Vasculitis 17

James A. Listman and Scott J. Schurman

Contents

Core Messages

Vasculitis can present with a myriad of signs and symptoms, some of which are classic, but in many instances the presentation overlaps with other diseases (Table 17.1).

The rarity of vasculitis in conjunction with an incomplete presentation may delay diagnosis, potentially increasing morbidity, and mortality.

From a nephrological perspective, nephritis or hypertension typically leads to consultation.

Work-up can be broad and might include laboratory testing, imaging, and biopsy (Table 17.2).

Therapeutic options and aggressiveness are often dictated more by the severity of symptoms than the etiology of the disease:

- Pulse dose steroids should be considered up front as empiric therapy as long as there is reasonable certainty regarding the absence of malignancy or underlying infection.
- Patients with an immediately life-threatening presentation should also be considered for therapeutic plasma exchange, though its benefit is not always clear in all forms of vasculitis.
- Cytotoxic agents have a proven role in most forms of vasculitis.
- IVIG is less well studied (the exception being Kawasaki syndrome), but the literature is full of anecdotal successes with its use.
- Newer immunomodulatory agents are also undergoing evaluation.

The outlook for many contemporary pediatric cases is not as bleak as it once was, particularly if the diagnosis is made early.

Case Vignette

NR was a 9-year-old, previously healthy, girl, who presented with a seven-day history of vomiting, watery diarrhea, weight loss, fever, and lethargy. The gastrointestinal losses were nonbloody, but her urine was dark brown the prior 2 days and was reduced in volume. She also had a rash on her left leg described as the remnants of an infected bug bite she developed 3 weeks prior. This responded well to a 2 week course of antibiotics. She was not taking medications chronically, but she was using acetaminophen for the fever. There was no history of upper or lower respiratory tract problems.

On physical examination, she was pale and appeared moderately ill and dehydrated. She had a temperature of 39 °C, a blood pressure of 133/75 mmHg, and a pulse of 114 beats per minute. The remainder of the examination was only remarkable for a 3 cm red and slightly raised circular lesion on the left lower leg.

Initial laboratory investigations showed normal white blood cell (WBC) and platelet counts, but marked anemia with a hemoglobin of 6.4 g dl^{-1}. The blood smear showed fragmented red blood cells (RBCs) and large platelets. Serum BUN and creatinine

S.G. Kiessling et al. (eds) *Pediatric Nephrology in the ICU*.

Table 17.1 Differential diagnosis

- Menigiococcal infection
- Malignancy
- Endocarditis
- SLE
- HSP
- Postinfectious GN
- Systemic polyangiitis (Wegener granulomatosis, microscopic polyangitis, polyarteritis nodosa)
- Renal vein thrombosis with pulmonary embolism
- Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura
- Goodpasture syndrome
- Chronic hepatitis B infection/pneumococcal infection/HIV
- Infiltrative diseases (sarcoidosis, histiocytic proliferative diseases)
- Drug reactions (hypersensitivity angiitis)

Table 17.2 Diagnostic tools for the evaluation of vasculitis

- Blood cultures
- Erythrocyte sedimentation rate/C-reactive protein
- White blood cell count
- Blood smear
- C3, C4, ANA
- Lumbar puncture (CNS involvement)
- Chronic hepatitis/HIV serologies
- Bone marrow aspirate (particularly with FUO or before empiric treatment)
- ANCA
- Anti-glomerular beasement mmbrane antibody
- Renal Ultrasound (including Doppler of renal vessels and inferior vena cava)
- Echocardiogram
- CT/MRI of head (for patients with CNS involvement)
- CTA/MRA or angiogram (if PAN or Takyasu arteritis are suspected)
- Biopsy of diseased tissue

were 80 and 7.5 mg dl^{-1}, respectively, accompanied by mildly disturbed electrolytes. Urinalysis showed dark yellow urine with a specific gravity of 1.020, a pH of 5, 2 + protein, and 25–50 RBCs, 3–10 WBCs, and 0–2 granular casts per high-power field. Renal ultrasound showed enlarged and echogenic kidneys with pulsatile flow in the renal vessels. Chest X-ray was negative.

Blood samples were sent off for the determination of C3 and C4 complement concentrations and antinuclear and antineutrophil antibody titers (ANA, ANCA), and the patient was admitted for hydration, supportive care, and possible dialysis.

Normal complement levels and a negative ANA titer were found on the first hospital day, but the ANCA titer returned strongly positive at 1:2,560, leading to additional testing showing cytoplasmic staining on immunofluorescence (cANCA) and detecting high levels of anti-proteinase 3 (PR 3) antibodies, but no anti-myeloperoxidase (MPO) antibodies. The patient was immediately given pulse-dose steroids and underwent a renal biopsy, which showed 100% of her glomeruli to be globally necrotic on light microscopy. The immunofluorescence and electron microscopy showed no evidence of immune complex disease or linear staining of anti-GBM antibody.

A diagnosis of atypical Wegener's granulomatosis (WG) was made, and no further immunosuppression was used because her kidneys did not appear salvageable. She was placed on chronic kidney disease medications and prepared for renal replacement therapy. On hospital day 14, she developed dyspnea and fever, followed by hemoptysis and seizure activity, consistent with pulmonary and central nervous system vasculitis. Pulse steroids and cylcophosphamide as well as therapeutic plasma exchange with intermittent IVIG replacement were initiated, eventually leading to stabilization and allowing discharge to home on hospital day 50 on chronic dialysis.

After 6 months, the cyclophosphamide was discontinued and her steroids tapered to a low dose, based on absence of symptoms and AP3 antibody levels that were still slightly above normal but dramatically improved.

After 2 years on dialysis, she received a LRD kidney transplant using standard immunosuppression. The graft remains stable 4 years later, and there has had been no recurrence of her original disease.

17.1 Background

Vasculitic conditions with renal involvement are an anomaly in most pediatric ICU settings where the more common entities one encounters include complications of infection (sepsis and respiratory failure), trauma, or babies with postoperative congenital heart disease. Furthermore, many of the more common

forms of vasculitis that the pediatric nephrologist see, e.g., systemic lupus erythematosus (SLE) and Henoch-Schönlein purpura (HSP), will be diagnosed outside the ICU setting, while the more rare forms, e.g. Wegener's granulomatosis (WG), microscopic polyarteritis (MPA), and polyarteritis nodosa (PAN), will primarily be seen in the ICU, probably due to delayed diagnosis because of their rarity and lack of specific diagnostic testing. Pediatric nephrologists often possess unique insights into the management of these diverse diseases because they frequently involve the kidney, require uncommon diagnostic testing (by pediatric standards), and require immunosuppressant therapy. Unfortunately, our treatment plans are often more art than science, as there is a paucity of controlled data for what constitutes optimally effective treatment for many vasculitic diseases, particularly in the maintenance phase of therapy. Therefore, historical outcome data and anecdotal experience form the basis for most management strategies. Exceptions include the treatment of moderately active SLE and WG/MPA, where there exists solid data to support a treatment plan. Newer therapies directed at specific inflammatory mediators are currently undergoing evaluation. Most therapeutic strategies are derived from studies in adult subjects or patients; the exceptions being Kawasaki syndrome or Takyasu's arteritis. Notwithstanding its relative high frequency in the pediatric population, HSP nephritis still has no clear treatment strategy primarily because so many patients improve spontaneously, and the frequency of the more severely-involved patients preclude easy study.

