



## Review Article – Meta-analysis

# Infections and systemic sclerosis: an emerging challenge<sup>☆</sup>

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### ABSTRACT

Mounting evidence has shown non-systemic sclerosis (SSc) related complications as a rising cause of hospital admission and mortality, out of which infections are among the top-five causes. Patients with SSc are at an increased risk of infection due to several features of the treatment options and the disease itself. For instance, lung involvement is associated with a higher frequency of respiratory infections, whereas the presence of digital ulcers or calcinosis may result in skin and soft tissue infections, and even osteomyelitis. On the other hand, the growing trend towards immunomodulation and immunosuppression in patients with autoimmune diseases will place SSc patients at a higher risk of infectious complications, including opportunistic infections. A low suspicion threshold and an increasing awareness among treating specialists, particularly rheumatologists, are warranted for prevention, early diagnosis and management of infectious complications. Nonetheless, data on risk management strategies in SSc, such as vaccination and antimicrobial prophylaxis, are scarce. A narrative non-systematic review was performed to provide an update of infectious complications in patients with SSc.

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## Infecciones y esclerosis sistémica: un desafío emergente

### R E S U M E N

#### Palabras clave:

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Medición de riesgo

La evidencia creciente muestra que las complicaciones no asociadas a la esclerosis sistémica (ES) son una causa cada vez más frecuente de hospitalización y mortalidad, dentro de las cuales las infecciones se encuentran entre las primeras cinco causas. Los pacientes con ES presentan un riesgo elevado de infección asociado a las opciones terapéuticas y por la enfermedad misma. Por ejemplo, el compromiso pulmonar se asocia a una mayor frecuencia de infecciones respiratorias, mientras que la presencia de úlceras digitales o calcinosis pueden resultar en infecciones de piel y tejidos blandos, e incluso osteomielitis. Por otro lado, la tendencia creciente hacia la inmunomodulación y la inmunosupresión como tratamiento de las enfermedades autoinmunes, pondrá a estos pacientes en un mayor riesgo de infecciones, incluidas las infecciones oportunistas. Son necesarios un umbral bajo de sospecha y un alto nivel de alerta entre las especialidades tratantes, particularmente los reumatólogos, para la prevención, el diagnóstico temprano y el manejo de las complicaciones infecciosas. Sin embargo, la información respecto a estrategias de gestión de riesgo en ES, como la vacunación o la profilaxis antibiótica, es escasa. Se realizó una revisión narrativa no sistemática que presenta una actualización sobre las complicaciones infecciosas en pacientes con ES.

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## Introduction

Systemic sclerosis (SSc), also called scleroderma, is an immune-mediated chronic connective tissue disease characterized by a disproportionate deposition of collagen in the skin and internal organs; fibrosis and vasculopathy are its main features.<sup>1,2</sup> Two main subsets, limited and diffuse, are described according to the extension of cutaneous involvement.<sup>3</sup> SSc presents the highest standardized mortality ratio (SMR, i.e., risk of death as compared with the general population) among rheumatic diseases.<sup>4</sup> As a systemic disease, a myriad of signs and symptoms may be present, particularly renal, cardiopulmonary, gastrointestinal, and musculoskeletal. Thus, its management is an increasing challenge for rheumatologists and related specialties.

With regard to infectious diseases, patients with SSc are at an increased risk of infection due to the disease itself, mainly respiratory infections due to interstitial lung disease (ILD)<sup>5</sup> and skin/soft tissue infections due to the presence of digital ulcers (DU) or calcinosis, that can progress to osteomyelitis.<sup>6,7</sup>

As well, the growing trend towards immunomodulation and immunosuppression will place SSc patients at a higher risk of infections, as increasingly observed in other autoimmune diseases,<sup>8</sup> including opportunistic infections (OIs). Medications such as cyclophosphamide (CYC), mycophenolate mofetil (MMF), methotrexate (MTX), azathioprine (AZA), glucocorticoids, and biological therapy (i.e., rituximab [RTX]) are recommended for the management of disease manifestations.<sup>9-12</sup> Several novel immunologic targets are under research with promising results.<sup>13</sup> In addition, the intravenous route of application of prostanoids and some immunosuppressants may generate an increased risk of infection. Further, the prolonged use of proton pump inhibitors (PPI)

and the use of antibiotic courses for microbial overgrowth are interventions to be considered as risk factors for infection.

Hereby, we offer an updated review of infectious diseases in patients with SSc, including their epidemiology, clinical manifestations and risk-management strategies.

## Methods

A narrative non-systematic review was performed. We completed a literature search in 4 databases (Cochrane Database, Medline, Embase and LILACS [which includes literature from Latin America]). Articles in English, Spanish, French, Italian, Portuguese and German were included. The search strategy included the following terms: "Systemic scleroderma", "Infection", "Infectious Disease Medicine", "Communicable Diseases". Gray literature was obtained using these terms in Google and a 'snowball' strategy was applied to retrieve useful literature from the revised articles' references.

## Infections and SSc: epidemiology

Recent advances in the treatment of SSc have influenced the causes of death and in-hospital admission. A shift from renal crisis to cardiovascular (e.g., congestive heart failure [CHF]), pulmonary (i.e., ILD and pulmonary artery hypertension [PAH]), neoplastic and infectious causes as main drivers of death and hospitalization has been observed.<sup>5,14-26</sup> A meta-analysis that included data until 2006 found a SMR of 3.53, which has not changed significantly over the last 40 years.<sup>14</sup> Rubio-Rivas et al. reported a lower SMR (2.72) using a similar approach; the authors estimated a cumulative survival from onset (first Raynaud's symptom) at 87% and 74% at 5 and 10 years, respectively, whereas from diagnosis the sur-

vival was 75% and 62%, respectively. Further, they described a trend towards improvement in mortality between the studies performed prior and after 1990, although statically significant only at 5-year survival from diagnosis (71% vs. 84%).<sup>27</sup> Previously, the main driver of death in patients with SSc was renal crisis. The use of angiotensin-converting enzyme inhibitors led to a profound reduction from 42% of cases to less than 6% in the early 2000s.<sup>22</sup> However, mounting evidence has shown that non-SSc-related causes for both death and admission are approaching 50%,<sup>14,15,17,20,22,23</sup> out of which infections are becoming an important cause.

### Infection as a cause of death

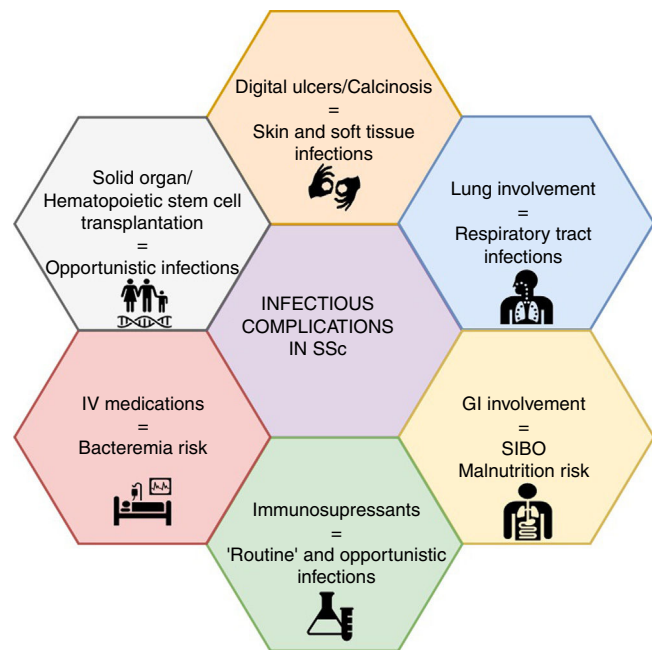
Two metaanalyses including data from 1960 to the first decade of the 2000s reported a 7% death frequency secondary to infection in SSc.<sup>14,19</sup> Further, reports from the international European Scleroderma Trials and Research (EUSTAR) database, ranked infections among the top-five causes of death.<sup>15,24</sup> A study using death certificates from France supported a similar frequency and reported infection as the cause of death in 11% of certificates. The authors reported a high mortality from lung infections and a five-fold higher rate of infectious deaths among patients with SSc compared with the general population<sup>24</sup>; similar evidence has been reported from several cohorts around the world.<sup>16,17,20,21,23,28</sup>

Some reports suggest a temporal shift in causes of death with infections being on the rise. Steen et al. reported that the proportion of infections as a cause of death among their cohort (1972–2001) ranged from 2% (1972–76) to 9% (1997–2001); although no statistical differences between periods were observed, a trend towards a higher frequency appears to be present.<sup>22</sup> Further, two studies with a 10-year difference in the USA, based on the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) databases and using a similar methodology, presented a significant rise in infections as a cause of death and admission<sup>26,29</sup>; Chung et al. (2002–2003) showed that infections were among the top-three causes of death, accounting for 13% of the events.<sup>26</sup> Whereas Poudel et al., ten years later (2012–2013) reported that the most common diagnoses of deceased inpatients were infection/septicemia (32.7%), followed by pulmonary (20%) and cardiovascular (15.7%) involvement. Infection (other than opportunistic) had a high adjusted OR for mortality (3.36, CI 2.73–4.41).<sup>29</sup>

