy. The incidence of hypertension or proteinuria is reported to be 36–70% even in the absence of active renal disease (Goldstein et al. 1992, Ronkainen et al. 2002). This may be due to the hormonal changes that take place during pregnancy, which affect cell-mediated immunity (Cummins et al. 2003). It has also been suggested that hyperfiltration during pregnancy could overload the surviving nephrons, which might cause further renal impairment (Goldstein et al. 1992, Ronkainen et al. 2002).
3 Aims of the research

The aims of the research were as follows:

- To describe the clinical features and clinical course of Henoch-Schönlein purpura (HSP) in a prospective setting (I, II, IV),
- To determine the follow-up time needed to diagnose Henoch-Schönlein purpura nephritis (HSN) (II),
- To study and compare the efficacy of cyclosporine A and methylprednisolone pulses for the treatment of severe HSN (III),
- To study the long-term outcome of HSP in unselected patients (IV), and
- To evaluate the effect of prophylactic prednisone treatment given at disease onset on the long-term outcome of HSP (IV).
4 Subjects and methods

4.1 Subjects

The population consisted of two prospective patient groups recruited from 5 university hospitals and 10 central hospitals in Finland: 176 children who had attended the randomized placebo-controlled prednisone trial (Ronkainen et al. 2006b) and 24 children recruited between December 1999 and April 2006 for a trial comparing CyA and MP pulses for the treatment of severe HSN (III). Five of the patients were enrolled in both trials. Papers I and II were based on both of the prospective patient groups and on 29 additional patients who had been diagnosed as having HSP during the recruitment period for the prednisone trial but did not take part in it. A total of 138 patients from the prednisone trial were enrolled in the 8-year follow-up study (IV). The enrolment procedure and HSP treatment protocol are described in Table 5.

Table 5. Enrolment and treatment of the patients described in papers I–IV.

<table>
<thead>
<tr>
<th>Papers</th>
<th>Prednisone versus placebo trial (Ronkainen et al. 2006b)</th>
<th>Patients with severe HSN</th>
<th>Additional patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II (n=223)</td>
<td>176</td>
<td>65 prednisone</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 CyA + ACEI*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 MP + ACEI*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>86 placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 CyA + ACEI*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 MP + ACEI*</td>
<td></td>
</tr>
<tr>
<td>III (n=24)</td>
<td>5</td>
<td>2 CyA + ACEI</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 MP + ACEI</td>
<td></td>
</tr>
<tr>
<td>IV (n=138)</td>
<td>138</td>
<td>70 prednisone</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 CyA + ACEI*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 MP + ACEI*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 CyA + ACEI*</td>
<td></td>
</tr>
</tbody>
</table>

ACEI angiotensin-converting enzyme inhibitor; CyA cyclosporine A; HSN Henoch-Schönlein purpura nephritis; MP methylprednisolone.

* Received later due to severe HSN.
Clinical course of extrarenal and renal manifestations of HSP during the first 6 months after onset (I, II). The course of extrarenal and renal HSP symptoms in 223 paediatric patients (122 boys, 101 girls) was assessed for 6 months from the time of diagnosis. The mean age of the patients was 7.1±3.5 years (range 1.6–16.7 years), and they were recruited a mean of 7±10.5 days (range 0–65 days) after the onset of the initial symptoms. One patient in the CyA vs. MP series was excluded on the grounds of missing data on the disease onset.

CyA vs. MP pulses for the treatment of severe HSN (III). The inclusion criteria were an age of 2–16 years and a clinical diagnosis of HSP with nephrotic-range proteinuria or crescentic glomerulonephritis with ISKDC grades III–VI in a kidney biopsy. A total of 24 patients (15 boys, 9 girls) with a mean age of 9.4 years (range 4–16 years) were enrolled at all the tertiary care paediatric nephrology units in Finland. Seven of the patients were assigned to CyA medication and eight to MP treatment by random allocation. An additional four patients were treated with CyA and five with MP according to the same protocol without randomization. There were no statistically significant differences at onset between randomized and non-randomized patients or between the CyA and MP-treated patients, as shown in Table 6. The CyA treatment was started a mean of 5 months after the initial diagnosis of HSP (range 1–31 months) and MP within 4 months (range 1–9 months). A total of six patients (1 CyA, 5 MP) had received corticosteroids for up to 3 months prior to inclusion in the trial, either for severe extrarenal HSP symptoms or as part of the early prednisone trial (Ronkainen et al. 2006b). The mean follow-up time was 6 years (range 2.2–10.4 years).

Outcome of HSP 8 years after treatment with a placebo or prednisone at onset (IV). Of the 171 patients completing the previous prednisone trial, 160 (94%) filled in a health questionnaire and 138 (81%) entered a further screening consisting of a urine analysis and blood pressure measurement. The mean follow-up time was 7.7 years (range 4.6–11.4 years). The patients who entered the screening were younger than those who did not (mean age 13.9 vs. 16.1 years, p=0.005, 95% CI -3.7 to -0.7 years), but there were no other differences between the two groups. A total of 17 patients with abnormal screening results underwent a control visit with further laboratory tests.
Table 6. Demographic and clinical features of the 24 patients with severe Henoch-Schönlein purpura nephritis at onset, by treatment group and randomization (III).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CyA (n=11)</th>
<th>MP (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized</td>
<td>Non-randomized</td>
</tr>
<tr>
<td>Gender</td>
<td>2 girls, 5 boys</td>
<td>1 girl, 3 boys</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>9.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Range</td>
<td>5.1–12.3</td>
<td>7.0–14.4</td>
</tr>
<tr>
<td>Mean 24-h urine protein</td>
<td>143</td>
<td>73</td>
</tr>
<tr>
<td>(mg/m²/h)</td>
<td>38–510</td>
<td>14–229</td>
</tr>
<tr>
<td>Mean serum albumin (g/l)</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Range</td>
<td>20–43</td>
<td>16–40</td>
</tr>
<tr>
<td>Haematuria N (%)</td>
<td>7/7 (100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Mean time from HSP</td>
<td>3.0</td>
<td>9.2</td>
</tr>
<tr>
<td>diagnosis to enrolment</td>
<td>0.8–11.8</td>
<td>1.7–30.6</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISKDC gradus II</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ISKDC gradus III</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

CyA cyclosporine A; ISKDC International Study of Kidney Disease in Children; MP methylprednisolone.

4.2 Methods for the studies on the clinical course of HSP during the 6 first months after onset (I, II)

The patients attended five control visits during the 6-month follow-up: at inclusion and at 1–2 weeks and 1, 3 and 6 months after diagnosis. The visits included laboratory tests and a clinical examination, including blood pressure measurement. The patients from the prednisone trial, 176/223 (79%), also monitored haematuria and proteinuria at home with daily urine dipstick tests for a month.

