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Review Article

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A Revolutionary Leap: Bridging The Gap in Antibiotic Resistance Against Pneumonia

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Abstract

Nafithromycin is India's first indigenous antibiotic designed to treat community-acquired bacterial pneumonia (CABP), a major health concern, especially for the elderly and those with underlying health issues. CABP is one of the leading causes of hospitalization, primarily caused by Streptococcus pneumoniae, although it can also involve various other bacteria. This antibiotic is a macrolide, which is known for several advantageous properties: good oral bioavailability and effective penetration of lung tissue, with a three-day course of treatment, this innovative antibiotic is ten times more effective than existing medications like azithromycin, thereby reducing recovery time. Additionally, it is safe for pediatric use and has immune-modulating effects. Its spectrum of activity includes atypical bacteria that can cause pneumonia, making it particularly useful in treating pneumococcal infections in outpatient and hospital settings. The global incidence of CABP ranges from 20 to 100 cases per 10,000 person-years, highlighting its prevalence. While many cases can be treated with oral antibiotics in outpatient settings, severe cases may require hospitalization, when there are complications or when oral treatments are ineffective. Nafithromycin is particularly important as it can address multidrug-resistant strains of both typical and atypical respiratory pathogens, including those resistant to penicillin and other macrolides. This innovative antibiotic offers a promising solution to the challenges posed by resistant bacterial infections in the treatment of CABP. It represents a significant advancement in the fight against bacterial pneumonia in India, providing an effective treatment option against resistant pathogens. It works by attaching itself to the bacterial ribosome and preventing the construction of proteins and subsequent translation. Overall, Nafithromycin was well tolerated across all dosages, with no severe adverse effects reported, showed moderate metabolism in most species, was well tolerated in human trials, and demonstrated favorable pharmacokinetic properties.

1. Introduction.

Community-acquired bacterial pneumonia (CABP), one of the most frequent illnesses that necessitates hospitalization, particularly in the elderly and those with comorbid disorders, remains a significant concern in the field of infectious diseases (1,2). Macrolides are "tailored" antibiotics for the treatment of pneumococcal infections in both outpatient and hospital settings because of their (i) oral bioavailability, (ii) exponential lung (site-of-infection) penetration, (iii) pharmacokinetics/pharmacodynamics (PK/PD) features that allow for less frequent dosing, (iv) pediatric-use safety, (iv) favorable immune-modulating activity, and most importantly (v) an activity spectrum that includes pneumonia-causing atypical bacteria (3). The incidence of CABP varies from 20 to 100 per 10,000 person-years worldwide (4).The primary cause of CABP is S. pneumoniae, even though it is a multi-aetiological infection (5,6), and is typically treated empirically with antibiotics in ambulatory settings; hospitalization is only necessary in severe cases, when oral medication fails, or when comorbidities occur (7). Pneumococcal strains that are resistant to penicillin and macrolides are among the multidrug-resistant (MDR) typical and atypical respiratory pathogens that can be covered by the innovative oral and intravenous lactone-ketolide Nafithromycin (8). (3R,3aS,4R,6R,8R,9R,10R,12R,15R,15aS,Z)-9-(((2S,3R,4S,6R)-4-(Dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-15-ethyl-8-methoxy-4,6,8,10,12,15a-hexamethyl-2,5,11,13-tetraoxo-N'-((S)-1-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)ethoxy)tetradecahydro-2H-furo[2,3-c][1]oxacyclotetradecine-3-carboximidamide; is its chemical name. (registration number 1691240-78-4 for Chemical Abstract Services)

In the United States of America, naftithromycin has completed phase I and phase II clinical trials. The U.S. Food and Drug Administration awarded its qualifying infectious disease product (QIDP) classification in 2015. The medication is currently seeking final approval from the Central Drugs Standard Control Organisation (CDSCO) after undergoing rigorous clinical studies in the United States, Europe, and India (11). The medication is currently seeking final approval from the Central Drugs Standard Control Organisation (CDSCO) after undergoing rigorous clinical studies in the United States, Europe, and India (11).

Erm, efflux, and ribosomal protein mutations are the three macrolide resistance mechanisms that this drug defeats in S. pneumoniae. In a worldwide surveillance investigation, this drug indicated strong effectiveness against respiratory infections, including S. pneumoniae, and is resistant to macrolide (12). High and prolonged exposures to it in lung epithelial lining fluid (ELF) were found in Phase 1 pulmonary pharmacokinetic investigation (69 times higher than the plasma unbound exposures). Furthermore, alveolar macrophages have far greater concentrations of the drug (2635 times) than plasma unbound exposures, which should help kill the pathogen intracellularly and deliver large drug concentrations at the infection site (13). The larger pulmonary exposures guarantee the effectiveness of the three-day, once-daily (OD) dosage schedule of naftithromycin for CABP and make it easier to achieve the PK/PD targets shown by the Monte Carlo simulation. Its safety and effectiveness have been proven by a worldwide Phase 2 research that compared a 3-day OD regimen with a 7-day OD regimen of moxifloxacin (ClinicalTrials.gov identifier NCT02903836).

