Do antibiotics cause mitochondrial and immune cell dysfunction? A literature review

Muska Miller1* and Mervyn Singer1

1Bloomsbury Institute of Intensive Care Medicine, Cruciform Building, University College London, Gower Street, London, WC1E 6BT, UK

*Corresponding author. E-mail: muska.miller@ucl.ac.uk

While antibiotics are clearly important treatments for infection, antibiotic-induced modulation of the immune system can have detrimental effects on pathogen clearance and immune functionality, increasing the risk of secondary infection. These injurious consequences may be mediated, at least in part, through effects on the mitochondria, the functioning of which is already compromised by the underlying septic process. Here, we review the complex interactions between antibiotic administration, immune cell and mitochondrial dysfunction.

Introduction

Antibiotics are key components of modern-day medicine. Yet, despite their numerous benefits, they carry a significant risk of detriment and thus represent a double-edged sword. Some harmful effects are overt and/or well recognized such as rashes, hepatic and renal dysfunction, overgrowth by opportunistic organisms, induction of resistance, and effects on the microbiome.1 However, other adverse consequences are less well appreciated, for instance effects on the efficacy of anti-cancer medications,2 organ–organ crosstalk3 and the Jarisch–Herxheimer reaction, in which release of pathogen constituents such as endotoxin and DNA activate proinflammatory pathways.3 Using a rat model of caecal ligation and puncture, Peng et al.4 demonstrated that ampicillin/subbactam improved survival but at the expense of a greater inflammatory response and more renal dysfunction.

The antimicrobial actions of antibiotics also impact directly, albeit to a lesser extent, upon mammalian cells. Antibiotics can affect immune and bioenergetic function and this may potentially compromise the host’s ability to both counter the infection and maintain organ functionality. Sepsis represents a dysregulated host response triggered by an infectious process that leads to organ dysfunction.7 As bioenergetic/metabolic shutdown is considered a likely key component underlying multi-organ dysfunction in sepsis,6 including the immune system, there may be an additional and crucial iatrogenic contribution from antibiotics.

It is thus timely to review current knowledge of how specific antibiotic classes affect immune cell processes including chemotaxis, phagocytosis, antigen presentation, cytotoxicity and antibody production, and what is known about their impact on mitochondria. We performed a detailed search of both clinical and preclinical literature using PubMed using the following criteria: (antibiotics OR antimicrobials OR aminoglycosides OR beta-lactams OR macrolides OR quinolones OR oxazolidinone) AND (immune OR mitochondria). All non-English reviews were excluded.

A brief overview of mitochondrial dysfunction in sepsis, with particular reference to immune cells, and the link to antibiotics

The link between antibiotics and mitochondria stems from the endosymbiotic theory, which proposes that mitochondria share common ancestry with Alphaproteobacteria such as Rickettsia, Anaplasma and Ehrlichia.7 Thus mitochondria may be particularly susceptible to antibiotic mechanisms acting on nucleic acid and protein synthesis and/or transport pathways. The ensuing inhibition of mitochondrial functionality and biogenesis may compromise energy substrate availability with downstream consequences on host cell functionality. Importantly, mitochondria do not simply act as intracellular powerhousees but also play other important roles to maintain homeostasis. These include biosynthesis (e.g. nucleotides, fatty acids and cholesterol), mediation of intracellular signalling, and production and sequestration of reactive oxygen species (ROS). Mitochondrial dysfunction is implicated in multiple conditions including sepsis, neurodegeneration, ageing and cancer cell metabolism.

In sepsis, mitochondrial dysfunction is strongly associated with illness severity and poor outcomes.6 Immune dysregulation is a major feature of sepsis and this is increasingly linked to bioenergetic dysfunction.3–11 Specific alterations are described in immune cell mitochondrial respiratory complex activity, oxygen consumption, mitochondrial membrane depolarization, apoptosis and ROS production.12–16 Release of mitochondrial DNA and cardiolipin are also sensed by immune cells as damage-associated molecular pathogens (DAMPs) that will further amplify the systemic inflammatory response.16,17 After the
initial immune activation, immunoparesis follows; this can persist for weeks, if not months, predisposing the patient to secondary infection. An increasing evidence base links immunoparesis, at least in part, to bioenergetic dysfunction.10