The aetiology of HSP was explored in detail by eliciting an extensive medical history and performing a throat culture, AST and streptodornase and viral antibody tests. A full blood cell count, ESR, CRP, serum albumin, SCr, C3, C4, immunoglobulin A, E, G and M, fecal occult blood, and α1-antitrypsin were measured at the time of diagnosis. The urine analysis included dipsticks, microscopy and protein assays. The criteria for haematuria, proteinuria, nephrotic-range proteinuria and nephrotic-nephritic syndrome are described in Table 7.
Table 7. Criteria for renal manifestations of Henoch-Schönlein purpura nephritis

<table>
<thead>
<tr>
<th>Renal manifestation</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematuria</td>
<td>$\geq 5$ Red blood cells/hpf or positive dipstick tests*</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Urine protein $&gt;200$ mg/l, urine albumin $&gt;30$ mg/l or positive dipstick tests*</td>
</tr>
<tr>
<td>Nephrotic-range proteinuria</td>
<td>24-hour urine protein $&gt;40$ mg/m$^2$/h</td>
</tr>
<tr>
<td>Nephrotic-nephritic syndrome</td>
<td>$&gt;200$ red blood cells/hpf and 24-hour urine protein $&gt;40$ mg/m$^2$/h and at least two of the following findings: oliguria, hypertension, renal dysfunction</td>
</tr>
</tbody>
</table>

Hpf: high-power field.

* + to ++ in 3 consecutive days or +++ in 2 consecutive days.

A recurrence was defined as an instance of a patient who had been asymptomatic for 1 month presenting with a new flare-up of skin lesions with or without other symptoms related to HSP. The mean blood pressure at the first three control visits was taken to describe the blood pressure at the acute phase of HSP. Hypertension was defined as systolic or diastolic blood pressure greater than the 95th percentile for the patient’s age and sex (National High Blood Pressure Education Program Working Group 1996).

4.3 Methods for studying the use of cyclosporine A and methylprednisolone pulses for treating severe HSN (III)

The patients in the CyA group received Sandimmun Neoral® at an initial oral dose of 5 mg/kg/day, after which the dosage was titrated by monitoring the whole-blood CyA concentration once a week until the therapeutic level was reached, and thereafter at each control visit. The target pre-dose blood concentration of CyA (C0) was 150–200 μg/l for the first 3 months followed by 80–100 μg/l for the following 9 months. In the event of SCr elevation, the dose was reduced or temporarily discontinued. The mean duration of CyA treatment was 1.2 years (range 0.9–1.7 years), due to variation in tapering of the treatment after 1 year.

The MP treatment consisted of three intravenous doses of MP 30 mg/kg (max. 1 g) given on alternate weekdays over a period of 1 week. On the intermediate days and for 1 month after the MP pulses, the patients received prednisone 30 mg/m$^2$ in two daily doses orally, after which the medication was gradually tapered over 3 months. The mean duration of prednisone treatment was 5 months (range 3.3–8.5 months). An ACTH tolerance test was performed before the discontinuation of treatment. All patients except for one in the MP group were
treated with ACEI enalapril at a dose of 0.1–0.5 mg/kg to reduce glomerular proteinuria.

The patients were monitored by means of ten visits to the outpatient clinic arranged 2 weeks and 1 month after discharge and at 3-month intervals thereafter for 2 years altogether. Clinical status was assessed at each control visit, including measurement of blood pressure and the following laboratory tests: full blood count, serum albumin, SCr, Cyst-C and urine dipsticks, microscopy and protein assays. Since the GFR measured by Cr-EDTA was unreliable due to heavy proteinuria and a false distribution volume, GFR was estimated by the formula of Schwartz et al. (1987). In the case of a continuation of nephrotic-range proteinuria or reduced GFR, an alternative immunosuppressive treatment for HSN was considered with CyA in the MP group and MP in the CyA group.

A renal biopsy was performed at enrolment and a control biopsy 2 years later. All the renal biopsies were examined by the same pathologist and paediatrician, both of whom were blinded with respect to the patients’ treatment groups and number of biopsies. The glomerular changes were graded according to the ISKDC classification and the semiquantitative scoring system described in Tables 3 and 4. Nephrotic-range proteinuria was defined as 24-h protein > 40 mg/m²/h. If necessary, 24-hour urine protein was estimated from the urine protein/creatinine ratio (UP/C) (Antunes et al. 2008). Haematuria was defined as > 5 red blood cells per high-power field (hpf). Remission was defined as proteinuria below the nephrotic-range, and impaired renal function as an eGFR < 80 ml/min/1.73 m². The primary outcomes were the duration of proteinuria and haematuria, the maintenance of renal function and the renal biopsy histology. The secondary outcome was the need for further medication for HSN.

4.4 Methods for studying the HSP outcome 8 years after treatment with a placebo or prednisone at onset (IV)

The patients in the initial prednisone trial, who had been randomized to receive either a placebo or prednisone 1 mg/kg for 2 weeks followed by a weaning dose for another 2 weeks, were traced by means of their social security numbers and recruited with invitation letters and telephone calls for a follow-up screening consisting of a urine analysis, blood pressure measurement and a health questionnaire. The urine analysis, performed at the nearest hospital or health care centre, included urine microscopy, urine protein (U-Prot) and UP/C. Haematuria was defined as red blood cells over 18 x 10⁶/l in the urine. If necessary, the quantity of red blood cells in urine per hpf, as used
in some centres, was transformed to the same unit (European Confederation of Laboratory 2000). The definition of proteinuria was \( \text{UP/C} > 20 \text{ g/mol Crea} \) or \( \text{U-Prot} > 300 \text{ mg/l} \). Hypertension was defined as the mean of three repeated measurements being greater than the 95th percentile for the patient’s age and gender in patients aged < 18 years (National High Blood Pressure Education Program Working Group 1996) and as systolic pressure above 140 mmHg or diastolic pressure above 90 mmHg in patients aged ≥ 18 years.

Patients with abnormal urine results or hypertension were invited to the same centre for a control visit, including a physical examination, measurement of blood pressure and laboratory tests (Scr, urea, Cyst-C, urine microscopy, U-Prot and UP/C). The eGFR was determined using the updated formula of Schwartz et al. (2009). Decreased renal function was defined as an eGFR of < 90 ml/min/1.73m².

The health questionnaire contained questions about recurrences of HSP symptoms, the occurrence of urine abnormalities or hypertension and any treatment received for HSP after finishing the 6-month follow-up of the previous trial. A history regarding the occurrence of HSP or IgAN in the family was collected, and also details about any pregnancies in the women.

### 4.5 Statistical methods (I–IV)

For the purposes of statistical analysis continuous data were described in terms of the mean and standard deviation (mean±Sd) and categorial variables in percentages. The statistical analyses were carried out using the \( \chi^2 \) test (I, II, IV) or Fisher’s exact test (III, IV) for categorial variables and Student’s two-tailed t test (I, II, IV) or Mann-Whitney U test (III) for continuous variables, and their corresponding 95% confidence intervals (CI) were calculated. Forward stepwise logistic regression was used for multivariate analysis to evaluate the risk factors for the development of nephritis (II). The nephritis-free survival time in the prednisone and placebo groups was calculated by the Kaplan-Meier method (II). The differences of proportions between the CyA and MP-treated patients (III) and between the patients with and without nephritis at the acute phase of HSP (IV) were tested with the binomial SND test.

