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.

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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 diseases[1–5].

Treatment with biological agents is associated with a small, but statistically significant increase of serious

infectious[6]. The risk is particularly high for some opportunistic infections and during the first months on biologics[7–9].

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 population.[10,11] 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

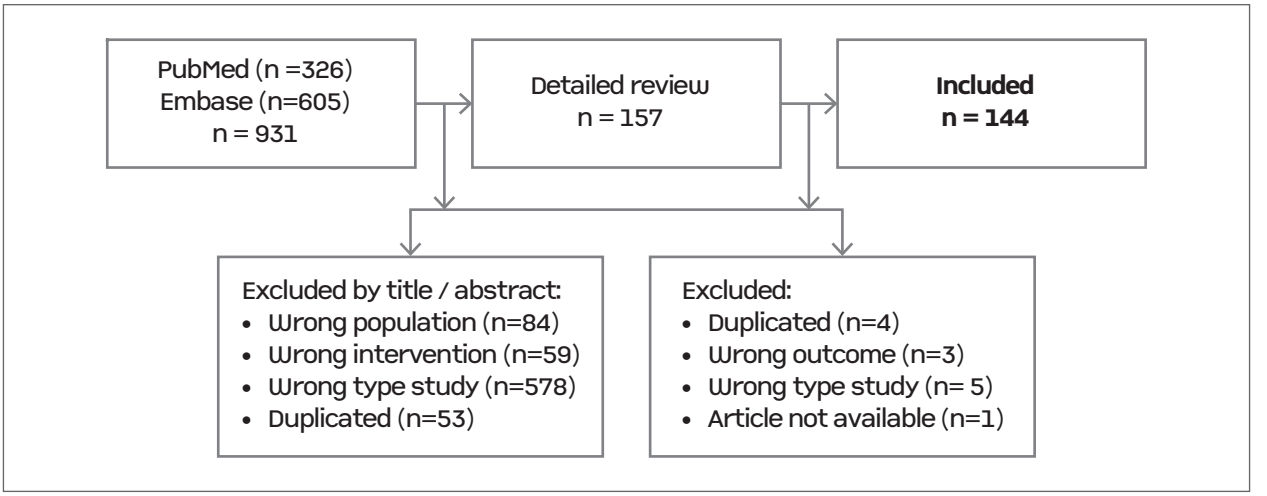

FIGURE 1. The search strategy for the systematic review

TABLE I. DISTRIBUTION OF THE INCLUDED STUDIES ACCORDING TO THE BIOLOGICAL AGENT AND TYPE OF INFECTION

Type of infection	Abatacept	Anakinra	Belimumab	RTX	TCZ	TNF-i	Total
Respiratory	13	2	4	15	14	35	80
Urinary	9	1	1	10	3	26	37
Gastrointestinal	5	0	0	7	5	9	21
Viral hepatitis	1	-		4		19	24
Skin/soft tissue	1	-	1	8	6	20	33
Osteoarticular	2	-	-	2	2	9	13
Opportunistic (viral)	2	-	-	5	2	7	14
Opportunistic (others)	3	-	1	3	1	26	33
Disseminated	1	-	-	-	1	5	6

RTX – Rituximab, TCZ – Tocilizumab, TNF-i – Tumour Necrosis Factor inhibitors. Some studies are quoted in more than one column because they address more than one class of biological drug or more than one type of infection.

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 [11,12]. In addition, exposure to medication should also be part of overall risk assessment.[13] 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.[14] 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)[15,16]. 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.[6] There is no conclusive data supporting the notion that methotrexate use (and other csDMARDs) increases the overall risk of infection[17,18].

For assessing the risk of infection in this population, it is also very important to evaluate the previous vaccination status[13].

TABLE II. RECOMMENDATIONS FOR THE MANAGEMENT OF INFECTIONS IN RHEUMATIC PATIENTS RECEIVING BIOLOGICAL THERAPIES

Recommendations	Level of evidence	Grade	Agreement mean (SD)
General			
1. Overall infection risk must be assessed in every rheumatic patient either candidate or on biological therapy.	3a	C	9.79 (0.62)
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.	4	C	9.84 (0.42)
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.	5	D	9.59 (0.63)
4. There should be a high index of suspicion for opportunistic infections.	5	D	9.45 (0.95)
5. Identification of the causative agent is recommended whenever possible.	5	D	9.45 (0.72)
6. Biological therapy should be discontinued at least during antimicrobial therapy.	5	D	8.82 (1.49)
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.	5	D	9.38 (1)
8. Permanent discontinuation of biological therapy should be considered in severe or recurrent infections.	5	D	9.44 (0.76)
9. The diagnostic / therapeutic decision-making should be shared with the patient.	5	D	9.48 (0.83)
Specific			
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.	5	D	9.35 (0.99)
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.	5	D	9.45 (0,78)
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.	5	D	9.04 (1.17)
4. Skin and soft tissue. Oral or intravenous empirical antibiotics should be initiated according to severity, with further adjustment guided by susceptibility tests.	4	C	9.32 (1.15)
5. Osteoarticular infections. Intravenous broad-spectrum empirical antibiotherapy 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.	2b	B	9.61 (0.68)
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.	4	C	9.61 (0.68)

TABLE III. IDENTIFIED RISK FACTORS FOR SPECIFIC INFECTIONS

Specific infections	Risk Factors
Upper or lower respiratory infections	Immunosuppression; COPD/Asthma; Diabetes mellitus and Heart Disease.
Urinary tract infections	Age ≥ 65 years; PDN ≥ 5-10mg or concomitant DMARDs; Disease duration> 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).
Skin and soft tissue infections	Diabetes mellitus; Prior skin infection; GCs; Advanced age.
Osteoarticular infections	Prosthesis; Opportunistic infections; GCs (PDN > 10mg); Advanced age; Existence of extra-articular manifestations (in RA); Depletion of B cells.
Disseminated infection	Advanced age; Longstanding rheumatic disease; Recurrent infections; Concomitant DMARDs and GC.

COPD – chronic obstructive pulmonary disease; PDN – prednisolone.

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[19,20].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[21].