The distinct structural features of the drug, including a hydrophilic alkyl aryl side chain with a chiral methyl and a double-bond amidoxime core without fluoro substitution, are responsible for these features (14). To evaluate its safety and effectiveness as a treatment for three days, once daily in adult patients with CABP in India, a phase 3 randomized, double-blinded, non-inferiority trial was initiated. Its in vitro activity against modern invasive and non-invasive S. pneumoniae isolates obtained from major Indian cities was examined before this investigation (15).

2. Nafithromycin: A Milestone for Public Health

On November 20, 2024, the Union Minister 'Dr. Jitendra Singh formally introduced naftromycin, also known as "Miqnaf," created by Wockhardt with assistance from the Biotechnology Industry Research Assistance Council (BIRAC), to treat drug-resistant bacteria that cause community-acquired bacterial pneumonia (CABP). With a three-day course of treatment, this innovative antibiotic is ten times more effective than existing medications, such as azithromycin, thereby reducing recovery time and enhancing patient outcomes. It is an essential weapon in combating the global health challenge of antimicrobial resistance (AMR) because it treats both normal and atypical drug-resistant bacteria. It has no serious medication interactions, few adverse effects, and excellent safety (16).

3. Etiology of CABP.

Streptococcus pneumoniae is the bacterium that causes the majority of CABP, accounting for up to

two-thirds of bacteremia cases and 30% of all cases. Atypical microbes such as Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella spp. Account for 20% of CABP, whereas Haemophilus influenzae accounts for 12% (17, 18, 19). According to recent research, Gram-negative bacilli such as Escherichia coli (11.5%), Klebsiella pneumoniae (4%) or P. aeruginosa (2.8%), and S. aureus (10.2%) are among its other aetiologies (20). Six percent of infections acquired in CABP are multidrug-resistant organisms (MDRO), which are linked to increased mortality. These include methicilin-susceptible Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase (ESBL) Enterobacteriaceae, and Pseudomonas aeruginosa. These pathogens are primarily observed in elderly patients who have previously been exposed to drugs (21).

4. Are New Antibiotics Needed for CABP?

Ongoing epidemiological shifts have raised certain concerns that warrant the development of novel antibiotics to treat CABP. With a prevalence of 20–40% in certain environments, S. pneumonia resistance to macrolides is noteworthy (22, 23). Globally, M. pneumoniae is also becoming resistant to macrolides (24). For these reasons, the 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA)guidelines, which advised macrolide monotherapy for outpatients, have been revised to a conditional recommendation due to concerns about macrolide resistance levels in the 2019 ATS/IDSA guidelines (25,26). Finally, concerns have been expressed about the widespread usage of fluoroquinolones in all CABP patients owing to the description of adverse outcomes associated with their use. Some of these adverse events, such as tendinopathy and tendon rupture, have been known for years; however, others, such as severe hypoglycemia, adverse psychiatric events, QT prolongation, and aortic rupture and dissection, have gained attention more recently because of their severity. The Food and Drug Administration has recommended that fluoroquinolones be reserved for patients with no other treatment options because of these factors (27).

5. Nafithromycin: A Drug of Choice

A multicenter, double-blind, phase 3 pneumonia study comparing moxifloxacin to Wockhardt NCE (new chemical entity), also known as naftromycin. The study findings demonstrated that a three-day ultrashort course of treatment is as effective as a seven-day course of moxifloxacin. The results of the phase 3 trial are consistent with those of phase 2 studies conducted in the US and Europe. According to US human lung penetration research, the drug has the ability to build up a high lung concentration over five days after only three days of dosage. It is eight times more common in human lung exposure than azithromycin, and its efficacy for some respiratory infections is 10–100 times greater (28). In the phase 3 research, 96.7% of patients experienced a clinical cure after three days of naftromycin treatment, compared to 94.5% in the moxifloxacin arm. A sizable fraction of research participants had infections caused by bacteria resistant to levofloxacin, amoxicillin + clavulanic acid, and azithromycin. Clinicians would be very interested in how this new drug might be used to treat such patients (29). There were no severe adverse events (AEs) in the phase 3 study; all that were reported were minor, and the investigators thought that most of them had little to do with the study medications, except for gastrointestinal and nausea symptoms. Additionally, the study demonstrates that it is the first macrolide to effectively complete clinical development for the indication of community-acquired bacterial pneumonia in 30 years (30).The macrolide antibiotics currently on the market, clarithromycin and azithromycin, were authorized in 1988 and 1991, respectively. Since then, no new macrolide antibiotics have been licensed, even though the World Health Organization estimates that pneumonia kills 2.5 million people globally each year (31). Pneumococcal infection is expected to have caused 151,768 fatalities in India, according to the infectious disease-related mortality burden published in the December 2022 issue of the Lancet. In summary, naftromycin has been a significant development in the last three decades for the treatment of pneumonia that is both safe and effective against resistant organisms in the community (32). It is an essential weapon in combating the worldwide health challenge of antimicrobial resistance (AMR) because it is made to treat both normal and atypical drug-resistant bacteria. It has no serious medication interactions, few adverse effects, and excellent safety (33).

