Management of infections in rheumatic patients receiving biological therapies.
The Portuguese Society of Rheumatology recommendations

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ABSTRACT

Introduction: Infections are a major cause of morbidity and mortality in systemic inflammatory rheumatic diseases and the management of infectious complications in patients under biological therapies deserves particular attention.

Objective: Develop evidence-based recommendations for the management of infections in rheumatic patients receiving biological therapies.

Methods: A search in PubMed (until 10 November 2014) and EMBASE (until 20 December 2014) databases was performed. Patients with systemic inflammatory rheumatic diseases treated with approved biologics in whom infections occurred were included. Search results were submitted to title and abstract selection, followed by detailed review of suitable studies. Information regarding presentation of the infectious complication, its diagnosis, treatment, and outcome, as well as maintenance or discontinuation of the biological agent was extracted and subsequently pooled according to the type of infection considered. Results of literature review were presented and critically reviewed in a dedicated meeting by a multidisciplinary panel. Recommendations were then formulated using the Delphi method. Finally, the level of agreement among rheumatologists was voted using an online survey.

Results: Fifteen recommendations were issued. Nine general recommendations concerned the assessment of infectious risk before and while on biologics, the procedures in case of suspected infection and the management of biologics during infectious complications. Six specific recommendations were developed for respiratory, urinary, gastrointestinal, skin, osteoarticular and disseminated infections.

Conclusion: These fifteen recommendations are intended to help rheumatologists in the management of infections in patients on biological therapy. They integrate an extensive literature review, expert opinion and inputs from Portuguese rheumatologists.

Keywords: Biologics; Infections; Treatment; Recommendations.

INTRODUCTION

Patients with systemic inflammatory rheumatic disease (SIRD) have increased morbidity and mortality due to infections. Highly active and long standing diseases are associated with amplified risk of infection. Death from infections in patients with Rheumatoid Arthritis (RA) is twice more common than in general population. In other SIRDs such as Systemic Lupus Erythematosus (SLE), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and systemic Vasculitis, infections have also been found to be a major cause of death. Additionally, SIRD patients have significantly increased risk of being hospitalized due to a serious infection. This increased risk can be attributed partly to the aberrant immune system and to the effect of immunosuppressive drugs used in the treatment of these diseases¹⁻⁵.

Treatment with biological agents is associated with a small, but statistically significant increase of serious
infectiouss. The risk is particularly high for some opportunistic infections and during the first months on biologics7–9.

OBJECTIVE

Develop evidence-based recommendations for the management of infections in SIRD patients receiving biological therapies.

METHODS

A systematic literature review (SLR) was performed, focused on the management of infections in rheumatic patients while on biological therapies. We searched in PubMed (until 10 November 2014) and EMBASE (until 20 December 2014) databases. We included adult patients with SIRD (RA, PsA Spondyloarthritis, Juvenile Idiopathic Arthritis and SLE), treated with approved biologics. The biological agents considered were TNF inhibitors (TNF-i), Rituximab, Abatacept, Tocilizumab, Belimumab, Anakinra and Ustekinumab. The outcomes of interest were respiratory, urinary, gastrointestinal, skin and soft tissue, osteoarticular, opportunistic (viral and others) and disseminated infections as well as viral hepatitis. Regarding the occurrence of infections we were particularly interested in their presentation, diagnostic procedures, treatment, maintenance or discontinuation of biological therapy and their outcome. We included randomized controlled trials, cohort studies, case-control studies and case series. The exclusion criteria were: non-rheumatic disease, no biological therapy, clinical cases, editorials, review articles, opinion pieces, letters, and no reference to the outcomes of interest. Eight independent reviewers performed a selection by title and abstract. Data were subsequently extracted from the eligible studies and pooled according to the type of infection. Thereafter, a descriptive analysis was performed.

SLR results were presented and critically reviewed by a multidisciplinary panel with 63 participants, including rheumatologists, an infectious diseases expert, a pulmonologist, other health professionals and patient representatives. The taskforce was subsequently divided in 6 breakout groups: each one discussed one topic and proposed recommendations. Preliminary statements were afterwards submitted to the appraisal of the entire taskforce and voted according to the Delphi method. A minimum concordance rate of 75% was considered necessary for the approval of each statement as a final recommendation. When below this level of agreement, the content and phrasing of each statement were discussed and reformulated until a suitable concordance rate was attained. Then, each statement was organized according to general principles and infection specific recommendations. Recommendations were sent to all rheumatologists and the final agreement was voted online in a 10-point numerical scale (one – fully disagree to ten – totally agree) by 55 rheumatologists.

RESULTS

Nine hundred and thirty one abstracts were retrieved. After title and abstract selection 157 manuscripts entered the detailed review, but 13 were excluded, leaving 144 papers in this phase (Figure 1).