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[22–31]. 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[23–31]. Safety data with other biological agents are scarce.

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[32–34]. 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[35,36]. 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[25,26,28,29,31,37–48].Of 8 patients medicated with Abatacept, those without prophylaxis, had a reactivation of hepatitis B (n=4).[49] Fourteen patients treated with Rituximab had no reactivation of hepatitis[50].

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 [51,52]. 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 <36ºC), hypotension, tachycardia, tachypnea, hypoxemia or abnormal state of consciousness, must be evaluated [52–54]. 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 [55].

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[39,56–68].

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 [39,57,62,69–96].

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 [97]. 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[98].

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 [19,99]. 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[3,8,56,57,61–68,70,72,73,76,78,79,81–84,86,90,96,100–146].

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[117,118,134,147]. 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[92,118,134,148]. The administration of the biologic must be postponed at least until the infection is resolved and always during antibiotic therapy, as mentioned before[82,130,147,148].

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[8,57,61–66,81,83,84,90,92,103,110,112,114–116,119,121,123,125,128,129,132,136–138,140,142,146,149–151].

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**[163] 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**[164] 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 400 mg PO qd[164] Duration: 7 days. **Community-Acquired Pneumonia requiring hospitalization**¤ [165] 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**[166–168] First Line° – Fosfomycin trometamol 3g PO single dose; Nitrofurantoin macrocrystal 100 mg PO qid for 5-7 days; Amoxicillin/Clavulanate 500/125mg PO tid for 5-7 days; TMP-SMX◊ 160/800 mg PO bid 3 days. Alternative – Ciprofloxacin 250 mg PO bid 3 days; Levofloxacin 250 mg PO qid 3 days; Ofloxacin 200 mg PO bid 3 days; Cephalosporin (e.g. cefuroxime) 500 mg PO bid 3 days. If failure of empirical therapy after 1-3 days or in severe conditions, use: Fluoroquinolone (if not used initially); Cephalosporin (3rd generation) or Carbapenem ± Aminoglycoside.[166] **Mild and moderate uncomplicated pyelonephritis**[167,168] Ceftriaxone 1g im or iv single dose followed by Cefuroxime 500mg PO bid, 7-14 days; Levofloxacin 750 mg PO qid 5 days. Duration: 1-2 weeks. **Severe acute pyelonephritis (complicated with sepsis)**[168] 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**[152] *- Mild-to-moderate severity*ŧ First Line – Cefoxitin 2g iv qid, Ertapenem 1g iv qd, Moxifloxacin 400mg iv qd. Alternative – Metronidazole 500mg iv every 8-12 h or 1500mg iv every qd + Cefazolin 1-2g iv tid, Cefuroxime 1.5g iv tid, Ceftriaxone 1-2g iv every 12-24 h, Cefotaxime 1-2g iv every 6-8 h, Ciprofloxacin 400mg iv bid or Levofloxacin 750mg iv qd. *High risk or severity*Φ First Line – Imipenem-cilastatin 500mg iv qid or 1g tid, Meropenem 1g iv tid or Piperacillin-tazobactam 4.5 g iv qid. Alternative – Metronidazole 500 mg every 8-12h or 1500mg qd + Cefepime 2g every 8-12h, Ceftazidime 2g tid, Ciprofloxacin 400 mg bid or Levofloxacin 750 mg qd. **Biliary Infections**[152] 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 diarrhea**[169] *Campylobacter* spp. – Azithromycin 500mg PO daily, 1-3days. *Escherichia coli* (enterotoxigenic, enteropathogenic, enteroinvasive) or empiric therapy of traveler's diarrhea – Ciprofloxacin 500mg PO bid, 1-3days.

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TABLE IV. CONTINUATION

	Non-typhoid Salmonella spp. – Ciprofloxacin 500mg PO bid, TMP-SMX 160/800 PO bid or Ceftriaxone 1g iv daily, 14 days. *Shigella* spp. – Ciprofloxacin 500mg PO bid or TMP-SMX 160/800 PO bid, 7 days. *Vibrio parahaemolyticus* (if severe illness) – Ciprofloxacin 500mg PO bid, 3 days. *Yersinia* spp. – Ciprofloxacin 500mg PO bid, TMP-SMX 160/800 PO bid or Doxycycline 100mg bid, 3 days.
Skin and soft tissues	**Nonpurulent[b] – Erysipelas/Cellulitis/Necrotizing infection**[169,170] - Mild Amoxicillin/Clavulanate 875/125mg PO bid, Cephalosporin (1st or 2nd generation), Flucloxacillin 500-1000 mg PO tid or Clindamycin 300mg PO qid. DURATION: 5 days. - Moderate Penicillin 2-4 million iv units every 4–6h, Cefazolin 1g iv tid or Clindamycin 600mg iv tid. DURATION: 5-7 days. - Severe Emergency surgical inspection/debridement and Vancomycin 15-20 mg/kg iv every 8-12h + Piperacillin-tazobactam 4.5g qid. DURATION: 5-7 days. **Purulent[c] – Furuncle/Carbuncle/Abscess**[169,170] - Mild Incision and drainage. - Moderate Incision and drainage. TMP-SMX 160/800mg PO bid or Doxycycline 100mg PO bid. DURATION: 5-7 days. - Severe Incision and drainage. Vancomycin 15-20mg/kg iv every 8-12h, Daptomycin, or Linezolid. DURATION: 5-7 days.
Bone and joints	**Septic arthritis**[171,172] - No risk factors for atypical organisms FIRST LINE – Flucloxacillin 2g iv tid, and/or Gentamicin iv. ALTERNATIVE – Clindamycin 450-600mg tid iv or Cephalosporin (2nd or 3rd generation) iv. DURATION: 2-4 weeks. - High risk of Gram-negative sepsis[d] Cefuroxime 1.5g tid iv or ceftriaxone 1-2g bid iv + Flucloxacillin 2g tid iv. DURATION: 2-4 weeks. - MRSA risk[e] Vancomycin 1g bid iv + Cephalosporin (2nd or 3rd generation) iv. - Suspected gonococcus or meningococcus Ceftriaxone 1g iv qd (or similar dependent on local policy or resistance). DURATION: 2-4 weeks. **Infection of articular prosthesis**[171,173] Orthopedics referral –> decision regarding retention or removal strategy. Pathogen-specific iv antibiotic therapy (2 to 6 weeks) followed by oral therapy (3-6 months). **Bacterial Osteomyelitis**[169,174] - Vertebral osteomyelitis FIRST LINE – Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv or Cefepime 2g iv tid.

