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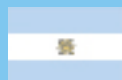
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MINIREVIEWS

- 16 Pediatric lupus nephritis: Management update
Sinha R, Raut S

Contents

World Journal of Nephrology
Volume 3 Number 2 May 6, 2014

APPENDIX I-V Instructions to authors

ABOUT COVER *World Journal of Nephrology* Editorial Board, Rajiv Sinha, MD, Assistant Professor, FRCPCH (UK), Institute of Child Health, Kolkata, India

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World Journal of Nephrology (*World J Nephrol*, *WJN*, online ISSN 2220-6124, DOI: 10.5527) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJN covers topics concerning kidney development, renal regeneration, kidney tumors, therapy of renal disease, hemodialysis, peritoneal dialysis, kidney transplantation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of nephrology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Pediatric lupus nephritis: Management update

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Abstract

Childhood-onset systemic lupus erythematosus (cSLE) is a severe multisystem autoimmune disease. Renal involvement occurs in the majority of cSLE patients and is often fatal. Renal biopsy is an important investigation in the management of lupus nephritis. Treatment of renal lupus consists of an induction phase and maintenance phase. Treatment of childhood lupus nephritis using steroids is associated with poor outcome and excess side-effects. The addition of cyclophosphamide to the treatment schedule has improved disease control. In view of treatment failure using these drugs and a tendency for non-adherence, many newer agents such as immune-modulators and monoclonal antibodies are being tried in patients with cSLE. Trials of these novel agents in the pediatric population are still lacking making a consensus in the management protocol of pediatric lupus nephritis difficult.

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Key words: Pediatric; Lupus nephritis; Management; Monoclonal antibody; Cyclophosphamide; Mycophenolate mofetil

Core tip: Childhood-onset systemic lupus erythematosus (cSLE) is a rare but severe autoimmune disease with multisystem involvement. Renal disease occurs in 50% to 75% of all cSLE patients and is a major cause of increased morbidity and mortality. Originally SLE nephritis was treated with steroids with a poor outcome which improved markedly with the introduction of cyclophosphamide, but at the cost of increased side effects which resulted in a further search for a less toxic, but equally effective regime. Here we discuss some newer drugs including immune-modulators and monoclonal antibodies in addition to azathioprine and mycophenolate mofetil, however, most of the evidence on these medications is restricted to adult literature and pediatric data are extrapolated from these trials.

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INTRODUCTION

Epidemiology

Childhood-onset systemic lupus erythematosus (cSLE) is a rare but severe autoimmune disease with multisystem involvement, the incidence is 0.3/100000-0.9/100000 children-per year with a prevalence of 3.3/100000-8.8/100000 children^[1]. A higher frequency of cSLE is reported in Asians, African Americans, Hispanics, and native Americans^[2]. Median age of onset of cSLE is between 11 and 12 years (rare below 5 years), and 80% of patients are female^[3]. cSLE follows a more severe disease course than adult-onset SLE, with higher morbidity and lower survival rates^[4].

Diagnosis of cSLE

Four out of 11 American College of Rheumatology (ACR) criteria have a sensitivity and specificity greater than 95% for the diagnosis of cSLE. These criteria are as follows: malar rash, discoid rash, photosensitivity rash, oral or nasopharyngeal ulceration, nonerosive arthritis,

Table 1 International society of nephrology/renal pathology society 2003 classification of lupus nephritis^[11,12]

Class	Name	Light microscopy	Immunofluorescence
I	Minimal mesangial LN	Normal	Mesangial immune deposits
II	Mesangial proliferative LN	Mesangial hypercellularity or mesangial matrix expansion	Mesangial immune deposits
III	Focal LN	Segmental, or global glomerulonephritis (< 50% of glomeruli)	Diffuse subendothelial immune deposits
IV	Diffuse LN	Segmental, or global glomerulonephritis LN (> 50% glomeruli)	Diffuse subendothelial immune deposits
	A		
	A/C		
V	Membranous LN	LN (> 90% globally Sclerosed glomeruli without residual activity)	Global or segmental subepithelial immune deposits
	A		
	A/C		
VI	Advanced sclerosing LN		

