Review

Clinical review: Vasculitis on the intensive care unit – part 2: treatment and prognosis

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Abstract

The second part of this review addresses the treatment and prognosis of the vasculitides Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome and polyarteritis nodosa. Treatment regimens consist of an initial remission phase with aggressive immunosuppression, followed by a more prolonged maintenance phase using less toxic agents and doses. This review focuses on the initial treatment of fulminant vasculitis, the mainstay of which remains immunosuppression with steroids and cyclophosphamide. For Wegener's granulomatosis and microscopic polyangiitis plasma exchange can be considered for first-line therapy in patients with acute renal failure and/or pulmonary haemorrhage. Refractory disease is rare and is usually due to inadequate treatment. The vasculitides provide a particular challenge for the critical care team. Particular aspects of major organ support related to these conditions are discussed. Effective treatment has revolutionized the prognosis of these conditions. However, mortality is still approximately 50% for those requiring admission to intensive care unit. Furthermore, there is a high morbidity associated with both the diseases themselves and the treatment.

Introduction

Systemic necrotizing vasculitis represents a major challenge in critical care units. The prognosis of a fulminating vasculitic illness is poor, with patients admitted to the intensive care unit (ICU) with suspected pulmonary vasculitis having a mortality between 25% and 50% [1]. Early and accurate diagnosis and aggressive treatment are essential to optimizing outcomes while avoiding unnecessary immunosuppressive therapy. In this second part of the review we consider the role played by the ICU in their treatment and look at the prognosis of the fulminant presentations. Although there is a firm evidence base for first-line treatment of the vasculitic process, the evidence for the treatment of resistant and severe disease relies more on small cases series and single centre experiences.

Treatment specific to the vasculitis

Corticosteroids/cyclophosphamide

The combination of high-dose corticosteroids and cyclophosphamide are the mainstay of treatment for the vasculitides, and disease resistance to this combination is rare [2–4]. Remission of Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) has been reported in up to 90% of cases, although one would expect this to be considerably less in the critical care population.

A trial of corticosteroids alone can be considered for cases of polyarteritis nodosa (PAN) or Churg–Strauss syndrome (CSS) that are not immediately life threatening. However, they should not be used alone in cases of WG, MPA, or the more fulminant presentations of PAN and CSS seen on critical care units [4–8].

Historically, cyclophosphamide has been given orally in the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. However, there is evidence that pulsed intravenous cyclophosphamide is at least as effective in attaining remission and may be less toxic, although this may be at the expense of a higher likelihood of relapse [9,10]. No difference has been demonstrated between monthly intravenous (0.6 g/m^2 body surface area) or daily oral regimens in CSS, whereas in PAN the question has not been systematically addressed [11]. The European Vasculitis Study Group is currently coordinating a large prospective study (the CYCLOPS trial) designed to provide more complete data on the role of intravenous

ANCA = antineutrophil cytoplasmic antibody; CSS = Churg–Strauss syndrome; ICU = intensive care unit; MPA = microscopic polyangiitis; PAN = polyarteritis nodosa; PE = plasma exchange; WG = Wegener's granulomatosis.

cyclophosphamide in ANCA-associated vasculitis. In the critically ill patient in whom there may be doubts about drug absorption, the intravenous route may be the only choice.

A typical regimen for a patient with fulminant multisystem disease is three daily doses of intravenous methylprednisolone (total daily dose dose 0.25–1 mg), followed by oral prednisolone (1 mg/kg) or equivalent. Intravenous cyclophosphamide (0.5–1 g/m^2 body surface area) is started at the same time as the methylprednisolone and repeated at intervals of between 1 and 4 weeks. Alternatively, oral cyclophosphamide 2–4 mg/kg per day is used if the gastrointestinal tract is competent. Less severe disease would demand lower doses of oral cyclophosphamide (1.5–2 mg/kg per day) and oral steroids (1 mg/kg) only.

