Review

Value of anti-infective chemoprophylaxis in primary systemic vasculitis: what is the evidence?

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Abstract

Although infections are a major concern in patients with primary systemic vasculitis, actual knowledge about risk factors and evidence concerning the use of anti-infective prophylaxis from clinical trials are scarce. The use of high dose glucocorticoids and cyclophosphamide pose a definite risk for infections. Bacterial infections are among the most frequent causes of death, with Staphylococcus aureus being the most common isolate. Concerning viral infections, cytomegalovirus and varicella-zoster virus reactivation represent the most frequent complications. The only prophylactic measure that is widely accepted is trimethoprim/sulfamethoxazole to avoid Pneumocystis jiroveci pneumonia in small vessel vasculitis patients with generalised disease receiving therapy for induction of remission.

Introduction

In patients with small vessel vasculitis (SVV), infectious complications are at least as often the cause of death as uncontrolled disease activity. For example, in the recently published MEPEX-trial about 25% of the patients did not survive the first year, and most of the deaths were attributable to overwhelming infectious complications [1]. Despite the fact that infections substantially contribute to morbidity and mortality in patients with primary systemic vasculitis (PSV), data on risk factors and on the burden of specific infectious agents are scarce. In oncology, recommendations for anti-infective chemoprophylaxis (AIP) are often derived from randomised controlled trials evaluating the effectiveness of the prophylactic intervention itself [2,3]. Such data are widely missing in PSV.

However, some conclusions might be drawn from therapeutic trials and cohort studies. For this purpose we analysed 35 such trials [4-37], which were selected according to quality, patient number and availability of at least some data on infectious complications (Table 1). Regarding AIP, these data still have to be interpreted with caution: infection rates are documented and published with varying degrees of accuracy depending on the design of the studies. Mild and moderate infections - that is, those not requiring hospitalisation - appear to be underestimated, whereas it can be assumed that deaths due to infections are reported thoroughly.

Furthermore, there are great variations in the use of AIP: some trials used routine prophylaxis against Pneumocystis jiroveci pneumonia (PCP; formerly named Pneumocystis carinii), other fungi and cytomegalovirus (CMV), and others did not. Most protocols left the use of AIP optional and in many the actual use was not even recorded, or at least not reported. Finally, the therapeutic intervention is given infrequently in sufficient detail; for example, the cumulative dose of glucocorticoids (GCs) is usually not mentioned.

When thinking about AIP, both the individual risk for the patient and the evidence for the efficiency and safety of the prophylactic intervention must be taken into account.

Factors influencing susceptibility to infections

Because, to date, no PSV trials have used infection as the primary endpoint, information on possible risk factors can only be retrieved from adverse event reporting in cohort studies or therapeutic trials. In Table 1 the rates of infections, serious infections and fatal infections in different entities and under distinct medication are summarised. In conjunction with data from other medical conditions the following conclusions might be drawn.

AAV = ANCA associated vasculitis; AIP = anti-infective prophylaxis; ANCA = antineutrophil cytoplasmic antibody; BSR = British Society for Rheumatology; CMV = cytomegalovirus; Cyc = cyclophosphamide; EULAR = European League Against Rheumatism; GC = glucocorticoid; GCA = giant cell arteritis; HZ = herpes zoster; MTX = methotrexate; PCP = Pneumocystis jiroveci pneumonia; PSV = primary systemic vasculitis; SVV = small vessel vasculitis; TB = tuberculosis; TNF = tumour necrosis factor; T/S = trimethoprim/sulfamethoxazole; VZV = varicella-zoster virus; WG = Wegener’s granulomatosis.
Table 1

Rates of infections, mortality and infection related mortality in major studies on primary systemic vasculitis

