International Journal of Research in Medical Sciences
Waghray P et al. Int J Res Med Sci. 2025 Jan;13(1):547-558
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20244169

Review Article

Role of clarithromycin in the management of multiple infection

Pradyut Waghray[1], Samir Bhargava[2], Devesh K. Joshi[3]*, Monil Gala[3], Snehal S. Muchhala[3], Bhavesh P. Kotak[3]

[1]Department of Pulmonology, Apollo Hospitals Jubilee hills, Hyderabad, Telangana, India
[2]Department of ENT, HBT Medical College and Dr. R.N. Cooper Hospital, Mumbai, Maharashtra, India
[3]Department of Medical Affairs, Dr. Reddy's Laboratories Ltd., Hyderabad, Telangana, India

Received: 28 October 2024
Revised: 07 December 2024
Accepted: 11 December 2024

***Correspondence:**
Dr. Devesh K. Joshi,
E-mail: deveshkj@drreddys.com

ABSTRACT

Clarithromycin, a second-generation semisynthetic macrolide antibiotic, is known for its broad-spectrum antibacterial activity, favorable pharmacokinetic profile, and stability at gastric pH, along with significant anti-inflammatory and immunomodulatory effects. It demonstrates superior efficacy and fewer side effects compared to other macrolides, making it a potent therapeutic option for various bacterial infections. Clarithromycin is approved for use in combination therapy to eradicate *Helicobacter pylori* and for treating mild to moderately severe respiratory infections such as acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP) including infections from *Chlamydia*, *Mycoplasma* spp., acute streptococcal pharyngitis, and skin and soft tissue infections. Apart from its usual listed uses, clarithromycin is used in multiple other infections, including upper respiratory tract infections (URTIs) like pharyngitis in penicillin-allergic patients, chronic pharyngitis related to gastroesophageal reflux disease (GERD), sore throat, acute laryngitis, and chronic rhinosinusitis. It is also effective for lower respiratory tract infections (LRTIs) related to chronic obstructive pulmonary disease (COPD), *Mycobacterium avium* complex (MAC) infections, bronchiectasis, and various other conditions including COVID-19, systemic lupus erythematosus (SLE), bronchiolitis obliterans syndrome post-lung transplant, and *H. influenzae* infections. During the COVID-19 pandemic, concerns about antimicrobial resistance from the overuse of antibiotics, including azithromycin, highlighted clarithromycin as a preferable alternative due to its superior pharmacodynamics and lower resistance risk. While clarithromycin has a favorable safety profile, it is associated with potential adverse effects such as cardiovascular risks and gastrointestinal disturbances. Its role as a reserve antibiotic highlights its importance in managing resistant infections and in situations where first-line treatments are ineffective or contraindicated.

Keywords: Macrolides, Azithromycin, Antibiotic resistance, Clarithromycin, Respiratory tract infections, COVID-19

INTRODUCTION

Macrolides are a proven and highly effective class of antibiotics for managing respiratory tract infections (RTIs) and are ranked among the most essential antibiotics globally by the World Health Organization (WHO). Their high tissue penetration and significant anti-inflammatory properties, through immune system modulation, make them a preferred treatment option in multiple infections.[1] The broad-spectrum activity of macrolides is attributed to their high affinity for bacterial ribosomes and the conserved ribosomal structure across various bacterial species. They are effective against a wide range of Gram-positive and Gram-negative pathogens, as well as species of *Chlamydia*, *Legionella*, *Mycobacteria*, and *Mycoplasma* makes them highly effective in managing RTIs.[2] Macrolides have evolved through four generations, each marked by distinct structural modifications and development stages.[3] First-generation macrolide erythromycin is effective against a broad range of bacteria

but is limited by gastrointestinal side effects and increasing bacterial resistance. Second-generation macrolides, such as clarithromycin and azithromycin, offer improved pharmacokinetics, enhanced tissue penetration, and a broader spectrum of activity.[4] However, the irrational use of azithromycin, especially during the COVID-19 pandemic, has significantly contributed to the increasing trends in resistance, particularly against common pathogens such as *Staphylococcus aureus* and *Neisseria gonorrhoeae.*[5] The widespread use of azithromycin without appropriate guidelines has worsened these resistance patterns, complicating treatment options for bacterial infections.[5] Telithromycin, a third-generation macrolide, was withdrawn due to severe side effects, while solithromycin, a fourth-generation macrolide, faced Food and Drug Administration (FDA) rejection over suspected toxicity despite structural modifications aimed at reducing these issues.[3]

Clarithromycin, a semisynthetic macrolide, is a newer molecule with improved pharmacokinetics, gastric pH stability, notable anti-inflammatory and immunomodulatory effects, and fewer adverse effects compared to erythromycin and azithromycin. It primarily inhibits bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome, blocking peptide translocation during translation, which is crucial for bacterial growth and replication.[2] Additionally, it possesses immunomodulatory properties by suppressing cytokines interleukin-6 (IL-6). While clarithromycin is effective in treating a variety of bacterial infections, including both primary and secondary infections, increasing resistance due to mutations in the 23S rRNA gene, particularly the A2143G mutation poses challenges and affects treatment efficacy.[6] It is an effective treatment for upper and lower RTIs, including pharyngitis, sinusitis, community-acquired pneumonia (CAP), bronchitis, skin and soft tissue infections, and atypical infections by inhibiting pathogens such as *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus.*[2] In addition, it is used for *Helicobacter pylori* infection, acute otitis media (AOM), and mycobacterial infections. It also treats whooping cough and reduces sepsis recurrence rates, indicating a role in immune restoration.[7,8] It is effective in patients with penicillin allergies or when first-line drugs such as amoxicillin/clavulanate or doxycycline are ineffective or contraindicated.[9] This review highlights the less common indications of clarithromycin, exploring its recent or under-explored uses. It also discusses clarithromycin's role in both primary and secondary infections, its therapeutic positioning, and comparison to azithromycin in the post-COVID setting.