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TABLE IV. CONTINUATION

	ALTERNATIVE – Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv and/or Ciprofloxacin 400mg iv tid. DURATION: 4-8 weeks. - Non vertebral bacterial Osteomyelitis Clindamycin, Rifampicin, Trimethoprim-sulfamethoxazole, Fluoroquinolones, Linezolid or Vancomycin iv. DURATION: 4-8 weeks. Disseminated
Sepsis with no clear source[169]	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 Ciprofloxacin 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**[54] Extended spectrum beta-lactam + aminoglycoside or a fluoroquinolones. **Suspected intra-abdominal sepsis**[169] Meropenem 1g iv tid ± Vancomycin (loading dose 20-25mg/Kg, followed by 15-20mg/Kg every 8h-12h) iv ± Gentamicin 3mg/kg iv id or 1g/Kg tid.

Adapted from[161-173]

† If intolerance to first line medications. ¤ In patients meeting a CRB-65 of one or more (except age ‡65 as the only criterion met), hospitalization should be seriously considered. ¤ Patients without findings reflecting acute respiratory failure, severe sepsis or septic shock and radiographic extension of infiltrates, as well as severely decompensated comorbidities, should prompt consideration of admission to the ICU or an intermediate care unit. ° In men a treatment duration of at least 7 days is recommended, preferably with TMP-SMX or a fluoroquinolone if in accordance with the susceptibility testing. ◊ If local resistance pattern is known (E. coli resistance < 20%). ᵏ Perforated or abscessed appendicitis and other infections of mild-to-moderate severity. ΦSevere physiologic disturbance, advanced age, or immunocompromised state. ᵇ Nonpurulent SSTIs. Mild infection: typical cellulitis/erysipelas with no focus of purulence. Moderate infection: typical cellulitis/erysipelas with systemic signs of infection. Severe infection: patients who have failed oral antibiotic treatment or those with systemic signs of infection (as defined above under purulent infection), or those who are immunocompromised, orthoses with clinical signs of deeper infection such as bullae, skins sloughing, hypotension or evidence of organ dysfunction. ᶜ Purulent skin and soft tissue infections (SSTIs). Mild infection: for purulent SSTI, incision and drainage is indicated. Moderate infection: patients with purulent infection with systemic signs of infection. Severe infection: patients who have failed incision and drainage plus oral antibiotics; orthoses with systemic signs of infection such as temperature >38°C, tachycardia (heart rate >90 beats per minute), tachypnea (respiratory rate >24 breaths per minute) or abnormal white blood cell count (<12000 or <400 cells/μL), or immunocompromised patients. d Elderly, frail, recurrent UTI, and recent abdominal surgery. e Known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors determined locally.

ICU – Intensive Care Unit; TMP – trimethoprim; SMX – sulfamethoxazole; qd - once daily; bid – twice a day; tid – three times a day; qid – four times a day.

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. LEVEL OF EVIDENCE 5, GRADE OF RECOMMENDATION: D.

Data regarding gastrointestinal infectious complications are scarce. The SLR retrieve 21 articles, including 27849 patients and a total of 229 (0.82%) cases with severe gastrointestinal infections events identified, but none was fatal. Those infections manifested as gastroenteritis, colitis, diverticulitis, abdominal abscesses, appendicitis, and cholangitis. Nevertheless, no evidence is available regarding the best treatment of abdominal infections in patients treated with biologics[3,62,63,81,92,93,102,110,115,119,121,125,126,128,132,136,139,140,146,149].

According to the expert panel, empiric antimicrobial therapy should be initiated once the patient receives a diagnosis of an intra-abdominal infection (except non-severe gastroenteritis) (Table IV). Regarding patients with septic shock, antibiotics should be administered as soon as possible, given the poor prognosis associated with delayed antimicrobial therapy.[152]

In the event of a newly diagnosed hepatotropic infection during biological treatment, viral replication should be accessed and it is advised to consult a hepatic diseases specialist. Biologic treatment should be stopped and, if indicated, antiviral therapy should be started.

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-i 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-i[3,39,62,65,70–73,76,81,83,93,96,102,104,108,110,112,114,115,119,121,125,127,128,131,132,135,141,143,144,146,149,150,153–157].

The panel suggest 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 antibiotherapy 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)[3,68,76,81,87,93,106,115,119,125,141,145,149,159–162]. 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 antibiotherapy 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 antibiotherapy 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[68,73,108,124,154,159]. 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)[68,73,108,154,159,160]. The epidemiological context should guide the diagnostic tests. These studies should include the collection of biological products for cultural examination, histology and serology[73,159,160]. Immunosuppressive treatment must be stopped and broad-spectrum empirical antibiotherapy 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[68,73,108,124,154,159]. 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 divulgation 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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REFERENCES

