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Primary glomerular diseases in the elderly

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Abstract

Primary glomerular diseases in the elderly population are a frustrating topic due to difficulties in both the diagnosis and decision making about treatment. The most frequent type of primary glomerular disease in elderly is membranous nephropathy; while its counterpart in younger population is IgA nephropathy. The most frequent cause of nephrotic syndrome in the elderly is also membranous nephropathy. Pauci-immune crescentic glomerulonephritis (GN) rate increases both in elderly and very elderly population. Pauci-immune crescentic GNs should be regarded as urgencies in elderly patients as in their younger counterparts due to potential for causing end-stage renal disease in case of delayed diagnosis and treatment, and also causing mortality due to alveolar hemorrhage in patients with pulmonary involvement. Renal biopsy is the inevitable diagnostic method in the elderly as in all other age groups. Renal biopsy prevents unnecessary treatments and provides prognostic data. So advanced age should not be the sole contraindication for renal biopsy. The course of primary glomerular diseases may differ in the elderly population. Acute kidney injury is more frequent in the course and renal functions may be worse at presentation. These patients are more prone to be hypertensive. The decision about adding immune suppressive therapies to conservative methods should be made considering many factors like co-morbidities, drug side effects and potential drug interactions, risk of infection, patient preference, life expectancy and renal functions at the time of diagnosis.

Key words: Elderly; Membranous nephropathy; Renal biopsy; Pauci-immune crescentic glomerulonephritis; Primary glomerular disease

Core tip: Primary glomerular diseases in the elderly population are a frustrating topic due to difficulties in both diagnosis and treatment. The most frequent type of primary glomerular disease and the most frequent cause of nephrotic syndrome is membranous nephropathy. The frequency of pauci-immune glomerulonephritides increases considerably in the very elderly population. Renal biopsy is the inevitable diagnostic method in the elderly as in all other age groups. The decision about adding immune suppressive therapies to conservative methods should be made considering many factors like co-morbidities, drug side effects, patient preference, life expectancy and renal functions at the time of diagnosis.

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INTRODUCTION

Primary glomerular diseases (PGD) in the elderly deserves mention under a heading separate from PGDs in young adults due to differences in epidemiological and clinical characteristics, and difficulties in diagnosis and decision making about diagnosis. Co-morbidities, shorter life expectancy, complications of renal biopsy and immunosuppressive medications are among the factors that challenge the clinicians about diagnosis and treatment. Paucity of clinical studies and so insufficiency of evidence and guidelines are other problems in the elderly population that increases progressively due to increased mean life expectancy[1]. First, general epidemiological and clinical characteristics of PGDs in the elderly will be mentioned followed by details about specific diseases.

The frequency of PGDs in the elderly may change in countries. Ethnic predisposition, different approaches about biopsy indications and differences in the methods and design of epidemiological studies are among the causes of this variability. We learn about epidemiological data about PGDs in the elderly, from glomerulonephritis or biopsy registries of countries. These studies may be classified as involving "elderly" (> 60-65 years) and "very elderly" (> 80-85 years) patients.

Some of the registries that you can gain information about epidemiological data in the elderly population in Europe are those of Italy, Spain, Czech Republic and Turkey[2-5]. Membranous nephropathy (MN) was reported in these studies as the most frequent PGD and the most frequent cause of nephrotic syndrome in patient older than 65 years. The PGD in the second order changes in different countries. The evaluation of pauci-immune crescentic glomerulonephritis (pauci-immune crescentic GN) within PGDs in some studies while within secondary glomerular diseases in the others leads to difficulties in evaluation of epidemiological studies. The most frequent biopsy indication is nephrotic syndrome as expected whether accompanied by acute kidney injury (AKI) or not. The manuscript by Yokoyama *et al*[6] who presented data of Japan Renal Biopsy Registry has a special place in the literature due the highest number of patients. Data of 2802 patients aged > 65 (group A) and 276 patients aged > 80 years (group B) were presented in this study. Forty-five percent of cases were PGDs. The most frequent PGDs in group A and B were MN, IgA nephropathy (IgAN) and minimal change disease (MCD) in order, while the most frequent diagnoses in elderly patients who had renal biopsy due to nephrotic syndrome were MN, MCD and focal segmental glomerulosclerosis (FSGS) with decreasing order. The most frequent biopsy indication was nephrotic syndrome in both groups, while rapidly progressive glomerulonephritis (RPGN) was the second most frequent cause in group B. When compared with patients aged less than 65 years, pauci-immune crescentic GN, MN, type 1 and 3 membranoproliferative glomerulonephritis (MPGN) were more frequent and IgAN was significantly less frequent in patients aged more than 65 years. The ratio of renal biopsies performed due to RPGN was higher in the elderly population compared to younger counterparts. There are also current studies presenting epidemiological data of elderly patients in a single center besides registry studies[7-10]. MN was again the most frequent diagnosis in these studies except in the study by Brown *et al*[10] in which pauci-immune crescentic GN was the most frequent PGD. Recent studies about the epidemiology of PGD in elderly are summarized in Table 1.