6. Use of Nafithromycin.

Pneumococcal strains resistant to penicillin and macrolides are among the MDR typical and atypical respiratory pathogens that can be covered by the innovative oral and intravenous lactone-ketolide naftimicin. In addition to other significant respiratory pathogens, such as H. influenzae, Moraxella catarrhalis, methicilin-resistant Staphylococcus aureus, and group A streptococci, preclinical research has demonstrated that naftimicin has pharmacodynamic activity against macrolide- and ketolide-resistant strains of Streptococcus

pneumoniae. According to global antimicrobial monitoring research conducted between 2013 and 2014, the MICs for 50% and 90% of isolates (MIC50 and MIC90) against S. pneumoniae were 0.015 mg/liter and 0.06 mg/liter, respectively. In vitro, naftimicin was 2–8 times more effective against S. pneumoniae than telithromycin, cethromycin, clindamycin, and clarithromycin (34).

In humans, it is moderately metabolized by CYP3A4. Its metabolites do not inhibit CYP2D6 and are weak inhibitors of CYP3A4 isoforms. It is significantly eliminated by the kidneys, thereby reducing the hepatic burden. In terms of hepatic safety, a repeat-dose trial revealed a large safety margin. Nafithromycin and ketolides are prescribed to treat CABP (35,36).

Its inhibitory potential does not depend on metabolism, and it has no CYP-inducing constraints; the drug has demonstrated reversible and mild inhibition of the CYP3A4 isoform. All of these characteristics are thought to be essential in avoiding liver damage caused by drugs and/or their metabolites that have hepatotoxic potential. Furthermore, ketolide medications with strong CYP3A4 inhibitory action impede their metabolism, which raises the risk of drug toxicity by causing the drugs to accumulate at ever higher levels with repeated dosage (37,38).

7. Mechanism of Action

The main way that macrolide antibiotics work is by attaching themselves to the bacterial ribosome and preventing the construction of proteins and subsequent translation. This is accomplished by causing steric obstruction of peptide transport by attaching to the ribosome's 50S subunit, more especially the 23S rRNA (39). Although these interactions are typically bacteriostatic, clarithromycin and azithromycin have bactericidal effects when they interact with S. pyogenes, S. pneumoniae, and H. influenzae (40). Kobuchi et al. (2016) state that macrolides such as azithromycin accumulate to high levels in the initial location where infections caused by bacteria begin, particularly within the interstitial spaces of soft tissue structures. The 23s rRNA domain V's peptidyl transferase ring is the primary binding site for macrolides and lincosamides like clindamycin, which block the exit tunnel for developing peptides. The lactone ring of the macrolide and the desosamine sugar regulate the interaction of hydrogen bond interactions with the peptidyl transferase cavityIn particular, a crucial ribosome nucleotide (E. coli's A2058), which is the focus of ribosomal alterations and susceptibility-mediating methylases that facilitate defense against macrolides, interacts with the desosamine sugar's 2′ OH (Weisblum 1995). Domain V of the 23s rRNA contains this nucleotide as well as others that are involved in building interactions with macrolides (41). Domain II associated with 23s rRNA can also help in the stabilizing adsorption of macrolides by having a carbamate ring at C11–12, as seen using telithromycin (42). Telithromycin's alkyl-aryl branch forms a new connection with the developing peptide exit channel by interacting with residue A752 of the second domain of 23s rRNA (43). The substitution of aryl side chains for the 3-O-cladinose also produces a unique interaction with the nascent peptide exit tunnel, as was shown in the case of carbamolides, which are duplicates of 3-O- carbamoyl erythromycin A (44). The fact that 14- and 15-membered macrolides allow 6–8 peptides to construct themselves in the ribosome while the ketolide telithromycin allows 9–10 amino acids to accumulate in the ribosome indicates that there is greater space within the peptidyl transferase domain with the ketolide (45). It has been demonstrated that certain macrolides, such as the ketolide subclass, have alternative modes of action in addition to 23s rRNA binding. According to Champney and Tober (2000) and Champney et al. (1998), these macrolides, in particular clarithromycin, prevent the production of the 50S subunit. They also control the synthesis of the 30S ribosomal subunit, along with some ketolide antibiotics. This form of action is preferred over steric translation inhibition by certain macrolides. For instance, roxithromycin, flurithromycin, and ketolide antibiotics block the production of the 30S ribosomal subunit in H. influenzae (46). No particular interactions between ribosomal proteins and macrolides have been discovered, despite studies demonstrating that mutations in the ribosomal protein genes L4 and L22, which are involved in forming peptide cellars, are the origin of macrolide resistance (47). It is hypothesized that a portion of a developing peptide, whose accumulation is believed to be fatal, is expressed by some synthetic macrolides, giving them their broad bactericidal action (48). The increased degree of translation that can be sustained with the most recent generations of macrolides, such telithromycin and solithromycin, depends on the composition of the developing peptide, the structure of the protein's N-terminal order, and the nature of the nascent peptide egress tunnel (49). Furthermore, 9-oxime ketolides cause slightly distinct antibacterial action and steric interference by interacting with the 23s rRNA within the ribosomal egress tunnel (50). Translational precision is generally lost due to the increased rates of stop codon readthrough caused by 16-membered macrolides, specifically tylosin and