### Infection as a cause of admission

Several cohorts have reported infections as a common cause of admission in patients with SSc, being ranked among the top three causes and as the most common non-SSc-related cause.<sup>17,18,21,26,29,30</sup> Respiratory, skin/soft tissue, gastrointestinal, and urinary tract systems are the most common sites of infection causing hospital admission, although their frequencies differ by cohort. Infections have been associated with higher costs, longer length of stay and mortality.<sup>29</sup>

The occurrence of infections in SSc may be explained by an increasing use of immunosuppressive agents. Poudel et al. explored this hypothesis by comparing non-SSc-related hospitalizations against SSc-related hospitalizations with



**Fig. 1 – Infectious complications and risk factors in systemic sclerosis.**

infection/septicemia, using a surrogate variable (a code for “chemotherapy” was available, which may represent the use of CYC or RTX, although it is not possible to ascertain). They found a significantly higher proportion of chemotherapy use in SSc hospitalizations with infection/septicemia, both in those who lived (9.2% vs. 4.1%,  $p < 0.0001$ ) and those who died (17.4% vs. 6.3%,  $p = 0.0005$ ). Those patients who died had higher proportions of PAH (43.3%), respiratory failure (72.4%), and CHF (38.4%), which may represent a more aggressive disease that required stronger immunosuppression and therefore, a higher risk of infection. Interestingly, the authors found that a higher income was associated with a higher risk of death. They proposed an access paradox, in which, among other causes, a higher income may represent a better access to immunosuppressive agents.<sup>29</sup> Conversely, another study analyzing the immunosuppressive therapy hypothesis found no statistical association between respiratory infection and the use of immunosuppressants as a group.<sup>17</sup> In this line, recent studies with Tocilizumab (TCZ)<sup>31,32</sup> and Abatacept (ABA)<sup>33</sup> do not support an increased risk of infections, as will be discussed later.

## Infections and SSc: organ-specific involvement

Infectious complications in SSc can be attributed to disease- or drug-associated factors (Fig. 1). The former appears to be more frequent, mainly represented by soft tissue and pulmonary infections.

### Skin and soft tissue infections

Skin involvement due to DU is one of the most frequent complications of SSc, and it can be associated with soft tissue

infection in 19–54% of patients.<sup>6,7,34–36</sup> The etiological mechanism of DU differs between ischemic ulcers, those related to articular deformities, and those associated with calcinosis.<sup>5</sup> With regard to infectious complications, literature reports do not usually discriminate by mechanism, thus defining a clear risk difference is difficult.

Nonetheless, particularly in the presence of calcinosis, the development of cellulitis is a frequent complication.<sup>37,38</sup> Progression to streptococcal pyomyositis,<sup>39</sup> and cases of necrotizing fasciitis<sup>40</sup> have also been reported.

Some studies have reported more infectious complications among the limited cutaneous SSc subset patients.<sup>41</sup> DU infections can progress to osteomyelitis, with an incidence as high as 8%, which can increase to 17% in patients with active DU<sup>6,42–44</sup> and 42% when those ulcers have any sign of infection.<sup>7</sup> The most frequently isolated pathogens are *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*, a pivotal information for the election of empiric antibiotic treatment.<sup>45</sup> Furthermore, disease related disability is worsened by these infections, since 8–16% of patients require surgical amputation as part of their management.<sup>46</sup> Patients who need surgical debridement, amputation or other acute intervention, will present an increased risk of wound infection, necrosis and slow wound healing, thus requiring a careful monitorization.<sup>47</sup>

### Respiratory involvement

In some SSc series, the respiratory system is the most frequent site of infectious complications, accounting for up to 24% of the reported events.<sup>8</sup> Diverse mechanisms have been proposed to explain this phenomenon, including ILD, which develops in almost 50–60 % of SSc patients, being the main cause of death in several series<sup>48,49</sup>; 40% of these deaths are attributed to lung infection.<sup>50</sup> Due to pulmonary structural involvement, bacterial infections are frequent (e.g., pneumonia with or without necrosis, lung abscess, empyema, etc.).<sup>51</sup> As patients with lung involvement present frequent flares, it is vital to rule out infectious complications as a cause of acute respiratory symptoms; early bronchoscopy may be necessary to identify infectious agents.<sup>52</sup> Procalcitonin has showed some usefulness in this scenario, where a positive value can suggest an active bacterial infection, although the threshold is not well established.<sup>53,54</sup>

On the other side, esophageal dysmotility has been associated with aspiration pneumonia (OR 1.23, CI 1.05–10.55), major infection (OR 3.22, CI 1.01–10.51)<sup>30</sup> and in-hospital death<sup>25</sup>; some authors have proposed that microaspiration may contribute to ILD.<sup>55,56</sup> Pneumonia may be difficult to distinguish from ILD.<sup>52</sup> Thus, Sehra et al.<sup>25</sup> proposed that “strict aspiration precautions should be considered for SSc patients who are admitted to the hospital, including simple measures like elevation of the head of the bed, avoiding over-sedation, and swallowing evaluations to probably help decrease in-hospital mortality”.

Bacterial pneumonia and TB have also been reported in SSc. Two population-based studies in Taiwan (2000–2006 and 2001–2012) explored the risk of TB in SSc<sup>57</sup> and rheumatic diseases,<sup>58</sup> compared to age-matched healthy patients. SSc

patients were found to have a significant 2.81-fold greater risk of overall TB infection (Incidence Rate Ratio [IRR] 2.81, CI 1.36–5.37) and 2.53-fold greater risk of pulmonary TB (IRR 2.53, CI 1.08–5.30); although non-significant, a trend towards a higher risk of extrapulmonary TB was reported (IRR 4.22, CI 0.27–17.57). SSc was found to be an independent risk factor for TB infection, with a hazard ratio (HR) of 2.99 (CI 1.58–5.63). Risk factors for TB in SSc were explored: age > 60 years and the presence of PAH were statistically significant in the multivariate analysis; interestingly, exposure to glucocorticoids or CYC were only significant in the univariate analysis.<sup>57</sup> Lu et al. reported similar findings, although their methods differed, as the authors pooled together data from SSc and inflammatory myositis as a group.<sup>58</sup> Moreover, among patients who received dexamethasone pulse therapy as part of their treatment, pulmonary TB was reported in 9% and extrapulmonary TB in 20%.<sup>59</sup> Extrapulmonary TB has also been associated with the use of CYC, high doses of glucocorticoids and Tumor Necrosis Factor (TNF)- $\alpha$  inhibitors.<sup>60,61</sup> Some series have reported non-TB mycobacteria infections in 18% of patients with ILD.<sup>62</sup>

Lung involvement by other opportunistic microorganisms include infection by *Pneumocystis jirovecii* which, although seldom reported in SSc patients,<sup>63,64</sup> has been associated with high dose glucocorticoids (i.e.,  $\geq 20$  mg/day in this study) or lower glucocorticoids doses with concomitant use of CYC<sup>65</sup> with a mortality close to 50%. Therefore, a low threshold of suspicion must be considered among rheumatologists and treating specialists to make the diagnosis in patients with highly immunosuppressive treatment who consult with progressive dyspnea and dry cough<sup>66</sup>; prophylaxis should be considered in high risk patients.<sup>67</sup>

*Aspergillus fumigatus* fungal ball has been found on large bullous spaces in patients with ILD, so it should be considered in patients with hemoptysis and lung masses.<sup>68</sup> A case of pulmonary actinomycosis in a patient on infliximab was reported.<sup>69</sup>

### Gastrointestinal involvement

Small intestinal bacterial overgrowth (SIBO) is a common gastrointestinal manifestation. Several antibiotics, such as amoxicillin, quinolones (e.g., ciprofloxacin), tetracyclines (e.g., doxycycline), metronidazole, minimally absorbable antibiotics (e.g., rifaximin) and trimethoprim/sulfamethoxazole (TMP/SMX) may be considered for SIBO treatment.<sup>70,71</sup> Cyclical courses may be given monthly during 10–14 days. From an infectious diseases perspective, one should not forget that the regular use of antibiotics is linked with antibiotic associated diarrhea and a higher risk of *Clostridioides difficile* infection.<sup>72,73</sup> Although clindamycin is often considered as the major driver of *C. difficile* infection, most of the mentioned antibiotics for the treatment of SIBO may be associated as well.<sup>73</sup> A myriad of symptoms may be present and range from mild to severe systemic compromise. The main acute symptoms that should prompt active search are malaise, abdominal pain, diarrhea, nausea, vomiting, fever and leukocytosis.<sup>74</sup> Moreover, the presence of gastrointestinal involvement has been related to a greater incidence of non-strongyloidiasis diarrhea (OR 2.28, CI 1.21–6.56).<sup>30</sup>

Interestingly, a high incidence of esophageal candidiasis was reported in the late 80s in patients with SSc who needed PPIs and was linked by the authors to esophageal dysmotility, rather than to immunosuppressive treatment.<sup>75,76</sup> Nonetheless, this phenomenon appears to be uncommon in recent literature. In fact, only one case was reported among the retrieved articles.<sup>30</sup> Further, in our experience, esophageal candidiasis is seldom seen in clinical practice.