| Study                        | Type of study | Indication | Intervention | Prophylaxis | N       | Follow up (months) | Reported infections (classified as serious) | Type of infections (number of patients) | Total deaths (%) | Death due to or in conjunction leading to death (number of patients) |
|------------------------------|---------------|------------|--------------|-------------|---------|-------------------|---------------------------------------------|----------------------------------------|------------------|---------------------------------------------------------------------|
| **Giant cell arteritis**     |               |            |              |             |         |                   |                                             |                                        |                  |                                                     |
| Matteson *et al.* 1996 [4]  | RCT           | GC ± MTX   | None         | INH AA      | 42      | 24                | 18 (4)                                     | Pneu (1), TB (1), PN (1), CC (1)   | 0                | NA                                                                 |
| Chevalet *et al.* 2000 [5]  | RCT           | GC ± initial GC iv pulse | None | 164 | 12 | 31 (22) | Pneu (20), Sep (1), Abs (1) | 5 (3) | 0 | NA |
| Jover *et al.* 2001 [6]     | RCT           | GC ± MTX   | INH AA       | 42          | 18 (4) | 3 (24) | 3 (6) | NI |
| Hoffman *et al.* 2002 [7]   | RCT           | GC ± MTX   | None         | 98          | 12     | 8 (0) | 0 | 0 | NA |
| Mazlumzadeh *et al.* 2006 [8] | RCT          | GC ± initial GC iv pulse | None | 27 | 12 | 18 (0) | 0 | 0 | NA |
| Hoffman *et al.* 2007 [9]   | RCT           | GC ± Inflix | TS           | 44          | 5.5    | 8 (0) | 0 | 0 | NA |
| Martinez-Taboada *et al.* 2007 [10] | RCT     | GC ± Eta   | INH AA       | 17          | 12     | 8 (0) | 0 | 0 | NA |
| **Takayasu arteritis**      |               |            |              |             |         |                   |                                             |                                        |                  |                                                     |
| Hoffman *et al.* 2004 [11]  | CS            | GC + Inflix or Eta | None         | 15          | 22     | 0 | 0 | NA |
| **Churg-Strauss syndrome/polyarteritis nodosa** | | | | | | | | | | |
| Cohen *et al.* 2007 [12]    | RCT           | GC + 6 pulse CY versus 12 pulse CY | TS recommended | 48 | 42 | 21 (Ni) | 4 (8) | 3 (75) | CMV (1), Pneu (1) and NI |
| Gayraud *et al.* 1997 [13]  | RCT           | GC + pulse CY versus oral CY | None | 25 | 60.8 | 7 (Ni) | 1 (4) | 1 (100) |
| Guillevin *et al.* 1995 [14] | RCT         | GC + pulse CY ± PE | TS | 62 | 33 | 8 (Ni) | 11 (17) | 2 (18) | 
| Guillevin *et al.* 1992 [15] | RCT         | GC ± PE | None | 78 | 44 | 8 (Ni) | 15 (19) | 2 (13) | Sep (1) and NI |
| Guillevin *et al.* 1991 [16] | RCT         | GC + PE ± CY | None | 71 | 69 | 8 (Ni) | 19 (27) | 5 (26) | Preu/Sep (4), TB (1) |
| **Microscopic polyangiitis**|               |            |              |             |         |                   |                                             |                                        |                  |                                                     |
| Nachman *et al.* 1996 [17]  | CS            | GC + CY    | NI           | 107         | 44     | 6 (6) | 2 (33) | Sep (2) |
| **Wegener's granulomatosis**|               |            |              |             |         |                   |                                             |                                        |                  |                                                     |
| Metzler *et al.* 2007 [18]  | RCT           | GC + Lef or MTX | None | 54 | 21 | 25 (0) | 0 | 0 | NA |
| WGET Research Group 2005 [19] | RCT, M | GC + CY/MTX ± Eta | TS | 174 | 27 | 8 (Ni) | 6 (3.5) | 2 (33) | Sep (2) |