APPROVED INDICATIONS AND GUIDELINES

According to USFDA guidelines, clarithromycin is approved for use in adults and children to treat various infections including pharyngitis, tonsillitis, and uncomplicated skin and skin structure infections caused by *Streptococcus pyogenes* or *Staphylococcus aureus*. It is also indicated for acute maxillary sinusitis, chronic bronchitis, CAP and infections due to *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *M. pneumoniae*, or *C. pneumoniae*. Additionally, it is prescribed for mycobacterial infections caused by *Mycobacterium avium* or *Mycobacterium intracellulare*, and the eradication of *H. pylori.*[10] The CDSCO has approved clarithromycin use as part of a combination therapy to eradicate *H. pylori* infections.[11] Clarithromycin tablets are also approved for treating mild to moderately severe infections, including acute exacerbation of chronic bronchitis, CAP including infections due to *chlamydia, mycoplasma spegiocella,* acute *streptococcal* pharyngitis and skin and soft tissue infections. Modified release (MR) tablets are prescribed for treating lower respiratory tract infections (LRTI), upper respiratory tract infections (URTI) and skin and soft tissue infections. Additionally, the CDSCO has recommended the topical use of clarithromycin for acne vulgaris.[11] Several organizations have developed guidelines recommending clarithromycin use as a first or second-line treatment. Table 1 lists various international guidelines and recommendations.[9,12-22]

BROADER THERAPEUTIC USES OF CLARITHROMYCIN

Upper respiratory tract infections

Streptococcal pharyngitis

Pharyngitis caused by group A beta-hemolytic *Streptococci* (GABHS) is considered the most clinically significant bacterial URTI. The American Academy of Family Physicians, the American Academy of Pediatrics, the AHA, the IDSA, and the WHO recommend clarithromycin for the treatment of GABHS recurrent pharyngitis in patients with type IV hypersensitivity reactions to the first-line drug penicillin and patients allergic to both penicillin and sulfisoxazole.[23]

Chronic pharyngitis due to gastroesophageal reflux disease

Sometimes patients with GERD experience laryngopharyngeal symptoms, including hoarseness, cough, and a sensation of a lump in the throat with symptoms of pharyngitis. In cases where GERD is accompanied by chronic *H. pylori* infection, the preferred initial treatment is often triple therapy including clarithromycin. For GERD-related chronic pharyngitis, clarithromycin may be included in the treatment plan if *H. pylori* co-infection is present. Eradicating *H. pylori* with triple therapy can help reduce gastric inflammation and acid production, potentially easing GERD symptoms and, consequently, chronic pharyngitis. The recommended first-line regimen includes a PPI combined with either clarithromycin and amoxicillin or metronidazole.[24]

Table 1: Guidelines recommending clarithromycin use in various infections.[9,12-22]

Guidelines	Condition	Recommendation for clarithromycin	Dosage
American College of Gastroenterology (ACG) (2017), ASEAN consensus (2018), Maastricht VI/Florence consensus report (2022)[12]	*H. pylori* infections (clarithromycin resistance <15%)	First-line use with clarithromycin triple therapy	500 mg BID with PPI + amoxicillin or metronidazole for 14 days
Centre for health protection (Hong Kong), Mahidol University (Bangkok, Thailand), Scientific Center of Children's Health (Russia), NICE (UK), Ben-Gurion University (Israel), American Health Association (AHA), Infectious Diseases Society of America (IDSA) and Sociedad Argentina de Infectología (Argentina)[9]	Sore throat (penicillin allergy)	Second-line treatment	250 mg to 500 mg BID (7-14 days)
Indian Council of Medical Research (ICMR) (2019)[13]	*Streptococcal pharyngitis* (penicillin allergy)	Recommended for anaphylactic treatment	500 mg BID for 10 days
ICMR (2019)[13]	Acute otitis media (penicillin allergy)	Anaphylactic treatment	500 mg BID
ICMR (2019)[13]	CAP	Alternative treatment for adult outpatients without co-morbidities	500 mg BID for 5 to 7 days
ICMR (2019)[13]	*Scrub typhus* (doxycycline-resistant strains)	Alternative treatment	500 mg BID
IDSA (2012)[14]	*Streptococcal pharyngitis* (penicillin allergy)	For penicillin-allergic patients	7.5 mg/kg/dose BID (max 250 mg per dose) for 10 days
IDSA (2014)[15]	Skin and soft tissue infections (nontuberculous mycobacteria)	Recommended as part of combination therapy	500 mg BID for 6-12 weeks
American Heart Association (AHA) (2009)[16]	Rheumatic fever prevention	Primary prevention for patients allergic to penicillin and sulfisoxazole	15 mg/kg/day divided BID (max 250 mg BID)
Skin and soft tissue infection guidelines (2022)[17]	Skin and soft tissue infections and diabetic foot ulcers	Monotherapy for mild to moderate cellulitis, erysipelas, impetigo, and infected diabetic foot ulcers	500 mg BID for 7-14 days
Australian Safety Guidelines (2022)[18]	CAP	Second-line treatment for low-severity (mild) CAP in children (≥2 months) and adults	Children: 7.5 mg/kg BID for 3 days (max 500 mg BID); adults: 500 mg BID
British Thoracic Society (BTS) (2019)[19]	CAP	Alternative to macrolides in patients with macrolide-resistance or contraindications to first-line therapy	500 mg BID for 7 days
Canadian Thoracic Society (CTS)[20]	CAP	Combination therapy for patients with comorbidities or severe CAP	500 mg BID for 7-14 days
National Institute for Health and Care Excellence (NICE)[21]	URTI	Second-line therapy for bacterial infections when first-line antibiotics are unsuitable	250-500 mg BID for 7-10 days

Continued.

Guidelines	Condition	Recommendation for clarithromycin	Dosage
Japanese Respiratory Society (JRS) (2021)[22]	*Mycoplasma pneumoniae* infections	First-line treatment for atypical pneumonia caused by *Mycoplasma pneumoniae*	500 mg BID for 7 days

BID: Bis in die (twice a day); PPI: Proton pump inhibitor

Sore throat/throat pain

Sore throat (acute pharyngitis) is a common issue globally, viral in 70%-95% of cases.[25] Leading healthcare organizations endorse the use of clarithromycin as a second-line treatment for sore throat in patients who are either allergic to or unresponsive to first-line antibiotics like penicillin V.[9] A meta-analysis study involving 1,184 patients with symptoms of streptococcal pharyngitis, showed that clarithromycin was significantly more effective than penicillin VK, achieving a cure rate of 95% compared to 87% with penicillin VK. Although clarithromycin is not typically recommended as a first-line treatment for URTIs, the meta-analysis results suggest that it remains a valid, effective, and generally well-tolerated option for patients with GABHS pharyngitis who do not respond to other medications.[26] Post COVID-19, for patients complaining of throat pain and not responding to antibiotics for 3-4 months, clarithromycin is effective and can be a drug of choice.