*Helicobacter pylori* prevalence in SSc patients is an interesting phenomenon, as it can be almost twice the one of immunocompetent population, although this prevalence is mainly driven by ELISA positivity.<sup>77</sup> Its occurrence has been associated with the presence of disease activity and severity, and its detection and eradication have shown significant improvement in SSc symptoms and disease activity.<sup>78,79</sup> Several eradication regimens are available and should be considered based on local epidemiology, patient preferences, risk factors and medical consideration.<sup>80</sup>

Another complication with the potential of infectious complications is the requirement of parenteral nutrition, mostly derived from gastrointestinal involvement, such as pseudo-obstruction, malabsorption, and malnutrition. It is considered as a safe intervention, although bacteremia incidence presents a variable rate (0.19–1 in 1000 catheter-days).<sup>81,82</sup>

### Opportunistic infections and others

The advent of biological therapy and the use of both glucocorticoids and other immunosuppressants in rheumatology practice render patients on these therapies prone to OI, for whom a specific definition has been proposed.<sup>83</sup> Currently, OIs in SSc are considered to be less frequent than in other rheumatic diseases, given that most of the available information is limited to case reports. Thus, recommendations for a prophylactic or diagnostic approach are difficult, but they should be considered in highly immunosuppressed patients.

Extrapolated data of OIs from other diseases in which similar therapies are used (e.g., rheumatic, malignancies, transplants, etc.) might be considered. This kind of infections has been described in patients with high immunosuppression requirements, especially with high glucocorticoids dose (i.e.,  $\geq 30$  mg/day), CYC or biological therapy.

Several different OIs have been reported in SSc, such as *P. jirovecii* pneumonia (as previously described)<sup>63–65</sup>; disseminated candidiasis on high glucocorticoids doses (i.e., prednisolone at a dose of 40 mg/day, followed by methylprednisolone pulse therapy)<sup>84</sup>; cryptococcosis, with pulmonary and extrapulmonary involvement<sup>85,86</sup>; cerebral toxoplasmosis<sup>87</sup>; tenosynovitis, septic arthritis and skin abscesses caused by atypical mycobacteria<sup>88–90</sup>; and infections by *Nocardia farcinica* with subcutaneous abscesses or pulmonary infections.<sup>91,92</sup>

Similarly, viral reactivations have been reported in patients on high immunosuppressive therapy. Cytomegalovirus (CMV) reactivations present similar complications to those described in other high risk groups, including splenic rupture, pneumonitis, pancreatitis, esophagitis or duodenal perforation, mainly related with high dose glucocorticoids and CYC.<sup>93–96</sup> Human Herpes Virus 6 (HHV6) asymptomatic reactivation has

been detected in SSc patients, although it may represent an epiphenomenon linked to immunosuppression, without clinical relevance.<sup>97</sup> There are also reports of a Herpes Simplex Virus (HSV) -1 necrotizing pleuritis<sup>98</sup> and parvovirus B19 alveolitis associated with ILD.<sup>99</sup> Herpes Zoster Virus (HZV) reactivations can happen in 5% of patients, mainly with cutaneous involvement, but complications such as Guillain-Barré syndrome, have been reported.<sup>100</sup> Hepatitis B Virus (HBV) reactivation prevalence in rheumatoid arthritis has been described in 3–3.5 %, but there are no data of its prevalence in SSc patients. Nevertheless, when high immunosuppressive doses are considered as part of SSc treatment, patients with a high risk profile (i.e., health care workers, high risk sexual activity, hemodialysis patients, injectable drug users, multiple sexual partners, and household contacts of HBV-infected individuals) must be screened for chronic HBV infection, and prophylaxis must be offered if indicated.<sup>101,102</sup> HBV reactivation must be suspected when an increase in liver enzymes is observed, mainly alanine aminotransferase, particularly in patients with evidence of past HBV infection (i.e., positive HBV core antibody).<sup>102</sup> If suspected, serum HBV DNA should be assessed and consultation with a specialist (e.g., gastroenterology, infectious diseases) is advisable. A low threshold of suspicion must be considered: although hepatotoxicity from medications is often seen, HBV reactivation may explain this finding and must be ruled out in at-risk patients.

Data on Human Papilloma Virus (HPV) infection incidence in SSc are contrasting, but up to a five-fold increased incidence when compared with healthy age matched controls has been reported.<sup>103,104</sup> Routinely gynecological screening must be considered based on national guidelines.

## Immunosuppressants and infections

Currently, treatment strategies are directed towards management for specific organ involvement and symptoms relief, with immunomodulation as a pivotal strategy for the management of skin, lung and articular involvement.<sup>9,10</sup> In selected patients, transplantation proceedings, such as hematopoietic stem cell transplantation (HSCT), are also available with a subsequent risk of infection.<sup>105</sup> Solid organ transplantation is also feasible and is particularly offered for patients with organ-specific involvement, including lung (i.e., ILD or PAH), heart, and kidney; even heart-lung transplant is possible in selected cases. Clinical and survival outcomes are comparable to those observed in patients without SSc, including infectious events,<sup>106–109</sup> for which recent guidelines have been issued.<sup>110</sup> Further, other frequent interventions, particularly intravenous medications, such as prostanoids may turn SSc patients more prone to infections.<sup>5</sup> Table 1 summarizes potential infectious complications/etiologies by immunosuppressant in patients with SSc.

### Synthetic immunosuppressants

#### Cyclophosphamide

CYC is an alkylating agent that inhibits DNA replication, particularly in hematopoietic cells and lymphocytes due to their high proliferation rate, ultimately leading to their

**Table 1 – Potential infectious complications/etiologies by immunosuppressant in patients with Systemic sclerosis.**

Glucocorticoids (146,148)	<ul style="list-style-type: none"> <li>• Bacteria: Gram-positive, Gram-negative, <i>Listeria monocytogenes</i>, <i>Nocardia spp</i>, TB, Non-TB- mycobacteria</li> <li>• Fungi: <i>Candida spp.</i>, <i>Aspergillus spp.</i>, <i>Pneumocystis jirovecii</i>, <i>Cryptococcus</i>, <i>Histoplasma capsulatum</i></li> <li>• Virus: HSV, HZV, CMV, EBV, Influenza, Adenovirus</li> <li>• Parasites: <i>Toxoplasma</i>, <i>Cryptosporidium spp</i>, <i>Strongyloides spp</i></li> </ul>
Cyclophosphamide (5,112,114,118–127,184,185)	<ul style="list-style-type: none"> <li>• Bacteria: Gram-positive, Gram-negative, mycobacteria</li> <li>• Fungi: <i>P.jirovecii</i>, <i>C. albicans</i>, invasive fungal disease</li> <li>• Virus: HSV, HZV, BK-virus and adenovirus associated hemorrhagic cystitis, JC-virus/PML, HBV reactivation</li> <li>• Increased risk of upper RTI, pneumonia, UTI, skin/soft tissue infection.</li> </ul>
Methotrexate (102,125,126,144,145)	<ul style="list-style-type: none"> <li>• Skin and soft tissue infections, RTI</li> <li>• Virus: HZV (debated)</li> </ul>
Azathioprine (102,112,115,125,126,135–138)	<ul style="list-style-type: none"> <li>• Virus: HZV, HSV, CMV, EBV</li> </ul>
Mycophenolate mofetil (113,116,117,129–132)	<ul style="list-style-type: none"> <li>• RTI, UTI and skin/soft tissue infection, pneumonia, HZV</li> </ul>
Rituximab (102,125,153–155,157,158,160)	<ul style="list-style-type: none"> <li>• Bacteria: Enterobacteria, Gram-positive.</li> <li>• Fungi: <i>P. jirovecii</i>, <i>A. fumigatus</i>, <i>Candida spp.</i></li> <li>• Virus: HBV reactivation, HZV, CMV, JC virus/PM</li> </ul>
Tocilizumab (31,102,125,126,162–165,168)	<ul style="list-style-type: none"> <li>• Bacteria: <i>S. aureus</i> (including disseminated infections), <i>E. coli</i>, <i>Streptococcus intermedius</i>, Non-TB-mycobacteria</li> <li>• Virus: HZV</li> <li>• Necrotizing skin and soft tissue infections</li> <li>• UTI, RTI, nasopharyngitis</li> </ul>
Abatacept (102,125,126,169–171,174)	<ul style="list-style-type: none"> <li>• Virus: HSV</li> <li>• Upper RTI, pneumonia, UTI</li> <li>• Seldom seen: OIs (peritoneal tuberculosis, fungal esophagitis, fungal eye infection, fungal sinusitis, and <i>Candida spp.</i>)</li> </ul>
TNF $\alpha$ inhibitors (69,177–180)	<ul style="list-style-type: none"> <li>• Bacteria: Non-TB-mycobacteria</li> <li>• Virus: HZV, HBV reactivation</li> <li>• Fungi: endemic mycoses, CMV, <i>P. jirovecii</i>, <i>Aspergillus spp.</i></li> <li>• RTIs, UTIs, gastrointestinal, skin/soft tissue infections</li> </ul>

CMV, Cytomegalovirus; EBV, Epstein-Barr Virus; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HSV, Herpes Simplex Virus; HZV, Herpes Zoster Virus; JC-virus, John Cunningham -virus; OI, Opportunistic Infection; PML, Progressive Multifocal Leukoencephalopathy; RTI, Respiratory Tract Infection; TB, Tuberculosis; TNF, Tumor Necrosis Factor; UTI, Urinary Tract Infection.

