Review

Antibiotic therapy in autoimmune disorders

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Practice Points

- Infections may trigger autoimmunity through several mechanisms most notably; 'molecular mimicry', 'epitope spreading' and 'bystander activation'.
- Minocycline, macrolides and fluoroquinolones may be recommended to patients with early and mild rheumatoid arthritis.
- Ciprofloxacin therapy may obviate chronic reactive arthritis in HLA-B27 patients, while antichlamydia-based antibiotic regimens may enhance chronicity.
- Trimethoprim/sulfamothoxazole should be part of the treatment protocol of granulomatosis with polyangitis.
- *Helicobacter pylori* eradication should be offered to all carriers with chronic thrombocytopenic purpura.
- Empiric antibiotic treatment should be considered as a standard part of the treatment protocol in catastrophic antiphosphlipid antibody syndrome.

SUMMARY: Antibiotics have been applied for the treatment of autoimmune diseases for over five decades, based on the premise that infections play a role in the initiation and propagation of these entities. The mechanisms by which an infection may trigger an autoimmune reaction include the so-called 'molecular mimicry', 'epitope spreading' or 'bystander activation'. The association between infection and autoimmunity may be directly evident, as in cases of reactive arthritis, or in a more roundabout manner, as exemplified by the association between anaerobic bacterial infection of the gums and rheumatoid arthritis. Moreover, some antibiotics have, in addition to

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their antibacterial effects, anti-inflammatory and immunomodulatory properties. In this review we focus on the rationale and possible benefits of antibiotic treatment in various autoimmune diseases, including rheumatoid arthritis, reactive arthritis, granulomatosis with polyangitis, immune thrombocytopenia purpura and the antiphospholipid syndrome.

Antibiotics have been applied for the treatment of autoimmune diseases for over five decades, based on the premise that infections play a role in the initiation and propagation of these entities.

There are several proposed mechanisms by which an infection may trigger an autoimmune reaction [1]. 'Molecular mimicry', in which the pathogen and host share a common epitope (i.e., proteins or DNA) resulting in the cross-activation of autoreactive T or B cells by pathogen-derived peptides is one of them [2,3]. The classic autoimmune disease rheumatic fever is thought to be triggered by an infectious origin probably via 'molecular mimicry' [4]. rheumatic fever is a systemic disease, affecting the heart, joints, CNS and the skin, following Streptococcal infection of the tonsils or the skin. In this disease, antibodies against group A β-hemolytic *Streptococcus* are also active against host target, including the heart and joints. Antibiotic treatment with penicillin is known to prevent the autoimmune reaction when given during the acute infection, or may prevent the continued deterioration when given for a long period of time even after the infection was eliminated.

Other mechanisms by which infections may trigger an autoimmune reaction include 'Epitope spreading', where an epitope is switched from a dominant to a cryptic position resulting in the creation of autoantibodies against the new epitope, is another possible initiator of autoimmunity [1]. Additional mechanisms include 'bystander activation', in which tissue damage results in the release of a new antigen, which activates autolymphocytes inducing an autoinflammatory microenvironment, leading in turn to the destruction of neighboring, uninfected cells [1].

The association between infection and autoimmunity may be directly evident, as in cases of reactive arthritis (ReA), where a history of a recent infection is elicited and in which bacterial products may be detected in joints long after all signs of infection have abated. Alternatively, infection may contribute to the autoimmune cascade in a more roundabout manner, as exemplified by the association between anaerobic bacterial infection of the gums (periodontitis) and rheumatoid arthritis (RA) [5]. Epidemiological studies have shown that periodontal disease is more frequent and more severe in patients with RA [6]. Also, the severity of periodontal disease was found to correlate with RA severity [7], and treating periodontal disease was demonstrated to improve clinical and laboratory parameters of the disease [8]. The presence of peripathogenic bacteria in the synovium of patients with RA suggests that joint seeding and localized inflammatory amplification may initiate and propogate inflammation [9]. Notably, the Gram-negative, anaerobic, coccobacillus *Porphyromonas gingivalis* has received considerable attention for its role in the development of periodontal disease and its association with RA. It was shown that anti-*P. gingivalis* antibodies were present in high titers in RA patients and that these antibodies were associated with the presence of anticitrullinated cyclic peptides [10]. Moreover, in rat models, arthritis was induced by implanting killed *P. gingivalis* organisms subcutaneously, suggesting a role for molecular mimicry [11]. Taken together, these findings suggest a pathological association between *P. gingivalis* and RA, hence the concept that antibiotics directed against *P. gingivalis* may be beneficial in the treatment of RA, especially in early disease.

