29 Influence of Antibacterial Drugs on Immune and Inflammatory Systems

Martina Bosnar, Vesna Eraković Haber, and Garry G. Graham

29.1 Introduction

Interference of ANTIBACTERIAL AGENTS with immune and inflammatory systems, and the possible clinical implications, has long been a focus of attention worldwide. In particular, toxic effects with immunological implications (neutropenia, ALLERGY, INFLAMMATION, etc.) influence the development and clinical use of these drugs. However, favourable effects are also very important. Possible effects of ANTIBACTERIAL AGENTS on immune and inflammatory systems are shown in Table 29.1 and in sections on individual ANTIBACTERIAL AGENTS.

ANTIBACTERIAL AGENTS may interact favourably with immune and inflammatory systems in three ways:

- ANTIBACTERIAL AGENTS stop the growth of, or kill, microorganisms which have initiated an acute excessive and/or chronic immunological or inflammatory state.
- ANTIBACTERIAL AGENTS may modify the actions of antibacterial host cells (MONOCYTES, NEUTROPHILS, etc.), which, together with the ANTIBACTERIAL AGENTS, combine to stop the growth of, or kill, the invading bacteria.
- ANTIBACTERIAL AGENTS may directly affect immune and inflammatory systems and modulate the inflammatory response or correct an immune dysfunction without direct effects on bacteria.

This chapter is concerned mainly with the third possibility with the particular aim of describing ANTIBACTERIAL AGENTS which are or may possibly be useful in the treatment of non-bacteriological immune or inflammatory diseases.

Several classes of ANTIBACTERIAL AGENTS may have activities within the third possibility, most importantly sulphones (dapsone), macrolides, rifampicin, tetracyclines and their analogues. This chapter places emphasis on the basic pharmacology and clinical uses of these four drug groups in isolation from their mechanisms in causing bacteriostatic or bactericidal actions. Actions of other ANTIBACTERIAL AGENTS with less clear non-antibacterial effects are discussed in lesser detail.

The pharmacological effects of the ANTIBACTERIAL AGENTS have been studied widely both in in vitro and in vivo experimental systems. The results of in vitro studies depend, however,

Final manuscript submitted on October 09, 2018.

M. Bosnar
In Vitro Pharmacology, Fidelta, Zagreb, Croatia
e-mail: martina.bosnar@glpg.com

V. Eraković Haber (✉)
Translational Research and Alliances, Fidelta, Zagreb, Croatia
e-mail: Vesna.ErakovicHaber@glpg.com

G. G. Graham (✉)
Department of Clinical Pharmacology, St Vincent's Hospital, Darlinghurst, NSW, Australia
e-mail: g.graham@unsw.edu.au

M. J. Parnham et al. (eds.), *Nijkamp and Parnham's Principles of Immunopharmacology*,
https://doi.org/10.1007/978-3-030-10811-3_29

on the cell type, the technique, the cell activation status, the composition of the media and the concentration of the drug. Table 29.1 shows possible pathophysiological functions and mediators which may be inhibited to produce IMMUNOMODULATION or ANTI-INFLAMMATORY effects of ANTIBACTERIAL AGENTS.

In analysing the effects of any drug in vitro, it is important to compare the effective concentrations with the unbound plasma concentrations produced by therapeutic dosage. There are, however, several reasons why these correlations are often imprecise.

- The effects of the drug may be competitive and therefore depend upon the concentration of the agonist or stimulant of the system.
- The drug may be taken up avidly, even covalently, by the cells used in in vitro incubations. Consequently, the inhibitory activity may decrease with increasing cell densities in the in vitro incubations, as was demonstrated with the gold drug, auranofin, which is bound strongly to NEUTROPHILS [1].

In vivo experimental studies are the gold standard, but are subject to multiple pitfalls, such as

Table 29.1 Possible modulation of immune and inflammatory processes by antibacterial agents

Inhibited function or mediator	Potential consequences	Main antibacterial agents
Respiratory burst/reactive oxygen species (ROS) (including hypochlorous acid)	Cell/tissue protection from ROS but oxidation to reactive metabolites to produce toxicity is possible	Aminoglycosides, dapsone, sulfapyridne, fluoroquinolones, isoniazid, macrolides, tetracyclines
Phagocytosis	Inhibited uptake of necrotic cell material but possible progress of inflammatory diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) (see Chap. 8)	Ciprofloxacin[a], dapsone, rifampicin
Expression and activity of nitric oxide synthase	Decreased inflammation	Moxifloxacin[a], rifampicin, tetracyclines, tigecycline
Matrix metalloproteinases	Decreased production of active forms of TGF-β and VEGF	Tetracyclines, CMT-3
Expression of cyclooxygenase (COX)/synthesis of prostaglandins	Antinociception and suppression of inflammation	Dapsone, fosfomycin, rifampicin, tetracyclines
Chemotaxis	Decreased access of neutrophils and other inflammatory cells to areas of inflammation	Aminoglycosides, dapsone, rifampicin
TNF	Suppressed inflammatory responses including lesser induction of COX and lipoxygenase enzymes	Dapsone, fluoroquinolones, fosfomycin, fusidic acid, rifampicin, tetracyclines
NF-κB and AP-1	Reduced induction of production of inflammatory cytokines	Ciprofloxacin, macrolides, tigecycline
IL-1	Inflammation decreased by multiple mechanisms	Beta-lactams, fluoroquinolones, fosfomycin, macrolides, tigecycline
IL-2	Decreased immune reactivity (see Chap. 25)	Fusidic acid, fluoroquinolones[a]
IL-6	Decreased acute phase reactants and decreased mobilisation of neutrophils into circulation and synovial fluid (see Chap. 34)	Ciprofloxacin, fosfomycin
IL-8	Decreased angiogenesis and chemotaxis, phagocytosis and respiratory burst of neutrophils	Fluoroquinolones[a], clarithromycin, tetracyclines
IL-10	Lessened downregulation of multiple mechanisms of inflammation including suppression of pro-inflammatory cytokines such as TNF and IL-1	Fluoroquinolones[a], fusidic acid

Note that inhibition of one factor typically leads to more general decreased activity of inflammatory pathways. Several possible immune and anti-inflammatory effects are also involved in their antibacterial actions

[a]Increased activity in some cases

species differences in the composition and functions of the IMMUNE SYSTEM [2], as well as ethical problems and interindividual variability in absorption, plasma concentrations, tissue distribution, metabolism and excretion. Furthermore, it is important to note that, within a particular group of ANTIBACTERIAL AGENTS, variable effects may be obtained. Thus, drugs within the one group of ANTIBACTERIAL AGENTS may have inconsistent pharmacological effects on mammalian systems. Despite these difficulties, major progress has been made in understanding the immune and ANTI-INFLAMMATORY effects of ANTIBACTERIAL AGENTS. Further, novel uses of these drugs and development of their analogues are potentially clinically important.

An early study suggested that the IMMUNOMODULATORY properties of ANTIBACTERIAL AGENTS could be predicted from their modes of action on microbial cells [3]. However, this hypothesis, in general, has not been confirmed.

There are two notable concerns with all ANTIBACTERIAL AGENTS, which may be used clinically for their non-antibacterial activities, possibly for long periods. The concerns are the possibilities of bacterial resistance and changes in gastrointestinal flora. In particular, many ANTIBACTERIAL AGENTS cause pseudomembranous colitis due to an overgrowth of *Clostridium difficile* in the colon. Symptoms range from mild diarrhoea to potentially life-threatening.

Some ANTIBACTERIAL AGENTS have been investigated in attempts to develop analogues which are not antibacterial but have retained their IMMUNOMODULATORY or ANTI-INFLAMMATORY actions. In particular, efforts have been made to synthesise macrolides and tetracyclines with ANTI-INFLAMMATORY actions without significant antibacterial actions (see sections on individual drug groups).

29.2 Aminoglycosides

Aminoglycosides interfere with bacterial protein synthesis by acting on the 30S ribosomal subunit. Although they are considered to be extracellular ANTIBACTERIAL AGENTS, they accumulate slowly in host cells (over days in MACROPHAGES) by fluid-phase pinocytosis.

The aminoglycosides are excreted unchanged to a very large extent, and, consequently, their dosage is reduced in renal impairment in line with their plasma concentrations.

Conflicting data exist on the in vitro inhibitory effect of aminoglycosides (at therapeutic concentrations) on the function of NEUTROPHILS. Inhibition of the respiratory burst is the most common observed effect [4, 5]. Suggested underlying mechanisms include binding to negatively charged membrane phospholipids (leading to membrane disturbances), specific binding to inositol biphosphate (resulting in phospholipase C inhibition) and protein kinase C (PKC) inhibition. Interstingly, amikacin at low concentrations (contrary to other aminoglycosides) enhances the respiratory burst of NEUTROPHILS *in vitro*,whereas supratherapeutic concentrations (> 1 g/l are inhibitory [5].

Most of the non-bacterial clinical interest in the aminoglycosides has been associated with their effects on congenital muscular dystrophic disease. Several trials on the use of aminoglycosides in cystic fibrosis have given encouraging results [6]. However, the need for pharmacokinetic monitoring to avoid toxicity may limit the possible use of aminoglycosides for long-term treatment of congenital muscular dystrophic disease or inflammatory diseases unless they are shown to be extremely beneficial.

29.3 Beta-Lactams

Five groups comprise the beta (β)-lactam, namely, penams (penicillins and β-lactamase inhibitors), penems (faropenem), carbapenems (imipenem, meropenem), cephems (cephalosporins, cephamycins, oxa- and carbacephems) and monobactams (aztreonam), all of which bind to various enzymes (penicillin-binding proteins) and the transpeptidase enzyme involved in the synthesis of PEPTIDOGLYCAN backbone which is normally responsible for the strength of bacterial cell walls.

Cefodizime, a cephalosporin, was the subject of worldwide interest in the 1990s and was referred to as an immune response modifier (IRM) antibiotic. Cefodizime showed a greater effect on Enterobacteriaceae infections than that expected from its in vitro antibacterial effects, even more so in immunocompromised animals [7]. Cefodizime demonstrates pleiotropic effects on immune and inflammatory parameters such as enhanced phagocyte function, B LYMPHOCYTE repressiveness and delayed HYPERSENSITIVITY and it may restore phagocytic activity and activity of NATURAL KILLER (NK) cells, as well as IL-1 and IFN-Y production, in immunocompromised patients and animals. Cefodizime also stimulates the proliferative response of LYMPHOCYTES, increases the phagocytic and bactericidal activity of NEUTROPHILS and downregulates the production of INFLAMMATORY CYTOKINES by stimulated MONOCYTES [7–9]. Another cephalosporin, cefaclor, is considered to "normalise" the immune and inflammatory systems during bacterial infections and may be useful in the clinical treatment of patients with immune disorders leading to chronic INFLAMMATION [10].

There is now little interest in the IRM activity of cefodizime, but further work on the non-antibacterial effects of cephalosporins and other beta-lactams on host cells is still required.