This table is based on references and author's experience.

apoptosis.<sup>111</sup> CYC appears as a first-line therapy for the treatment of ILD and is considered in severe skin involvement.<sup>9</sup> This agent has been associated with respiratory infections, although the presence of lung structural changes that may account for an increased risk of infections should not be disregarded.<sup>5</sup> Data on CYC and infections will be approached from two standpoints: regular- and high-dose, as infection risk is expected to differ. Although a recommended standard regular dose is lacking,<sup>10</sup> a dose of 500–600 mg/m<sup>2</sup> on a monthly basis is widely accepted, which will be discussed in this subheading. In contrast, high doses exceed this dosage and are mainly reported in Hematopoietic Stem Cell Transplant (HSCT) trials, a subject that will be addressed later.

Randomized controlled trials of CYC compared with a variety of interventions have shed light onto this subject. Ludici

et al. reported UTIs in 6 patients (13.3%) and respiratory infections in 4 (8.8%).<sup>112</sup> A recent metanalysis of CYC in connective tissue disease-associated ILD found no difference in pneumonia rates when compared either to placebo or MMF<sup>113</sup>; only two studies versus placebo were included: one study reported 6 out of 79 patients with pneumonia, as the only recorded infectious event,<sup>114</sup> and, the other study reported no differences in infections between groups, although 13.6% (n=3) patients in the intervention group presented intercurrent upper respiratory infection<sup>115</sup> with a more intense immunosuppressive therapy (i.e., glucocorticoids plus CYC followed by AZA). The comparison of CYC against MMF found similar results.<sup>113,116,117</sup> In a metanalysis of 18 studies up to 2010 of CYC for lung involvement, Poormoghim et al reported only one discontinuation of CYC due to pneumonia and only one episode of HZV.<sup>118</sup>

Some other infectious complications have been reported. For instance, one of the frequent adverse events during CYC therapy is hematuria, which is usually considered secondary to CYC itself.<sup>118</sup> However, BK-virus associated hemorrhagic cystitis in a patient with SSC treated with CYC has been reported, thus highlighting the need to rule out an infectious cause.<sup>119</sup> Further, a case of hemorrhagic cystitis associated to adenovirus was described in a HSCT, probably secondary to CYC mobilization (considered as a high-dose).<sup>120</sup>

Although infections due to CYC appear to be rather infrequent, the experience in other rheumatic disease should prompt awareness. Woytala et al reported infections in 37% of patients (n = 24) with different rheumatic diseases, including skin, upper and lower respiratory, and UTIs; few episodes of HZV (3%) were observed.<sup>121</sup> Experience in systemic lupus erythematosus (SLE) has suggested an increased risk of infection from a variety of etiologies<sup>122-124</sup>; CYC has been considered as a low risk medication for progressive multifocal leukoencephalopathy (PML).<sup>125,126</sup> An association with HZV appears to be present in rheumatoid arthritis (RA) on CYC.<sup>126</sup> HBV reactivation has been reported in the literature and a shorter period to reactivation (8 weeks) compared to other immunosuppressants was identified.<sup>127</sup>

In conclusion, an increased risk of upper respiratory infections and probably UTIs appears to be associated with CYC. However, treatment interruption is not often needed.

#### *Mycophenolate mofetil*

MMF is a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is pivotal for the proliferation of T and B lymphocytes.<sup>111,128</sup> MMF is recommended among the first line therapies for ILD,<sup>9</sup> although its safety in SSC treatment appears as an objective in the research agenda.<sup>10</sup>

A systematic review on MMF safety in SSc reported 34 infection events in 487 included patients, including respiratory (n = 11), skin (n = 4), and UTIs (n = 2).<sup>129</sup> Boulos et al. reported only one discontinuation due to recurrent infections after 5 years on therapy in patients treated with MMF (n = 74).<sup>130</sup> Gordon et al.<sup>131</sup> compared MMF alone vs. MMF plus belimumab in 20 patients, with a 1:1 randomization. No differences in infection rates were observed. Naidu et al. reported a similar infection rate compared to placebo in Indian patients.<sup>132</sup>

A recent metanalysis of CYC in ILD in SSc that included two studies,<sup>113,116,117</sup> found no difference in pneumonia rates when comparing MMF with CYC.

Data from renal transplant and SLE patients have reported a decreased production of IgG and IgM, thus increasing infection risk and suppressing response to some vaccines.<sup>133</sup>

These findings support an acceptable safety profile of MMF from an infectious risk standpoint, and may support its election over CYC, although evidence from lupus nephritis appears to show no difference between both.<sup>134</sup>

#### *Azathioprine*

Azathioprine (AZA) is a cytotoxic agent that interferes with DNA and RNA cycles through the insertion of 6-thioguanine nucleotide.<sup>111</sup> AZA is considered as a second line agent for maintenance therapy in ILD.<sup>9</sup> Evidence of infections in SSc is scarce and its safety in these patients appears as an objective in the research agenda.<sup>10</sup> Ludici et al. did not report infectious

events in 24 patients on AZA,<sup>112</sup> whereas Dheda et al. found one episode of TB in 8 patients assessed.<sup>115</sup> Nonetheless, some evidence from the treatment of inflammatory bowel disease suggests a 3-fold increased risk of OIs with the use of AZA, particularly viral (i.e., HZV, HSV, CMV, Epstein-Barr Virus [EBV]),<sup>135</sup> and a 7% frequency of infectious events.<sup>136-138</sup> An association with HZV appears to be present in RA on AZA.<sup>126</sup>

#### *Methotrexate*

Methotrexate (MTX) is a folic acid analogue that inhibits dihydrofolate reductase activity, thus undermining lymphocyte proliferation and promoting an anti-inflammatory milieu.<sup>139</sup> MTX should be considered for the management of skin and articular involvement in SSc.<sup>9,10</sup>

The evidence from randomized controlled trials in the management of SSc has shown infections as a rare event in this population, with doses up to 25 mg/week.<sup>140-143</sup> Evidence from IBD treatment appears to support its safety.<sup>138</sup> MTX has been associated with a mild increased risk of infection, particularly skin/soft tissue and respiratory tract infections, in patients with rheumatoid arthritis (RA).<sup>144,145</sup> Although an increased risk of HZV has been suggested, a large national database-based study in the USA found no association.<sup>126</sup>

#### *Glucocorticoids*

Glucocorticoids influence the inflammatory response through several pathways. Specifically, by a reduction in the innate response and in the production of inflammatory cytokines, an inhibition of both classic and alternative pathways of the complement system, and a reduced capacity for antigen presentation, lymphocyte proliferation and differentiation; a shift towards a Th2 phenotype is generated.<sup>146</sup> Low dose glucocorticoids have been recommended, mainly based on expert opinion, for the management of articular symptoms<sup>9</sup> and some evidence for myositis is available, although its use is debated; however, a wide share of patients with SSc receive them as comedication with other immunosuppressants.<sup>147</sup> Immunological alterations explain the increased risk of infectious events due to both intra- or extra-cellular microorganisms, including bacteria, fungi, virus, mycobacteria and parasites<sup>146</sup>; OIs, such as *P. jirovecii* pneumonia, TB and HZV are increasing major concerns.<sup>148</sup> High-dose glucocorticoids have been associated to an increased risk of fatal infections in patients with autoimmune diseases.<sup>149,150</sup>

#### **Biological immunosuppressants as potential novel interventions for SSc**

##### *Rituximab*

Rituximab (RTX) is a monoclonal antibody that targets CD20 and depletes most of B-cells virtually sparing plasmatic cells, thus altering several immunologic pathways.<sup>13,151</sup> Although not readily approved by regulatory agencies for the treatment of SSc, RTX is recommended by experts for the treatment of refractory ILD and articular involvement.<sup>9</sup> Mounting evidence supports its efficacy, either alone or in combination, for these systems and even in skin involvement.<sup>152-155</sup> Infectious disease risk appears to depend on the underlying diagnosis, as it may be as high as 50% in patients with lymphoma or below 5% in patients with RA or systemic vasculitis. Hypogamma-

globulinemia is the main driver of infection in these patients, in whom the highest risk occurs during the first 3 months of therapy, although substantial risk is present thereafter.<sup>156</sup> Neutropenia can also occur and severe neutropenia is reported in up to 30% of patients. Early neutropenia is rare, nonetheless, the so-called late-onset neutropenia is observed in up to 15% of patients 1–5 months after the end of therapy. Its mechanism is still unknown as is considered to be immune-mediated; it can persist for months, may resolve spontaneously, and in persistent cases, its response to granulocyte colony-stimulating factor therapy is poor or transient. Its impact on infection risk remains to be elucidated.<sup>157</sup> Different microorganisms have been reported as etiologies of infectious events on RTX for both neoplastic and autoimmune diseases, particularly by *Enterobacteriaceae*. Further, OIs have been reported including *P. jirovecii* pneumonia, *A. fumigatus*, *Candida* spp., HZV, CMV and PML,<sup>158</sup> although for the latter, RTX has been considered as a low risk medication.<sup>125</sup> However, evidence is conflicting as data derived from RA did not revealed an increased risk of OIs nor viral reactivations, although the lack of long-term follow-up hampers to ascertain this risk.<sup>159</sup> Regarding specific data on SSc, Thibaut et al. reported in a literature review that infectious events are frequent, but usually not severe.<sup>153</sup> Melsens et al. did not report infectious complications in 17 patients with SSc.<sup>154</sup> Noteworthy, interim results from the EUSTAR Network reported infections in 76 out of 248 (30%) patients with SSc using RTX.<sup>155</sup>

