Mortality in systemic vasculitis: a systematic review

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Abbreviations:

ANCA:	Antineutrophil cytoplasm antibody
BVAS:	Birmingham Vasculitis Activity Score
CI:	Confidence Interval
HR:	Hazard ratio
IVIG:	Intravenous immunoglobulin
MeSH:	Medical Subject heading
PR3:	Proteinase 3
RR:	Relative risk
SIR:	Standardised incidence ratios
VDI:	Vasculitis damage index

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ABSTRACT

There has been a considerable improvement in the survival of patients with systemic vasculitis since the introduction of immunosuppressive therapy and improved diagnostic tools to allow earlier diagnosis. We review the published literature on current risk of mortality in patients with small vessel antineutrophil cytoplasm antibody-(ANCA) associated vasculitis including Wegener's granulomatosis (survival rate of approximately 75% at 5 years), microscopic polyangiitis (survival rate of 45% to 75% at 5 years), Churg-Strauss syndrome (survival rate of 68% to 100% at 5 years), and Henoch-Schönlein purpura (survival rate of 75% in adult-onset, greater in childhood onset); medium vessel vasculitis including polyarteritis nodosa (survival rate of 75% to 80% at 5 years), Kawasaki disease (survival rate of greater than 99% at 5 years); large vessel vasculitis including giant cell arteritis (survival rate equivalent to the age-matched population), and Takayasu arteritis (survival of 70% to 93% at 5 years). Mortality rates are falling as a result of more effective intervention but remain elevated substantially in severe disease. Early deaths are usually attributable to active vasculitis with multiorgan failure or infection, or both. The incidence of late deaths may be increased by long-term effects of therapy and development of comorbidities. These findings highlight the need to improve early diagnosis and initiation of targeted therapy, thereby reducing treatment-related toxicity and comorbidities.

Introduction

Untreated systemic vasculitis is associated with high mortality rates, especially in patients with what we now recognise as anti-neutrophil cytoplasm antibody- (ANCA) associated systemic vasculitis. Even milder forms of disease carry a poor prognosis, with a 40% death rate in patients with non-renal Wegener's granulomatosis (1). The introduction of glucocorticoids extended survival for about 12 months but over 5 years, glucocorticoids were not found to affect mortality resulting from multisystem disease. By contrast, immunosuppressive agents converted an 80% mortality rate associated with no treatment into an 80% survival since the 1970s, rising to over 90% survival at 18 months for generalized ANCA associated vasculitis as demonstrated in a recent study in 2003 (2). Cyclophosphamide (3) in particular changed the outlook for patients with severe vasculitis. Survival of patients with generalised vasculitis using cyclophosphamide for 3 to 6 months plus high dose glucocorticoid, followed by low-dose azathioprine and low-dose glucocorticoid is now greater than 90% after 18 months follow-up (3). The likelihood of survival after 5 years from the initial episode of ANCA-associated vasculitis is more than 70% (4-7). Despite the improved survival with treatment, relapse and low grade persistent disease manifestations are common and require ongoing immunosuppression, resulting in poor quality survival (3, 4, 8, 9). In medium vessel vasculitis there have been significant improvements in outcome of polyarteritis nodosa as a result of better treatment of hepatitis B infection. Improved recognition of Kawasaki disease results in earlier treatment. Growing awareness of the potential for aneurysm formation and ischaemic complications in large vessel disease suggests that a more aggressive course may be required in some patients. These complications are more commonly recognised in Takayasu arteritis.

We undertook a systematic literature review of clinical trials and studies of primary small vessel vasculitis in order to define disease-specific survival, causes of death, and prognostic factors for survival. We have excluded cryoglobulinaemic vasculitis, since it

is addressed in a separate paper in this volume. We have also excluded isolated cutaneous vasculitis.

Methods

A literature search was performed (Fig. 1) using the Sheffield Hallam University LitSearch website (2008) and the MEDLINE (Cambridge Scientific Abstracts) database. The keywords vasculitis and mortality were used initially to identify appropriate articles. The individual syndromes identified by the Chapel Hill consensus (Wegener's granulomatosis, Churg-Strauss, microscopic polyangiitis, Henoch-Schönlein, polyarteritis nodosa, Kawasaki disease, giant cell arteritis, and Takayasu arteritis) were then used as keywords, in combination with mortality, to identify further articles of interest. Abstracts were obtained for all and scrutinised to determine their relevance. Where appropriate the original article was then obtained and reviewed. References were also reviewed to identify other potentially eligible papers. All English-language peer-reviewed articles published between 1950 and 29 April 2008 were considered eligible.

Mortality in Wegener's granulomatosis

Wegener's granulomatosis is an ANCA-associated vasculitis affecting small and medium-sized vessels. It was initially characterised by a triad of ear, nose and throat, pulmonary, and renal involvement (10), although it is now recognised that this involvement can be highly variable and can include other organs and tissues.

Mortality rates

The use of glucocorticoids and cyclophosphamide has resulted in much lower mortality rates than those published in early studies of Wegener's granulomatosis (11). A summary of published data (Table I) suggests improved mortality rates.