Continued overleaf
| Study                        | Type of study | Indication | Intervention                          | Prophylaxis                  | N  | Follow up (months) | Reported serious infections (number of patients) | Type of serious infections      | Total deaths (%) | Death due to or in conjunction with infection (% of total deaths) | Type of infection leading to death (number of patients) |
|-----------------------------|---------------|------------|---------------------------------------|------------------------------|----|-------------------|-----------------------------------------------|------------------------------|-----------------|-----------------------------------------------------------------|--------------------------------------------------|
| **Wegener's granulomatosis** (continued) |               |            |                                       |                              |    |                   |                                               |                              |                 |                                                                 |                                                   |
| Schmitt *et al.* 2004 [20]  | UCT I         |            | GC + ATG                             | Optional TS, optional fung, optional CMV | 15  | 21.8              | NI (6)                                        | Pneu (2), Abs (1), UTI (1), CMV (1), Col (1) | 2 (13)          | 1 (50)                                                          | Pneu (1)                                          |
| Metzler *et al.* 2004 [21]  | UCT M         |            | GC + Lef                             | None                         | 20  | 21                | 9 (1)                                        | Pneu (1)                                | 0               | 0                                                              | NA                                                |
| Bligny *et al.* 2004 [22]  | CS I, M       |            | Mainly GC + CY                       | TS or Penta in most patients | 93  | 54                | NI (54)                                       | PCP (12), Asp (5), VZV (3), CMV (6), Sep (8), Papo (1), TB (4), Abs (1), Toxo (2) | 25 (27)         | 13 (52)                                                         | PCP (5), CMV (2), Pneu (3), Asp (3), TB (1), Papo (1) |
| Reinhold-Keller *et al.* 2002 [23] | UCT M         |            | GC + MTX                             | None                         | 71  | 25.2              | 7 (0)                                         | NA                                        | 2 (3)           | 0                                                              | NA                                                |
| Mahr *et al.* 2001 [24]     | CS I          |            | GC + CY                              | TS in most patients          | 49  | 23                | NI (31)                                       | PCP (19), Asp (5), CMV (5), TB (2), VZV (2), Papo (1), Sep (2), SA (1) | 18 (37)         | 7 (39)                                                          | PCP (5), Sep (1), Pneu (3), Asp (2), Papo (1), CMV (1) |
| Reinhold-Keller *et al.* 2000 [25] | CS I, M      |            | Mainly GC + CY followed by MTX or TS | TS in case of CY             | 155 | 84                | NI (56)                                       | Pneu (32), Sep (10), CMV (3), PCP (1)    | 22 (14)         | 5 (23)                                                          | Sep (4), Pneu (1)                                  |
| Guillevin *et al.* 1997 [26] | RCT I         |            | GC + oral CY versus GC + pulse CY    | TS in most patients after high incidence of PCP in the first patients | 50  | 27                | NI (25)                                       | Pneu (3), Sep (3), SA (1), CMV (4), Papo (1), PCP (10) | 19 (38)         | 9 (47)                                                          | PCP (6), Pneu (1), Sep (1), Papo (1)               |
| de Groot *et al.* 1996 [27] | RCT M         |            | MTX versus TS ± GC                   | No additional                | 65  | 22                | NI                                            | NI                                        | 0               | 0                                                              | NA                                                |
| Stegeman *et al.* 1996 [28] | RCT M         |            | Placebo versus TS                    | No additional                | 81  | 24                | NI                                            | NI                                        | 1 (1.2)         | 0                                                              | NA                                                |
| Sneller *et al.* 1995 [29]  | UCT I         |            | GC + MTX                             | None                         | 42  | 19                | NI (4)                                        | PCP (4)                                  | 3 (7)           | 2 (67)                                                          | PCP (2), Cryp (1)                                  |

**ANCA-associated vasculitis**

| Study                        | Type of study | Indication | Intervention                          | Prophylaxis                  | N  | Follow up (months) | Reported serious infections (number of patients) | Type of serious infections      | Total deaths (%) | Death due to or in conjunction with infection (% of total deaths) | Type of infection leading to death (number of patients) |
|-----------------------------|---------------|------------|---------------------------------------|------------------------------|----|-------------------|-----------------------------------------------|------------------------------|-----------------|-----------------------------------------------------------------|--------------------------------------------------|
| Pagnoux *et al.* 2008 [30]  | RCT M         |            | GC + MTX versus Aza                   | TS or Penta                  | 126 | 12                | 46 (6)                                        | Sep (2)                                   | 1 (0.8)         | 1 (100)                                                         | Sep (1)                                          |

*Continued overleaf*
| Study | Indication | Intervention | Prophylaxis | N | Follow up (months) | Type of infections (number of patients) | Type of serious infections (number of patients) | Total deaths (%) | Death due to or in conjunction with infection (% of total deaths) | Type of infection leading to death (number of patients) |
|-------|------------|--------------|-------------|---|-------------------|-------------------------------------|-----------------------------------------------|----------------|------------------------------------------------|-----------------------------------------------|
| Walsh et al. 2008 [31] | UCT | I | GC + Campath-1H | Acyc, fungi | 71 | 60 | 31 (21) | Staph (10), CMV (2), PCP (2), Asp (2), Sal (19), Pseu (1), Acti (1) | 31 (44) | 12 (39) | NI |
| Jayne et al. 2007 [1] | RCT | I | GC + oral CY + PE versus iv GC pulse | TS suggested | 137 | 12 | 61 (37) | NI | 35 (26) | 19 (54) | NI |
| de Groot et al. 2005 [32] | RCT | I | GC + CY versus MTX | Optional TS | 100 | 18 | 18 (8) | CMV (1), SA (1), Cory (1), Pneu (2), UTI (1) | 4 (4) | 1 (25) | CMV (1) |
| Booth et al. 2004 [33] | UCT | I | GC + Inflix ± CY | TS, fungi | 32 | 16.8 | NI (7) | Pneu (3), Sep (1), Abs (1), Opht (1) | 2 (6) | 1 (50) | Pneu (1) |
| Birck et al. 2003 [34] | UCT | I | GC + DSG | NI | 20 | 12 | NI | NI | 1 (5) | 1 (100) | PCP (1) |
| Jayne et al. 2003 [35] | RCT | I, M | GC + oral CY followed by GC + oral CY versus Aza | TS recommended | 155 | 18 | 33 (11) | NI | 8 (5) | 5 (63) | Pneu (2) and NI |
| Haubitz et al. 1998 [36] | RCT | I | GC + oral CY versus pulse CY | None | 47 | 40 | NI (13) | Sep (4), Pneu (5), VZV (1), CMV (1), Endo (1), SD (1) | 3 (6) | 3 (100) | Sep (3) |
| de Groot et al. 2009 [37] | RCT | I | GC + oral CY versus pulse CY | TS | 149 | 18 | 51 (17) | Pneu (3), Sep (3), Div (1), PCP (1), HSV (1), Abs (1) | 14 (9.4) | 6 (43) | Sep (6), PCP (1) |