One of the major concerns of RTX, is its increased risk of reactivation of latent HBV infection, that is considered the highest among all the available biologics: a rate of up to 16.9%, although this information comes from patients on concomitant antineoplastic agents.<sup>160</sup> This risk appears to be lower among rheumatic diseases (<10%), thus, close monitoring is advised.<sup>102</sup>

#### Tocilizumab

Tocilizumab is a humanized monoclonal antibody directed towards IL-6 receptor.<sup>161</sup> TCZ is considered a promising molecule in the treatment of SSc and is recommended as an alternative in articular involvement.<sup>9,13</sup> The FaSScinate phase 2 study explored its utility in SSc and reported that up to 56% of patients (n = 24) presented at least one infectious event. Noteworthy, this frequency did not differ from the placebo arm, although serious infectious events were more frequent in the TCZ arm (16% vs. 5%). One death due to lung infection was reported. The most frequent infections were nasopharyngitis (n = 5), UTI (n = 3) and HZV (n = 3).<sup>31</sup> Data from the phase 3 trial did not report an increased risk of infection when compared to placebo.<sup>32</sup> Noteworthy, Distler & Distler expressed a relevant concern on infectious disease risk: the authors of the study reported two events of proximal interphalangeal joint osteomyelitis in patients receiving TCZ, probably associated with digital ulcers. As TCZ inhibition of IL-6 has been shown to blunt PCR elevation and probably signs of infection, a low threshold of clinical suspicion is warranted<sup>162</sup>; from an infectious disease perspective, the follow-up of osteomyelitis under IL-6 inhibition may present a major challenge. Evidence from RA experience has suggested an increased risk of necrotizing skin infections, as well as *S. aureus* and non-TB mycobacteria disseminated infections.<sup>163-166</sup> Neutropenia was observed

in up to 30% of RA patients in pivotal studies, although less than 5% presented severe neutropenia. Its mechanism is still unknown, although a redistribution of the neutrophil compartment has been proposed. Its consequences on infection risk are unclear, although data from RA trials do not support an association with an increased risk; dose interruption is an effective risk mitigation strategy that yields a rapid recovery of neutrophil counts.<sup>167,168</sup>

#### Abatacept

Abatacept is a soluble fusion molecule formed by the extracellular domain of CTLA-4, which inhibits the activation of T lymphocytes through its union with CD80 and CD86, thus blocking the interaction with CD28.<sup>161</sup> The efficacy of ABA in the management of skin and articular involvement in SSc has been suggested.<sup>13</sup> Chakravarty et al. (n = 10) found no statistical differences in infection rate between the intervention and the control group; two events of upper respiratory infection were reported in the ABA arm.<sup>169</sup> Similarly, a retrospective study (n = 11) in patients with articular involvement reported 3 infectious events: two episodes of bronchitis and one HSV infection.<sup>170</sup> Results from a phase 2 trial in SSc suggested a comparable infection risk profile between ABA and placebo.<sup>32</sup> Pooled-evidence from RA studies does not support an increased risk for infection compared to other therapies,<sup>171-173</sup> although the long-term extension (5 years) report of the ACQUIRE study showed that 70% of patients experienced an infectious event during follow up, mainly mild or moderate.<sup>174</sup>

#### Belimumab

In a pilot study, Gordon et al compared MMF alone vs. MMF plus belimumab (BEL) in 20 patients, with a 1:1 randomization. Although no differences between the interventions in the assessed outcomes were observed, basic science evidence supports its potential use<sup>13</sup> and the authors suggest the performance of a larger clinical trial.<sup>131</sup> No differences in infection rates were observed, with 18 in the MMF/BEL vs. 16 in the MMF alone. The most frequent infections in the MMF/BEL were upper respiratory involvement (n = 5), UTI (n = 3) and HSV stomatitis (n = 2).

#### Tumor necrosis factor $\alpha$ inhibitors

Tumor Necrosis Factor (TNF)  $\alpha$  inhibitors might play a role in the management of articular compromise, although they are not currently recommended by experts as a first line therapy.<sup>9,13,175</sup> Data for etanercept, adalimumab and infliximab have been reported from small studies in patients with SSc.<sup>176,177</sup> Regarding infectious disease risk, a low frequency of events has been reported: uncomplicated HZV (although this patient received concomitant prednisone and AZA),<sup>177</sup> infected DU and one sepsis episode.<sup>178</sup> Lam et al. reported no cases of OIs in 18 patients.<sup>179</sup> Anecdotally, one case of pulmonary actinomycosis was reported on infliximab.<sup>69</sup> Nonetheless, safety concerns based on data from other autoimmune/autoinflammatory diseases should be considered. Patients on TNF- $\alpha$  inhibitors may present a doubled risk of serious infections compared to placebo.<sup>180</sup> Several infectious complications have been reported, namely respiratory infections, UTIs, gastrointestinal infections, skin/soft



tissue infections, HZV, and HBV reactivation.<sup>180</sup> OIs have been described, such as endemic mycoses, CMV, *P. jirovecii* pneumonia, *Aspergillus* spp., among others, in which atypical manifestations may be observed.<sup>180</sup> As TB infection is a major concern on TNF- $\alpha$  inhibitors, active screening prior to biologic application must be performed. Non-TB-mycobacteria infections may be observed.<sup>180</sup>

### Hematopoietic stem cell transplant and high dose CYC

Hematopoietic Stem Cell Transplant (HSCT) is an emerging therapeutic strategy in selected patients with SSC. The procedure is performed in three main phases: 1) mobilization of stem cells from the bone marrow to the peripheral blood using priming agents (i.e., high dose CYC), followed by the collection of the mobilized stem cells; 2) immunoablation or myeloablation through the administration of conditioning regimens (i.e., total body irradiation or alkylating agents); 3) infusion of autologous CD4+ stem cells, the so-called "transplantation".<sup>181,182</sup>

Infectious complications are usual in the vast majority of transplantation procedures and three risk phases have been proposed. The first phase is known as 'early pre-engraftment', which occurs previous to the "transplantation" during the first 2–4 weeks, and is characterized by infections due to mucositis and neutropenia. The most frequent etiologies are bacterial (Gram-positive or Gram-negative), HSV and *Candida* spp. The second phase is known as 'early post-engraftment', and occurs from days 30–100 after the "transplantation". The most frequent etiologies are bacterial, fungal (e.g., *Aspergillus* spp., *P. jirovecii*), and viral (e.g., CMV, EBV) infections. The last phase is known as 'late post-engraftment' and is characterized by infections due to encapsulated bacteria, *Nocardia* spp., *Aspergillus* spp., *P. jirovecii*, CMV, EBV, among others. Nonetheless, an increased incidence of respiratory virus infections and complications is present throughout all the phases.<sup>105</sup> These periods are as applicable in patients with refractory systemic autoimmune diseases undergoing autologous stem cell transplantation. Szodoray et al. reported that immune reconstitution started with CD56 + NK cells around day 30, followed by CD8 + T cells around day 60 post transplantation. The number of B cells and CD4 + T cells became normal within 150 days.<sup>183</sup>

The HSCT experience in SSC has illustrated the risk of infection. The SCOT trial compared CYC in a high dose regimen (i.e., initial intravenous dose of 500 mg/m<sup>2</sup>, followed by 11 monthly infusions of 750 mg/m<sup>2</sup>) with HSCT (which included a mobilization dose of CYC of 120 mg/Kg), and reported a similar infection rate among both groups. In the CYC arm, 84% of patients (n = 31) presented an infectious disease during follow-up, although only 9 patients presented a serious infection. The most frequent infections were UTIs (40%) and upper respiratory infections (21.6%); up to 10% of patients presented an infected DU. In contrast, in the HSCT group 97% of patients (n = 33) presented an infectious episode and serious infections appeared to be more frequent. The most frequent infections were HZV (38.2%), upper respiratory infection (26.5%) and pneumonia (26.5%); bacteremia was reported in 11.8% of patients. Varicella Zoster occurred in 12 patients

in the HSCT compared to 1 in the CYC arm. Five cases of CMV reactivation were observed in the HSCT arm.<sup>184</sup>