Statistical significance was defined as \( p<0.05 \). The SND tests were performed using StatsDirect (Windows version 2.7.8, StatsDirect Ltd., Altrincham, Cheshire, UK) and all the other statistical analyses using the Statistical Package for the Social Sciences (SPSS, Windows versions 16.0–19.0, SPSS Inc., Chicago, IL, USA).
4.6 Ethical issues

The trial reported in paper III and the extension to the previous prednisone trial, as reported in paper IV, were approved by the local ethics committees. Written informed consent was obtained from all the patients or their parents. The trial in paper III was registered with ClinicalTrials.gov under the code NCT00425724, and the protocol was approved by the National Agency for Medicines (Lääkelaitos, Helsinki, Finland).
5 Results

5.1 Clinical course of HSP within 6 months of onset (I, II)

Purpura and petechiae were the first finding at presentation in 73% of cases (157/216), but were preceded by joint symptoms in 15%, GI symptoms in 11% or both in 1%, by a mean interval of 4±3.7 days (range 1–19 days). Joint and GI symptoms were typically present at an early phase in the disease, but could appear for the first time up to 1 month after the time of diagnosis. Ninety percent of the patients presented with joint symptoms, 57% with abdominal pain and 8% with melena. The scrotum was affected by oedema in 14% of the boys. The abdominal pain of 17 (8%) patients required admission to hospital (I).

The fecal occult blood and α1-antitrypsin tests were positive in 22% (26/117) and 9% (7/77) of cases, respectively, suggesting mucosal injury. Of these patients, only 10/26 (38%) and 1/7 (14%) had abdominal pain at the time of the test. A low serum albumin level (range 25–36.9 g/l) without proteinuria was observed in 44/179 (25%) of the patients, indicating protein leakage into the bowel, and an additional 12 patients developed hypoalbuminaemia without proteinuria later during the follow-up. Severe protein-losing enteropathy was observed in seven patients, taking the form of abdominal pain, oedema and serum albumin ≤ 30 g/l (I).

Nephritis occurred in 102/223 (46%) of the patients, consisting of isolated haematuria in 14, isolated proteinuria in 9, both haematuria and proteinuria in 58, nephrotic-range proteinuria in 20 and nephrotic-nephritic syndrome in 1. Nephritis occurred on average 14 days after the disease onset (range 0–101 days) and in 87% within a month. The incidence rates of nephritis after 1 and 2 months were 14% and 2%, respectively. The patient with the latest onset of nephritis, at day 101, had a recurrence of HSP skin symptoms the same time. As seen in Figure 3, early prednisone treatment did not affect the frequency or timing of the appearance of HSN (II).
Fig. 3. Timing of the onset of HSN in patients treated with early prednisone (n=40) and in non-treated patients (n=62). Only the patients presenting with nephritis were included in the analyses (II).

Patients with severe HSN requiring immunosuppressant therapy also had extrarenal symptoms more frequently during the 6-month period. The patients treated with prednisone had symptoms slightly less frequently than those without treatment, but only during the first month, i.e. at the time of medication (Figure 4) (I). Mild hypertension was detected in 20/160 (13%) of the cases during the first month. Significant hypertension was diagnosed and treated only in the one patient with nephrotic-nephritic syndrome, however (II). HSP recurrences occurred in 25% of the patients during the 6 first months after diagnosis, with no difference between the prednisone-treated and non-treated patients (I).
5.2 Laboratory findings at HSP onset (I)

Signs of streptococcal infection were found in 71/199 (36%) of the patients; the throat culture was positive for GABS in 50/165 (30%), AST was elevated in 19/159 (12%) and streptodornase antibodies were elevated in 41/140 (30%). Elevated antibody titres of parainfluenza, adeno, cytomegalio, influenza A and B, mycoplasma, entero, respiratory syncytial and coxsackie viruses were found in 89/149 (60%) of the patients. HSP had been preceded by URTI in 72% of the patients, in 53% of whom it had occurred within 2 weeks prior to the HSP onset. Tonsillitis, gastroenteritis and other febrile infections prior to HSP onset were also observed.

At the time of diagnosis, 93/181 (51%) had elevated ESR (30±17.7, range 16–103 mm/h), 77/206 (37%) had elevated CRP (30±25.3, range 11–158 mg/l)
and 12/213 (6%) had leukocytosis (17±2.9, range 14–24 x 10^9/l), possibly indicating a previous infection. HSP occurred more commonly at the coldest time of the year, as 78% of cases were diagnosed between September and March. A decreased C3 level was found only in 2 patients.

5.3 Risk factors for developing HSN (II)

The occurrence of HSN increased significantly with age (p<0.001 for the linear trend), the patients with nephritis being significantly older than those without (8.2±3.8 vs. 6.2±3.0 years, p<0.001, 95% CI for the difference 1.1–2.9), but nephritis also occurred in young children, 24% being aged 1–4 years. The 42 patients affected by nephrotic-range proteinuria or persistent nephritis for over 1 month were older than those with nephritis lasting under 4 weeks and with non-nephrotic proteinuria (9.1±3.8 vs. 7.5±3.6 years, p=0.038, 95% CI for the difference 0.9–3.1).

Multivariate analysis showed that age over 8 years at onset (odds ratio [OR] 2.7, p=0.002, 95% CI 1.4–5.1), abdominal pain (OR 2.1, p=0.017, 95% CI 1.1–3.7) and HSP recurrences (OR 3.1, p=0.002, 95% CI 1.5–6.3) were independent risk factors for developing nephritis. Previous URTI (68% vs. 51%; p=0.058) and streptococcal infection (42% vs. 30%; p=0.077) tended to be more common in the patients with HSN. None of the other numerous laboratory tests performed at the onset of HSP predicted the development of HSN.