spiracin (51). It is uncertain what pharmacokinetic characteristics at the infection site may enable mediation of the bactericidal or bacteriostatic actions considering rocitamycin has demonstrated bactericidal activity in vitro but rapidly transforms into bacteriostatic metabolites in vivo (52). One macrolide with a completely bactericidal mechanism of action is fidaxomicin. Its peculiar 18-membered ring layout within macrolide antibiotics enables it to bind to and inhibit RNA polymerase, albeit its precise mode of action is still understood (53). Additional characteristics of macrolides include gastrointestinal motor stimulation, immunomodulation, anti-inflammatory, and anticancer effects. Additionally, at least one instance of antiviral properties against rhinovirus was previously reported for the oleandomycin derivative Mac5, however it was unclear how this occurred (54). It appears that the antibacterial properties of 14-membered macrolides have nothing to do with their reported intestinal motor-stimulating actions (motilide) (55). It has been possible to create non-antibiotic "motilides" that are more effective than erythromycin at promoting stomach emptying (56). Most likely, motilide activity results from the beta-turn shape of the macrolide ring, which resembles a functional component with motilin, a type of peptide that causes duodenal contractions (57). According to Asakawa et al. (2003), these motilides may be helpful in the treatment of anorexia-cachexia linked to delayed stomach transit. In many nations, diffuse panbronchiolitis, an inflammatory airway condition, has been treated with low dosages of antibacterial macrolides such as erythromycin, clarithromycin, azithromycin, and roxithromycin (58). Erythromycin and a number of its derivatives, some of which have only limited antibacterial activity, inhibit the release of interleukin-8, which may reduce inflammation, particularly in bronchial epithelial cells (59). Clarithromycin reduces T cell production of interleukin-2, along with josamycin and midecamycin (60), whereas erythromycin and certain derivatives limit leukocyte chemotaxis (61), suggesting an additional role in lowering inflammation. Several erythromycin's intermediate metabolites promote monocyte differentiation, suggesting that the drug's effects are due to its metabolism rather than its antibacterial properties (62). Azithromycin's immunomodulatory impact is used in clinical settings to treat a variety of chronic lung disorders by promoting function and reducing mucus secretion in airway epithelial cells (63). The macrolide rapamycin (sirolimus) has immunosuppressive qualities in addition to anticancer ones. To combat efflux-based medication resistance in the treatment of breast cancer, rapamycin can be coupled with a chemosensitizer, such as piperine, in a nanoparticle formulation (64). Additional interactions between macrolides and the immune system include encouraging the recruitment of macrophages and increasing the synthesis of C–C motif chemokine ligand2 by macrophages (65). Similarly, neutrophil migration is stimulated in vitro by erythromycin (and roxithromycin) (Anderson 1989). The research of the immunomodulatory effects of macrolides has led to the exploration of non-antibacterial erythromycin derivatives. Less potent macrolides are being created to block the inflammasome known as NLRP3 and decrease inflammation in chronic lung illnesses without affecting the rise in bacterial resistance rates (66). It is widely recognized that several non-antibacterial macrolides can alter the immune system. As a calcineurin inhibitor, tacrolimus is a macrolide immunosuppressant/immunomodulator that inhibits T-cell activation (67).