Recent articles have been published about epidemiological data of very elderly patients although the age limit is variable[11-15]. Although all cases are not PGDs in these studies, they provide important information about PGDs in the very elderly population. The most frequent PGD in studies originating from United States[11,14] was pauci-immune crescentic GN, while it was MN in other studies from European and Asian countries. Biopsy indications in these studies follow the same order, and provide clues about behavior regarding biopsy indication in this special age group in these countries. The most frequent biopsy indication is AKI in United States, while it is nephrotic syndrome in other European and Asian countries. Studies performed with very elderly patients are summarized in Table 2.

Although renal biopsy is the inevitable diagnostic method in glomerular diseases, it is not performed in some of the patients due to various factors including co-existing systemic diseases, shorter life expectancy, reluctance of the clinicians about biopsy and immunosuppressive treatment and patient preference. There are studies in the literature reporting that bleeding risk after renal biopsy in elderly patients is not different from other age groups[16,17]. But, the possibility that clinicians would have performed renal biopsy in elderly patients with lower risk in these studies in which data of biopsy series are presented, should be kept in mind. As well known, the most important predictor of bleeding complication is serum creatinine level[17]. This complication is more common in patients with renal failure compared to patients without. The concern of clinicians about this complication is not undue considering physiological changes related to age, co-existing systemic diseases (hypertension, atherosclerosis, diabetes mellitus, amyloidosis), and overestimation of glomerular filtration rate with creatinine level due to decreased muscle mass. When possible complications of immunosuppressive treatment add on these concerns, some clinicians prefer conservative methods without performing renal biopsy. Some other clinicians on the other hand try empiric

Table 1 Recent epidemiological studies in the elderly

Country	Ref.	Date	Number of cases	Age	The most frequent PGDs
Italy[1]	Vendemia *et al*[2]	2001	280	> 65	1. MN 2. Pauci-immune GN 3. MPGN
Turkey	Ozturk *et al*[5]	2014	150	> 60	1. MN 2. Pauci-immune GN 3. FSGS
Japan	Yokoyama *et al*[6]	2012	2802	> 65	1. MN 2. IgAN 3. MCD
Brasil	Carmo *et al*[7]	2010	113	> 60	1. MN 2. FSGS 3. MCD
South Africa	Okpechi *et al*[8]	2013	111	> 60	1. MN 2. IgAN 3. Pauci-immune GN
China	Jin *et al*[9]	2014	851	> 65	1. MN 2. IgAN 3. MCD
Ireland	Brown *et al*[10]	2012	236	> 65	1. Pauci-immune GN 2. MN 3. IgAN

[1]Only patients with PGDs were included in this study, while other studies included patients with secondary glomerular diseases also. FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; IgAN: IgA nephropathy; MCD: Minimal change disease; MN: Membranous nephropathy; MPGN: Membranoproliferative glomerulonephritis; PGD: Primary glomerular disease.

immunosuppressive treatment without biopsy. Yoon *et al*[18] evaluated this subject in their study. They evaluated renal and patient survival rates of 99 patients (age > 60 years) presenting with nephrotic syndrome who were grouped as those who had renal biopsy (n = 64) and those who did not (n = 35). The major defect of this study was the lower mean age and better renal functions in the group who had renal biopsy. Although complete remission was more frequent (45% *vs* 26%, P = 0.013) in the biopsy group in which statistically significantly more patients had immunosuppressive therapy (P < 0.005), renal survival rates were similar. Patient survival was lower in the group without biopsy which was not a surprise considering significantly higher mean age.

On the other hand, there are factors that lead the clinician towards biopsy like need of urgent diagnosis for optimum treatment of pauci-immune glomerulonephritides presenting as RPGN; the risk of not giving specific treatment considering more susceptibility of elderly to infective and thrombotic complications of nephrotic syndrome[19,20]; prevention of unnecessary treatments by renal biopsy; and provision of prognostic data. Studies with very elderly patients revealed that therapeutic approach may change 40%-67% with renal biopsy[11,14]. So, advanced age should not be the sole contraindication for renal biopsy. The clinician has to decide respecting the preference of the patient within this multifactorial equation.

Renal biopsy in elderly has the potential to be problematic for pathologists as well as clinicians. Varying degrees of "background" glomerulosclerosis, tubular atrophy, arteriolar hyalinosis that may be seen as a result of both senility and co-morbidities may superimpose primary and secondary glomerular diseases[21].

