Enhanced Steroid Therapy in Adult Minimal Change Nephrotic Syndrome: A Systematic Review and Meta-analysis

Lingfei Zhao, Jun Cheng, Jingyi Zhou, Congcong Wu and Jianghua Chen

Abstract

The best regimen for adult minimal change nephrotic syndrome (MCNS) is still unknown. Due to an excessive number of adverse events caused by oral steroid monotherapy, enhanced steroid therapy (low dose of prednisolone with a short course of methylprednisolone or with another immunosuppressant) has been studied extensively for years. In this study, the PubMed, Embase, EBSCO and Cochrane Library databases were searched for clinical trials which compared enhanced steroid therapy with oral steroid monotherapy in adult MCNS and a meta-analysis was performed. Seven studies involving 357 patients were included. We found that patients treated with enhanced steroid therapy responded more quickly to complete remission (CR) [mean difference = -9.52, 95% confidence interval (CI): -12.66--6.39, p<0.00001] and showed fewer adverse events [risk ratio (RR) = 0.72, 95% CI: 0.54-0.97, p=0.03] than patients receiving oral steroid monotherapy. The CR rate (RR= 0.96, 95% CI: 0.83-1.10, p=0.53) and relapse rate (RR=0.87, 95% CI: 0.57-1.34, p=0.53) were similar in both groups.

Key words: adult minimal change nephrotic syndrome, enhanced steroid therapy, meta-analysis

(DOI: 10.2169/internalmedicine.54.3927)

Introduction

Minimal change disease (MCD) is a common cause for idiopathic nephrotic syndrome (INS) among adults and accounts for 25% of all cases (1). In renal biopsies, glomerular lesions are not present on light microscopy (or only minimal mesangial prominence), immunofluorescence microscopy is negative (or only exhibits low-level staining for C3 and IgM), and foot process effacement is visible on electron microscopy, but not electron-dense deposits (2). In general, MCD is regarded as a self-limiting and relatively benign disease, and the risk of end-stage renal disease (ESRD) in these patients is extremely low. However, persistent proteinuria in these patients can result in severe hypoalbuminemia, edema, hyperlipidemia, recurrent infections, cardiovascular disease, and progression to renal failure (3). Therefore, active therapy and quick remission is of great importance for these patients.

Most of our treatment experience for MCD comes from pediatric patients. However, unlike the good response to steroids in children, the response rate is slower in adults (4), and 5-30% of adults with MCD do not respond to initial steroid therapy. Furthermore, for those who respond to steroid therapy, 30-62% will experience a single relapse and up to 39% will have frequent relapses (5).

Repeated and prolonged steroid therapy places patients at risk for developing cushingoid obesity, hypertension, infections, psychological disturbances, osteoporosis and cardiovascular morbidity later in life (6). Especially for women, cosmetic problems during treatment are of great concern for such patients. Pulse therapy and immunosuppressant combination therapy have been increasing in popularity in recent years. These two treatment strategies are both able to induce stronger immune suppression in the early duration of therapy to achieve a quick remission and use lower doses of steroid in the maintenance phase to avoid the adverse events caused by high-dose, long-term steroid use. Due to the ad-
verse events caused by oral steroid monotherapy, patient compliance is low. Therefore, we combined pulse therapy with immunosuppressant combination therapy as enhanced steroid therapy and performed a meta-analysis to evaluate the use of enhanced steroid therapy with oral steroid monotherapy for adult minimal change nephrotic syndrome (MCNS).

Materials and Methods

Search strategy

We conducted a search on the PubMed, Embase, EBSCO and Cochrane Library databases from 1970-July 29, 2014 using the key words “minimal change nephropathy,” “minimal change disease,” and “minimal change nephrotic syndrome” with “corticosteroid” or “steroid.” All clinical trials which compared enhanced steroid therapy with oral steroid monotherapy were identified. There were no language restrictions on inclusion for the meta-analysis. References of the articles acquired were also searched. The abstracts of the articles were independently analyzed by two of the authors (L.F. Zhao and J. Cheng) to ascertain inclusion criteria conformity. Disagreements between these two investigators were solved after discussions until reaching a consensus.