Large differences in infection-related mortality between the different indications can be observed. Mortality from infections is much less frequent in giant cell arteritis than in ANCA-associated vasculitis. In small vessel vasculitis the phase of induction of remission confers much more susceptibility to infections than the maintenance phase. Bacterial infections are the most frequently mentioned causes of death. Types of infections are given as clinical conditions or causative agents as information was available. aThe sum might be smaller than the number of serious infections due to missing information. bThe sum might be higher than the number of deaths as in some patients more than one infection was involved. Types of study are: CS, cohort study; RCT, randomized controlled trial; UCT, open label uncontrolled trial. Indications are: I, induction therapy; M, maintenance. Interventions are: ATG, anti-thymocyte globulin; Aza, azathioprine; CY, cyclophosphamide; DSG, deoxypergualin; Eta, etanercept; GC, glucocorticoid; Inflix, infliximab; Lef, leflunomide; MTX, methotrexate; PE, plasma separation; TS, trimethoprim/sulfamethoxazole. Prophylaxis: Acyc, acyclovir; fungi, anti-fungal prophylaxis using ether nystatin, fluconazole or amphotericin; INH, isoniazid; Penta, pentamide; TS, trimethoprim/sulfamethoxazole. Types of infection are: Abs, abscess; Acti, Actinomyces sp.; Asp, aspergillosis; CC, cholecystitis; CMV, cytomegalovirus; Col, colitis; Cory, Corynebacterium sp.; Cryp, cryptococcus; Div, diverticulitis; End, endocarditis; Histo, histoplasmosis; HSV, herpes simplex virus; Ophth, ophthalmitis; Papo, papovavirus encephalitis; PCP, Pneumocystis jiroveci pneumonia; PN, pyelonephritis; Pneu, pneumonia; Pseu, Pseudomonas sp.; SA, septic arthritis; Sal, Salmonella sp.; SD, spondylodiscitis; Sep, septicaemia; Sig, sigmoiditis; Staph, Staphylococcus sp.; TB, tuberculosis; Toxo, toxoplasmosis; UTI, urinary tract infection; VZV, varicella zoster virus. Other abbreviations: AA, as appropriate; ANCA, antineutrophil cytoplasmic antibody; iv, intravenous; NA, not applicable; NI, no information.
Medication

It is obvious that immunosuppressive medication is a major risk factor for infections [38]. A high GC dose (often defined as more than 30 mg per day prednisolone-equivalent), especially in the form of intravenous methylprednisolone, is a significant risk factor [1,39]. With respect to common clinical experience, its importance seems to be underestimated in clinical trials because, for example, the cumulative GC dose is not usually stated. In a study on giant cell arteritis (GCA) solely treated with GCs, 86% of the patients experienced severe GC-related adverse events, including severe infections in 31% [40]. Schmidt and colleagues [41] reported a relative risk of severe infections - that is, infections leading to hospitalisation - of 2.44 in the first 6 months of GC treatment in a large GCA trial and increased infection-related mortality. Rising awareness of GC complications, including infections, makes GC sparing an increasingly important aim. According to the European League Against Rheumatism (EULAR) recommendations for conducting clinical trials in PSV, protocols should be designed to reduce patients' total exposure to GCs, which includes recording cumulative GC doses and the use of GC-sparing drugs like methotrexate (MTX) [42].

Although some trials using cyclophosphamide (Cyc) report very low rates of infectious complications [17,33], Cyc use in SVV is associated with higher rates of infections and fatalities than the use of medium potent immunosuppressants such as MTX, azathioprine or leflunomide [22,24,26]. Among the latter no differences concerning rates and types of infections can be derived from the available data. When analysing infectious complications, it has to be taken into account that treatment changes over time. For example, the CYCAZAREM-trial demonstrated that oral Cyc could safely be substituted by azathioprine after achieving remission, leading to much lower cumulative Cyc doses [35]. The use of Campath-1H, a monoclonal antibody to CD52 that leads to lymphocyte depletion and profound neutropenia, was associated with high rates of infectious complications, as was expected from its use in haematology [32]. A clear association of drugs with specific types of infections, as is known for tuberculosis (TB) and anti-TNF-α agents, can not be derived from the still limited data from PSV trials.