Primary glomerular diseases in the elderly present as nephrotic syndrome, nephritic syndrome, RPGN, asymptomatic urine abnormalities or chronic glomerulonephritis as in other age groups. But nephrotic syndrome and acute nephritic syndrome including RPGN comprises most of the cases as can be understood from biopsy indications in reported by biopsy series. PGDs causing nephrotic syndrome are MN, FSGS and MDH, while MPGN, IgAN and pauci-immune crescentic GNs comprise the major causes of nephritic syndrome. But different and complex forms of presentation are not rare. As an example, AKI superimposed on nephrotic syndrome is more frequent in elderly population. Some of the authors consider AKI on the basis of nephrotic syndrome as idiopathic if there is no clear reason as drug use, exposure to radio contrast agent or interstitial nephritis[22].

The treatment of PGDs in the elderly causes difficulties as the diagnosis. Co-morbidities, the number of pills that the patients take, potential drug interactions, risk of infection, patient preference, expected life expectancy, renal functions at the time of diagnosis, increased drug toxicity risk due to age related decreased in drug metabolism and excretion[23,24] are some of the factors effective on the decision of the clinician about treatment. Moreover, disease specific secondary causes should be searched for promptly as well as

Table 2 Recent epidemiological studies in the very elderly population

Country	Ref.	Date	Number of cases	Age	The most frequent PGD
Japonya	Yokoyama *et al*[6]	2012	276	> 80	1. MN 2. IgAN 3. MCD
United States	Moutzouris *et al*[11]	2009	235	> 80	1. Pauci-immune GN 2. MN 3. IgAN
Italy	Rollino *et al*[12]	2014	131	> 75	1. MN 2. Pauci-immune GN 3. IgAN
Japan	Omokawa *et al*[13]	2012	73	> 80	1. MN 2. MCD
United States	Nair *et al*[14]	2004	100	> 80	1. Pauci-immune GN 2. MN
Spain	Verde *et al*[15]	2012	71	> 85	1. MN 2. Pauci-immune GN 3. IgAN

GN: Glomerulonephritis; IgAN: IgA nephropathy; MCD: Minimal change disease; MN: Membranous nephropathy; PGD: Primary glomerular disease.

any contraindication for treatment and screening for malignancy appropriate for the age group should be performed.

Conservative methods are the sine qua non of treatment of patients with nephrotic syndrome in this age group. Salt restriction, smoking cessation, diuretics, renin-angiotensin-aldosterone system blockers, statins, anticoagulant agents and pneumococcal vaccination are the components of conservative treatment[25,26]. Anticoagulation is recommended in patients with serum albumin level below 2 g/dL and co-existing risk factors if bleeding risk not high. But treatment decision should be individualized as in all cases. An article reporting the importance of forming a scaling system for thrombosis and bleeding before decision about anticoagulant use has been published recently[27].

Immunosuppressive therapy should be considered in cases with nephrotic proteinuria in spite of conservative methods, progressively declining renal functions, life threatening complications of nephrotic syndrome like thrombosis, and patients with RPGN. No guideline has been developed up to now for glomerulonephritides in the elderly. "Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis" published in 2012 helps the clinicians caring elderly patients. But it is difficult to adopt all recommendations to old patients. The clinician has to choose the correct treatment method considering both positive and negative sides together. All medications should be used in doses appropriate for the renal function of the patient.

MEMBRANOUS NEPHROPATHY

The most frequent PGD in adult population all over the world is IgAN as is well known[28,29]. But MN with its frequency increasing with aging, is the most common PGD and the most common reason of nephrotic syndrome in elderly. AKI is more frequent in the course of disease compared to other PGDs. Advanced age has been reported to be a risk factor for AKI in patients with MN[30]. Moreover, hypertension and worse renal functions at the time of presentation are expected to be more prevalent in elderly patients. There are studies reporting increased risk of thrombotic[31] and infectious[32] complications compared to adult patients.

The PGD that is most associated with malignancies is MN, and it is speculated that it accompanies tumors in 10% of cases[33,34]. M type anti phospholipase A2 antibodies that started a new era protects from unnecessary interventional investigations[35,36]. There is a tendency to screen patients with M type anti phospholipase A2 antibodies in accordance with age; while more complicated screening is necessary in those without anti phospholipase A2 antibody[37]. Another difference is in the subtypes of IgG on immune fluorescent microscopy, although not routinely studied. IgG4 predominates in primary MN, while IgG1 and/or IgG2 staining is expected to be positive in MN associated with malignancies[36]. Malignancies are usually clinically evident at the time of diagnosis of nephrotic syndrome. However, there are reported cases with malignancies reported late in the course. Some authors think that screening for cancer should be repeated within 5-10 years in cases with histological and serological testing resembling secondary MN[38,39]. History of medications, screening for infection (hepatitis B and malaria) and evaluation for systemic lupus erythematosus should not be forgotten. Nonsteroidal anti-inflammatory drugs (NSAID) are in the first order among drugs related with MN. NSAIDs may cause MN and MDH as well as non-glomerular diseases[40,41].