Inclusion criteria

We included all clinical trials which meet all of the following criteria: (i) the study was a trial of adult MCNS and (ii) the study compared enhanced steroid therapy with oral steroid monotherapy.

Exclusion criteria

Studies enrolling pediatric patients, patients with secondary MCD, patients who had any type of focal segmental glomerulosclerosis (FSGS) were excluded.

Data extraction

Data extraction was performed for all included trials by the two reviewers (L.F. Zhao and J. Cheng) independently. Disagreements between these two reviewers were solved by discussion. We extracted data from each study including the authors’ names, year of publication, design of the trial, patient characteristics, sample size, study drugs, doses, duration of the study, duration of the follow-up and the following reported outcomes; (i) complete remission (CR) and relapse rate in the treatment, (ii) duration to CR in the treatment and (iii) adverse events in the treatment.

Quality assessment

We assessed the quality of random controlled trials (RCTs) using a modified Jadad scoring system, to ensure that the studies included adequate randomization (2 = described in detail with proper method of randomization, 1= randomized but not reported in detail, 0 = not randomized), allocation concealment (2 = described that would not allow investigator/participant to know or influence the intervention group before an eligible participant enrolled in the study (7), 1 = stated allocation concealment but did not provide detailed information, 0 = not proper), blinding (2 = double-blind,1 = single-blind, 0 = open-label), completeness of the follow-up (1 = reported numbers and reasons, 0 = not reported), and we performed an intention-to-treat analysis. The maximum score was 7 points, and more than 4 points represented a high-quality study.

We also accessed the quality of the cohort studies using the Newcastle-Ottawa scale (8), including selection (0 to 4 points), comparability (0 to 1 points), and outcome (0 to 3 points). The maximum score was 8 points, representing the highest methodological quality.

Statistical analysis

Data were pooled using a fixed-effect model, unless they had significant heterogeneity, in which results were confirmed using a random-effect statistical model. For dichotomous outcomes (CR rate, relapse rate, adverse events), the results were expressed as the risk ratio (RR) with 95% confidence intervals (CI). For continuous outcomes (duration to CR), the results were expressed using the weighted mean difference (WMD) with 95% CIs. We also assessed the heterogeneity of results by calculating a chi-square test and evaluated the extent of inconsistency using the I² measure. I² values >25%, >50%, and >75% were defined as mild, moderate, and severe heterogeneity, respectively. A sensitivity analysis and subgroup analysis were performed to assess the effects of select measures of study quality and clinical factors on heterogeneity using the Stata 11.0 statistical software package (Stata Corp., College Station, USA). All other statistical analyses were performed using the Review Manager 5.1 statistical software package (Cochrane Collaboration, Oxford, UK) for the meta-analysis. Statistical significant was considered to be present at p<0.05.

Results

Included studies

The electronic and manual search retrieved 1,359 citations. Of these, seven trials (9-15), with a total of 357 patients, were included in this analysis (Fig. 1).

Based on the clinical features of the studies, we divided the reports into two subgroups, the combination group and pulse group. The combination group (9-11) compared low-dose steroid plus an immunosuppressant with traditional 1 mg/kg/day prednisolone therapy, while the pulse group (12-15) compared low dose steroid plus a short course of methylprednisolone with traditional 1 mg/kg/day prednisolone therapy. Details of the interventions, baseline patient characteristics, study period, and follow-up are summarized in Table 1. And the quality assessment is shown in Table 2.
Effect on CR rate

All of the seven studies were conducted to determine the effectiveness of enhanced steroid therapy on inducing CR rate in a total of 357 patients with adult MCNS (9-15). In these studies, 169 patients were assigned to the enhanced treatment group and 188 patients were assigned to the control group.