Of the 144 papers included, 80 concerned to respiratory tract infections, 37 to urinary tract infections, 21 to gastrointestinal infections, 24 to viral hepatitis, 33 to skin and soft tissue infections, 13 to osteoarticular infections, 47 to opportunistic infections (viral and others) and 6 to disseminated infections. Table I summarizes study distribution according to the type of infections and biological therapy. Of note, several papers concerned more than one type of infection and more than one type of biological agent.

RECOMMENDATIONS

Nine general principles and six infection specific recommendations were issued, reaching a high level of agreement among Portuguese Rheumatologists (Table II).

GENERAL PRINCIPLES

1. OVERALL INFECTION RISK MUST BE ASSESSED IN EVERY RHEUMATIC PATIENT EITHER CANDIDATE OR ON BIOLOGICAL THERAPY. LEVEL OF EVIDENCE: 3A, GRADE OF RECOMMENDATION: C.

The particular risk of infectious complications in patients with SIRD is estimated to be about 2-fold higher than in the general population10,11. Identified risk factors include demographics and disease characteristics, comorbidities, medication as well as the epidemiological context (Table III). Along with older age (>65 years) and impaired function, the presence of diabetes
mellitus, chronic pulmonary disease, impaired renal function, previous infections, alcoholism and hypogammaglobinaemia, are independently associated with the susceptibility to infections. Local specific infection risk factors such as bronchiectasis, urethral catheterization, vesicoureteral reflux and other anatomical changes, history of skin ulcers, previous septic arthritis and prosthetic joint must also be addressed in infection risk evaluation. In addition, exposure to medication should also be part of overall risk assessment. Glucocorticoids (GCs) and some conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may impair the response to pathogens and consequently predispose to infection. Use of medium to high dose GCs, particularly in prolonged use, has been linked to serious infections requiring hospitalization. In a large cohort study, a dose-dependent effect was suggested. The incidence rate ratio (IRR) of serious infections was significantly increased in patients treated with GCs, being higher in patients treated with ≥15 mg/day (IRR=4.7) compared to patients treated with 7.5-14 mg/day (IRR=2.1). For low-dose GCs (in some studies defined as ≤5 mg and others as ≤7.5 mg), there was no increased risk, or the risk was only slightly increased. There is no conclusive data supporting the notion that methotrexate use (and other csDMARDs) increases the overall risk of infection.