It has been shown that corticosteroid therapy alone in elderly patients with MN is not enough and actually, it is related with more complication[42,43]. Ponticelli

protocol (in which steroids are used in combination with either chlorambucil or cyclophosphamide) can be tried[44]. KDIGO guideline proposes immunosuppressive treatment in patients with severe life-threatening symptoms and findings, proteinuria more than 4 g/d in spite of conservative methods, or at least 30% increase in serum creatinine level within the last 6-12 mo[26]. However, there are no up-to-date randomized controlled trials about side effect profile and efficacy of steroid treatment in old patients. Besides, studies about the role of cyclosporine plus low dose steroid, and mycophenolate mofetil are not enough also. We can mention a study in which mizoribin was used in a few old patients. But the number of patients is not enough, and mizoribin group was not compared with patients receiving only steroid treatment[45].

MINIMAL CHANGE DISEASE

Minimal change disease which is one of the important causes of nephrotic syndrome in elderly presents withy hypertension and AKI more compared with younger population. Some authors believe that AKI superimposed on nephrotic syndrome in elderly is commonly associated with MCD, and elderly patients are more prone to acute tubular necrosis[46,47]. Relapses are rarer in patients older than 40 years compared to patients younger than 40 years[47,48]. All immunosuppressive medications used in the treatment of glomerulonephritis have been tried with considerable success, although steroids remain to be the mainstay of treatment[26].

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

We do not have enough data in the literature about the clinical characteristics and treatment of FSGF in the elderly. Tip variant of FSGS has been reported to be the histologic type presenting with sudden onset of severe nephrotic syndrome and also the type which is the most sensitive to steroid treatment. Tip lesions ten de be more prevalent in older patients[49,50]. Important predictors of renal prognosis are the magnitude of proteinuria, the level of kidney function, and the amount of tubulointerstitial injury[51]. Corticosteroids are the first line treatment in appropriate patients while second line treatment with cyclosporine plus low dose steroid may be preferred in cases for which there is considerable risk for corticosteroid side effects[26]. Evaluation for secondary causes of FSGS should not be omitted. Interferons[52] and intravenous use of bisphosphonates (especially pamidronate)[53] which are commonly prescribed in this population are examples for causes of secondary FSGS. American Society of Clinical Oncology published an update for use of bisphosphonates in multiple myeloma including knowledge about dose reduction in case of decreased renal function[54].

IGA NEPHROPATHY

IgA nephropathy is associated with more severe renal manifestations at presentation in the elderly. It has been reported in Spanish Registry of Glomerulonephritis that 27.8% of patients with IgAN older than 65 years presented as AKI[3]. This ratio reached to 53% in another study with the emphasis that tubular injury is more prominent than glomerular damage in these patients[55]. Advanced age has been determines as a risk factor for progression to end-stage renal disease (ESRD) which was found to be 1.95 times more common compared to young adults[56]. An article has been published recently reporting that 70% of patients reach ESRD within 20 years[57]. The only immunosuppressive medication proved to be effective in IgAN is corticosteroids. Although persistent proteinuria in spite of conservative measures is an indication for corticosteroid treatment according to KDIGO guideline, it may not be wise to give corticosteroid treatment to elderly patients with normal renal functions, blood pressure and non-nephrotic range proteinuria, especially in the presence of comorbidities. However, IgAN presenting as crescentic glomerulonephritis should be treated as pauci-immune crescentic glomerulonephritis[26].

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Primary MGPN is a rare disease. So, secondary causes, especially monoclonal gammopathies and hepatitis C infection, should be ruled out case of pathological diagnosis of MPGN[58,59]. Although usually not responsive, corticosteroid + mycophenolate mofetil or corticosteroid + oral cyclophosphamide may be tried in patients with MPGN type Ⅰ presenting with nephrotic syndrome and/or rapid increase in creatinine levels[26,60]. But patients and relatives should be informed thoroughly about the low response rates before deciding for immunosuppressive treatment.

PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS

Pauci-immune crescentic GN is disease group with increased rate both in elderly and very elderly population[61]. This group represents renal involvement in anti-glomerular basement membrane disease and anti-neutrophil cytoplasmic autoantibody associated vasculitides. Renopulmonary syndrome is the more frequent type of presentation although isolated renal involvement may also be seen. The first explanation for increased frequency is the peak that the systemic vasculitides show between ages 65-74 years[62]. Moreover, presentation with RPGN increases the probability of performing renal biopsy in these patients for whom