Helicobacter pylori is an infectious agent noteworthy for its association with autoimmunity. Anti-*H. pylori* antibodies have been associated with antiphospholipid syndrome, giant cell arteritis, systemic sclerosis and primary biliary cirrhosis. Also, *H. pylori* infection has been implicated in the causation of various autoimmune diseases including immune thrombocytopenic purpura, autoimmune chronic gastritis and RA.

The persistent presence of *H. pylori* in gastric mucosa results in chronic immune system activation with ongoing cytokine signaling, infiltration of gastric mucosa by neutrophils, macrophages and lymphocytes, as well as production of antibodies and effector T cells [12]. Molecular mimicry between *H. pylori* antigen and the H^+/K^+-ATPase (the 'autoantigen') leads to autoimmune chronic gastritis, where the

activated $CD4^+$ T lymphocytes cross react with H^+/K^+-ATPase and *H. pylori* antigens [13].

That being said, evidence indicates an overall downregulation of the host immune response in *H. pylori*-infected individuals [12] and this bacteria is also thought to play a protective role in the development of multiple sclerosis, systemic lupus erythematosus and inflammatory bowel disease.

Whether these links are epiphenomenal or *H. pylori* does play a causative role in the autoimmune diseases remains uncertain. The negative associations could possibly support the notion that in susceptible individuals infections that may protect from the development of autoimmune diseases.

While these examples highlight the potential use of antibiotics in curtailing infections which may initiate an autoimmune cascade, antibiotics are also utilized for their anti-inflammatory and immunomodulatory properties. Tetracyclines, for instance, were shown to inhibit the activity of antiphospholipase A2, scavenge free radicals and inhibit various matrix metalloproteinases [14,15] as well as impair lymphocyte [16] activity and impart chondroprotective properties [17].

While single infectious agents promote our understanding of autoimmunity by clarifying the basic concepts of molecular mimicry, epitope spreading and bystander activation, as noted above, 'real-life' autoimmune disease is more likely the result of exposure to numerous infectious agents rather than a single inciter. Moreover, the concept of 'superorganism' and 'microbiome', describing the ensemble of human and nonhuman (microorganism) cells that constitute the human body, which has been developed by Nobel laureate Joshua Lederberg over the last decade, further complicates our understanding of autoimmunity. It seems that the intestinal microbiota are able to shape the immune system to maintain homeostasis and healthy states or promote inflammation when the composition of the microbiota community becomes imbalanced. Therefore the effect of antibiotics in autoimmune diseases is undoubtedly more far-reaching than fathomed at this time point.

The following review shall elaborate on the rationale and possible benefits of antibiotic treatment in various autoimmune diseases.

Rheumatoid arthritis

RA, the most common, chronic, inflammatory joint disease, may be complicated by substantial joint damage and disability [18]. Antibiotics have been administered sporadically in the past in RA, in an attempt to retard disease progression, with minimal benefit. The newly recognized importance of periodontal disease in the pathogenesis of RA has sparked new interest in the use of antibiotics in the treatment and prevention of this common disease. These studies are summarized in **Table 1**.

Tetracyclines

Tetracyclines are a group of broad-spectrum antibiotics used in the treatment of infections of the respiratory tract, urinary tract and intestines. They were first advocated as therapeutic candidates in RA by scientists who presumed that mycoplasma infection triggers the disease and proposed prolonged antibiotic therapy with the aim of eradicating the bacteria [19]. Anecdotal use of tetracyclines in the treatment of RA persisted during the 1970s and early 1980s yet the rheumatology community remained reserved in judging their efficacy.

In the late 1980s, the anti-inflammatory properties of tetracyclines were discovered leading to renewed interest in these drugs in the treatment for RA. Two small, but positive studies, published in the early 1990s, paved the way to larger trials, suggesting that the tetracycline derivate – minocycline, indeed exerts substantial antirheumatic properties [20,21].

The first of these trials was a multicenter double-blinded, randomized controlled study conducted in The Netherlands. A total of 80 patients with a history of more than 10 years of active RA, who had failed more than one disease-modifying antirheumatic drug (DMARD), were divided into two groups. The study group received 200 mg of minocycline once daily on top of their regular therapy, while the control group received placebo. At the end of 26 weeks, there was a pronounced improvement in laboratory parameters of disease activity in the minocycline-treated patients. Alas, improvement in clinical parameters was less impressive [22].

In the second trial, 219 RA patients, who had failed one or more DMARDs were allocated to therapy with 200 mg/day of minocycline in place of the previous DMARD, or to placebo. A significant improvement in joint tenderness and swelling as well as in laboratory parameters including hematocrit, erythrocyte sedimentation rate (ESR), platelet count and IgM rheumatoid

Table 1. Antibiotic use in rheumatoid arthritis.