Acute laryngitis

Clarithromycin, at 250 mg twice daily, can help relieve voice disturbances and cough. A Russian study with 145 patients compared fusafungine (6 times daily), fusafungine with clarithromycin (250 mg twice daily), and no treatment, showing significant improvement by day 5 in both the fusafungine (RR 1.50; P = 0.04) and fusafungine plus clarithromycin groups (RR 1.47; p = 0.05).[27] Naik *et al.* noted clarithromycin's effectiveness against atypical pathogens like *Chlamydia pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae* and *Legionella spp*. and its use for respiratory infections like laryngitis and CAP due to its anti-inflammatory and immunomodulatory effects.[2]

Chronic rhinosinusitis and persistent postnasal drip

Clarithromycin may offer advantages over azithromycin in treating erythromycin-resistant *Streptococcus pneumoniae* strains with low-level resistance. It can lead to quicker symptom relief by day 14 in patients with uncomplicated acute rhinosinusitis (ARS), as shown by quality of life (QoL) surveys, compared to amoxicillin/clavulanate.[28] CRS is a persistent inflammatory condition affecting the nasal cavity and sinuses. Current treatments, including endoscopic sinus surgery (ESS) and standard postoperative care such as antibiotics, intranasal corticosteroids, mucolytics, oral hormones, and nasal irrigation, can achieve clinical cure rates of 75% to 98%. However, about 10% of CRS patients show little improvement in symptoms or local signs after these treatments. These patients are classified as having "refractory CRS" (RCRS). Clarithromycin may be considered as the preferred therapy option for managing CRS.[29] Low-dose clarithromycin exhibits immunomodulatory effects in managing post-surgery CRS and is effective in patients with CRS without nasal polyps (CRSsNP) by suppressing IL-8 and myeloperoxidase production, leading to improved QoL.[30] Clarithromycin also improves symptoms in CRS with nasal polyps and is beneficial as an adjuvant with intranasal steroids in recurrent CRS cases. Combining clarithromycin with oral corticosteroids after ESS has been shown to alleviate postnasal drip and enhance both subjective and objective outcomes in patients with CRSwNP.[31] In a randomized, double-blind, placebo-controlled trial, adding clarithromycin to oral prednisolone after ESS for CRSwNP significantly improved visual analog scale (VAS), sino-nasal outcome test (SNOT-22), and Lund-Kennedy endoscopy scores (LKES) at 8, 12, and 24 weeks, compared to placebo or prednisolone alone, with the greatest benefit seen in patients without tissue eosinophilia.[31] The adjuvant administration of clarithromycin is also beneficial in recurrent CRS with nasal polyps unresponsive to both medical and surgical interventions. A randomized study on 60 patients post-functional endoscopic sinus surgery (FESS) showed that a 3-month low-dose clarithromycin course (250 mg/day) significantly improved Lund-Mackay Score (LMS) (5.90 versus 8.45, p<0.001) and endoscopic scores compared to the non-macrolide group, suggesting it is effective and safe in preventing early recurrence of CRSwNP and improving QoL.[32]

In another study of 66 patients with CRS and nasal polyposis, those treated with clarithromycin (250 mg/day) for 12 or 24 weeks post-FESS showed significant improvements in SNOT-20 scores compared to the control group, suggesting long-term clarithromycin may help prevent early relapse of nasal polyps.[33]

In a prospective study of 18 patients with RCRS unresponsive to surgery and standard treatment, low-dose clarithromycin (250 mg daily for 12 weeks) significantly improved symptoms like nasal congestion, rhinorrhea, and postnasal drip by week 4. By week 12, both symptoms and endoscopic scores had further improved, *S. pneumoniae* levels decreased, while nasal flora composition remained unchanged.[34] In another prospective, randomized, controlled trial, to assess the effectiveness of clarithromycin (250 mg daily for 12 weeks) in improving PPND without sinus involvement, long-duration clarithromycin treatment demonstrated promising efficacy in reducing PPND symptoms severity as measured by the

VAS with improved QoL.[35] These studies suggest that clarithromycin is effective in reducing postnasal drip symptoms in patients with RCRS or PPND.

Lower respiratory tract infections

Community acquired pneumonia

A recent meta-analysis showed that erythromycin was less effective, with reduced rates of clinical success, clinical cure, radiological success and had an increased risk of adverse effects (AEs) than clarithromycin as an empiric treatment for CAP.[36] It is suggested that erythromycin should be avoided in most CAP patients when both azithromycin and clarithromycin are available. Both azithromycin and clarithromycin, when combined with a beta-lactam, show considerable clinical success, with clarithromycin achieving a 75.42% success rate at doses of 300 mg-1000 mg per day for 5 or 7 days. Patients receiving a clarithromycin-based regimen had fewer hospitalization days compared to those on an azithromycin-based regimen. Therefore, clarithromycin-based combinations may be preferred for shorter hospital stays in CAP treatment.[37]

The recent ACCESS trial found that adding clarithromycin to standard beta-lactam macrolide (BLM) antibiotic treatment in hospitalized adults with CAP led to an early clinical response and reduced inflammatory markers in 68% of patients, compared to 38% in the placebo group, highlighting its potential benefit in treating hospitalized pneumonia.[19] ICMR recommends the alternative treatment with clarithromycin in adult CAP outpatients without co-morbidities.[13]

Chronic obstructive pulmonary disorder and acute exacerbations of chronic bronchitis

Clarithromycin use is suggested in COPD and AECB. As per one of the studies, patients with chronic bronchitis or COPD treated with clarithromycin experienced fewer prior exacerbations and clinical visits. Additionally, sputum purulence, expectoration, and dyspnoea resolved in 89%, 88.5%, and 81% of patients, respectively.[38] A phase 3 clinical trial comparing clarithromycin with amoxicillin/clavulanic acid (500 mg/125 mg TID) in adult patients with AECB found that clarithromycin had better efficacy and tolerability, with fewer adverse events and discontinuations, and a higher patient compliance rate of 95%.[39] Another study showed that clarithromycin was comparable to cefixime for pneumonia and acute bacterial exacerbations of bronchitis with mild to moderate severity, caused by pathogens including *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.[40]

Mycobacterium avium complex infections

While clarithromycin monotherapy is contraindicated due to its potential to induce drug-resistant bacterial strains, it is an essential component in the recommended combination therapy for MAC, along with rifampicin and ethambutol.[41] The use of clarithromycin resulted in a significant reduction of over 99% in MAC bacteremia in individuals with HIV infection.[42] This decrease was observed following the administration of all three doses (500/1000/2000 mg BID) of clarithromycin.[42] The drug is well-tolerated in patients with advanced AIDS and is linked to a decreased frequency of hospitalization and reduction in mortality rates.[43]