Class V may occur in combination with class III or IV, in which case both will be diagnosed. LN: Lupus nephritis.

serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and antinuclear antibody^[5]. Although still not widely used, the newer systemic lupus international collaborating clinics (SLICC) criteria have been introduced for the classification of SLE^[6]. According to the SLICC rule for the classification of SLE, the patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunologic criterion OR the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded DNA antibodies.

Renal involvement

Renal disease occurs in 50% to 75% of all cSLE patients, mostly within the first 2 years after diagnosis^[7]. Lupus nephritis (LN) is more common in males and in non-White populations^[8,9]. Initial manifestations of renal disease range from minimal proteinuria and microscopic hematuria to nephrotic-range proteinuria, urinary casts, severe hypertension, peripheral edema, and renal insufficiency or acute renal failure. SLE most commonly affects the glomerulus (*i.e.*, lupus nephritis), but can also involve the renal interstitium. It can also present with features of thrombotic microangiopathy including both atypical hemolytic uremic syndrome as well as thrombotic thrombocytopenic purpura.

CASE DEFINITION FOR LN

As per the ACR criteria, LN is defined as: persistent proteinuria *i.e.*, 0.5 g per day [a spot urine protein/creatinine ratio of 0.5 can be substituted] or greater than 3+ by dipstick; and/or cellular casts including red blood cells (RBCs), granular, tubular, or mixed^[10]. An additional, perhaps optimal, criterion is a renal biopsy sample demonstrating immune complex-mediated glomerulonephritis compatible with LN^[11]. As the severity of the nephritis may not correlate with the severity of the clinical signs and symptoms, a renal biopsy should be performed for any suspicion of glomerulonephritis, including persistent mild proteinuria.

INDICATIONS FOR RENAL BIOPSY IN PATIENTS WITH CSLE^[12]

Increased serum creatinine without compelling alternative causes, such as sepsis, hypovolemia, or medication.

Confirmed proteinuria of 1.0 g per 24 h (either 24-h urine specimens or spot protein/creatinine ratios are acceptable).

Combinations of the following, assuming the findings are confirmed in at least 2 tests performed within a short period of time and in the absence of alternative causes: (1) Proteinuria: 0.5 g per 24 h plus hematuria, defined as 5 RBCs per hpf; and (2) Proteinuria: 0.5 g per 24 h plus cellular casts.

Renal biopsy should be reported as per the International Society of Nephrology/Renal Pathology classification (Table 1). Recent modifications of the activity and chronicity index not only help in acute management, but also help in prognostication.

TREATMENT

Originally SLE nephritis was treated by steroids with a poor outcome which improved markedly with the introduction of cyclophosphamide. The first controlled trial reporting the short-term efficacy of cyclophosphamide for lupus nephritis in adults was published in 1971^[13]. Initially this combination was advocated for a prolonged period, but unfortunately the improved outcome was found to be associated with long-term side effects, which resulted in a further search for a less toxic, but equally effective regime. Most of the studies have been performed in adults and to a large extent the current recommendations are borrowed heavily from adult studies. The current therapeutic strategy for SLE nephritis distinguishes two distinct phases of treatment. The first phase is INDUCTION therapy which aims to control disease activity by inducing remission of disease flare (which may be the initial presentation or represent a new flare). It is at this point that potential organ-threatening and/or life-

threatening disease needs to be aggressively treated. The second phase is MAINTENANCE, wherein the target is to avoid relapses and control the disease by limiting inflammation and damage.