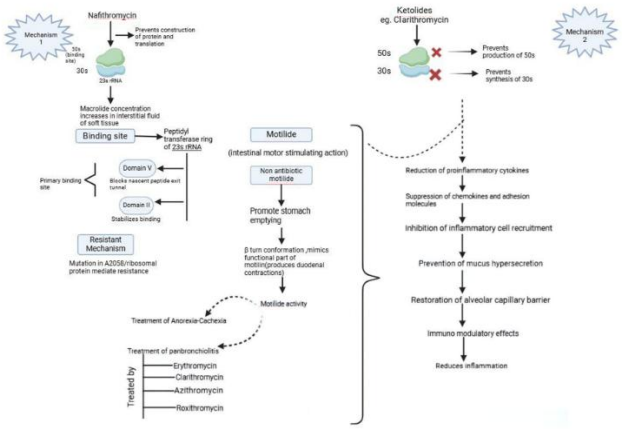

FIGURE:1; Mechanism of Action (68).

8. In- Vitro Drug Metabolism

In vitro metabolite profile analysis revealed that naftithromycin is moderately metabolized in all species studied, except in rats and rabbits, where it is slightly metabolized. Different species had varying proportions of metabolites. Metabolites were found in similar amounts in humans and dogs, but in monkeys, the quantities were larger. Fewer metabolites were found in rats and rabbits. Six metabolites were identified (69).

9. Testing And Trials

In two phase 1 randomized, double-blind, placebo-controlled trials, naftromycin was administered to healthy adults. The effects of food on the bioavailability of the drug were examined at 400 and 800 mg doses in a first-in-human trial, which

involved administering individuals single ascending oral doses of the antibiotic (100–1,200 mg) either fasted or fed. In the second study, multiple ascending oral doses of 600, 800, or 1,000 mg of the drug were administered once daily for seven days under fed conditions. In general, the drug was well tolerated at all dosages, with no significant adverse effects observed. The plasma AUC0-t increased by approximately 1.2-fold when administered under fed conditions compared with fasting. From time zero to time t, the area under the concentration–time curve (AUC0–t) varied from 0.54 to 22.53 h·mg/liter, while the mean maximum plasma concentration (C_{max}) varied from 0.099 to 1.742 mg/liter. The 600- and 800-mg dose samples reached a steady state after three days, whereas the 1,000-mg sample reached a steady state after four days. The Cmax of the antibiotic on day 7 in a multiple-dose study varied between 1.340 and 2.987 mg/liter, whereas the AUC during the last dosing period (AUC0–24) varied between 13.48 and 43.46 h·mg/liter. Both single- and multiple-dosing regimens enhanced plasma exposure to this drug in a dose-proportional manner. Further research into this antibiotic is supported by human pharmacokinetic profile data, tolerability, and safety. On the seventh session of therapy, the patient experienced a moderate buildup of naftromycin. (With registration codes NCT03926962 and NCT03979859, ClinicalTrials.gov has registered this study.) (70).

10. Discussion

Because of their (i) ease of dosage and (ii) broad-spectrum pathogen coverage, which ensures the effectiveness of monotherapy, macrolides have long been the treatment of choice for CABP and other pneumococcal infections. However, increasing resistance to macrolides has severely limited their use alone, forcing physicians to use a compromised treatment approach that combines macrolides with β-lactams (71).

High frequencies of macrolide non-susceptibility (>60%) were observed in the current panel of multicenter Indian pneumococcal isolates, which is consistent with a previous report (72). The increased clindamycin susceptibility rate compared to that for macrolides indicates a high frequency of efflux as a resistance mechanism affecting macrolides (73). The minimum inhibitory concentration (MIC) profile of naficithromycin, which shows strong efficacy against macrolide-, penicillin-, and quinolone-non-susceptible pneumococci, is consistent with the results of an earlier global surveillance trial (MIC90 of 0.06 mg/L) (74).

In conclusion, the characteristics of Nafithromycin, including its strong activity against S. pneumoniae and other respiratory pathogens, high and prolonged lung concentrations, and documented anti-inflammatory and immunomodulatory effects, suggest that it may be a promising treatment for CABP infections (75).

11. ABBREVIATIONS

PK	Pharmacokinetics
PD	Pharmacodynamics
CABP	Community-Acquired Bacterial Pneumonia
MDR	Multi-Drug Resistant
QIDP	Qualifying Infection Disease Product
CDSCO	Central Drug Standard Control Organisation
ELF	Epithelial Lining Fluid
OD	Once a Day
BIRAC	Biotechnology Industry Research Assistance Council
AMR	Anti-Microbial Resistance
MDRO	Multi-drug Resistant Organisms
MRSA	Methicillin-Susceptible Staphylococcus Aureus
ESBL	Extended Spectrum Beta-Lactamase
ATS	American Thoracic Society
IDSA	Infectious Disease Society of America
NCE	New Chemical Entity
AEs	Adverse Events
MIC	Minimum Inhibitory Concentration

Submission Declaration:

The authors confirm that the work is original and have read and approved the final manuscript for submission. The authors confirm that the work is original and have read and approved the final manuscript for submission.