the clinicians may prefer to remain conservative otherwise. Pauci-immune crescentic GNs should be regarded as urgencies in elderly patients as in their younger counterparts due to potential for causing ESRD in case of delayed diagnosis and treatment, and also causing mortality due to alveolar hemorrhage in patients with pulmonary involvement[63]. Renal biopsy should be scheduled immediately and serum samples should be taken for determination of anti-neutrophilic cytoplasmic antibody, anti-glomerular basal membrane antibody and then immunosuppressive treatment should be started as soon as possible. In the absence of absolute contraindications, pulse corticosteroid and cyclophosphamide treatment should be started together with plasma exchange in the presence of alveolar hemorrhage or rapid decline in renal functions[26]. In case of vasculitides limited to kidney, decision about treatment and its duration should be made regarding comorbidities and activity/chronicity of lesions on renal biopsy. Renal survival in anti-glomerular basal membrane disease is related with creatinine levels at the time of admission[64]. So, early diagnosis and treatment have prime importance. Independent determinants of mortality in anti neutrophil cytoplasmic autoantibody-associated vasculitides have been found to be advanced age and pulmonary infections[65]. KDIGO guideline recommends crescentic forms of any PGDs to be considered as pauci-immune GN and treated so[26].

As a conclusion, PGDs in elderly are a group of diseases that challenges the clinicians in both diagnosis and treatment. Although MN is the most common PGD in this age group, crescentic glomerulonephritides should always be considered due to irretrievable results.

REFERENCES

1 **Stevens LA**, Li S, Wang C, Huang C, Becker BN, Bomback AS, Brown WW, Burrows NR, Jurkovitz CT, McFarlane SI, Norris KC, Shlipak M, Whaley-Connell AT, Chen SC, Bakris GL, McCullough PA. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2010; **55**: S23-S33 [PMID: 20172445 DOI: 10.1053/j.ajkd.2009.09.035]

2 **Vendemia F**, Gesualdo L, Schena FP, D'Amico G. Epidemiology of primary glomerulonephritis in the elderly. Report from the Italian Registry of Renal Biopsy. *J Nephrol* 2001; **14**: 340-352 [PMID: 11730266]

3 **Rivera F**, López-Gómez JM, Pérez-García R. Frequency of renal pathology in Spain 1994-1999. *Nephrol Dial Transplant* 2002; **17**: 1594-1602 [PMID: 12198210 DOI: 10.1093/ndt/17.9.1594]

4 **Rychlík I**, Jancová E, Tesar V, Kolsky A, Lácha J, Stejskal J, Stejskalová A, Dusek J, Herout V. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000. *Nephrol Dial Transplant* 2004; **19**: 3040-3049 [PMID: 15507479 DOI: 10.1093/ndt/gfh521]

5 **Ozturk S**, Sumnu A, Seyahi N, Gullulu M, Sipahioglu M, Artan S, Bicik Z, Kutlay S, Keles M, Oygar D, Odabas AR, Kayatas M, Dursun B, Sayarlioglu H, Trablus S, Taymez DG, Ozdemir AA, Sahin GM, Altun B, Azak A, Altintepe L, Suleymanlar G, Koc M, Selcuk Y, Kazancioglu R, Erkoc R, Gursu M, Kucuk M, Akcaoglu SA, Yıldız A, Unal A, Akarsu O, Ates K, Cankaya E, Turkmen A. Demographic and clinical characteristics of primary glomerular diseases in Turkey. *Int Urol Nephrol* 2014; **46**: 2347-2355 [PMID: 25269407 DOI: 10.1007/s11255-014-0838-3]

6 **Yokoyama H**, Sugiyama H, Sato H, Taguchi T, Nagata M, Matsuo S, Makino H, Watanabe T, Saito T, Kiyohara Y, Nishi S, Iida H, Morozumi K, Fukatsu A, Sasaki T, Tsuruya K, Kohda Y, Higuchi M, Kiyomoto H, Goto S, Hattori M, Hataya H, Kagami S, Yoshikawa N, Fukasawa Y, Ueda Y, Kitamura H, Shimizu A, Oka K, Nakagawa N, Ito T, Uchida S, Furuichi K, Nakaya I, Umemura S, Hiromura K, Yoshimura M, Hirawa N, Shigematsu T, Fukagawa M, Hiramatsu M, Terada Y, Uemura O, Kawata T, Matsunaga A, Kuroki A, Mori Y, Mitsuiki K, Yoshida H. Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). *Clin Exp Nephrol* 2012; **16**: 903-920 [PMID: 23053590 DOI: 10.1007/s10157-012-0673-8]

7 **Carmo PA**, Kirsztajn GM, Carmo WB, Franco MF, Bastos MG. Histopathological findings in elderly patients. *J Bras Nefrol* 2010; **32**: 286-291 [PMID: 21103693]

8 **Okpechi IG**, Ayodele OE, Rayner BL, Swanepoel CR. Kidney disease in elderly South Africans. *Clin Nephrol* 2013; **79**: 269-276 [PMID: 23195833 DOI: 10.5414/CN107746]

9 **Jin B**, Zeng C, Ge Y, Le W, Xie H, Chen H, Liang S, Xu F, Jiang S, Liu Z. The spectrum of biopsy-proven kidney diseases in elderly Chinese patients. *Nephrol Dial Transplant* 2014; **29**: 2251-2259 [PMID: 25034755 DOI: 10.1093/ndt/gfu239]