Bronchiectasis

Th17 cells play a crucial role in neutrophilic inflammation and tissue injury in non-cystic fibrosis bronchiectasis (NCFB). Clarithromycin is used in treating infectious exacerbations of NCFB. According to the British Thoracic Society guidelines, clarithromycin 500 mg twice daily is recommended as a first-line therapy for bronchiectasis, particularly for hospitalized patients who are allergic to penicillin.[44] One of the studies involving 22 patients with stable NCFB, who were treated with a daily 500-mg dose of clarithromycin for 12 weeks, has shown that a low dose of clarithromycin has anti-inflammatory and immunomodulatory effects with a significant decrease in absolute counts of CD4+IL17+ cells in peripheral blood and IL-17 levels in exhaled breath condensate.[45]

Another study on children with bronchiectasis found clarithromycin reduced IL-8 levels, total cell count, and neutrophil ratios in bronchoalveolar lavage fluid after 3 months of daily treatment with decrease in sputum production and increase in macrophage ratios.[46]

Other infections

COVID-19

The COVID-19 pandemic led to the overuse of antibiotics without appropriate clinical rationale, resulting in significant public health concerns regarding antibiotic resistance. A recent meta-analysis including 28 studies showed that fluoroquinolones (20.0%) followed by macrolides (18.9%), beta-lactam/ beta-lactamase inhibitors (15.0%), and cephalosporins (15.0%) were the most frequently given groups of antibiotics in patients with COVID-19, however, the prevalence of bacterial coinfection was only 8.6%.[47] The overuse of azithromycin during COVID-19 treatment potentially contributed to resistance development, necessitating alternatives like clarithromycin. Clarithromycin shows better pharmacodynamic parameters, with a time above mutant prevention concentration (MPC) of 24 hours compared to azithromycin's 0 hours, and higher values of both area under curve (AUC) 24/MPC (96 versus 0.85) and maximum concentration (C_{max})/MPC (7.5 versus 0.1).[48] These parameters make clarithromycin least likely to increase the chances of developing resistance.[48]

In healthy volunteer peripheral blood mononuclear cells (PBMCs), clarithromycin increased IL-2 and decreased

IL-10 in both CD8+ and CD4+ T cells, while combining it with amoxicillin led to changes in several cytokines, including an increase in CD8+ IL-6 and decreases in TNF-α and IFN-α. Azithromycin alone also increased IL-2 in CD8+ and CD4+ T cells but had no impact on monocyte phagocytosis.[49] Multiple studies have failed to show any benefit of azithromycin alone, in reducing symptoms or hospitalization in patients with moderate COVID-19 disease. Clarithromycin demonstrated a more favorable impact on lung function, potentially due to its anti-inflammatory properties.

Systemic lupus erythematosus

In patients with SLE, clarithromycin has been used to elevate blood levels of tacrolimus, by inhibiting its metabolism, resulting in increased trough concentrations.[50] In one case study, a patient with SLE was treated with clarithromycin to boost tacrolimus blood levels, an immunosuppressive drug associated with the induction of microangiopathic hemolytic anemia, a condition similar to thrombotic thrombocytopenic purpura.[50]

Bronchiolitis obliterans syndrome (BOS) in lung transplant

Clarithromycin may help prevent BOS in lung transplant recipients and stabilize the lung function. Studies have shown that long-term clarithromycin treatment can significantly increase forced expiratory volume (FEV1) in more than one-third of patients with BOS, with outcomes comparable to azithromycin. In another study evaluating clarithromycin for BOS on 31 patients, 12 (39%) responded to clarithromycin, with 10 of these patients showing improvement within the first 3 months.[51] Responders showed a significant FEV1 increase of 732 ml ($p<0.001$) over 6 months, with the pre-treatment decline of 181 ml/month slowing to 25 ml/month during clarithromycin therapy.[51] A study on lung transplant recipients found that adding clarithromycin to immunosuppressive therapy reduced cyclosporine doses from 9.9 to 5.8 mg/kg/day at 1 month and to 4.1 mg/kg/day at 1 year, without increasing infection or rejection rates.[52]

Haemophilus influenzae infection

Clarithromycin is highly effective against *H. influenzae*, due to its metabolite, 14-hydroxy clarithromycin, even in cases where the bacteria are resistant to ampicillin, which makes it a valuable treatment option in clinical practice.[2] In a clinical study combining clarithromycin with carbocysteine, it reduced persistent middle ear inflammation after AOM caused by *H. influenzae* in children ($p=0.097$).[53] Another study aimed to compare the safety and efficacy of clarithromycin-naproxen-oseltamivir combination therapy to that of oseltamivir therapy alone, reported that decrease in virus titer from days 1 to 3 was more pronounced in the combination group than in the oseltamivir group (39% versus 19%, $p=0.001$).[54] Combination treatment with clarithromycin, naproxen and oseltamivir lowers 30-day mortality, fewer high dependency unit admissions, shorter hospital stays, significantly lower virus titer and pneumonia severity index from days 1-3, and fewer nasopharyngeal aspirate specimens with neuraminidase-inhibitor-resistant A(H3N2) virus quasispecies ≥5% on days 1-2.[55] In another open-label study involving 79 influenza patients, the clarithromycin group showed a significantly higher rate of improvement in rhinorrhea compared to control.[56]

An *in-vitro* study using human tracheal epithelial cells infected with influenza A (H3N2) showed that clarithromycin decreased viral titers, cytokine levels in supernatants, viral RNA in cells, and susceptibility to infection. It also reduced the expression of the SAα2, 6Gal receptor for the virus on the tracheal mucosal surface and lowered the number and fluorescence intensity of acidic endosomes involved in viral entry. Additionally, clarithromycin reduced the levels of NF-κB proteins (p50 and p65) in nuclear extracts, suggesting it may help modulate airway inflammation in influenza infections.[57]

CLARITHROMYCIN WITH OTHER ANTIBIOTICS

Modifying the structure of erythromycin by introducing a methoxy group or a methyl-substituted nitrogen into the lactone ring enhances the stability of clarithromycin in acidic conditions. This results in improved pharmacokinetic properties and greater efficacy against bacteria. When patients with pneumonia do not respond to macrolides, clarithromycin may be beneficial. It specifically downregulates the transcription of the gene responsible for pneumolysin production, though it upregulates the autolysis-related *lytA* gene, leading to the release of bacterial DNA.[58] Macrolide resistance poses a significant challenge in treating bacterial infections, leading to poorer outcomes and higher illness rates. Clarithromycin remains a potent and valuable option for managing bacterial infections, as it remains effective when resistance is controlled and managed appropriately.