An analysis of the treatment effect on the CR rate was plotted in Fig. 2. Forest plots displayed the results of the meta-analysis for the combination group (RR=1.05, 95% CI: 0.90-1.23, p=0.54), pulse group (RR=0.84, 95% CI: 0.63-1.13, p=0.25) and overall (RR=0.96, 95% CI: 0.83-1.10, p=0.53). The test for subgroup differences was not significant (p=0.19) and the results showed that there were no significant differences in the CR rate between the two groups (Fig. 2).

Effect on mean time to CR

Five studies assessed the effect of mean time to CR in a total of 299 patients with adult MCNS (9, 10, 12, 14, 15). Patients were assigned to the enhanced treatment group (n=141) or the control group (n=158).

An analysis of the treatment effect on the mean time to CR was plotted in Fig. 3. Forest plots displayed the results of the meta-analysis for the combination group (MD=-8.08, 95% CI: -12.52-3.64, p=0.0004), pulse group (MD=-10.95, 95% CI: -15.38-6.53, p=0.00001) and overall (MD=-9.52, 95% CI: -12.66-6.39, p=0.00001). The test for subgroup differences was not significant (p=0.37). Our meta-analysis indicated that treatment with enhanced steroid therapy induced an earlier CR compared with the control group (Fig. 3).

Effect on relapse rate

Six of the seven studies, involving 308 patients, published the effect of enhanced steroid therapy on the relapse rate in adult patients with MCNS (9-13, 15). Patients were assigned to the enhanced treatment group (n=144) and the control group (n=164).

An analysis of the effect of treatment on the relapse rate was plotted in Fig. 4. Forest plots displayed the results of the meta-analysis for the combination group (RR=0.6, 95% CI: 0.35-1.05, p=0.07), pulse group (RR=1.08, 95% CI: 0.57-2.02, p=0.82) and overall (RR=0.87, 95% CI: 0.57-1.34, p=0.53). The test for subgroup differences was not significant (p=0.18). According to our meta-analysis in which the weight of individual studies was taken into account, there were no significant differences in the relapse rate between the two groups (Fig. 4).

Adverse events of treatment

Four studies reported treatment-related adverse events in details (9, 11, 14, 15). We classified adverse events into serious or less serious based on the guidelines by ICH in 1994 which defined a serious adverse event (experience) or reaction as any untoward medical occurrence that (at any dose) resulted in death, life threatening, persistent or significant disability/incapacity, congenital anomaly/birth defects, inpatient hospitalization or prolongation of existing hospitalization (16). Cates et al. also used a similar classification scheme to evaluate drug-related adverse events in their study (17). Thus we included serious infection, leucopenia, gastroduodenal bleeding and aseptic osteonecrosis as serious adverse events, while diabetes, hepatitis B virus (HBV) reactivation, gastrointestinal syndrome, cataract and cosmetic problem were considered to be less serious adverse events.

The specific adverse events are summarized in Table 3, and an analysis of the effect of treatment on the adverse events was plotted in Fig. 5. Forest plots displayed the results of the meta-analysis for serious adverse events (RR=0.76, 95% CI: 0.43-1.34, p=0.34), less serious adverse events (RR=0.71, 95% CI: 0.43-1.34, p=0.34), less serious adverse events (RR=0.71, 95% CI: 0.51-0.99, p=0.04) and overall (RR=0.72, 95% CI: 0.54-0.97, p=0.03; Fig. 5). Furthermore, although Imbasciati et al. (13) did not describe adult patients who had cosmetic problems in detail, there were fewer patients in the enhanced treatment group who developed obesity, facies, striae or other cosmetic problems.

Therefore, our meta-analysis indicated that treatment with enhanced steroid therapy can effectively decrease the frequency of adverse events.