The rapidity at which vasculitis is recognized generally depends on the patients presenting symptoms (Table 17.3). Constitutional symptoms are typically the first signs of more indolent disease, but multiple-organ involvement becomes more apparent with time. In our experience, a CNS presentation (for example seizure) due to hypertensive encephalopathy or microangiopathy oftentimes delays the diagnosis of vasculitis because the initial workup is often directed more toward infectious etiologies or CVA. Furthermore, use of benzodiazepine anticonvulsants and sedatives may obscure significantly elevated blood pressure that might clue the clinician in to renal involvement. Once the elevated blood pressure or hematuria comes to light, a more directed differential diagnosis ensues. In contrast, respiratory disease with hemoptysis and associated hematuria are usually sufficient enough to bring pulmonary/renal syndromes to mind immediately. Vasculitis should also be considered in the differential of a purpuric rash particularly if purpura fulminans is ruled out on clinical grounds. When vasculitis is considered in the differential, rapid diagnostic and therapeutic interventions are warranted and need to be prioritized accordingly. It almost goes without saying that once vasculitis is seriously considered in the differential diagnosis of a critical ill child, high dose corticosteroid therapy should not be withheld as there is minimal

Table 17.3 Signs and symptoms of vasculitis

Feature	Entity	Comment
Fever, chills, night sweats	All	Frequent
Malaise	All	Frequent
Weight loss	All	Weight gain if nephrotic
Myalgias	All	Frequent
Arthralgia/arthritis	Collagen vascular disease, HSP, Wegener's	
CNS (seizure, mental states change)	Potentially all except Bechet's and Kawasaki	Primary CNS involvement or hypertensive
Hypertension	Most syndromes	May present with seizure or CVA
Hematuria	Many (immune complex diseaswes, nectrotizing lesions of smaller vessels)	Less likely in large vessel disease
Dyspnea	Systemic necrotizing vasculitis	Common
Rash	All (includes papules, purpura, nodules, livedo reticularis, necrosis, and Reynaud's)	Classic distributions in immune complex diseases like SLE and HSP
Upper respiratory tract	Systemic necrotizing vasculitis	Common
Eyes	Kawasaki's, Wegener's, and Bechet's syndromes	Common

complications associated its short-term use, and there is sufficient historical evidence that corticosteroid therapy dramatically improves the survival of patients with life-threatening secondary or idiopathic vasculitis. In some instances, it may prove useful to seek assistance from our adult nephrology colleagues who may have considerable more experience with "adult" forms of vasculitis. Bone marrow aspiration for histology and culturing is prudent in patients in whom one is less decisive in declaring a primary diagnosis before using high dose steroids or cytotoxic agents.

17.2 Pathogenesis and Classification

The pathogenesis of vasculitis remains uncertain and controversial. Virtually all components of the immune response are implicated in the pathogenesis of vasculitis. The process probably begins with endothelial activation via induction of adhesion molecules and consequent attachment and transmigration of leukocytes, culminating in the release of proteases and cytotoxic substances [31]. The specific inciting events remain obscure, although several mechanisms have been proposed: Deposition of immune complexes in HSP, superantigen in Kawasaki syndrome, defects in cell-mediated cytotoxicity in PAN, and anti-endothelial antibodies (not to be confused with ANCA) in virtually all forms of vasculitis, including WG [1, 17, 21, 23, 66, 72]. Unfortunately, it remains a nontrivial task to detect anti-endothelial antibodies making their pathogenic relevance in some forms of vasculitis uncertain. SLE can cause vascular injury by a few mechanisms, including immune complex deposition, causing glomerulonephritis (GN) or a rash, or anti-endothelial cell antibodies (e.g., antiphospholipid antibodies) that can cause thrombosis of small or medium-sized vessels. Therapeutic plasma exchange would appear to lend itself well to processes that involve circulating factors, although, the utility of this approach is not uniformly apparent in these diseases.

One of the major hurdles for clinicians remains concise definitions of vasculitic conditions, particularly of the idiopathic variety. Strictly speaking, vasculitis describes and inflammatory lesion of blood vessels. Neutrophil infiltration with necrosis (leukocytoclastic reaction), immune complex deposition, and granuloma formation are some of the more common characteristic findings. Vasculitis may occur as just one manifestation of a more complex disease state (collagen vascular disease or chronic infections like Hepatitis B) or is the defining characteristic of the disease. The secondary forms are generally easier to diagnose because of the availability of sensitive and specific tests. Idiopathic forms of vasculitis may be more difficult to diagnose because of the lack of specific serologic testing. This problem is best illustrated by the pediatric experience with Kawasaki disease in infants who often have a more atypical presentation and are diagnosed at autopsy after succumbing to a catastrophic event. Other examples include clinical situations where disease manifestations are more indolent or develop sequentially over time. HSP, on the other hand, is often easily diagnosed on clinical grounds alone, as are ANCA-associated conditions in the right clinical context.

The most accepted stratifications subdivide vasculitis first by vessel size with further subdivision based upon histologic criteria. Diagnostic tests such as ANCA have previously not been used in the standard classifications, but their diagnostic value is well recognized in the literature. Until recently, classification relied upon criteria set forth in adults only. However, in 2005, several international pediatric organizations with an interest in vasculitic diseases convened for the purpose of establishing a pediatric-specific classification (Table 17.4) [65]. This classification borrows from the standard Chapel Hill criteria that rely upon vessel size to stratify the idiopathic forms of disease, which might fail to detect many patients with idiopathic vasculitis [75]. The main differences are the inclusion of phenotypes encountered primarily in children such as Kawasaki syndrome and the exclusion of those that are extremely rare or never seen in childhood [12]. The classification also includes secondary forms of vasculitis. Furthermore, this group took advantage of newer radiographic and serologic techniques to assist with development of diagnostic criteria for many of the idiopathic forms of vasculitis. Prospective studies to validate these criteria are ongoing.

Hopefully, with time, the pediatric classification will gain acceptance and help categorize patients in a standardized way that will assist future therapeutic trials. Of course, such stratifications do not necessarily shed insight into the pathogenesis of these syndromes. In fact, some argue that stratifying vasculitic diseases has minimal value in terms of treatment because of the considerable overlap in many patients' phenotypes and treatment regimens. Nevertheless, this classification, representing an uniform scheme to support the study

Table 17.4 New classification of childhood vasculitis

	Renal involvement
I Predominantly large vessel vasculitis	
Takayasu arteritis	Yes
II Predominantly medium-sized vessel vasculitis	
› Childhood polyarteritis nodosa	Yes
› Cutaneous polyarteritis	
› Kawasaki disease	Rare
III Predominantly small vessels vasculitis	
(A) Granulomatous	
› Wegener's granulomatosis	Yes
› Churg-Strauss syndrome	
(B) Nongranulomatous	
› Microscopic polyangiitis	Yes
› Henoch- Schönlein purpura	Yes
› Isolated cutaneous leucocytoclastic vasculitis	
› Hypocomplementic urticarial vasculitis	
IV Other vasculitides	
› Behcet disease	
› Vasculitis secondary to infections (including hepatitis B-associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis	Yes
› Vasculitis associated with connective tissue diseases	Yes
› Isolated vasculitis of the central nervous system	
› Cogan syndrome	
› Unclassified	Yes

of these rare disease, is the basis for the more detailed outline presented below of those idiopathic varieties of vasculitis that are likely to include renal involvement.