Combination therapy

A combination of clarithromycin with beta-lactams may offer superior treatment for CAP in hospitalized patients compared to fluoroquinolones, as it also helps in mitigating inflammation associated with the condition. A retrospective analysis involving 1,174 patients with CAP found that clarithromycin 500 mg twice daily was more effective than fluoroquinolones (moxifloxacin 400 mg once daily and levofloxacin 500 mg twice daily), with higher rate of CAP resolution compared to both the fluoroquinolone group and the BLM group.[59] Furthermore, evidence suggests that macrolide-based combination therapies lead to lower mortality rates compared to those that do not include macrolides.[60] While comparing treatment alone with clarithromycin, findings from a meta-analysis indicated that clarithromycin use did not elevate

the risk of adverse events in patients with sepsis or septic shock.[61] In another study involving 600 patients with sepsis, it was found that while intravenous clarithromycin did not impact overall mortality, it shortened the time to infection resolution, particularly in those with severe sepsis or septic shock. These findings suggest that patients in intensive care may be managed better with clarithromycin, either alone or as combination therapy.

Clarithromycin versus amoxicillin-clavulanate

Amoxicillin clavulanate is one of the most commonly used antibiotics in emergencies and primary care settings. However, the most common complaint remains diarrhea with moderate risk of secondary *Clostridioides difficile* colitis. Also, high doses of penicillins can lead to seizures, which is particularly concerning for patients with impaired renal function.[62]

A meta-analysis of clinical trials showed that clinical success rates for clarithromycin ranged from 85.8% to 97.9%, while for amoxicillin, 84.2% to 96.8%. This suggests that clarithromycin is a legitimate and effective alternative to amoxicillin for treating acute maxillary sinusitis in adults.[63] Clarithromycin can also be prescribed as an alternative for patients who experience diarrhea as an adverse effect from amoxicillin-clavulanate.[63]

Clarithromycin versus azithromycin

Clarithromycin offers superior benefits over azithromycin, improving survival rates for severe CAP and proving more effective in post-exposure prophylaxis against inhalation anthrax, with a 67% survival rate compared to 50% for azithromycin.[64] The irrational use and improper prescription of macrolides, including the repurposing of azithromycin for COVID-19, have contributed to increased bacterial resistance. In critically ill COVID-19 patients, clarithromycin showed a significant survival benefit over non-macrolide antibiotics, likely due to its immunomodulatory effects that enhance T cell responses-a benefit not seen with azithromycin. These effects could contribute to its superior effectiveness in treating viral infections and improving patient outcomes. Studies have indicated that clarithromycin demonstrates greater clinical efficacy compared to the combination of azithromycin and hydroxychloroquine, suggesting that clarithromycin may be more effective than azithromycin, especially given the reported ineffectiveness of hydroxychloroquine.[65]

ADVERSE EFFECTS

Macrolides have been linked to QT interval prolongation, which can increase the risk of serious cardiovascular events like ventricular arrhythmias (VA) and all-cause mortality. Research indicates that macrolides can lead to significant alterations in cardiac repolarization, thereby prolonging the QT interval, particularly in patients with pre-existing cardiac conditions or those on concurrent medications that also affect QT duration.[66] It has also been associated with a higher risk of myocardial infarction, VA and sudden cardiac death, though this risk is relatively lower compared to that of azithromycin.[67] Several studies have reported rare adverse effects associated with its use, including seizures, status epilepticus, mania, agitation, and delirium.[68]

Another rare but serious adverse effect associated with intravenous clarithromycin is severe vesiculobullous skin reactions and vein thrombosis.[69] Furthermore, intravenous administration of clarithromycin requires monitoring due to higher reported rates of infusion site pain and superficial thrombophlebitis. It is classified as a category C drug by the FDA and should be used cautiously during pregnancy.

DRUG INTERACTIONS

Clarithromycin is associated with numerous significant drug interactions, primarily due to its strong inhibitory effects on CYP3A4 and P-glycoprotein. These interactions can lead to increased plasma concentrations of other medications, potentially resulting in adverse effects.

Calcium channel blockers

Clarithromycin inhibits the metabolism of calcium channel blockers like amlodipine via CYP3A4.[70] This co-administration increases the amlodipine's bioavailability, potentially causing hypotension due to elevated plasma concentrations and reduced drug clearance.[70]

Statins

By inhibiting CYP3A4, clarithromycin can significantly increase the concentration of statins in the bloodstream, heightening the risk of muscle toxicity (e.g., myopathy or rhabdomyolysis).[71] Specifically, clarithromycin raises the systemic exposure to simvastatin and lovastatin more than fivefold, moderately increases the levels of atorvastatin and pitavastatin (2- to 4-fold), and slightly increases pravastatin exposure (around 2-fold), with little effect on fluvastatin or rosuvastatin.[71]

Oral hypoglycemic

Clarithromycin can amplify the hypoglycemic effects of drugs like sulfonylureas and insulin, raising the risk of hypoglycemia. Patients with end-stage renal disease can experience refractory hypoglycemia due to this interaction.[72]

Antiepileptics

Clarithromycin inhibits the metabolism of antiepileptic drugs such as carbamazepine and phenytoin through CYP3A4 inhibition, leading to elevated plasma levels of these drugs and potential toxicity, including symptoms like dizziness, nausea, and ataxia.[73]

Colchicine

Clarithromycin significantly extends the half-life of colchicine by inhibiting CYP3A4, increasing the risk of severe toxicity, especially in elderly patients. Adverse effects can be severe, sometimes resembling systemic diseases, with reports of fatalities due to this interaction.[74]

QT interval prolongation

Clarithromycin is known to prolong the QT interval, increasing the risk of a potentially life-threatening arrhythmia called torsades de pointes, especially when combined with other QT-prolonging drugs. This risk is heightened when clarithromycin is used with antipsychotics (e.g., haloperidol, quetiapine), antiarrhythmics (e.g., amiodarone, sotalol), antidepressants (e.g., citalopram, escitalopram), or methadone.[75] Additionally, bilastine, an antiallergic drug, should be used cautiously with clarithromycin as it may contribute to QT prolongation.

DISCUSSION

Macrolides, including clarithromycin, are widely recognized for their efficacy in treating respiratory, gastrointestinal, and systemic bacterial infections. They are considered to be highly effective antibiotics due to their exceptional ability to penetrate tissues, extended duration of tissue persistence, and favorable safety profile after oral administration. Among macrolides, clarithromycin stands out due to its broad-spectrum activity and immunomodulatory effects, which position it well as a primary treatment for systemic infections, demonstrating effectiveness in resolving conditions such as pneumonia, URTIs, LRTIs, AOM, and other bacterial infections. Compared to other macrolides, it offers superior pharmacodynamic profile, including a longer half-life and better tissue concentration. This leads to enhanced antibacterial efficacy, especially in managing resistant bacterial strains.