For assessing the risk of infection in this population, it is also very important to evaluate the previous vaccination status.
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade</th>
<th>Agreement mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
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</tr>
<tr>
<td>1. Overall infection risk must be assessed in every rheumatic patient either candidate or on biological therapy.</td>
<td>3a</td>
<td>C</td>
<td>9.79 (0.62)</td>
</tr>
<tr>
<td>2. Screening of chronic infections – tuberculosis, HIV, HBV, and HCV – should be performed in accordance to the national guidelines prior to the introduction of biological therapy. Screening of other infections can be considered in view of the epidemiological context.</td>
<td>4</td>
<td>C</td>
<td>9.84 (0.42)</td>
</tr>
<tr>
<td>3. In the event of suspected active infection, the severity of the situation must be evaluated and postponing the administration of the biologic is advised.</td>
<td>5</td>
<td>D</td>
<td>9.59 (0.63)</td>
</tr>
<tr>
<td>4. There should be a high index of suspicion for opportunistic infections.</td>
<td>5</td>
<td>D</td>
<td>9.45 (0.93)</td>
</tr>
<tr>
<td>5. Identification of the causative agent is recommended whenever possible.</td>
<td>5</td>
<td>D</td>
<td>9.45 (0.72)</td>
</tr>
<tr>
<td>6. Biological therapy should be discontinued at least during antimicrobial therapy.</td>
<td>5</td>
<td>D</td>
<td>8.82 (1.49)</td>
</tr>
<tr>
<td>7. Reintroduction of biological therapies after resolution of an infectious episode should be decided on a case-by-case basis, taking into account the activity of the rheumatic disease and the risk of reinfection.</td>
<td>5</td>
<td>D</td>
<td>9.38 (1)</td>
</tr>
<tr>
<td>8. Permanent discontinuation of biological therapy should be considered in severe or recurrent infections.</td>
<td>5</td>
<td>D</td>
<td>9.44 (0.76)</td>
</tr>
<tr>
<td>9. The diagnostic / therapeutic decision-making should be shared with the patient.</td>
<td>5</td>
<td>D</td>
<td>9.48 (0.83)</td>
</tr>
<tr>
<td><strong>Specific</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Upper or lower respiratory infections. If no signs of severity consider symptomatic treatment and/or empirical oral antibiotic therapy and monitor evolution. In severe infections intravenous antibiotic therapy should be promptly initiated and whenever possible guided by antibiotic susceptibility testing.</td>
<td>5</td>
<td>D</td>
<td>9.35 (0.99)</td>
</tr>
<tr>
<td>2. Urinary tract infections. If severe, intravenous antibiotics are recommended. Consider repeat urine culture prior to reintroduction of the biologic. Evidence is lacking regarding management of asymptomatic bacteriuria in rheumatic patients under biologics.</td>
<td>5</td>
<td>D</td>
<td>9.45 (0.78)</td>
</tr>
<tr>
<td>3. Gastrointestinal infections. If severe antibiotics directed to the identified causal agent or empirical broad-spectrum antibiotics should be started. In the event of elevated transaminases of unknown aetiology viral hepatitis screening should be repeated. In presence of active viral hepatitis biological therapy should be discontinued until full evaluation.</td>
<td>5</td>
<td>D</td>
<td>9.04 (1.17)</td>
</tr>
<tr>
<td>4. Skin and soft tissue. Oral or intravenous empirical antibiotics should be initiated according to severity, with further adjustment guided by susceptibility tests.</td>
<td>4</td>
<td>C</td>
<td>9.32 (1.15)</td>
</tr>
<tr>
<td>5. Osteoarticular infections. Intravenous broad-spectrum empirical antibiotic therapy must be promptly started with subsequent adjustment according to antibiotic susceptibility testing. Opportunistic infections and associated osteomyelitis have to be considered in the evaluation of joint infections. Assessment by an orthopaedic surgeon is recommended, particularly in patients with osteomyelitis or joint prosthesis.</td>
<td>2b</td>
<td>B</td>
<td>9.61 (0.68)</td>
</tr>
<tr>
<td>6. Disseminated infection. Epidemiological context should guide diagnostic studies. Immunosuppressive treatment must be stopped and broad-spectrum empirical antibiotherapy introduced immediately. In the absence of clinical response after 48-72 hours, consider less common agents such as fungi, viruses, parasites and mycobacteria.</td>
<td>4</td>
<td>C</td>
<td>9.61 (0.68)</td>
</tr>
</tbody>
</table>
2. Screening of Chronic Infections – Tuberculosis, HIV, HBV, and HCV – Should Be Performed in Accordance to the National Guidelines Prior to the Introduction of Biological Therapy. Screening of other infections can be considered in view of the epidemiological context. Level of evidence: 4, Grade of recommendation: C.

The presence of active infections is a contraindication for starting biological therapy. Suspension of the biological therapy is mandatory in all active viral infections with organ damage. Chronic infections, such as tuberculosis, HIV, hepatitis B and C also pose constraints to the use of these medications and must be proactively screened. Until 2014, Portugal was a country with an intermediate incidence rate of tuberculosis and specific recommendations for screening and treatment of latent tuberculosis were published.

Although infection by a hepatotropic virus (HBV and HCV) is usually considered a contraindication for anti-TNF therapies, their use can be justified after a careful risk/benefit assessment. Recommendations for screening before TNF inhibitors seem to be quite safe in patients with chronic hepatitis C with low to moderate chronic activity on histopathological examination (Knodell Histology Activity Index ≤ 12, with or without fibrosis) independently of viral load. In our SLR we found 9 studies including a total of 52 patients with chronic hepatitis C treated with TNF-i, 48 of them did not receive prophylaxis or treatment for hepatitis C. After a medium follow up of 18 months only one patient stopped the biologic. The others did not develop neither symptoms of viral liver disease nor persistent elevation of liver enzymes (more than twice the upper limit of normal), though some variation of liver enzymes was seen (less than twice the upper limit of normal). Although these studies suggest a good safety profile for anti-TNF therapies in patients with HCV infection, their use should be monitored carefully.

Concerning patients with chronic HBV infection, the introduction of biological therapy should be done only after a thorough clinical and laboratorial assessment, evaluation by a liver disease specialist and, when indicated, initiation of appropriate antiviral therapy/prophylactic antiviral therapy. Although rarely, reactivation of “resolved” hepatitis B (AgHBs negative/anti-HBc positive) can also occur under biologics and guidelines for the screening and management of those patients were published. Of our SLR we obtained information from 19 studies, corresponding to a total of 527 patients with chronic hepatitis B infection or past “resolved” hepatitis B. In total, 28 out of 505 patients (5.5%) under TNF-i reactivated hepatitis B after a mean follow-up of 18.5 months (10 under chemoprophylaxis) and no recurrence was seen in patients with “resolved” hepatitis B. In total, 28 out of 505 patients (5.5%) under TNF-i reactivated hepatitis B after a mean follow-up of 18.5 months (10 under chemoprophylaxis) and no recurrence was seen in patients with “resolved” hepatitis B. Of 8 patients medicated with Abatacept, those without prophylaxis, had a reactivation of hepatitis B (n=4). Fourteen patients treated with Rituximab had no reactivation of hepatitis.