29.4 Fluoroquinolones

The fluoroquinolones are synthetic antibacterial drugs whose activity is due to their inhibition of bacterial TOPOISOMERASE II and thus on DNA replication. Mammalian cells also contain an TOPOISOMERASE II, but it is unclear if an interaction with the enzyme is responsible for any of the therapeutic or adverse effects of fluoroquinolones.

The best-known fluoroquinolone is ciprofloxacin (Fig. 29.1) which is eliminated by both excretion of the unchanged drug and metabolism. Its TERMINAL HALF-LIFE is approximately 4 h, and it is usually administered twice daily. Peak concentrations of unbound ciprofloxacin in plasma are approximately 1800 µg/L (5–6 µmol/L).

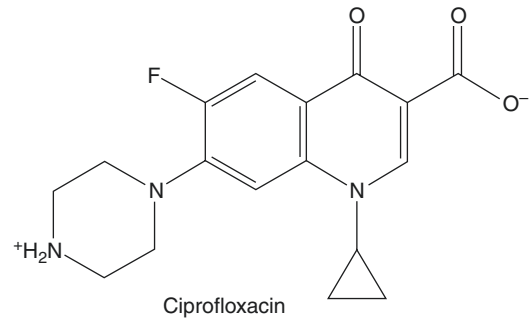


Fig. 29.1 Structure of ciprofloxacin in the unionised form. Like other fluoroquinolones, ciprofloxacin has both acidic (-COOH) and basic (amino group in the piperazine ring system). Consequently, the major species at physiological pH is the zwitterion with no net charge

To date, fluoroquinolones have not proven beneficial in inflammatory diseases. Interest in the potential immunostimulating properties of some fluoroquinolones is, however, growing. Ciprofloxacin, in combination with other drugs, such as pentoxifylline (a vasodilator), accelerates NEUTROPHIL recovery in breast cancer during or following chemotherapy [11].

29.4.1 Basic Immunomodulatory and Anti-inflammatory Pharmacology of Fluoroquinolones

It is difficult to categorise the in vitro pharmacological activities of the fluoroquinolones as they have a variety of effects (increase, decrease, no effect) on PHAGOCYTOSIS, adhesion, and respiratory burst of MONOCYTES and NEUTROPHILS. Their effects on the respiratory burst appear to depend on the animal species and the fluoroquinolone structure. High concentrations decrease levels of the INFLAMMATORY CYTOKINES which have been induced by TNF-α in human cell lines (Table 29.2).

Stimulation of some immune or inflammatory systems in vitro has been reported (Table 29.2). These effects are inconsistent with suppression of immune or inflammatory systems. However,

Table 29.2 Experimental pharmacological actions showing modulation of immune and inflammatory processes by fluoroquinolones

Pharmacological actions	References
In vitro	
Ciprofloxacin increases phagocytosis, intracellular killing, myeloperoxidase activity and malondialdehyde (a marker of lipid peroxidation) levels in neutrophils of healthy subjects and patients with allergic asthma	[52]
Ciprofloxacin increases the production of PGE_2 by monocytes but inhibits the production of IFN-γ and TNF-α after induction by advanced glycation end products (AGE-2 and AGE-3). Proliferation of induced monocytes is also inhibited	[53]
Ciprofloxacin increases the synthesis of IL-2 by PHA-stimulated human lymphocytes. By contrast, IL-1 and IFN-γ are inhibited but to a small degree	[54]
In a lung epithelial cell line, moxifloxacin inhibits the production of nitric oxide (NO) due to reduced expression of inducible NO synthase (iNOS). It also inhibits the expression of NF-κB	[55]
Moxifloxacin decreases TNF-α-induced levels of IL-6, IL-8, p65 factor-κB and phosphorylated ERK in a cystic fibrosis cell line to a much greater extent than ciprofloxacin	[56]
Ex vivo	
After 7 days treatment with ciprofloxacin, LPS-stimulated human monocytes in vitro produce more IL-1, IL-6 and TNF-α	[57]
In vivo	
Ciprofloxacin, trovafloxacin and tosufloxacin (100 mg/kg) diminish serum levels of tumour necrosis factor-α (TNF-α). Levofloxacin (100 mg/kg) does not affect the TNF-α level, whereas a lower dose (10 mg/kg) increases TNF-α level	[58]
Ciprofloxacin treatment decreases colonic inflammation in a model of colitis in mice. Also levels of IL-1β, IL-8, and TNF-α in colon homogenate are decreased	[59]
Ciprofloxacin treatment ameliorates changes in body weight, diarrhoea, colon length and histology in a colitis model. Also NF-κB and TNF-α expression in colon tissue is decreased	[60]

the potential value of fluoroquinolones as immune and ANTI-INFLAMMATORY agents is shown by increases in CYTOKINE responses in rats and mice in vivo (Table 29.2). The fluoroquinolones also decrease the severity of models of colitis in mice and rats where they probably have an ANTI-INFLAMMATORY effect in addition to their antibacterial actions. Further work on the IMMUNOMODULATORY and ANTI-INFLAMMATORY effects of this drug group is required.

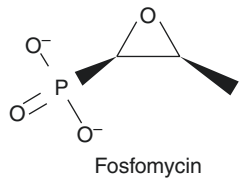
29.4.2 Adverse Reactions of Fluoroquinolones

The adverse effects of the fluoroquinolones present a problem for their potential clinical use as non-ANTIBACTERIAL AGENTS. Adverse effects include low incidences of colitis, liver failure, tendon rupture and cardiac arrhythmias, particularly in combination with other drugs which may prolong QT INTERVAL (e.g. some anti-arrhythmics, tricyclic antidepressants and antipsychotic drugs). The Food and Drug Administration of the USA (FDA) recommends that patients should be checked for low blood sugar and adverse mental effects such as disorientation, memory impairment and delirium.

29.5 Fosfomycin

Fosfomycin (1-*cis*-1,2-epoxypropylphosphoric acid) (Fig. 29.2) is a broad-spectrum bactericidal antibiotic which interferes with bacterial cell wall biosynthesis by inhibiting pyruvate-uridine-diphosphate-*N*-acetylglucosamine transferase.

Fosfomycin is a highly ionised compound at physiological pH values which, not surprisingly, enters bacterial cells by a transporter. The glycerol-3-phosphate transporter in bacteria but its transporter into mammalian cells has not been recorded. It is accumulated twofold by NEUTROPHILS. Its availability is about 50% and has a TERMINAL HALF-LIFE of approximately 10 h which is



Fosfomycin

Fig. 29.2 Structure of fosfomycin in the ionised form. Fosfomycin is a strong acid which is present as the anion at physiological pH values. It is available as its sodium and calcium salts and also a salt with an organic base

Table 29.3 Experimental pharmacological actions showing modulation of immune and inflammatory processes by fosfomycin

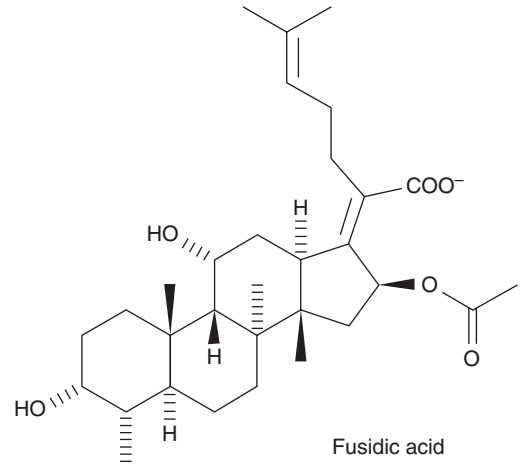
Pharmacological actions	References
In vitro	
Fosfomycin suppresses NF-κB activation in two human cell lines	[61]
Fosfomycin decreases the levels of IL-6 and TNF-α after the addition of LPS to human blood	[62]
In vivo	
In mice injected with LPS, fosfomycin significantly lowers peak serum levels of TNF-α and IL-1β	[63]
In a rat air pouch model, after carrageenan challenge, fosfomycin decreases the inflammation in the pouch tissues. Also the amounts of PGE_2, TNF-α as well as mRNA encoding COX-2 are reduced	[64]

extended in impairment of kidney function as it is excreted unchanged in urine.

Fosfomycin shows several potential immune and ANTI-INFLAMMATORY effects in in vitro and in vivo systems (Table 29.3). However, following the administration of bacterial LPS to human subjects, fosfomycin did not alter the levels of TNF-α, IL-1β or IL-6 proteins of mRNA [12]. Further work on the immune and ANTI-INFLAMMATORY effects of fosfomycin is required.

29.6 Fusidic Acid

Fusidic acid is a steroid derivative (Fig. 29.3) which is used mainly as an antistaphylococcal agent which interferes with bacterial biosynthesis of proteins. It has an oral BIOAVAILABILITY of about 50% and a TERMINAL HALF-LIFE of elimination of about 10 h after oral dosage.



Fusidic acid

Fig. 29.3 Structure of fusidic acid in the ionised form. Fusidic acid is carboxylic acid which is available as its sodium salt

Table 29.4 Experimental pharmacological actions showing modulation of immune and inflammatory processes by fusidic acid

Pharmacological actions	References
Fusidic acid reduces peak plasma values of TNF-α and increases the survival of neonatal mice and reduces plasma TNF-α in endotoxic shock	[65]
Fusidic acid protected mice from concanavalin-A (ConA)-induced hepatitis. This was accompanied by markedly diminished plasma levels of IL-2, IFN-γ and TNF-α but increased levels of IL-6	[66]
Fusidic acid is beneficial in the treatment of experimental autoimmune neuritis in rats (a model of Guillain-Barré syndrome). Serum levels of interferon-γ, IL-10 and TNF-α decreased	[67]
Fusidic acid reduces tissue oedema in rats after the local injection of formalin	[68]

Fusidic acid has several ANTI-INFLAMMATORY effects in mice and rats in vivo, particularly by decreasing the release of TNF (Table 29.4). These effects require further study.

29.7 Isoniazid

Isoniazid is an antituberculous agent whose antimycobacterial activity has been attributed to its oxidative metabolism by mycobacterial peroxidases. Isoniazid is an irreversible inhibitor of the

mammalian enzyme, MYELOPEROXIDASE [13, 14]. Isoniazid therefore decreases the formation of major products, hypochlorous, hypobromous and hypothiocyanous acids of the respiratory burst of NEUTROPHILS. These oxidants are antibacterial but may also cause tissue damage. Isoniazid has, however, not been tested for activity against purely inflammatory diseases in vivo.

29.8 Lincosamides

Clindamycin (Fig. 29.4) is a semisynthetic antibiotic derived from lincomycin, but clindamycin is now the more widely used drug of this group in modern medical practice. Both antibiotics interact with bacterial protein synthesis at the level of the 50S ribosomal subunit. The nucleoside transport system has been suggested to explain the cellular accumulation of clindamycin (12- to 20-fold). Clindamycin is eliminated by hepatic metabolism with a TERMINAL HALF-LIFE of 2–3 h. Orally, it is generally administered twice daily.