5.4 Cyclosporine A vs. methylprednisolone pulses for severe HSN (III)

All the CyA-treated patients achieved remission of nephrotic-range proteinuria within 3 months with the initial treatment, contrary to the situation in the MP group, where remission was achieved more slowly and not at all with the initial treatment in 6/13 (46%). Two of the patients treated initially with MP never achieved remission. The difference in treatment response was statistically significant at 1 and 3 months (p=0.040 and 0.016, respectively), as shown in Figure 5. The difference in the 3-month treatment response was also statistically significant when analysed in the randomized patients only. The disappearance of haematuria showed no difference between the treatment groups, as shown in Figure 6.
The clinical characteristics at 2 years and at the latest examination after a mean of 6.1 years (range 2.2–10.4 years) showed that all the parameters tended to be better in the CyA group (Table 8). At the latest point, 16 patients (8 CyA, 8 MP) had no renal symptoms and six (3 CyA, 3 MP) had persistent nephropathy but normal renal function. One of the MP-treated patients had received a kidney transplant 6 years after the onset of HSN and one had reduced renal function (SCr 143 µmol/l). In 6/13 MP patients (46%) additional immunosuppressive treatment had to be started after a mean of 1.6 years (range 0.2–2.7 years), while none of the CyA-treated patients needed any additional treatment. The difference was statistically significant whether analysed in all the patients (difference in proportion 46%, p=0.008) or in the randomized patients only (difference in proportion 50%, p=0.0385). Five out of the six patients not responding to MP did respond to CyA.
Table 8. Outcome of Henoch-Schönlein purpura nephritis in patients treated with CyA and MP, as assessed 2 years after enrolment and at the latest follow-up at a mean of 6.1 years (range 2.2–10.4 years) (III).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CyA (n=11)</th>
<th>MP (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-year</td>
<td>Latest</td>
<td>2-year</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>control</td>
<td>control</td>
</tr>
<tr>
<td>24-h urine protein (mg/h/m²)</td>
<td>Mean (Sd)</td>
<td>Mean (Sd)</td>
<td>Mean (Sd)</td>
</tr>
<tr>
<td>Haematuria N (%)</td>
<td>4/11 (36%)</td>
<td>0/10 (0%)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>SCR (μmol/l) Mean (Sd)</td>
<td>47 (113)</td>
<td>56 (164)</td>
<td>55 (216)</td>
</tr>
<tr>
<td>Cyst-C* (mg/l) Mean (Sd)</td>
<td>0.77 (0.23)</td>
<td>0.77 (0.11)</td>
<td>0.81 (0.14)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²) Mean (Sd)</td>
<td>170 (18)</td>
<td>166 (33)</td>
<td>147 (33)</td>
</tr>
</tbody>
</table>

CyA cyclosporine A; Cyst-C cystatin C; eGFR estimated glomerular filtration rate; MP methylprednisolone; SCR serum creatinine; SD standard deviation.

* Cyst-C assay missing for three (2 CyA, 1 MP) and for eight patients (1 CyA, 7 MP) at the 2- and 6-year control visits, respectively.

Renal biopsies were performed on all the patients at onset and on 6/11 of the CyA-treated and 12/13 of the MP-treated patients after a mean of 2.0 years. In one MP case the control biopsy was performed after only 9 months due to a poor response to treatment. The ISKDC grade of the control biopsy had improved in four CyA-treated patients and remained the same in two, while eight MP-treated patients had an improved grade, three remained the same, and one had deteriorated. The biopsy outcome measured by the semiquantitative grading system introduced in Table 4 showed no statistically significant differences between the treatment groups (Figure 7). The mean tubulointerstitial index in the CyA group was not significantly higher than in the MP group, suggesting that the CyA treatment was not markedly nephrotoxic. Of the five CyA patients without a control biopsy, three had no proteinuria and two had proteinuria of 10.7 and 15.8 mg/m²/h, respectively, with normal renal function at the 2-year control. The only MP-treated patient without a control biopsy had nephrotic-range proteinuria at the 2-year control. IgA deposits in one MP-treated patient had disappeared in the control biopsy.
Fig 7. Activity, chronicity, tubulointerstitial, and total indices of renal biopsies at enrolment and 2 years later in patients treated with CyA or MP (III).

Side-effects of cytotoxic treatment were reported in 82% of cases in the CyA group and 92% in the MP group. MP was replaced by CyA after 2 months in one patient due to depression, oedema, hypertension and persistent proteinuria. In one MP-treated patient, the remission was initially achieved using CyA, but the medication was changed to MMF later because of hypertension and a decrease in GFR. The other patients’ side-effects were mild and reversible. ACEI treatment was tolerated well without any reported side-effects. The most common side-effects of CyA were hirsutism (82%), gingival hypertrophy (45%) and transient elevation in SCr (45%). Mild signs of tubulus atrophy were found in all the CyA-treated patients who underwent a control biopsy as compared with 5/12 of the MP-treated patients, one of whom had received CyA prior to the control biopsy. The other reported side-effects included anaemia in two patients and headache in one. The most frequent side-effects of the MP and prednisone treatments were weight gain (91%), Cushing’s syndrome (58%), mood fluctuations (50%) and striae (33%). Hirsutism and gastric irritation occurred in two patients (15%). Three patients showed hypocortisolism in the ACTH test.

5.5 Long-term outcome of HSP 8 years after treatment with a placebo or prednisone at onset (IV)

Of the 138 patients attending the follow-up screening, haematuria was recorded in seven, proteinuria in three and both in two. Protein and erythrocytes in the spot
urine analysis were higher in the patients who had had nephritis at the acute phase of the disease (mean U-Prot 144 mg/l vs. 92 mg/l, p=0.042, 95% CI 2–103 mg/l and mean U-Erythrocytes 8 vs. 5 x 10⁹/l, p=0.025, 95% CI 0.4–5.6, respectively). There were no differences between the patients who had received prednisone or a placebo. Elevated blood pressure was recorded in 7 patients, one of whom also had haematuria. Nineteen of the 138 patients (14%) with hypertension or urine abnormalities in the screening had had nephritis more frequently during the 6 months following disease onset than those with normal screening results (OR 3.6, p=0.022, 95% CI 1.3–10.0). There were no differences between the patients who had received early prednisone and those with placebo treatment.

Seventeen of the 19 patients with abnormalities in the screening came for the control visit. Haematuria was observed in 2 cases, proteinuria in 1, both haematuria and proteinuria in 1 and elevated blood pressure in 4. The mean eGFR was 100 ml/min/1.73m² (range 76–121 ml/min/1.73m²) and it was decreased in two patients, with 76 and 86 ml/min/1.73m² respectively. Both of them had received early prednisone treatment. The first patient had been treated with CyA due to severe HSN and he presented with haematuria in the screening. The second patient had normal urine and blood pressure results but had frequent HSP skin relapses for 10 years. One patient with proteinuria was referred for a kidney biopsy 11 years after HSP onset on the basis of the screening results. The biopsy showed no IgA deposits or any other pathological abnormalities. One patient with previous severe HSP had severe hypertension, with a mean blood pressure of 160/111 mmHg in 24-h ambulatory measurement, but with no urine abnormalities.