Types of vasculitis

As shown in Table 1, there are large differences regarding the forms of PSV and their infection-related mortality. Infections and mortality from infectious complications are much more prevalent in SVV than in large vessel vasculitis. In GCA trials, mortality ranged from 0 to 0.03 deaths per patient year and infections caused 0 to 33% of these deaths [4-11]. In SVV this range was 0 to 0.26 deaths per patient year and infections were involved in 0 to 100% of the fatal events [1,17-37].

Interestingly, in most published clinical trials in GCA, PCP prophylaxis was not used. Despite the fact that high doses of GCs are a major risk factor for the development of PCP, no case of PCP has been reported within these trials [4-10]. In contrast, patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), especially those with Wegener's granulomatosis (WG), are at high risk for PCP that can not be attributed only to medication [18-29]. There is evidence that at least some entities within the group of PSV confer an altered function of the immune defence per se. In WG, for instance, the granulomatous inflammation of the upper respiratory tract leads to destruction of the barrier function of the surfaces, possibly allowing for invasion of pathogens [43]. It may also be possible that a primary barrier deficiency not only promotes infections but has a role in the aetiology of the disease itself [44].

Disease stage and phase of therapy

In PSV, and especially in SVV, the therapeutic approach usually consists of an induction of remission and a maintenance phase (for review, see [45]). For induction, more aggressive regimens, including Cyc and higher GC doses, are utilised. Furthermore, in SVV the selection of drugs depends on the stage of the disease: in the localised and early systemic stage - that is, disease without threatened vital organ function - induction of remission is usually attempted with medium potent immunosuppressants such as MTX, whereas in generalised and severe disease - that is, with threatened vital organ function or organ failure, respectively - Cyc is used.

In SVV the induction of the remission period is the most vulnerable phase concerning infections and mortality. From studies assessing only maintenance of remission, published mortality rates ranged from 0 to 0.01 deaths per patient year and infections did not significantly contribute to those fatalities [18,21,23,27,28,30]. In contrast, trials on induction of remission in SVV reported mortality rates up to 0.26 per patient year. In those trials infections were responsible for the fatal events in up to 100%, and about 50% of deaths, on average, were due to infections [1,17,20,22,24,26,29,31-37]. Accordingly, mortality was higher in study populations with more severe disease. The highest reported rate was in SVV patients who presented initially with organ (renal) failure [1]. But even in this population, in which one might expect a higher contribution of uncontrolled disease to the death rate, infections are involved in more than 50% of the fatal outcomes.

Types of infection and options for prophylaxis

Bacterial infections

In PSV trials Staphylococcus aureus is the isolate for which fatal outcome has been reported most frequently. As demonstrated in surgical patients and patients on dialysis, prophylactic topical treatment with mupirocin ointment for nasal carriers of S. aureus leads to a significant reduction in the rate of infections with this agent (relative risk 0.55 according to [46]). Especially in WG, the incidence of nasal
incidence of PCP is up to 20% [26] and many fatalities have undergone induction therapy. Without using prophylaxis the risk of PCP is especially high in patients with SVV colonisation with *S. aureus* [28]. It is not clear whether this effect is achieved by its antibiotic or its immunomodulatory properties. Although its primary end point was relapse rates, the study by Stegeman and colleagues [28] clearly demonstrated a reduction in respiratory-tract as well as non-respiratory-tract infections using T/S in WG patients in remission. This study can be regarded as the only large scale trial of anti-infective prophylaxis in vasculitis.

As topical mupirocin does not cause serious adverse events [46], it is used in some vasculitis centres during the high risk phase of induction of remission in SVV (seven subsequent days three times daily per month). One concern, however, is that with mupirocin there is an increase in infections other than those due to *S. aureus* [46]. For reasons of possible development of resistance as well as compliance problems, long-term use should be avoided.