Clindamycin was presented as a possible IMMUNOMODULATORY DRUG in infection in the early 1980s. However, controversial effects on phagocyte functions (stimulation, inhibition or no action) have been reported with various techniques and drug concentrations. Interest in the ANTI-INFLAMMATORY effects of clindamycin was stimulated by its potential prophylactic effect in LPS-induced septic shock (see Chap. 26), through inhibition of PRO-INFLAMMATORY CYTOKINE release in vitro and in vivo [15]. Interestingly, modulation of CYTOKINE release in vitro is not accompanied by a parallel change in mRNA expression [16]. In dogs infected with *Babesia gibsoni*, a protozoal parasite which is rare in man, clindamycin does not eliminate the parasite but may stimulate humoral and immune responses to decrease the numbers of the infecting protozoa [17].

The relationship between the therapeutic plasma concentrations of clindamycin and its modulating effect on immunological processes is required for a better understanding of its potential non-antibacterial effects in clinical medicine.

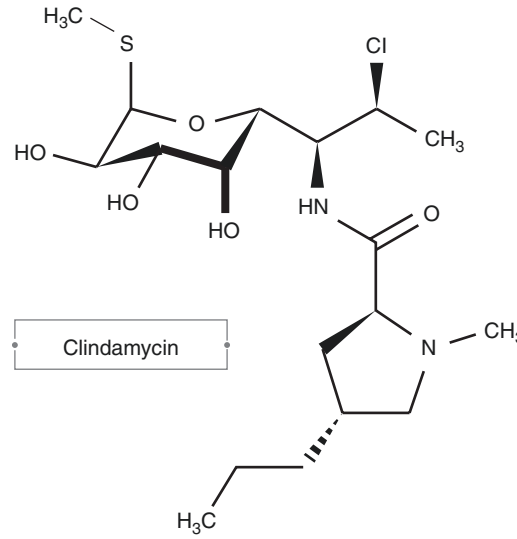


Fig. 29.4 Structure of unionised clindamycin. It is available mainly as the hydrochloride for oral and topical use, while the phosphate ester is included in solution for intravenous use

29.9 Macrolides

Macrolides are widely used antibacterial drugs, which impair bacterial protein synthesis by acting on the 50S bacterial ribosomal subunit. Erythromycin is the original antibiotic in this class.

29.9.1 Chemistry of Macrolides

Macrolide antibiotics have a 12- to 16-membered ring structure containing a lactone group (internal ester) with substitutions by 2 amino groups and/or neutral sugars (Fig. 29.5). Modern semi-synthetic derivatives of erythromycin, azithromycin, roxithromycin and clarithromycin have been obtained by adding new substituents or by introducing a nitrogen atom into the ring structure. These have antibacterial activity. Extensive derivatisation of the scaffold has also resulted in a number of non-ANTIBACTERIAL macrolides with IMMUNOMODULATORY/ANTI-INFLAMMATORY activities [18].

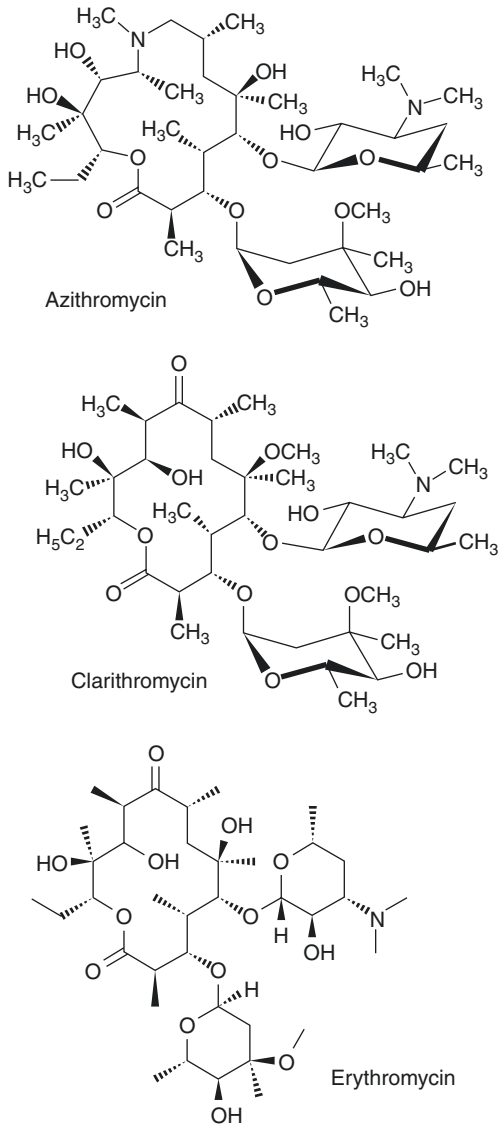


Fig. 29.5 Structures of macrolide antibiotics in the unionised forms. Erythromycin is available as the unionised form, a salt with stearic acid and an ester with ethyl succinic acid for oral dosage. It is also available as the lactobionate salt for intravenous infusion

29.9.2 Metabolism and Pharmacokinetics of Macrolides

The macrolides are eliminated primarily by metabolism. The TERMINAL HALF-LIVES are very much dependent upon the macrolide, ranging from approximately 1.6 h (erythromycin), 3.5 h (clarithromycin), 12 h (roxithromycin) to 40 h (azithromycin). The long TERMINAL HALF-LIFE of azithromycin makes it suitable for long-term dosage where it is often administered every second day. The macrolides are taken up by NEUTROPHILS and MACROPHAGES and concentrate, like other cationic drugs, in the lysosomes, making it difficult to compare concentrations in plasma with those in experiments in vitro (see Sect. 29.1). However, this leucocyte accumulation may act to deliver macrolides to sites of INFLAMMATION and infection.

Erythromycin is unstable in the stomach and is administered orally in two forms: either the base form in ENTERIC-COATED tablets or as the ester form with ethyl succinic acid. The latter form is hydrolysed after absorption from the gastrointestinal tract.

29.9.3 Basic Immune and Anti-inflammatory Pharmacology of Macrolides

The macrolides have several cellular effects both in vitro and in vivo (Table 29.5). These pleiotropic effects indicate that there are several cellular targets of their actions. Among the cellular mechanisms of action, inhibition of MAP kinase/ERK pathway and consequent suppression of transcription factor activation have been suggested. Furthermore, the pharmacological effects of the individual macrolides often vary between the various members of drug class. A non-antibacterial analogue of erythromycin (EM703) has potential ANTI-INFLAMMATORY actions which are indicated by its inhibition of the respiratory burst of NEUTROPHILS (Table 29.5).

29.9.4 Immune and Anti-inflammatory Clinical Effects of Macrolides

Macrolides display IMMUNOMODULATORY properties that may confer beneficial effects on patients with respiratory diseases associated with

Table 29.5 Experimental pharmacological actions showing modulation of immune and inflammatory processes by macrolides

Pharmacological actions	References
In vitro	
Clarithromycin suppresses LPS-induced IL-8 production by human monocytes and human epithelial cells through inhibition of AP-1 and NF-κB transcription factors	[69, 70]
Clarithromycin inhibits NF-κB activation in human mononuclear cells and pulmonary epithelial cells	[71]
Macrolides inhibit the release of a variety of inflammatory cytokines and chemokines in sputum cells isolated from steroid-naïve patients with chronic obstructive pulmonary disease (COPD)	[72]
Azithromycin attenuates LPS-induced production and expression of pro-inflammatory cytokines in alveolar macrophages through inhibition of AP-1	[73]
Azithromycin inhibits specifically the production of pro-inflammatory cytokines IL-1α and IL-1β by human monocytes after stimulation by LPS. There is no inhibition of several other cytokines. Inhibition of the inflammasome/IL-1β axis indicates potential activity in ASTHMA (see Chap. 9)	[74]
The non-antibacterial analogue of erythromycin (EM703) suppresses the production of superoxide by human neutrophils after stimulation by LPS or fMLP	[75]

chronic INFLAMMATION. The macrolides attenuate inflammatory responses in the lung, regulate mucus production and decrease bronchial responsiveness. Panbronchiolitis and cystic fibrosis are the two main clinical indications for macrolide action, but their use in other respiratory diseases is being investigated. Most clinical research has been centred on azithromycin.

29.9.4.1 Diffuse Panbronchiolitis

Diffuse panbronchiolitis is a potentially fatal disease which is an inflammatory disease of bronchioles. It is found most commonly in patients of Asian descent. Erythromycin or azithromycin is recommended widely for the treatment of diffuse panbronchiolitis, with azithromycin favoured because of its long TERMINAL HALF-LIFE. Dosage is once daily to once every 2 or 3 days [19, 20].

29.9.4.2 Cystic Fibrosis (CF)

There is fair evidence for the long-term use of azithromycin in the treatment of cystic fibrosis in patients with and without infection with *Pseudomonas aeruginosa* [19–22]. However, the EFFICACY often decreases markedly after treatment for 1 year with no significant effect after treatment for 3 years. Nevertheless, azithromycin is recommended by the Cystic Fibrosis Foundation for patients who are more than 6 years old [23]. Non-cystic fibrosis bronchiectasis is also treated usefully by azithromycin [23].

29.9.4.3 Asthma

A recent conclusion is that macrolides do not have significant activity in the treatment of acute or chronic ASTHMA [24, 25], although, possible benefits of macrolides in patients with non-eosinophilic ASTHMA was noted in two studies [26]. This finding requires further study.

29.9.4.4 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a major chronic disease. Azithromycin decreases the frequency of acute exacerbations even in patients with optimal treatment with bronchodilators [23] (see also Chap. 23).

29.9.4.5 Bronchiolitis Obliterans Syndrome (BOS)

BOS is major problem after lung transplantation. Some, but not all patients, respond with an improvement in FEV1 during treatment with azithromycin (250 mg every second day) [27, 28].

29.9.5 Adverse Effects of Macrolides

The macrolides are generally well tolerated although gastrointestinal adverse effects, such as discomfort, nausea, etc., are well known and often lead to cessation of their use. The cardiovascular effects of the macrolides are of considerable interest. Prolongation of the QT

INTERVAL is of concern, but patients' underlying cardiac pathophysiology makes it difficult to make definite conclusions about cardiac adverse effects [23]. Nevertheless, they should be taken with care by patients with a history of arrhythmias or taking antiarrhythmic drugs. Because of their antibiotic activities, overgrowth with *Clostridium difficile* is possible, and patients with severe diarrhoea should be examined carefully.

29.10 Rifampicin and Related Drugs

Rifampicin (rifampin) is a member of the ansamycin group of macrocyclic antibiotics. Rifampicin is a major antibiotic for the treatment of tuberculosis, while rifaximin is used for INFLAMMATORY BOWEL DISEASES and travellers' diarrhoea which is not due to species of *Campylobacter*, *Salmonella* or *Shigella*. Rifampicin and the related antibiotics bind to the DNA-dependent RNA polymerase and, thereby, inhibit RNA synthesis and bacterial proliferation.