The ASTIS trial compared CYC (i.e., 750 mg/m<sup>2</sup> monthly for 12 months) with HSCT (i.e., mobilization dose of CYC of 200 mg/Kg for 4 days); viral infection or reactivation after randomization were recorded. Infections were infrequent among the CYC group (n = 77) with only one episode of HSV primary infection. In contrast, 27.8% of patients (n = 22) in the HSCT group presented an infectious disease. Reactivation of EBV (12.5%), HSV (22%) and recurrent CMV (18.7%) were the most frequent phenomena.<sup>185</sup>

The ASSIST trial compared CYC (i.e., 1000 mg/m<sup>2</sup> monthly for 12 months) with HSCT (i.e., mobilization dose of CYC of 200 mg/Kg for 4 days). The authors reported only one episode of cellulitis on CYC and one episode of *C. difficile* positive stool sample in both arms, *Micrococcus* bacteremia and CMV reactivation were observed in the HSCT arm.<sup>186</sup>

Del Papa et al., in a retrospective study of HSCT in SSC, recorded eight cases of fever of unknown origin, five cases of fever with positive blood culture and three cases of pneumonia. All the observed infections resolved with adequate antibiotic treatment.<sup>182</sup>

### Solid organ transplantation

Solid organ transplant recipients also have an increased risk of infectious complications, in close relation to the dose and type of immunosuppressive drugs used. Other factors related include surgical complications, prolonged hospitalization, other invasive procedures, and viral reactivations, mainly CMV, with increased risk of opportunistic infections, allograft injury and rejection.<sup>187,188</sup>

In any post-transplant patient, the risk of infection is a function of the net state of immunosuppression. As described in bone marrow transplant recipients, the risk of infection has been divided into three periods, the first is referred as "early period", which includes infections within the first month post transplantation and is characterized by health care-related infections, donor derived infections (e.g., HSV, rabies, HIV, *Trypanosoma cruzi*) and recipient derived infections, usually related to previous colonization. The second or "intermediate period" includes infections during the period from 1 to 6 months after transplantation. It is characterized by the greatest risk of opportunistic infections, mainly intracellular microorganisms, including *P. jirovecii*, TB, *Cryptococcus neoformans*, CMV, EBV, *Toxoplasma gondii*, among others. The third or "late period" occurs after the sixth month post transplantation and is characterized by an increased incidence of community acquired infections, mainly pneumonia and UTIs. Infections by *Aspergillus* spp., Zygomycota, CMV infections (colitis and retinitis), and post transplantation lymphoproliferative disorder, associated in most cases to EBV have been described.<sup>188</sup>

In solid organ transplant recipients, the most common site of infection is the allograft. In SSC patients, the most frequently transplanted organ is the lung. Bacterial infection is the most frequent infectious complication (35–66%) for recipients with unilateral or bilateral lung transplant. Bacterial infections presenting in the immediate post transplantation period usually show relation with pre-transplantation colonization, the surgical procedure itself and accompanying

technical complications, intubation or prolonged hospitalization. Late onset bacterial infections are related to increased immunosuppression due to rejection, invasive diagnostic procedures and the development of bronchiolitis obliterans.<sup>189</sup>

### Other therapies and their potential risk of infection

The intravenous route of some therapies for SSc management should raise awareness towards the potential for infectious complications. Prostanoids (e.g., epoprostenol, treprostinil) are recommended for the management of PAH, Raynaud's phenomenon and DU.<sup>9,10</sup> Cellulitis and sepsis have been described with their application. Among the most frequent sepsis etiologies are *Staphylococcus epidermidis*, *Micrococcus* spp., *S. aureus*, *Pseudomonas* spp., and *Enterobacter* spp.<sup>190,191</sup> A higher infection rate associated with treprostinil compared to epoprostenol has been suggested.<sup>5,192,193</sup>

In patients with gastroesophageal reflux disease or gastrointestinal dysmotility, the use of high dose PPIs is recommended.<sup>9</sup> Recently, the prolonged use of PPIs has been associated with a higher risk of *C. difficile* infection<sup>73,194,195</sup> and community-acquired pneumonia, although evidence for the latter is conflicting.<sup>196-199</sup>

With regard to ILD management with anti-fibrotic therapy, current evidence supports its efficacy in SSc. Nintedanib is not associated with an increased risk of infection in SSc or other patient population.<sup>200-203</sup> As observed with most tyrosine kinase inhibitors, a common side effect is diarrhea, which has not been associated with an infectious etiology. Although its cause is still unknown, receptor inhabitation and direct mucosal damage have been proposed.<sup>204,205</sup> On the other hand, although direct evidence of pirfenidone in SSc is lacking, trials are ongoing; to date, pirfenidone has not been associated with an increased risk of infection in other patient population.<sup>206,207</sup>

Other therapeutic strategies addressing several domains of the disease have not been associated with a higher risk of infection in SSc. These include phosphodiesterase-5 inhibitors, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonist, endothelin receptor antagonists, and riociguat.<sup>10,208-213</sup>

## Infection prevention

Risk management strategies, including prophylaxis and vaccination must be considered within the bundle of care. [Table 2 and 3](#) summarize screening recommendations, potential prophylaxis and available prophylactic therapies to be considered in patients with SSC. Several recommendations guidelines for the prevention of infection in patients receiving immunosuppressive treatments are available.<sup>157,168,214-223</sup> However, there is a lack of information in the literature on infectious diseases prevention in patients with SSc, probably due to the low incidence of the disease. Thus, extrapolated data from other diseases, in which similar therapies are used (e.g., rheumatic, malignancies, transplants, etc.), might be considered. When considering vaccination and chemoprophylaxis for patients with SSc, the first thought a rheumatologist should have is: how immunosuppressed is my patient and

what is the mechanism of immunosuppression? One shall not forget an increased risk of infections due to the disease itself. Vaccination, screening for latent or active infections, and several other measures for infection prevention should be performed prior to immunosuppressive agent application (215,223,224)

### Antibiotic prophylaxis: when to consider

As shown, the most frequently used immunosuppressants in SSc may increase the risk of infectious complications.<sup>5</sup> Experience from other autoimmune diseases has suggested the protective effect of chemoprophylaxis whenever immunosuppression is necessary.<sup>67</sup>

A particular interest and evidence for *P. jirovecii* pneumonia are available, in which contrasting incidences are identified depending on the underlying disease, from as low as 0.1% in RA to as high as 12% in granulomatosis with polyangiitis.<sup>225</sup> One shall consider that *P. jirovecii* pneumonia has a low rate among patients with rheumatic diseases, although its course tends to be severe and potentially fatal.<sup>226</sup> For instance, recent guidelines for the management of ANCA-associated vasculitis "encourage the use of prophylaxis against *P. jirovecii* in all patients treated with CYC, where not contraindicated".<sup>227,228</sup> Mounting evidence supports the utility of prophylaxis in patients on glucocorticoids, particularly in those with high doses ( $\geq 30$  mg/day), since a dose-dependent risk is observed.<sup>67,229</sup> In addition, the use of RTX also appears to be associated with a higher risk of *P. jirovecii* pneumonia and a protective effect of prophylaxis has been reported.<sup>230</sup> Winthrop & Baddley recently proposed a tailored prophylaxis schema for different autoimmune rheumatic diseases on glucocorticoids, in which SSc patients with  $\geq 30$  mg/day dose would benefit and those with doses below 15 mg/day would not; those patients who receive between 15 mg and 30 mg/day should be assessed on an individual risk basis, based on the presence of at least one of these factors: baseline lymphopenia, low CD4 count, CYC use, anti-TNF or RTX use, initial glucocorticoids dose  $\geq 60$  mg/day ([Table 3](#)). Nonetheless, these recommendations are based on expert opinion and the authors advocate for further studies<sup>67</sup>; some other authors believe that "more personalized risk assessments are needed to inform *P. jirovecii* pneumonia prophylaxis", as data are contrasting.<sup>226</sup> There are no studies in SSc showing these outcomes, probably due to the difficulty in gathering large cohorts of patients with this disease. However, there are reports of SSC patients on these therapies who develop opportunistic infections by *Mycobacterium avium intracellulare* and *P. jirovecii*.<sup>231</sup>

As the optimal TMP/SMX prophylactic dose in rheumatic diseases is unclear, an open RCT in Japan explored this subject. Patients were mainly exposed to glucocorticoids ( $>0.6$  mg/Kg/day), and received a daily low dose TMP/SMX (80 mg/400 mg, or 40 mg/200 mg, or escalating dose from 8 mg/40 mg until 40 mg/200 mg was reached); no events of *P. jirovecii* pneumonia were observed in any group. The authors suggested a better tolerability and safety of 40 mg/200 mg doses.<sup>232</sup> Recommended regimens for ANCA-associated vasculitis prophylaxis on CYC are: TMP/SMX 160 mg/800 mg on alternate days or 80 mg/400 mg every day. In case of adverse reaction or contraindication, pentamidine, atovaquone or