Besides topical treatment, systemic antibiotics are another option for AIP, although they have not been used in PSV remission induction trials so far. From randomised controlled trials using, for example, levofloxacin in patients with malignancies during chemotherapy-induced neutropenia (<500 neutrophils per microlitre), it is known that a reduction in the incidence of neutropenic fever and hospitalisation can be achieved [2,3]. An effect on mortality has not been demonstrated and there are concerns regarding the long-term outcome of such interventions on microbial resistance in the community. As the treatment of PSV using standard protocols does not usually lead to prolonged neutropenia and the effectiveness of chemotherapy is well documented, it can be considered that levofloxacin with regard to mortality has not been proven in patients treated with more intense chemotherapy, there is no standard setting for which the use of systemic antibacterial prophylaxis can be recommended. Although clear evidence for its use during induction of remission - apart from PCP-prophylaxis - is missing, T/S has proven its ability to reduce bacterial infections in patients with WG [28] and, therefore, might be considered in high-risk patients.

Other antibiotics, such as levofloxacin, might only be considered in refractory heavily pre-treated PSV patients undergoing salvage therapy with drugs known to induce severe neutropenia - for example, campath-1H.

**Pneumocystis jiroveci**

The risk of PCP is especially high in patients with SVV undergoing induction therapy. Without using prophylaxis the incidence of PCP is up to 20% [26] and many fatalities have been reported in earlier trials [22,24,26,29]. It has to be mentioned, however, that the causes of deaths in those patients were multi-factorial and often due to several infectious agents simultaneously. Furthermore, some of the mentioned studies referred to the same patient population [22,24,26]. In a retrospective analysis, Ognibene and colleagues [51] found an estimated PCP incidence of 6% in a cohort of 180 WG patients. PCP occurred during induction of remission. Estimating the risk of PCP during induction of remission is further complicated as therapeutic strategies have changed over time, leading to lower cumulative Cyc doses and less frequent use of high dose intravenous GCs. Simultaneously, T/S use as PCP prophylaxis has gained widespread acceptance. Unlike in HIV infection, where a low CD4 count is the strongest risk factor, such factors are insufficiently defined in PSV patients. There is evidence that older age is an independent risk factor [52]. Patients with WG seem to be at increased risk compared to other AAV or PSV patients in general. In WG a low lymphocyte count before and during therapy is associated with PCP [51,52]. Generally speaking, prolonged (>1 month) GC use at doses >15 to 20 mg per day is the best defined risk factor [53,54]. Other immunosuppressants, especially Cyc, also increase the risk of PCP [54].

Although, as for all other potential indications for AIP, there are no clinical trial data on PCP prophylaxis in PSV patients, there is some evidence for its use in SVV (level B to C): infection rates were much higher in trials not using prophylaxis than in those recommending it [22,26]. Mahr and colleagues [24] introduced T/S prophylaxis during an ongoing protocol as a reaction to high rates of PCP and reported effectiveness. In their analysis, Chung and colleagues [55] concluded that PCP prophylaxis is cost-effective in WG patients unless the annual incidence of PCP fell below 0.2%. According to the EULAR recommendations, T/S prophylaxis is encouraged in all patients being treated with Cyc [56]. The British Society for Rheumatology (BSR) formally recommends PCP prophylaxis at a dose of 960 mg T/S thrice weekly or of 300 mg inhaled pentamidine in all AAV patients treated with GCs and Cyc [57].

Even though PCP is rare in large vessel vasculitis, the use of T/S prophylaxis in all PSV patients receiving GCs >15 mg per day and a GC-sparing immunosuppressant (for example, MTX) might be considered. As severe adverse event rates with T/S are generally low and cessation of the medication is reported in only about 3% of non-HIV-infected patients [58], generous use seems to be appropriate considering the still severe prognosis of PCP in this patient population [59]. However, the potential interaction of MTX and T/S has to be taken into account and strict folate substitution is mandatory. Furthermore, it has to be stressed that there is only little evidence from trials to support T/S prophylaxis in patients receiving medium potency immunosuppression. Its use should be discussed individually according to local praxis.
It is not clear for how long PCP prophylaxis should be given. In some centres one criterion to stop PCP prophylaxis is a GC dose tapered below 15 mg per day and/or the cessation of Cyc therapy. This praxis is based on the observation that PCP in non-HIV patients under GC medication occurred mainly with doses above 15 mg per day [54]. In analogy to experiences in HIV patients, it has been suggested to measure CD4 cell counts and to stop prophylaxis when this value is above 200 per cubic millimetre [60]. However, other risk factors such as impaired cell functions are under-estimated by this approach.