Class I / II LN are milder and generally do not require immunosuppressive treatment, whereas class III / IV needs to be treated aggressively^[14]. Research studies over the last decade have shown increasing evidence of the efficacy of mycophenolate mofetil (MMF)/azathioprine (AZA) with a better side effect profile as compared to cyclophosphamide (CyC). Despite this, as shown by the recently conducted consensus meeting of pediatric rheumatologists and nephrologists in North America, the majority still prefer CyC as the induction agent^[15]. Most of the studies on the use of MMF in children have only been case series. The largest series included 31 children or young people who were treated with MMF (either initially or switched from AZA) and showed that 73% had a good response without any recorded major side-effects^[16]. Among the multiple adult studies, the first comparative study on MMF compared with CyC was published in Hong Kong in 2000^[17]. MMF and CyC showed similar rates of improvement and of complete remission, 81% and 76%, respectively. Patients experienced fewer side-effects with MMF treatment. Subsequently Contreras *et al*^[18], studied 59 adults with lupus nephritis who were initially treated with 4-7 mo infusions of CyC and then randomized to quarterly infusions of CyC or oral MMF or AZA. Patients treated with AZA or MMF showed fewer flares than those treated with CyC, six, three, and eight flares, respectively. Patients treated with MMF experienced fewer side-effects than those treated with CyC except for an increased risk of gastrointestinal symptoms and diarrhea with MMF. To date, the biggest study, the aspreva lupus management study (ALMS) attempted to determine the efficacy of MMF as an induction agent for LN. The study included 370 patients with class III through V lupus nephritis^[19] and consisted of one 24-wk induction phase and thereafter a 3-year maintenance phase. The results did not show any difference between the percentages of patients responding to treatment (56.2% in the MMF group, and 53.0% in the CyC group). There was also no significant difference in the rate of side-effects and a tendency for more severe adverse events in the MMF group ($P = 0.07$). In a sub-analysis of the ALMS, Isenberg *et al*^[20] showed that response varied with race, in that Black and Hispanic patients responded better to MMF (60.4%) compared to CyC (38.5%), $P = 0.03$. In a recently published meta-analysis, Touma *et al*^[21] looked at the cumulative evidence for MMF/CyC as induction treatment. Four trials with 668 patients were included and no difference in clinical efficacy was found between the two drugs. MMF did, however, show significantly less alopecia (RR = 5.77; 95%CI: 1.56-21.38), but other side-effects were not significantly different. Researchers have also studied patients with class V nephritis (*i.e.*, a membranous pattern on kidney biopsy) and found no differences between the MMF and CyC-treated groups^[22]. Based on these studies, the ACR has published their recommendation on

SLE nephritis, albeit targeted primarily towards the adult population.

ACR recommendation

As per the ACR recent recommendation for class III/IV LN, MMF and glucocorticoids (GC) can be used as induction agents for African-American and Hispanic patients, whereas CyC and GC remain the first choice for White populations. MMF and GC are agents of choice in isolated class V LN^[10]. In mixed cases such as class V with III or IV LN, the treatment should be similar to that for class III/IV LN. Other induction modalities that can be tried in refractory cases include intravenous immunoglobulin, plasma exchange and B-lymphocyte depletion agents such as Rituximab^[23,24] (Figures 1 and 2).

The ACR recommends either MMF or AZA and low dose steroid for the maintenance phase. MMF has been shown to be statistically better than AZA in terms of time to treatment failure (a composite including death, end stage renal disease, doubling of serum creatinine, and renal flare)^[25].

In patients who fail to respond after 6 mo of treatment with GC plus MMF or CyC, the ACR recommend a switch of immunosuppressive agent from either CyC to MMF or from MMF to CyC, and these changes are accompanied by IV pulses of GCs.

Adherence

Non-adherence to immunosuppressive agents can be common in the adolescent age group^[14], resulting in relapse of symptoms and sometimes an acute presentation with renal failure after initial successful treatment. Intravenous agents, such as CyC or rituximab can be considered in this situation, to ensure adherence and disease control.