Recurrences of HSP skin symptoms after the initial 6-month follow-up were reported in the health questionnaire by 15 patients. The first recurrence had appeared 1–8 years after the onset of HSP in 5 cases. These included a patient with a mild initial disease without nephritis or any recurrences. She had normal results in the screening but one year later, 8 years after the initial onset, she developed a HSP recurrence with skin, joint and renal manifestations during an URTI. On account of nephrotic-range proteinuria and haematuria she underwent a kidney biopsy showing ISKDC gradus II, and her nephritis subsided spontaneously. In 2 male patients the purpura and petechiae had been appearing frequently for 8 to 10 years after the initial disease onset. Both of them had normal urine tests in the screening, but one had hypertension. The skin symptoms had been provoked by physical and emotional stress in one case and by URTI in the other. The aunt of one of these patients had been diagnosed earlier as having IgAN. There were 2 other self-reported familial cases of IgAN, and altogether 10
cases of HSP in 5 families, including two first-degree relatives. Of the 12 women aged ≥ 18 years, two had had altogether 5 full-term pregnancies, which had all been complicated by proteinuria. Both of them had had mild HSN during the acute phase of HSP, but their 8-year screening results were normal.
6 Discussion

6.1 Study design and patient series (I–IV)

Clinical course of extrarenal and renal manifestations of HSP (I, II). These studies present the largest published prospective series of patients with HSP (Table 1). The 111 patients who received no treatment describe the natural course of HSP, representing a control group for comparison of the efficacy of early prednisone treatment with respect to the clinical course of HSP. The 23 patients with severe HSN represent a more severe form within the wide spectrum of HSP. The series can be considered unselected, as only 18/223 (8%) of the patients were recruited at tertiary centres after the establishment of severe HSN.

CyA vs. MP pulses for treating severe HSN (III). The patients were recruited during a period of 7.25 years from all the tertiary paediatric nephrology units in Finland and include all the patients affected by severe HSN during this time. It can be therefore concluded that the annual incidence of nephrotic-range HSN in Finland was 2.6 per million children under 15 years of age during this time, since one of the patients was 16 years old and another 4 presented with proteinuria below the nephrotic-range at onset. The incidence is similar to the figure of 2 per million reported previous for Finnish children (Ronkainen et al. 2003a). A third of the patients, 4 in the CyA group and 5 in the MP group, were treated according to the same protocol but without randomization. This was because they refused either the CyA or the MP treatment, probably partly on account of previous participation in the prednisone trial in 2 cases. The demographic and clinical characteristics of the patients on enrolment were nevertheless similar in the randomized and non-randomized groups, as shown in Table 6, and therefore the results were combined and analysed together. The statistically significant differences that were found between the CyA and MP groups concerning the remission of proteinuria at 3 months and the need for additional immunosuppressive treatment also remained when the analyses were performed separately for the randomized patients only.

Outcome of HSP 8 years after treatment with a placebo or prednisone at onset (IV). The high participation rates of 94% for the health questionnaire and 81% for the screening consisting of a urine analysis and blood pressure measurement is attributable to the fact that it is possible in Finland to trace the phone number and address of any citizen via the National Population Registration
Centre if his or her social security code is known. The patients were contacted with repeated invitation letters and phone calls. Those not electing to participate were significantly older than those participating, which might be explained by the fact that their parents remembered the initial HSP disease better and attached more importance to health check-ups than did the adolescents themselves. There were no differences between the participating and non-participating patients with respect to signs and symptoms of the initial HSP disease itself. The results of a random urine analysis and blood pressure measurement might not have been reliable, since 9/17 (53%) of those with abnormal screening results had normal results at the control visit.

6.2 Clinical course of extrarenal HSP symptoms during the first 6 months after onset (I)

As shown in Tables 1 and 2, the mean age of 7.1 years, and the slight predominance of boys, 55%, in the present series are consistent with previous reports. The ranges of variation between individual studies are quite large, however. The prevalences of joint symptoms (91% vs. 68%) and recurrences (36% vs. 17%) were higher in the prospective studies, possibly due to recall bias and limitation in the documentation of HSP symptoms in the medical records in the retrospective studies. In some cases the patient series may have been selected, or may even have included patients who had been misdiagnosed, as not all the HSP patients were reported to have petechiae (Potts et al. 1987, Nong et al. 2007, Fretzayas et al. 2008), or else no symptoms other than petechiae were observed at presentation (Muslu et al. 2002, Peru et al. 2008). The 1990 ACR criteria for vasculitides (Mills et al. 1990), which have been the most widely applied classification criteria for HSP in children until recently, have been criticized for controversialities that might result in an overdiagnosis of HSP (Ozen 2005). The new EULAR and PRES criteria, with a sensitivity of 100% and a specificity of 87% for the diagnosis of HSP (Ozen et al. 2010) should therefore be preferred in the future.

The positive fecal occult blood and α1-antitrypsin results for the patients without GI symptoms suggest mucosal injury even in the absence of abdominal pain. Protein-losing enteropathy occurred in seven (3%) patients in the present series and another 49 patients (22%) had a subnormal serum albumin level without renal loss. It is therefore warranted to assay serum albumin even in patients without any proteinuria, and even those without GI symptoms. Protein-
losing enteropathy has previously been considered a very rare feature of HSP, with virtually only 8 reported cases (Nakamura et al. 2010). It can be assumed that this is partly due to the fact that serum albumin has not been routinely measured and that the oedema caused by hypoalbuminaemia has been interpreted as due to the leukocytoclastic vasculitis itself. The role of vasculitis and inflammation in the pathogenesis of hypoalbuminemia cannot be ruled out, however, especially in patients with no confirmation of mucosal injury by means of further tests.

6.3 Recurrences of HSP (I, IV)

The extrarenal symptoms of HSP are reported to be self-limiting within 6–8 weeks (Saulsbury 1999), while recurrences beyond 4 months are rare (Saulsbury 1999, Prais et al. 2007). It is of note that 17% of the present non-treated patients, 16% of the prednisone-treated patients and 74% of the patients with severe HSN still had extrarenal or renal symptoms related to HSP at the 6-month control (I). The frequency rates of 25% for recurrences during the first 6 months and 27% during a mean of 8 years after HSP onset were similar to those reported in the literature (Tables 1 and 2) (I, IV). The highest incidence of recurrences, 66%, was reported in a small prospective study and can probably be explained by the definition of recurrence, with a shorter asymptomatic period of only 2 weeks and a broader scale of signs and symptoms (Fretzayas et al. 2008).

The mean number of recurrences has been reported in the literature to be 2.3 (range 1–40) at a mean of 2.8±4.2 months after the initial HSP onset, and the latest recurrences to occur up to 4 years (Fretzayas et al. 2008). The present findings show that frequent HSP recurrences are possible even up to a decade from the initial disease onset and that these are often triggered by URTI. The reported case of severe late-onset nephritis during a recurrence of HSP skin manifestations warrants follow-up urine analyses during and after HSP recurrences (IV).

6.4 Renal manifestations of HSP within 6 months of onset (I, II)

The reported incidence of HSN varies greatly depending both on the definition of renal disease and on the method of detection, and also according to the nature of the patient series (from primary care vs. a tertiary referral centre). The occurrence of urinary findings in the present series (II) is same as in the large systematic
review of over thousand patients by Narchi (2005). In both of them nephritis consisted of haematuria and/or proteinuria in 79% of cases and acute nephritic and/or nephrotic syndrome in 21%.