10 **Brown CM**, Scheven L, O'Kelly P, Dorman AM, Walshe JJ. Renal histology in the elderly: indications and outcomes. *J Nephrol* 2012; **25**: 240-244 [PMID: 21725922 DOI: 10.5301/JN.2011.8447]

11 **Moutzouris DA**, Herlitz L, Appel GB, Markowitz GS, Freudenthal B, Radhakrishnan J, D'Agati VD. Renal biopsy in the very elderly. *Clin J Am Soc Nephrol* 2009; **4**: 1073-1082 [PMID: 19443626 DOI: 10.2215/CJN.00990209]

12 **Rollino C**, Ferro M, Beltrame G, Quattrocchio G, Massara C, Quarello F, Roccatello D. Renal biopsy in patients over 75: 131 cases. *Clin Nephrol* 2014; **82**: 225-230 [PMID: 25161113 DOI: 10.5414/CN108258]

13 **Omokawa A**, Komatsuda A, Nara M, Fujiwara T, Sato R, Togashi M, Okuyama S, Sawada K, Wakui H. Renal biopsy in patients aged 80 years and older: a single-center experience in Japan. *Clin Nephrol* 2012; **77**: 461-467 [PMID: 22595388 DOI: 10.5414/CN107368]

14 **Nair R**, Bell JM, Walker PD. Renal biopsy in patients aged 80 years and older. *Am J Kidney Dis* 2004; **44**: 618-626 [PMID: 15384012 DOI: 10.1053/j.ajkd.2004.05.044]

15 **Verde E**, Quiroga B, Rivera F, López-Gómez JM. Renal biopsy in very elderly patients: data from the Spanish Registry of Glomerulonephritis. *Am J Nephrol* 2012; **35**: 230-237 [PMID: 22343659 DOI: 10.1159/000336307]

16 **Parrish AE**. Complications of percutaneous renal biopsy: a review of 37 years' experience. *Clin Nephrol* 1992; **38**: 135-141 [PMID: 1395165]

17 **Whittier WL**, Korbet SM. Timing of complications in percutaneous renal biopsy. *J Am Soc Nephrol* 2004; **15**: 142-147 [PMID: 14694166 DOI: 10.1097/01.ASN.0000102472.37947.14]

18 **Yoon HE**, Shin MJ, Kim YS, Choi BS, Kim BS, Choi YJ, Kim YO, Yoon SA, Kim YS, Yang CW. Clinical impact of renal biopsy on outcomes in elderly patients with nephrotic syndrome. *Nephron Clin Pract* 2011; **117**: c20-c27 [PMID: 20689321 DOI: 10.1159/000319643]

19 **Abrass CK**. Treatment of membranous nephropathy in the elderly. *Semin Nephrol* 2003; **23**: 373-378 [PMID: 12923725 DOI: 10.1016/S0270-9295(03)00053-6]

20 **Cameron JS**. Nephrotic syndrome in the elderly. *Semin Nephrol* 1996; **16**: 319-329 [PMID: 8829270]

21 **Rule AD**, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, Textor SC, Stegall MD. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010; **152**: 561-567 [PMID: 20439574 DOI: 10.7326/0003-4819-152-9-201005040-00006]

22 **Tavares MB**, Chagas de Almeida Mda C, Martins RT, de Sousa AC, Martinelli R, dos-Santos WL. Acute tubular necrosis and renal failure in patients with glomerular disease. *Ren Fail* 2012; **34**:

1252-1257 [PMID: 23002699 DOI: 10.3109/0886022X.2012.723582]
23 **Mangoni AA**, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6-14 [PMID: 14678335 DOI: 10.1046/j.1365-2125.2003.02007.x]
24 **Shi S**, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab* 2011; **12**: 601-610 [PMID: 21495970 DOI: 10.2174/138920011796504527]
25 **Petrovichev NN**. [Change in the mitotic activity of hepatocytes and resorption of necrotic areas in the formation of liver cirrhosis]. *Biull Eksp Biol Med* 1976; **81**: 617-618 [PMID: 181102 DOI: 10.1111/j.1440-1797.2007.00890.x]
26 **International Society of Nephrology.** KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl* 2012; **2**: 142 [DOI: 10.1038/kisup.2012.12]
27 **Lee T**, Biddle AK, Lionaki S, Derebail VK, Barbour SJ, Tannous S, Hladunewich MA, Hu Y, Poulton CJ, Mahoney SL, Charles Jennette J, Hogan SL, Falk RJ, Cattran DC, Reich HN, Nachman PH. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. *Kidney Int* 2014; **85**: 1412-1420 [PMID: 24336031 DOI: 10.1038/ki.2013.476]
28 **Galla JH**. IgA nephropathy. *Kidney Int* 1995; **47**: 377-387 [PMID: 7723227 DOI: 10.1038/ki.1995.50]
29 **Donadio JV**, Grande JP. IgA nephropathy. *N Engl J Med* 2002; **347**: 738-748 [PMID: 12213946 DOI: 10.1056/NEJMra020109]
30 **Smith JD**, Hayslett JP. Reversible renal failure in the nephrotic syndrome. *Am J Kidney Dis* 1992; **19**: 201-213 [PMID: 1553965 DOI: 10.1016/S0272-6386(13)80001-7]
31 **O'Callaghan CA**, Hicks J, Doll H, Sacks SH, Cameron JS. Characteristics and outcome of membranous nephropathy in older patients. *Int Urol Nephrol* 2002; **33**: 157-165 [PMID: 12090324 DOI: 10.1023/A: 1014404006045]
32 **Yamaguchi M**, Ando M, Yamamoto R, Akiyama S, Kato S, Katsuno T, Kosugi T, Sato W, Tsuboi N, Yasuda Y, Mizuno M, Ito Y, Matsuo S, Maruyama S. Patient age and the prognosis of idiopathic membranous nephropathy. *PLoS One* 2014; **9**: e110376 [PMID: 25330372 DOI: 10.1371/journal.pone.0110376]
33 **Lefaucheur C**, Stengel B, Nochy D, Martel P, Hill GS, Jacquot C, Rossert J. Membranous nephropathy and cancer: Epidemiologic evidence and determinants of high-risk cancer association. *Kidney Int* 2006; **70**: 1510-1517 [PMID: 16941021 DOI: 10.1038/sj.ki.5001790]
34 **Beck LH**. Membranous nephropathy and malignancy. *Semin Nephrol* 2010; **30**: 635-644 [PMID: 21146128 DOI: 10.1016/j.semnephrol.2010.09.011]
35 **Beck LH**, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361**: 11-21 [PMID: 19571279 DOI: 10.1056/NEJMoa0810457]
36 **Larsen CP**, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. *Mod Pathol* 2013; **26**: 709-715 [PMID: 23196797 DOI: 10.1038/modpathol.2012.207]
37 **Timmermans SA**, Ayalon R, van Paassen P, Beck LH, van Rie H, Wirtz JJ, Verseput GH, Frenken LA, Salant DJ, Cohen Tervaert JW. Anti-phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. *Am J Kidney Dis* 2013; **62**: 1223-1225 [PMID: 24021909 DOI: 10.1053/j.ajkd.2013.07.019]
38 **Bjørneklett R**, Vikse BE, Svarstad E, Aasarød K, Bostad L, Langmark F, Iversen BM. Long-term risk of cancer in membranous nephropathy patients. *Am J Kidney Dis* 2007; **50**: 396-403 [PMID: 17720518 DOI: 10.1053/j.ajkd.2007.06.003]
39 **Beck LH,** Salant DJ. Causes and diagnosis of membranous nephropathy. In: UpToDate. Glassock RJ, Fervenza FC, editors. Waltham, MA: UpToDate. Available from: URL: http://www.uptodate.com/contents/causes-and-diagnosis-of-membranous-nephropathy
40 **Radford MG**, Holley KE, Grande JP, Larson TS, Wagoner RD, Donadio JV, McCarthy JT. Reversible membranous nephropathy associated with the use of nonsteroidal anti-inflammatory drugs. *JAMA* 1996; **276**: 466-469 [PMID: 8691554 DOI: 10.1001/jama.1996.03540060042033]
41 **Mihovilovic K**, Ljubanovic D, Knotek M. Safe administration of celecoxib to a patient with repeated episodes of nephrotic syndrome induced by NSAIDs. *Clin Drug Investig* 2011; **31**: 351-355 [PMID: 21271751 DOI: 10.2165/11586340-000000000-00000]
42 **Zent R**, Nagai R, Cattran DC. Idiopathic membranous nephropathy in the elderly: a comparative study. *Am J Kidney Dis* 1997; **29**: 200-206 [PMID: 9016890 DOI: 10.1016/S0272-6386(97)90030-5]
43 **Passerini P**, Como G, Viganò E, Melis P, Pozzi C, Altieri P, Ponticelli C. Idiopathic membranous nephropathy in the elderly. *Nephrol Dial Transplant* 1993; **8**: 1321-1325 [PMID: 8159299]
44 **Ponticelli C**, Zucchelli P, Passerini P, Cagnoli L, Cesana B, Pozzi C, Pasquali S, Imbasciati E, Grassi C, Redaelli B. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1989; **320**: 8-13 [PMID: 2642605 DOI: 10.1056/NEJM198901053200102]
45 **Ito T**, Mochizuki K, Oka T, Hanada K, Tanabe K. Study of mizoribine therapy in elderly patients with membranous nephropathy: comparison with patients not receiving mizoribine. *Int Urol Nephrol* 2015; **47**: 131-135 [PMID: 25298141]
46 **Haas M**, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. *Am J Kidney Dis* 2000; **35**: 433-447 [PMID: 10692269 DOI: 10.1016/S0272-6386(00)70196-X]
47 **Waldman M**, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, D'Agati V, Appel G. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2007; **2**: 445-453 [PMID: 17699450 DOI: 10.2215/CJN.03531006]
48 **Nakayama M**, Katafuchi R, Yanase T, Ikeda K, Tanaka H, Fujimi S. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. *Am J Kidney Dis* 2002; **39**: 503-512 [PMID: 11877569 DOI: 10.1053/ajkd.2002.31400]
49 **Chun MJ**, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. *J Am Soc Nephrol* 2004; **15**: 2169-2177 [PMID: 15284302 DOI: 10.1097/01.ASN.0000135051.62500.97]
50 **Thomas DB**, Franceschini N, Hogan SL, Ten Holder S, Jennette CE, Falk RJ, Jennette JC. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006; **69**: 920-926 [PMID: 16518352 DOI: 10.1038/sj.ki.5000160]
51 **Chitalia VC**, Wells JE, Robson RA, Searle M, Lynn KL. Predicting renal survival in primary focal glomerulosclerosis from the time of presentation. *Kidney Int* 1999; **56**: 2236-2242 [PMID: 10594800 DOI: 10.1038/sj.ki.4491164]
52 **Markowitz GS**, Nasr SH, Stokes MB, D'Agati VD. Treatment with IFN-{alpha}, -{beta}, or -{gamma} is associated with collapsing focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; **5**: 607-615 [PMID: 20203164 DOI: 10.2215/CJN.07311009]
53 **Markowitz GS**, Appel GB, Fine PL, Fenves AZ, Loon NR, Jagannath S, Kuhn JA, Dratch AD, D'Agati VD. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* 2001; **12**: 1164-1172 [PMID: 11373339]
54 **Kyle RA**, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, Orlowski RZ, Roodman DG, Twilde P, Anderson K. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2007; **25**: 2464-2472 [PMID: 17515569 DOI: 10.1200/JCO.2007.12.1269]
55 **Wen YK**, Chen ML. Differences in new-onset IgA nephropathy between young adults and the elderly. *Ren Fail* 2010; **32**: 343-348 [PMID: 20370450 DOI: 10.3109/08860221003611687]
56 **Duan ZY**, Cai GY, Chen YZ, Liang S, Liu SW, Wu J, Qiu Q, Lin SP, Zhang XG, Chen XM. Aging promotes progression of IgA nephropathy: a systematic review and meta-analysis. *Am J Nephrol* 2013; **38**: 241-252 [PMID: 24021632 DOI: 10.1159/000354646]
57 **Oshima Y**, Moriyama T, Itabashi M, Takei T, Nitta K. Characteristics