17.3 Clincopathologic Correlates

17.3.1 Henoch-Schönlein Purpura

HSP is an idiopathic systemic immune complex disease, primarily of the immunoglobulin A (IgA) class, that occurs uncommonly in childhood and even more rarely in adults [71]. It is well described in any general textbook of Pediatrics and Medicine. The most defining and required feature for the diagnosis of HSP is its rash, a palpable purpura generally present in the lower extremities. HSP is generally not a diagnostic dilemma if the classic tetrad of abdominal pain, arthritis/arthralgia, purpuric rash (confined to buttocks and legs), and nephritis are present (Table 17.5). On many occasions, however, there is limited expression of the disease or staggering of symptoms, resulting in a delayed diagnosis. For example, orchitis is a common but sometimes underappreciated complication in male patients. In contrast, fulminant, and potentially lethal, presentations are also possible, e.g., acute abdomen, CNS vasculitis, or pul-

Table 17.5 Classification criteria for Henoch-Schönlein purpura

Palpable purpura (mandatory criterion) in the presence of at least one of the following four features:
› Diffuse abdominal pain
› Any biopsy showing predominant IgA deposition
› Arthritis[a] or arthralgia
› Renal involvement (any haematuria and/or proteinuria)

[a] Acute, any joint

monary hemorrhage. The differential diagnosis includes other forms of vasculitis such as SLE, necrotizing vasculitis, hypersensitivity angiitis, and infection, in particular with pneumoccous. In difficult cases, biopsy of the skin lesions can be diagnostic and shows a leukocytoclastic reaction in small vessel walls staining positive for IgA deposits on immunofluorescence. When HSP afflicts the kidney, the findings mimic the full spectrum of those found in IgA nephropathy.

Despite the risk for severe organ involvement, the reality is that for most patients, HSP follows a relatively benign course, particularly for those with no or minimal renal involvement. However, it is this renal involvement that causes the most morbidity and worry for parents and clinicians [56]. 1.4% of pediatric renal transplants in North America over the past 20 years are done because of end-stage renal disease (ESRD) caused by HSP, and this rate is similar in Europe. Other pediatric patients with HSP are left with a chronic glomerulonephritis (GN) essentially identical to IgA nephropathy and, accordingly, an uncertain fate into adulthood. There is a smaller subset of patients that presents with a rapidly progressive GN, which may well require admission to the ICU, or chronic and relapsing GN that places the nephrologist at a crossroads because there is a paucity of data to guide when or how to treat such patients – all in the face of success treating other vasculitic diseases of the kidney (e.g., SLE or WG) with aggressive immunosuppresion.

Evidence of nephritis can be found in 20–50% of children with HSP [77]. There is no correlation between the severity of nonrenal symptoms and the risk of nephritis, and most patients who develop nephritis do so within one month of presentation, although exceptions abound [49, 55, 68, 83]. The most common renal manifestation is microscopic hematuria with or without nonnephrotic proteinuria. Fortunately, most patients with these findings remit spontaneously over the course of several weeks to months [68, 77]. Approximately, one-third of patients with renal involvement will have evidence of a more active nephritis heralded by gross hematuria, hypertension, edema, and/or renal failure. Patients with severe nephrotic syndrome or renal failure are predictably at greatest risk for progression. Their GN may be rapidly or more slowly progressive, with the latter frequently associated with relapsing disease. Other patients may seemingly completely recover. Defining the risk for progression in any individual patient is complicated by epidemiologic data that are mired by center effect. For example, in a series of 275 hospitalized children with HSP reported by Stewart et al., 20% had any renal manifestation, but only 18% of these had true GN or nephrotic syndrome, and only 1 of 10 patients in this category developed ESRD [77]. This low risk contrasts with the findings of many older case series that generally include only those patients who present with significant renal manifestations and were referred specifically because of their renal involvement (reviewed in [55]). For example, in the classic series of Habib et al., more than half of patients who presented with severe nephrotic syndrome (defined as serum total protein less than 5 mg dl^{-1}) or renal failure (defined as serum creatinine greater than 2 mg dl^{-1} or glomerular filtration rate less than 50% of normal) developed terminal renal failure, despite treatment attempts in at least some of these patients [48]. It is not clear how many of the patients in the Stewart series met the threshold for severe nephrotic syndrome or renal failure because serum protein or severity of azotemia at presentation were not mentioned, but it was probably a very small fraction. The low number of severe cases in the Stewart series also derives from the population base of only 155,000 vs most, if not all, of France for the Habib series.

Renal biopsy may be valuable for prognostication in selected cases. Patients with minor urine abnormalities do not require biopsy because, historically, they recover, and most would show only mesangial proliferation. The findings become more varied with the more advanced cases. Besides mesangial proliferation, one sees variable degrees of endocapillary involvement that may be focal and segmental or diffusely proliferative. This distinction probably has minimal significance as the more worrisome findings are the degree of necrosis and extracapillary crescent formation present. If greater than 50% of glomeruli have crescents, there is an associated 20–50% risk of ESRD within months to several years of presentation [49, 79]. The rate of complete recovery is low, and most patients have residual renal manifestations. This risk of ESRD falls to 5–10% if less than 50% of glomeruli feature crescents. Patients with greater than 80% crescents almost uniformly progress to ESRD, at least if untreated [48]. Thus, biopsy can help coarsely predict a patient's risk for progression or recovery. However, there is a cautionary note here for those with chronic urinary findings and even for those who seemingly completely recover with normal renal function and urinalysis. Two long-term studies have shown that a significant proportion of patients with persistent abnormalities

progress to some degree of chronic kidney disease (CKD) or ESRD, and even a minority of patients who completely recover showed progression later on in life, with pregnancy being a particularly notable risk factor for this progression [29, 69]. These authors found that neither clinical nor histologic severity could predict with certainty an individual patient's outcome. They hypothesize that patients who had early complete remission probably sustained significant early nephron loss when younger, followed by chronic hyperfiltration injury with time and growth. Therefore, long-term monitoring for recurrence of proteinuria or hypertension seems prudent for such patients, particularly in women planning a pregnancy.

For the majority of patients, HSP is, as mentioned earlier, a self-limiting disease that waxes and wanes over a few weeks to months. GI complaints and joint pain respond well to brief courses of corticosteroid therapy. However, treatment of HSP nephritis remains controversial because some patients with very active disease spontaneously improve over many months to years. Therefore, each case demands an individualized approach weighing the benefits and risks of treatment. Studies of HSP nephritis treatment fall into two categories: (1) those that treat with corticosteroid therapy at diagnosis of HSP with the goal of preventing nephritis; (2) those that treat after nephritis is diagnosed (generally treating those with the more severe presentations). Previously, most studies concluded that steroid treatment at onset of HSP had no impact on development of renal disease but was beneficial for symptomatic relief of abdominal and joint pain. However, these studies generally used only short courses of therapy (1–2 weeks) and most were probably underpowered. A more recent placebo-controlled study of 171 patients using one month of steroid therapy (starting at $1\,mg/kda^{-1}\ day^{-1}$) showed no difference in risk of developing nephritis compared with placebo, but the severity was less and improved more quickly in the steroid-treated group [68]. The results were particularly striking for subjects over 6 years of age. The treated patients also showed significant improvement in nonrenal manifestations. The risks associated with this relatively modest dosing of steroid therapy were no different than the placebo-treated group. These results suggest that higher risk patients (those over age 6 in this trial) might benefit from such an approach. The main caveat is that if treatment is initiated, it should be for longer duration then many typically use.