Cytomegalovirus
CMV is a herpesvirus that leads to latent infection. Its prevalence ranges between 60 and 100%, depending on the geographic area [61]. CMV reactivation leads to a high burden of morbidity and mortality in immunocompromised persons, an interrelation best studied in transplantation medicine [62]. The spectrum of manifestations ranges from non-symptomatic infection to life-threatening disease, for example, pneumonia. The scale of this problem in rheumatology and especially in PSV patients is insufficiently defined but appears to be less severe in most cases. In vasculitis patients leucopenia is the most frequent manifestation. However, in clinical trials some cases of CMV illness have been described with a relatively high proportion of fatal outcomes [20,22,25]. Large scale underreporting must be assumed, since until recent years reliable detection methods have been missing and the awareness of this problem appears to be still low. Mori and colleagues [63] found a high incidence of CMV reactivation in CMV-seropositive patients with connective tissue disease undergoing immuno-suppressive therapy. A recent study by Takizawa and colleagues [39] suggests that GC use, especially in the form of pulsed methylprednisolone as well as other immuno-suppressants, primarily Cyc, are the major risks factors for CMV reactivation in rheumatic diseases. In PSV, and especially in WG, CMV reactivation is an important differential diagnosis if leucopenia occurs.

In solid organ transplant recipients prophylaxis with, for example, ganciclovir or valganciclovir reduces CMV disease [64]. If CMV disease occurs in severely compromised patients with rheumatic diseases, anti-viral therapy might be without benefit as reported by Takizawa and colleagues [39] in a cohort of 85 patients. As CMV itself leads to further immunosuppression, fatal co-infections are promoted [39]. Taken together, these are arguments in favour of anti-viral prophylaxis in CMV-seropositive PSV patients undergoing intense immunosuppression. However, as data from clinical trials are missing, no evidence-based recommendation as to which patients should be introduced to prophylaxis can be given. In praxis prophylaxis (valganciclovir 900 mg once daily) might be considered only in severely ill PSV patients who need high dose methylprednisolone pulses or Cyc, especially if they had experienced earlier CMV reactivations. An alternative to this, as well as for other latently infected patients who need intense immunosuppression, is the pre-emptive approach, which also has been proven to be effective in organ-transplant recipients [65]. This requires quantitative monitoring of CMV - for example, by measurement of early antigen (pp65)-positive cells. Takizawa and colleagues [39] suggested a threshold of 5.6 pp65 positive cells per 10^6 polymorphonuclear cells. Measurement of early antigen is increasingly replaced by quantitative CMV-PCR, which is currently the method of first choice.

Varicella zoster virus
Varicella zoster virus (VZV) reactivation leads to herpes zoster (HZ). Whereas age is the most important risk factor for the development of HZ [66], autoimmune diseases and especially immunosuppressive therapy with Cyc and GCs further increases the probability of reactivation [67]. Several PSV trials report relatively high numbers of VZV reactivation and HZ [28]. However, underreporting of this usually non-life-threatening condition is likely. HZ causes substantial morbidity, especially when post-herpetic neuralgia develops, which is the case in up to 20% of the elderly population [68].

Despite these facts, no trial in PSV has included VZV prophylaxis to our knowledge, although it is feasible and effective at least in patients receiving haematopoietic stem cell transplantation using, for example, aciclovir (2 × 800 mg per day) or valaciclovir [69]. The reason for not administering VZV prophylaxis in PSV may be the high potential for drug interactions and adverse events, especially in patients with renal impairment and the non-life- or organ-threatening nature of HZ in this population. In general, VZV prophylaxis is not recommended in PSV patients. It might be considered only in selected patients who have experienced several VZV reactivations and have an ongoing need for intense immunosuppression. More importantly, patients should be trained to recognise the early signs and symptoms of HZ to enable the immediate start of anti-viral therapy in the case of possible HZ.

Vaccination to avoid HZ is available and effective [70]. In the US it is recommended by the Advisory Committee on Immunization Practices for all persons older than 60 years [70] but it is not recommended in patients under immuno-suppressive medication [71]. Whether patients in remission from PSV under mild immunosuppression may benefit from vaccination warrants further investigation.

Fungi
Invasive fungal infections (other than PCP) are rare in PSV. Risk factors for the development of pulmonary Aspergillus sp. infections are prolonged episodes of neutropenia and prolonged use of high-dose GCs [72]. Few cases of invasive Aspergillus infections and fatalities in PSV have been reported [13,22,24].
There is generally no indication for the prophylactic use of systemic anti-mycotics in PSV but aspergillosis should be considered as a differential diagnosis in patients if fever of unknown origin does not resolve under a calculated antibiotic therapy.

In contrast to invasive aspergillosis, Candida infections of mucosal membranes are a frequent complication of GC treatment, although leading to invasive candidiasis only very rarely. Nonetheless, oral candidiasis or candida esophagitis are painful and might hinder oral nutrition. In critically ill patients and solid organ transplant recipients prophylaxis using fluconazole is effective in avoiding invasive candidiasis \[73,74\]. Using topical non-absorbable antifungal prophylaxis in immunocompetent critically ill patients leads also to a significant reduction in fungal (mainly non-invasive) infections \[75\]. According to the BSR, prophylaxis with nystatin, amphotericin or fluconazole should be considered in all AAV patients receiving high-dose immunosuppressive therapy \[57\].