The present results are in accordance with previous observations that 75–100% of patients developing HSN do so within the first 4 weeks after the onset of HSP, and virtually all within 3 months (Saulsbury 1999, Fretzayas et al. 2008). On the other hand, 27% of the HSN cases were discovered over 6 months after the diagnosis of HSP in a retrospective Thai study (Pabunruang et al. 2002). The frequency of urine testing was not described, and it can be suggested that the delay in diagnosing HSN may have originated from differences in the local healthcare system and the study setup, and from the infrequent testing of urine. The occurrence of nephritis was infrequent after 1 month. Ten patients had to be screened in order to diagnose a new case of nephritis 1 month after the onset of HSP, and as many as 50 patients 2 months after (II). According to the systematic review by Narchi (2005), the cumulative proportion of patients with HSP developing HSN by 1.5 months was 91% and by 6 months 97%, respectively. These data may be interpreted as suggesting that all patients with HSP should be tested at least for 6 months. On the basis of the present prospectively and systematically collected data on frequent urine testing it can be suggested that weekly urine dipstick tests are necessary only for 2 months from the onset of HSP. Beyond that point frequent routine follow-up are neither cost-effective nor necessary in patients with no urine abnormalities at that stage. The length of the follow-up time should be increased beyond 6 months on an individual basis in the case of HSP recurrence, however, and in those developing nephritis, since 18% of the patients still had some renal findings after 6 months (I).

Frequent urine analysis and follow-up is important, as even patients with mild and transient HSN at onset may run a risk of severe long-term complications (Goldstein et al. 1992, Ronkainen et al. 2002). In accordance with this, the renal histology was reported to be normal in only two out of 10 patients 2–9 years after apparently completely healed mild HSN (Algoet & Proesmans 2003).

6.5 Risk factors for HSN (II)

Renal involvement in HSP has been reported to be more frequent and more severe in children older than 4–10 years (Kaku et al. 1998, Sano et al. 2002, Shin et al. 2006a), and in agreement with this, the present results show a linear trend between the age at onset and the occurrence of nephritis (p<0.0001), so that age
over 8 years carries a 2.7-fold risk. HSN may develop at any age, however, as witnessed by the fact that 24% of the present patients with nephritis were aged 1–4 years. Severe GI symptoms and recurrences of purpura have also been described as independent risk factors for the occurrence of HSN (Sano et al. 2002, Rigante et al. 2005, Shin et al. 2006a, de Almeida et al. 2007). Accordingly, the present multivariate analysis showed that the occurrence of nephritis was 2.1-fold in patients with abdominal pain and 3.1-fold in patients with HSP recurrences. GI symptoms and recurrences could be indicators of extensive, active HSP vasculitis, while there are virtually no theories to explain why older age is associated with an elevated risk of nephritis.

Data on other risk factors implicated in HSN are contradictory. Arthritis has been reported both to protect the patient from nephritis (Shin et al. 2006a) and to increase the risk (Mir et al. 2007). The present study showed no association between the occurrence of arthritis and nephritis. URTI (Gonzalez-Gay et al. 2004) and streptococcal infection (Al-Sheyyab et al. 1999) have been thought to precede HSN, and this was the trend in the present study, although it did not reach statistical significance.

Early laboratory markers associated with HSN have been widely studied, since these would allow targeting more frequent urine testing and possible prophylactic treatment at those with an increased risk of HSN, but no such markers have been found. Elevated serum levels of IgA (Fretzayas et al. 2008) and IgM (Similä et al. 1977) were more frequent in patients with HSN in individual studies, but the results have not been confirmed by others. In the present work no correlation could be demonstrated between any of the laboratory tests taken at the onset of the disease and the development of HSN.

6.6 Triggers of HSP (I)

The majority of the present patients had a potential trigger event before the onset of HSP, including a previous infection. On the other hand, this may only depict a normal course of life. The incidence of URTI before HSP onset has been reported to be 36–64% (Fischer et al. 1990, Balmelli et al. 1996, Calvino et al. 2001, Gonzalez-Gay et al. 2004, Fretzayas et al. 2008), and the figure was even higher in the present study, 73%. Patients with previous URTI have been reported to have a decreased risk of GI problems (Nong et al. 2007) or an increased risk of nephritis (Gonzalez-Gay et al. 2004), but the present results showed no clear association between a history of URTI and the clinical features of HSP.
The present data support previous notions of an infectious trigger in the pathogenesis of HSP, although no single pathogen appears to be the dominant precipitating cause of HSP (Saulsbury 1999). Among the present patients, 122/201 (61%) had positive serological tests or microbiological cultures at the time of diagnosis, and the most common pathogen, GABS, was observed in 71/122 (58%) of these. Streptococcal infection did not induce changes in the level of complement component C3, which is in contrast to the situation in post-streptococcal glomerulonephritis, in which it has been suggested that the decreased level of C3 may be caused by activation of the complement alternative pathway (Payne et al. 2008). Elevation in various viral antibodies was observed, but the lack of systematically taken control serum samples complicates the interpretation, and these elevated levels may merely indicate old-standing immunity. The elevated ESR and CRP levels may mean that a recent infection was implicated, or else the reason for these laboratory abnormalities might lie in the vasculitis and inflammation inherent in HSP.

6.7 The role of corticosteroids in the clinical course of HSP (I, II, IV)

Corticosteroids were postulated to benefit children with HSP in the 1950s since they were effective in the treatment of most other vasculitides in children and adults (Allen et al. 1960). The recent Cochrane review has nevertheless concluded that corticosteroids are efficient for treating the extrarenal symptoms of HSP but do not reduce the risk of the development or persistence of kidney disease (Chartapisak et al. 2009). Accordingly, the HSP-related symptoms recorded here were slightly less frequent only during the 1-month prednisone treatment as compared with the situation in non-treated patients. Corticosteroid treatment did not alter the clinical course of extrarenal or renal manifestations during the first 6 months after onset and should not be used routinely but individually, in cases of severe symptoms. The present study also clearly demonstrated that early prednisone treatment did not prevent or mask the development of HSN.

It has been suggested in a retrospective study that corticosteroid treatment may increase the frequency of HSP recurrences, 13% of the patients concerned having received corticosteroids for severe abdominal pain or nephropathy (Trapani et al. 2005). The association between corticosteroid therapy and HSP recurrences has not been confirmed anywhere else, however, not even in the present study with its randomized prospective setting (I). It can therefore be
suggested that a severe disease at onset constitutes a major risk factor for recurrences rather than the treatment as such.

The Cochrane review on the effectiveness of early corticosteroids for treating HSP was based on 5 RCTs with a follow-up period of 6–12 months (Chartapisak et al. 2009). The present study now represents the longest follow-up after a RCT, and shows that early prednisone treatment does not improve the long-term outcome of HSP and should therefore not be routinely used (IV).