Indicators of poor prognosis

Analysis of study populations has identified factors associated with a poor prognosis in Wegener's granulomatosis. Increased age and evidence of renal impairment are consistently shown to confer a poor prognosis (7, 11-14). Lack of ear, nose and throat (ENT) involvement has also been shown to be a significant indicator of increased risk of mortality (7, 11) with other studies showing a trend towards significance (12, 13, 15, 16). Luqmani *et al*. (16) showed that an absence of renal involvement was highly favourable with a 100% 5-year survival rate compared to approximately 70% in those with renal disease. Studies of ANCA-associated vasculitides have shown an increased risk of mortality in patients who are PR3-ANCA positive and at high titre, compared to patients who are ANCA negative or have low titre ANCA (17, 18). A summary of the findings is presented in Table II.

Patients with Wegener's granulomatosis admitted to intensive care (ICU) have a mortality rate of 29.4%, chiefly due to infection (reported in 40% of cases) (19), according to a study by Burkhardt and colleagues. The risk factors for an unfavourable outcome included ICU stay of greater than 10 days, early use of cyclophosphamide, and a high (>20) acute physiology and chronic health evaluation II (APACHE II) score. The authors proposed that these features all increased susceptibility to infection. Interestingly, glucocorticoid use, degree of renal impairment, and age had no statistically significant influence on survival in this study.

Causes of death

Early (less than 1 year)

Sepsis is a significant early cause of mortality in Wegener's granulomatosis. Mahr *et al*. (12) found infection to be related to 39% of all deaths (7 cases),

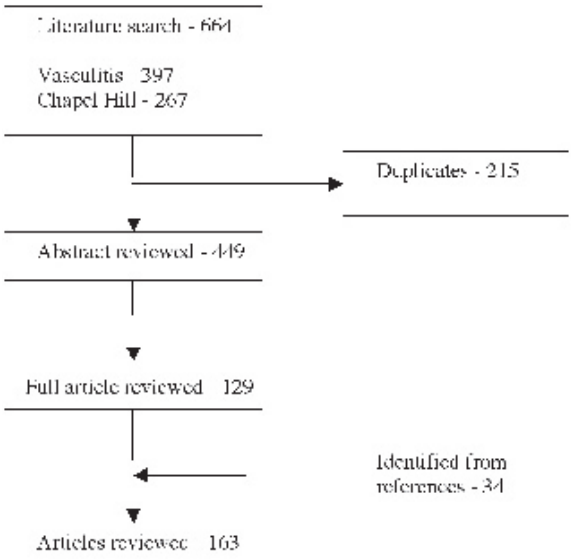

Fig. 1. Literature search summary.

Table I. Wegener's granulomatosis mortality rates.

Mortality rate	Study population (n)	Authors	Nationality
97% 2-y survival 88% 10-y survival	155	Reinhold-Keller et al. (14)	German
93% 1-y survival 79% 5-y survival 75% 10-y survival	56	Koldingsnes & Nossent (11)	Norwegian
75•9% 5-y survival	57	Lane *et al*. (15)	British
74% 5-y survival	93	Bligny *et al*. (7)	French
88% 2-y survival 74% 5-y survival	108 With renal involvement	Aasarød *et al*. (6)	Norwegian
67•5% 2-y survival	49	Mahr *et al*. (12)	French
59% survival at 35 months	23	Kamali *et al*. (20)	Turkish

Table II. Predictors of mortality in Wegener's granulomatosis.

Factor	Relative risk (significance at p<0•05 or less)	95% Confidence interval	Source
Increasing age	Not stated [a]		Aasarød *et al*. (6)
	HR=3•4 (>52 yrs)*	1•03 - 11•21	Bligny *et al*. (7)
	HR=2•18*	1•38 - 3•42	Koldingsnes & Nossent (11)
	RR=3•6 (>57 yrs)*	2•5 - 4•6	Mahr *et al*. (12)
	HR=5•45 (>50 yrs)*	1•97 - 15•02	Reinhold-Keller *et al*. (14)
Lack of ENT involvement	35% 5-y survival *vs*. 82%		Bligny *et al*. (7)
Lung involvement	HR=3•75 (at diagnosis)*	1•26 - 11•16	Reinhold-Keller *et al*. (14)
Raised serum creatinine	58% 5-y survival *vs*. 82% (> 160 μmol.l^{-1})		Bligny *et al*. (7)
	HR=1•35 [a]	1•11 - 1•65	Koldingsnes & Nossent (11)
	HR=5•72 (> 1•5mg.dl^{-1})	1•05 - 31•12	Pavone *et al*. (13)
	RR=3•5 (>18 mg.dl^{-1})*	2•5 - 4•5	Mahr *et al*. (12)
	HR=5•42*	1•76 -16•68	Reinhold-Keller *et al*. (14)
Dialysis dependence	HR=8•20*	2•02 - 33•11	Koldingsnes & Nossent (11)
	RR=3•58 (<1yr; DD at diagnosis)* †	1•01 - 12•7	Slot *et al*. (90)
	RR=4•15 (>1yr; DD during follow up) * †	1•43 - 12•0	Slot *et al*. (90)
Low serum albumin	RR=4•5 (Alb<30g.l^{-1})	1•3 - 16•0	Aasarød *et al*. (6)
High level of PR3-ANCA	RR=2•7 (> 550 U)	1•5 - 4•8	Westman *et al*. (18)
	69% 5-y survival *vs*. 93%		Weidner *et al*. (17)