When renal disease manifests as nephritic/nephrotic syndromes, biopsy may assist with decisions about treatment, particularly if crescentic GN is present. The rationale to treat is derived historically from the earlier successes using immunosuppression for other vasculitic diseases and is colored by the experience in larger centers were several patients with more severe renal manifestations had progressed to terminal renal failure before dialysis was a viable option [49]. To date, there is only one controlled trial of 56 subjects comparing supportive therapy with treatment using a single agent, oral cyclophosphamide for 42 days, done by the International Study of Kidney Diseases in Children (ISKDC) [79]. This trial showed no benefit of therapy. However, this study, in our view, suffers from small numbers of patients in the highest risk group for progression (≥50% crescents) and, of these most had exactly 50% crescents. Other nonrandomized trials using other strategies suggest a benefit, but also suffer from small patient numbers and the use of historical controls. These include use of various combinations of oral cytotoxic agents with or without steroids [48], pulse-dose steroids followed by oral steroids for several months [60], and pulse steroids followed by daily steroids and daily cyclophosphamide [63]. However, it is hard to ignore these particular data because disease severity in these studies is rather high compared with the ISKDC study, and results compare favorably to historical controls. Figure 17.1 aims to assist with the interpretation of these data, stratified by study, treatment status, and percentage of crescents. One point of clarification here is that the treated and untreated subjects from the ISKDC study are combined in this figure because there was no trend for improvement with treatment. Therefore, the results from this study may serve as historical control for the other studies. The outcomes include complete recovery, partial response (criteria vary by study), and ESRD, and are shown as raw numbers. The one clear message from these data is that patients with less than 50% crescents showed no benefit from treatment regardless of approach. This is because most patients fully recover spontaneously and the risk of ESRD is probably under 10%. Therefore, large numbers of patients would need to be treated to show any potential benefit of therapy in patients with less than 50% crescents. These data become more complex for subjects with ≥50% crescents. Starting with the Levy study, most untreated patients died from terminal renal failure. That trend changed when treatment (mostly chlorambucil and/or steroids) was used, with approximately one-half of the treated patients apparently recovering fully.

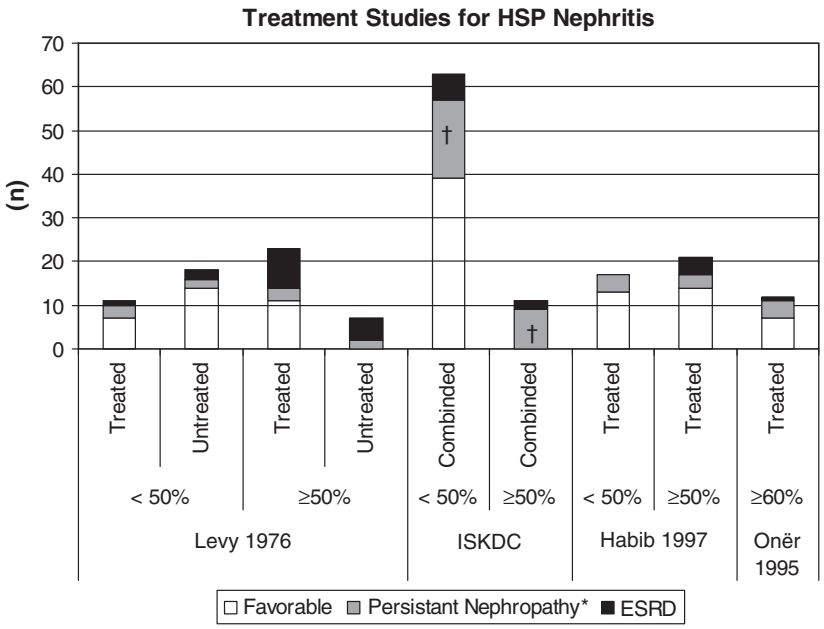

Fig. 17.1 Compilation of outcome data from four studies using various therapies for severe HSP nephritis. The studies stratify patients by the indicated percentage of crescents at presentation. The study details are as follows: Levy et al. (1976) reports retrospective outcomes of treated patients compared with historical controls. Most patients were treated with chlorambucil with or without steroids; The ISKDC study is the only controlled trial comparing oral cyclophosphamide to no treatment (results are combined because no difference was found in outcomes between groups); Habib (1997) used pulse-dose steroids and oral steroids and compared with historic controls; Onër used more aggressive therapy with pulse steroids (3 doses), daily cyclophosphamide (for 2 months) and daily maintainance steroids (for 3 months). *Criteria for persistent nephropathy vary between studies. Levy's definition uses proteinuria 0.5 g day^{-1} +/- microsopic hematuria. The ISKDC definition was, more broadly, any urinary abnormalities and included subjects with CKD. Habib's definition was proteinuria >20 mg; kg^{-1} day^{-1} with normal or mild GFR reduction (50–75 ml min^{-1} 1.73 m^{-2}). Onër's definition was any proteinuria. † In the ISKDC study, persistent nephropathy was further segregated: In the group with <50% crescents, most patients had minimal clinical renal findings, while most in the 50% group had heavy proteinuria or CKD. Therefore, these subjects are comparatively more severely affected than the comparable group in the Levy study

The parallel control (combined) group from the ISKDC study had no patient with greater than 50% crescents go on to full recovery, 1/3 of them progressing to ESRD, and most of the remaining having CKD, e.g., at least heavy proteinuria. Although the rate of ESRD was lower in the ISKDC study compared with the untreated patients from the Levy study, it should be recalled that the distribution of histologic severity in the ISCKD study was weighted toward 50% crescents, while the Levy study had more dispersion in this regard. Thus, this difference would portend a better prognosis in the ISKDC study group. Despite this skewing, the treated patients in this category of the Levy study still did better than the ISKDC controls. Habib's 1997 study also shows a favorably outcome when using pulse dose steroids, followed by daily oral steroids (a few patients with ≥80% crescents also received oral cyclophosphamide), with a significant fraction fully recovering. Onër's 1995 study shows even more promise when using more aggressive immunosuppression, including pulse steroids, daily steroids, and daily cyclophosphamide. This was a small study, but disease severity was very high (≥60% crescents), and nearly all patients fully recovered. Even two patients with persistent findings were early in their course and showed a trend toward improvement. The only patient who developed ESRD was lost to follow-up for a time. Finally, plasmapheresis may also be of benefit for patients with severe HSP nephritis [34]. A high proportion (6/9) of patients in this study had complete or nearly complete recovery (normal renal function and normal urinalysis or microhematuria only) following treatment with therapeutic plasma exchange, despite all patients presenting with renal failure, nephrotic syndrome, and most with greater than 50% crescents – historically a group expected to likely have CKD or ESRD. Thus, and while these data are not definitive, there remains a suggestion that treatment is beneficial and perhaps the intensity of immunosuppression or absence

of steroid therapy might explain the lack of treatment effect in the ISKDC study.

Despite the uncertainty of the data above, there is room for reason when approaching a patient with HSP nephritis. Certainly, a patient with significant nephrosis but a non-crescentic lesion might benefit from some form of steroid therapy if for nothing else but to hasten recovery. The associated risk of several weeks of steroid use is minimal. Alternatively, one could resort to an angiotensin-converting enzyme inhibitor and diruetics for control of edema while observing clinical trends before intervening with immunosuppression. Those patients with significant or worsening azotemia and ≥50% nonsclerotic crescentic lesions on biopsy are considered by many as candidates for more aggressive therapy with steroids and cytotoxic agents, and one wonders if mycophenolate mofetil could work as well as cyclophosphamide. The rare patient with more immediately life-threatening disease (i.e., pulmonary hemorrhage or CNS involvement) may also benefit from therapeutic plasma exchange [10, 84].

17.3.2 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a relatively common disease affecting serosal surfaces, vessel walls, and bone marrow elements. Because these structures exist throughout the body, SLE can present with any number of signs and symptoms. Fortunately, many children (usually adolescent girls) with SLE will present with classic features beginning with the non-healing sunburn of the face with butterfly distribution and eventual onset of malaise and arthritis. Patients with more advanced disease will develop GN with or without nephrotic syndrome. Occasionally, and especially in African-Americans and male patients, SLE may present more dramatically with seizures (either from hypertension or CNS vasculitis), pulmonary hemorrhage, or heart failure from pericarditis. Males in particular may rarely even present only with nephritis and thus not fit the classic diagnostic criteria for SLE, even though a biopsy demonstrates *sine que non* features of lupus nephritis (see below). Because of this heterogeneity, any sick patient presenting with hematuria or, more generally, as a diagnostic dilemma should have a complement C3 level and ANA titers performed as part of their work-up.