Aminoglycosides

Data on immunomodulatory effects of aminoglycosides are conflicting.18–21 In some studies, therapeutic levels of gentamicin and amikacin reduced polymorphonucleocyte (PMN) chemotaxis.22,23 On the other hand, others reported no influence on either chemotaxis or phagocytosis but an inhibitory effect on PMN bactericidal activity.24,25 At therapeutic doses, amikacin increased superoxide production in stimulated PMNs but this was reduced at high doses (1–5 mg/L).26 Gentamicin, netilmicin and tobramycin, however, had no impact.26 Gentamicin and amikacin at high concentrations (>40 mg/L) also inhibited macrophage activation.27

Deleterious effects of aminoglycosides on mitochondrial function are also described. This mechanism has been implicated, at least in part, in the complications of ototoxicity and nephrotoxicity28–30 as aminoglycosides act on the mitochondrial ribosomal A site, which has structural similarity to bacterial ribosomes. This may activate phosphatidylinositol phospholipase C,13 increasing intracellular calcium12 and ultimately leading to a proinflammatory response via activation of extracellular signal-regulated kinases (ERKs).31 In renal and sensory hair-cell mitochondria, gentamicin inhibited oxidative phosphorylation and mitochondrial membrane potential, increasing ROS and apoptosis.34–42 Kanamycin reduced mitochondrial membrane potential, electron transport chain activity and ATP production in epithelial cells.43 Aminoglycosides could also chelate mitochondrial iron, forming a highly oxidant Fe(II)–aminoglycoside complex that causes oxidative damage and death in sensory hair cells.44 Gentamicin may mobilize iron from mitochondria in a time- and dose-dependent manner via generation of hydrogen peroxide.45 To our knowledge, no study has yet investigated aminoglycoside effects on mitochondrial function in immune cells.

β-Lactams

β-Lactams have known immunomodulatory functions in hypersensitivity46–48 and cancer.49,50 However, reported effects on immune cells in the context of infection have been conflicting.51 It remains unclear whether these effects are direct or secondary to release of pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved molecules released by killed bacteria.52–55 Variations in β-lactam-induced endotoxin release can influence cell death processes; when added to a co-culture of PMNs and Escherichia coli, ampicillin and cephalosporins produced a marked release of endotoxin with resulting PMN necrosis, whereas imipenem generated significantly lower levels of endotoxin and induced apoptotic cell death.56 β-Lactams also reduce granulopaiesis and may even cause neutropenia.57,58 Paradoxically, amoxicillin increased dendritic cell maturation and expression of activation markers such as HLA-DR, CD86 and CD80.58

There are also conflicting data on chemotaxis and phagocytosis. Some studies found penicillins, carbapenems and cephalosporins had no effect on PMN chemotaxis,59–62 whereas others reported ampicillin and cephalosporins reduced chemotaxis across a broad concentration range.63,66,67 Yet other papers found cephalosporins and carbapenems increased chemotaxis of PMNs and murine macrophages, respectively.58–72 Similarly, for phagocytosis, some studies found no effect of cephalosporins on PMN phagocytosis at therapeutic doses,53,66,73 some found cephalosporins and carbapenems increased human PMN and murine macrophage phagocytosis,68,69,72,74–76 while others reported that piperacillin, cephalosporins and meropenem reduced phagocytic activity in PMNs, monocytes and rat leucocytes, respectively.61,67,77 Cefotaxime, faropenem, amoxicillin, clavulanic acid and imipenem increased the respiratory burst and superoxide production in PMNs.54,76,78–80 On the other hand, meropenem reduced superoxide release but had no effect on PMN killing of Candida albicans.71 In a cell-free system, ampicillin and various cephalosporins could scavenge hypochlorous acid (HOCl).81 With this wide variation in findings, no solid conclusions can be drawn.