Treatment related morbidity and mortality are frequently seen with this regimen and may be minimized by early dose reductions or substitutions for less toxic agents. This must be balanced against the risk for disease relapse. Oral steroids should not be reduced for at least 1 month after remission. Until recently many centres would continue the cyclophosphamide for up to 12 months after remission in ANCA-associated conditions. In PAN there is evidence that 12 months of monthly intravenous cyclophosphamide is associated with lower mortality than 6 months of therapy. Recently, data have shown no increased incidence of relapse if cyclophosphamide is substituted for azathioprine (2 mg/kg per day) after 3 months in WG or MPA [12]. There are no data for this approach in either CSS or PAN [13].

Disease that is truly resistant to a corticosteroid/cyclophosphamide regimen is rare, but it is more common in fulminant disease [4]. Care should be taken to ensure that the ongoing or deteriorating condition is due to active vasculitis and not irreversible organ damage, drug toxicity, or sepsis. Inadequate drug therapy is the most common cause of treatment failure. In cases in which cyclophosphamide and corticosteroids have failed to suppress the vasculitic activity, or in which side effects are unacceptable, there is scarce information to guide the next step.

Further treatment strategies

Plasma exchange

The role of plasma exchange (PE) is still far from clear. However, it would appear to be most useful in the ANCA-associated vasculitides. It is an intellectually attractive therapeutic option, given the likely pathogenic role of ANCA in these conditions. Initial trials showed benefit when PE was used in addition to a corticosteroid and cyclophosphamide regimen, but only in cases in which there was dialysis dependence at presentation [14,15] or concurrent anti-glomerular basement membrane disease (a rare overlap). No evidence of additional benefit has been observed in less severe disease [16]. PE has also been used in some centres for fulminant disease causing pulmonary–renal failure requiring organ support [17] or for severe pulmonary haemorrhage, in which it has theoretical benefits. Recently, the completion of a large multicentre, international trial has clarified the role of PE in vasculitis. The MEPEX trial compared the use of oral cyclophosphamide and either PE followed by oral prednisolone or three pulses of daily intravenous methylprednisolone (15 mg/kg) followed by oral prednisolone. The 151 patients included had either WG or MPA and a serum creatinine concentration greater than 500 μmol/l. Early follow-up data suggest that the PE group exhibited improved dialysis independence at 3 months, whether they were dialysis dependent at presentation or not [18]. There were no differences in mortality. PE is not without potentially serious complications such as infection, cardiovascular compromise and electrolyte disturbance. Therefore, longer term follow-up data will clearly be important.

There is no evidence that PE is of additional value in CSS and PAN [19].

The patient with a diagnosis of either WG or MPA, particularly those with acute renal failure and/or severe pulmonary haemorrhage, may benefit from PE (if it is available locally) and cyclophosphamide as first-line therapy. There are few data to support the use of a combination of PE, methylprednisolone and cyclophosphamide for initial treatment.

Hepatitis B associated polyarteritis nodosa

Immunosuppressive regimens alone are associated with an adverse prognosis in hepatitis B associated PAN [20,21]. However, several small series and case reports of short courses of steroids combined with antivirals and PE or interferon-α have demonstrated more success [22–26]. Extrapolation of these results to the ICU environment is necessary because there are no data specifically relating to this severe end of the spectrum. A typical regimen might be prednisolone 1 mg/kg daily for 1 week, rapidly tapering off over the next week, followed by lamivudine 100 mg/day (reduced if renal function impaired) for at least 6 months, together with serial PEs. These are performed three times per week for 3 weeks, twice per week for 2 weeks, and then once per week until loss of hepatitis B e antigen and development of hepatitis B e antibody occurs in the patient's serum, or sustained clinical recovery for 2–3 months has been achieved.