Additionally, the current research indicated that clarithromycin exhibits a lower resistance rate compared to other macrolides, even under COVID-19 conditions. Post COVID-19, clarithromycin has been considered a more favorable option than azithromycin, as studies indicate that azithromycin misuse during the pandemic contributed to a rise in antimicrobial resistance. Pharmacodynamic modeling and epidemiological data suggest that increased resistance to azithromycin compared to clarithromycin can be attributed to differences in their pharmacokinetics, potency, and mutant-prevention concentrations (MPC). It's pharmacokinetic properties, such as a longer time above the MPC, make it less prone to induce resistance, offering a safer therapeutic alternative.[48] When compared to amoxicillin-clavulanate, clarithromycin can also be used in primary care settings in patients experiencing diarrhoea with the former antibiotic, demonstrates superior activity against specific pathogens like MAC, and is particularly useful in patients allergic to penicillin.[62] Additionally, clarithromycin's immune-modulating effects give it an edge over amoxicillin-clavulanate in certain inflammatory conditions.

Although clarithromycin is highly effective, the question remains whether it should be chosen when patients do not respond to other macrolides. In such cases, exploring alternative antibiotic classes may be prudent, particularly in patients with resistant infections. However, clarithromycin may still offer clinical benefits in cases where other macrolides fail.

Regarding its role in primary versus secondary infections, clarithromycin remains a front-line treatment for primary bacterial infections, caused by H. *pylori*, URTIs, LRTIs, and certain infections in patients unresponsive or allergic to penicillin.[9,13,14,16,23] In secondary infections, particularly those arising from viral illnesses, clarithromycin is effective in preventing bacterial superinfections by modulating immune responses and preventing bacterial adhesion to infected cells. It plays a role in preventing secondary bacterial infections in patients with rhinovirus by inhibiting pathways that facilitate bacterial attachment. Additionally, clarithromycin has shown promise in managing viral infections like influenza and COVID-19 by reducing inflammation and improving clinical outcomes.[56] Clarithromycin has been recommended for use in patients with ampicillin-resistant infections and has led to a notable decrease of over 99% in MAC bacteremia among HIV-infected individuals.[42]

Finally, the continued use of clarithromycin as a reserve drug is supported by its efficacy in resistant bacterial infections. While it is recommended for certain primary indications, its reserve status is crucial to prevent overuse and minimize the risk of resistance. While considering the therapeutic potential of clarithromycin, it has also been reported to show various side effects, like potentially elevating the risk of cardiovascular disease. Additionally, clarithromycin is classified as a Category C drug. Overall, clarithromycin remains a valuable antibiotic, especially in scenarios where first-line treatments fail or are contraindicated.

CONCLUSION

In conclusion, clarithromycin remains a critical antimicrobial agent in multiple primary infections. Its immunomodulatory properties and ability to inhibit bacterial adhesion also make it effective in preventing secondary bacterial infections following viral illnesses like rhinovirus, influenza, and COVID-19. With demonstrated efficacy in resistant cases, clarithromycin's broad-spectrum application and safety profile support its continued use in various clinical scenarios. It is positioned as a reserve antibiotic and should remain so to minimize the risks of ever-increasing antibiotic resistance.

ACKNOWLEDGEMENTS

The authors would like to thank NeoCrest Life Sciences Consulting Private Limited for providing medical writing assistance for this manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The immunomodulatory effects of macrolides—a systematic review of the underlying mechanisms. Front Immunol. 2018;9:302.
2. Naik P, Prabhat D, Shrivastava R, Nair A, Khandke DA. Clarithromycin: overview and its current clinical utility in the treatment of respiratory tract infections. Int J Res Med Sci. 2024;12(2):1.
3. Jednačak T, Mikulandra I, Novak P. Advanced Methods for Studying Structure and Interactions of Macrolide Antibiotics. Int J Mol Sci. 2020;21(20):7799.
4. Zuckerman J. Macrolides and ketolides: Azithromycin, clarithromycin, telithromycin. Infect Dis Clin North Am. 2004;18:621-49.
5. Tanwir S, Sabah A, Khatoon A, Afridi FI. Increased antimicrobial resistance against azithromycin during COVID: role of irrational utilization. J Pak Med Assoc. 2024;74(2):258-71.
6. Lee JW. Clarithromycin. Helicobacter pylori: Springer. 2024;485-95.
7. Karakike E, Scicluna BP, Roumpoutsou M, Mitrou I, Karampela N, Karageorgos A, et al. Effect of intravenous clarithromycin in patients with sepsis, respiratory and multiple organ dysfunction syndrome: a randomized clinical trial. Crit Care. 2022;26(1):183.
8. Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J. Cochrane Review: Antibiotics for whooping cough (pertussis). Evidence-Based Child Health. 2012;7(3):893-956.
9. Coutinho G, Duerden M, Sessa A, Caretta-Barradas S, Altiner A. Worldwide comparison of treatment guidelines for sore throat. Int J Clin Pract. 2021;75(5):e13879.
10. Clarithromycin approved uses- USFDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050662s044s050,50698s026s030,050775s015s019lbl.pdf. Accessed on 12 October 2024.
11. Clarithromycin approved drug-CDSCO. 2022. Available at: https://cdscoonline.gov.in/CDSCO/Drugs. Accessed on 12 October 2024.
12. Aumpan N, Mahachai V, Vilaichone Rk. Management of Helicobacter pylori infection. JGH Open. 2023;7(1):3-15.
13. Gopalkrishnan R, Walia K, Ohri V. Treatment Guidelines for Antimicrobial Use in Common Syndromes 2nd edition: Indian Council of Medical Research. 2019. Available at: https://main.icmr.nic.in/sites/default/files/guidelines/Treatment_Guidelines_2019_Final.pdf. Accessed on 12 October 2024.
14. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012;55(10):e86-102.
15. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-52.
16. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009;119(11):1541-51.
17. Agwuh K. Skin and Soft Tissue Infection Guideline, including Diabetic Foot Ulcer Infection. 2022. Available at: https://www.dbth.nhs.uk/wp-content/uploads/2022/. Accessed on 12 October 2024.
18. Antibiotic prescribing in primary care: Therapeutic Guidelines summary table 2023. Australian Commission on Safety and Quality in Health. 2023. Available at: https://www.safetyandquality.gov.au/sites/default/files/2023-05/gpsummary_v15.pdf. Accessed on 12 October 2024.
19. Giamarellos-Bourboulis EJ, Siampanos A, Bolanou A, Doulou S, Kakavoulis N, Tsiakos K, et al. Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial. Lancet Resp Med. 2024;12(4):294-304.
20. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH, and the Canadian Community-Acquired Pneumonia Working G. Canadian Guidelines for the Initial Management of Community-Acquired Pneumonia: An Evidence-Based Update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis. 2000;31(2):383-421.
21. Kim NN, Marikar D. Antibiotic prescribing for upper respiratory tract infections: NICE guidelines. Arch Dis Child Educ Pract Ed. 2020;105(2):104-6.
22. Goto H. Multicenter surveillance of adult atypical pneumonia in Japan: its clinical features, and efficacy and safety of clarithromycin. J Infect Chemother. 2011;17(1):97-104.