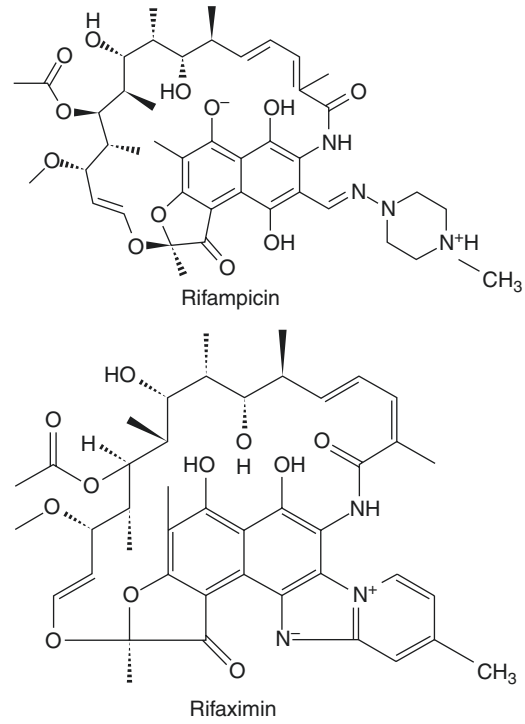


Fig. 29.6 Structures of rifampicin (upper) and rifaximin (lower) in the ZWITTERION forms at physiological pH values. Several ZWITTERION forms of rifaximin may exist and one such form is shown

29.10.1 Chemistry of Rifampicin and Analogues

Rifampicin and rifaximin are ZWITTERIONS at physiological pH values (Fig. 29.6). Several crystal forms of rifaximin exist. These have different absorption characteristics after oral administration (see below).

29.10.2 Metabolism and Pharmacokinetics of Rifampicin and Analogues

Rifampicin and rifaximin are incompletely absorbed after oral dosage, in part, due to their ionised ZWITTERION structures (Fig. 29.6). The absorption of rifaximin is reduced further due its slow dissolution. The alpha-crystalline form is less soluble than that of other crystalline forms, and, in order to achieve maximal availability in the colon, the alpha form is probably the optimal form for the treatment of ulcerative colitis [29]. The TERMINAL HALF-LIFE of rifampicin is approximately 4 h.

29.10.3 Basic Immune and Anti-inflammatory Pharmacology of Rifampicin and Analogues

Rifampicin has potential ANTI-INFLAMMATORY and immunological effects because of its activity in several cellular systems in vitro (Table 29.6). Some effects, such as inhibition of chemotaxis and PHAGOCYTOSIS, are produced in vitro at therapeutic unbound concentrations in plasma. However, several other effects are produced well above therapeutic concentrations in plasma (Table 29.6), and, consequently, some of their clinical relevance is often discounted but cannot be rejected totally at this stage.

Table 29.6 Experimental pharmacological actions showing modulation of immune and inflammatory processes by rifampicin and analogues

Pharmacological effects	References
Effects on inflammatory cells—in vitro	
Therapeutic concentrations of rifampicin decrease chemotaxis of neutrophils	[76]
Supratherapeutic concentrations of rifampicin inhibit production of TNF-α and IL-1β while enhancing IL-6 and IL-10 secretion	[77]
Rifampicin inhibits zymosan phagocytosis and TNF-α production with partial effects at therapeutic concentrations	[78]
Rifampicin and related antibiotics inhibit proliferation of mononuclear cells induced by phytohaemagglutinin, concanavalin A and bacterial superantigen toxic shock syndrome toxin 1	[79]
Supratherapeutic concentrations of rifampicin inhibit both TNF-α and PMA-induced NF-κB activation in Jurkat T cells	[80]
Effects on non-inflammatory cells—in vitro	
Supratherapeutic concentrations of rifampicin inhibit IL-1β-stimulated arachidonic acid release and prostaglandin E2 (PGE_2) production in an alveolar epithelial cell line	[81]
Supratherapeutic concentrations of rifampicin augment cytokine-induced iNOS and consequently NO production in an alveolar cell line	[82]
Rifampicin enhances iNOS expression and production of NO and IL-8 as well as synthesis of IL-1β, IL-8 and IFN-γ-induced protein-10 in HepG2 liver epithelial cells	[83]

The ability of rifampicin to increase the serum levels of IL-10 (Table 29.6) indicates a potential mechanism increased immunosuppressant or ANTI-INFLAMMATORY effects as this CYTOKINE is considered to have ANTI-INFLAMMATORY actions by several mechanisms including the suppression of LPS-induced secretion of PRO-INFLAMMATORY CYTOKINES.

Apart from its direct antibacterial activity, several mechanisms have been suggested for the ANTI-INFLAMMATORY or immunosuppressive actions of rifaximin on the gastrointestinal tract (Table 29.6) [30, 31]. An important mode of action of rifampicin and rifaximin is the activation of pregnane X receptor, which is a nuclear receptor and transcription factor that regulates INFLAMMATION (Table 29.6) [31].

29.10.4 Immune and Anti-inflammatory Clinical Effects of Rifampicin and Analogues

29.10.4.1 Rheumatoid Arthritis

The first trials of rifampicin in early disease showed a possible improvement in RHEUMATOID ARTHRITIS, but later studies showed no improvement [32–34]. Intraarticular injection of rifampicin has been tested but did not improve response to intraarticular CORTICOSTEROID alone [35]. Further studies have not been considered worthwhile because of adverse effects, doubtful clinical effects and weak effects in vitro. The improved modern treatments of RHEUMATOID ARTHRITIS with METHOTREXATE and BIOLOGICALS also have decreased interest in the possible anti-antirheumatic actions of rifampicin (see Chap. 34).

29.10.4.2 Crohn's Disease and Ulcerative Colitis

Rifaximin is beneficial in the treatment of CROHN'S DISEASE and ulcerative colitis although possibly not as effective as other drugs [30, 31, 36] (see Chap. 35). Rifaximin may, however, be useful in combination with other drugs.

29.10.5 Adverse Effects of Rifampicin and Analogues

Liver dysfunction may be produced by rifampicin and should be checked routinely. The severe syndrome drug reaction with eosinophilia and systemic symptom (DRESS) has also been reported.

29.10.6 Drug Interactions of Rifampicin and Analogues

Rifampicin and rifaximin induce the metabolism of drugs by cytochrome P450 3A4 and several cytochrome P450 Cs and transport by P-glycoprotein [37]. The result is that the plasma concentrations of many other drugs are greatly reduced by concurrent dosage with rifampicin and rifaximin. It is strongly advised to check for interactions with any drugs that are taken with rifampicin or rifaximin. Induction of the metabolism of dapsone has been reported (see Sect. 29.11 below).

29.11 Sulphones/Sulphonamides

The major sulphone drug is dapsone (4,4′ diaminophenyl sulphone) (Fig. 29.7) which was initially developed as an antitubercular drug. It was tested in leprosy in the early 1950s and is still a part of drug combinations used in this disease. Apart from its use in leprosy, dapsone is administered orally for several cutaneous diseases, particularly dermatitis herpetiformis [38]. Dapsone is also applied locally for the treatment of acne vulgaris because of its antibacterial and ANTI-INFLAMMATORY actions.

The immunosuppressive and ANTI-INFLAMMATORY activities of two groups, sulphones and sulphonamides, are discussed together in this section because of their similar basic and clinical pharmacological properties. SULFAPYRIDNE is no longer used as an antibacterial agent, but it is still of research and clinical interest as it is the major metabolite of SULFASALAZINE, a widely used drug for RHEUMATOID ARTHRITIS and ulcerative colitis (Fig. 29.7) (see Chap. 34).

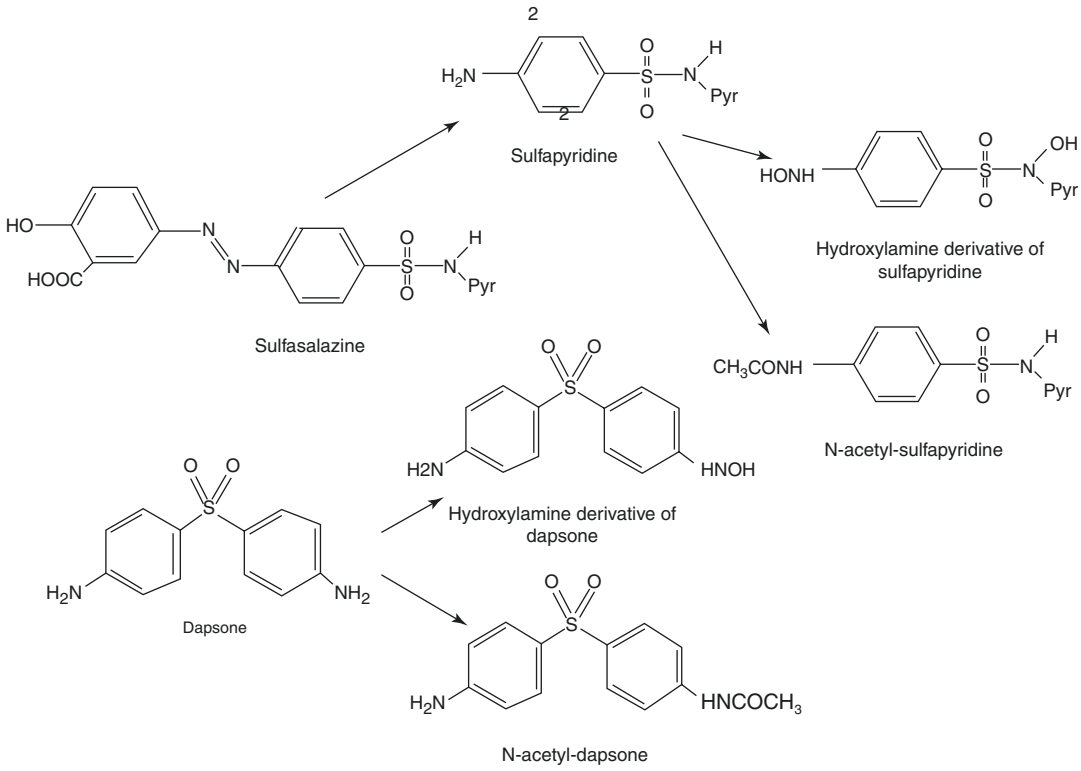


Fig. 29.7 Structures and metabolism of dapsone and sulfapyridine. Sulfapyridine is a metabolite of sulfasalazine. Both dapsone and sulfapyridine are metabolised to reactive hydroxylamine derivatives and also by acetylation, as shown

29.11.1 Metabolism and Pharmacokinetics of Dapsone and Sulfapyridine

The TERMINAL HALF-LIFE OF ELIMINATION of dapsone is about 30 h but is very variable. As a result, dapsone is usually administered once daily, sometimes twice daily. Dapsone is an amino compound which is both acetylated and also oxidised by cytochrome P450 enzymes. Resulting from its two major modes of elimination, the half-life is longer in genetic slow acetylators, while its oxidative metabolism is induced by rifampicin with which it may be administered. SULFAPYRIDNE has a half-life of approximately 14 h in slow acetylators but about 6 h in fast acetylators.

29.11.2 Basic Immune and Anti-inflammatory Pharmacology of Dapsone and Sulphonamides

The antibacterial activities of dapsone and the sulphonamides are due to inhibition of dihydropteroate synthase.