The histopathology of SLE nephritis is well documented elsewhere [1, 17, 49, 67]. Most children with evidence of nephritis have either diffuse proliferative GN (World Health Organization class IV) or focal proiferative GN (class III) with immune complexes staining positive for IgG, IgA, C3, C1q, and fibrin ("full house"). Prognosis is poor if untreated and, historically, was improved with liberal use of steroids [13, 76, 78]. However, a significant fraction of patients were still likely to progress to ESRD without the addition of a second immunosuppressant [4]. Induction therapy with pulse steroids followed by oral steroids and pulse Cyclophosphamide given as six monthly IV doses followed by quarterly infusions for a total of 2 years became the standard of care in the late 1980s after the landmark studies from the NIH [3, 7]. To shorten exposure to cyclophosphamide therapy, some advocated abbreviated courses of pulse cyclophosphamide to be replaced by oral azothiaprine or mycophenolate mofetil. Indeed, treatment of SLE nephritis has been revolutionized after more recent controlled trials comparing mycophenolate mofetil to intravenous cyclophosphamide for the induction of remission and the prolongation of renal survival reported equal or superior outcomes with the former [27, 38, 64]. The incidence of side effects was also reduced with mycophenolate mofetil, whose dose may need to be increased to 3 g daily for optimal effect in adults. Mycophenolate mofetil, like calcineurin inhibitors and anti-CD20 monoclonal antibodies, can also serve to salvage patients who fail to adequately respond to standard induction therapy [9, 14, 28, 57, 74, 82].

Most patients will show resolution of systemic symptoms over days or weeks following the start of induction therapy. The serologic markers of disease, including C3 or antidoublestranded DNA will then start to normalize followed by a gradual improvement in the signs of nephritis or nephrotic syndrome with less active urinary sediment, reduction in proteinruia, and increase in serum albumin if the patient was nephrotic. ACE inhibitors and antihypertensives are often required. During this window, the steroids will be tapered. If progress slows or reverses during the steroid taper, one can either increase the dose of the cytotoxic agent or add a salvage drug. The basal level of immunosuppression needed to prevent flares is often individualized, based on the patient's response. Daily low dose prednisone historically was a staple and still may be suitable for patients who presented with less disease activity or who responded quickly to induction therapy. However, compliance is at times a challenge for these patients who are often adolescents, particularly during the transition to independence. Furthermore, a significant proportion of children with

SLE nephritis will experience flares. Vigilance is critical to pick up relapses early. If mild and the inciting cause is known and corrected, a short boost in steroid therapy (1–2 weeks) is generally sufficient to reverse the flare. A common example is a stable patient on maintenance therapy from the Northern latitudes who experience arthralgias, rash, and mildly reduced C3 after a spring break trip to Florida. If the GN flares spontaneously, pulse dose steroids (orally or intravenous), followed by an increase in daily maintenance dosing, is helpful but indicates that the patient will require an increase in basal immunosuppression to maintain remission. In this situation, the addition of one of a calcineurin inhibitor, azathioprine or mycophenolate mofetil should be considered. High risk patients, including African-Americans, males, or those who required salvage therapy, should remain on mycophenolate mofetil, azothioprine, or cyclosporine and may be tapered to alternate day low-dose corticosteroid therapy [11, 58, 62]. The role of therapeutic plasma exchange in SLE GN was addressed in one controlled trial that showed no improvement when pheresis was added to standard therapy with corticosteroids and pulse cyclophosphamide [50]. Other smaller studies have shown more rapid remission of nephritis, but no difference in long-term outcome.

Patients with immediately life-threatening disease involving multiple organs including the CNS should be treated with pulse dose steroids and cyclophosphamide. There may be justification for therapeutic plasma exchange or IVIG to immediately lower the levels of circulating autoantibodies or block low affinity Fc receptors, respectively. If pheresis is entertained, the timing in relation to cyclophosphamide dosing may be critical, based on small trials [15, 16]. Anti-CD20 antibody to reduce numbers of circulating B cells may also be beneficial. One series reports rapid response to therapy in ten patients with CNS manifestations, a group with significant morbidity [81]. Anti-CD20 antibody is currently being investigated for the treatment of SLE GN. Finally, bone marrow transplant has been used with varying degrees of success in patients with severe and unremitting disease [2].

17.3.3 Wegener Granulomatosis and Microscopic Polyangiitis

Wegener granulomatosis (WG) is a vasculitis affecting a broad range of vessels including small to medium-sized arteries, venules, arterioles, and occasionally large arteries [36]. The classic defining feature is the presence of granuloma formation in the larger vessels. The disease tends to start in the respiratory tract (both upper and lower) where it can cause a variety of symptoms including sinusitis, chronic rhinitis (complicated by saddle nose deformity), chronic otitis media, dyspnea, and most notably pulmonary hemorrhage. Constitutional symptoms are common. WG will then classically spread to the kidney and cause RPGN, but it can also affect a number of other organs, including the joints, skin, eyes, and brain. Microscopic polyangiitis (MPA) shares many common clinical features with WG but the pathology is confined to only smaller vessels. MPA usually presents in the reverse order of WG by starting in the kidney and then spreading to the lung or other organs. Many patients present with limited disease to the kidney only (pauci-immune crescentic GN). Both WG and MPA are associated with a positive ANCA, which is typically negative in PAN or other forms of vasculitis. The distinguishing characteristics of MPA are its predilection for small vessels (arterioles, capillaries, and venules), absence of granulomas, and a different pattern of ANCA staining. A positive cANCA test is found in up to 90% or more of adult WG patients [22], and a pANCA is found in most cases of MPA/pauci-immune crescentic GN [61]. In fact, a positive ANCA test is now included as one diagnostic criterion for WG in the pediatric schema shown in Table 17.6. Generally, however, patients with WG or MPA are frequently still lumped together in many clinical trials, cementing the relationship between the two diseases.

WG and MPA are extremely rare in children. Review of cases from one large children's hospital showed that a majority of patients presented with constitutional symptoms and overt pulmonary-renal syndrome (dyspnea and/or hemaptysis with

Table 17.6 Classification criteria for Wegener's granulomatosis

Three of the following six features should be present:
› Abnormal urinalysis[a]
› Granulomatous inflammation on biopsy[b]
› Nasal sinus inflammation
› Subglottic, tracheal, or endobronchial stenosis
› Abnormal chest X ray or CT
› PR3 ANCA or C-ANCA staining

[a] Haematuria and/or significant proteinuria
[b] If a kidney biopsy is done it characteristically shows necrotizing pauciimmune glomerulonephritis

RPGN) [41]. Younger patients are also more likely to develop subglottic stenosis [70]. Adults, in contrast, tend not to develop constitutional symptoms or glomerulonephritis until later in their course [17]. Therefore, it may be easier to diagnosis WG in a pediatric patient. The histopathology shows microvascular necrosis and granulomatous changes in the larger vessels of involved tissues of the respiratory tract. However, renal pathology usually does not show granulomatosis changes, making kidney tissue less useful for diagnostic purposes compared with lung or upper airway biopsy. Renal histology generally shows segmental or global necrotizing lesions of the glomerulus and/or cresentic lesions, similar to what one sees with MPA. Thus, if multiple organs are involved, it is advisable to biopsy nonrenal tissues to confirm the diagnosis of WG. Of course, if readily available, the pattern of ANCA staining can also resolve diagnostics uncertainties. Importantly, immunofluoresent staining will not reveal antibasement membrane Ig deposits in a linear pattern characteristic of Goodpasture syndrome or stain for granular deposits of IgG, IgA, C3, Clq, and fibrin characteristic of SLE GN.