Author (year)	Antibiotic	Patient population	Study design	Patients (n)	Duration of treatment and follow up	Outcome	Ref.
Kloppenburg *et al.* (1994)	Minocycline 200 mg q.d. (on top of regular treatment)	Active RA for more than 10 years, after failure of one or more DMARD	Multicenter, double-blinded, randomized, placebo-controlled	80	26 weeks	Improvement in laboratory parameters	[22]
Tilley *et al.* (1995)	Minocycline 200 mg q.d., instead of regular treatment	Active RA, after failure of one or more DMARD	Multicenter, double-blinded, randomized, placebo-controlled	219	1 year	Improvement in clinical and laboratory parameters	[23]
O'Dell *et al.* (1999)	Minocycline 100 mg b.i.d.	Newly diagnosed RA	Double-blinded, randomized, placebo-controlled	46	4 years	Improvement in clinical and laboratory parameters	[25]
O'Dell *et al.* (2001)	Minocycline 100 mg b.i.d. versus hydroxychloroquine 200 mg b.i.d.	Newly diagnosed RA	Double-blinded, randomized controlled	60	2 years	Improvement in clinical parameters	[28]
van der Laan *et al.* (2001)	Doxycycline 100 mg q.d.	Active RA, after failure of one DMARD	Double-blinded, randomized placebo-controlled	66	36 weeks	No improvement	[29]
O'Dell *et al.* (2006)	Doxycycline 100 mg q.d. versus doxycycline 20 mg q.d. versus placebo. All with MTX	Newly diagnosed RA	Double-blinded, randomized, placebo-controlled	66	2 years	Improvement in clinical parameters with no difference between high or low dose doxyciline	[30]
Ogrendik (2007)	Clarithromycin 500 mg q.d.	Active RA, after failure of one or more DMARD	Double-blinded, randomized, placebo-controlled	81	6 months	Improvement in clinical and laboratory parameters	[32]
Ogrendik & Karagoz (2011)	Roxithromycin 300 mg q.d.	Active RA	Double-blinded, randomized, placebo-controlled	100	6 months	Improvement in clinical parameters	[33]
Ogrendik (2007)	Levofloxacine 500 mg q.d.	Active RA despite treatment with MTX	Double-blinded, randomized, placebo-controlled	66	6 months	Improvement in clinical and laboratory parameters	[34]
Smith *et al.* (2011)	Tetracycline 250 mg b.i.d., 3 times per week + iv. clindamycin (tapering doses)	Active RA, after failure of one DMARD	Double-blinded, randomized, placebo-controlled	50	25 weeks	No improvement	[35]

b.i.d: Two times a day; DMARD: Disease-modifying antirheumatic drug; iv.: Intravenous; MTX: Methotrexate; q.d.: Once a day; RA: Rheumatoid arthritis.

factor levels were noted among patients treated with minocycline [23].

Finally, minocycline was given to 46 newly diagnosed RA patients in a 6-month double-blinded, randomized controlled trial. These patients, who had not received DMARDs or steroids in the past, were allocated into a 100 mg minocycline twice-daily (b.i.d.) group and a control group. At the end of 3 months, 65% of the study population versus 13% of the controls improved by 50% or more in morning stiffness, joint tenderness, joint swelling and ESR levels [24]. Moreover, after 4 years of follow-up, eight patients (40%) initially randomized to minocycline were still receiving this compound and were in remission without additional DMARD therapy [25].

The sum of these studies prompted the expert opinion published in 2000, supporting the use of minocycline in early RA [26,27]. However, only in 2001 was the efficacy of minocycline compared with that of a conventional DMARD, hydroxychloroquine, utilizing the American College of Rheumatology (ACR) response criteria to measure outcome. In a double-blinded randomized controlled study, 60 patients with newly diagnosed RA, who had not been previously treated with DMARDs, were randomized to receive minocycline, 100 mg b.i.d., or hydroxychloroquine, 200 mg b.i.d., in addition to low-dose prednisone. After 2 years of follow up, patients in the minocycline group were more likely to achieve an ACR50 response compared with hydroxychloroquine-treated patients (60% compared with 33%, respectively; $p = 0.04$) and were also receiving less prednisone (mean dose of 0.81 and 3.21 mg/day, in the minocycline and hydroxychloroquine groups, respectively; $p < 0.01$). In addition, patients treated with minocycline were more likely to have been completely tapered off prednisone ($p = 0.03$) [28].