<table>
<thead>
<tr>
<th>Specific infections</th>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Upper or lower respiratory infections</td>
<td>Immunosuppression; COPD/Asthma; Diabetes mellitus and Heart Disease.</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Age ≥ 65 years; PDN ≥ 5-10mg or concomitant DMARDs; Disease duration&gt; 10 years; COPD/Asthma; Smoking; Diabetes mellitus; Heart disease; Chronic renal disease; Recurrent infections; Charlson comorbidity index ≥2; Hypogamaglobulinemia or low IgG (in case of Rituximab).</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>Diabetes mellitus; Prior skin infection; GCs; Advanced age.</td>
</tr>
<tr>
<td>Osteoarticular infections</td>
<td>Prophylaxis; Opportunistic infections; GCs (PDN &gt; 10mg); Advanced age; Existence of extra-articular manifestations (in RA); Depletion of B cells.</td>
</tr>
<tr>
<td>Disseminated infection</td>
<td>Advanced age; Longstanding rheumatic disease; Recurrent infections; Concomitant DMARDs and GC.</td>
</tr>
</tbody>
</table>

COPD – chronic obstructive pulmonary disease; PDN – prednisolone.
3. In the event of suspected active infection, the severity of the situation must be evaluated and postponing the administration of the biologic is advised. Level of evidence: 5, Grade of recommendation: D.

There is some evidence that under biological therapy infections may have an atypical presentation and a more severe course. In the event of a suspected active infection, a careful clinical evaluation must be done and appropriate additional tests must be carried out in order to clearly identify the type and location of infection. The presence of signs of severe illness such as fever (body temperature >38.3°C) or hypothermia (body temperature <36°C), hypotension, tachycardia, tachypnea, hypoxemia or abnormal state of consciousness, must be evaluated. Although we could not always clearly identify in the literature information regarding the action taken with respect to the administration of biological drug in a patient with suspected infection, the panel considered advisable to postpone the administration of the biologic until the severity of the situation is clarified as well as during antibiotic therapy.

4. There should be a high index of suspicion for opportunistic infections. Level of evidence: 5, Grade of recommendation: D.

Opportunistic infections should always be suspected in immunocompromised patients. The epidemiologic context must be taken into account since there is a geographical variability in the incidence of some opportunistic infections such as tuberculosis. Concerning viral opportunistic infections the SLR depicted 14 studies (population range from 4 to 59066 patients, mostly with RA). The rate of opportunistic infections for each biological agent ranged between 0.2-6.25% and Herpes Zoster was the main microorganism identified. In 3 studies the biological agent was suspended and in 1 study maintained. Most studies showed a good outcome with the exception of 3 patients under Rituximab and John Cunningham (JC) virus infection, who had a fatal outcome.

The main risk factor identified for viral opportunistic infections was concomitant therapy with GCs in a dosage greater than or equal to 10 mg/day and csDMARDs.

Regarding non-viral opportunistic infections, we retrieved 40 studies with a population range from 2 to 141,134 patients, also mostly with RA. Opportunistic infections were reported in 0.23% of the patients. The most common bacterial agents were nontuberculous mycobacteria followed by Mycobacterium tuberculosis, either pulmonary or extra-pulmonary/disseminated infections. The most common fungal agents were Pneumocystis jirovecii and Candida spp. There were also reports of infection caused by Listeria spp, Leishmania spp, Cryptococcus spp, Salmonella spp and Histoplasma spp. Of the 460 patients with non-viral opportunistic infections, 38 had a fatal outcome.

5. Identification of the causative agent is recommended whenever possible. Level of evidence: 5, Level of recommendation: D.

A wide variety of microorganisms can cause infections in SIRD patients under biologics. A rapid and accurate diagnosis of infection and identification of the causative microorganism is crucial to ensure effective antimicrobial therapy. Thus, cultures, serological tests or even more invasive diagnostic procedures should be performed before starting empirical treatment, in order to identify the causative agent and its susceptibility. This way, it will be possible to accurately determine the need for specific antimicrobial therapy and treatment duration, to adjust treatment using the narrowest spectrum and shortest duration of therapy, and switch to oral agents as soon as possible.

6. Biological therapy should be discontinued at least during antimicrobial therapy. Level of evidence: 5, Level of recommendation: D.