Historically, WG was associated with nearly 100% mortality within a few months of diagnosis [17, 55]. That changed dramatically after uncontrolled studies showed remarkable improvement in survival with use of corticosteroid therapy [36]. Later uncontrolled trials showed even better outcomes with the combination of steroids and cyclophosphamide [18, 19, 36]. Both IV (500–1,000 mg/M2 monthly) and oral cyclophosphamide (2 mg kg^{-1} daily) have been used, and there was anecdotal evidence that oral therapy is more effective [30]. However, the European Vasculitis Study Group (EUVAS) recently completed a controlled trial comparing the two approaches and it appears that there was no difference in outcomes (personnel communication with Dr. Caroline Savage). Furthermore, the IV route probably has less toxicity associated with it [44, 52]. Azothiaprine or methotrexate may also be safely substituted for cyclophosphamide after achieving remission to reduce the risk of toxicity [42, 45]. Patients with severe renal dysfunction also appear to have better outcomes when several courses of therapeutic plasma exchange are used [42]. The typical patient will be treated with cyclophosphamide for 6 months with the dose adjusted to prevent neutropenia (a particular problem in patients with renal failure). This is accompanied by pulse-dose steroids followed by a tapering oral dose. With life-threatening disease, therapeutic plasma exchange has been reported to be beneficial. Another promising option is the use of mycophenolate mofetil, which was shown in a single center study to have a significantly higher rate of remission compared with cyclophosphamide after 6 months of therapy [37]. The maintenance phase of therapy will include a less toxic cytotoxic agent and low dose corticosteroid therapy. The duration of therapy will be on the order of years for more severe cases of ANCA positive disease. Adults with WG can be successfully weaned from therapy after five years of remission and relatively low ANCA levels [46]. Numerous options are available for salvage therapy or for the treatment of relapsing disease, including IVIG, anti-thymocyte globulin, anti-CD20 antibody, mycophenolate mofetil, high-dose azothioprine, and infliximab [5, 6, 8, 35, 43, 44, 54, 73, 80]. A thorough set of guidelines was recently published by experts in the field from Great Britain and is as a useful clinical tool as of this writing [46].

17.3.4 Polyarteritis Nodosa

PAN is a necrotizing vasculitis of small to medium-sized muscular arteries and adjacent veins [17, 49, 67]. Often insidious at onset, disease activity is segmental and can occur at the bifurcation of vessels in any organ. Histopathology shows fibrinoid necrosis of the entire vessel wall, possibly resulting in aneurysms or vascular occlusion. Constitutional symptoms occur frequently on presentation, and muscle and bone aches as well as rashes are common features. Erythematous and painful nodules in the extremities are characteristic, but livedo reticularis, purpura, and gangrene can also occur. Abdominal pain or an acute abdomen is also frequent. Renovascular hypertension may be the initial presentation, with minimal findings on UA because of only larger vessel involvement, and has historically been a leading cause of death [17, 49, 55]. Mono or polyneuropathy are classic findings, particularly in association with hypertension. CNS symptoms are also relatively common, and pulmonary hemorrhage is possible. Finally, myocardial infarction may be recognized, usually after the patient succumbs. As with most idiopathic vasculitides, there is no diagnostic test specific for PAN. Possible laboratory findings include elevated erythrocyte sedimentation rate, elevated serum immunoglobulin concentrations, and, not infrequently, leukocytosis with eosinophilia. The latter can help distinguish PAN from other necrotizing vasculitides. The diagnosis is confirmed either by biopsy

Table 17.7 Classification criteria for childhood polyarteritis nodosa

A systemic illness characterized by the presence of either a biopsy showing small and mid-size artery necrotising vasculitis OR angiographic abnormalities[a] (aneurysms or occlusions) (mandatory criteria), plus at least two of the following:

- Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions)
- Myalgia or muscle tenderness
- Systemic hypertension, relative to childhood normative data
- Mononeuropathy or polyneuropathy
- Abnormal urine analysis and/or impaired renal function[b]
- Testicular pain or tenderness
- Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system)

[a] Should include conventional angiography if magnetic resonance angiography is negative

[b] Glomerular filtration rate of less than 50% normal for age

or more easily with angiography showing the classic aneurysms in the involved organs. MRA angiography is now a suitable substitute to standard angiography for making the diagnosis and is included in the new pediatric classification of PAN (Table 17. 7). PAN can also be secondary to collagen vascular disease, hairy cell leukemia, and chronic hepatitis B infection. Therefore, evidence of these conditions should be sought.

The prognosis of untreated PAN is grim, with most patients dying from myocardial infarction, hypertensive encephalopathy, or renal failure. Five-year survival untreated is only 13%, but treatment has improved this rate to 80% [24, 26]. Steroids are effective in about one half of patients, and addition of a cytoxic agent provides further therapeutic benefit [47]. Therefore, general recommendations are to use corticosteroid therapy initially only for patients with mild disease (constitutional symptoms +/− skin involvement). For children, we recommend 2 mg kg^{-1} day^{-1} of steroids up to 60–80 mg for at least one month, followed by tapering determined by clinical and inflammatory biomarker response for a total duration of at least 6 months. Treatment of moderately severe disease with solid organ involvement should also include either oral or pulse cyclophosphamide (the latter probably being less toxic but also less convenient), using standard immunosuppressant dosing (oral 2 mg^{-1} kg^{-1} day^{-1} with a maximum of 100 mg daily or 500–1,000 mg m^{-2} intravenously every month) [25], titrating dosing to response and keeping absolute neutrophil counts above 1,500. These protocols are generally used for 6 months. Those patients who require prolonged therapy to retain remission may benefit from a switch to a less toxic agent, such as azothiaprine. Patients with immediately life-threatening disease with neurologic complications should also receive pulse dose steroids. Therapeutic plasma exchange has not shown to be effective when added to steroids alone or steroids plus cyclophosphamide in at least two controlled trials [32, 33], although there was a trend for improved survival in both studies, and the sample size may have resulted in a type 2 error. Therefore, in a critically ill patient, we still would consider therapeutic plasma exchange at least in the acute phase of the illness. Finally, newer immunomodulatory agents have been used anecdotally. Several reports have shown a positive outcome of therapy with tumor necrosis factor-alpha blockade in patients with chronic disease that failed to remit with steroid and cytotoxic therapy, including one pediatric patient [20]. Other options include interferon-alpha (particularly for hepatitis B-related PAN), intravenous immunoglobulin, and mycophenolate mofetil, although the efficacy of these agents is circumstantial at this writing.