An additional double-blinded, placebo-controlled crossover trial was performed in 2001, studying the effect of another tetracycline compound doxycycline, in RA [29]. In this study, 66 patients with stable RA were randomized to receive either low-dose (100 mg/day) doxycycline or placebo, and followed for 36 weeks. Lamentably, doxycycline therapy had no effect on any of the clinical, laboratory or radiographic parameters assessed. It was speculated that the disparity in therapeutic efficacy between minocycline and doxycycline was a result of distinct chemical properties, most notably the enhanced lipophilicity of minocycline compared with doxycycline, which favors its distribution within the synovium. Presumably, the enhanced lipophilicity of minocycline also enables it to more readily penetrate the blood–brain barrier and act on the parts of the CNS that influence the immune system, contributing to its immunosuppressive effects. However, one should bear in mind that most of the positive effects attributed to minocycline were noted in populations with early RA which were not exposed to prior DMARD therapy, whereas the study with doxycycline was performed in patients with well-established RA. Indeed, when doxycycline was tested in patients with early RA (in combination with methotrexate [MTX]) it proved to have a beneficial effect on the ACR50 response [30].

Macrolides

Macrolides are a group of antibiotics that are used in the treatment of infections caused by Gram-positive, as well as oral anaerobic, bacteria in addition to possessing inherent anti-inflammatory properties [31]. The discovery of the association between RA and periodontitis, discussed previously, prompted the 2007 study that tested the efficacy of 500 mg of clarithromycin in patients with active RA who had had an inadequate response to at least one previous DMARD [32]. At 6 months, significantly more patients on clarithromycin therapy achieved an ACR20 and/or 50 response, exhibited reductions in ESR and CRP levels and reported an improvement in quality of life. Similar results were demonstrated in a study that tested the effects of a different macrolide – roxithromycine, 300 mg/day in RA patients [33].

Quinolones

Quinolones are antibiotics with activity against anaerobic bacteria. In total, 76 patients with active RA on MTX therapy were allocated to combination therapy with levofloxacin and MTX versus metothrexate and placebo in a randomized, double-blinded study. At 6 months, a significant improvement in all measures of disease activity was noted including a significant reduction in the number of swollen joints in the study group. A significant improvement in secondary end points including a reduction in pain and duration of morning stiffness, improvement in the quality of life, physician's and patient's global assessments, as well as in objective laboratory measures was also noted [34]. The effect of levofloxacin was attributed to its activity against oral anaerobic bacteria, as previously discussed.

These small trials with positive results using a macrolide or a quinolone raise the need for more large-scale trials comparing the addition of a macrolide or a quinolone to the conventional treatment protocol, including the use of biological treatment, for severe active RA.

Combined antibiotic treatment

The effect of combined therapy with intravenous clindamycin in a tapering dose and oral tetracycline 250 mg b.i.d., 3 days a week, was investigated in 50 patients with active RA who

had failed therapy with MTX or sulphasalazine alone. The trial was stopped early owing to lack of improvement in any of the designated outcomes, which was ascribed, retrospectively, to an insufficient dose of tetracycline [35].

H. pylori eradication in RA

As previously discussed, *H. pylori* infection has been associated not only with chronic gastritis and peptic ulcers, but also with many extraintestinal disorders and autoimmune diseases. Zentilin *et al.* studied the effect of *H. pylori* eradication on the outcome of patients with RA [36]. A total of 58 patients with active RA and dyspepsia were divided into two groups. The first, which consisted of 28 patients who had tested positive for a urea breath test for *H. pylori*, received eradication therapy with amoxicillin, whereas the second group, which suffered from dyspepsia but was negative for *H. pylori*, received no therapy. At the end of a 2-year follow-up, a significant reduction in the number of swollen joints and laboratory markers was noted in the first group, in which *H. pylori* was eradicated. This is a small preliminary study, regarding the possible association between RA and *H. pylori*. More large-scale randomized controlled studies are necessary to better define this association.

Summary of antibiotic therapy in RA

The sum of evidence suggests that antibiotics may have a role in DMARD-naive, early RA patients (minocycline) as well as in addition to standard DMARD therapy in established disease (macrolides and quinolones). The beneficial effects of the antibiotic in these cases may be ascribed to immunomodulatory effects in the former, or antibacterial effects, specifically – antioral bacteria, in the latter. The data regarding *H. pylori* eradication in RA are not strong enough at this point in order to issue a recommendation. Antibiotic therapy has yet to be assessed in RA patients treated with biologics.

Reactive arthritis

ReA is an inflammatory arthritis that typically develops 1–4 weeks following gastrointestinal or genitourinary bacterial infections. Various bacteria have been implicated in the cause of ReA, most notably, *Chlamydia trachomatis*, as well as *Salmonella*, *Shigella*, *Campylobacter* sp. and *Yersinia entrocolitica*. Approximately half of the individuals infected with ReA experience spontaneous resolution within 6 months while the other half continue to suffer from chronic symptoms.

On account of ReA being triggered by a preceding bacterial infection and as bacteria or bacterial products may be detected in patients joints by various techniques, the utilization of antibiotics in this entity is clear. The studies regarding antibiotic treatment for ReA are summarized in **Table 2**.