DD: Dialysis dependent; HR: Hazard ratio; RR: Relative risk.
* Multivariate analysis; [a] Univariate analysis; PR3: Proteinase 3; † with renal involvement.

and all except one of the seven occured within the first 6 months of diagnosis. Bligny *et al*. (7) found infection to be implicated in 48% of deaths, with the majority occurring within 6 months. Other studies have shown lower rates of infection (6, 15, 20). Infections have been shown to be related to prednisolone dosage, with higher doses associated with more infections (11, 14, 21). Whether this was due to the dose itself or the severity of disease requiring such doses, is not proven. Other causes of early mortality include disease activity, acute renal failure, and alveolar haemorrhage (6, 7, 11, 12, 14, 15, 21).

Zycinska *et al*. (22) looked specifically at predicting the risk of early death and found that dialysed patients had a risk 16 times higher than nondialysed patients (p<0.02) and those with a cough a risk 15 times higher than those without (p<0.05).

Late
(greater than 1 year post-diagnosis)

Late causes of death are similar to those seen in early disease. Despite evidence of endothelial dysfunction in Wegener's granulomatosis (23), the levels of cardiovascular disease are much less than those described in large vessel vasculitides. However, definitive information is limited by the absence of long-term studies.

An increased risk of malignancy is recognised, both secondary to the disease and also to treatment. Knight *et al*. (24) found 110 cancers in 1065 hospitalised Wegener's granulomatosis patients, a 2-fold increase compared to the general population. Standardised incidence ratios (SIR) were used to estimate the relative risk. The increase was most pronounced for bladder cancer (SIR = 4.8), squamous cell carcinoma (SIR=7.3), leukaemia (SIR=5.7), and malignant lymphomas (SIR=4.2).

Further analysis of the same cohort revealed that cyclophosphamide use was associated with bladder cancer risk (25). The risk doubled with every 10-g increment in the cumulative dose of cyclophosphamide. Treatment with cyclophosphamide for longer than 1 year was associated with an 8-fold increase in overall mortality. The absolute risk for bladder cancer was 10% 16 years after a diagnosis of Wegener's granulomatosis. Faurschou *et al*. (26) assessed the malignancy risk associated with cyclophosphamide, identifying an increased risk for acute myeloid leukaemia (SIR=19.6), bladder cancer (SIR=3.6) and nonmelanoma skin cancer (SIR=4.7). The risk of these malignancies was not increased in patients who did not receive cyclophosphamide or only had a cumulative dose less than or equal to 36 g. Those patients receiving more than 36 g had a 60-fold increased risk of acute myeloid leukaemia and a 10-fold increased risk of bladder cancer. These cancers were diagnosed between 7 and 18.5 years after initiation of cyclophosphamide therapy.

The role of clinical assessment tools in vasculitis

Vasculitis assessment tools have been used in an effort to predict mortality. Conclusions on their use are complicated by the retrospective nature of many of the studies, relying on a high quality of note-keeping and patient recall to produce accurate scores.

The Birmingham vasculitis activity score (BVAS) has been assessed as a potential predictor of mortality in a number of studies (7, 11, 12, 28). Luqmani *et al*. (28) suggested that higher BVAS scores were associated with reduced survival. Gayraud *et al*. (29) and Luqmani *et al*. (28) both showed that BVAS does give prognostic data for groups but not necessarily for individuals. The disease extent index has not been shown to predict earlier mortality (7, 11).

Summary

Mortality in Wegener's granulomatosis has been significantly reduced as a result of glucocorticoid and cyclophosphamide use. Tertiary centre retrospective studies introduce a potential bias to most of the published results. However, a number of indicators of poor prognosis have been identified that can be used to guide treatment. The predominant causes of both early and late deaths are sepsis, renal disease, and disease activity. Treatment may result in significant morbidity and mortality with increased glucocorticoid dosage

related to increased infection rates. Higher cyclophosphamide dosages are associated with an increased risk of malignancy, particularly acute myeloid leukaemia and bladder cancer. It is difficult to attribute the increased mortality directly to treatment because severe disease, which requires increased levels of treatment, may in itself increase the risk of malignancy (92). Clinical assessment tools can be used to estimate survival rates.

The current lack of large-scale long-term prospective trials should be addressed because they have the potential to improve our ability to predict those patients most at risk of death and therefore guide therapy more effectively and safely. An alternative to controlled trials is to follow cohorts of patients in well-maintained longitudinal databases.