17.3.5 Takayasu Arteritis

Takayasu arteritis (TA) is strictly a large vessel arteritis that typically involves the major branches of the aorta, especially those coming off the aortic arch. However, it can also affect the aorta's main branches at any level [39, 51], and it may be limited to only the descending thoracic or abdominal aorta in a minority of patients. In the later stages, the pulmonary artery can also be affected. The afflicted region will show mononuclear infiltrates in all layers, with more involved sections containing granulomas with giant cells and central necrosis [67]. Resulting fibrosis will lead to narrowing of the branch orifices (accounting for the past name of pulseless disease). TA tends to afflict younger females and is more prevalent in East Asian populations and South America, but is less frequent in North America. It usually begins with constitutional symptoms and body aches for weeks to months before more significant symptoms occur. Frequently, these will include visual disturbance (Takayasu retinopathy), focal neurologic deficits, claudication, and intestinal angina. Hypertension is common. Of note, blood pressure readings are often lower in the upper extremities compared with the lower extremities (termed reverse coarctation) because of occlusion of

Take-Home Pearls

- Order a C3 and ANA in any patient with nephritis (even in suspected cases of HSP).
- Order a renal ultrasound for the evaluation of hematuria even if you think you know the diagnosis.
- Consider vasculitis in any patient with nephritis and rash.
- Order an ANCA titer for patients presenting with significant renal dysfunction (and ask for rapid turn-around).
- You do not always need to wait for the biopsy before treating with pulse steroids when vasculitis is suspected. It will not obscure the histology and has minimal risks.
- Increase the dose of mycophenolate mofetil to 3 g day^{-1} for older SLE patients who do not seem to be responding.
- Remember antimicrobial prophylaxis for immunocompromised patients.
- Remain vigilant: follow the patients who have life-threatening vasculitis regularly even when they are quiescent during the maintenance phase of therapy.

the subclavian arteries. Historically, many patients die from heart failure or sudden death from cerebral vascular accidents or rupture of the aorta. Patients who survive the first few years could only do so with neurologic deficits. Survival depends on the severity of complications at diagnosis, age at onset, and duration of elevated sedimentation rate [40]. In the current era, diagnosis can be made by CT or MR angiography, which can show mural changes at the common aortic sites and, in the case of MRA, thickening of the vessel wall in early stages of the disease [59, 85]. Treatment with immunosuppression, surgery, and stents has dramatically influenced the outcome in affected individuals. There is no consensus for treatment of TA, but corticosteroids are a mainstay, with addition of cytotoxic agents in more severe cases [53]. Surgical intervention or stent placement is necessary in patients with renovascular hypertension or ischemic symptoms.

References

1. Adler SG, Cohen AH, Glassock RJ, Chapter 31: Secondary Glomerular Disease. In: B. M. Brenner (1996) The Kidney. W.B. Saunders Company
2. Alderuccio F, Siatskas C, Chan J, et al. (2006) Haematopoietic stem cell gene therapy to treat autoimmune disease. Curr Stem Cell Res Ther 1:279–87
3. Austin HA, 3rd, Klippel JH, Balow JE, et al. (1986) Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 314:614–19
4. Balow JE, Austin HA, III, Muenz LR, et al. (1984) Effect of treatment on the evolution of renal abnormalities in lupus nephritis. N Engl J Med 311:491–5
5. Benenson E, Fries JWU, Heilig B, et al. (2005) High-dose azathioprine pulse therapy as a new treatment option in patients with active Wegener's granulomatosis and lupus nephritis refractory or intolerant to cyclophosphamide. Clin Rheumatol 24:251
6. Booth A, Harper L, Hammad T, et al. (2004) Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 15:717–21
7. Boumpas DT, Austin HA, III, Vaughn EM, et al. (1992) Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 340:741–5
8. Brik R, Gepstein V, Shahar E, et al. (2007) Tumor necrosis factor blockade in the management of children with orphan diseases. Clin Rheumatol 26:1783–5
9. Carroll RP, Brown F, Kerr PG (2007) Anti-CD20 antibody treatment in refractory Class IV lupus nephritis. Nephrol Dial Transpl 22:291–3
10. Chen CL, Chiou YH, Wu CY, et al. (2000) Cerebral vasculitis in Henoch-Schonlein purpura: a case report with sequential magnetic resonance imaging changes and treated with plasmapheresis alone. Pediatr Nephrol 15:276–8
11. Contreras G, Tozman E, Nahar N, et al. (2005) Maintenance therapies for proliferative lupus nephritis: mycophenolate mofetil, azathioprine and intravenous cyclophosphamide. Lupus 14 Suppl 1:s33–s38
12. Dillon M, Ozen S (2006) A new international classification of childhood vasculitis. Pediatric Nephrology 21:1219
13. Donadio JV, Jr., Holley KE, Wagoner RD, et al. (1972) Treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. Ann Intern Med 77:829–35
14. Dooley MA, Cosio FG, Nachman PH, et al. (1999) Mycophenolate mofetil therapy in lupus nephritis: clinical observations. J Am Soc Nephrol 10:833–9
15. Euler HH, Schroeder JO, Harten P, et al. (1994) Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis Rheum 37: 1784–94
16. Euler HH, Schwab UM, Schroeder JO, et al. (1996) The Lupus Plasmapheresis Study Group: rationale and updated interim report. Artif Organs 20:356–9
17. Fauci AS, The Vasculitic Sydromes. In: A. S. Fauci, E. Braunwald, K. J. Isselbacher, J. D. Wilson, M. J.B., D. L. Kasper, S. L. Hauser and D. L. Longo (1998) Principles of Internal Medicine. McGraw-Hill, New York
18. Fauci AS, Haynes BF, Katz P, et al. (1983) Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 98:76–85
19. Fauci AS, Wolff SM (1973) Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine (Baltimore) 52:535–61
20. Feinstein J, Arroyo R (2005) Successful treatment of childhood onset refractory polyarteritis nodosa with tumor necrosis factor alpha blockade. J Clin Rheumatol 11:219–22

21. Finkielman JD, Lee AS, Hummel AM, et al. (2007) ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 120:643 e9–e14
22. Finkielman JD, Lee AS, Hummel AM, et al. (2007) ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 120:643.e9
23. Florey OJ, Johns M, Esho OO, et al. (2007) Antiendothelial cell antibodies mediate enhanced leukocyte adhesion to cytokine-activated endothelial cells through a novel mechanism requiring cooperation between Fc γ RIIa and CXCR1/2. Blood 109:3881–9
24. Frohnert PP, Sheps SG (1967) Long-term follow-up study of periarteritis nodosa. Am J Med 43:8–14
25. Gayraud M, Guillevin L, Cohen P, et al. (1997) Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. Br J Rheumatol 36:1290–7
26. Gayraud M, Guillevin L, le Toumelin P, et al. (2001) Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 44:666–75
27. Ginzler EM, Dooley MA, Aranow C, et al. (2005) Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 353:2219–28
28. Glicklich D, Acharya A (1998) Mycophenolate mofetil therapy for lupus nephritis refractory to intravenous cyclophosphamide. Am J Kidney Dis 32:318–22
29. Goldstein AR, White RHR, Akuse R, et al. (1992) Long-term follow-up of childhood Henoch-Schonlein nephritis. The Lancet 339:280
30. Guillevin L, Cordier JF, Lhote F, et al. (1997) A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 40:2187–98
31. Guillevin L, Dorner T (2007) Vasculitis: mechanisms involved and clinical manifestations. Arthritis Res Ther 9:S9
32. Guillevin L, Fain O, Lhote F, et al. (1992) Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. Arthritis Rheum 35:208–15
33. Guillevin L, Lhote F, Cohen P, et al. (1995) Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum 38:1638–45
34. Hattori M, Ito K, Konomoto T, et al. (1999) Plasmapheresis as the sole therapy for rapidly progressive Henoch-Schonlein purpura nephritis in children. Am J Kidney Dis 33:427–33
35. Hellmich B, Lamprecht P, Gross W (2006) Advances in the therapy of Wegener's granulomatosis. Curr Opin Rheumatol 18:25–32
36. Hoffman GS, Kerr GS, Leavitt RY, et al. (1992) Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 116:488–98
37. Hu W, Liu C, Xie H, et al. (2007) Mycophenolate mofetil versus cyclophosphamide for inducing remission of anca vasculitis with moderate renal involvement. Nephrol Dial Transplant: doi: 10.1093/ndt/gfm780
38. Hu W, Liu Z, Chen H, et al. (2002) Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chin Med J (Engl) 115:705–9
39. Ishikawa K (1978) Natural history and classification of occlusive thromboaortopathy (Takayasu's disease). Circulation 57:27–35
40. Ishikawa K, Maetani S (1994) Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. Circulation 90:1855–60
41. J. D. Akikusa, Schneider R, Harvey EA, Hebert D, Thorner PS, Laxer RM, Silverman ED (2007) Clinical features and outcome of pediatric Wegener's granulomatosis. Arthritis Care Res 57:837–844
42. Jayne D, Rasmussen N, Andrassy K, et al. (2003) A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44
43. Keogh KA, Ytterberg SR, Fervenza FC, et al. (2006) Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 173:180–187
44. Koldingsnes W, Gran JT, Omdal R, et al. (1998) Wegener's granulomatosis: long-term follow-up of patients treated with pulse cyclophosphamide. Br J Rheumatol 37:659–64
45. Langford C, Talar-Williams C, Barron K, et al. (1999) A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 42:2666–2673
46. Lapraik C, Watts R, Bacon P, et al. (2007) BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology 46:1615–16
47. Leib ES, Restivo C, Paulus HE (1979) Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. Am J Med 67:941–7
48. Levy M, Broyer M, Arsan A, et al. (1976) Anaphylactoid purpura nephritis in childhood: natural history and immunopathology. Adv Nephrol Necker Hosp 6:183–228
49. Levy M, Gagnadoux MF, Chapter 5: Glomerular Nephropathies in Systemic Disease. In: P. Royer, R. Habib, H. Mathieu and M. Broyer (1974) Pediatric Nephrology. W.B. Saunders Company
50. Lewis E, Hunsicker L, Lan S, et al. (1992) A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med 326:1373–1379
51. Lupi-Herrera E, Sanchez-Torres G, Marcushamer J, et al. (1977) Takayasu's arteritis. Clinical study of 107 cases. Am Heart J 93:94–103
52. M. Haubitz, et al. (1998) Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: A prospective, randomized study. Arthritis Rheum 41:1835–44