The ANTI-INFLAMMATORY activity of dapsone is indicated by several in vitro and in vivo findings (Table 29.7). The activity of dapsone in rats with implants of carrageenan and cotton pellets is notable because inhibition of INFLAMMATION caused by these treatments is characteristic of the (aspirin-like) non-steroidal ANTI-INFLAMMATORY drugs (see Chap. 33).

There is considerable interest in the ANTI-INFLAMMATORY pharmacology of sulphonamides because the well-known drug, SULFASALAZINE, is metabolised to aminosalicylate and SULFAPYRIDNE (see Chap. 34). Both metabolites are active in the treatment of RHEUMATOID ARTHRITIS, but only the parent, SULFASALAZINE, is used clinically [39]. Like dapsone, SULFAPYRIDNE is active in the treatment of neutrophilic diseases [38]. In particular, SULFAPYRIDNE and dapsone are active in many patients with ocular cicatricial pemphigoid [40].

The antirheumatic activity of SULFAPYRIDNE and some other sulphonamides is backed up by limited experimental pharmacology (Table 29.8). Like dapsone, sulfamethizole decreases the INFLAMMATION caused by carrageenan and cotton pellets (Table 29.8). SULFAPYRIDNE reacts readily with (scavenges) hydroxyl radicals which can be derived from superoxide which is formed in turn from superoxide from the oxidative burst of NEUTROPHILS and MONOCYTES (Table 29.8). Hydroxyl radicals react readily with

Table 29.7 Experimental pharmacological actions showing modulation of immune and inflammatory processes by dapsone

Pharmacological actions	References
In vitro	
In neutrophils, dapsone inhibits myeloperoxidase	[84, 85]
Dapsone inhibits the production of prostaglandin D_2 by rat mast cells	[86]
In vivo	
Dapsone shows anti-inflammatory activity in carrageenan and cotton pellet tests in rats	[87]
Normalisation of mucociliary transport by dapsone after intratracheal administration of LPS to ferrets	[88]
Improved neurological function by dapsone together with increases in the amount of spared tissue after spinal cord injury in rats by inhibiting apoptosis	[89]

Table 29.8 Experimental pharmacological actions showing modulation of immune and inflammatory processess by sulphonamides

Pharmacological actions	References
In vitro	
Sulfapyridne inhibits myeloperoxidase[a]	[85]
Sulfapyridne reacts readily with hydroxyl radical and other free radicals	[90, 91]
Sulfapyridne inhibits ROS of neutrophils after stimulation by receptor, fMLP and calcium ionophore	[92]
40% reduction in mRNA for TNF-α and 50% increase in mRNA for tissue inhibitor of metalloproteinase in rheumatoid synovial fibroblasts	[93]
In vivo	
Sulfamethizole decreases the inflammation caused by carrageenan and cotton pellets.[a] Other sulphonamides, sulphadiazine and sulphanilamide inactive	[87]

[a]Activity also shown by dapsone

biological molecules, and it is doubtful that scavenging could lead to a selective action of SULFAPYRIDNE.

29.11.3 Adverse Effects of Dapsone and Sulfapyridine

The major adverse effects of dapsone and SULFAPYRIDNE are haemolysis and methemoglobinuria. AGRANULOYTOSIS and skin rashes also occur but are uncommon. The adverse effects of both drugs are probably derived from reactive metabolites, particularly the hydroxylamine derivatives which may be cytotoxic [41] (Fig. 29.7). These are formed by oxidation of the amino groups of both dapsone and SULFAPYRIDNE, by MYELOPEROXIDASE and cytochrome P450 enzymes. Alternatively, the reactive metabolites could induce the production of antibodies that could cause the destruction of NEUTROPHIL precursors. In skin, the target cells may be keratinocytes which subsequently activate DENDRITIC CELLS and initiate an immune response within the skin [42].

29.12 Tetracyclines and Related Drugs

The tetracyclines are a group of widely used broad-spectrum antibiotics including minocycline, doxycycline and an individual antibiotic which is termed tetracycline. The tetracyclines interfere with bacterial protein synthesis, by acting on the 30S ribosomal subunit. The tetracyclines have multiple ANTI-INFLAMMATORY and IMMUNOMODULATORY effects which may make them useful in several chronic non-antibacterial diseases.

The tetracycline molecule has been chemically modified in multiple ways, generating second series of semisynthetic tetracyclines (e.g. doxycycline and minocycline) which have both antibiotic and ANTI-INFLAMMATORY properties. A new family of compounds called chemically modified tetracyclines (CMTs) lack antimicrobial activity but have retained some ANTI-INFLAMMATORY actions.

29.12.1 Chemistry of Tetracyclines

The tetracyclines are organic bases with p*K*a values of about 8 and are, therefore, largely present as the cationic (ionised forms) in blood. They are usually administered as their hydrochloride salts (Fig. 29.8). Many chemical analogues of the tetracyclines have been synthesised. The best known is CMT-3 which is a neutral unionised compound (Fig. 29.8).

29.12.2 Metabolism and Pharmacokinetics of Tetracyclines

The tetracyclines are well absorbed and have similar ranges of TERMINAL HALF-LIVES but different modes of elimination (Table 29.9). The dosage of tetracycline and doxycycline should be reduced in renal impairment because of their significant renal excretion. CMT-3 has a long TERMINAL HALF-LIFE (about 57 h) which allows dosage every day or every second day [43].

The tetracyclines are taken up by NEUTROPHILS by saturable, sodium-dependent transport [44]. The observed cellular/extracellular concentration ratios are greater than 60 for minocycline and >7 for doxycycline.

29.12.3 Basic Immune and Anti-inflammatory Pharmacology of Tetracyclines

There are two aspects of the activity of tetracyclines in pharmacological systems in vitro: inhibition of the respiratory burst and suppression of the release of INFLAMMATORY MEDIATORS by NEUTROPHILS. Many reports show the inhibitory action of tetracyclines on various phagocyte functions in vitro (Table 29.10). The production of REACTIVE OXYGEN SPECIES is apparently reduced, but the underlying mechanisms may include chelation of Ca^{2+} or Mg^{2+} or Zn^{2+} and scavenging of reactive products of the respiratory burst of NEUTROPHILS. These chelating actions make

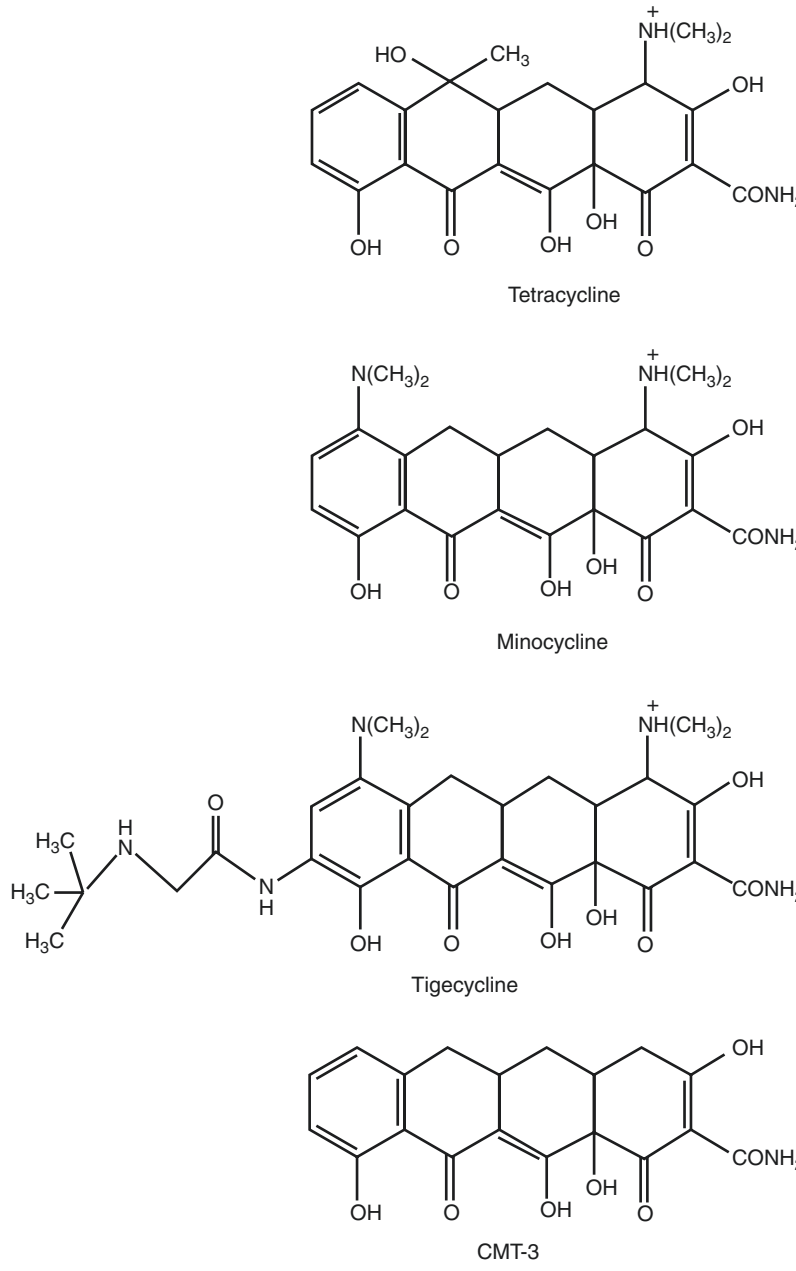


Fig. 29.8 Structures of tetracycline, minocycline and tigecycline in their ionised forms. CMT-3 is a non-antibacterial analogue which is not ionisable

Table 29.9 Pharmacokinetic properties and urinary excretion of tetracyclines

	Tetracycline	Doxycycline	Minocycline
Terminal half-life (h)	6–12	18–22	11–22
% Excretion unchanged in urine	60	40	10

Table 29.10 Experimental pharmacological actions showing modulation of immune and inflammatory processes by tetracyclines

Pharmacological actions	References
In vitro	
Tetracyclines inhibit the respiratory burst (including the production of hypochlorous acid) by neutrophils	[48, 49, 94]
Tetracyclines inhibit matrix metalloproteinases, particularly metalloproteinase-8 through binding to zinc or calcium	[48, 49, 94]
Doxycycline reduces the production of IL-8 and TNF-α by a human mast cell line	[50]
Tetracyclines decrease expression of iNOS by J774 macrophage cell line	[95]
Several proteins (including vimentin and heat shock protein 60) are downregulated by LPS in J774 cells	[95]
Minocycline inhibits collagenase derived from rat gingiva	[94]
Minocycline inhibits the synthesis of prostaglandin E2 and NO due to downregulation of COX-2 and iNOS	[96]
IgE production by PMBCs from with asthma patients is reduced when the cells were co-cultured with IL-4 and CD40 in the presence of minocycline or doxycycline	[97]
CMT-3 inhibits metalloproteinases and human leukocyte elastase by direct inhibition of the enzymes and by decreasing the breakdown of endogenous inhibitors of these enzymes (α_1-proteinase inhibitor and tissue inhibitors of matrix metalloproteinases)	[43]
In vivo	
Doxycycline and minocycline produce antinociception resulting from pain produced by the injection of formalin into the hind paw of the mouse, the carrageenan-induced oedema of the rat paw and leukocyte migration into the mice peritoneal cavity	[98]
CMT-3 prevents respiratory distress syndrome in pigs after the induction of sepsis and ischaemia/reperfusion injury	[99]
Oxytetracycline treatment inhibits influx of inflammatory cells, goblet-cell hyperplasia and concentrations of soluble inflammatory mediators in ovalbumin-induced asthma model in mice	[100]
Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease	[101]
CMT-3 decreases brain concentration of TNF-α and activation of microglia after administration of LPS to mice	[102]

it very difficult to correlate therapeutic plasma concentrations with the concentrations in the in vitro experiments. Furthermore, tetracyclines are oxidisable by hypochlorous acid, potentially making the inhibition dependent upon the molecular ratio of concentrations of tetracycline to the yield of hypochlorous acid.