of IgA nephropathy in advanced-age patients. *Int Urol Nephrol* 2015; **47**: 137-145 [PMID: 25388352]

58 **Sethi S**, Zand L, Leung N, Smith RJ, Jevremonic D, Herrmann SS, Fervenza FC. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol* 2010; **5**: 770-782 [PMID: 20185597 DOI: 10.2215/CJN.06760909]

59 **Johnson RJ**, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Corey L, Wener MH, Alpers CE. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 1993; **328**: 465-470 [PMID: 7678440 DOI: 10.1056/NEJM199302183280703]

60 **Jones G**, Juszczak M, Kingdon E, Harber M, Sweny P, Burns A. Treatment of idiopathic membranoproliferative glomerulonephritis with mycophenolate mofetil and steroids. *Nephrol Dial Transplant* 2004; **19**: 3160-3164 [PMID: 15479745 DOI: 10.1093/ndt/gfh526]

61 **Abrass CK.** Glomerular Disease in the Elderly. In: Online Geriatric Nephrology Curriculum. Chicago: American Society of Nephrology, 2009. Available form: URL: https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter10.pdf

62 **Watts RA**, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000; **43**: 414-419 [PMID: 10693883 DOI: 10.1002/1529-0131(200002)43: 2<414: : AID-ANR23>3.0.CO; 2-0]

63 **Ponticelli C,** Passerini P, Cresseri D. Primary glomerular diseases in the elderly. *Geriatr Nephrol Urol* 1996; **6**: 105-112 [DOI: 10.1007/BF00451114]

64 **Cui Z**, Zhao J, Jia XY, Zhu SN, Zhao MH. Clinical features and outcomes of anti-glomerular basement membrane disease in older patients. *Am J Kidney Dis* 2011; **57**: 575-582 [PMID: 21168945 DOI: 10.1053/j.ajkd.2010.09.022]

65 **Chen M**, Yu F, Zhang Y, Zhao MH. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. *Medicine* (Baltimore) 2008; **87**: 203-209 [PMID: 18626303 DOI: 10.1097/MD.0b013e31817c744b]

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