Mortality in microscopic polyangiitis

Microscopic polyangiitis is a necrotizing vasculitis associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Necrotizing glomerulonephritis is common and pulmonary capillaritis is also seen (30). Previously a subset of polyarteritis nodosa, microscopic polyangiitis is distinguished from classic polyarteritis nodosa by the presence of small vessel disease, irrespective of medium vessel involvement (31).

Mortality rates

Five-year survival rates vary among studies. Guillevin *et al*. (5) found a rate of 74% in a cohort of French microscopic polyangiitis patients whereas Hattori *et al*. (32) found a rate of 58% in Japanese microscopic polyangiitis patients with peripheral neuropathy. In a general hospital setting in the UK, a 5-year survival rate of 45.1% was found (15). When comparing outcome in small vessel vasculitides (13, 29), mortality rates in microscopic polyangiitis have been shown to be significantly higher than those in Churg-Strauss syndrome (32) and Wegener's granulomatosis (18).

Indicators of poor prognosis

Older age is reported as a significant factor in one study of poor prognosis in microscopic polyangiitis (13) but not in another (15). Renal involvement is a significant factor in predicting poor survival, either in the form of proteinuria (>1g per day) or raised creatinine levels (5, 13). Additional evidence has been found to support a predictive role for hepatic or cerebral involvement, raised inflammatory markers, and high titres of PR3-ANCA (13, 18, 33).

A 5-factor score has been used in patient evaluation, with the following components: proteinuria >1 g per day; serum creatinine >1.58 $mg.dl^{-1}$; gastrointestinal involvement; cardiomyopathy; and CNS involvement. Higher 5-factor scores have been shown prospectively and retrospectively to be correlated significantly with lower survival (5, 29). The Birmingham vasculitis activity score (BVAS) has been shown to be of use retrospectively in one study (29) but not in others (5, 15).

Causes of death

Disease activity, sepsis (either primary or secondary to treatment) and cardiovascular disease are the primary causes of death in microscopic polyangiitis, with malignancy an additional common late cause (5, 15, 18, 33).

Summary

Microscopic polyangiitis is a vasculitis with a significant mortality risk. Early aggressive treatment can influence factors associated with poor prognosis and potentially improve survival rates. There is an absence of large-scale prospective trials in microscopic polyangiitis.

Mortality in Churg-Strauss syndrome

Churg-Strauss syndrome is a small and medium vessel necrotizing vasculitis associated with eosinophil-rich and granulomatous inflammation involving the respiratory tract, with associated asthma and eosinophilia (34).

Mortality rates

Mortality rates in Churg-Strauss syndrome are much lower than in Wegener's granulomatosis and microscopic polyangiitis, with 5-year survival rates greater than 90%. Published rates are summarised in Table III.

Indicators of poor prognosis

The high survival rates and low study population numbers make it difficult to identify statistically significant indicators of poor prognosis in Churg-Strauss syndrome. Renal involvement is less pronounced than in the other small vessel vasculitides (13, 32 35). Cardiovascular disease has been shown to be implicated in 83% of Churg-Strauss syndrome deaths. Cardiomyopathy has been shown to be a poor prognostic marker for Churg-Strauss syndrome patients (HR = 3.39; 95% CI 1.6 to 7.3) (33).

Five-factor scores greater than 2 are associated with an increased risk of death, while a 5-factor score of zero confers a better prognosis (33). Gayraud *et al*. (29) also showed an association between increasing 5-factor score and mortality.

Summary

Churg-Strauss syndrome has a better prognosis than other vasculitides. Cardiovascular disease is a significant cause of mortality. The 5-factor score can identify patients at increased risk of premature death. Further research incorporating larger numbers of patients is required to identify possible risk factors for Churg-Strauss syndrome-related mortality.

Mortality in Henoch-Schönlein purpura

Henoch-Schönlein purpura is primarily a vasculitis of children, though it can also affect adults (36). It is characterised by deposition of IgA immune complexes, resulting in a small vessel vasculitis that can cause skin, joint and gastrointestinal symptoms (34). The long-term prognosis of the condition is primarily related to the degree of renal involvement (36), with adults more at risk of developing significant renal disease (37).

Narchi (38) showed in a systematic review of paediatric Henoch-Schönlein purpura that there was no risk of developing renal disease if patients had normal urinalysis within the first 6 months of presentation. Isolated haematuria or proteinuria resulted in long-term renal impairment in only 1.6% of cases. In

Table III. Survival rates in Churg-Strauss syndrome.

Survival rates	Population (n)	Population characteristics	Source
100% 5-y survival rate	23	Italian	Pavone *et al*. (13)
97% 5-y survival rate	30	Japanese with peripheral neuropathy	Hattori *et al*. (32)
93•7% 1-y survival rate 90% 5-y survival rate	32	Spanish	Solans *et al*. (35)
75% 5-y survival rate	64	French	Gayraud *et al*. (29)
68•1% 5-y survival rate	18	UK	Lane *et al*. (15)

those with nephritic or nephrotic syndrome at presentation, renal impairment increased to 19.5%, with females 2.5 times more at risk than males.

