


percentage of normal glomeruli in the diagnostic biopsy [8,9].
However, even in those presenting with severe histological
findings and very low numbers of normal glomeruli, treatment
should be given as the chance of renal recovery is greater than
for therapy-related death [10].
Ear, nose and throat disease in GPA has a high risk of causing
irreversible damage and chronic symptomatology. Collapse of
the bridge of the nose can be corrected by bone or cartilage
grafts and restorative procedures should only be performed
when the disease is thoroughly controlled. Damage to the nasal
mucosa results in nasal crusting which provides a focus for
infection as well as causing nasal obstruction. Regular nasal
douching and use of a topical aseptic cream, such as, mupirocin,
Hearing loss is usually caused by eustachian tube obstruction
and recurrent otitis media but may also result from damage to
the eighth cranial nerve. Subglottic, tracheal or bronchial
stenoses can be fibrotic in origin reflecting previous episodes
of vasculitic damage to the airways. Physical dilatation can
restore the lumen but multiple procedures may be required.
The long-term outcome of alveolar haemorrhage is usually
good with stable lung function but a minority of patients
present with overlapping features of ANCA vasculitis and
pulmonary fibrosis [12,13]. The lung fibrosis can precede or
follow vasculitis and be progressive leading to respiratory
failure despite control of vasculitis. This pattern is more
commonly associated with the MPO-ANCA subtype.
AAV is also associated with an increased risk of venous throm-
boembolism, especially when the disease is active [14,15].
Autoantibodies to plasminogen and tissue plasminogen acti-
vator occur in the sera of 25% and 14% of AAV patients. Their
presence has been associated with more severe renal out-
comes and increased risk for thromboembolic events [16].
Avoidance of classical risk factors for venous thromboembolism
is important, as well as the use of prophylaxis during prolonged
immobility.
Despite resolution of disease activity, poor quality of life often
persists in AAV patients with fatigue described as the main
contributor [17,18]. Despite many patients having significant
organ damage, quality of life measures do not appear to
correlate with the extent of damage [17,19]. The mechanisms
of fatigue are complex, and likely to involve a balance between
disease and psychosocial factors.

**Morbidity due to treatment**

Improvement in survival has resulted from improved treatment
strategies; however adverse events associated with these
treatments are now an important cause of death and morbidity.
Infection is common. In one study, 25% of patients recruited to
four EUVAS studies developed infection within the first year
following diagnosis. Respiratory tract and generalised septi-
caemia were the most common infections [20]. Both corticos-
teroid and cytotoxic therapy are known to contribute to the
increased risk of infection [21].
 Opportunistic infections are also increased in patients with AAV
treated with immunosuppression. The occurrence of Herpes
Zoster Varicells (HZV), shingles, occurs more often in AAV
patients, with a frequency of 4.5 episodes of HZV/100
patient-years, than a healthy population [21,22].
*Pneumocystis jiroveci* infection (previously known as
*Pneumocystis carinii*) is reported in patients with AAV with
an incidence of 0.85–12% [23–25]. The presentation of
*Pneumocystis* infection and HZV often occurs when immuno-
suppressive therapy is most intensive, although not always.
The use of rituximab is increasing in patients with AAV. Infection
associated with this therapy remains a concern, as there were
no differences in the infection rates in the two published trials
that compared cyclophosphamide to rituximab as induction
therapy [26,27]. However, this may relate to glucocorticoid
use as infection rates are low in RA patients treated with
rituximab [28]. Predictors of infection in those receiving
rituximab include low IgG before treatment, chronic lung and
cardiac disease [29]. The risk of progressive multifocal leu-
koencephalopathy continues to cause concern [30].
Those at risk of infection should be identified and interventions
undertaken to reduce risk. Factors predictive of infection include
age, severity of renal dysfunction, leucopenia and intensity and
duration of immunosuppression [20,31,32]. Guidelines advocate
the use of prophylaxis against *P. jiroveci* in patients receiving
cyclophosphamide [33]. Leucopenia is common, especially in
those receiving oral cyclophosphamide [20] and should be
avoided with close monitoring. Leucopenic patients can safely
be treated with G-CSF [34] although a recent study in an animal
model of AAV suggests G-CSF may exacerbate disease [35].
Influenza vaccinations are safe and effective in AAV without
association with relapse [36]. Pneumococcal vaccination is
recommended but response rates are often poor when using
the polysaccharide vaccine, pneumovax. Live vaccines should
be avoided in all patients taking immunosuppressives or pre-
dnisolone doses above 5 mg/d. In those AAV patients on
standard maintenance therapy, maintenance of protective
levels of antibody to other vaccines such as diphtheria, tetanus
and polio may be shorter than in immunocompetent patients
and may require more frequent booster vaccinations [37]. AAV
patients who receive rituximab may be unable to respond to
vaccination with new antigens although they do maintain their
recall responses and respond to booster vaccination [38].
Other adverse events are specific to treatments. Glucocorticoids
are known to have a broad adverse event profile, including
steroid-associated diabetes, avascular necrosis and ocular cat-
aract formation, and these should all be monitored for during
treatment. Prophylaxis against osteoporosis and peptic ulcer-
anoma has become routine, especially in those receiving high dose
corticosteroids. Reduced bone mineral density is common in
patients with AAV; in one study of 99 patients with AAV, 57% had osteopenia and 21% had osteoporosis in at least one site [39]. Studies report fractures rates of 2.5–15% [40,41]. The adverse events specific to cyclophosphamide, other than infection and bone marrow suppression, include hair loss, hemorrhagic cystitis and infertility. Hemorrhagic cystitis is reported to occur with a frequency of 0.5/100 patient-years and is associated with oral cyclophosphamide use and total cumulative dose [42]. Prevention of hemorrhagic cystitis is important as an episode increases the risk of bladder cancer 5–7 times. The risk of hemorrhagic cystitis can be reduced by concomitant treatment with mesna, which binds to the cyclophosphamide toxic metabolite, acronolein [33,43]. Few studies have addressed the risk of infertility in AAV. However, in general, the risk of ovarian failure is dependent on the cumulative dose of cyclophosphamide and the age of the patient, with older women being at higher risk [44,45]. Minimising the dose of cyclophosphamide is therefore important, as well as the continuing development of methods of fertility preservation [46,47]. Patients should be counselled as to the risk of infertility, and cryopreservation of sperm and oocytes should be offered if appropriate [48].