The tetracyclines inhibit metalloproteinases, particularly the matrix metalloproteinases which breakdown several INFLAMMATORY CYTOKINES and many proteins in the intracellular matrix. Matrix metalloproteinases also convert several factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), into their active forms. Overall, inhibition of matrix metalloproteinases may be responsible for much of the ANTI-INFLAMMATORY activity of tetracyclines.

The anti-oxidative actions of the tetracyclines indicate their potential use in the treatment of inflammatory states. Tetracyclines also inhibit several inflammatory diseases in mice and other experimental animals [10]. Treatment of these experimental conditions is consistent with their value in several chronic diseases in people.

29.12.4 Immune and Anti-inflammatory Clinical Effects of Tetracyclines

The tetracyclines have been tested in several inflammatory disease states, while CMT-3 may have activity in Kaposi's sarcoma but not in other sarcomas.

29.12.4.1 Rheumatoid Arthritis

Minocycline and doxycycline relieve the symptoms of RHEUMATOID ARTHRITIS with a better response seen in early-onset seropositive disease. A meta-analysis of ten studies indicates the activity of tetracyclines [45]. Two studies lasted 48 weeks but showed no significant reduction in erosions or joint space narrowing. Treatment of this disease by these tetracyclines is uncommon. Furthermore, alternative antirheumatic drugs are available (see Chap. 34), and it is unlikely that the tetracyclines will achieve widespread use in RHEUMATOID ARTHRITIS.

29.12.4.2 Osteoarthritis

Osteoarthritis may have an inflammatory component. Doxycycline slows the progression of osteoarthritis to a small degree, but there is no reduction in pain or disability [46, 47]. However, some patients may respond to a greater degree than others.

29.12.4.3 Dermatological Diseases

The tetracyclines are useful in treating inflammatory lesions of rosacea and acne such as erythema, papules, pustules and blepharitis but not sebaceous changes that do not appear to be inflammatory [48, 49]. Doses of doxycycline that are low (typically 20 mg twice daily) and considered insufficient for antibacterial activity appear active in the treatment of rosacea and acne. Several other uncommon dermatological diseases have also responded to tetracyclines. These include blistering disorders, chronic wounds (inability of wounds to heal) and GRANULOCYTE disorders (including sarcoidosis) [48, 49].

29.12.4.4 Periodontal Disease

Low-dose doxycycline is approved for treatment of periodontitis (pyorrhoea), a disease in which there is excessive INFLAMMATION due to bacteria adhering to the teeth [48].

29.12.4.5 Asthma

Minocycline lessens symptoms of ASTHMA and allows reduction in the dose of CORTICOSTEROIDS [50] (see also Chap. 23). Serum concentrations of IMMUNOGLOBULIN E decrease during treatment with minocycline without effects on immunoglobulins A, G and M.

29.12.5 Adverse Effects of Tetracyclines

The use of tetracyclines has been limited because of concerns about the development of resistant organisms resulting from their antibiotic activity. This is not a problem with the nonantibiotic CMTs which appear to have lesser adverse effects although a small proportion of patients have developed a lupus-like syndrome.

A variety of adverse effects have been associated with treatment by tetracyclines:

- Continued therapy for more than 2 years is associated with hyperpigmentation of skin and nails in 10–20% of patients and may take a year to resolve.
- Up to age of about 8 years, the tetracyclines may cause discolouration of teeth and hypoplasia of dental enamel, and their use should be avoided.
- Tetracyclines cause discolouration of babies' teeth following administration in the second half of pregnancy, and their use should be avoided at this time.
- Tetracyclines may depress prothrombin activity, and the dosage of warfarin should be decreased accordingly.
- Capsules of tetracyclines have caused ulceration of the oesophagus due to their retention in the oesophagus. They should be taken with milk or food to prevent this.
- The tetracyclines may cause supersensitivity to ultraviolet light (excessive sunburn). This adverse effect is also seen with some CMTs.
- Minocycline is associated with autoimmune reactions, a lupus-like syndrome and hepatitis, which are not shown by other tetracyclines. This tetracycline is metabolised by hepatic cytochrome P450 systems and the NEUTROPHIL enzyme, MYELOPEROXIDASE, to reactive products which may cause adverse effects specific to minocycline [51]. Appropriate monitoring is therefore indicated in patients early in polyarthritis when diagnostic uncertainty may still exist.

29.12.6 Drug Interactions of Tetracyclines

- The absorption of tetracyclines is reduced by complexation with iron salts and by both calcium and bismuth antacids. The combinations should be avoided. Alternatively, a 3 h delay between the administration of the tetracycline and the interacting compounds should decrease the extent of the interactions.
- The EFFICACY of oral anticoagulants (warfarin) may be increased, and oral contraceptives may become ineffective, both interactions occurring because of changes in the gut flora due to the antibiotic activities of the tetracyclines.

29.13 Tigecycline

Tigecycline is the first clinically available drug in a new class of antibiotics termed the glycylcyclines. Structurally, it is tetracycline with a central four-ring carbocyclic skeleton and is closely related to minocycline (Fig. 29.8).

Tigecycline has actions both in vitro and in vivo which indicate modulation of immunological and inflammatory processes. Both inhibition and activation have been reported (Table 29.11). As yet, tigecycline has not been tested for immunological or inflammatory diseases in people.

29.14 Conclusions and Future Research

It is now widely acknowledged that in addition to their antibacterial activity, several ANTIBACTERIAL AGENTS display IMMUNOMODULATORY and ANTI-INFLAMMATORY properties with potential therapeutic importance. Modulation of immune functions is presently a major focus of attention, particularly in inflammatory diseases and cancer. In particular, sulphones (dapsone), tetracyclines, macrolides and rifampicin and their analogues show inhibitory activity towards several initiators of the inflammatory cascade, as well as to mediators of tissue damage. However, lengthy administration and absence of selectivity of these antimicrobial immunomodulators can lead to the induction of microbial resistance. As a result, intensive research is ongoing, to identify IMMUNOMODULATORY antibiotic derivatives which are devoid of antibacterial activity, most notably with tetracycline and macrolide derivatives.

Finally, recent discoveries related to the role that MICROBIOTA plays, both in health and disease, may shed new light on possible ways in which ANTIBACTERIAL AGENTS can influence numerous pathological conditions.

Acknowledgement This is an update of the chapter from the third edition, written by Marie-Therese Labro, who died in 2016.

Table 29.11 Experimental pharmacological actions showing modulation of immune and inflammatory processes by tigecycline

Pharmacological actions	References
In vitro	
In a murine model of *Mycoplasma pneumoniae* pneumonia, tigecycline treatment has a modest microbiological effect, but it significantly decreases histological evidence of lung inflammation and reduces pulmonary cytokines and chemokines	[103]
Tigecycline has no influence on cytokine production by LPS—triggered human blood	[104]
Tigecycline prevents LPS-induced release of pro-inflammatory and mediators of apoptosis, NF-κB, TNF-α, IL-1β and NO, in neuronal cells	[105]
In the therapeutic concentration range, tigecycline potentiates the pro-inflammatory functions of human neutrophils in vitro by acting as a calcium ionophore	[106]
In vivo	
Tigecycline decreases hypotension but not inflammatory cytokines in pigs after infusion of endotoxin. This is a sterile model of sepsis	[107]

Selected Readings

Garrido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169(2):337–52.

Parnham MJ, Haber Erakovic V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014;143(2):225–45.

Rothstein DM. Rifamycins, alone and in combination. Cold Spring Harbor Perspect Med. 2016;6(7):a027011.