6.8 Cyclosporine A vs. methylprednisolone pulses for severe HSN (III)

Data on the treatment of severe HSN are controversial and scarce, with a lack of controlled trials (Chartapisak et al. 2009). Morbidity among these patients is high, and randomized studies are needed for optimizing their treatment. The only RCT on the treatment of severe HSN beside the present study randomized 56 children during the period 1973–1980 to receive supportive therapy with or without cyclophosphamide for 42 days. Cyclophosphamide was no more effective in preventing persistent kidney disease than the supportive treatment when assessed 7 years later (Tarshish et al. 2004). The optimal management of IgAN has remained equally uncertain (Samuels et al. 2003).

Corticosteroids have been most widely used for treating severe HSN, often in combination with other treatments (Bogdanovic 2009). Due to the many side-effects of corticosteroids, steroid-sparing treatments would present benefits for the often long-lasting treatment of severe HSN. The few previous case reports have yielded promising results in the case of CyA treatment, but the optimal dose, target C0 level and duration of CyA treatment for HSN are not known. In the case reports the treatment time has varied between 2 and 55 months and the C0 level between 50 and 200 μg/l (Huang et al. 2003, Ronkainen et al. 2003b, Someya et al. 2004, Shin et al. 2005a, Shin et al. 2005c, Shin et al. 2006b, Park et al. 2011). Since the metabolism of CyA is very variable and individual in children, monitoring of the CyA concentration at 2 h post dose (C2) has been introduced, and this has been shown to be a significantly more accurate predictor of drug exposure than C0 (Levy 2001). C2 monitoring was not included in the present study, however, since it was not in clinical use in Finland at the time of planning the protocol. The data obtained in a 2-year trial showed that the rate for sustained remission was higher and the hazard ratio for relapses lower when CyA was employed for treating frequently relapsing nephrotic syndrome using a C0 of 60–
100 μg/l compared with treatment at a fixed CyA dose of 2.5 mg/kg/day (Ishikura et al. 2008). The study further concluded that CyA given according to targeted C0 levels is an effective and safe treatment for children with nephrotic syndrome, which is confirmed by the present results.

Although in most studies patients with HSN have been treated with various combinations of corticosteroids and CyA (Huang et al. 2003, Someya et al. 2004, Shin et al. 2005a, Shin et al. 2005c), the present results suggest that CyA alone is effective in treating HSN. It has also been reported to be effective as a rescue therapy for HSN when other treatments have failed (Huang et al. 2003, Ronkainen et al. 2003b, Someya et al. 2004, Park et al. 2011). In accordance, five of the six patients who had not responded to initial MP treatment responded to CyA. In the only non-responding case CyA was started 1.5 years after the initiation of MP and at that point the kidney histology had deteriorated to ISKDC grade IV. None of the patients became dependent on CyA, contrary to previous reports of CyA dependence in 21–43% of the patients treated (Ronkainen et al. 2003b, Park et al. 2011). The treatment for these CyA-dependent patients was started significantly later, however (Ronkainen et al. 2003b).

One known adverse effect of CyA is nephrotoxicity, which is characterized by arteriolopathy and striped interstitial fibrosis with tubular atrophy. It has been reported that arteriolopathy resolves itself after the withdrawal of CyA, whereas tubulointerstitial and focal glomerular lesions do not (Hamahira et al. 2001). In order to avoid nephrotoxicity, the dose of CyA should be individually titrated according to C0 and C2, as discussed above. CyA-induced nephrotoxicity is rare in HSN patients, however, and was seen previously in only one out of 24 patients who had had a control biopsy (Shin et al. 2005c, Shin et al. 2006b, Park et al. 2011).

Corticosteroids have been used in HSN alone or in combination with other drugs. The benefit of MP and prednisolone for the treatment of IgAN in adults and children was first reported in a Finnish study (Mustonen et al. 1983). Corticosteroid treatment with MP followed by prednisone was employed by Niaudet & Habib (1998) in a prospective uncontrolled study of HSN in 38 paediatric patients, 27 of whom recovered fully during the mean follow-up of 5.6 years (range 1–16 years). Three still had minimal urinary abnormalities, four had persistent nephropathy and four suffered renal failure. Twelve of these patients were treated with additional immunosuppressive therapy. The present results regarding the efficacy of MP treatment are in accordance with these observations.
The ISKDC classification for the histological findings in HSN, introduced over 30 years ago (Counahan et al. 1977), is based merely on the frequency of crescents and does not seem to correlate with the prognosis for HSN, possibly due to the more aggressive treatment of severe cases. It has therefore been suggested (Davin 2011) that it should be replaced by a more detailed histological classification similar to that recently published for IgAN (Working Group of the International IgA Nephropathy Network and the Renal Pathology Society 2009).

In the present study the kidney biopsies were evaluated using both the ISKDC classification and a semiquantitative scoring system (Table 4) including most of the features suggested for the new histopathological classification (Davin 2011). Neither method revealed any significant differences in the biopsy outcome. The results are hampered by the poor coverage of the control biopsies obtained from the CyA-treated patients with a good outcome, however, i.e. 45%. This was due to parental non-consent because of clinical remission. Elsewhere, the parents of 2/8 patients with a good response to CyA treatment were also reluctant to allow a follow-up biopsy to be performed (Shin et al. 2005c). The disappearance of IgA deposits in the control biopsy, as seen in one of the present patients, has also been described by other authors (Niaudet & Habib 1998, Algoet & Proesmans 2003, Shin et al. 2005a, Shin et al. 2005b). It should be remembered, though, that apart from recovery, disappearance of the deposits may also reflect complete fibrosis of the glomeruli (Niaudet et al. 1984).

All the CyA-treated patients had normal renal function at the latest examination, while one MP-treated patient had decreased eGFR and another had progressed to ESRD. Since Cr-EDTA measurement proved to be an unreliable method for GFR evaluation on account of serious proteinuria and a false distribution volume, GFR was estimated by the Schwartz formula. This may have given artificially high values in some patients due to nephrotic-range proteinuria and hyperfiltration. The updated Schwartz formula (Schwartz et al. 2009) which seems to give a more reliable estimate of GFR (Kivelä et al. 2011), could not be used because of the missing Cyst-C values. The good outcomes reported here may partially be attributed to the fact that treatment was started at an early phase in the disease, i.e., by a mean of 4.5 months. In addition, a total of six patients (one CyA, five MP) had been receiving corticosteroids for up to 3 months prior to inclusion in the study, either due to severe extrarenal HSP symptoms or as a part of the randomized prednisone trial (Ronkainen et al. 2006b). The results support previous reports (Niaudet & Habib 1998, Ronkainen et al. 2003b, Tanaka et al.)
2003) showing that immunosuppressive treatment for HSN should be started early, before irreversible fibrosis of the glomeruli or any decline in renal function occurs.