Butani and Morgenstern (39) examined 53 paediatric patients diagnosed with Henoch-Schönlein purpura glomerulonephritis between 1953 and 1990. Of these 66% had normal renal function and urinalysis but 21% had either died of complications related to renal disease (6%) or required a renal transplant (15%). The median time to end stage renal disease was 11 years (95% CI 2.3 - 24.2 y). The only statistically significant association with poor prognosis was the use of cytotoxic medication. Considering the study spanned a 37-year period, it was interesting to note that the date of diagnosis had no influence on outcome.

Adult-onset Henoch-Schönlein purpura is a more severe syndrome than paediatric Henoch-Schönlein purpura (36, 37), with higher rates of renal insufficiency (approximately 30% *vs*. 10%). Pillebout *et al*. (36) studied specifically adult-onset Henoch-Schönlein purpura. The 5-year survival rate was 75%. The most frequent cause of death in this cohort was carcinoma, primarily of the lung and gut, followed by infection and then cardiovascular disease. At the end of the follow-up period, only 20% of total cases were in complete remission with no clinical evidence of renal involvement. Univariate analysis identified statistically significant risk factors for severe chronic renal impairment; these included age over 50 years (relative risk (RR)=2.5) and the presence of renal failure at onset (RR=5.7). The glomerular classification at biopsy was also predictive of renal outcome ($p<0.001$). In their series macroscopic haematuria and proteinuria >1 $g.l^{-1}$ at the time of biopsy correlated to the creatinine clearance at the end of follow up, but nephrotic levels of proteinuria were not predictive of a poor outcome. Treatment studies provide some evidence of benefit from glucocorticoids. One study reported evidence that glucocorticoids may reduce the risk of renal involvement (60), though other studies have failed to confirm this (36, 40). There is only one randomised controlled trial of cyclophosphamide, which showed no effect on long-term prognosis (41).

Pregnancy in patients with previous Henoch-Schönlein purpura is associated with an increased incidence of hypertension, proteinuria, and pre-eclampsia (40, 42). A diagnosis of Henoch-Schönlein purpura either in childhood or as an adult is a risk factor for pregnant women developing these conditions, irrespective of previous renal status. This suggests that close surveillance of previous Henoch-Schönlein purpura patients during pregnancy is warranted.

Summary

The long-term prognosis of patients with Henoch-Schönlein purpura is related to the development of renal disease, the incidence of which is greater in adult-onset Henoch-Schönlein purpura compared to childhood-onset disease. The severity of renal disease at diagnosis is associated with a worse prognosis. There is limited evidence to support the use of immunosuppressive treatment.

Mortality in polyarteritis nodosa

Polyarteritis nodosa is a necrotizing vasculitis involving medium-sized and small arteries, in the absence of glomerulonephritis and small vessel involvement (34). The presence of these features results in a diagnosis of microscopic polyangiitis. The American College of Rheumatology criteria differ in being a combination of clinical signs and symptoms that also include hepatitis B-related polyarteritis nodosa as a primary vasculitis (43). Prior to this time, a diagnosis of polyarteritis nodosa potentially included a number of other forms of primary vasculitis and, in trials involving patients diagnosed before this period, it has been necessary to apply diagnostic criteria retrospectively.

Mortality rates

Reported survival rates for polyarteritis nodosa are similar to those seen in microscopic polyangiitis and Churg-Strauss syndrome (29, 44) at around 75% to 80%. Survival is greater for hepatitis B-related polyarteritis nodosa, with a reported 5-year survival rate of 83%, in part as a result of the introduction of antiviral treatments (45).

Predictors for survival

The majority of deaths from polyarteritis nodosa are due to active vasculitis (29, 33, 46). Survival is improved with the use of cyclophosphamide in cases with an initial 5-factor score ≥2 (29). Gastrointestinal involvement is often seen and previously had a very poor prognosis (47). Improved surgical management and aggressive medical treatment have improved survival rates to 77% in acute abdomen and 91% for other GI involvement (48). Statistically significant predictors of mortality are shown in Table IV.

Treatment with antiviral agents has a significant influence on hepatitis B-related polyarteritis nodosa as part of a protocol including the use of glucocorticoids and plasma exchange. Guillevin *et al*. (45) found that 75% of those treated had no evidence of vasculitis after therapy. Nineteen of 35 patients were considered "cured" (no serological evidence of viral replication), and complete virus eradication was achieved in 25%, but it is not clear for how long eradication was successful; the implication from the studies reviewed was that this was permanent eradication.

Potentially lethal complications from treatment remain a significant issue in polyarteritis nodosa. Such complications include immunosuppression-related sepsis and cyclophosphamide-related bladder cancer (29)

Summary

Survival rates in polyarteritis nodosa are similar to those seen in microscopic polyangiitis and Churg-Strauss syndrome. Improved management is resulting in a decrease in mortality. Treatment of hepatitis B-related polyarteritis nodosa has the potential to result in a cure.

Table IV. Predictors of mortality in polyarteritis nodosa.