1. Thomas E, Symmons DP, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: A 20 year followup study. J Rheumatol. 2003;30:958--965.
2. Kang I, Park SH. Infectious complications in SLE after immunosuppressive therapies. Curr Opin Rheumatol. 2003;15:528-534. doi:10.1097/00132980-200312000-00015.
3. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007;56:1125--1133. doi:10.1002/art.22504.
4. Ranjan P, Chakrawarty A, Kumari A, Kumar J. Immunization in Patients with Rheumatic Diseases: A Practical Guide for General Practitioners. J Clin Diagnostic Res. 2015;9:OE01-OE04.
5. Curtis JR, Xi J, Patkar N, Xie A, Saag KG, Martin C. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007;56:4226-4227. doi:10.1002/art.23050.
6. Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014;73:529--535. doi:10.1136/annrheumdis-2013-204575.
7. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emph. Rheumatology (Oxford). 2011;50:124-131. doi:10.1093/rheumatology/keq242.
8. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003;48:2122-2127. doi:10.1002/art.11137.
9. Che H, Lukas C, Morel J, Combe B. Risk of herpes/herpes zoster during anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Systematic review and meta-analysis. Joint Bone Spine. 2014;81:215-221. doi:10.1016/j.jbspin.2013.07.009.
10. Glück T, Müller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases. Clin Infect Dis. 2008;46:1459-1465. doi:10.1086/587063.
11. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel S. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46:2287-2293.
12. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002;46:2294-2300. doi:10.1002/art.10529.
13. Cordeiro I, Ac D, Jf F, et al. Recommendations for Vaccination in Adult Patients with Systemic Inflammatory Rheumatic Diseases from the Portuguese Society of Rheumatology. :1-20.
14. Widdifield J, Bernatsky S, Paterson JM, et al. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res. 2013;65:353-361. doi:10.1002/acr.21812.
15. Santiago T, Jacobs JW, Saag KG, Buttgereit F, Pereira da Silva JA. Balancing the benefits and risks of low-dose glucocorticoid in rheumatoid arthritis. Acta Reumatol Port. 2015;2015:10-22.
16. Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011;70:1914-1920. doi:10.1136/ard.2011.151043.
17. Solomon DH, Lunt M, Schneeweiss S. The risk of infection associated with tumor necrosis factor alpha antagonists: making sense of epidemiologic evidence. Arthritis Rheum. 2008;58:919-928. doi:10.1002/art.23396.
18. Beukelman T, Xie F, Chen L, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012;64:2773-2780. doi:10.1002/art.34458; 10.1002/art.34458.
19. Fonseca JE, Bernardes M, Canhão H, et al. Portuguese guidelines for the use of biological agents in rheumatoid arthritis - October 2011 update. Acta Reumatol Port. 2011;36:385—388. http://europepmc.org/abstract/MED/22472929.
20. Mourão AF, Fonseca JE, Canhão H, et al. Guia prático de utilização de terapêuticas biotecnológicas na artrite reumatóide-actualização de dezembro 2011. Acta Reumatol Port. 2011;36:389-395.

21. Diniz A, Duarte R, Bettencourt J, Melo T de, Gomes M, Oliveira O. Infeção por VIH, SIDA e Tuberculose em números – 2015. Direcção Geral de Saúde. 2015.
22. Pompili M. Tumor necrosis factor-α inhibitors and chronic hepatitis C: A comprehensive literature review. World J Gastroenterol. 2013;19:7867. doi:10.3748/wjg.v19.i44.7867.
23. Parke F a, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum. 2004;51:800-804. doi:10.1002/art.20702.
24. Aslanidis S, Vassiliadis T, Pyrpasopoulou A, Douloumpakas I, Zamboulis C. Inhibition of TNFα does not induce viral reactivation in patients with chronic hepatitis C infection: Two cases. Clin Rheumatol. 2007;26:261-264. doi:10.1007/s10067-006--0394-z.
25. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-α therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology. 2006;45:1294-1297. doi:10.1093/rheumatology/kel123.
26. Cansu DÜ, Ka ifo lu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol. 2008;35:421-424. doi:08/13/012 [pii].
27. Giannitti C, Benucci M, Caporali R, et al. Efficacy and safety of anti-TNF-alpha therapy combined with cyclosporine A in patients with rheumatoid arthritis and concomitant hepatitis C virus infection. Int J Immunopathol Pharmacol. 2009;22:543--546.
28. Li S, Kaur PP, Chan V, Berney S. Use of tumor necrosis factor-α (TNF-) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: A retrospective record review of 11 patients. Clin Rheumatol. 2009;28:787-791. doi:10.1007/s10067-009-1149-4.
29. Caporali R, Bobbio-Pallavicini F, Atzeni F, et al. Safety of tumor necrosis factor α blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res. 2010;62:749-754. doi:10.1002/acr.20130.
30. Costa L, Caso F, Atteno M, et al. Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: A retrospective observational multicenter study on 15 patients. Clin Rheumatol. 2014;33:273-276. doi:10.1007/s10067-013-2378-0.
31. Ballanti E, Conigliaro P, Chimenti MS, et al. Use of Anti-Tumor Necrosis Factor Alpha Therapy in Patients with Concurrent Rheumatoid Arthritis and Hepatitis B or Hepatitis C: A Retrospective Analysis of 32 Patients. Drug Dev Res. 2014;75:S42-S45. doi:10.1002/ddr.21193.
32. Singh JA, Saag KG, Bridges SLJ, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68:1-25. doi:10.1002/acr.22783.
33. Sagnelli E, Pisaturo M, Martini S, Filippini P, Sagnelli C, Coppola N. Clinical impact of occult hepatitis B virus infection in immunosuppressed patients. World J Hepatol. 2014;6:384-393. doi:10.4254/wjh.v6.i6.384.
34. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:215-219. doi:10.1053/j.gastro.2014.10.039.
35. Nunes J, Marinho RT, Fonseca JE, Pereira da Silva JA, Velosa J. Prophylaxis of hepatitis B reactivation with immunosuppressive therapy in rheumatic diseases. Orientations for clinical practice. Acta Reumatol Port. 2011;36:110-118. doi:10.1080/09523360600802562.
36. Lee YH, Bae SC, Song GG. Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumour necrosis factor therapy. Clin Exp Rheumatol. 2013;31:118-121.
37. Sakellariou GT, Chatzigiannis I. Long-term anti-TNFalpha therapy for ankylosing spondylitis in two patients with chronic HBV infection. Clin Rheumatol. 2007;26:950-952. doi:10.1007/s10067-006-0392-1.
38. Charpin C, Guis S, Colson P, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. Arthritis Res Ther. 2009;11:R179. doi:10.1186/ar2868.
39. Suwannalai P, Auethavekiat P, Udomsubpayakul U, Janvitayanujit S. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: A retrospective study a the university-based hospital. Int J Rheum Dis. 2009;12:118-124. doi:10.1111/j.1756-185X.2009.01393.x.
40. Chung SJ, Kim JK, Park MC, Park YB, Lee SK. Reactivation of hepatitis B viral infection in inactive HBsAg carriers following anti-tumor necrosis factor-?? therapy. J Rheumatol. 2009;36:2416-2420. doi:10.3899/jrheum.081324.
41. Vassilopoulos D, Apostolopoulou a, Hadziyannis E, et al. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2010;69:1352-1355. doi:10.1136/ard.2009.127233.
42. Lan J-L, Chen Y-M, Hsieh T-Y, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis. 2011;70:1719-1725. doi:10.1136/ard.2010.148783.
43. Tamori A, Koike T, Goto H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: Evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol. 2011;46:556-564. doi:10.1007/s00535-010-0367-5.
44. Ryu HH, Lee EY, Shin K, et al. Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNFα agents: A retrospective analysis of 49 cases. Clin Rheumatol. 2012;31(6):931-936. doi:10.1007/s10067-012-1960-1.
45. Zhang X, Zhang F, Wu D, Bao C, Zhu P. Safety of infliximab therapy in rheumatoid arthritis patients with previous exposure to hepatitis B virus Patient selection. 2013;:1-5.
46. Giardina AR, Ferraro D, Ciccia F, et al. No detection of occult HBV-DNA in patients with various rheumatic diseases treated with anti-TNF agents: A two-year prospective study. Clin Exp Rheumatol. 2013;31:25-30.
47. Laurenti R, Giovannangeli F, Gubinelli E, et al. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: A retrospective case series of 8 patients. Clin Dev Immunol. 2013;2013. doi:10.1155/2013/410521.
48. Ye H, Zhang XW, Mu R, et al. Anti-TNF therapy in patients with HBV infection-analysis of 87 patients with inflammatory arthritis. Clin Rheumatol. 2014;33:119-123. doi:10.1007/s10067-013-2385-1.