23. Kalra MG, Higgins KE, Perez ED. Common questions about streptococcal pharyngitis. Am Fam Physician. 2016;94(1):24-31.
24. Onyekwere CA, Odiagah JN, Igetei R, Emanuel AOD, Ekere F, Smith S. Rabeprazole, clarithromycin, and amoxicillin Helicobacter pylori eradication therapy: report of an efficacy study. World J Gastroenterol. 2014;20(13):3615.
25. Worrall G. Acute sore throat. Can Fam Physician. 2011;57(7):791-4.
26. Hoban DJ, Nauta J. Clinical And Bacteriological Impact Of Clarithromycin In Streptococcal Pharyngitis: Findings From A Meta-Analysis Of Clinical Trials. Drug Des Devel Ther. 2019;13:3551-8.
27. Reveiz L, Cardona AF. Antibiotics for acute laryngitis in adults. Cochrane Database Syst Rev. 2015;2015(5):CD004783.
28. Rechtweg JS, Moinuddin R, Houser SM, Mamikoglu B, Corey JP. Quality of life in treatment of acute rhinosinusitis with clarithromycin and amoxicillin/clavulanate. Laryngoscope. 2004;114(5):806-10.
29. Bhargava SK, Peethambaran K. Pharmacotherapy of Chronic Rhinosinusitis with a Focus on Clarithromycin: An Expert Opinion. J Assoc Physicians India. 2018;66(10):74-9.
30. Luo Q, Chen F, Liu W, Li Z, Xu R, Fan Y, et al. Evaluation of long-term clarithromycin treatment in adult Chinese Patients with chronic rhinosinusitis without nasal polyps. ORL J Otorhinolaryngol Relat Spec. 2011;73(4):206-11.
31. Lin CF, Wang MC, Merton AT, Ho NH, Wu PS, Hsu AT, et al. Add-on effect of clarithromycin to oral steroids as post- operative therapy for chronic rhinosinusitis with nasal polyps: a randomised controlled trial. Rhinology. 2020;58(6):550-8.
32. Perot B, Baban M. The Role of the Macrolide in Preventing Recurrence of the Nasal Polyposis after Fess. Pak J Med Health Sci. 2021;14(3):1291-5.
33. Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. Int Forum Allergy Rhinol. 2014;4(7):533-41.
34. Chen H, Zhou B, Huang Q, Li C, Wu Y, Huang Z, et al. Efficacy and Safety of Long-Term Low-Dose Clarithromycin in Patients With Refractory Chronic Sinusitis After Endoscopic Sinus Surgery: A Prospective Clinical Trial. Ear Nose Throat J. 2024;103(1):NP31-9.
35. El-Shinnawi M, Loizou P, Barbaccia C, Varma A. Management of Persistent Postnasal Drip Without Sinus Affection. Am J Interdisciplin Res Innov. 2024;3:1-6.
36. Ashy N, Alharbi L, Alkhamisi R, Alradadi R, Eljaaly K. Efficacy of erythromycin compared to clarithromycin and azithromycin in adults or adolescents with community-acquired pneumonia: A Systematic Review and meta-analysis of randomized controlled trials. J Infect Chemother. 2022;28(8):1148-52.
37. Al-Salloum J, Gillani SW, Mahmood RK, Gulam SM. Comparative efficacy of azithromycin versus clarithromycin in combination with beta-lactams to treat community-acquired pneumonia in hospitalized patients: a systematic review. J Int Med Res. 2021;49(10):3000605211049943.
38. Miravitlles M, Llor C, Naberan K, Cots JM, Molina J. Effect of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and chronic obstructive pulmonary disease in primary care. Clin Drug Investig. 2004;24:63-72.
39. Martinot JB, Carr WD, Cullen S, Heredia Budo JL, Bauer K, MacLeod C, et al. A comparative study of clarithromycin modified release and amoxicillin/clavulanic acid in the treatment of acute exacerbation of chronic bronchitis. Adv Ther. 2001;18(1):1-11.
40. Neu HC, Chick TW. Efficacy and safety of clarithromycin compared to cefixime as outpatient treatment of lower respiratory tract infections. Chest. 1993;104(5):1393-9.
41. Yamazaki Y, Ushiki A, Kubo K, Tanabe Y, Koyama S. Antimicrobial and anti-inflammatory effects of clarithromycin on Mycobacterium avium complex replication in cultured human bronchial epithelial cells. J Infect Chemother. 2012;18(5):683-8.
42. Chaisson RE, Benson CA, Dube MP, Heifets LB, Korvick JA, Elkin S, et al. Clarithromycin therapy for bacteremic Mycobacterium avium complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Ann Intern Med. 1994;121(12):905-11.
43. Pierce M, Crampton S, Henry D, Heifets L, LaMarca A, Montecalvo M, et al. A randomized trial of clarithromycin as prophylaxis against disseminated Mycobacterium avium complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med. 1996;335(6):384-91.
44. Gassiep I, Chaudhuri A. Is there a role for antimicrobial stewardship in bronchiectasis? Chron Respir Dis. 2015;12(3):274-5.
45. Fouka E, Lamprianidou E, Arvanitidis K, Filidou E, Kolios G, Miltiades P, et al. Low-Dose Clarithromycin Therapy Modulates Th17 Response In Non-Cystic Fibrosis Bronchiectasis Patients. Lung. 2014;192(6):849-55.
46. Yalçin E, Kiper N, Ozçelik U, Doğru D, Firat P, Sahin A, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. J Clin Pharm Ther. 2006;31(1):49-55.
47. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021;27(4):520-31.
48. Metzler K, Drlica K, Blondeau JM. Minimal inhibitory and mutant prevention concentrations of azithromycin, clarithromycin and erythromycin for