Factor	Relative risk (significant at $p \leq 0{\cdot}05$)	95% Confidence interval	Source
Increasing age	HR=1•04*	1•02 - 1•05	Bourgarit *et al*. (33)
CNS involvement	HR=3•4 [a]	1•4 - 8•2	Bourgarit *et al*. (33)
	HR=6•7 [b]	2•9 - 15•5	Bourgarit *et al*. (33)
Cardiac involvement	HR=2•47 [a]	1•3 - 4•8	Bourgarit *et al*. (33)
Cardiomyopathy	HR=3•54 [b]	1•2 - 10•7	Bourgarit *et al*. (33)
Gastrointestinal involvement	Not stated*		Guillevin *et al*. (46)
Proteinuria (>1 $g.d^{-1}$)	Not stated*		Guillevin *et al*. (46)

* Multivariate analysis; [a] Nonhepatitis B-related polyarteritis nodosa; [b] Hepatitis B-related polyarteritis nodosa; HR: Hazard ratio.

Mortality in Kawasaki disease

Kawasaki disease is an acute multisystem medium vessel vasculitis that primarily affects young children. It was first described in Japanese children (49) and has since been shown to have substantial ethnic and geographical variability. The incidence of Kawasaki disease has been increasing in recent years with rates described in children under five of 112 per 100,000 in Japan (50) and 8.1 per 100,000 in the UK (51).

The diagnosis of Kawasaki disease is based on clinical criteria and the exclusion of other conditions, including sepsis (52). Treatment is aimed at reducing inflammation and preventing vascular complications. The mainstays of treatment are aspirin and intravenous immunoglobulin (IVIG) (52, 53). The dose of IVIG has been shown to be related directly to the reduction in risk of developing coronary artery abnormalities (54). In other words, the highest doses of IVIG were associated with the lowest risk.

Virtually all the mortality associated with Kawasaki disease is attributable to involvement of the cardiovascular system. Between 20% and 40% of untreated Kawasaki disease patients will develop coronary artery abnormalities. Males and young children are most at risk (55). Coronary artery abnormalities develop within 8 weeks of Kawasaki disease onset (56). Approximately half of these lesions will regress to normal within 5 years (57, 58). Meta-analysis of treatment studies showed that a single high dose of IVIG (>1$g.kg^{-1}$) in combination with aspirin reduced coronary artery abnormality formation from 23% to 2.3% (54). Glucocorticoids, widely used in the treatment of other vasculitides, are associated with an increased rate of coronary artery abnormality formation (59), but their use remains controversial (52).

The Kawasaki Disease Follow-up Group in Japan has published by far the largest study, monitoring a cohort of 6576 patients with a history of Kawasaki disease since 1991. There were 8 deaths in the acute phase of the disease (0.12%), giving a standardised mortality ratio (SMR) of 8.2 (61). Twenty-seven patients died during the study, a number not significantly different from that expected in an age-matched population. Singh *et al*. (53) reported no deaths in their 10-year review of the acute management of Kawasaki disease patients in India.

Concern remains over the long-term effects of Kawasaki disease on future cardiac health. Iemura *et al*. (62) showed that even in patients with regressed coronary artery abnormalities, vascular wall function and morphology remained abnormal. They also showed normal function in patients who had not developed coronary lesions in the acute phase.

Burn *et al*. (63) reviewed 74 published cases of coronary artery disease attributed to previous childhood Kawasaki disease Twelve of these patients succumbed to sudden death, in an age range of 12 to 39 years old. More than 80% of presentations were related to strenuous exercise. Nearly half of all cases had no risk factors for cardiovascular disease other than previous Kawasaki disease. In patients who survived the acute phase of disease, the mortality rate was significantly increased in males with cardiac sequelae compared to the general population (SMR of 2.55) (61).

Summary

These results underline the need for strict risk factor control and regular review of all patients who develop cardiovascular sequelae of Kawasaki disease (Table V). Further studies of mortality rates beyond 40 years of age are needed to further elucidate the prevalence and severity of cardiovascular sequelae of Kawasaki disease.

Mortality in giant cell arteritis

Giant cell arteritis is a vasculitis characterised by granulomatous involvement of large and medium-sized blood vessels, particularly the extracranial branches of the carotid artery (64, 65). The frequency of giant cell arteritis increases with age, peaking in the eighth decade (66).

There is debate on the effect that giant cell arteritis has on mortality rates. Nordberg and Bengtsson (67) showed in a study of 284 participants that giant cell arteritis patients had a significantly increased rate of dying from vascular disorders in the initial few months of diagnosis. After 4 months, this risk

was similar to that found in the general population. Gran *et al*. (68) and Matteson *et al*. (69) reported no significant difference in mortality between those with giant cell arteritis and controls. In contrast, a study of 136 giant cell arteritis patients in Sweden reported increased mortality rates for women (SMR 1.42) and men (SMR 1.24) (70), usually secondary to cardiovascular complications. A summary of studies published is shown in Table VI. Mortality is given as standardised mortality ratios (SMR), where available.