RECENT ADVANCES IN SLE MEDICATIONS

Despite advances in treatment, mortality related to SLE nephritis has been static over the last decade and morbidity continues to be a major factor. Hence, there is a strong need for more effective drugs with, if possible, fewer side-effects. Studies are particularly required in children, as due to a lack of pediatric studies drugs trialed on adults are still been tried in children with severe lupus nephritis. We will discuss some of the newer medicines, however, most of the evidence on these medications is restricted to adult literature.

Rituximab

Rituximab, a chimeric antibody targeting CD20-positive cells, was first used by Tullus^[26] in 2000 in a girl with class V lupus nephritis and therapy-resistant nephrotic syndrome. The therapeutic response was remarkable and her proteinuria improved so much that her serum albumin normalized. Many other clinicians have had similar clinical experiences and several case series have published positive results^[14,27]. Unfortunately the first randomized

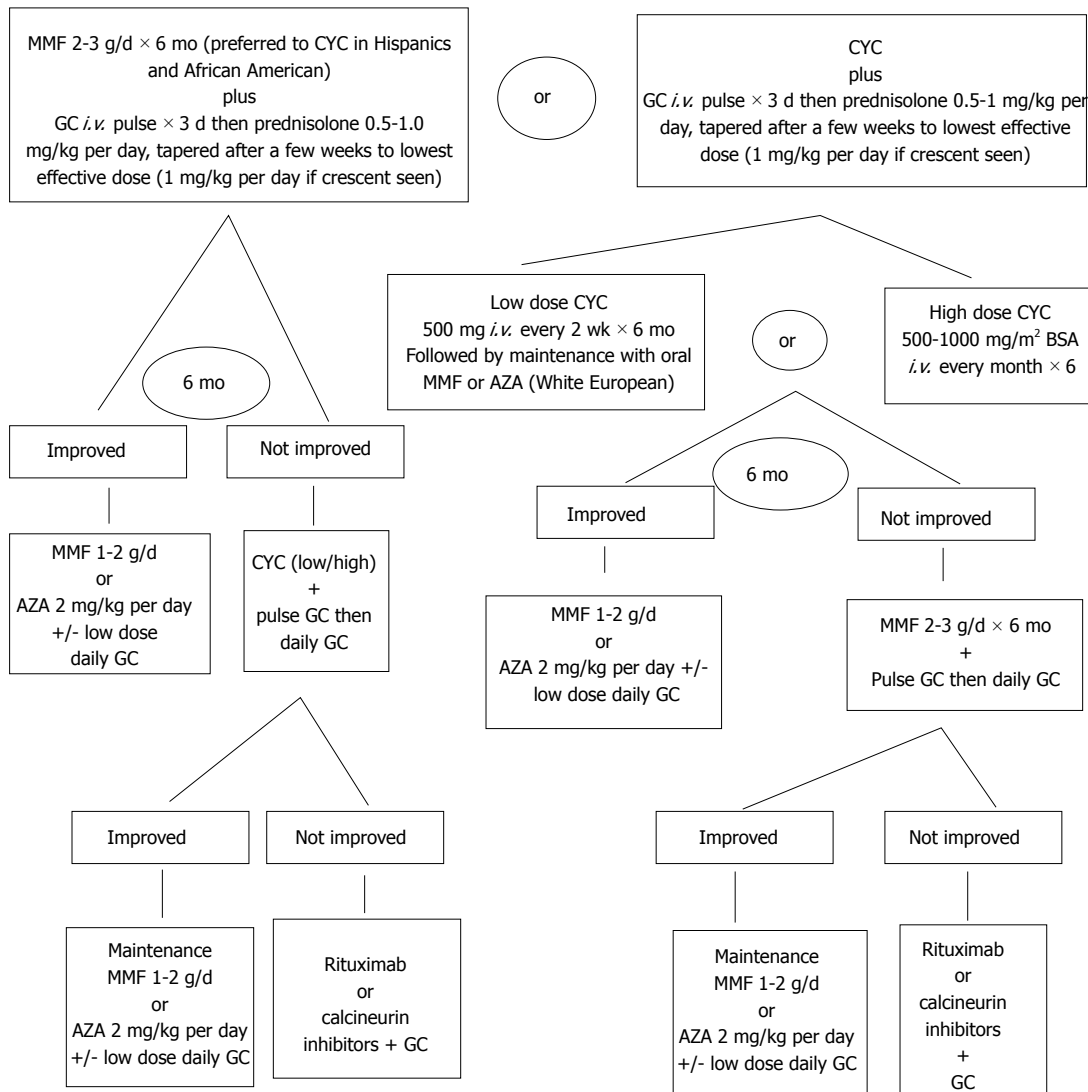


Figure 1 Class III/IV lupus nephritis induction therapy. MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; GC: Glucocorticoids; iv: Intravenous; AZA: Azathioprine; BSA: Body surface area.

controlled trial, EXPLORER, which included 237 patients with moderate to severe extra-renal lupus did not find any difference between rituximab and placebo^[28]. Another large randomized placebo-controlled study on rituximab, the LUNAR trial^[29], which included 144 patients with class III or IV lupus nephritis showed that only 30.6% of the patients in the placebo group and 25.4% of the rituximab-treated patient fulfilled the criteria for a complete response. Greater improvements in complement levels ($P = 0.025$) and antibodies to dsDNA ($P = 0.007$) were recorded in the rituximab group compared to the placebo group^[30].

