Recommendations for vaccination in patients with auto-inflammatory rheumatic diseases: a proposal to EULAR

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1. Introduction
Among the auto-inflammatory rheumatic diseases (AIRD) rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren’s syndrome (SjS), systemic sclerosis (SScl), and Wegener’s granulomatosis (WG) are the most prevalent. The prevalences of these separate diseases are 860, 23.8, 14.4, 4.4 and 3.0 per 100 000 persons respectively, and varies between populations depending on geographic and racial background.¹ The prevalence of polymyositis/dermatomyositis (PM/DM), also considered as one of the AIRD, is unclear, because of the heterogeneity of the diseases and the changes in diagnostic criteria. Patients with AIRD have a reduced life expectancy and in the most prevalent AIRD, RA, there is a one in three chance of becoming disabled.² Mortality seems to be highest in SScl: 24% in 5 years.³ A considerable part of death can be ascribed to infection, as will be further discussed in the next chapters. Therefore, aside from aggressive treatment of the AIRD, efforts should be made to prevent infections in these patients.

2. Infection in auto-inflammatory rheumatic diseases

Infection risk in auto-inflammatory rheumatic diseases

Patients with AIRD are at increased risk of contracting infectious diseases.⁴⁻⁷ These infections are a major cause of death and hospitalization in this patient group (also see next section). The increased susceptibility to infection can be contributed to several factors: 1. the immunosuppressive effect of the underlying auto-immune disease such as lymphopenia in SLE or neutropenia in Felty’s syndrome; 2. the creation of a “locus minoris resistantiae” as a sequel of the AIRD, for example destructed joints in RA or the (upper) respiratory tract in WG; 3. the immunomodulatory medications these patients generally need to be treated with, e.g. (high dose) corticosteroids, MTX or biological agents, and even stem cell transplantations are performed for treatment of several AIRD.⁸ The biologicals are of particular interest since increasingly more indications are being recognized for these agents, they are increasingly used earlier in the course of AIRD, and newer agents have become available.⁹⁻²⁰; 4. non-disease related factors like excessive alcohol use or diabetes mellitus.
can also contribute to the increased infection risk\textsuperscript{21}.

**Infection-related morbidity and mortality**

In a recent review of mainly prospective and retrospective cohort studies infection-related mortality in AIRD-patients varied between 1.2\% and 36\% (median 5.2\%). Median all-cause-mortality was 20\%. Treatment regimens and duration of follow-up varied greatly in these studies, as did the year of publication: from 1976 to 2005\textsuperscript{4}. Hence the results might not be representative for the current era and therefore we summarize the results of more recent papers (when available) on infection-related morbidity and mortality in patients with different AIRD.

**RA**
The incidence of infection in RA-patients is 19.64/100 person-years. Objectively confirmed infections occur 1.5 times more often in RA-patients compared with matched persons without inflammatory arthritis, while infections requiring hospitalization are almost twice as frequent in RA-patients\textsuperscript{6}. Infection-related mortality was significantly increased in a large prospective cohort study on 3501 RA-patients with a long follow-up; non-pulmonary and pulmonary infections were observed as the cause of death 6.2 and 5.3 times more often, respectively, than expected\textsuperscript{7}.

**SLE**
During a mean follow-up of 21 months 36\% of 110 SLE-patients developed at least one infection as compared to 22\% in controls\textsuperscript{5}. Infections occurred in 25\% of 1000 European SLE-patients during a 10 year follow-up. Mortality in this cohort was 6.8\% after a follow-up of 10 years, 25\% was contributed to infection\textsuperscript{22}. Pneumonia was the most common infection as the cause of death in both studies. In a smaller British retrospective cohort study (300 patients) from 1978 to 2000 mortality was 15\%, 17\% was due to infection\textsuperscript{23}. In both studies the frequency of hospitalization was not mentioned. The median mortality in SLE due to infection in a review of 17 studies was 4.7\%\textsuperscript{4}.

**Sjögren’s syndrome**
To date, no data are available on infection risk and infection-related mortality in patients with Sjögren’s syndrome.

**Systemic sclerosis**
Steen et al. showed that systemic sclerosis goes along with an infection-related mortality of 2.1\% (8.8\% of all death) in a prospective long-term follow-up study from 1972 up till 2002\textsuperscript{3}. In a Thai study infection-related mortality in systemic sclerosis was higher: 11.2\% (41.9\% of all death), most often from a pulmonary focus. Almost half of all participants was lost to follow-up in this study\textsuperscript{24}.

**Wegener’s granulomatosis**
In Wegener’s granulomatosis patients infection-related mortality was 3.2\% in two prospective studies (respectively 23\% and 16\% of overall mortality) after a median follow-up of respectively 7 and 8 years\textsuperscript{25;26}. This was comparable with an infection-related mortality of
4.6% (19% of all death) in Wegener’s patients with renal involvement in a Norwegian study.

**Polymyositis/dermatomyositis (PM/DM)**

Mortality to infection in PM/DM is also high: 22.2% due to opportunistic infections, compared with 14.5% due to non-opportunistic infections in a retrospective evaluation of 156 PM/DM-patients.