Data on the effects of β-lactams on cytokine release are also inconsistent. In endotoxin-stimulated PBMCs, penicillin (at 5–80 mg/mL) did not affect TNF-α release over a 3 day study period.82 However, meropenem reduced TNF-α release from endotoxin-stimulated monocytes after a 4 h incubation but did not affect IL-1α, IL-6 or IL-8.73 By contrast, a study using endotoxin-stimulated PBMCs found that piperacillin (at 100 mg/L) and co-amoxiclav (at therapeutic doses) increased release of TNF-α, IL-1β, IL-6 and IL-8 and increased expression of TLR2 mRNA, but reduced TLR4 mRNA expression.77–83 A further study using monocytes incubated with Staphylococcus epidermidis, however, found no effect of β-lactams on TNF-α release.84 In various studies on endotoxin-stimulated monocytes, penicillin and various cephalosporins inhibited IFN-γ activity,85 IL-10 release86 and CD14 expression.87 Penicillins could also conjugate with human IFN-γ, TNF-α, IL-1β, IL-4 and IL-13 but selectively disrupt IFN-γ-dependent immune responses.85,87,88

In terms of adaptive immunity, benzylpenicillin, carbenicillin, cefazolin and cefalotin did not affect lymphocyte mitogenic responses after 3 days of incubation.89 However, moxalactam at different concentrations reduced chemical-induced lymphocyte proliferation.90 Long-term ceftriaxone use increased the peripheral blood CD4/CD8 cell ratio but reduced the number of CD4+CD25+ cells.91

There is a scarcity of literature on the effects of β-lactams on immune cell mitochondria. Studies have mostly focused upon effects on hepatic and renal mitochondria. Cephalosporin nephrotoxicity was partially explained by effects on mitochondrial anionic substrate transport (e.g. glutamate and malate).92,93 Cefaloglycin competitively reduced carnitine-facilitated pyruvate oxidation and palmitoylcarnitine-mediated mitochondrial respiration, thereby reducing β-oxidation of fat and inhibiting activity of the tricarboxylic acid cycle.93 In renal mitochondria, imipenem, cefaloridine and cefaloglycin reduced mitochondrial respiration while imipenem and cefaloglycin reduced oxidation of butyrate, valerate and pyruvate as early as 30–90 min.94 Another study demonstrated that cephalosporins and penicillins could both reduce carnitine transport in a dose-dependent manner.95 In rat liver mitochondria, co-amoxiclav increased ATPase activity and induced opening of the mitochondrial transition pore to increase release of cytochrome c, thereby triggering
activation of caspase-9 and -3 and apoptosis. In neurons, piperacillin lowered mitochondrial membrane potential, reducing respiration and ATP production, but increased mitochondrial superoxide.

**Glycopeptides**

Naturally occurring glycopeptides are involved in both innate and adaptive immune responses, including immunoglobulins, cytokines, chemokines, complement, adhesion molecules and various receptors. Glycopeptides also affect the immune system, mostly by inducing adverse reactions via mast cell degranulation or neutrophin and decimation of gut microbiota. An in vivo murine study found that vancomycin produced neutropenia and lymphocytosis in peripheral populations but increased T-helper cells and reduced T-cytotoxic cells within the spleen.

In the context of infection, there is a plethora of conflicting reports. Teicoplanin at half its MIC enhanced macrophage phagocytosis of Staphylococcus aureus, whereas teicoplanin and vancomycin (at concentrations of 10–100 µg/mL) increased intracellular killing of phagocytosed organisms in both PMNs and monocytes. At high teicoplanin concentrations (500 µg/mL), adherence, chemotaxis, phagocytosis and killing of C. albicans by PMNs were significantly inhibited, while vancomycin (at 0.002 mg/mL) reduced PMN adherence and phagocytosis. Conversely, other studies found that therapeutic concentrations of teicoplanin and vancomycin did not affect chemotaxis, adherence nor phagocytosis of human PMNs.

There are similar conflicting findings in terms of cytokine release. In LPS-stimulated monocytes, vancomycin increased TNF-α, IL-6 and IL-10 and expression of multiple toll-like receptors (TLRs). Other studies, however, reported a decrease in TNF-α production in PBMCs following an 18 h incubation with vancomycin and a reduction in IL-8, IL-1β and TNF-α with teicoplanin.

We could find no studies investigating the effects of glycopeptides on immune cell mitochondria. Vancomycin (at ~0.033 mg/mL) inhibited protein and glycoprotein synthesis in isolated rat liver mitochondria and brain mitochondria. Mitochondrial dysfunction has been postulated to be the cause of glycopeptide nephrotoxicity, particularly through an increase in ROS production. In porcine proximal tubular epithelial cell lines, vancomycin (at 2 mM concentration) increased mitochondrial ROS production, reduced mitochondrial membrane potential, impaired activity of complex I of the electron transport chain, and increased apoptosis via activation of caspase-3, -7 and -9. These effects may be mediated by peroxidation of the mitochondrial membrane protein cardiolipin and could be partially or wholly mitigated by antioxidants such as vitamin E and MitoTEMPO.