Belimumab

Belimumab is a fully humanized monoclonal antibody that binds to soluble B-lymphocyte stimulator (BLyS) and acts as a specific inhibitor of its biological activity. BLyS, also known as B-cell activating factor (BAFF) is an immunomodulatory cytokine that promotes B-cell survival, B-cell differentiation, and immunoglobulin class switch-

ing. A phase III randomized double-blind placebo controlled study showed significant benefit, but to date, there is not enough data to recommend its use in children with lupus nephritis^[31].

Ocrelizumab

Ocrelizumab is a fully humanized antibody that targets CD20-positive B cells. It is a “next-generation rituximab” and the potential problem of human anti-chimeric antibody development is hopefully ameliorated. The BELONG study, 2010 was set up to study the efficacy of ocrelizumab in 381 patients with lupus nephritis^[32] and the results are awaited.

Epratuzumab

Epratuzumab is a monoclonal antibody against CD22, another B-cell-specific surface antigen. Early open data in a few patients have shown positive results^[33]. A study involving 227 patients found that a dose of 600 mg weekly was associated with greater british isles lupus activity

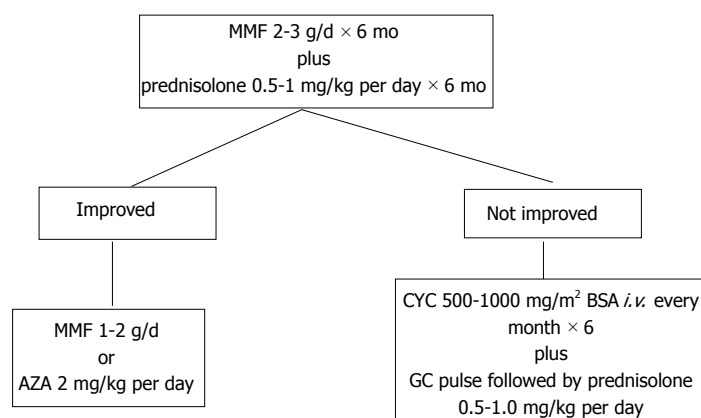


Figure 2 Treatment of class V without proliferative changes and with nephrotic range proteinuria (> 3 g/24 h). MMF: Mycophenolate mofetil; AZA: Azathioprine; CYC: Cyclophosphamide; GC: Glucocorticoids.