**Infection focus, causative micro-organisms, and risk factors for infection in AIRD**

Patients with RA are at increased risk of developing pneumonia and other respiratory tract infections, besides bone, joint, and soft tissue infections. RA-patients are at increased risk to develop herpes zoster, however, causative micro-organisms of other infections in RA are not specified in the different studies. For frequently occurring respiratory tract infections, the common respiratory pathogens, like *Streptococcus pneumoniae*, *Haemophilus influenzae B* and *Influenza*-virus, are most likely also the most important causative micro-organisms in patients with AIRD.

Increasing age, presence of extraarticular manifestations of RA, leukopenia, and comorbidities (chronic lung disease, alcoholism, organic brain disease, and diabetes mellitus), as well as use of corticosteroids, are strong predictors of infection in RA. Steroids increase pneumonia risk even at doses as low as ≤5mg/day and raise the risk of herpes zoster. Notably, use of disease-modifying antirheumatic drugs was not associated with increased risk of infection in multivariate analyses, after adjustment for demographic characteristics, comorbidities, and disease-related variables in this study. However, in other studies leflunomide has been associated with pneumonia and tuberculosis. Anti-TNFα agents, in particular when combined with methotrexate (MTX), raise the risk for infection, mainly for pneumonia. Possibly, etanercept is less immunosuppressive than infliximab and adalimumab. Postmarketing surveillance studies and retrospective cohort studies clearly point in the direction of increased risk for mycobacterial infection in patients on TNFα-blockers. Also opportunistic infections with other intracellular microorganisms has been described in several case reports. A recent meta-analysis of RCT’s showed no increased infection risk for rituximab and abatacept, but does demonstrate an increased infection risk for patients on high doses of anakinra. Again, the most prevalent infectious manifestation was pneumonia.

In SLE herpes zoster is the most prevalent infection. Pneumonia also occurs more frequently, especially during high dose corticosteroids. Besides *Varicella zoster*, *Staphylococcus aureus*, *Escherichia coli*, *Candida* spp. and *Salmonella* spp. were relatively often cultured from several foci. Treatment of SLE often comprises high dose steroids combined with cyclophosphamide, azathioprine or mycophenolate mofetil. Mycophenolate mofetil might lead to less infections when given in conjunction with steroids than cyclophosphamide or azathioprine. The latter two do not differ in infection risk. There are no studies that differentiate between infection risk caused by the disease or by it’s treatment.
Patients treated for WG with or without renal involvement more often develop bacterial upper and lower respiratory infections, but also opportunistic infections, e.g. *Pneumocystis jiroveci* pneumonia, herpes zoster and invasive fungal infections. Daily steroid use was strongly associated with infectious complications \(^{25,27}\).

Mainly aspiration pneumonia (52% of all infections) and opportunistic infections (35%) complicate PM/DM. The latter were predominantly caused by *Pneumocystis jiroveci*, *Candida* sp., mycobacteria and cytomegalovirus. Only the mean daily dose of steroids was higher in patients developing opportunistic infections \(^{28}\).

Hardly any data on risk factors for infection and causative micro-organisms in patients with SSc or SjS are available.

### 2. Prevention of infection in AIRD: usefulness of vaccination

Obviously, prevention of infections in patients suffering from AIRD is important. Vaccination might reduce infection rates in these patients. Many guidelines recommend vaccination for Influenza and *Streptococcus pneumoniae* in immunocompromised patients, and almost all patients with AIRD should be considered as such. However, still the larger part of the immunocompromised patients do not receive the recommended immunizations \(^{43}\).

No quantitatively and qualitatively adequate trials are available that studied the usefulness of vaccination strategies in patients with AIRD on relevant clinical endpoints, i.e. reduction in mortality and morbidity caused by infection. One small trial in patients with either SLE or RA showed reduction in the occurrence of viral infections, acute bronchitis or pneumonia, but the differences could also be contributed to age \(^{44}\). Therefore, recommendations can only be based on extrapolation from other patient populations (for example, vaccination for Influenza and *Streptococcus pneumoniae* in elderly patients has been proven to be efficacious \(^{45-47}\)) and surrogate parameters (e.g. humoral immune responses after vaccination). Many studies performed so far evaluated serologic responses to vaccination in patients with different AIRD, whether or not treated with immunomodulatory medications. However, it is still not known what the best correlates of protection are, especially for immunocompromised or elderly patients. For example, T-cell immune responses have been shown to be of major importance to prevent elderly from contracting clinical disease from *Influenza* \(^{48}\). Our group is working on humoral and cellular responses to trivalent Influenza subunit vaccine in SLE and WG-patients, as well as in RA-patients at defined time intervals after treatment with rituximab \(^{49,50}\).