Most studies did not specify whether biological agent was stopped or not. Nevertheless, the panel concluded that it is reasonable to discontinue the biological agent during the treatment of infections with antimicrobials, specifically in case of moderate to severe, recurrent or opportunistic infections.

7. Reintroduction of biological therapies after resolution of an infectious episode should be decided on a case-by-case basis, taking into account the activity of the rheumatic disease and the risk of reinfection. Level of evidence: 5, Level of recommendation: D.

After the occurrence of a serious bacterial infection, the biological therapy should not be started until complete clinical resolution. In the absence of signs of infection, the biologic is usually started one week after stopping the anti-infective treatment. Given the scarcity of data, we cannot recommend the reintroduction of biological therapies after an episode of active tuberculosis. In this case
reintroduction should be decided on a case-by-case basis and only after the complete normalization of all clinical, radiological and laboratorial signs of active disease. A multidisciplinary approach should be sought.

**8. Permanent discontinuation of biological therapy should be considered in severe or recurrent infections. Level of evidence: 5, Level of recommendation: D.**

There is still a lack of evidence in the literature regarding the permanent discontinuation of the biological therapy due to infections. The panel consider that permanent discontinuation should be pondered in all patients with severe or recurrent infections. The individual risk factors for infection such as age and comorbidities, the epidemiologic context, the SIRD and disease activity, as well as concomitant medications (GCs and csDMARDs) should be taken in account.

**9. The diagnostic/therapeutic decision-making should be shared with the patient. Level of evidence: 5, Level of recommendation: D.**

Shared decision making is an approach where clinicians and patients share the best available evidence when faced with the task of making decisions. Despite the lack of evidence regarding the best management of infections in patients under biological therapy, patients should be encouraged to learn about different treatment options, their benefits and harms, and communicate their preferences. Therefore, shared decision-making can ensure that the decision taken meets the clinical as well as psychosocial needs of the patient.

**SPECIFIC INFECTIONS**

1. **Upper and lower respiratory infections. If no signs of severity consider symptomatic treatment and/or empirical oral antibiotic therapy and monitor evolution. In severe infections intravenous antibiotic therapy should be promptly initiated and whenever possible guided by antibiotic susceptibility testing. Level of evidence: 5, Level of recommendation: D.**

From the data of the SLR performed, we conclude that infections of the upper respiratory tract were the most frequently found in patients treated with biological agents. Of the 95,533 patients under biologics, there were 10,292 (10.77%) cases of respiratory infections, mostly upper respiratory infections occurring in 2896 (3.03%) cases and, more specifically, nasopharyngitis in 2059 (2.16%) cases. Severe pneumonia was reported less frequently in 863 (0.9%) patients, and in all cases the biological agent was interrupted and patients admitted for intravenous (iv) antibiotic therapy.

In patients with upper or lower respiratory tract infections, without signs of severity, either symptomatic treatment or oral antibiotics, depending on the type of infection, are acceptable therapeutic options (Table IV). The choice of the antibiotic should follow the existing standards of antibiotic treatment for different types of infection. These patients need to be monitored tightly and if there is no clinical improvement or if clinical worsening occurs, the patient should be hospitalized and iv broad spectrum antibiotics administered. The administration of the biologic must be postponed at least until the infection is resolved and always during antibiotic therapy, as mentioned before.

2. **Urinary tract infections. If severe, intravenous antibiotics are recommended. Consider repeat urine culture prior to reintroduction of the biologic. Evidence is lacking regarding management of asymptomatic bacteriuria in rheumatic patients under biologics. Level of evidence 5, Grade of recommendation: D.**

Thirty-seven studies reported urinary tract infections (UTIs) in patients while taking biological treatment. These studies included a total of 59680 patients with identification of 778 UTIs, 41 (5%) of them classified as serious, including 3 urinary sepsis, one fatal. Biological treatment was maintained in 5 studies despite the reported infection. None of the studies addressed the problem of asymptomatic bacteriuria.

The panel considered important the collection of urine culture before initiating antibiotic therapy, while ordering other tests should depend on the clinical manifestations. The choice of the antibiotic should follow the guidelines for the general population (Table IV). None of the studies addressed the problem of asymptomatic bacteriuria, therefore, there is currently no evidence on its best approach.

3. **Gastrointestinal infections. If severe, antibiotics directed to the identified causal agent or empirical broad-spectrum antibiotics should be started. In the event**
### TABLE IV. SUGGESTED EMPIRIC ANTIBIOTIC THERAPY FOR COMMUNITY ACQUIRED INFECTIONS

#### Upper respiratory tract

**Acute bacterial rhinosinusitis**

**First Line** – Amoxicillin with or without Clavulanate, PO, for 5 to 10 days.  
**Alternative (if penicillin allergy)** – Doxycycline PO or a respiratory quinolone.