References

1. Rudkowski R, Ziegler JB, Graham GG, Champion GD. Auranofin inhibits the activation pathways of polymorphonuclear leukocytes at multiple sites. Biochem Pharmacol. 1991;41:1921–9.
2. Haley P. Species differences in the structure and function of the immune system. Toxicology. 2003;188:49–71.
3. Thong YH. Immunomodulation by antimicrobial drugs. Med Hypotheses. 1982;8:361–70.
4. Umeki S. Action of gentamycin through inhibitory effect on neutrophil NADPH oxidase activity. Comp Biochem Physiol B Biochem Mol Biol. 1995;110(4):817–21.
5. Gressier B, Brunet C, Dine T, Luyckx M, Ballester L, Cazin M, et al. In vitro activity of aminoglycosides on the respiratory burst response in human polymorphonuclear neutrophils. Methods Find Exp Clin Pharmacol. 1998;20(10):19–24.
6. Sermet-Gaudelus I, Renouil M, Fajac A, Bidou L, Parbaille B, Pierrot S, et al. In vitro prediction of stop-codon suppression by intravenous gentamicin in patients with cystic fibrosis: a pilot study. BMC Med. 2007;5:5.
7. Labro MT. Cefodizime as a biological response modifier: a review of its in-vivo, ex-vivo and in-vitro immunomodulatory properties. J Antimicrob Chemother. 1990;26(Suppl C):37–47.
8. Meloni F, Ballabio P, Bianchi L, Grassi FA, Gialdroni Grassi GG. Cefodizime modulates in vitro tumor necrosis factor-alpha, interleukin-6 and interleukin-8 release from human peripheral monocytes. Chemotherapy. 1995;41(4):289–95.
9. Fietta A, Bersani C, Bertoletti R, Grassi F, Grassi G. In vitro and ex vivo enhancement of nonspecific phagocytosis by cefodizime. Chemotherapy. 1988;34(5):430–6.
10. Dabrowski MP, Stankiewicz W. Desirable and undesirable immunotropic effects of antibiotics: immunomodulating properties of cefaclor. J Chemother. 2001;13(6):615–20.
11. Bensinger WI, Buckner CD, Lilleby K, Holmberg L, Storb R, Slattery JT. Dose escalation of busulfan with pentoxifylline and ciprofloxacin in patients with breast cancer undergoing autologous transplants. Oncology. 2004;67(5–6):368–75.
12. Sauermann R, Marsik C, Steiner I, Seir K, Cvitko T, Zeitlinger M, et al. Immunomodulatory effects of fosfomycin in experimental human endotoxemia. Antimicrob Agents Chemother. 2007;51(5):1879–81.
13. Hassan HM, Guo H, Yousef BA, Guerram M, Hamdi AM, Zhang L, et al. Role of inflammatory and oxidative Stress, cytochrome P450 2E1, and bile acid disturbance in rat liver Injury induced by Isoniazid and lipopolysaccharide cotreatment. Antimicrob Agents Chemother. 2016;60(9):5265–93.
14. Maiocchi SL, Morris JC, Rees MD, Thomas SR. Regulation of the nitric oxide oxidase activity of myeloperoxidase by pharmacological agents. Biochem Pharmacol. 2017;135(1):90–115.
15. Hirata N, Hiramatsu K, Kishi K, Yamasaki T, Ichimiya T, Nasu M. Pretreatment of mice with clindamycin improves survival of endotoxic shock by modulating the release of inflammatory cytokines. Antimicrob Agents Chemother. 2001;45(9):2638–42.
16. Nakano T, Hiramatsu K, Kishi K, Hirata N, Kadota J, Nasu M. Clindamycin modulates inflammatory-cytokine induction in lipopolysaccharide-stimulated mouse peritoneal macrophages. Antimicrob Agents Chemother. 2003;47(1):363–7.
17. Wulansari R, Wijaya A, Ano H, Horii Y, Makimura S. Lymphocyte subsets and specific IgG antibody levels in clindamycin-treated and untreated dogs experimentally infected with Babesia gibsoni. J Vet Med Sci. 2003;65:579–84.
18. Haber VE, Bosnar M, Kragol G. The design of novel classes of macrolides for neutrophil-dominated inflammatory diseases. Future Med Chem. 2014;6:657–74.
19. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. J Antimicrob Chemother. 2004;54:21–8.
20. Li H, Zhou Y, Fan F, Zhang Y, Li X, Yu H, et al. Effect of azithromycin on patients with diffuse panbronchiolitis: retrospective study of 51 cases. Intern Med. 2011;50(16):1663–9.
21. Southern KW, Barker PM. Azithromycin for cystic fibrosis. Eur Respir J. 2004;24:834–8.
22. Saiman L. The use of macrolide antibiotics in patients with cystic fibrosis. Curr Opin Pulmon Med. 2004;10:515–23.
23. Cramer CL, Patterson A, Alchakaki A, Soubani AO. Immunomodulatory indications of azithromycin in respiratory disease: a concise review for the clinician. Postgrad Med. 2017;129(5):493–9.
24. Johnston SL, Szigeti M, Cross M, Brightling C, Chaudhuri R, Harrison T, et al. Azithromycin for acute exacerbations of asthma: the AZALEA randomized clinical trial. JAMA Intern Med. 2016;176(11):1630–7.
25. Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, Gibson PG. Macrolides for chronic asthma. Cochrane Data Sys Rev. 2005;(4):CD002997.

26. Kew KM, Undela K, Kotortsi I, Ferrara G. Macrolides for chronic asthma. Cochrane Data Sys Rev. 2015;(9):CD002997.
27. Hayes D. A review of bronchiolitis obliterans syndrome and therapeutic strategies. J Cardiothorac Surg. 2011;6:92.
28. Corris PA, Ryan VA, Small T, Lordan J, Fisher AJ, Meachery G, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. Thorax. 2015;70(5):442–50.
29. Blandizzi C, Viscomi G, Marzo A, Scarpignato C. Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers. Pharmacol Res. 2014;85(1): 39–44.
30. DuPont HL. Therapeutic effects and mechanisms of action of rifaximin in gastrointestinal diseases. Mayo Clin Proc. 2015;90(8):1116–24.
31. Sartor RB. Review article: The potential mechanisms of action of rifaximin in the management of inflammatory bowel diseases. Aliment Pharmacol Ther. 2016;43(Suppl 1):27–36.
32. McConkey B, Situnayake RD. Effects of rifampicin with and without isoniazid in rheumatoid arthritis. J Rheumatol. 1988;15(1):46–50.
33. Cox NL, Prowse MV, Maddison MC, Maddison PJ. Treatment of early rheumatoid arthritis with rifampicin. Ann Rheum Dis. 1992;51(1):32–4.
34. Borg AA, Davis MJ, Fowler PD, Shadforth MF, Dawes PT. Rifampicin in early rheumatoid arthritis. Scand J Rheumatol. 1993;22(1):39–42.
35. Blyth T, Stirling A, Coote J, Land D, Hunter JA. Injection of the rheumatoid knee: does intra-articular methotrexate or rifampicin add to the benefits of triamcinolone hexacetonide? Br J Rheumatol. 1998;37(7):770–2.
36. Guslandi M, Giollo P, Testoni PA. Corticosteroid-sparing effect of rifaximin, a nonabsorbable oral antibiotic, in active ulcerative colitis: preliminary clinical experience. Curr Ther Res. 2004;65(3):292–6.
37. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet. 2003;42(9):819–50.
38. Dallegri F, Ottonello L, Bevilacqua M. Possible modes of action of nimesulide in controlling neutrophilic inflammation. Arzneimittelforschung. 1995;45(10):1114–7.
39. Neumann VC, Taggart AJ, Le Gallez P, Astbury C, Hill J, Bird HA. A study to determine the active moiety of sulphasalazine in rheumatoid arthritis. J Rheumatol. 1986;13(2):285–7.
40. Elder MJ, Leonard J, Dart JKG. Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. Br J Ophthalmol. 1996;80:549–52.
41. Uetrecht J. Drug metabolism by leukocytes and its role in drug-induced lupus and other idiosyncratic drug reactions. Crit Rev Toxicol. 1990;20(4): 213–35.
42. Khan FD, Vyas PM, Gaspari AA, Svensson CK. Effect of arylhydroxylamine metabolites of sulfamethoxazole and dapsone on stress signal expression in human keratinocytes. J Pharmacol Exp Ther. 2007;323:771–7.
43. Gu Y, Lee HM, Simon SR, Golub LM. Chemically modified tetracycline-3 (CMT-3): a novel inhibitor of the serine proteinase, elastase. Pharmacol Res. 2011;64(6):595–601.
44. Walters JD. Characterization of minocycline transport by human neutrophils. J Periodontol. 2006;77:1964–8.
45. Stone M, Fortin PR, Pacheco-Tena C, Inman RD. Should tetracycline treatment be usedmore extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. J Rheumatol. 2003;30(10):2112–22.
46. Snijders GF, van den Ende CH, van Riel PL, van den Hoogen FH, den Broeder AA. The effects of doxycycline on reducing symptoms in knee osteoarthritis: results from a triple-blinded randomised controlled trial. Ann Rheum Dis. 2011;70(7):1191.
47. da Costa BR, Nësch E, Reichenbach S, Juni P, Rutjes AWS. Doxycycline for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2012;(11):CD007323.
48. Korting HC, Schöllmann C. Tetracycline actions relevant to rosacea treatment. Skin Pharmacol Physiol. 2009;22(6):287–94.
49. Monk E, Shalita A, Siegel DM. Clinical applications of non-antimicrobial tetracyclines in dermatology. Pharmacol Res. 2011;63(2):130–45.
50. Joks R, Durkin HG. Non-antibiotic properties of tetracyclines as anti-allergy and asthma drugs. Pharmacol Res. 2011;64(6):602–9.
51. Mannargudi B, McNally D, Reynolds W, Uetrecht J. Bioactivation of minocycline to reactive intermediates by myeloperoxidase, horse peroxidase, and hepatic microsomes: implications for minocycline-induced lupus and hepatitis. Drug Metab Dispos. 2009;37(9):1806–18.
52. Rayaman P, Rayaman E, Cevikbas A, Demirtunc R, Sehirli AO, Alagoz SG, et al. Effect of antibiotics on polymorphonuclear leukocyte functions and myeloperoxidase activity, glutathione and malondialdehyde levels in allergic asthma. Polish J Microbiol. 2015;64(1):69–72.
53. Mori S, Takahashi HK, Liu K, Wake H, Zhang J, Liu T, et al. Ciprofloxacin inhibits advanced glycation end products-induced adhesion molecule expression on human monocytes. Br J Pharmacol. 2010;161:229–40.
54. Riesbeck K, Forsgren A. Selective enhancement of synthesis of interleukin-2 in lymphocytes in the presence of ciprofloxacin. Eur J Clin Microbiol Infect Dis. 1990;9:409–13.
55. Werber S, Shalit I, Fabian I, Steuer G, Weiss T, Blau H. Moxifloxacin inhibits cytokine-induced MAP kinase and NF-kB activation as well as nitric oxide synthesis in a human respiratory epithelial cell line. J Antimicrob Chemother. 2005;55:293–300.