Conflict of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this study.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Ethics Statement:

This review paper **does not** involve experimental research, human subjects, or animal studies that require ethical approval; instead, it is based entirely on publicly available literature. For academic openness and integrity, all acknowledged sources are appropriately

referenced. I have exercised all my powers to provide an objective, accurate, and thorough literature review free from any conflicts of interest that could affect the interpretation of the data. The development of this study did not involve any instances of scientific misconduct, data manipulation, or plagiarism. Let me know if you need refinement

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REFERENCES

1. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. The Lancet. 2015 Sep 12;386(9998):1097-108. doi:10.1016/S0140-6736(15)60733-4

2. Bordon J, Slomka M, Gupta R, Furmanek S, Cavallazzi R, Sethi S, Niederman M, Ramirez JA, University of Louisville Pneumonia Study Group. Hospitalization due to community-acquired pneumonia in patients with chronic obstructive pulmonary disease: incidence, epidemiology, and outcomes. Clinical microbiology and infection. 2020 Feb 1;26(2):220-6. doi:10.1016/j.cmi.2019.06.025

3. Amsden GW. Pneumococcal macrolide resistance—myth or reality?. Journal of Antimicrobial Chemotherapy. 1999 Jul 1;44(1):1-6. https://doi.org/10.1093/jac/44.1.1

4. Cools F, Delputte P, Cos P. The search for novel treatment strategies for Streptococcus pneumoniae infections. FEMS Microbiology Reviews. 2021 Jul;45(4):fuaa072. https://doi.org/10.1093/femsre/fuaa072

5. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, Chappell JD. Community-acquired pneumonia requiring hospitalization among US adults. New England Journal of Medicine. 2015 Jul 30;373(5):415-27. https://doi.org/10.1056/NEJMoa1500245

6. Feldman C, Anderson R. The role of Streptococcus pneumoniae in community-acquired pneumonia. InSeminars in Respiratory and Critical Care Medicine 2016 Dec (Vol. 37, No. 06, pp. 806-818). Thieme Medical Publishers. https://doi.org/10.1055/s-0036-1592074

7. Kaysin A, Viera AJ. Community-acquired pneumonia in adults: diagnosis and management. American family physician. 2016 Nov 1;94(9):698-706.

8. Flamm RK, Rhomberg PR, Sader HS. In vitro activity of the novel lactone ketolide nafithromycin (WCK 4873) against contemporary clinical bacteria from a global surveillance program. Antimicrobial agents and chemotherapy. 2017 Dec;61(12):10-128. https://doi.org/10.1128/aac.01230-17

9. Farrell DJ, Sader HS, Rhomberg PR, Flamm RK, Jones RN. In vitro activity of WCK 4873 (nafithromycin) against resistant subsets of Streptococcus pneumoniae from a global surveillance program (2014). American Society for Microbiology (ASM Microbe). 2016.

10. Bhawsar S, Tadiparthi R, Kayastha AK, Dixit P, Pavase L, Mishra A, Chavan V, Birajdar S, Shaikh M, Yeole R, Bhagwat S. Nafithromycin (MIQNAF®): ultramodern lactone ketolide designed to treat community acquired bacterial pneumonia (CABP). Medicinal Chemistry Research. 2024 Oct;33(10):1715-33.

11. Meshram N, Harane S, Kale V, Biyani D, Umekar MJ. Regulatory overview on new drugs and clinical trials rules, 2019. International Journal Of Drug Regulatory Affairs. 2023;11(1):31-42. DOI https://doi.org/10.22270/ijdra.v11i1.578

12. Flamm RK, Rhomberg PR, Sader HS. In vitro activity of the novel lactone ketolide nafithromycin (WCK 4873) against contemporary clinical bacteria from a global surveillance program. Antimicrobial agents and chemotherapy. 2017 Dec;61(12):10-128. https://doi.org/10.1128/aac.01230-17

13. Rodvold KA, Gotfried MH, Chugh R, Gupta M, Friedland HD, Bhatia A. Comparison of plasma and intrapulmonary concentrations of nafithromycin (WCK 4873) in healthy adult subjects. Antimicrobial agents and chemotherapy. 2017 Sep;61(9):10-128. https://doi.org/10.1128/aac.01096-17