Acute ReA

The effect of a short course of antibiotic treatment in the acute phase of postenteric ReA was studied by Fryden *et al.* in 1990 [37]. In this randomized placebo-controlled study, 40 patients were assigned to a 10–14 day course of antibiotic treatment or placebo. Choice of antibiotic therapy was determined according to the suspected pathogen. No difference was noted between the groups at 18 months of follow-up.

Sieper *et al.* assessed the effect of ciprofloxacin administered for 3 months in 55 patients and showed a beneficial effect of ciprofloxacin over placebo in the subgroup who developed ReA postchlamydia infection [38]. A similar study was conducted by Yli-Kerttula *et al.* in 2000 [39]. A total of 62 patients with acute ReA received either ciprofloxacin (500 mg b.i.d.) or placebo for 3 months. After 1 year of follow-up, clinical and laboratory parameters improved to a similar extent in both groups. Interestingly, despite a similar outcome at 1 year, a significantly lower incidence of chronic arthritis was evident in patients originally allocated to treatment with ciprofloxacin after 4–7 years [40]. Early treatment with ciprofloxacin was also associated with a lower incidence of ankylosing spondylitis and anterior uveitis in the future.

The evidence that antibiotic treatment may improve outcome in ReA developing postchlamydia infection, gave rise to studies using specific antichlamydia antibiotics Putschky *et al.* for example, compared a long (100 mg b.i.d. for 4 months) with a short (100 mg b.i.d. for 10 days) course of doxycycline in the acute phase of postchlamydia ReA [41]. Surprisingly, clinical and laboratory outcome were no different among the two groups. Contrary to expectations, a favorable trend for a better clinical response was discerned in the short course antibiotic group. The unfavorable outcome of long term antibiotic treatment is supported by studies showing persistence of chlamydia in affected joints after such treatment [42].

Table 2. Antibiotic use in reactive arthritis.

Author (year)	Antibiotic	Patient population	Study design	Patients (n)	Duration of therapy	Follow-up period	Outcome	Ref.
Fryden *et al.* (1990)	According to the suspected pathogen	Acute post-enteric ReA	Multicenter randomized, placebo-controlled	40	10–14 days	18 months	No clinical or laboratory improvement	[37]
Sieper *et al.* (1999)	Ciprofloxacin 500 mg b.i.d.	Acute ReA	Double-blinded, randomized, placebo-controlled	55	3 months	1 year	A mild clinical improvement only in postchlamydia	[38]
Yli-Kerttula *et al.* (2000)	Ciprofloxacin 500 mg b.i.d.	Acute ReA	Double-blinded, randomized, placebo-controlled	62	3 months	1 year	Both groups improved the same	[39]
Yli-Kerttula *et al.* (2003)	Ciprofloxacin 500 mg b.i.d.	Acute ReA	Double-blinded, randomized, placebo-controlled	53	3 months	4–7 years	Significantly less chronic arthritis in the study group	[40]
Putschky *et al.* (2006)	Doxycycline 100 mg b.i.d.	Acute postchlamydia ReA	Double-blinded, randomized placebo-controlled	32	10 days versus 4 months	4 months	No difference between the two groups	[41]
Kvien *et al.* (2004)	Azithromycin 1 g once weekly	Acute ReA	Double-blinded, randomized, placebo-controlled	152	3 months	6 months	No clinical or laboratory improvement	[43]
Smieja *et al.* (2001)	Doxycycline 100 mg b.i.d.	Chronic ReA	Double-blinded, randomized, placebo-controlled	37	3 months	3 months	No clinical improvement	[44]
Carter *et al.* (2010)	Doxycycline 100 mg b.i.d. versus azithromycin 500 mg q.d. both on top of rifampin 300 mg q.d.	Post chlamydia chronic ReA	Double-blinded, randomized, placebo-controlled	42	6 months	9 months	A clinical and laboratory improvement in both treatment groups	[45]

b.i.d: Two times a day; q.d.: Once a day; ReA: Reactive arthritis.

A second study, using a different anti-chlamydia regiment – azithromycin – beginning in the acute phase of ReA was conducted by Kvien *et al.* In total, 152 patients with acute ReA (less than 2 months duration) received one dose of azithromycin followed by weekly azithromycin or placebo for 3 months. No differences in any clinical or laboratory parameters were observed after 24 weeks, although the postchlamydia ReA subgroup was not analyzed separately due to its small size [43].

Chronic ReA

The efficacy of doxycycline in chronic ReA was assessed by Smieja *et al.* in a double-blinded placebo-controlled study, in which 37 patients with ReA of more than 4 months duration, were treated with doxycycline (100 mg b.i.d.) or placebo. At 3 months follow-up, no differences were observed between the two treatment groups. Moreover, the subgroup with postchlamydia ReA (11 patients) did not show better results than the rest of the study population [44].