Another in vitro study, however, found that vancomycin (at 1, 2.5 and 5 mM concentrations) increased oxygen consumption and ATP concentrations in proximal tubular epithelial cell lines.

**Quinolones**

The reported immunomodulatory effects of quinolones are more consistent, particularly in hypersensitivity reactions but also on the gut microbiota. Quinolones (at 5–100 mg/L) reduced pro-inflammatory cytokine and chemokine release (e.g. IL-1, IL-6, IL-8, TNF-α, JFN-γ and GM-CSF) partially by down-regulation of NF-κB, ERK and c-Jun-N-terminal kinase (JNK). Quinolones also increased IL-8 and TNF-α mRNA and IL-2 production.

Most reports show that quinolones do not affect chemotaxis or phagocytosis at therapeutic doses; however, at high concentrations they do inhibit both phagocytosis and the respiratory burst. Ciprofloxacin may also increase phagocytosis and intracellular killing of organisms.

Quinolones at concentrations of >50 mg/L can inhibit mammalian cell growth by blocking cell cycle progression. The increase in thymidine uptake has been attributed to increasing IL-2 production. In lymphocytes, proliferation was inhibited by up-regulating Fas ligand, caspase-8 and -3 activity.
In vitro ofloxacin (at 10 or 100 mg/L) did not induce apoptosis in isolated lymphocytes.\textsuperscript{210} Quinolones damage mitochondria by targeting mitochondrial topoisomerases.\textsuperscript{211} These influence mitochondrial DNA (mtDNA) topology and structural availability for DNA replication. TOP2 induces mtDNA supercoiling which, on inhibition by quinolones, accumulates and prevents mtDNA replication.\textsuperscript{211,212} Ciprofloxacin induces mtDNA loss, decreases electron transport chain complex I activity (as this is mtDNA encoded),\textsuperscript{213} and decreases mitochondrial membrane potential.\textsuperscript{214} This may be beneficial in colorectal and bladder cancer where quinolones have inhibited mtDNA synthesis, reduced mitochondrial membrane potential, up-regulated Bax expression and activity of caspase-3, -8 and -9, resulting in apoptosis.\textsuperscript{215,216} In breast cancer, quinolones reduced mitochondrial membrane potential and ATP production by suppression of the PI3K/Akt/mTOR and mitogen-activated protein kinase (MAPK)/ERK signalling pathways.\textsuperscript{217} In lung cancer, quinolones disrupted activity of complexes I and III, reduced ATP production and increased ROS production.\textsuperscript{218}

**Oxazolidinones**

Prolonged use of oxazolidinones is associated with myelosuppression, metabolic acidosis with hyperlactataemia, and peripheral and ophthalmic neuropathies. Myelosuppression occurs due to reduced maturation of myeloprogenitor cells, mediated by impaired mitochondrial protein synthesis, complex IV activity and mitochondrial oxidative metabolism.\textsuperscript{219–222} In addition to inhibition of fatty acid synthesis,\textsuperscript{223} these bioenergetic effects have been implicated in oxazolidinone-induced lactic acidosis.\textsuperscript{224–226} Linezolid inhibits mitochondrial translation by binding ribosomal peptidyl transferases and interfering with the binding of aminoacyl-tRNAs.\textsuperscript{219,221} This process impairs the coordinated assembly of the electron transport chain from mitochondrial- and nuclear-encoded genes.\textsuperscript{227}

Multiple in vitro studies have shown that oxazolidinones reduce cytokine production (e.g. TNF-α, IL-6, IFN-γ and IL-10)\textsuperscript{228–236} and phagocytosis, but exert no effect on killing capacity.\textsuperscript{237} Oxazolidinones also have no effect on chemotaxis, phagocytosis or the respiratory burst.\textsuperscript{238–240}

There are limited studies of the effect of oxazolidinones on mitochondrial functionality in muscle, liver and kidney.\textsuperscript{222,226,224,241} One clinical study did show impaired mitochondrial complex IV in PBMCs taken from patients on long-term linezolid therapy developing lactic acidosis and weakness.\textsuperscript{242}