Other novel treatments

As the pathogenesis of these conditions becomes clearer, and understanding of the respective roles of the cell-mediated and humoral immune systems improves, novel therapies are being developed based on this theoretical knowledge. Options currently under investigation include anti-tumour necrosis factor antibodies, anti-T-cell or anti-B-cell antibodies, pooled intravenous immunoglobulin and other chemotherapeutic agents. Most have been reported only in very small numbers of patients (often only one), and so conclusions on their efficacy cannot reliably be drawn.

However, it appears that there may be evidence to recommend intravenous immunoglobulin in CSS that has not responded to conventional treatment [27,28].

Possible complications of therapy

Superadded infection

Treatment for small vessel vasculitis is potent and highly toxic. Although the near universal mortality associated with untreated disease justifies its use, every care needs to be taken to minimize its adverse consequences. In the short term this requires regular monitoring for significant bone marrow suppression. Vigilance is also needed for superadded infection. Severe treatment-related infections occur in approximately 10% of cases treated with cyclophosphamide and are a significant cause of mortality [11]. Although the evidence is lacking for its unequivocal recommendation, many would view prophylaxis against *Pneumocystis carinii* pneumonia with co-trimoxazole as mandatory for all patients on high-dose cyclophosphamide.

Bone protection

Although the consequences of the bone demineralization related to high-dose steroid use will not be apparent for many months, or possibly years, the most rapid loss occurs soon after starting treatment [29]. Bone protection, in the form of bisphosphonates, with or without vitamin D and calcium supplementation, should be prescribed from the onset in any patient expected to have a prolonged course of steroids.

Intensive care unit specific management

Airway management

WG classically involves the upper respiratory tract, which in approximately 16% of cases results in subglottic stenosis [5,30,31]. The implications for airway management include potentially difficult intubation requiring a smaller diameter endotracheal tube, and consequently tracheostomy may be required in approximately 50% of cases (80% will need some form of surgical intervention ranging from dilatation to reconstruction) [5,30].

Respiratory management

Small vessel vasculitis in the lung involves destruction of arterioles, capillaries and venules by infiltration of activated neutrophils leading to interstitial oedema and diffuse alveolar haemorrhage. Care should be taken to avoid exacerbation of pulmonary oedema and haemorrhage. Such patients may require invasive haemodynamic monitoring [1].

Pulmonary oedema, haemorrhage and the potential for development of the acute respiratory distress syndrome will reduce lung compliance. Large tidal volumes or pressure changes may further exacerbate damage to the pulmonary microvasculature, and it would therefore seem prudent to adopt a protective ventilation strategy. Current evidence supports aiming for tidal volumes of 6 ml/kg and inspiratory plateau pressures below 30 cmH_2O, while using appropriate levels of positive end-expiratory pressure to improve functional residual capacity and alveolar recruitment [32]. In a small series of seven patients with fulminant vasculitis admitted to ICU, two subsequently developed tension pneumothoracies where protective ventilation strategies were not employed [33].

Cardiovascular management

In addition to the impaired gas exchange caused by pulmonary haemorrhage, large volumes of blood may be lost into the alveolar space before haemorrhage becomes apparent as haemoptysis. As a result, patients with severe systemic vasculitis are often anaemic. This combination of hypoxia and anaemia may dramatically reduce oxygen delivery to the tissues.

On admission to the ICU patients with fulminant vasculitis may be hypotensive because of a combination of dehydration, haemorrhage and systemic inflammatory response syndrome. As such they may require ionotropic/vasopressor support [33].

Hypertension can be problematic in PAN. This is due to activation of the renin–angiotensin–aldosterone axis as a consequence of renal ischaemia. Therefore, an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker may be helpful, although care must be taken to ensure that they do not contribute to a further decline in renal function.

Renal management

Renal replacement therapy may be required acutely during treatment of the vasculitis, and in 20–40% of cases this will need to continue in the long term [4]. Unfortunately, of those who avoid long-term renal replacement therapy initially, many will progress to end-stage renal failure.