Carter *et al.* examined the effect of a long-term combined antibiotic treatment in chronic ReA post chlamydia infection [45]. In this double-blinded, triple placebo-controlled trial, 42 patients with chronic (at least 6 months) ReA were divided into three groups. The first group (12 patients) received long-term antibiotic treatment with doxycycline and rifampin, the second group received azithromycin and rifampin (15 patients) and the third group received placebo. Treatment was given for 6 months and assessments were performed at 9 months. Clinical and laboratory markers significantly improved in both treatment groups compared with the placebo group, suggesting that long-term combined antibiotic treatment may have a role in treating chronic ReA due to chlamydia infection. The difference between these two small, but well-conducted, trials may be due

to the addition of rifampin in the second trial. More large-scale randomized controlled trials are needed for further recommendations.

■ Summary of antibiotic therapy in ReA

Somewhat unpredictably, antibiotics seem to have a limited and, in certain instances, even a counterproductive role in ReA despite the recognized infectious trigger of the disease. Aversion of chronic disease, especially in HLAB27-positive patients, was noted in only a single study in which ciprofloxacin therapy was instituted in acute ReA. However, other studies have mostly shown a neutral effect on the acute and chronic course of the disease, whereas in chlamydia-induced ReA, early use of antibiotics was associated with persistent disease. Until larger scale studies become available, it may be prudent to withhold antibiotics in ReA.

Systemic vasculitis

The systemic vasculitides are characterized by inflammation of blood vessels occurring in a variety of organ systems. Although the pathophysiology and etiology of these diseases has not been fully elucidated, bacterial infections have been recognized in both the induction and reactivation of some of these disorders. 'Granulomatosis with polyangitis' (GPA, Wegener's granulomatosis) is a small–medium vessel sized vasculitis associated with PR3-antineutrophil cytoplasmic antibodies manifested by granulomatous inflammation in the upper and lower airways as well as necrotizing glomerulonephritis. Stegeman *et al.* described the association between chronic nasal carriage of *S. aureus* and a relapse of GPA in their cohort of 57 patients with GPA followed for a median of three years. A total of 63% of the patients had chronic nasal carriage of *S. aureus*, which was found to be an independent risk factor for relapse (adjusted relative risk: 7.16; 95% CI: 1.63–31.50) [46]. The association between GPA, nasal carriage of *S. aureus* and disease relapse was confirmed by others [47,48]. Presumably, colonization with *S. aureus* induces the production of low-grade proinflamatory cytokines that prime neutrophil/monocytes for antineutrophil cytoplasmic antibodies-induced activation, or alternatively, a superantigen from the bacteria stimulates autoreactive lymphocytes [49].

The evidence that chronic bacterial infection may play a role in the pathogenesis of GPA prompted several trials which aimed to study the effect of antibiotic treatment on the clinical course of the disease. DeRemee *et al.* was first to demonstrate an improved clinical outcome in 11 patients with GPA who received trimethoprim/sulfamethoxazole (TMP-SMX) [50]. This observation led to a number of case reports and case series that reported a possible beneficial effect of TMP-SMX in patients with GPA with or without cytotoxic treatment [51–53]. The impression from the sum of these reports was that TMP-SMX may be beneficial in patients with chronic nasal carriage of *S. aureus* and a limited disease. Noncarriers of *S. aureus*, as well as those with a more generalized disease, tended not to achieve remission or to relapse often on this treatment [54]. However, to date, no randomized control trial studying the effect of TMP-SMX in acute GPA has been conducted.

Conversely, the effect of maintenance prophylactic treatment with TMP-SMX on relapses in GPA was assessed in several controlled trials. Stegeman *et al.*, conducted a double-blinded, placebo-controlled, multicenter trial, in order to assess the efficacy of TMP-SMX on the number of relapses in patients with GPA in remission [55]. In total, 81 patients were randomly assigned to receive TMP-SMX (800 mg of SMX and 160 mg of TMP) or placebo twice daily for 24 months, on top of their usual medications. After 24 months, 82% of the study patients were in remission as compared with 60% of the controls (relative risk: 0.4; 95% CI: 0.17–0.98). Disease involving the upper airways was the most prominently reduced (10 vs 32.5% in the study and control groups, respectively). Notwithstanding, nausea and anorexia led to discontinuation of therapy in 20% of the patients. The protective effect of TMP-SMX was ascribed to the elimination of *S. aureus* from the upper airways although no actual data on carriage post-therapy was presented. A reduction in respiratory and nonrespiratory infections among the study group possibly attenuates potential triggers for relapse. The utility of TMP-SMX in maintaining remission in patients with GPA was assessed by Zycinska *et al.* [56]. In a prospective, double-blinded, placebo-controlled study, 31 patients with GPA in remission were assigned to TMP-SMX (800 mg of SMX and 160 mg of TMP, twice daily) or placebo. At the end of 18 months follow-up, 75% of the study group was in remission versus 55% of the control group (hazard ratio: 0.8;

95% CI: 0.21–1.2). TMP-SMX treatment was an independent predictor of disease-free interval (0.4; 95% CI: 0.12–0.69), whereas *S. aureus* chronic nasal carriage was an independent risk factor for disease relapse (6.15; 95% CI: 2.15–33.2).