#### Lower respiratory tract

**Community-Acquired Pneumonia**

**First Line** – Amoxicillin 1g PO tid plus one of the following:  
Azithromycin 500mg/day PO; Clarithromycin 500mg PO bid or Doxycycline 200mg PO first dose and then 100mg bid.  
**Alternative** – Levofloxacin 500mg PO qd or Moxifloxacin 400mg PO qd  
**Duration:** 7 days.

**Community-Acquired Pneumonia requiring hospitalization**

**Non-ICU patients** – Aminopenicillin ± Macrolide or Aminopenicillin/b-lactamase inhibitor ± Macrolide or Non-antipseudomonal cephalosporin or Cefotaxime/Ceftriaxone ± Macrolide; Levofloxacin/Moxifloxacin or Penicillin G ± macrolide.  
**Duration:** 8 days.

#### Urinary tract

**Acute uncomplicated cystitis**

**First Line** – Fosfomycin trometamol 3g PO single dose; Nitrofurantoin macrocrystal 100mg PO qid for 5-7 days; Amoxicillin/Clavulanate 500/125mg PO tid for 5-7 days; TMP-SMX 160/800mg PO bid 3 days.  
**Alternative** – Ciprofloxacin 250mg PO qid 3 days; Levofloxacin 250mg PO qd 3 days; Ofloxacin 200mg PO bid 3 days; Cefalosporin (e.g. cefuroxime) 500mg PO bid 3 days.  
If failure of empirical therapy after 1-3 days or in severe conditions, use: Fluoroquinolone (if not used initially); Cefalosporin (3rd generation) or Carbapenem ± Aminoglycoside.

**Mild and moderate uncomplicated pyelonephritis**

Ceftriaxone 1g im or iv single dose followed by Cefuroxime 500mg PO bid, 7-14 days; Levofloxacin 750mg PO qid 5 days.  
**Duration:** 1-2 weeks.

**Severe acute pyelonephritis (complicated with sepsis)**

**First Line** – Ceftriaxone 2g iv qd. Duration – to decide in hospital.  
**Alternative** – Gentamicin 5mg/Kg/day iv followed by therapeutic adjusted to the susceptibility tests. Duration – to decide in hospital.

#### Gastrointestinal

**Extra-biliary complicated intra-abdominal infections**

- **Mild-to-moderate severity**

  **First Line** – Cefoxitin 2g iv qid, Ertaopenem 1g iv qd, Moxifloxacin 400mg iv qd.  
  **Alternative** – Metronidazole 500mg iv every 8-12h or 1500mg iv every qd + Cefazolin 1-2g iv tid, Cefuroxime 1.5g iv tid, Ceftriaxone 1-2g iv every 12-24h, Cefotaxime 1-2g iv every 6-8h, Ciprofloxacin 400mg iv bid or Levofloxacin 750mg iv qd.  
  **High risk or severity**

  **First Line** – Imipenem-cilastatin 500mg iv qid or 1g tid, Meropenem 1g iv tid or Piperacillin-tazobactam 4.5g iv qid.  
  **Alternative** – Metronidazole 500mg every 8-12h or 1500mg qd + Cefepime 2g every 8-12h, Cefazidine 2g tid, Ciprofloxacin 400mg bid or Levofloxacin 750mg qd.

**Biliary Infections**

Metronidazole 500mg iv qid or 1g iv tid + Meropenem 1g iv tid or Piperacillin-tazobactam 4.5g iv tid, Cefepime 2g iv every 8-12h, Ciprofloxacin 400mg iv bid or Levofloxacin 750mg iv qd.

**Infectious diarrheaa**

*Campylobacter* spp. – Azithromycin 500mg PO daily, 1-3 days.  
*Escherichia coli* (enterotoxigenic, enteropathogenic, enteroinvasive) or empiric therapy of traveler’s diarrhea – Ciprofloxacin 500mg PO bid, 1-3 days.

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### TABLE IV. CONTINUATION

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-typhoid Salmonella spp.</strong></td>
<td>Ciprofloxacin 500mg PO bid, TMP-SMX 160/800 PO bid or Ceftriaxone 1g iv daily, 14 days.</td>
</tr>
<tr>
<td><strong>Shigella spp.</strong></td>
<td>Ciprofloxacin 500mg PO bid or TMP-SMX 160/800 PO bid, 7 days.</td>
</tr>
<tr>
<td><strong>Vibrio parahaemolyticus</strong> (if severe illness)</td>
<td>Ciprofloxacin 500mg PO bid, 3 days.</td>
</tr>
<tr>
<td><strong>Yersinia spp.</strong></td>
<td>Ciprofloxacin 500mg PO bid, TMP-SMX 160/800 PO bid or Doxycycline 100mg bid, 3 days.</td>
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</tbody>
</table>