**Table 2 – Screening recommendations and available prophylactic therapies proposed for autoimmune diseases.**

Recommendation by infectious disease	Available therapies
<p><b>Tuberculosis (TB)</b> Screening: TST or IGRA (based on local guidelines).</p> <p>TST <math>\geq</math> 5 mm or IGRA (+): 1) Rule out active TB (Chest X-rays, sputum smear and culture). 2) ID/ TB specialist consult should be considered. 3) Initiate LTBI treatment</p> <p>TST &lt; 5 mm or IGRA (-): 1) Routine screening is not recommended and should be based on suggestive symptoms or potential TB exposure. <b>P. jirovecii pneumonia<sup>a</sup></b></p> <p>To be considered in patients receiving CYC, GC or RTX.</p>	<p>Isoniazid 300 mg PO/day + Pyridoxine 50 mg PO/day for nine months (270 doses)</p> <p>Other therapies are available and should be considered based on the patient history and the medical concept.</p> <p>Should be given for at least one month prior to immunosuppression</p> <p>TMP/SMX 800 mg/160 mg PO on alternate days or 400 mg/80 mg PO every day<sup>b</sup></p> <p>In case of adverse reaction, other therapies may be considered – ID specialist consult should be considered.</p>
<p><b>Hepatitis B Virus (HBV)</b> Screening should be considered in every patient prior to immunosuppressive therapy. Baseline HBV profile should include: antiHbs, HbsAg, and antiHbc.</p> <p>1) antiHbs (-), HbsAg (-), antiHbc (-): vaccination should be initiated.</p> <p>2) antiHbs (-), HbsAg (+/-) antiHbc (+): Prophylaxis should be considered. Complete profile must be performed, including: HbeAg, antiHbeAg, ALT, serum HBV DNA.</p> <p>3) antiHbs (+), HbAg (-), antiHbc (+/-): patient is protected (previous vaccination or resolved infection).</p>	<p>ID specialist consult must be considered.</p> <p>Several options are available, including lamivudine, tenofovir (TDF, TAF), entecavir.</p> <p>Major concern: patients receiving RTX.</p>
<p><b>Herpes Zoster Virus</b> Suggested by some authors for patients exposed to CYC<sup>236</sup>. No consensus available. Patients must be individualized.</p>	<p>ID specialist consult must be considered. Valacyclovir?</p>
<p><b>Herpes Simplex Virus</b> No consensus available. Suppressive therapy may be considered if recurrent episodes (&gt;= 3/year) occur. Patients must be individualized.</p>	<p>ID specialist consult must be considered. Acyclovir: suppressive therapy dose.</p>
<p><b>Helminths and amoebas</b> Antiparasitic prophylaxis should be considered, particularly if biological therapy or GC are planned. Amebiasis prophylaxis in endemic regions has been proposed; repeated every year if immunosuppression persists or potential exposure (e.g., still living in endemic area).</p>	<p>Helminthic superinfection: ivermectin (200ug/Kg/day [i.e., one drop per Kg]), two doses 15 days apart; or albendazole 400 mg/day, for 3 days Amebiasis (endemic regions): secnidazole 2 g, single dose</p>
<p>antiHbc, Hepatitis B virus total core antibody; antiHbeAg, Hepatitis B virus E antigen antibody; antiHbs, Hepatitis B virus surface antibody; CYC, Cyclophosphamide; GC, Glucocorticoids; HbeAg, Hepatitis B virus E antigen; HbsAG, Hepatitis B virus surface antigen; ID, Infectious diseases; IGRA, Interferon Gamma Release Assay; LTBI, Latent TB Infection; RTX, Rituximab; TAF, Tenofovir Alafenamide Fumarate; TDF, Tenofovir Disoproxil Fumarate; TMP/SMX, Trimethoprim/Sulfamethoxazole; TNE, Tumor Necrosis Factor; TST, Tuberculin Skin Test. This table is based on references and author's experience.</p> <p><sup>a</sup> Based on expert recommendations, however, current data are contrasting. Lower TMP/SMX doses have been proposed. <sup>b</sup> Regimen proposed for ANCA-associated vasculitis.</p>	

dapsone are alternatives,<sup>227,228</sup> however, only the latter is available in Colombia. In this scenario, an infectious diseases specialist consultation is advisable. As quality evidence is unavailable regarding doses, one might extrapolate recommended doses for human immunodeficiency virus (HIV), namely dapsone 100 mg/day or, in situations in which the recommended agents cannot be administered or are not tol-

erated, clindamycin plus primaquine.<sup>233</sup> British guidelines on ANCA-associated vasculitis suggest the use of similar prophylaxis regimen in any patient with immunosuppression, including RTX.<sup>234</sup> Some authors have suggested that one shall not rely solely on CD4-cell count for the guidance of *P. jirovecii* prophylaxis in autoimmune/inflammatory diseases.<sup>235</sup>

**Table 3 – Potential prophylaxis to be considered in patients with SSC.**

	CYC	Glucocorticoids (GC)			RTX	Others <sup>f</sup>
		<15 mg	15–30 mg	>30 mg		
TB	Every patient should be screened. Treatment for LTBI positive patients must be administered at least one month prior to immunosuppression. ID specialist consultation advisable.					
PCP <sup>a</sup>	Y	N	Y <sup>b</sup>	Y	Y? <sup>c</sup>	N?
HBV	Prophylaxis must be considered in patients with HbsAg (+/-) and antiHbc (+). ID specialist consultation must be performed.					
HZV	?	?	?	?	?	?
HSV	Consider if recurrent (>= 3 per year). ID specialist consultation must be performed.					
Parasites <sup>d</sup>	Consider particularly when GCs or biologics are planned.					
Others <sup>e</sup>	No evidence. Patients must be individualized. ID specialist consultation must be performed.					

antiHbc, HBV total core antibody; CYC, Cyclophosphamide; GC, Glucocorticoids; HbsAg, HBV surface antigen; HBV, Hepatitis B virus; HSV, Herpes Simplex Virus; HZV, Herpes Zoster Virus; ID, Infectious diseases; LTBI, Latent TB Infection; PCP, *Pneumocystis jirovecii* pneumonia; RTX, Rituximab; TB, Tuberculosis.

This table is based on references and author's experience.

<sup>a</sup> Based on expert recommendations, however current data are contrasting.

<sup>b</sup> Additional risk factors: baseline lymphopenia, low CD4 count, CYC use, TNF  $\alpha$  inhibitors or RTX use, initial GC use >60 mg.

<sup>c</sup> Prophylaxis has been suggested for patients on RTX based on an apparent increased risk.

<sup>d</sup> Refers to helminths and amoebas.

<sup>e</sup> Including: *Candida spp.*, *Cryptococcus spp.*, *Toxoplasma*, Endemic mycoses (e.g., Histoplasmosis), *Leishmania spp.*, etc.

<sup>f</sup> Including: Methotrexate, Mycophenolate Mophetil, Azathioprine, Abatacept, Tocilizumab, Tumor Necrosis Factor  $\alpha$  inhibitor, Belimumab.

The incidence of HZV in patients under immunosuppression is an increasing challenge, however, the utility of prophylaxis among patients with autoimmune rheumatic diseases is unclear and safety data for vaccination are lacking. A recent study in patients receiving CYC for SLE or vasculitis explored the effect of anti-viral prophylaxis with valacyclovir. The authors reported an increased risk of HZV in patients with lymphopenia <500/ $\mu$ L at CYC initiation (HR 4.36, CI 0.51-37-31) and suggested that valacyclovir should be considered in these scenarios; none of the 19 patients receiving valacyclovir presented HZV. Interestingly, a higher risk of HZV has been found in SLE, which may suggest a different risk based on the underlying disease.<sup>236</sup> Data are lacking for SSc.

As aforementioned, SSc patients are at an increased risk of TB (and probably non-TB-mycobacteria) infection due to the disease itself (particularly in the presence of pulmonary involvement and PAH) and to pharmacological immunosuppression.<sup>57,58</sup> Glucocorticoids and TNF- $\alpha$  inhibitors are well-known risk factors for TB.<sup>237,238</sup> Therefore, screening for TB infection using either a tuberculin skin test or an interferon gamma release assay is the basis of active disease prevention, and should be implemented in patients who will undergo immunosuppression.<sup>215,224</sup> Whenever latent TB infection is detected, it must be treated according to guidelines.<sup>224,239</sup> Expert recommendations for RA suggest to screen for pulmonary non-TB-mycobacteria prior to biologic therapy in patients with lung structural abnormalities (particularly bronchiectasis) or those with unexplained chronic cough. Although there is a higher risk of non-TB-mycobacteria in patients with ILD, such as SSc,<sup>62</sup> data to support the need of prophylaxis are not available.<sup>238</sup>

## Vaccines

Some preventable infectious diseases, such as influenza and pneumococcal pneumonia, may manifest more severely in patients with SSc. For instance, patients with ILD who become

infected by influenza are at greater risk of respiratory failure and morbidity. Therefore, vaccination becomes an important strategy of care.<sup>240</sup> However, safety and efficacy of vaccination in patients on immunosuppressive therapy and patients with autoimmunity has always concerned clinicians, as some studies have shown immunosuppressive therapy may hamper immunologic response to vaccination.<sup>241,242</sup> These beliefs may explain a low vaccination rate against influenza in these patients, as described in a French cohort of patients with systemic autoimmune diseases on immunosuppressive therapy.<sup>243</sup>