53. M. Vanoli, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, Schieppati A, Baldissera E, Bertolini G; Itaka Study Group. (2005) Takayasu's arteritis: a study of 104 Italian patients. Arthritis Care Res 53:100–7
54. Martinez V, Cohen P, Pagnoux C, et al. (2008) Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum 58:308–17
55. McLean R, Michael A, Fish A, et al., Chapter 25: Systemic Lupus Erytmatosus, Anaphylactoid Purpura and Vasculitis Syndromes. In: M. I. Rubin (1975) Pediatric Nephrology. The WIlliams and Wilkins Company, Baltimore
56. Meadow SR (1978) The prognosis of Henoch Schoenlein nephritis. Clin Nephrol 9:87–90
57. Mok CC, Tong KH, To CH, et al. (2005) Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study. Kidney Int 68:813–7
58. Moroni G, Doria A, Mosca M, et al. (2006) A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. Clin J Am Soc Nephrol 1:925–32
59. Nastri MV, Baptista LP, Baroni RH, et al. (2004) Gadolinium-enhanced three-dimensional MR angiography of Takayasu arteritis. Radiographics 24:773–86
60. Niaudet P, Habib R (1998) Methylprednisolone pulse therapy in the treatment of severe forms of Schonlein- Henoch purpura nephritis. Pediatr Nephrol 12:238–43
61. Niles JL, Pan GL, Collins AB, et al. (1991) Antigen-specific radioimmunoassays for anti-neutrophil cytoplasmic antibodies in the diagnosis of rapidly progressive glomerulonephritis. J Am Soc Nephrol 2:27–36
62. Ogawa H, Kameda H, Nagasawa H, et al. (2007) Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. Mod Rheumatol 17:92–7
63. Oner A, Tinaztepe K, Erdogan O (1995) The effect of triple therapy on rapidly progressive type of Henoch-Schonlein nephritis. Pediatr Nephrol 9:6–10
64. Ong LM, Hooi LS, Lim TO, et al. (2005) Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology (Carlton) 10:504–10
65. Ozen S, Ruperto N, Dillon MJ, et al. (2006) EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 65:936–941
66. Park MC, Park YB, Jung SY, et al. (2006) Anti-endothelial cell antibodies and antiphospholipid antibodies in Takayasu's arteritis: correlations of their titers and isotype distributions with disease activity. Clin Exp Rheumatol 24: (2 Suppl 41) S10–S16
67. Robbins S, Cotran R, Kumar V, Inflammation - The Vasculitides. In: (1984) Pathologic Basis of Disease. W. B. Saunders Company, Philadelphia
68. Ronkainen J, Koskimies O, Ala-Houhala M, et al. (2006) Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr 149:241
69. Ronkainen J, Nuutinen M, Koskimies O (2002) The adult kidney 24 years after childhood Henoch-Schonlein purpura: a retrospective cohort study. Lancet 360:666
70. Rottem M, Fauci AS, Hallahan CW, et al. (1993) Wegener granulomatosis in children and adolescents: clinical presentation and outcome. J Pediatr 122:26–31
71. Saulsbury FT (1999) Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. Medicine (Baltimore) 78:395–409
72. Savage CO, Pottinger BE, Gaskin G, et al. (1991) Vascular damage in Wegener's granulomatosis and microscopic polyarteritis: presence of anti-endothelial cell antibodies and their relation to anti-neutrophil cytoplasm antibodies. Clin Exp Immunol 85:14–9
73. Schmitt WH, Hagen EC, Neumann I, et al. (2004) Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. Kidney Int 65:1440
74. Smith KGC, Jones RB, Burns SM, et al. (2006) Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthritis Rheum 54:2970–82
75. Sorensen SF, Slot O, Tvede N, et al. (2000) A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. Ann Rheum Dis 59:478–82
76. Steinberg A, Kaltreider H, Staples P, et al. (1971) Cyclophosphamide in lupus nephritis: a controlled trial. Ann Intern Med 75:165–71
77. Stewart M, Savage JM, Bell B, et al. (1988) Long term renal prognosis of Henoch-Schönlein Purpura in an unselected childhood population. Eur J Pediatr 147:113
78. Sztejnbok M, Stweard A, Diamond H, et al. (1971) Azothioprine in the treatment of systemic lupus erythematosus: a controlled study. Arthritis Rheum 14:639–45
79. Tarshish P, Bernstein J, Edelmann CM, Jr. (2004) Henoch-Schonlein purpura nephritis: course of disease and efficacy of cyclophosphamide. Pediatr Nephrol 19:51–6
80. The Wegener's Granulomatosis Etanercept Trial Research G (2005) Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 352:351–61
81. Tokunaga M, Saito K, Kawabata D, et al. (2007) Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis 66:470–5
82. van Vollenhoven RF, Gunnarsson I, Welin-Henriksson E, et al. (2004) Biopsy-verified response of severe lupus nephritis to treatment with rituximab (anti-CD20 monoclonal antibody) plus cyclophosphamide after biopsy-documented failure to respond to cyclophosphamide alone. Scand J Rheumatol 33:423–7
83. Wedgwood RJ, Klaus MH (1955) Anaphylactoid purpura (Schonlein-Henoch syndrome): a long-term follow- up study with special reference to renal involvement. Pediatrics 16:196–206
84. Wen YK, Yang Y, Chang CC (2005) Cerebral vasculitis and intracerebral hemorrhage in Henoch-Schonlein purpura treated with plasmapheresis. Pediatr Nephrol 20:223–5
85. Yamada I, Nakagawa T, Himeno Y, et al. (1998) Takayasu arteritis: evaluation of the thoracic aorta with CT angiography. Radiology 209:103–9