The use of cytotoxic therapy increases the risk of malignancy. Studies with long follow-up times reveal increased incidence of malignancy with greater than a twofold increase on the background population. The increased risk varies according to the organ affected: 4.8–33-fold increase in bladder cancer rates, a 10-fold increase in non-melanoma skin cancer and 4.2–11-fold increases in lymphoma [21,48–51]. More recent publications are contradictory about the risk of malignancy using current cyclophosphamide regimens, as proposed by the EUVAS trials. At 5 years follow-up, the risk of malignancy is only increased for non-melanoma skin cancers in those patients recruited to four EUVAS trials [52] but a French study suggests that urinary tract cancer remains increased at 5 years follow-up [42]. Azathioprine increases the risk of skin cancer.

There is considerable evidence that the risk of cardiovascular disease is elevated in patients with AAV [53,54] although the aetiology of this is unclear with both disease and therapy factors being implicated. Risk factors include MPO-ANCA positivity, hypertension and kidney disease as well as traditional risk factors [55,56]. Endothelial dysfunction, possibly related to inflammation, is present in AAV [57,58] and is a risk factor for cardiovascular disease. Treatment with corticosteroids may also increase cardiovascular disease risk further [59,60]. In the light of current studies, AAV patients with traditional cardiovascular risk factors should be identified and treated to prevent disease.

Conclusions

AASV is a chronic relapsing/remitting inflammatory disease requiring prolonged treatment. The impact of disease and therapy on patient’s physical and emotional well-being is significant, with many patients experiencing reduced quality of life despite successful therapy. The mortality incurred by patients suffering from AASV has fallen steadily but the chronic relapsing nature of the disease, without definitive treatments that offer cure, continues to extract a heavy toll on the health of afflicted individuals. The challenge for the future is to develop specific therapies to cure disease with improved side-effect profiles. Until then, we need to manage our current therapies more effectively with improved prevention of toxicities associated with therapy.

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References


Lectures

L43. Seropositive and negative ANCA-associated vasculitis, anti-MPO and PR3-vasculitis: Different outcomes?

Clinical definition of ANCA-associated vasculitis (AAV) and association with serotype

The AAV comprise a heterogeneous group of the three distinct forms, namely microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly: Wegener’s granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly: Churg-Strauss syndrome). From the clinical point of view and according to the disease definitions and classification criteria, they share the manifestation of small- to medium-size vessel vasculitis which is strongly associated with anti-neutrophil cytoplasm antibodies (ANCA). Whereas MPA has no additional features and seems to represent a mere vasculitic disease, GPA is characterised by a granulomatous inflammatory process predominantly occurring in the upper and lower respiratory tract and asthma, eosinophilia and granulomatous inflammation are additional hallmarks of EGPA. Interestingly, GPA and EGPA seem to follow a stage-wise course. In GPA, the initial stage is referred to as localized GPA which is defined by upper and lower respiratory disease and no clinical signs of vasculitis. Nearly half of the patients with localized disease are ANCA-negative. Upon the evolvement of vasculitic symptoms (early systemic, generalized and severe disease), the vast majority of patients are ANCA-positive. Persistent localized disease in GPA is rare (5% of patients). Therefore, GPA cohorts are mainly represented by patients with systemic, ANCA-positive disease. Asthma followed by marked eosinophilia and subsequent vasculitis manifestations marks the disease course in EGPA. A predominant vasculitic phenotype with strong ANCA association can be distinguished from a phenotype with predominant eosinophil-associated organ manifestations that is usually ANCA-negative. All in all, only 40% of EGPA patients are ANCA-positive.

In MPA, which is characterised by systemic vasculitis manifestations only, most patients are ANCA-positive. Therefore, seronegative AAV is mainly represented by the initial stages of GPA and EGPA and the “eosinophilic” EGPA phenotype. It is not clear why GPA has a strong association with ANCA directed against proteinase 3 (PR3-ANCA) whereas MPA and EGPA are predominantly associated with ANCA against myeloperoxidase (MPO-ANCA). Importantly, the first genome-wide association study in GPA and MPA clearly identified that GPA and MPA are genetically distinct diseases. Yet, the study also revealed that the association with identified significant single nucleotide polymorphisms (SNPs) was stronger with the ANCA type (PR3-ANCA vs. MPO-ANCA) than with the clinical syndrome questioning the classification of patients on clinical and histopathological grounds. The GWAS results are supported by several recent clinical studies demonstrating that allocation to ANCA-serotype as well as specific organ involvement may also be relevant with respect to outcome.

Apart from AAV disease type and ANCA-serotype, outcome is also influenced by intensity and duration of immunosuppressive treatment, pattern of organ involvement as well as age and gender.

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