clinical isolates of Streptococcus pneumoniae. J Antimicrob Chemother. 2013;68(3):631-5.
49. Snow TAC, Longobardo A, Brealey D, Down J, Satta G, Singer M, et al. Beneficial ex vivo immunomodulatory and clinical effects of clarithromycin in COVID-19. J Infect Chemother. 2022;28(7):948-54.
50. Ohe M, Kataoka H, Mukai M. A case of lupus nephritis treated with clarithromycin, tacrolimus, and glucocorticoids. Kaohsiung J Med Sci. 2016;32(9):484-5.
51. Benden C, Boehler A. Long-term clarithromycin therapy in the management of lung transplant recipients. Transplantation. 2009;87(10):1538-40.
52. Knower MT, Labella-Walker K, McFadden PM, Kantrow SP, Valentine VG. Clarithromycin for safe and cost-effective reduction of cyclosporine doses in lung allograft recipients. South Med J. 2000;93(11):1087-92.
53. Iino Y, Yoshida N, Kato T, Kakizaki K, Miyazawa T, Kakuta H. Clinical effects of clarithromycin on persistent inflammation following Haemophilus influenzae-positive acute otitis media. Acta Otolaryngol. 2015;135(3):217-25.
54. Lee C-W, Tai Y-L, Huang L-M, Chi H, Huang F-Y, Chiu N-C, et al. Efficacy of clarithromycin-naproxen-oseltamivir combination therapy versus oseltamivir alone in hospitalized pediatric influenza patients. J Microbiol Immunol Infect. 2021;54(5):876-84.
55. Hung IF, To KK, Chan JF, Cheng VC, Liu KS, Tam A, et al. Efficacy of clarithromycin-naproxen-oseltamivir combination in the treatment of patients hospitalized for influenza A (H3N2) infection: an open-label randomized, controlled, phase IIb/III trial. Chest. 2017;151(5):1069-80.
56. Higashi F, Kubo H, Yasuda H, Nukiwa T, Yamaya M. Additional treatment with clarithromycin reduces fever duration in patients with influenza. Resp Investig. 2014;52(5):302-9.
57. Yamaya M, Shinya K, Hatachi Y, Kubo H, Asada M, Yasuda H, et al. Clarithromycin inhibits type a seasonal influenza virus infection in human airway epithelial cells. J Pharmacol Exp Ther. 2010;333(1):81-90.
58. Domon H, Isono T, Hiyoshi T, Tamura H, Sasagawa K, Maekawa T, et al. Clarithromycin Inhibits Pneumolysin Production via Downregulation of ply Gene Transcription despite Autolysis Activation. Microbiol Spectr. 2021;9(2):e0031821.
59. Kyriazopoulou E, Sinapidis D, Halvatzis S, Velissaris D, Alexiou N, Kosmas V, et al. Survival benefit associated with clarithromycin in severe community-acquired pneumonia: A matched comparator study. Int J Antimicrob Agents. 2020;55(1):105836.
60. Lee JH, Kim HJ, Kim YH. Is β-Lactam Plus Macrolide More Effective than β-Lactam Plus Fluoroquinolone among Patients with Severe Community-Acquired Pneumonia?: a Systemic Review and Meta-Analysis. J Korean Med Sci. 2017;32(1):77-84.
61. Zhao P, Yao R, Yang J, Wen W, Yao Y, Du X. Efficacy and safety of clarithromycin for patients with sepsis or septic shock: a systematic review and meta-analysis. Emerg Crit Care Med. 2024;4(2).
62. Evans J, Hanoodi M, Wittler M. Amoxicillin clavulanate. 2023 Aug 16. StatPearls. Treasure Island (FL): StatPearls Publishing. 2023.
63. Hoban DJ, Nauta J. Clarithromycin Amoxicillin alone or with Clavulanate in Acute Maxillary Sinusitis: A Meta-analysis of Clinical Trials. Open Infect Dis J. 2021;13.
64. Slay RM, Hewitt JA, Crumrine M. Determination of the Postexposure Prophylactic Benefit of Oral Azithromycin and Clarithromycin Against Inhalation Anthrax in Cynomolgus Macaques. Clin Infect Dis. 2022;75(3):S411-s6.
65. Tsiakos K, Tsakiris A, Tsibris G, Voutsinas PM, Panagopoulos P, Kosmidou M, et al. Early Start of Oral Clarithromycin Is Associated with Better Outcome in COVID-19 of Moderate Severity: The ACHIEVE Open-Label Single-Arm Trial. Infect Dis Ther. 2021;10(4):2333-51.
66. Júnior VCR, Sabattini AC. Impact of Azithromycin on the Predisposition to Cardiac Arrhythmias in Adult Patients: A Systematic Review. SCT Proceedings in Interdisciplinary Insights and Innovations. 2024;2:329.
67. Alispahic IA, Eklöf J, Sivapalan P, Jordan AR, Harboe ZB, Biering-Sørensen T, et al. Risk of Mortality and Cardiovascular Events in Patients with Chronic Obstructive Pulmonary Disease Treated with Azithromycin, Roxithromycin, Clarithromycin, and Amoxicillin. J Clin Med. 2024;13(7).
68. Seetharam R, Iyer RB, Nooraine J, Ramachandran J. Clarithromycin-induced Seizures and Status Epilepticus. Indian J Crit Care Med. 2021;25(8):945-7.
69. Kuçukbayrak A, Senel E, Kücükbayrak ZS, Gunay E, Simsek E. Vesiculobullous eruption of the right arm after intravenous clarithromycin. Indian J Pharmacol. 2011;43(1):82-3.
70. Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, et al. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013;310(23):2544-53.
71. Hougaard Christensen MM, Bruun Haastrup M, Øhlenschlæger T, Esbech P, Arnspang Pedersen S, Bach Dunvald AC, et al. Interaction potential between clarithromycin and individual statins—A systematic review. Basic Clin Pharmacol Toxicol. 2020;126(4):307-17.
72. Ruan XC, Tan PY, Tan Y. Clarithromycin and glipizide drug-drug interaction leading to refractory hypoglycemia. Cureus. 2019;11(6).
73. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006;61(3):246-55.
74. Villa Zapata L, Hansten PD, Horn JR, Boyce RD, Gephart S, Subbian V, et al. Evidence of Clinically Meaningful Drug–Drug Interaction With

Concomitant Use of Colchicine and Clarithromycin. Drug Safety. 2020;43(7):661-8.
75. Vieweg WVR, Hancox JC, Hasnain M, Koneru JN, Gysel M, Baranchuk A. Clarithromycin, QTc interval prolongation and torsades de pointes: the need to study case reports. Therap Adv Infect Dis. 2013;1(4):121-38.

Cite this article as: Waghray P, Bhargava S, Joshi DK, Gala M, Muchhala SS, Kotak BP. Role of clarithromycin in the management of multiple infection. Int J Res Med Sci 2025;13:547-58.