## Influenza

Recent research on influenza vaccination in patients with SSc has proven that different presentations of the influenza vaccine are not only safe in this population, but effective. A study by Sampaio-Barros et al. evaluating the outcomes of vaccination with H1N1 vaccine, found that there were no statistically significant differences in seroprotection (83.7 vs. 76.1%;  $P=0.20$ ) or seroconversion (76.1 vs. 72.8%;  $P=0.61$ ) rates between SSc patients and healthy controls, despite receiving different immunosuppressive medications. A similar incidence of systemic side effects after vaccination was also observed (25 vs. 31.5%;  $P=0.33$ ).<sup>244</sup> Another study by Setti et al., assessed the effectiveness of influenza AH3N2/AH1N1/B vaccine in individuals with SSc compared to a healthy control group. Although a higher effectiveness was observed in the control group, a good humoral response was achieved by SSc patients with no higher incidence of adverse effects or alterations in the course of the disease, proving its safety and efficacy.<sup>240</sup>

## Pneumococcal pneumonia

Public health authorities recommend vaccination for *Streptococcus pneumoniae* (PCV13 or PPVP23) in immunocompromised adults<sup>245</sup> and different studies have described a fair immune response to pneumococcal vaccine in patients with SSc. A

**Table 4 – Major recommendations for vaccination in patients with autoimmune inflammatory rheumatic diseases and patients with altered immunocompetence.**

Recommendation	EULAR (2011) <sup>(221)</sup>	IDSA (2013) <sup>(222)</sup>	ACIN (2016) <sup>(223)</sup>	ASOREUMA (2016) <sup>(216)</sup>	Pérez- Díaz et al. (2016) <sup>(215)</sup>	CDC (2018) <sup>(222)</sup>
• Assess which vaccines were previously administered to the patient	X	X	X	X	X	X
• Live vaccines must be administered 4wk before immunosuppression		X			X	X
• All inactivated vaccines, according to age, should be administered >2 wk before immunosuppression	X	X	X		X	X
• Vaccines should be administered if the inflammatory and autoimmune disease is stable	X		X			
• Live and live attenuated vaccines should not be administered to patients with high-grade immunosuppression	X	X	X	X	X	X
• Vaccination should be administered before starting rituximab or after 6 months of ceasing therapy						X
• Inactivated vaccines can be administered in patients on DMARDS and TNF- $\alpha$ blockers	X				X	X
• Live vaccines can be administered one month after stopping high dose corticosteroids before						
• Low dose corticosteroids do not contraindicate live vaccines						
• Live vaccines should be withheld for 3 months after Anti-TNF $\alpha$ or B-cell antibodies are stopped						
• Those who live in a household with immunocompromised patients should be vaccinated following the recommendations of the annually updated schedule, except for oral polio		X	X			X
• Varicella vaccine should be administered to patients without evidence of varicella immunity with low-level immunosuppression or $\geq$ 4 wk prior to immunosuppression		X	X		X	
• Administer Zoster vaccine to patients aged $\geq$ 60 years prior to immunosuppressive therapy or with mild immunosuppressive therapy	X	X	X		X	

– Table 4 (Continued)

Recommendation	EULAR (2011) <sup>(221)</sup>	IDSA (2013) <sup>(222)</sup>	ACIN (2016) <sup>(223)</sup>	ASOREUMA (2016) <sup>(216)</sup>	Pérez- Díaz et al. (2016) <sup>(215)</sup>	CDC (2018) <sup>(222)</sup>
• Administer Zoster vaccine to patients $\geq 50$ years with immunity for varicella and will be on high grade immunosuppression.		X	X		X	
• Annual inactivated influenza vaccination should be administered	X	X	X	X	X	X
• PPSV23 and PCV13 polysaccharide pneumococcal vaccination should be administered	X	X	X	X	X	X
• Tetanus toxoid vaccination should be administered as in the general population 6mo after rituximab	X		X	X	X	X
• Hepatitis A and B vaccinations are recommended in patients at risk of contracting those diseases.	X		X	X	X	
• Hepatitis B vaccine is strongly recommended		X	X	X	X	
• Vaccinate against HPV as recommended for general populations specially patients with SLE	X		X	X	X	
• Do not vaccinate with tuberculosis vaccine BCG	X		X	X	X	
• Oral polio vaccine is not recommended			X	X		
• Avoid yellow fever vaccine		X	X	X	X	X
High level immunosuppression:						
• Prednisone at doses $\geq 20$ mg/day or equivalent for $\geq 14$ days						
• Certain biologic immune modulators: TNF- $\alpha$ blockers or rituximab						
• After HSCT, high level immunosuppression is highly variable and depends on:						
• Type of transplant						
• Type of donor						
• Stem cell source						
• Complications (GVHD)						
Low level immunosuppression:						
• Methotrexate at doses $\leq 0.4$ mg/kg/week						
• Azathioprine $\leq 3$ mg/kg/day						
• 6 mercaptopurine $\leq 1.5$ mg/kg/day						
• Prednisone $< 20$ mg/day or equivalent for less than 14 days						
ACIN, Asociación Colombiana de Infectología (Colombian Association of Infectious Diseases); ASOREUMA, Asociación Colombiana de Reumatología (Colombian Association of Rheumatology); BCG, Bacillus Calmette-Guerin; CDC, Centers for Disease Control; DMARDS, Disease-modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; GVHD, Graft-vs-Host disease; Hib, <i>Haemophilus influenzae</i> b; IDSA, Infectious Diseases Society of America; HSCT, Hematopoietic Stem Cell Transplantation; PCV, Pneumococcal conjugate vaccine; PPSV, Pneumococcal polysaccharide vaccine; SLE, Systemic lupus erythematosus; TNF- $\alpha$ , Tumor necrosis factor $\alpha$ .						

study by Hesselstrand et al., comparing the immune response of patients with SSc with or without DMARDs (disease-modifying antirheumatic drugs) against a control group, receiving the PPVP23 or the PCV13 pneumococcal vaccine, found that the production of antibodies against pneumococcal serotypes in SSc patients without DMARDs was similar to that of the healthy control group. No differences were described between the PPVP23 and the PCV13 vaccine. However, patients on DMARDs had a lower antibody production.<sup>246</sup> Other study by Mercado et al. described the immunogenicity of different pneumococcal antigens after vaccination with the PPVP23 in a group of 18 patients with SSc. They found that after vaccination, all patients had a two-fold rise in antibodies against the different antigens despite being treated with CYC. No differences were observed between limited SSc and diffuse SSc.<sup>247</sup>

Additional recommendations for immunization in patients with autoimmune inflammatory rheumatic diseases from the CDC,<sup>222</sup> the Infectious Diseases Society of Colombia (ACIN),<sup>222</sup> the Infectious Diseases Society of America (IDSA),<sup>222</sup> the Colombian Association of Rheumatology (ASOREUMA)<sup>216</sup> and the European League Against Rheumatism (EULAR),<sup>221</sup> are summarized in Table 4. Novel interventions adapted to the South American context should be assessed for future recommendations on vaccination in patients with autoimmune diseases, such as vaccination for dengue virus, meningococcal disease and vaccination with the recently developed inactivated vaccine for HZV (Shingrix), which has shown to be more effective in preventing HZV and postherpetic neuralgia.<sup>248</sup>

### Pre-treatment considerations

A baseline screening for different infectious diseases should be considered, as strong immunosuppression in patients with SSc is expected. Interpretation of screening tests has been discussed elegantly elsewhere.<sup>102,215,224</sup> This screening should be based on local epidemiology, which should always include: TB, HIV, Hepatitis A Virus, HBV, Hepatitis C Virus, Toxoplasma, EBV, CMV, Varicella Zoster Virus, syphilis and a stool test. Some other entities to be considered are: Chagas (*Trypanosoma cruzi*) and Human T Lymphocyte Virus 1-2.<sup>215</sup> Screening for histoplasmosis is not routinely recommended and should only be considered in endemic areas.<sup>215</sup> Antiparasitic prophylaxis should be considered, particularly if biological therapy or glucocorticoids are planned. To prevent helminthic superinfection, the use of ivermectin (200ug/Kg/day [i.e., one drop per Kg]) in two doses 15 days apart, or albendazole 400 mg/day for 3 days is recommended.<sup>223</sup> Amebiasis prophylaxis in endemic regions has been proposed using secnidazole 2 grams in a single dose, and repeating it every year if immunosuppression persists or if the patient is still living in an endemic area.<sup>215</sup>

### Conclusion

Infections are a growing concern in the management of SSc, as evidence suggests them as a rising cause of admission and mortality. Most of the studies on this issue come from the USA and Europe, with few studies from Asia, which may not represent Latin-American populations, thus, local studies are warranted. Patients with SSc present a higher risk

of infectious complications due to the structural damage of the disease and immunosuppressive treatment. Novel therapeutic agents have shown promising results; however, an increasing incidence of infections may be expected as has been observed in other rheumatic diseases. Data on the effects of antimicrobial prophylaxis and risk management strategies in SSc are lacking, although experience from other autoimmune diseases may shed light on this issue. An increasing awareness among treating specialties, particularly rheumatologists is warranted. The wide adoption of risk management strategies, including underused measures such as vaccination, is necessary.

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