Sensitivity analysis and publication bias

Our analyses were robust in both the choice of models and the statistical methods utilized. The sensitivity analysis indicated that the study by Shinzawa et al. was the main source of heterogeneity on the CR rate and relapse rate seen in the meta-analysis. However, after excluding this study, the results of our meta-analysis remained unchanged. No publication bias was detected due to the low number of studies included in the meta-analysis.
Table 1. Characteristics of the Included Studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Baseline characteristics</th>
<th>Mean age (years)</th>
<th>Drugs</th>
<th>Treatment length (months)</th>
<th>Follow-up (months)</th>
<th>Cases (n)</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>prospective nonrandomized single center study</td>
<td>4 relapse and 20 first episode patients</td>
<td>32.0±13.8</td>
<td>CsA (2-3mg/kg/day) + PMT (1,000mg for 3 days)</td>
<td>12</td>
<td>38.9±16.3</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>prospective randomized trial</td>
<td>first relapse patients</td>
<td>33.0±9.3</td>
<td>CsA(600-800ng/mL for C2) + PSL(0.8 mg/kg/day)</td>
<td>6</td>
<td>NM</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>prospective cohort study</td>
<td>30 MCD and 11 slight mesangial proliferative glomerulonephritis*</td>
<td>NM</td>
<td>MMF(0.5-1g bid) + PSL(0.5 mg/kg/day)</td>
<td>9</td>
<td>15</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>retrospective cohort study</td>
<td>first episode patients</td>
<td>34.0±17.5</td>
<td>PMT(1,000mg for 3 days) + PSL 30-40mg/day</td>
<td>3</td>
<td>12</td>
<td>29</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>prospective randomized multicenter study</td>
<td>first episode patients</td>
<td>NM</td>
<td>PMT(20 mg/kg/day for 3 days) + PSL(0.5 mg/kg/day)</td>
<td>6</td>
<td>12-24</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>prospective randomized single center study</td>
<td>first episode patientsb</td>
<td>24.5±10.2</td>
<td>PMT(20 mg/kg/day for 3 days)</td>
<td>1-1.5</td>
<td>36</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>retrospective multicenter cohort study</td>
<td>first episode patients</td>
<td>NM</td>
<td>PMT(0.5g or 1g for 3 days) + PSLc</td>
<td>NM</td>
<td>43</td>
<td>65</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

MCD: minimal change disease, CsA: cyclosporin A, MMF: mycophenolate mofetil, PMT: pulse methylprednisolone therapy, PSL: prednisolone, NM: not mentioned
* Slight mesangial proliferative glomerulonephritis is a type of glomerulonephritis with slight mesangial proliferative on light microscopy. Its clinical manifestation is similar to MCD,
  with good response to steroid therapy and frequent relapse rate.

Discussion

Therapeutic approaches for adult MCNS have been attempted in the last four decades, but the ideal regimen, which comprises rapid induction, long time remission and few adverse events, is far from established. Steroids are recommended as a first-line therapy according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline (18). However, the response to steroid therapy appears to be lower and slower to develop in adults than in children (19). Furthermore, many adverse events, especially cosmetic issues caused by steroid use, are substantial issues for some nephrotic patients in regards to their social lives. Due to common relapsing and the significant toxicity of repeated steroid treatment, adult MCNS remains a therapeutic challenge for clinical nephrologists. Thus, we performed this meta-analysis to determine the most suitable therapeutic regimen, focusing on the balance between therapeutic effect and adverse events.

To the best of our knowledge, this is the first meta-analysis for adult MCNS. Our results indicate that enhanced steroid therapy is safer and more effective than oral steroid monotherapy for adult MCNS. Enhanced steroid therapy not only leads to a quicker effect on CR (MD=-9.52, 95% CI: -12.66--6.39, p<0.00001), but also causes fewer adverse events (RR=0.72, 95% CI: 0.54-0.97, p=0.03) than oral steroid monotherapy. The CR rate (RR=0.96, 95% CI: 0.83-1.10, p=0.53) and relapse rate (RR=0.87, 95% CI: 0.57-1.34, p=0.53) were found to be similar in both the treatment
Why does the initial use of enhanced steroid therapy contribute to earlier remission in MCD? Although the precise MCD pathogenesis remains unknown, many studies have indicated that immunological factors, especially T cells, play an important role in the process (20). Perturbations in T cells may do a lot of damage to glomerular podocytes (21), leading to a reduced expression of nephrin (21-23) and destabilization of the actin cytoskeleton (24), which thus leads to massive proteinuria in MCD. In addition to its immunomodulatory effect, cyclosporine A (CsA) and steroid therapy can also directly affect podocytes (24, 25). Faul et al. found that the beneficial effect of CsA on proteinuria was not only dependent on nuclear factor of activated T cells (NFAT) inhibition in T cells, but rather resulted from the stabilization of the actin cytoskeleton in kidney podocytes (24). Xing et al. found that dexamethasone promoted the expression of nephrin and other proteinuria-associated factors in human podocytes in a dose-dependent manner (25). These findings may explain why enhanced steroid therapy can induce earlier remission than oral steroid monotherapy.