In praxi amphotericin suspension in all patients under long term GC medication with a dose of >15 mg prednisolone per day can be recommended because it is effective, non-absorbable and associated, therefore, with very few side effects. According to a meta-analysis, the non-absorbable nystatin is not more effective in avoiding fungal colonisation than placebo and can not be recommended \[76\]. Additionally, all patients should be instructed to perform daily self-inspections of the mouth in order to detect mucosal candidiasis early.

**Mycobacterium tuberculosis**

Only a few cases of TB have been reported in PSV trials, although some of these have been fatal \[16\]. PSV studies

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**Table 2**

**Possible use of anti-infective chemoprophylaxis in primary systemic vasculitis patients**

| Infectious agent       | Prophylactic measure                                      | Appropriate clinical situation                                                                 | Level of evidence |
|------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------|
| *Pneumocystis jiroveci*| Trimethoprim/sulfamethoxazole 960 mg thrice weekly. Alternative: monthly aerosolized pentamidine (300 mg) | Should be given to all patients receiving long term glucocorticoid >15 mg/day and additional intense immunosuppression | B to C            |
| *S. aureus*            | Nasal mupirocin ointment three times daily for 7 consecutive days per month | Might be given to patients with generalised SVV who are *S. aureus* carriers during induction of remission | C                 |
| *Mycobacterium tuberculosis* | Isoniazid 5 mg/kg per day up to 300 mg plus pyridoxin (vitamin B6). Alternative: rifampin 10 mg/kg per day up to 800 mg | If latent tuberculosis is detected and immunosuppression necessary, especially when infliximab is used | C                 |
| *Varicella-zoster virus* | Aciclovir 2 × 800 mg per day | Generally not recommended, but might be considered in very selected cases with several reactivations and ongoing need for intense immunosuppression | C                 |
|                        | Zoster vaccine | Not recommended | C                 |
| *Cytomegalovirus*      | Valganciclovir 1 × 900 mg per day | Not generally recommended, but might be considered in selected severe cases with earlier reactivations and ongoing need for intense immunosuppression | C                 |
| *Aspergillus* sp.      | For example, posaconazole | Not recommended | C                 |
| *Candida* sp.          | Oral amphotericin B suspension, 4 × 1 ml (= 100 mg) per day | Should be considered in patients with long term glucocorticoid therapy >15 mg/day | C                 |

*Level of evidence: A = evidence from at least one properly performed randomized controlled trial or meta-analysis of several controlled trials; B = well-conducted clinical studies, but no randomized clinical trials - evidence may be extensive but essentially descriptive; C = evidence obtained from expert committee reports or opinions, and/or clinical experience of respected authorities.*
using TNF-α blocking agents included TB screening as a reaction to TB reactivations in early rheumatoid arthritis trials. Therefore, TB reactivation has not been seen in those studies [9,10,19]. While a general prophylaxis is clearly not indicated, screening for latent TB should be part of the work-up in PSV patients. For this purpose a full history, physical examination and a chest X-ray is recommended by the BSR guidelines [57], procedures that can be considered to be part of routine care. If latent TB is detected in a patient planned to start induction therapy for PVS, we recommend TB prophylaxis. According to a recent study, rifampin over 4 months might be safer and associated with better adherence than standard 9-month isoniazid [77]. As long as further trials are unavailable, we consider isoniazid plus vitamin B supplementation to be the standard of care, with rifampin being a good alternative in case of incompatibility.

In some PSV, especially in WG, infliximab is used as salvage therapy. In such cases screening and prophylaxis for TB should be performed as recommended for the use of infliximab in rheumatoid arthritis [78].

Conclusion
Infections significantly contribute to morbidity and mortality in PSV patients. There are three ways of targeting this problem: recognizing and minimising risk factors, implementing prophylaxis where appropriate and ensuring early diagnosis and targeted therapy if infections occur. Although there is an ongoing need for better definitions of risk factors, from the available data it is quite clear that prolonged high-dose GC dose use is of central significance. Therefore, the reduction of GC dose must be a major aim in daily praxis as well as in future studies. To date, the only prophylactic measure that is recommended by national [57] and international guidelines [56] is T/S to avoid PCP in SVV patients undergoing intensive immunosuppression. Further prophylaxis might be useful in specific clinical situations, as summarised in Table 2.

Competing interests
The authors declare that they have no competing interests.

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