**Conclusions**

Different classes of antibiotics exert varying immunomodulatory and bioenergetic effects with more consistent findings reported for quinolones and macrolides. This variation may be partially explained by differences in study methodology, cell types studied and underlying disease. Most studies to date have used in vitro or animal models and clinical data are relatively scarce. In many of these studies, supratherapeutic antibiotic concentrations have been used so the relevance to clinically relevant dosing regimens remains uncertain. Nonetheless, recommendations to increase antibiotic dose and/or frequency in critically ill patients, e.g. for quinolones and pipercillin/tazobactam, allied with an impaired ability to metabolize/excrete antibiotics due to concurrent organ dysfunction, altered volumes of distribution and protein binding, and the widening use of combination therapies to cover potentially resistant organisms will enhance the risk of potential toxicity.

No hard and fast recommendations can be made at present but we hope this review reignites interest in this forgotten area. Newer technologies should be utilized as many of the studies are now rather dated, and studies should be ideally performed on patient samples taken sequentially over the duration of a course of treatment. Better recognition of any impact on immune or bioenergetic functionality will also require concurrent therapeutic drug monitoring as wide variation in blood concentrations is recognized in critically ill patients wholargely receive fixed doses of antibiotic.\textsuperscript{243,244}

**Acknowledgements**

Muska Miller thanks The London Clinic for their support.

**Funding**

This study was carried out as part of our routine work.

**Transparency declarations**

None to declare.

**References**

11. Japiassu AM, Santiago APSA, d’Avila JC et al. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is...


38 Yang CL, Du XH, Han YX. Renal cortical mitochondria are the source of oxygen free radicals enhanced by gentamicin. Ren Fail 1995; 17: 21–6.


107. Cheng RY, Li M, Li SS et al. Vancomycin and ceftriaxone can damage intestinal microbiota and affect the development of the intestinal tract and immune system to different degrees in neonatal mice. Pathog Dis 2017; 5: https://doi.org/10.1093/femsmpdf/tfx104.
and heart of mice infected with in
presses induction of monocyte chemoattractant protein-1 and matrix
Chemother 2002; 149 150
peptidoglycan-induced activation of human monocyte-derived dendritic
inhibits lipopolysaccharide- or poly(I:C)-induced but not
29
Kamoi H, Kurihara N, Fujiwara H
κ
lipopolysaccharide-induced interleukin-8 production by human mono-
146
macrolide antibiotics.

 ⟨⟩
143
murine Langerhans cells.
modulates antigen-presenting and interleukin-1
148
macrolides inhibit interleukin-8 release by human eosinophils from atopic
Kohyama TH, Takizawa S, Kawasaki N et al. Fourteen-member
macrolides include interleukin-8 release by human eosinophils from atopi

 Riicentini GL, Peroni DG, Bodini A et al. Azithromycin reduces bron-
chial hyperresponsiveness and neutrophilic airway inflammation in asth-

 Fonseca-Aten M, Okada PJ, Bowieare KL et al. Effect of clarithromy-
cin on cytokines and chemokines in children with an acute exacerbation
of recurrent wheezing: a double-blind, randomized, placebo-controlled

 Amayasu H, Yoshida S, Ebana S et al. Clarithromycin suppresses
bronchial hyperresponsiveness associated with eosinophilic inflamm-

 Kraft M, Cassell GH, Pak J et al. Mycoplasma pneumoniae and
Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest 2002;
121: 1782–8.

 Simpson JL, Powell H, Boyle MJ et al. Clarithromycin targets neutro-
philic airway inflammation in refractory asthma. Am J Respir Crit Care Med

 Shoji T, Yoshida S, Sakamoto H et al. Anti-inflammatory effect of rox-
ithromycin in patients with aspirin-intolerant asthma. Clin Exp Allergy

 Kamoi H, Kuribara N, Fujihara H et al. The macrolide antibacterial
roxithromycin reduces bronchial hyperresponsiveness and superoxide
anion production by polymorphonuclear leukocytes in patients with asth-

 Parnham MJ, Culic O, Erakovic V et al. Modulation of neutrophil and
inflammation markers in chronic obstructive pulmonary disease by short-