14. Bhavsar S, Ravikumar T, Gupta S, Pawar S, Dabhade S, Kayastha AK, Deshpande P, Yeole R, Nandanwar M, Bhagwat S, Patel M. WCK 4873 (INN: Nafithromycin): Structure–activity relationship (SAR) identifying a novel lactone ketolide with activity against Streptococcus pneumoniae (SPN) and Streptococcus pyogenes (SPY). Results in Chemistry. 2023 Jan 1;5:100757. https://doi.org/10.1016/j.rechem.2022.100757

15. Veeraraghavan B, Varghese R, Saigal K, Balasubramanian S, Bai PS, Lal Y B, Neeravi A, Baskar P, Anandhan K, Kumar CG, Jayaraman Y. Activity of novel lactone ketolide nafithromycin against multicentric invasive and non-invasive

pneumococcal isolates collected in India. JAC-Antimicrobial Resistance. 2021 Jun 1;3(2):dlab066. https://doi.org/10.1093/jacamr/dlab066

16. Rathore IA, Malik S, Singh A, Tandon VR, Mahajan A. Nafithromycin: Pioneering India's Indigenous Antibiotic Revolution. JK Science: Journal of Medical Education & Research. 2025 Jan 10;27(1):1-2.

17. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. The Lancet. 2015 Sep 12;386(9998):1097-108.

18. File TM. Community-acquired pneumonia. The Lancet. 2003 Dec 13;362(9400):1991-2001.

19. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax. 2001 Apr 1;56(4):296-301. https://doi.org/10.1136/thorax.56.4.296

20. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson IF, Hill AT, Templeton KE. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clinical Infectious Diseases. 2016 Apr 1;62(7):817-23. https://doi.org/10.1093/cid/civ1214

21. Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, Puig de la Bellacasa J, Menéndez R, Mensa J, Torres A. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. Annals of the American Thoracic Society. 2015 Feb;12(2):153-60. https://doi.org/10.1513/AnnalsATS.201407-305OC

22. Cherazard R, Epstein M, Doan TL, Salim T, Bharti S, Smith MA. Antimicrobial resistant Streptococcus pneumoniae: prevalence, mechanisms, and clinical implications. American journal of therapeutics. 2017 May 1;24(3):e361-9. *DOI:* 10.1097/MJT.0000000000000551

23. Schroeder MR, Stephens DS. Macrolide resistance in Streptococcus pneumoniae. Frontiers in cellular and infection microbiology. 2016 Sep 21;6:98.doi:10.3389/ fcimb.2016.00098.

24. Haran JP, Volturo GA. Macrolide resistance in cases of community-acquired bacterial pneumonia in the emergency department. The Journal of emergency medicine. 2018 Sep 1;55(3):347-53. doi:10.1016/j. jemermed.2018.04.031.

25. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. American journal of respiratory and critical care medicine. 2019 Oct 1;200(7):e45-67. doi:10.1164/rccm.201908-1581ST.

26. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File Jr TM, Musher DM, Niederman MS, Torres A. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical infectious diseases. 2007 Mar 1;44(Supplement_2): S27-72. doi:10.1086/511159.

27. Buehrle DJ, Wagener MM, Clancy CJ. Outpatient fluoroquinolone prescription fills in the United States, 2014 to 2020: assessing the impact of Food and Drug Administration safety warnings. Antimicrobial agents and chemotherapy. 2021 Jun 17;65(7):10-128.

28. Rodvold KA, Gotfried MH, Danziger LH, Servi RJ. Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. Antimicrobial Agents and Chemotherapy. 1997 Jun;41(6):1399-402. https://doi.org/10.1128/aac.41.6.1399

29. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MK. Antibiotic resistance: a rundown of a global crisis. Infection and drug resistance. 2018 Oct 10:1645-58.

30. Saxena D, Dasgupta A, Chopra S. Nafithromycin. Ketolide antibiotic, Treatment of community-acquired bacterial pneumonia. Drugs of the Future. 2022 Dec;47(12). DOI: 10.1358/dof.2022.47.12.3441829

31. Scheld WM, Whitman MS, Tunkel AR. Azithromycin and clarithromycin overview and comparison with erythromycin. Infection Control & Hospital Epidemiology. 1992 Jun;13(6):357-68.

32. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. US pneumonia hospitalizations, a decade of pneumococcal conjugate vaccine use. The New England journal of medicine. 2013 Jul 7;369(2):155. DOI: 10.1056/NEJMoa1209165

33. Rathore IA, Malik S, Singh A, Tandon VR, Mahajan A. Nafithromycin: Pioneering India's Indigenous Antibiotic Revolution. JK Science:

Journal of Medical Education & Research. 2025 Jan 10;27(1):1-2.