49. Kim PS, Ho GY, Prete PE, Furst DE. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. Arthritis Care Res (Hoboken). 2012;64:1265-1268. doi:10.1002/acr.21654.
50. Mitroulis I, Hatzara C, Kandili A, Hadziyannis E, Vassilopoulos D. Long-term safety of rituximab in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2013;72:308-310. doi:10.1136/annrheumdis-2012-202088.
51. Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum. 2007;56:2896-2904. doi:10.1002/art.22808.
52. Kling A, Mjörndal T, Rantapää-Dahlqvist S. Sepsis as a possible adverse drug reaction in patients with rheumatoid arthritis treated with TNFalpha antagonists. J Clin Rheumatol. 2004;10:119-122. doi:10.1097/01.rhu.0000128734.07926.8e.
53. Marik PE. Fever in the ICU. Chest. 2000;117:855-869. doi:10.1378/chest.117.3.855.
54. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165-228. doi:10.1007/s00134-012-2769-8.
55. Yazdanpanah Y, Chêne G, Losina E, et al. Incidence of primary opportunistic infections in two human immunodeficiency virus-infected French clinical cohorts. Int J Epidemiol. 2001;30:864-871. doi:10.1093/ije/30.4.864.
56. Winthrop KL, Baddley JW, Chen L, et al. Association Between the Initiation of Anti–Tumor Necrosis Factor Therapy and the Risk of Herpes Zoster. Jama. 2013;309):887. doi:10.1001/jama.2013.1099.
57. Tak PP, Rigby W, Rubbert-Roth a., et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. Ann Rheum Dis. 2012;71:351-357. doi:10.1136/annrheumdis-2011-200170.
58. García-Doval I, Pérez-Zafrilla B, Descalzo MA, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Ann Rheum Dis. 2010;69:1751-1755. doi:10.1136/ard.2009.125658.
59. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009;301:737-744. doi:10.1001/jama.2009.146.
60. Wendling D, Streit G, Toussirot E, Prati C. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. Jt Bone Spine. 2008;75:540-543. doi:10.1016/j.jbspin.2007.10.011.
61. Walker UA, Courvoisier DS, Dudler J, et al. Do new biologics meet the unmet medical need in rheumatoid arthritis? Safety and efficacy of abatacept following B-cell depletion. Rheumatology. 2011;50:243-244. doi:10.1093/rheumatology/keq258.
62. Cobo-Ibanez T, Descalzo M, Loza-Santamara E, Carmona L, Munoz-Fernandez S. Serious infections in patients with rheumatoid arthritis and other immune-mediated connective tissue diseases exposed to anti-TNF or rituximab: Data from the Spanish registry BIOBADASER 2.0. Rheumatol Int. 2014;34:953-961. doi:10.1007/s00296-014-2945-y.
63. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: A twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014;66:379-389. doi:10.1002/art.38260.
64. Illei GG, Shirota Y, Yarboro CH, et al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010;62:542-552. doi:10.1002/art.27221.
65. Smith KGC, Jones RB, Burns SM, Jayne DRW. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthritis Rheum. 2006;54:2970-2982. doi:10.1002/art.22046.
66. Saougou I, Markatseli TE, Papagoras C, Voulgari P V., Alamanos Y, Drosos AA. Sustained Clinical Response in Psoriatic Arthritis Patients Treated with Anti-TNF Agents: A 5-year Open-Label Observational Cohort Study. Semin Arthritis Rheum. 2011;40:398-406. doi:10.1016/j.semarthrit.2010.07.004.
67. Genovese MC, Tena CP, Covarrubias A, et al. Subcutaneous abatacept for the treatment of rheumatoid arthritis: Longterm data from the ACQUIRE trial. J Rheumatol. 2014;41:629-639. doi:10.3899/jrheum.130112.
68. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014;73:86-94. doi:10.1136/annrheumdis-2013-203843.
69. Kilic O, Kasapcopur O, Camcioglu Y, Cokugras H, Arisoy N, Akcakaya N. Is it safe to use anti-TNF-α agents for tuberculosis in children suffering with chronic rheumatic disease? Rheumatol Int. 2012;32:2675-2679. doi:10.1007/s00296-011-2030-8.
70. Yoo IK, Choung RS, Hyun JJ, et al. Incidences of serious infections and tuberculosis among patients receiving anti-tumor necrosis factor-alfa therapy. Yonsei Med J. 2014;55:442-448. doi:10.3349/ymj.2014.55.2.442.
71. Steyaert S, Stappaerts G, Mareen P, Dierick J. Soft tissue infections with atypical mycobacteria in two patients with inflammatory rheumatic diseases using TNF-inhibitors and/or Leflunomide. Acta Clin Belg. 2011;66:144-147. doi:10.2143/ACB.66.2.2062537.
72. Alawneh KM, Ayesh MH, Khassawneh BY, Saadeh SS, Smadi M, Bashaireh K. Anti-TNF therapy in Jordan: a focus on severe infections and tuberculosis. Biologics. 2014;8:193-198. doi:10.2147/BTT.S59574.
73. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-?? therapy. Emerg Infect Dis. 2009;15:1556-1561. doi:10.3201/eid1510.090310.
74. Schoffelen T, Kampschreur LM, van Roeden SE, et al. Coxiella burnetii infection (Q fever) in rheumatoid arthritis patients with and without anti-TNFalpha therapy. Ann Rheum Dis. 2014;73:1436-1438.
75. Ke W-M, Chen L-S, Parng I-M, Chen W-W, On AWF. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. Int J Tuberc Lung Dis. 2013;17:1590-1595. doi:10.5588/ijtld.13.0368.
76. Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF, Griffin MR. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford). 2010;49:82-90. doi:10.1093/rheumatology/kep325.
77. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of

tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2009;69:522-528. doi:10.1136/ard.2009.118935.
78. Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007; 357:1874-1876. doi:10.1056/NEJMc070728.
79. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis. 2007;66:732-739. doi:10.1136/ard.2006.066761.
80. Gómez-Reino JJ, Carmona L, Rodríguez Valverde V, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis Rheum. 2003;48:2122-2127. doi:10.1002/art.11137.
81. Yang C-T, Kuo C-F, Luo S-F, Yu K-H. Discontinuation of anti-TNF-α therapy in a Chinese cohort of patients with rheumatoid arthritis. Clin Rheumatol. 2012;31:1549-1557. doi:10.1007/s10067-012-2047-8.
82. Keystone EC, Cohen SB, Emery P, et al. Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-Year data from the REFLEX study. J Rheumatol. 2012;39:2238-2246. doi:10.3899/jrheum.120573.
83. Nguyen-Khoa BA, Goehring EL, Alexander KA, Dong W, Napalkov P, Jones JK. Risk of Significant Infection in Rheumatoid Arthritis Patients Switching Anti-Tumor Necrosis Factor-α Drugs. Semin Arthritis Rheum. 2012;42:119-126. doi:10.1016/j.semarthrit.2012.04.001.
84. Schiff M, Keiserman M, Codding C, et al. Clinical response and tolerability to abatacept in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST Study. Ann Rheum Dis. 2011;70:2003-2007. doi:10.1136/annrheumdis-2011-200316.
85. Knight A, Hallenberg H, Baecklund E. Efficacy and safety of rituximab as maintenance therapy for relapsing granulomatosis with polyangiitis - A case series. Clin Rheumatol. 2014;33:841-848. doi:10.1007/s10067-013-2351-y.
86. Simon TA, Askling J, Lacaille D, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. Arthritis Res Ther. 2010;12:R67. doi:10.1186/ar2984.
87. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54:2807-2816. doi:10.1002/art.22070.
88. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor α antagonists infliximab and etanercept. Arthritis Rheum. 2002;46(10):2565-2570. doi:10.1002/art.10583.
89. Bonilla-Abadia F, Betancurt JF, Pineda JC, Vélez JD, Tobón GJ, Cañas CA. Pneumocystis jirovecii pneumonia in two patients with systemic lupus erythematosus after rituximab therapy. Clin Rheumatol. 2014;33:415-418. doi:10.1007/s10067-013-2475-0.
90. Merrill JT, Ginzler EM, Wallace DJ, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum. 2012;64:3364-3373. doi:10.1002/art.34564.
91. Tsai MJ, Chow CW, Lin FC, Shang SC. Pneumocystis jiroveci pneumonia in patients with systemic lupus erythematosus after rituximab therapy. Lupus. 2012;21:914-918.
92. Kremer JM, Peterfy C, Russell AS, et al. Longterm safety, efficacy, and inhibition of structural damage progression over 5 years of treatment with abatacept in patients with rheumatoid arthritis in the abatacept in inadequate responders to methotrexate trial. J Rheumatol. 2014;41:1077-1087. doi:10.3899/jrheum.130263.
93. M. W, M. G, F. P, et al. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) - Results from a nationwide cohort in Germany (GRAID). Lupus. 2013;22(2013):1142-1149.
94. Tony H-P, Burmester G, Schulze-Koops H, et al. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Res Ther. 2011;13:R75. doi:10.1186/ar3337.
95. Esposito M, Giunta A, Mazzotta A, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: An observational long-term study. Dermatology. 2013;225:312-319. doi:10.1159/000345623.
96. Wendler J, Burmester GR, Sörensen H, et al. Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. Arthritis Res Ther. 2014;16:R80. doi:10.1186/ar4521.
97. Seifert H. The clinical importance of microbiological findings in the diagnosis and management of bloodstream infections. Clin Infect Dis. 2009;48 Suppl 4(Supplement 4):S238-S245. doi:10.1086/598188.
98. Bodey GP. Managing Infections in the Immunocompromised Patient. Clin Infect Dis. 2005;40(Supplement 4):S239-S239. doi:10.1086/427328.
99. Mourão* AF, Fonseca* JE, , Helena Canhão, Maria José Santos, Alexandra Bernardo AC, et al. Guia prático de utilização de terapêuticas biotecnológicas na artrite reumatóide – actualização de Dezembro 2011. Acta Reumatol Port.
100. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385-2395. doi:10.1056/NEJMoa1112802.
101. Kawada J-I, Kitagawa Y, Iwata N, Ito Y. Clinical characteristics of influenza virus infection in juvenile idiopathic arthritis patients treated with tocilizumab. Mod Rheumatol. 2013;23:972-976. doi:10.1007/s10165-012-0780-0.
102. Yokota S, Imagawa T, Mori M, et al. Longterm Safety and Effectiveness of the Anti-interleukin 6 Receptor Monoclonal Antibody Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis in Japan. J Rheumatol. 2014;41:759-767. doi:10.3899/jrheum.130690.
103. Gerloni V, Pontikaki I, Gattinara M, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor α monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: Results of an open-label prospective study. Arthritis Rheum. 2005;52:548-553. doi:10.1002/art.20793.
104. Germano V, Cattaruzza MS, Osborn J, et al. Infection risk in