### Skin and soft tissues

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonpurulent</strong> – Erysipelas/Cellulitis/Necrotizing infection[^100,170]</td>
<td><strong>Mild</strong>&lt;br&gt;Amoxicillin/Clavulanate 875/125mg PO bid, Cephalosporin (1st or 2nd generation), Flucloxacillin 500-1000 mg PO tid or Clindamycin 300mg PO qid. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 5 days. &lt;br&gt;&lt;br&gt;- <strong>Moderate</strong>&lt;br&gt;Penicillin 2-4 million iv units every 4–6h, Cefazolin 1g iv tid or Clindamycin 600mg iv tid. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 5-7 days. &lt;br&gt;&lt;br&gt;- <strong>Severe</strong>&lt;br&gt;Emergency surgical inspection/debridement and Vancomycin 15-20 mg/kg iv every 8-12h + Piperacillin-tazobactam 4.5g qid. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 5-7 days.</td>
</tr>
<tr>
<td><strong>Purulent</strong> – Furuncle/Carbuncle/Abscess[^100,170]</td>
<td><strong>Mild</strong>&lt;br&gt;Incision and drainage. &lt;br&gt;&lt;br&gt;- <strong>Moderate</strong>&lt;br&gt;Incision and drainage. TMP-SMX 160/800mg PO bid or Doxycycline 100mg PO bid. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 5-7 days. &lt;br&gt;&lt;br&gt;- <strong>Severe</strong>&lt;br&gt;Incision and drainage. Vancomycin 15-20mg/kg iv every 8-12h, Daptomycin, or Linezolid. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 5-7 days.</td>
</tr>
</tbody>
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### Bone and joints

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatment Options</th>
</tr>
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<tbody>
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<td><strong>Septic arthritis[^171,172]</strong>&lt;br&gt;- No risk factors for atypical organisms</td>
<td><strong>FIRST LINE</strong> – Flucloxacillin 2g iv tid, and/or Gentamicin iv. &lt;br&gt;&lt;br&gt;<strong>ALTERNATIVE</strong> – Clindamycinconstantly 450-600mg tid iv or Cefalosporin (2nd or 3rd generation) iv. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 2-4 weeks. &lt;br&gt;&lt;br&gt;- <strong>High risk of Gram-negative sepsis[^4]</strong>&lt;br&gt;Cefuroxime 1.5g tid iv or ceftriaxone 1-2g bid iv + Flucloxacillin 2g tid iv. &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 2-4 weeks. &lt;br&gt;&lt;br&gt;- <strong>MRSA risk[^6]</strong>&lt;br&gt;Vancomycin 1g bid iv + Cefalosporin (2nd or 3rd generation) iv. &lt;br&gt;&lt;br&gt;- <strong>Suspected gonococcus or meningococcus</strong>&lt;br&gt;Ceftriaxone 1g iv qd (or similar dependent on local policy or resistance). &lt;br&gt;&lt;br&gt;<strong>DURATION:</strong> 2-4 weeks.</td>
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<td><strong>Infection of articular prosthesis[^171,173]</strong>&lt;br&gt;- Orthopedics referral ➔ decision regarding retention or removal strategy</td>
<td>Pathogen-specific iv antibiotic therapy (2 to 6 weeks) followed by oral therapy (3-6 months). &lt;br&gt;&lt;br&gt;<strong>Bacterial Osteomyelitis[^100,174]</strong>&lt;br&gt;- Vertebral osteomyelitis&lt;br&gt;&lt;br&gt;<strong>FIRST LINE</strong> – Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv or Cefepime 2g iv tid.</td>
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Table IV. Continuation

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<th>Diagnosis</th>
<th>Treatment</th>
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| **Sepsis with no clear source**  | **First Line** – Piperacillin-tazobactam 4.5g iv tid or Cefepime 2g iv tid ± Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv ± Gentamicin 3mg/kg iv qd or 1g/Kg iv tid.  
**Alternative** – Aztreonam 2g iv tid or Cefepime 400mg iv tid + Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv + Gentamicin 3mg/kg iv qd or 1g/Kg iv tid.  
**Severe infections + respiratory failure**†  
Extended spectrum beta-lactam + aminoglycoside or a fluoroquinolone.  
**Suspected intra-abdominal sepsis**Royal |}
4. Skin and soft tissue infections. Oral or intravenous empirical antibiotics should be initiated according to the severity, with further adjustment guided by susceptibility tests. Level of evidence: 4, Grade of recommendation: C.