The relationship between earlier induction of remission and earlier relapse is still controversial. Some studies found that earlier induction of remission may be related to earlier relapse (19, 26). Others observed that no correlation between the response time to remission and time to relapse (4, 27). Shinzawa et al. reported that earlier induction could decrease the rate of relapse (15). However, according to our meta-analysis, earlier induction after enhanced steroid therapy does not cause earlier relapse, and a decrease in the long-term dosage of steroids is recommended.
High-dose, long-term steroid use is associated with an excess of adverse events, and some of which are dosage-related. In the Hopkins Lupus Cohort Study, results indicated that an increasing cumulative steroid dose was associated with a significantly increased risk of osteoporotic fractures, symptomatic coronary artery disease, cataracts, diabetes, pulmonary fibrosis, and cognitive impairment/psychosis (28). The prolongation of hospitalization, which in turn results in an increase in medical expenses, is a big burden for both individuals and nations. Data from the Healthcare Cost and Utilization Project indicated that steroid therapy was the most common specific cause of adverse events, accounting for 10.3% of all drug-related adverse events and 141,000 hospital stays in the United States in 2004 (29). Furthermore, Shah et al. found that patients with systemic lupus erythematosus (SLE) receiving steroid therapy spend an additional $784 per year treating adverse events attributable to steroid use than steroid nonusers (30). Therefore, there is an urgent need to establish a specific therapy strategy for elderly and female patients. According to our meta-analysis, enhanced steroid therapy causes fewer adverse events and less adverse cosmetic effects, and thereby is a suitable regimen for these patients.

Age is considered to be related to both the treatment effect as well as to the occurrence of adverse events. The age at onset was found to be inversely correlated with the relapse rate in adult MCD patients and most studies have suggested that elderly patients tended to have fewer relapses than young patients (4, 5, 31-33). Conversely, age was found to be positively correlated with adverse events. Shinzawa et al. observed that older patients were significantly more vulnerable to severe infection, diabetes, and cataract compared with younger patients, and this phenomenon was not related to the cumulative steroid dose (31). Huang et al. also confirmed that high-dose and long-term corticosteroid treatment had a more significant impact in the elderly and resulted in a higher incidence of hyperglycemia, hypertension, osteoporosis, and severe infection (32). Because of the low relapse rate and severe steroid-related adverse events, a treatment strategy that suppresses not only the relapse of proteinuria but also steroid-related adverse events needs to be carefully devised, keeping in mind the risk stratification.