Sepsis

In a study of 26 patients with systemic necrotizing vasculitis admitted to the ICU, there was a 15% ICU mortality rate, with 75% of deaths due to sepsis [34]. The risk for acquiring nosocomial infections is high because of the immuno-suppressive therapy. The diagnosis of infection may be hampered not only through use of immunosuppressants but also by the disease process itself, as discussed in part 1 of this review. Treatment with activated protein C has been shown to reduce mortality in severe sepsis, and its use should be considered for appropriate patients [35].

Gastrointestinal tract

Gastrointestinal involvement may include diarrhoea, gastro-intestinal haemorrhage, or perforation, and this may be exacerbated, or indeed masked, by high-dose steroid therapy. In common with other critically ill patients, early enteral feeding and gastric protection is recommended where possible.

Metabolic management

In common with all critically ill patients, blood glucose should be tightly controlled to within normal limits using insulin infusions where necessary [36].

Prophylaxis for deep vein thrombosis

Deep vein thrombosis prophylaxis should be administered appropriately, bearing in mind the potential for pulmonary and gastrointestinal haemorrhage.

Prognosis

Untreated, these conditions have a very bleak outlook. Historically, 90% of WG/MPA patients died within 2 years; CSS was nearly universally fatal, with 50% of deaths within the first year. PAN had a 5-year survival of 13%, again with most deaths occurring in the early stages of the disease. However, the advent of effective treatment has dramatically altered these figures. Overall, 5-year survival is now in the region of 70–80% for all four conditions. Fulminant cases still represent a greater problem, and 25–50% survival would be more realistic for the ICU population [3,4,6,8,17,37,38].

Attempts have been made to identify those patients at highest risk. Unsurprisingly, those with a high Acute Physiology and Chronic Health Evaluation II score, Simplified Acute Physiology Score II or Birmingham Vasculitis Activity Score have a high mortality [34,39]. One series found the presence of cardiac, gastrointestinal, central nervous system or renal disease (a high creatinine or proteinuria >1 g/24 hours) to be adverse indicators of outcome for CSS. The presence of all of these factors reduced the 5-year survival to 50% [38]. In PAN, renal, gastrointestinal, or cardiac involvement are also adverse prognostic indicators [8]. Despite the often severe nature of their initial presentation to the ICU, a trial of full therapy should be made before decisions on futility are made.

The principal causes of early death are related to the disease in approximately half of cases (pulmonary–renal failure, cardiac involvement). However, with newer therapies between 23% and 50% of deaths may be attributable to the adverse effects of treatment (sepsis, malignancy) [37,40,41].

There is a very high morbidity associated with these conditions, caused by irreversible organ damage that occurs before treatment is effective. For example, progression to end-stage renal failure eventually occurs in up to 20–25% of patients with WG or MPA in the absence of active inflammation [3,4,40]. A significant proportion may also be due to toxicity of the treatment. Long-term corticosteroid use has well documented consequences, whereas prolonged oral cyclophosphamide use carries a life-long increased risk for bladder carcinoma, cutaneous squamous cell carcinomas, myelodysplasia and lymphoma. Some estimates put the yearly risk for malignancy at around 2.5 times normal, but this is probably an underestimate [5]. Up to 50% of women given cyclophosphamide for WG become infertile or amenorrhoeic in some series [5].

Conclusion

The modern treatment of vasculitis has revolutionized the outlook for these conditions. From near universal mortality within years, or even months, the expectation now favours survival past 5 years, and even in the ICU population respectable results are possible. However, treatment is not without cost, and a high percentage of those surviving will have considerable morbidity related either to the underlying condition or to the treatment itself. New, more specific treatments are under investigation, and have the potential to improve this even further and perhaps reduce the associated morbidity.