The striking feature of these results is that, whilst there is a tendency towards increased mortality rates, very few studies showed statistical significance. This observation suggests that the studies may be underpowered. A detailed meta-analysis might clarify this matter further. Death due to cardiovascular disease does appear to be increased in patients with giant cell arteritis (67, 70, 71), possibly secondary to glucocorticoid use or the disease itself, or both. The data would also suggest that tight control of risk factors for ischaemic heart disease should be promoted in this population. Mortality secondary to malignancy appears to be reduced (70) and may reflect greater surveillance in patients with giant cell arteritis.

Summary

There is limited and contradictory evidence concerning a possible increased mortality rate in patients with giant cell arteritis over the normal population. Tight control of cardiovascular risk factors should be promoted in these patients. Malignancy rates have not been shown to be increased.

Table V. Positive and negative risk factors for Kawasaki disease cardiac complications.

Risk factors for cardiac complications subsequent to Kawasaki disease	
Increased risk	Reduced risk
Male	Female
Giant coronary artery abnormality formation (>8mm)	No coronary artery abnormality formation
Young age	
No IVIG treatment	Use of IVIG
Proximal coronary artery abnormalities	Distal coronary artery abnormalities

IVIG: Intravenous immunoglobulin.

Table VI. Summary of study data in giant cell arteritis.

Mortality	Number of patients	Risk factors identified	Source
RR 1•22	42 Norway	No evidence for effect of disease activity	Gran *et al*. (68)
♁ SMR 1•42* ♂ SMR 1•24	136 Sweden	Male Hypertension Age in women	Uddhamar *et al*. (70)
SMR 1•20 CVS SMR 1•44*	284 Sweden	Increased risk in first 4 months	Nordborg & Bengtsson (67)
Increased risk for females only* (rate not stated)	90 United Kingdom	Visual loss Prednisolone maintenance dose > 10mg	Graham *et al*. (91)
SMR 1•03	214 USA	None*	Matteson *et al*. (69)
No increase in mortality rate	210 Spain	IHD Age Hypertension	Gonzalez-Gay *et al*. (71)
SMR 1•62 in proven IHD cases	IHD subgroup 19	Normal temporal artery at biopsy	
SMR 2•12	43 Israel	None stated	Nesher *et al*. (88)
No increase in mortality rate	173 USA	None stated	Salvarani *et al*. (89)

RR: Relative risk; SMR: Standardised mortality rati; CVS: Cardiovascular-related death; IHD: Ischaemic heart disease; * statistically significant.

Mortality in Takayasu arteritis

Takayasu arteritis is a large vessel vasculitis of unknown aetiology primarily affecting the aorta and its principal branches. It was first described in 1908 (72), but the diagnosis has been greatly enhanced with the development of non-invasive vascular imaging. Subsequent studies have shown that, although the disease was previously regarded as relatively benign, patients often continue to develop new and progressive lesions despite a lack of symptoms (73-75).

Takayasu arteritis has been thought to be a disease primarily affecting young Asian women. However, it is now known to affect both sexes, with wide geographical and ethnic variation. The mainstay of treatment is a combination of medical and surgical therapies, with limited evidence supporting the use of anti-TNF agents in refractory cases (76).

A number of case series of patients with Takayasu arteritis have reported mortality rates and risk factors (73, 77-82). Comparing data between these studies is limited by the low incidence of Takayasu arteritis and the variety of criteria used to diagnose the condition. Some of these series span many decades, during which time there have been substantial improvements in general medical and surgical care. Retrospective application of American College of Rheumatology criteria can result in significant numbers of Takayasu arteritis cases being excluded from studies (83), complicating the interpretation of some of the longitudinal data.

In all of the Takayasu arteritis studies reviewed, the most frequent age of presentation was between 25 and 30 years, with the majority of patients being female (range 61% to 97%). Approximately 20% of patients present before the age of 20 and 20% after the age of 40 (82, 83).

Table VII shows the reported mortality figures for the studies reviewed. The wide variability in mortality rates (from under 3% to over 20%) reflects the variety of study populations, variable reporting practices, and range of

Table VII. Reported mortality rates in Takayasu arteritis.

Study	Population	Deaths (%)	Reported causes of death (in order of frequency)
Mwipatayi *et al*. (81) South Africa 1952-2002	272	57 (21•0)	Cardiac Failure Renal failure Stroke Ruptured aneurysm Postoperative complications
Jain *et al*. (79) India 16-y study	69*	12 (17•3)	Heart failure Renal failure Ischaemic complications
Ishikawa and Maetani (78) Japan 1957-1990	120	16 (17•1)	Congestive heart failure Cerebrovascular accident Postoperative complications
Dabague *et al*. (77) Mexico 1957-1994	237	22 (9•3)	Surgical complications Infections Atherosclerosis
Park *et al*. (82) South Korea 1991-2003	108	7 (6•5)	Congestive heart failure Ischaemic heart disease Cerebrovascular accident
Kerr *et al*. (80) USA 1970-1990	60	2 (3•3)	Widespread vascular lesions but clinically in remission Suicide
Maksimowicz-McKinnon *et al*. (73) USA 1992-2004	75	2 (2•7)	Postoperative complications Cerebrovascular disease

* follow up participants only.