**Table 3.** Adverse Events Observed in Patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Serious infection</th>
<th>Leukopenia</th>
<th>Gastrointestinal bleeding</th>
<th>Aseptic osteonecrosis</th>
<th>Diabetes</th>
<th>HBV reactivation</th>
<th>Gastrointestinal symptoms</th>
<th>Cataract</th>
<th>Cosmetic problems</th>
<th>Serious adverse events</th>
<th>Less serious adverse events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>0 vs. 1</td>
<td>0 vs. 1</td>
<td>0 vs. 1</td>
<td>7 vs. 14</td>
<td>4 vs. 3</td>
<td>0 vs. 2</td>
<td>7 vs. 6</td>
<td>11 vs. 14</td>
<td>4 vs. 5</td>
<td>8 vs. 11</td>
<td>16 vs. 19</td>
<td>24 vs. 30</td>
</tr>
<tr>
<td>11</td>
<td>5 vs. 6</td>
<td>2 vs. 0</td>
<td>0 vs. 1</td>
<td>0 vs. 1</td>
<td>7 vs. 6</td>
<td>11 vs. 17</td>
<td>18 vs. 23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0 vs. 1</td>
<td>1 vs. 1</td>
<td>12 vs. 14</td>
<td>7 vs. 14</td>
<td>4 vs. 3</td>
<td>11 vs. 17</td>
<td>18 vs. 23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>7 vs. 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For certain patients, providers should carefully consider steroid therapy when making treatment decisions. Elderly patients tend to develop more frequent and severe adverse events compared with young patients (31, 32). In addition, women may feel that oral steroid monotherapy impairs their social lives due to adverse cosmetic problems. In fact, many young women in our hospital refused oral steroid monotherapy, due to the potential of adverse cosmetic effects. Therefore, there is an urgent need to establish a specific therapy strategy for elderly and female patients. According to our meta-analysis, enhanced steroid therapy causes fewer adverse events and less adverse cosmetic effects, and thereby is a suitable regimen for these patients.
by age (31). Nolasco et al. suggested that endoxan may be used as the primary first-line treatment in adult-onset MCD patients older than 65 years of age because results in fewer adverse events than corticosteroid treatment (19). Regarding the mean time to remission, the results varied in different studies. Shinzawa et al. indicated that compared with younger patients 15-29 years of age at kidney biopsy, elderly patients 60 years of age developed remission significantly later (31) while other studies suggested that the age of onset in MCD cases was not significantly correlated with the time interval to remission (4, 32, 33). Despite these contradicting results, our meta-analysis suggests enhanced steroid therapy, which leads to quicker remission and fewer adverse events is a suitable therapy strategy for elderly patients.

CsA nephrotoxicity is a major concern and the reason for its restrictive use in renal disease. However, recent reports have shown that a low dose of CsA had little effect on renal function. Matsumoto et al. tested oral CsA treatment (2-3 mg/kg/day) which was slowly tapered after intravenous pulse methylprednisolone in 12 patients (9). The patients’ renal functions were stable after 12 months of treatment. Similar results were also obtained from other groups. Kranz et al. evaluated the impact of CsA therapy in patients with corticosteroid-dependent nephritic-syndrome (SDNS) on the long-term renal function (34). The CsA dose was adjusted to a target blood level of 80-120 ng/mL and they found that the glomerular filtration rate (GFR) showed a drop during the first year but remained stable thereafter. No CsA toxicity was found in the patient biopsy specimens. Kim et al. retrospectively analyzed the clinical and laboratory findings of 58 children with MCNS who were treated with CsA, and they concluded that the medium CsA level was an independent and significant risk factor for the development of CsA-associated nephrotoxicity (35). Taken together, these studies suggest that low-dose, tapered CsA therapy is safe for MCNS patients, however the CsA concentrations should be closely monitored.

There are some limitations associated with this meta-analysis, although our meta-analysis provides new treatment strategies for adult MCNS. First, the number of included studies was small, and the quality of the studies was not high. Second, the does and type of drugs prescribed varied among the included studies (i.e. the agents used in the enhanced treatment group). Finally, the follow-up time in the studies was short and none of these studies assessed the outcome of renal death (defined as end-stage renal disease).

Therefore, multicenter, well-designed RCTs with large sample populations and a long-term follow-up are necessary to confirm our findings.

**Conclusion**

The current cumulative evidence suggests that enhanced steroid therapy is safer and more effective than oral steroid monotherapy for adult MCNS. However, these findings need to be confirmed by multicenter RCTs with large sample populations and a long-term follow-up.

**The authors state that they have no Conflict of Interest (COI).**

**Financial Support**

This study was supported by the Medical Research Fund from the Bureau of Health, Zhejiang Province (2013KYA072) and Project supported by National Key Technology R&D Program (No. 2013BAI09B04). The funding sources had no influence on data analysis or preparation of this manuscript.

**References**

1. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal changes and