56. Blau H, Klein K, Shalit I, Halperin D, Fabian I. Moxifloxacin but not ciprofloxacin or azithromycin selectively inhibits IL-8, IL-6, ERK1/2, JNK, and NF-kappaB activation in a cystic fibrosis epithelial cell line. Am J Physiol Lung Cell Mol Physiol. 2007;292(1):L343–52.
57. Bailly S, Fay M, Ferrua B, Gougerot-Pocidalo MA. Ciprofloxacin treatment in vivo increases the ex vivo capacity of lipopolysaccharide-stimulated human monocytes to produce IL-1, IL-6 and tumour necrosis factor-alpha. Clin Exp Immunol. 1991;85:331–4.
58. Ogino H, Fujii M, Ono M, Maezawa K, Hori S, Kizu J. In vivo and in vitro effects of fluoroquinolones on lipopolysaccharide-induced pro-inflammatory cytokine production. J Infect Chemother. 2009;15(3):166–73.
59. Lahat G, Halperin D, Barazovsky E, Shalit I, Rabau M, Klausner J, et al. Immunomodulatory effects of ciprofloxacin in TNBS-induced colitis in mice. Inflamm Bowel Dis. 2007;13(5):557–65.
60. Toklu HZ, Kabasakal L, Imeryuz N, Kan B, Celikel C, Cetinel S, et al. A study comparing the efficacy of antimicrobial agents versus enzyme (P-gp) inducers in the treatment of 2,4,6 trinitrobenzenesulfonic acid-induced colitis in rats. J Physiol Pharmacol. 2013;64:439–51.
61. Yoneshima Y, Ichiyama T, Ayukawa H, Matsubara T, Furukawa S. Fosfomycin inhibits NF-kappaB activation in U-937 and Jurkat cells. Int J Antimicrob Agents. 2003;21(6):589–92.
62. Zeitlinger M, Marsik C, Steiner I, Sauermann R, Seir K, Jilma B, et al. Immunomodulatory effects of fosfomycin in an endotoxin model in human blood. J Antimicrob Chemother. 2007;59(2):219–23.
63. Matsumoto T, Tateda K, Miyazaki S, Furuya N, Ohno A, Ishii Y, et al. Fosfomycin alters lipopolysaccharide-induced inflammatory cytokine production in mice. Antimicrob Agents Chemother. 1999;43(3):697–8.
64. Morikawa K, Nonaka M, Torii I, Morikawa S. Modulatory effect of fosfomycin on acute inflammation in the rat air pouch model. Int J Antimicrob Agents. 2003;21(4):334–9.
65. Genovese F, Mancuso G, Cuzzola M, Cusumano V, Nicoletti F, Bendtzen K, et al. Improved survival and antagonistic effect of sodium fusidate on tumor necrosis factor alpha in a neonatal mouse model of endotoxin shock. Antimicrob Agents Chemother. 1996;40:1733–5.
66. Nicoletti F, Beltrami B, Raschi E, Di Marco R, Magro G, Grasso S, et al. Protection from concanavalin A (Con A)-induced T cell-dependent hepatic lesions and modulation of cytokine release in mice by sodium fusidate. Clin Exp Immunol. 1997;110(3):479–84.
67. Di Marco R, Khademi M, Wallstrom E, Muhallab S, Nicoletti F, Olsson T. Amelioration of experimental allergic neuritis by sodium fusidate (fusidin): suppression of IFN-gamma and TNF-alpha and enhancement of IL-10. J Autoimmun. 1999;13(2):187–95.
68. Kilic FS, Erol K, Batu O, Yildirim E, Usluer G. The effects of fusidic acid on the inflammatory response in rats. Pharmacol Res. 2002;45(4):265–7.
69. Kikuchi T, Hagiwara K, Honda Y, Gomi K, Kobayashi T, Takahashi H, et al. Clarithromycin suppresses lipopolysaccharide-induced interleukin-8 production by human monocytes through AP-1 and NF-kappa B transcription factors. J Antimicrob Chemother. 2002;45(5):745–55.
70. Abe S, Nakamura H, Inoue S, Takeda H, Saito H, Kato S, et al. Interleukin-8 gene repression by clarithromycin is mediated by the activator protein-1 binding site in human bronchial epithelial cells. Am J Respir Cell Mol Biol. 2000;22(1):51–60.
71. Ichiyama T, Nishikawa M, Yoshitomi T, Hasegawa S, Matsubara T, Hayashi T, et al. Clarithromycin inhibits NF-kB activation in human peripheral blood mononuclear cells and pulmonary epithelial cells. Antimicrob Agents Chemother. 2001;45(1):44–7.
72. Marjanović N, Bosnar M, Michielin F, Willé DR, Anić-Milić T, OgnjenČulić O, et al. Macrolide antibiotics broadly and distinctively inhibit cytokine and chemokine production by COPD sputum cells in vitro. Pharmacol Res. 2011;63(5):389–97.
73. Bosnar M, Snježana Čužić S, Bošnjak B, Nujić K, Ergović G, Marjanović N, et al. Azithromycin inhibits macrophage interleukin-1β production through inhibition of activator protein-1 in lipopolysaccharide-induced murine pulmonary neutrophilia. Int Immunopharmacol. 2011;11:424–34.
74. Gualdoni GA, Lingscheid T, Schmetterer KG, Hennig A, Steinberger P, Zlabinger GJ. Azithromycin inhibits IL-1 secretion and non-canonical inflammasome activation. Sci Rep. 2015;5:12016.
75. Nozoe K, Aida Y, Fukuda T, Sanui T, Nishimura F. Mechanisms of the macrolide-induced inhibition of superoxide generation by neutrophils. Inflammation. 2016;39(3):1039–48.
76. Gray GD, Smith CW, Hollers JC, Chenoweth DE, Fiegel VD, Nelson RD. Rifampin affects polymorphonuclear leukocyte interactions with bacterial and synthetic chemotaxins but not interactions with serum-derived chemotaxins. Antimicrob Agents Chemother. 1983;24:777–83.
77. Ziglam HM, Daniels I, Finch RG. Immunomodulating activity of rifampicin. J Chemother. 2004;16(4):357–61.
78. Mlambo G, Sigola LB. Rifampicin and dexamethasone have similar effects on macrophage phagocytosis of zymosan, but differ in their effects on nitrite and TNF-α production. Int Immunopharmacol. 2003;3:513–22.
79. Maeda M, Ishii H, Tanaka S, Onda K, Hirano T. Suppressive efficacies of antimicrobial agents against human peripheral-blood mononuclear cells stimulated with T cell mitogen and bacterial superantigen. Arzneimittelforschung. 2011;60:760–8.

80. Pahlevan AA, Wright DJM, Bradley L, Smith C, Foxwell BMJ. Potential of rifamides to inhibit TNF-induced NF-kappaB activation. J Antimicrob Chemother. 2002;49:531–4.
81. Yuhas Y, Azoulay-Alfaguter I, Berent E, Ashkenazi S. Rifampin inhibits prostaglandin E2 production and arachidonic acid release in human alveolar epithelial cells. Antimicrob Agents Chemother. 2007;51(12):4225–30.
82. Yuhas Y, Berent E, Ovadiah H, Azoulay I, Ashkenazi S. Rifampin augments cytokine-induced nitric oxide production in human alveolar epithelial cells. Antimicrob Agents Chemother. 2006;50(1):396–8.
83. Yuhas Y, Berent E, Ashkenazi S. Effect of rifampin on production of inflammatory mediators in HepG2 liver epithelial cells. Antimicrob Agents Chemother. 2011;55(12):5541–6.
84. Stendahl O, Molin L, Dahlgren C. The inhibition of polymorphonuclear leukocyte cytotoxicity by dapsone. A possible mechanism in the treatment of dermatitis herpetiformis. J Clin Invest. 1978;62(1):214–20.
85. Ottonello L, Dapino P, Scirocco MC, Balbi A, Bevilacqua M, Dallegri F. Sulphonamides as anti-inflammatory agents: old drugs for new therapeutic strategies in neutrophilic inflammation? Clin Sci. 1995;88(3):331–6.
86. Ruzicka T, Wasserman SI, Soter NA, Printz MP. Inhibition of rat mast cell arachidonic acid cyclooxygenase by dapsone. J Allergy Clin Immunol. 1983;72:365–70.
87. Hiremath SV, Gouripur VV, Patil PA. The anti-inflammatory activity of some sulphonamides in albino rats. Ind J Med Res. 1996;103:120–5.
88. Kanoh S, Tanabe T, Rubin BK. Dapsone inhibits IL-8 secretion from human bronchial epithelial cells stimulated with lipopolysaccharide and resolves airway inflammation in the ferret. Chest. 2011;140:980–90.
89. Ríos C, Orozco-Suarez S, Salgado-Ceballos H, Mendez-Armenta M, Nava-Ruiz C, Santander I, et al. Anti-apoptotic effects of dapsone after spinal cord injury in rats. Neurochem Res. 2015;40:1243–51.
90. Aruoma OI, Wasil M, Halliwell B, Hoey BM, Butler J. The scavenging of oxidants by sulphasalazine and its metabolites. A possible contribution to their anti-inflammatory effects? Biochem Pharmacol. 1987;36(21):3739–42.
91. Joshi R, Kumar S, Unnikrishnan M, Mukherjee T. Free radical scavenging reactions of sulfasalazine, 5-aminosalicylic acid and sulfapyridine: mechanistic aspects and antioxidant activity. Free Rad Res. 2009;39(11):1163–72.
92. Kanerud L, Hafstrom I, Ringertz B. Effect of sulphasalazine and sulphapyridine on neutrophil superoxide production: role of cytosolic free calcium. Ann Rheum Dis. 1990;49(5):296–300.
93. Minghetti PP, Blackburn WDJ. Effects of sulfasalazine and its metabolites on steady state messenger RNA concentrations for inflammatory cytokines, matrix metalloproteinases, and tissue inhibitors of metalloproteinase in rheumatoid synovial fibroblasts. J Rheumatol. 2000;27(3):653–60.
94. Griffin MO, Fricovsky E, Ceballos G, Villarreal F. Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature. Am J Physiol Renal Physiol. 2010;299:C539–48.
95. Dunston CR, Griffiths HR, Lambert PA, Staddon S, Vernallis AB. Proteomic analysis of the anti-inflammatory action of minocycline. Proteomics. 2011;11:42–51.
96. Kim SS, Kong PJ, Kim BS, Sheen DH, Nam SY, Chun W. Inhibitory action of minocycline on lipopolysaccharide-induced release of nitric oxide and prostaglandin E2 in BV2 microglial cells. Arch Pharm Res. 2004;27(3):314–8.
97. Smith-Norowitz TA, Bluth MH, Drew H, Norowitz KB, Chice S, Shah VN, et al. Effect of minocycline and doxycycline on IgE responses. Ann Allergy Asthma Immunol. 2002;89:172–9.
98. Leite LM, Carvalho AGG, Ferreira PL, Pessoa IX, Goncalves DO, Lopes ADA, et al. Anti-inflammatory properties of doxycycline and minocycline in experimental models: an in vivo and in vitro comparative study. Inflammopharmacology. 2011;19(2):99–110.
99. Roy SK, Kubiak BD, Albert SP, Vieau CJ, Gatto L, Golub L. Chemically modified tetracycline 3 prevents acute respiratory distress syndrome in a porcine model of sepsis + ischemia/reperfusion-induced lung injury. Shock. 2012;37(4):424–32.
100. Ci X, Chu X, Chen C, Li X, Yan S, Wang X, et al. Oxytetracycline attenuates allergic airway inflammation in mice via inhibition of the NF-κB pathway. J Clin Immunol. 2011;31:216–27.
101. Du Y, Ma Z, Lin S, Dodel RC, Gao F, Bales KR, et al. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. Proc Natl Acad Sci U S A. 2001;98:14669–74.
102. Edan RA, Luqmani YA, Masocha W. COL-3, a chemically modified tetracycline, inhibits lipopolysaccharide-induced microglia activation and cytokine expression in the brain. PLoS One. 2013;8(2):e57827.
103. Salvatore CM, Techasaensiri C, Tagliabue C, Katz K, Leos N, Gomez AM, et al. Tigecycline therapy significantly reduces the concentrations of inflammatory pulmonary cytokines and chemokines in a murine model of Mycoplasma pneumoniae pneumonia. Antimicrob Agents Chemother. 2009;53:1546–51.
104. Traunmüller F, Thallinger C, Hausdorfer J, Lambers C, Tzaneva S, Kampitsch T, et al. Tigecycline has no effect on cytokine release in an ex vivo endotoxin model of human whole blood. Int J Antimicrob Agents. 2009;33:583–6.

105. Yagnik RM, Benzeroual KE. Tigecycline prevents LPS-induced release of pro-inflammatory and apoptotic mediators in neuronal cells. Toxicol In Vitro. 2013;27:686–93.
106. Cockeran R, Mutepe ND, Theron AJ, Tintinger GR, Steel HC, Stivaktas PI, et al. Calcium-dependent potentiation of the pro-inflammatory functions of human neutrophils by tigecycline in vitro. J Antimicrob Chemother. 2012;67:130–7.
107. von Seth M, Sjolin J, Larsson A, Eriksson M, Hillered L, Lipcsey M. Effects of tigecycline and doxycycline on inflammation and hemodynamics in porcine endotoxemia: a prospective, randomized, and placebo-controlled trial. Shock. 2015;43(6):604–11.