Table VIII. Survival rates in 108 patients with Takayasu arteritis.

	5-y survival	10-y survival
Overall	92•9%	87•2%
One or less complication	100%	96•8%
Two or more complications	69•9%	36•7%

Park *et al*. (2005) (82)

study periods. Park *et al*. (82) examined the influence of serious complications on survival rates. Complications were defined as a life threatening or disabling condition attributable to Takayasu arteritis. They included valvular heart disease, stroke, heart failure, retinopathy, and renovascular hypertension. The presence of two or more serious complications led to significantly greater 5- and 10-year mortality rates (Table VIII). Clinical manifestations, intitial disease activity, angiographic classification, laboratory findings, and presence and frequency of relapses were not associated significantly with mortality.

Ishikawa and Maetini (78) showed an overall survival rate of 82.9% at 15 years postdiagnosis. The median age at time of death was 48 years (range 21-65). They also identified different survival rates depending on date of diagnosis. Those diagnosed with Takayasu arteritis between 1957 and 1975 had a 14-year survival rate of 79.9% compared to 96.5% in those diagnosed between 1976 and 1990. The presence of a major complication (retinal microaneurysm formation; brachial pressure ≥200 systolic or ≥110 diastolic (or popliteal ≥230 or 110 respectively); aortic regurgitation ≥grade 3; aortic or arterial aneurysm ≥ twice normal diameter) or a progressive course (increasingly symptomatic) were found to be associated significantly with mortality. In addition, a low ESR (<20 $mm.h^{-1}$) predicted poorer outcomes (Table IX). The lack of a significant inflammatory response may result in undertreatment.

Summary

Takayasu arteritis has an overall 10-year survival rate of approximately 90%, although this rate is rate reduced by the presence of complications as listed above. Optimal management of these factors has the potential to reduce mortality. There is an absence of prospective and randomised controlled trial data in Takayasu arteritis.

Conclusions

Despite advances in immunosuppressive treatments, we recognise that not all patients survive their disease. Early deaths are due primarily to active disease or infection, or both. The mortality of ANCA-associated vasculitis is generally greater than for other types of vasculitis. Late deaths (after the first year) are more likely to occur as a result of the increasing burden of comorbidities but can also relate to flares of disease and infection. Improvement in the management of comorbidities may account for a significant reduction in deaths, especially better management of infection and more effective surgical intervention, for example in polyarteritis nodosa or Takayasu arteritis.

Age emerges as a significant risk factor in most diseases, particularly over longer periods of observation. Whether this reflects limited reserve function in organs affected or some more generalised association with increased comorbidity is not entirely clear. In patients with giant cell arteritis, the risk of cardiovascular complications has previously been explained by the overlapping arteritis and atherosclerosis, based on histological observations (84). However, a recent study failed to demonstrate any association between carotid intima-media thickness and disease activity in patients with giant cell arteritis (85).

The absence of upper airway involvement in Wegener's granulomatosis may reflect a bias in disease recognition. Patients who develop upper airway disease will usually have symptoms that encourage them to get medical attention. By contrast, new onset glomerulonephritis may be asymptomatic, so that by the time the patient comes to medical attention damage may already have occurred, leading to reduced organ

Table IX. Prognostic effect of clinical characteristics in Takayasu arteritis.

Major complication	-	-	-	+	-	+	+	+
Progressive course	-	-	+	-	+	-	+	+
Low ESR (< 20 $mm.h^{-1}$)	-	+	-	-	+	+	-	+
15-y survival rate		100%			83•6%		43•0%	

+ = Presence; - = Absence
Ishikawa & Maetani (1994) (78)

function and increased mortality risk (86). The presence of persistently high levels of PR3 ANCA is a risk for relapse as well as mortality in Wegener's granulomatosis, although ANCA titres are not a reliable guide to therapy (87). Cardiovascular involvement, although uncommon, is the most pertinent complicating feature of Churg-Strauss syndrome. By contrast with other forms of small vessel vasculitis, Henoch-Schönlein purpura is associated with a very low mortality, unless there is significant renal disease at onset. Unlike other forms of vasculitis, there is no demonstrable benefit from the use of current immunosuppressive therapy.

The acute mortality risk in Kawasaki disease is an important driver for early diagnosis and treatment. For children with this disease who develop permanent abnormalities of coronary arteries, premature death from heart disease may result in a substantial increase in late mortality.

In less common forms of vasculitis such as Takayasu arteritis it is difficult to extrapolate from limited data. Whilst the outcome overall is better than for small vessel ANCA-related disease, significant racial variation and heterogeneity is seen in the vascular territory affected. The different therapeutic regimens applied and the ability to detect sub-clinical disease with modern imaging could account for the very substantial differences in reported outcome.

The 5-factor score remains an important indicator of future outcome and has been used to determine initial therapy. BVAS is better suited to providing support for current management of the patient. If we can develop more effective clinical scores or biomarkers to identify patients most at risk of death or severe organ dysfunction/failure and identify the mechanisms responsible, targeted therapy will become a more practical and effective approach to improving outcome in systemic vasculitis.

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