 Pukalsky AL, Shmarina GV, Kaprano N et al. Anti-inflammatory and
immunomodulating effects of clarithromycin in patients with cystic

and interleukin 6 production induced by heat-killed Streptococcus pneu-

 Iaino A, Ialenti A, Maffa P et al. Anti-inflammatory activity of

 Ohshima A, Tokura Y, Wakita H et al. Roxithromycin down-
modulates antigen-presenting and interleukin-1 β-producing abilities of

 Kikuchi T, Hagiwara K, Honda Y et al. Clarithromycin suppresses
lipopolysaccharide-induced interleukin-8 production by human mono-
cytes through AP-1 and NF-kB transcription factors. J Antimicrob

 Yasumori M, Oshimia Y, Omata N et al. Erythromycin differentially
inhibits lipopolysaccharide- or poly(I:C)-induced but not peptide glycogen-induced activation of human monocyte-derived dendritic

 Takahashi E, Indalao IL, Sawabuchi T et al. Clarithromycin sup-
presses induction of monocyte chemoattractant protein-1 and matrix
metalloproteinase-9 and improves pathological changes in the lungs
and heart of mice infected with influenza A virus. Comp Immunol

 Banerjee D, Honeybourne D, Khair OA. The effect of oral clarithromy-
cin on bronchial airway inflammation in moderate-to-severe stable

 Cameron EJ, Chaudhuri R, Mair F et al. Randomised controlled trial of

 Iino Y, Sasaki Y, Kojima C et al. Effect of macrolides on the expression
of HLA-DR and costimulatory molecules on antigen-presenting cells

 Karrow NA, McCoy JA, Brown RD et al. Evaluation of the immunomo-
dulatory effects of the macrolide antibiotic, clarithromycin, in female
B6C3F1 mice: a 28-day oral gavage study. Drug Chem Toxicol 2001; 24:
19–37.

 Kanno S, Adachi M, Asano K et al. Influences of roxithromycin on

 Anderson R. Erythromycin and roxithromycin potentiate human
neutrophil locomotion in vitro by inhibition of leuko-attractant activated

 Yamaryo T, Oishi K, Yoshimine H et al. Fourteen-member macrolides
promote the phosphatidylserine receptor-dependent phagocytosis of
apoptotic neutrophils by alveolar macrophages. Antimicrob Agents

 Hodge S, Hodge G, Brozyna S et al. Azithromycin increases phagocy-
osis of apoptotic bronchial epithelial cells by alveolar macrophages. Eur
Respir J 2006; 28: 486–95.

 Herrera-Insua J, Jacques-Polak Z, Murray BE et al. The effect of anti-
biotic exposure on adherence to neutrophils of Enterococcus faecium

 Nama T, Hayashi M, Yoshizawa I et al. A comparative investigation of
the restorative effects of roxithromycin on neutrophil activities. Int J

 Scaglione F, Ferrara F, Dugnani S et al. Immunostimulation by clari-
thromycin in healthy volunteers and chronic bronchitis patients. J
Chemother 1993; 5: 228–32.

 Wenisch C, Parschalk B, Zedtwitz-Liebenstein K et al. Effect of single
oral dose of azithromycin, clarithromycin, and roxithromycin on poly-
morphonuclear leukocyte function assessed ex vivo by flow cytometry.

 Ortega E, Escobar MA, Gafario JJ et al. Modification of phagocytosis
and cytokine production in peritoneal and splenic murine cells by eryth-
53: 367–70.

 Braga PC, Maci S, Dal Sasso M et al. Effects of rokitamycin on phago-
cytosis and release of oxidant radicals of human polymorphonuclear leu-

 Mitsuyama T, Tanaka T, Hitaka K et al. Inhibition by erythromycin of
superoxide anion production by human polymorphonuclear leukocytes
through the action of cyclic AMP-dependent protein kinase. Respiration

 Cui CH, Honda K, Saito N et al. Effect of roxithromycin on eotaxin-
primed reactive oxygen species from eosinophils. Int Arch Allerg

 Eswarappa SM, Basu N, Joy O et al. Folimycin (concanamycin A) inhib-
hits LPS-induced nitric oxide production and reduces surface localization

 Mizuno S, Kadota JI, Tokimatsu I et al. Clarithromycin and azithro-
mycin induce apoptosis of activated lymphocytes via down-regulation

 Ishimatsu Y, Kadota JI, Iwashita T et al. Macrolide antibiotics induce
apoptosis of human peripheral lymphocytes in vitro. Int J Antimicrob