rheumatoid arthritis and spondyloarthropathy patients under treatment with DMARDs, corticosteroids and TNF-α antagonists. J Transl Med. 2014;12:77. doi:10.1186/1479-5876-12--77.
105. Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis. 2015;74:538-546. doi:10.1136/annrheumdis-2013-204195.
106. Son J-H, Cha S-W. Anti-TNF-alpha therapy for ankylosing spondylitis. Clin Orthop Surg. 2010;2:28-33. doi:10.4055/cios.2010.2.1.28.
107. Abreu C, Magro F, Santos-Antunes J, et al. Tuberculosis in anti-TNF-α treated patients remains a problem in countries with an intermediate incidence: analysis of 25 patients matched with a control population. J Crohns Colitis. 2013;7:e486-e492. doi:10.1016/j.crohns.2013.03.004.
108. Salmon-Ceron D, Tubach F, Lortholary O, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2011;70:616-623. doi:10.1136/ard.2010.137422.
109. Chen DY, Shen GH, Chen YM, Chen HH, Hsieh CW, Lan JL. Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFalpha inhibitors: the utility of IFN-gamma assay. Ann Rheum Dis. 2012;71(2):231-237. doi:10.1136/annrheumdis-2011-200489.
110. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. Ann Rheum Dis. 2011;70:2148-2151. doi:10.1136/ard.2011.151092.
111. Hoshi D, Nakajima A, Inoue E, et al. Incidence of serious respiratory infections in patients with rheumatoid arthritis treated with tocilizumab. Mod Rheumatol. 2012;22:122-127. doi:10.1007/s10165-011-0488-6.
112. Curtis JR, Xie F, Chen L, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011;70(8):1401-1406. doi:10.1136/ard.2010.146365.
113. Komano Y, Tanaka M, Nanki T, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: A report from the registry of Japanese rheumatoid arthritis patients for long-term safety. J Rheumatol. 2011;38:1258-1264. doi:10.3899/jrheum.101009.
114. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010;69:380-386. doi:10.1136/ard.2008.089276.
115. Genovese MC, Breedveld FC, Emery P, et al. Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients. Ann Rheum Dis. 2009;68:1894-1897. doi:10.1136/ard.2008.101675.
116. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009;68:1708-1714. doi:10.1136/ard.2008.099218.
117. Fujiwara H, Nishimoto N, Hamano Y, et al. Masked early symptoms of pneumonia in patients with rheumatoid arthritis during tocilizumab treatment: A report of two cases. Mod Rheumatol. 2009;19:64-68. doi:10.1007/s10165-008-0111-7.
118. Miller KL, Sawitzke AD, Doane J. Abatacept and serious respiratory infections in patients with previous lung disease. Clin Rheumatol. 2008;27:1569-1571. doi:10.1007/s10067-008-0979-9.
119. Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology. 2007;46: -1122-1125. doi:10.1093/rheumatology/kem033.
120. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis. 2007;66:228-234. doi:10.1136/ard.2006.055111.
121. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-α blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. Rheumatology. 2007;46:327-334. doi:10.1093/rheumatology/kel236.
122. Imaizumi K, Sugishita M, Usui M, Kawabe T, Hashimoto N, Hasegawa Y. Pulmonary infectious complications associated with anti-TNFalpha therapy (infliximab) for rheumatoid arthritis. Intern Med. 2006;45:685-688. doi:10.2169/internalmedicine.45.1623.
123. Neven N, Vis M, Voskuyl AE, et al. Adverse events in patients with rheumatoid arthritis treated with infliximab in daily clinical practice. Ann Rheumatol Dis. 2005;66:645-655. doi:10.1136/ard.2004.028597.
124. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004;50:1959-1966. doi:10.1002/art.20454.
125. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003;42:617-621. doi:10.1093/rheumatology/keg263.
126. Fleischmann RM, Halland AM, Brzosko M, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol. 2013;40:113-126. doi:10.3899/jrheum.120447.
127. Xanthouli P, Sailer S, Fiehn C. Rituximab (RTX) as an Alternative to TNF-Alpha Antagonists in Patients with Rheumatoid Arthritis and High Risk of Severe Infections: A Systematic Analysis of the Experience in One Center. Open Rheumatol J. 2012;6:286-289. doi:10.2174/1874312901206010286.
128. Atzeni F, Sarzi-Puttini P, Botsios C, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev. 2012;12:225-229. doi:10.1016/j.autrev.2012.06.008.
129. Thyagarajan V, Norman H, Alexander KA, Napalkov P, Enger C. Risk of Mortality, Fatal Infection, and Fatal Malignancy Related to Use of Anti-Tumor Necrosis Factor-α Biologics by Rheumatoid Arthritis Patients. Semin Arthritis Rheum. 2012;42:223-233. doi:10.1016/j.semarthrit.2012.05.004.
130. Bykerk VP, Ostör AJK, Alvaro-Gracia J, et al. Tocilizumab in

patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. Ann Rheum Dis. 2012; 71:1950-1954. doi:10.1136/annrheumdis-2011-201087.
131. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structu. Arthritis Rheum. 2011;63:609-621. doi:10.1002/art.30158.
132. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010;62:2625-2632. doi:10.1002/art.27555.
133. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum. 2007;56:1754-1764. doi:10.1002/art.22600.
134. Popa C, Leandro MJ, Cambridge G, Edwards JCW. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology. 2007;46:626-630. doi:10.1093/rheumatology/kel393.
135. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006;54:2817-2829. doi:10.1002/art.22033.
136. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793-2806. doi:10.1002/art.22025.
137. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54:1390-1400. doi:10.1002/art.21778.
138. Heiberg MS, Kaufmann C, Rødevand E, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007;66:1038-1042. doi:10.1136/ard.2006.064808.
139. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: The randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62:222-233. doi:10.1002/art.27233.
140. Tanaka Y, Yamamoto K, Takeuchi T, et al. A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. Mod Rheumatol. 2007;17:191-197. doi:10.1007/s10165-007-0565-z.
141. Weisman MH, Moreland LW, Furst DE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: A pilot study. Clin Ther. 2003;25(6):1700-1721. doi:10.1016/S0149-2918(03)80164-9.
142. Nash P, Nayiager S, Genovese MC, et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study. Arthritis Care Res (Hoboken). 2013;65:718-728. doi:10.1002/acr.21876.
143. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet (London, England). 2013;381(9877):1541-1550. doi:10.1016/S0140-6736(13)60250-0.
144. Weinblatt ME, Moreland LW, Westhovens R, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: Integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. J Rheumatol. 2013;40:787-797. doi:10.3899/jrheum.120906.
145. Burmester G, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid art. Ann Rheum Dis. 2014;73:69-74. doi:10.1136/annrheumdis-2013-203523.
146. Koike T, Harigai M, Inokuma S, et al. Effectiveness and safety of tocilizumab: Postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41:15-23. doi:10.3899/jrheum.130466.
147. Bello S, Serafino L, Bonali C, et al. Incidence of influenza-like illness into a cohort of patients affected and treated with biological agents. 2012;64:299-306.
148. Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008;67:547-554. doi:10.1136/ard.2007.074773.
149. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65:28-38. doi:10.1002/art.37711.
150. Ye Y, Qian J, Gu Y, Chen X, Ye S. Rituximab in the treatment of severe lupus myelopathy. Clin Rheumatol. 2011;30:981-986. doi:10.1007/s10067-011-1714-5.
151. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum. 2004;50:3161-3169. doi:10.1002/art.20576.
152. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133-164. doi:10.1086/649554.
153. Trachana M, Pratsidou-Gertsi P, Pardalos G, Kozeis N, Badouraki M, Kanakoudi-Tsakalidou F. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. Scand J Rheumatol. 2011;40:101-107. doi:10.3109/03009742.2010.517546.
154. Audring H, Kary S, Burmester G, et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor- a antagonists. 2007:486-491.

155. Momohara S, Kawakami K, Iwamoto T, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. Mod Rheumatol. 2011;21:469-475. doi:10.1007/s10165-011-0423-x.
156. van Vollenhoven RF, Emery P, Bingham CO, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013; 72:1496-1502. doi:10.1136/annrheumdis-2012-201956.
157. Wasson NJ, Varley CD, Schwab P, Fu R, Winthrop KL. "Serious skin & soft tissue infections in rheumatoid arthritis patients taking anti-tumor necrosis factor alpha drugs: a nested case-control study". BMC Infect Dis. 2013;13:533. doi:10.1186/1471-2334-13-533.
158. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology. 2010;49:2217-2219. doi:10.1093/rheumatology/keq249a.
159. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum. 2005;52:1986-1992. doi:10.1002/art.21137.
160. Nguyen MT, Podenphant J, Ravn P. Three cases of severely disseminated Staphylococcus aureus infection in patients treated with tocilizumab. BMJ Case Rep. 2013;2013(January):10.1136/bcr-2012-007413. doi:10.1136/bcr-2012-007413; 10.1136/bcr-2012-007413.
161. Meyer A, Theulin A, Chatelus E, et al. Campylobacter fetus infection in three rheumatoid arthritis patients treated with rituximab. Ann Rheum Dis. 2012;71:1094-1095. doi:10.1136/annrheumdis-2011-200719.
162. Terrier B, Amoura Z, Ravaud P, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the French autoimmunity and rituximab registry. Arthritis Rheum. 2010;62:2458-2466. doi:10.1002/art.27541.
163. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. Otolaryngol Head Neck Surg. 2015;152(2 suppl):S1-S39. doi:10.1177/0194599815572097.
164. Monteiro ME, Santos I, Caetano P, Pinto D, Heleno B. Orientação n.o 045/2011: Antibioterapia na Pneumonia Adquirida na Comunidade em Adultos Imunocompetentes. Direcção-Geral Saúde. 2011:1-17.
165. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R and, Verheij M, Joint Taskforce of the European Respiratory Society Diseases. ES for CM and I. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infect. 2011;17:1-24. doi:10.1136/pgmj.64.752.478-a.
166. Bishop MC, Botto H, Lobel B, Naber KG, Palou J. Orientações sobre infecções urológicas. 2009;(Tabela 1):152-168.
167. Grabe M, Bartoletti R, Bjerklund-Johansen TE, et al. Guidelines on Urological Infections. Eur Assoc Urol. 2015:33-40.
168. George HM, George HM. Norma no 015/2011 de 30/08/2011. Terapêutica de infeções do aparelho urinário (comunidade). 2014:1-10.
169. Johns Hopkins Medicine. Antibiotic Guidelines 2015-2016: Treatment Recommendations for adult inpatients. Antibiot Guidel 2015-2016 Treat Recomm adult inpatients. 2016:110-124.
170. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59. doi:10.1093/cid/ciu296.
171. George HM. Duração de Terapêutica Antibiótica. 2015.
172. Coakley G, Mathews C, Field M, et al. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. Rheumatology (Oxford). 2006;45:1039-1041. doi:10.1093/rheumatology/kel163a.
173. Minassian AM, Osmon DR, Berendt AR. Clinical guidelines in the management of prosthetic joint infection. J Antimicrob Chemother. 2014;69(SUPPL1):29-35. doi:10.1093/jac/dku253.
174. Concia E, Prandini N, Massari L, et al. Osteomyelitis: clinical update for practical guidelines. Nucl Med Commun. 2006; 27:645-660.