Table 2 Monitoring schedule for systemic lupus erythematosus nephritis^[10]

Stage of disease	Blood pressure	Urinalysis	Protein/creatinine ratio	Serum creatinine	C3/C4 level	Anti-DNA
Active nephritis at onset of treatment	1	1	1	1	2	3
Previous active nephritis, none currently	3	3	3	3	3	6
No prior or current nephritis	3	6	6	6	6	6

grading improvement^[34].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor. In a phase I study of 16 patients with mild to moderate lupus, tocilizumab was found to be well tolerated, significantly reducing plasma cells and dsDNA suggesting a good clinical response^[35]. Further studies seem warranted.

Abetimus

Abetimus is an immunomodulating agent designed to induce tolerance in B cells directed against dsDNA and to reduce anti-dsDNA levels. It is a synthetic molecule consisting of four double-stranded oligodeoxyribonucleotides attached to non-immunogenic polyethylene glycol. Abetimus works through the formation and clearance of drug antibody complexes and by tolerating anti-dsDNA specific B cells. Cardiel *et al.*^[36], 2008 in a 22-mo study of 317 patients showed that abetimus failed to prolong time to flare compared to the placebo.

Atacicept

Atacicept is a receptor analogue that binds both BAFF and a proliferation-inducing ligand to related members of the tumor necrosis factor superfamily. A phase II study of atacicept showed a marked reduction in B cells and immunoglobulin levels and a short term side-effect profile similar to placebo^[37].

Rigeromid

Rigerimod is a spliceosomal peptide that is recognized by CD4⁺ T cells from patients with lupus, but not from those with other autoimmune diseases. In a 12-wk study, 150 patients with lupus and high SLE Disease Activity

Index scores (Safety of estrogens in lupus erythematosus national assessment) were given three infusions of two different doses of rigerimod or placebo followed by 12 wk of observation. The treatment seemed to be well tolerated and a statistically significant reduction in disease activity was recorded^[38]. Longer-term studies are needed.

Abatacept

Abatacept is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7 which selectively modulates the CD80/CD86:CD28 co-stimulatory signal. A recent 12-mo double-blind placebo-controlled study in 118 lupus patients failed to meet the primary end point of a reduction in new flares^[39]. Serious adverse events were higher in the abatacept group compared with the placebo group (20% *vs* 7%).

Infliximab

The use of infliximab in lupus has been surrounded with major worries. Long-term use of infliximab in lupus patients can cause severe side-effects, including severe infections and even cerebral lymphoma^[40].

ADJUNCTIVE TREATMENTS

The ACR recommended that all SLE patients with nephritis be treated with a background of hydroxychloroquine (HCQ), unless there is a contraindication^[11]. HCQ treatment may reduce the risk of renal damage and clotting events in SLE^[41-43]. Medications to control high blood pressure (anti-hypertensive), fluid overload (diuretics), proteinuria (angiotensin converting enzyme inhibitors), hypercoagulability (aspirin or other anticoagulants) and lipid control (statins)^[22,44,45] are mainstays of adjunctive

tive treatment. Dietary restriction may be necessary in terms of sodium, protein and calories. Unlike adults, these recommendations must be adjusted to take into account the growth and developmental status of the child. Infection is the most common cause of death in cSLE due to immune suppression^[46]. Infections can be difficult to differentiate from a flare of SLE disease activity. C-reactive protein monitoring can be useful as most SLE patients have normal levels, except during inter-current infections.

RECOMMENDED MONITORING OF LUPUS NEPHRITIS

SLE is a chronic disease with the possibility of frequent flare-ups. Hence, these children need to be followed up regularly (Table 2). Compliance can be a major issue and needs to be addressed during each clinic visit^[47].

CONCLUSION

In conclusion, the outcome of lupus nephritis is primarily dependent on histological classification at presentation. Early renal biopsy in all children with features of lupus nephritis to decide on induction therapy, aggressive treatment of hypertension and other adjunct therapy is recommended to improve mortality and morbidity of such patients.

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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Books

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Conference paper

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Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and position-

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