### 3. Safety of vaccination in patients with AIRD

Although several case reports and case series suggest a relation between exacerbations of the underlying auto-immune disease and vaccination in patients with AIRD, many prospective studies did not show any significant increase in flare-ups of AIRD after different kinds of vaccination \(^{51-53}\).
An other safety issue to be addressed is the chance of occurrence of an active infection resulting from vaccination of immunocompromised patients with vaccines with live attenuated micro-organisms (e.g. BCG, Varicella zoster, Yellow Fever). The potential benefits of vaccination should outweigh the potential harm of vaccination and this is an important issue to be addressed in EULAR-recommendations on vaccination in patients with AIRD.

4. Which vaccinations for patients with AIRD should be considered?

Vaccinations for patients with AIRD can be subcategorised in three categories:

1. “standard”: vaccines that should (have) be(en) administered to every person (e.g. diphtheria, tetanus)

2. “extra”: vaccines that should be provided to AIRD-patients because of their increased susceptibility to (potentially) vaccine-preventable infections due to their immunocompromised state (e.g. for Influenza, Streptococcus pneumoniae)

3. “specific”: vaccines that should be provided to AIRD-patients when they might be exposed to a (potentially) vaccine-preventable infection (e.g. hepatitis A and B, Neisseria meningitides, Rabies, Yellow fever). This is of particular importance with regard to the increasing travel movements of people from developed countries to places all over the world.

For these three categories of vaccines evidence should be collected regarding their efficacy and safety. Also recommendations should be given to avoid exposure to certain pathogens when vaccination can not be given because of increased risks of this vaccination (e.g. live attenuated vaccine) or when efficacy of particular vaccinations is unlikely. This mainly concerns category 3 (“specific”)-vaccinations

5. Which patients should be vaccinated?

In respect of the increasing use immunosuppressive drugs, including biological agents, particular attention should be paid to the vaccination of patients treated with these drugs. Type and time of vaccination are matters to be dealt with.

6. Summary

Patients with AIRD are at increased risk for infections, which lead to considerable morbidity and mortality. Vaccination is an attractive preventive measure against infection in this category of patients, but because of the underlying AIRD and the immunosuppressive medication most of the AIRD-patients use, there are concerns about the efficacy and safety of vaccination. Moreover, it is unknown what the best correlates of protection are for many vaccinations in general, and in patients with AIRD in particular. Recommendations based on the evidence from currently available literature will be of great help for clinicians (GP’s,
internists, rheumatologists, and clinical immunologists) with regard to decision-making on vaccination of this patient group, and can increase the implementation of the recommended immunizations in AIRD-patients. Several categories of vaccination ("standard", "extra", and "specific") need to be addressed.

7. The development of recommendations on vaccination in patients with AIRD

If the EULAR decides to support the development of recommendations on vaccination in patients with AIRD, steering group committee members will be approached on the short term. The proposed person to be in charge of the literature search will be Sander van Assen, MD, internist/infectious disease-physician, and the proposed convenors of the project will be Marc Bijl, MD/PhD, internist/rheumatologist and Cees Kallenberg, MD/PhD, clinical immunologist. A list of proposed members of this EULAR-guideline preparing committee can be found as appendix 1.

Literature will be searched using PubMed, Embase, and Cochrane databases. The AGREE instrument (AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. www.agreecollaboration.org) will be used as the framework for assessing the quality of guideline. The Delphi method will be used to agree on the propositions regarding vaccination in AIRD-patients.

The initially proposed questions to be answered will be:

1. Is vaccination indicated for patients with AIRD (in particular those on specific immunosuppressives/biologicals)?

2. What are the risks of vaccination of patients with AIRD?

   3a. Which "standard" vaccinations should be offered to patients with AIRD?
   3b. Which "extra" vaccinations should be offered to patients with AIRD?
   3c. Which "specific" vaccinations should be offered to patients with AIRD?

4a. Which "standard" vaccinations are contraindicated in patients with AIRD?
   4b. Which "extra" vaccinations are contraindicated in patients with AIRD?
   4c. Which "specific" vaccinations are contraindicated in patients with AIRD?

5. What is the best timing for vaccination of patients with AIRD?

6. Should vaccination responses after vaccination be checked, and if so, how?

Presentation and dissemination of the recommendations will be by presentation at the annual EULAR scientific meeting and meeting of the different national associations for Rheumatic Disease, and by publication in the Annals of Rheumatic Diseases. The issues of financial support and planning of meetings of the members of the steering group will be addressed in detail later on in the process. Finally, appendix 2 shows the estimated costs for the preparation of the proposed EULAR-recommendations for vaccination in patients with auto-inflammatory rheumatic diseases.
Reference List


(44) Stojanovich L. Influenza vaccination of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Clin Dev Immunol 2006; 13(2-4):373-375.


Appendix 1. List of proposed participants

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Appendix 2. Estimated costs for the preparation of the proposed EULAR-recommendations

- Salary fellow (S. van Assen, internist-infectiologist): € 10,000,-
- Statistical support: € 10,000,-
- 2 Meetings in EULAR-building, Zürich, Switzerland
  € 1,000/participant; 16 participants: € 32,000,-

- Total estimated budget: € 52,000,-