On the ICU the vasculitides present particular challenges for airway management and vital organ support, but although the evidence base in this area is thin, relying mainly on cases series, some specific recommendations are possible.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Griffith M, Brett S: **The pulmonary physician in critical care – illustrative case 3: pulmonary vasculitis.** *Thorax* 2003, **58:**543-546.
2. Fauci AS, Katz P, Haynes BF, Wolff SM: **Cyclophosphamide therapy of severe systemic necrotizing vasculitis.** *N Engl J Med* 1979, **301:**235-238.
3. Slot MC, Tervaert JW, Franssen CF, Stegeman CA: **Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement.** *Kidney Int* 2003, **63:** 670-677.
4. Nachman PH, Hogan SL, Jennette JC, Falk RJ: **Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis.** *J Am Soc Nephrol* 1996, **7:**33-39.
5. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS: **Wegener granulomatosis: an analysis of 158 patients.** *Ann Intern Med* 1992, **116:**488-498.
6. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, Jarrousse B: **Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg–Strauss syndrome: analysis of four prospective trials including 278 patients.** *Arthritis Rheum* 2001, **44:**666-675.
7. Clutterbuck EJ, Evans DJ, Pusey CD: **Renal involvement in Churg–Strauss syndrome.** *Nephrol Dial Transplant* 1990, **5:** 161-167.
8. Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B: **Clinical findings and prognosis of polyarteritis nodosa and Churg–Strauss angiitis: a study in 165 patients.** *Br J Rheumatol* 1988, **27:**258-264.
9. Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, Lesavre P, Jacquot C, Bindi P, Bielefeld P, *et al.*: **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* 1997, **40:**2187-2198.
10. de Groot K, Adu D, Savage CO: **The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review.** *Nephrol Dial Transplant* 2001, **16:**2018-2027.
11. Conron M, Beynon HL: **Churg–Strauss syndrome.** *Thorax* 2000, **55:**870-877.
12. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, Ekstrand A, Gaskin G, Gregorini G, de Groot K, *et al.*: **A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies.** *N Engl J Med* 2003, **349:**36-44.
13. Guillevin L, Cohen P, Mahr A, Arene JP, Mouthon L, Puechal X, Pertuiset E, Gilson B, Hamidou M, Lanoux P, *et al.*: **Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients.** *Arthritis Rheum* 2003, **49:**93-100.

14. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM: **Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies.** *Kidney Int* 1991, **40:**757-763.
15. Cole E, Cattran D, Magil A, Greenwood C, Churchill D, Sutton D, Clark W, Morrin P, Posen G, Bernstein K, *et al.*: **A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group.** *Am J Kidney Dis* 1992, **20:**261-269.
16. Guillevin L, Cevallos R, Durand-Gasselin B, Lhote F, Jarrousse B, Callard P: **Treatment of glomerulonephritis in microscopic polyangiitis and Churg–Strauss syndrome. Indications of plasma exchanges, Meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis.** *Ann Med Interne (Paris)* 1997, **148:**198-204.
17. Gallagher H, Kwan JT, Jayne DR: **Pulmonary renal syndrome: a 4-year, single-center experience.** *Am J Kidney Dis* 2002, **39:** 42-47.
18. Gaskin G, Jayne DR, European Vasculitis Study Group: **Adjunctive plasma exchange is superior to methylprednisolone in acute renal failure due to anti-neutrophil cytoplasmic antibody-associated glomerulonephritis.** In *The Renal Association: 9–11 October 2002; London*. London: The Renal Association; 2002:8.
19. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, Leon A, Bussel A: **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* 1995, **38:** 1638-1645.
20. Guillevin L, Lhote F, Jarrousse B, Bironne P, Barrier J, Deny P, Trepo C, Kahn MF, Godeau P: **Polyarteritis nodosa related to hepatitis B virus. A retrospective study of 66 patients.** *Ann Med Interne (Paris)* 1992, **Suppl 1:**63-74.
21. Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, Noel LH, Trepo C: **Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients.** *Medicine (Baltimore)* 1995, **74:**238-253.
22. Guillevin L, Mahr A, Cohen P, Larroche C, Queyrel V, Loustaud-Ratti V, Imbert B, Hausfater P, Roudier J, Bielefeld P, *et al.*: **Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa.** *Arthritis Rheum* 2004, **51:**482-487.
23. Erhardt A, Sagir A, Guillevin L, Neuen-Jacob E, Haussinger D: **Successful treatment of hepatitis B virus associated polyarteritis nodosa with a combination of prednisolone, alpha-interferon and lamivudine.** *J Hepatol* 2000, **33:**677-683.
24. Guillevin L, Lhote F, Leon A, Fauvelle F, Vivitski L, Trepo C: **Treatment of polyarteritis nodosa related to hepatitis B virus with short term steroid therapy associated with antiviral agents and plasma exchanges. A prospective trial in 33 patients.** *J Rheumatol* 1993, **20:**289-298.
25. Guillevin L, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, Pourrat J, Christoforov B, Trepo C: **Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges.** *Ann Rheum Dis* 1994, **53**:334-337.
26. Wicki J, Olivieri J, Pizzolato G, Sarasin F, Guillevin L, Dayer JM, Chizzolini C: **Successful treatment of polyarteritis nodosa related to hepatitis B virus with a combination of lamivudine and interferon alpha.** *Rheumatology (Oxford)* 1999, **38:**183-185.
27. Hamilos DL, Christensen J: **Treatment of Churg–Strauss syndrome with high-dose intravenous immunoglobulin.** *J Allergy Clin Immunol* 1991, **88:**823-824.
28. Tsurikisawa N, Taniguchi M, Saito H, Himeno H, Ishibashi A, Suzuki S, Akiyama K: **Treatment of Churg–Strauss syndrome with high-dose intravenous immunoglobulin.** *Ann Allergy Asthma Immunol* 2004, **92:**80-87.
29. Reid IR, Heap SW: **Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy.** *Arch Intern Med* 1990, **150:**2545-2548.
30. Gluth MB, Shinners PA, Kasperbauer JL: **Subglottic stenosis associated with Wegener's granulomatosis.** *Laryngoscope* 2003, **113:**1304-1307.
31. Langford CA, Sneller MC, Hallahan CW, Hoffman GS, Kammerer WA, Talar-Williams C, Fauci AS, Lebovics RS: **Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis.** *Arthritis Rheum* 1996, **39:**1754-1760.
32. Moloney ED, Griffiths MJ: **Protective ventilation of patients with acute respiratory distress syndrome.** *Br J Anaesth* 2004, **92:** 261-270.
33. Soding PF, Lockwood CM, Park GR: **The intensive care of patients with fulminant vasculitis.** *Anaesth Intensive Care* 1994, **22:**81-89.
34. Cruz BA, Ramanoelina J, Mahr A, Cohen P, Mouthon L, Cohen Y, Hoang P, Guillevin L: **Prognosis and outcome of 26 patients with systemic necrotizing vasculitis admitted to the intensive care unit.** *Rheumatology (Oxford)* 2003, **42:**1183-1188.
35. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, *et al.*: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344:**699-709.
36. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients.** *N Engl J Med* 2001, **345:**1359-1367.
37. Matteson EL, Gold KN, Bloch DA, Hunder GG: **Long-term survival of patients with Wegener's granulomatosis from the American College of Rheumatology Wegener's Granulomatosis Classification Criteria Cohort.** *Am J Med* 1996, **101:**129-134.
38. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P: **Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients.** *Medicine (Baltimore)* 1996, **75:**17-28.
39. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D: **Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis.** *QJM* 1994, **87:**671-678.
40. Aasarod K, Iversen BM, Hammerstrom J, Bostad L, Vatten L, Jorstad S: **Wegener's granulomatosis: clinical course in 108 patients with renal involvement.** *Nephrol Dial Transplant* 2000, **15:**611-618.
41. Guillevin L, Jarrousse B, Lok C, Lhote F, Jais JP, Le Thi Huong Du D, Bussel A: **Longterm followup after treatment of polyarteritis nodosa and Churg–Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa.** *J Rheumatol* 1991, **18:**567-574.