The beneficial effect of TMP-SMX in GPA, hitherto delineated, was questioned by de Groot *et al.* [57,58]. In their first study, the efficacy of TMP-SMX (800 mg of SMX and 160 mg of TMP, twice daily) compared with MTX, in maintaining remission in 65 patients with GPA, was assessed. MTX alone maintained remission in 86% of the patients versus 58% with TMP-SMX ($p < 0.05$). Importantly, all of the patients relapsed when low-dose prednisone was added to TMP-SMX. In the second study, TMP-SMX was shown to be effective in inducing remission when given to patients in the initial phase of GPA (58% success rate), but was ineffective in maintaining remission in patients with generalized GPA (42% relapse rate versus 29% in the untreated group).

Antibiotics in systemic vasculitis

Studies conducted on antibiotic use in systemic vasculitis have centered on the role of TMP-SMX in GPA. Taken together it seems that TMP-SMX is effective in inducing and maintaining remission in GPA, more so in mild and limited disease, possibly through elimination of chronic *S. aureus* nasal carriage.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder, characterized by antibodies to platelets, resulting in thrombocytopenia. Generally this disorder is highly responsive to steroids, Rho(D) immunoglobulin or intravenous immunoglobulin. Some cases are refractory, requiring more extreme therapeutic measures such as splenectomy or chronic steroid treatment. As indicated by its name, the cause for ITP is unknown. Gasbarrini *et al.* were first to report a possible association between ITP and *H. pylori*, a bacteria that has been implicated in gastritis and peptic disease [59]. In their report, *H. pylori* was identified by '^{13}C urea breath test' in 11 patients with ITP. Eradication of the bacteria employing amoxicillin (1000 mg b.i.d.), clarithromycin (250 mg three times a day) and pentoprazole (40 mg once daily) led to resolution of the ITP in eight cases (73%) as well as to higher platelets counts after 4 months. As mentioned previously, it was speculated that the association between *H. pylori* and ITP may be a product of the immunologic response to the bacteria resulting in the release of cytokines and autoantibodies. In a prospective open study conducted in 2001, *H. pylori* was found by ^{13}C urea breath test in 43.3% (13/30) ITP patients that were assessed [60]. Eradication was successful in 12 of the 13 patients, after which complete response was noted in four patients and partial response in two more. The only patient that failed eradication remained with low platelet counts. The favorable outcome was achieved over 8 months of follow-up. In contrast to these favorable results, other prospective open studies failed to demonstrate a beneficial effect of eradication of *H. pylori* in patients with ITP [61,62]. To our knowledge, the only randomized control trial was carried out in Japan in 2004 by Suzuki *et al.* [63]. In this randomized controlled trial, 25 patients with chronic ITP on no current treatment and with a positive breath test for *H. pylori*, were randomly assigned to eradication therapy versus observation. In total, 46% (six/13) of the study group increased their platelet counts at 6 months follow-up, while no change was noted among the control group. After 6 months, the control group received eradication therapy yielding a 30% response (four/12) exemplified by elevation of platelet counts. There was no difference in clinical characteristics or *H. pylori* virulence factors between the responders and nonresponders. In 2007, Franchini *et al.* published a meta-analysis on the effect of *H. pylori* eradication in chronic ITP [64]. Data on 788 ITP patients was collected from 17 studies (16 with a prospective cohort design and one randomized trial). A statistically significant difference in the increase in platelet count was documented in patients in whom *H. pylori* eradication was successful compared with controls: 40.77 platelets (95% CI: 20.92–60.63) compared with untreated patients; 52.16 platelets (95% CI: 34.26–70.05) compared with patients who failed eradication and 46.35 platelets (95% CI: 27.79–64.91) compared with *H. pylori*-negative patients. Moreover, in the meta-regression model, the success of *H. pylori* eradication was highly significant as an explanatory variable for platelet count increase. Not surprisingly, the beneficial effect of *H. pylori* eradication was only demonstrated in patients with chronic ITP that were found to be positive for *H. pylori*. As

demonstrated by Arnold *et al.* in their systemic review, *H. pylori* eradication therapy was found to be of little benefit for *H. pylori*-negative patients with chronic ITP [65].