The present results indicate that CyA is not inferior to MP for the treatment of severe HSN, since remission was achieved faster and all the patients responded to the treatment with no need for additional immunosuppressive therapy. The renal survival rate in the CyA group was 100%, compared with 85% in the MP group. All these parameters argue in favour of CyA rather than MP, even though there were no differences in the biopsy outcome after 2 years. The immunosuppressive action of CyA stems from its inhibition of the activity and immune response of T lymphocytes. Glucocorticoids are also efficient in reducing the development and functioning of T cells. It has recently been suggested that the beneficial effect of CyA on proteinuria is not dependent on hampered T cell function, but rather results from stabilization of the actin cytoskeleton in the kidney podocytes (Faul et al. 2008), which might explain the beneficial effect of the CyA treatment on severe HSN compared with corticosteroids.

Since high-dose corticosteroids have been most widely used for treating severe HSN (Bogdanovic 2009), a multicentre and probably multinational RCT with strictly defined clinical and histological criteria and standardized treatment protocol should be arranged to compare these treatments in an adequately powered setting. The study should also have sufficiently long follow-up, as progression to ESRD may take decades. Severe HSN is rare, however, and as shown in the present study, it may be difficult to obtain enough patients for randomization.

6.9 Long-term outcome of HSP 8 years after a placebo or prednisone at onset (IV)

This study represents the largest and longest prospective survey of HSP outcomes in unselected patients. In fact, there are only a few other long-term follow-up studies available that involve unselected patients. These were based on data for 43–74 paediatric patients followed up for 6–8.3 years (Koskimies et al. 1981, Stewart et al. 1988, Calvino et al. 2001, Garcia-Porrua et al. 2002, Fretzayas et al. 2008), although some only included patients with renal manifestations at the acute phase of the disease (Koskimies et al. 1981, Stewart et al. 1988). The long-term follow-up studies of HSP on selected patient series have contained a high proportion of severe HSN cases, and have therefore resulted in poorer outcomes (Counahan et al. 1977, Goldstein et al. 1992, Schärer et al. 1999, Ronkainen et al.)
The present study shows that the prognosis for unselected patients with HSP is good. The mean values for protein and erythrocytes in the urine were statistically significantly higher in the patients who had had nephritis during the initial 6-month follow-up than in those who did not have nephritis, but the mean values in both groups were within the normal range. Of the patients 3% had persistent proteinuria and/or haematuria and 1% had slightly decreased eGFR. Relapses of HSN and progression to ESRD may develop even decades later, however (Goldstein et al. 1992, Ronkainen et al. 2002). As seen in one of the present patients, the first episode of nephritis may develop almost a decade after the mild initial disease without nephritis. The results are similar to those of the prospective study on Greek children, with a frequency of 3% for persistent occult haematuria after 7.3 years (Fretzayas et al. 2008). Higher frequencies of 11–12% for persistent urinary abnormalities with normal renal function have been reported elsewhere (Calvino et al. 2001, Garcia-Porrua et al. 2002). The outcome in studies on unselected patients with HSN has been poorer, as the incidence of ESRD or death was 2–3% and that of CKD 5–7% (Koskimies et al. 1981, Stewart et al. 1988). In the present study the frequency of urinary abnormalities based on a single spot urine test was higher, i.e. 9%. The other reports do not mention whether the outcome results were based on a single urine test or not. The existence of HSN at the acute phase of HSP was associated with a 3.6-fold risk of haematuria, proteinuria, or hypertension 8 years later, which is a consistent finding with that the patients with HSN have a worse prognosis than those without (Goldstein et al. 1992, Ronkainen et al. 2002).

Five per cent of the present patients had hypertension in the screening, and this was confirmed at the control visit for 4/7 of them. It is unclear whether hypertension without urinary abnormalities is connected in any way with a previous HSP disease. According to the definition used here, 5% of all children have high blood pressure values (above the 95th percentile; National High Blood Pressure Education Program Working Group 1996). The only one of the previous studies that gives data on this matter reported that all the patients had normal blood pressure after a mean follow-up of 8 years (Stewart et al. 1988).

The present results support reports of an increased risk of pregnancy complications in HSP patients, since proteinuria occurred in all five pregnancies experienced during the 8-year follow-up. Two long-term follow-up studies have reported frequencies of 36% and 70%, for full-term pregnancies being
complicated by hypertension, proteinuria or pre-eclampsia, even in the absence of active renal disease (Goldstein et al. 1992, Ronkainen et al. 2002).

The present 8-year follow-up study represents the longest follow-up after a RCT, and shows that early prednisone treatment does not improve the long-term outcome of HSP and should therefore not be routinely used. This is in accordance with the fact that early prednisone treatment did not prevent the development of nephritis in the acute phase of HSP, which in turn determines the long-term outcome of HSP in the light of the present results.
7 Conclusions

The conclusions to be drawn from this work are:

- Patients with severe nephritis more frequently have extrarenal symptoms during the first 6 months after disease onset (I). Protein loss via the intestine is more common in Henoch-Schönlein purpura (HSP) than has previously been described, warranting the monitoring of serum albumin level even in patients without proteinuria (I).

- Henoch-Schönlein purpura nephritis (HSN) develops early. The present results suggest that weekly urine dipstick tests are indicated for 2 months after the onset of HSP and individually for over 6 months in cases of HSN or HSP recurrence (II). Oral prednisone therapy does not affect the frequency or timing of HSN (II).

- Cyclosporine A is not inferior to methylprednisolone pulses for the treatment of severe HSN, representing an efficient, safe steroid-sparing treatment for this disease (III).

- Henoch-Schönlein purpura carries a good prognosis, but skin relapses may occur for as long as a decade and may be accompanied by late-onset nephritis (IV). The occurrence of hypertension and renal abnormalities after 8 years was associated with the initial occurrence of HSN, warranting a long-term follow-up of these patients (IV).

- Early prednisone treatment does not affect the long-term outcome of HSP and should not be routinely used (IV).
References


List of original publications

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:


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Original publications are not included in the electronic version of the thesis.
1135. Liukkonen, Timo (2011) Low-grade inflammation in depression, anxiety and sleep disturbances


1140. Kangas, Maarit (2011) Development of accelerometry-based fall detection : from laboratory environment to real life

1141. Määtä, Tuomo (2011) Down syndrome, health and disability : A population-based case record and follow-up study

1142. Leskelä, Tarja (2011) Human δ opioid receptor Phe27 and Cys27 variants : The role of heteromerization and pharmacological chaperones in receptor processing and trafficking

1143. Karjalainen, Minna (2011) Genetic predisposition to spontaneous preterm birth : approaches to identify susceptibility genes

1144. Saaristo, Timo (2011) Assessment of risk and prevention of type 2 diabetes in primary health care

1145. Vuononvirta, Tiina (2011) Etäterveydenhuollon käyttöönotto terveydenhuollon verkostoissa


1147. Katisko, Jani (2012) Intraoperative imaging guided delineation and localization of regions of surgical interest : Feasibility study


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