From a total of 53799 patients under biologic therapy reported in 33 studies included in this review, 707 (1.31%) developed skin or soft tissue infections (SSTI) after a medium exposure of 10.8 months. Only 156 (0.28%) patients had severe complications. Biologics were stopped in 2 (0.004%) cases. Overall, the use of TNF-α in RA was not associated with increased risk of severe SSTI. However, patients with diabetes mellitus and those with a history of prior skin infection were significantly more likely to develop severe SSTI (Table III). There was also a small but significant risk of SSTI associated with concomitant use of corticosteroids and advanced age at the start of the TNF-α treatment (3,39,62,65,67,70–73,76,81,93,96,102,104,108,110,112,114,115,119,121,123,127,128,131,132,135,141,143,146,149,150,153–157).

The panel suggests that biological therapy should be initiated with caution, after discussing the relative risks and benefits, in cases of chronic (example: chronic infected leg ulcers) and recurrent skin and soft tissue infections. 158.

5. Osteoarticular infections. Intravenous broad-spectrum empirical antimicrobial therapy must be promptly started with subsequent adjustment according to antibiotic susceptibility testing. Opportunistic infections and associated osteomyelitis have to be considered in the evaluation of joint infections. Assessment by an orthopaedic surgeon is recommended, particularly in patients with osteomyelitis or joint prosthesis. Level of evidence 2b, Grade of recommendation: B.

Osteoarticular infections are always severe and require prolonged hospitalization. In our SLR, 579 severe osteoarticular infections occurred in a total of 11232 patients under biologics (5.1%), in some cases with isolation of opportunistic agents. The most frequent specific risk factors were joint prosthesis, therapy with GCs (prednisolone more than 10 mg), opportunistic infections, advanced age, existence of extra-articular manifestations in RA, depletion of B cells, so in the evaluation of joint infections, these specific risks (Table III) 158,70,81,87,93,106,115,119,123,141,143,149,159–162. Assessment by an orthopaedic surgeon should be requested, namely when concomitant osteomyelitis is suspected or infection of a prosthetic joint is involved. Intravenous broad-spectrum empirical antimicrobial therapy should be promptly started and subsequently adjusted according to the antimicrobial susceptibility testing (Table IV). After complete resolution of infection, the reintroduction of the biological must be weighted based on the activity of rheumatic disease and the risk of reinfection.

6. Disseminated infection. Epidemiological context should guide diagnostic studies. Immunosuppressive treatment must be stopped and broad-spectrum empirical antimicrobial therapy introduced immediately. In the absence of clinical response after 48-72 hours, consider less common agents such as fungi, viruses, parasites and mycobacteria. Level of evidence: 4, Grade of recommendation: C. Disseminated infection means the involvement of multiple organs by the same pathogen. In patients under biological therapy, disseminated infections are severe and often caused by opportunistic agents 158,73,108,124,159,159. In our SLR, 23 out of 3668 patients under biologics (0.6%), developed a disseminated infection, with the highest risk between 8-36 months after initiating biologics and in patients with advance age, long-standing rheumatic disease, history of recurrent infections, comorbidities, treated with concomitant csDMARDs and GCs (Table III) 108,73,108,154,159,160. The epidemiological context should guide the diagnostic tests. These studies should include the collection of biological products for cultural examination, histology and serology. 153,159,160 Immunosuppressive treatment must be stopped and broad-spectrum empirical antimicrobial therapy introduced immediately (Table IV). In the absence of clinical response after 48-72 hours, consider less common agents such as fungi, viruses, parasites and mycobacteria 158,73,108,124,154,159. After complete resolution of infection, reintroduction of biologic must be weighted based on the activity of rheumatic disease and risk of reinfection 108,160.

Discussion

Although infections occur frequently and may be severe in patients under biological therapies, the best management remains mostly empirical. After an extensive literature review, we did not retrieve necessary information about the best management of infections in pa-
tients under biologics. There is no sufficient data on the clinical presentation or the laboratorial features of the infectious disease, the treatment, discontinuation of the biologic and other anti-rheumatic medications and their reintroduction. Given the scarcity of data from the literature, most of the recommendations are primarily based on expert opinion.

CONCLUSIONS

These fifteen recommendations, integrating an extensive literature review and the opinion of clinical experts, were issued to help the clinical decision.

There is a scarcity of evidence concerning the best management of infections in patients treated with biologics. Most RCTs lack information on the management of infectious complications arising during treatment with biologics. Registries can provide useful information to fill this gap. As more information becomes available, these recommendations will be updated.

For divulagão purposes, the current paper will be published in a MEDLINE-indexed journal and freely available online at the website of the Portuguese Society of Rheumatology. All members of the Society will be notified by email and/or newsletter after publication.

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