Summary of antibiotic therapy in ITP

An increased association of *H. pylori* carriage has been noted in numerous autoimmune diseases suggesting a causal, if yet unproved, relationship. Based on the meta-analysis cited, provision of antibiotic therapy to *H. pylori*-positive patients with chronic ITP should be routinely initiated prior to more expensive and more immune-suppressive therapy.

Antiphospholipid antibody syndrome

The classic antiphosphlipid antibody syndrome (APS) is characterized by the presence of antiphospholipid antibodies acting mainly through B2GP1, recurrent fetal losses and thromboembolic events. 'Catastrophic APS' is an unusual and life-threatening manifestation of the APS defined by Asherson *et al.* in 1992 [66]. The syndrome is characterized by the rapid development of multiple blood clots in several organs; most commonly the heart, lungs, nervous system and kidneys. An association between APS and infections was documented by Cervera *et al.* who described 100 cases of APS that were preceded by an infection, typically pneumonia, cellulitis, urinary tract infections and HIV [67]. Others have described an association of APS with *Streptococcus* spp. *M. pneumonia*, *Coxiella burnetti* and *Mycobacterium leprae* [67]. The association between catastrophic APS and infection is even more remarkable as Asherson *et al.* had documented that 24% of cases of catastrophic APS develop in these clinical situations [68]. The proposed mechanisms by which infection induces APS include molecular mimicry between the pathogen and the B2GP1 molecule, polyclonal activation of lymphocytes and stimulation of cytokines by proteins of the infectious agent [69]. Blank *et al.* showed that infecting mice with various agents including *Haemophilus influenza, Neisseria gonorrhea* and *Tetanus toxoid* produce a hexapeptide which is in turn recognized by a pathogenic anti-B2GP1 antibody. The induction of this hexapeptide leads to clinical and laboratory manifestations of APS in association with elevated titers of anti-B2GP1 [70].

Cicconi *et al.* described a 33 year old woman with APS in which eradication of *H. pylori* resulted in the disappearance of antiphospholipid antibodies with improvement of all clinical signs and symptoms [71].

Summary of antibiotic therapy in APS

Despite the evidence that links infections to APS, data proving the efficacy of antibiotic treatment in these acute situations are lacking. Notwithstanding, due to the severity of the clinical situation, it is our common practice to administer antibiotic therapy to all patients with catastrophic APS, even when an infectious cause is obscure.

Undifferentiated connective tissue disease

Undifferentiated connective tissue disease (UCTD) is an autoimmune disease with symptoms/signs of connective tissue disease, and the presence of one or more positive autoimmune disease tests, but with insufficient criteria to make a definitive diagnosis. Moskowitz *et al.* studied the effect of a 12-week course of clarithromycin in seven patients suffering from UCTD [72]. In this open label study, clinical improvement was noted in six of the seven patients at the end of the treatment course.

When this limited amount of data are taken together with the recognition that UCTD is a mixed entity which tends to develop over time into an established disease, and as antibiotic therapy has shown a limited benefit in most autoimmune disease entities, we see no role for therapeutic antibiotics in UCTD at this point.

Conclusion

The potential beneficial role of antibiotics in the treatment of autoimmune diseases is based on two main premises. The first is the assumption that eradication of an infectious process, which may both initiate and propagate autoimmunity, will curtail an ongoing stimulus and lead to disease amelioration. Second, several antibiotics have shown to have inherent anti-inflammatory properties, and as such were utilized as a DMARD. In some instances, as in the case of RA, antibiotics were assessed in small, but well-designed trials showing substantial effects in early and mild disease. Given the newly recognized importance of periodontal disease in RA as well as the cost of the newer biologic and nonbiologic DMARDS, we suggest a revival of minocycline, macrolide and quinolone use in early and mild RA, as well as in cases where

periodontal disease is evident. Finer tuning of these recommendations deserves larger scale clinical studies. Similarly, the recommendation for TMP-SMX therapy in GPA is well founded and is the mainstay of treatment in mild disease. A less recognized association that is highlighted in the present review is the beneficial effect of *H. pylori* eradication in chronic ITP, which is consolidated by a meta-analysis. One should consider testing for *H. pylori* carriage in all such patients, most definitely before immunosuppressive agents are added and splenectomy is performed. As for catastrophic APS, despite the lack of published cases on the role of antibiotics in this clinical scenario, we believe that the evidence pointing to an infectious process in the initiation of this calamity is reason enough to institute prompt antibiotic therapy in all cases.

Future perspective

Controlled trials studying the effect of antibiotics in autoimmune diseases are needed.

Trials should be conducted in life-threatening diseases for which effective therapies are lacking and which have not yet been intensively investigated, such as catastrophic APS, acute and chronic GPA, and chronic ITP.

Controlled trials to establish the efficacy of antibiotics in the treatment of RA, in which a bacterial culprit has been identified (i.e., periodontitis), and in which uncontrolled studies in early disease have shown promise, should be performed.

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