34. Iwanowski P, Bhatia A, Gupta M, Patel A, Chavan R, Yeole R, Friedland D. Safety, tolerability, and pharmacokinetics of oral nafithromycin (WCK 4873) after single or multiple doses and effects of food on single-dose bioavailability in healthy adult subjects. Antimicrobial agents and chemotherapy. 2019 Dec;63(12):10-128. https://doi.org/10.1128/aac.01253-19

35. Brown SJ, Desmond PV. Hepatotoxicity of antimicrobial agents. InSeminars in liver disease 2002 (Vol. 22, No. 02, pp. 157-168). Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.:+ 1 (212) 584-4662.

36. Clay KD. Severe Hepatotoxicity of Telithromycin. Annals of Internal Medicine. 2006 Sep 19;145(6):472.

37. Brinker AD, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM, Seeff LB. Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. Hepatology. 2009 Jan;49(1):250-7.

38. Georgopapadakou NH. The wobbly status of ketolides: where do we stand?. Expert Opinion on Investigational Drugs. 2014 Oct 1;23(10):1313-9. https://doi.org/10.1517/13543784.2014.954036

39. Schlünzen F, Zarivach R, Harms J, Bashan A, Tocilj A, Albrecht R, Yonath A, Franceschi F. Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. Nature. 2001 Oct 25;413(6858):814-21.

40. Zuckerman M, Kuhlman DM. Personality and risk-taking: common bisocial factors. Journal of personality. 2000 Dec;68(6):999-1029. https://doi.org/10.1111/1467-6494.00124

41. Schlünzen F, Zarivach R, Harms J, Bashan A, Tocilj A, Albrecht R, Yonath A, Franceschi F. Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. Nature. 2001 Oct 25;413(6858):814-21.

42. Douthwaite S, Hansen LH, Mauvais P. Macrolide–ketolide inhibition of MLS-resistant ribosomes is improved by alternative drug interaction with domain II of 23S rRNA. Molecular microbiology. 2000 Apr;36(1):183-93. https://doi.org/10.1046/j.1365-2958.2000.01841.x

43. Dunkle JA, Xiong L, Mankin AS, Cate JH. Structures of the Escherichia coli ribosome with antibiotics bound near the peptidyl transferase center explain spectra of drug action. Proceedings of the national academy of sciences. 2010 Oct 5;107(40):17152-7. https://doi.org/10.1073/pnas.1007988107

44. Magee CA, Miller LM, Heaven PC. Personality trait change and life satisfaction in adults: The roles of age and hedonic balance. Personality and individual differences. 2013 Oct 1;55(6):694-8. https://doi.org/10.1016/j.paid.2013.05.022

45. Tenson T, Lovmar M, Ehrenberg M. The mechanism of action of macrolides, lincosamides and streptogramin B reveals the nascent peptide exit path in the ribosome. Journal of molecular biology. 2003 Jul 25;330(5):1005-14.https://doi.org/10.1016/S0022-2836(03)00662-4Get rights and content.

46. Mabe S, Eller J, Champney WS. Structure–Activity Relationships for Three Macrolide Antibiotics in Haemophilus influenzae. Current Microbiology. 2004 Oct;49:248-54.

47. Vester B, Douthwaite S. Macrolide resistance conferred by base substitutions in 23S rRNA. Antimicrobial agents and chemotherapy. 2001 Jan 1;45(1):1-2. https://doi.org/10.1128/aac.45.1.1-12.2001

48. Zhanel GG, Dueck M, Hoban DJ, Vercaigne LM, Embil JM, Gin AS, Karlowsky JA. Review of macrolides and ketolides: focus on respiratory tract infections. Drugs. 2001 Apr;61:443-98.

49. Agouridas C, Denis A, Auger JM, Benedetti Y, Bonnefoy A, Bretin F, Chantot JF, Dussarat A, Fromentin C, D'Ambrières SG, Lachaud S. Synthesis and antibacterial activity of ketolides (6-O-methyl-3-oxoerythromycin derivatives): a new class of antibacterials highly potent against macrolide-resistant and-susceptible respiratory pathogens. Journal of medicinal chemistry. 1998 Oct 8;41(21):4080-100.

50. Bryskier A. Antimicrobial agents: antibacterials and antifungals. 2005 Nov 2.

51. Kannan K, Mankin AS. Macrolide antibiotics in the ribosome exit tunnel: species-specific binding and action. Annals of the New York Academy of Sciences. 2011 Dec;1241(1):33-47.

https://doi.org/10.1111/j.1749-6632.2011.06315.x

52. Hardy SJ, Holmgren J, Johansson S, Sanchez J, Hirst TR. Coordinated assembly of multisubunit proteins: oligomerization of bacterial enterotoxins in vivo and in vitro. Proceedings of the National Academy of Sciences. 1988 Oct;85(19):7109-13. https://doi.org/10.1073/pnas.85.19.7109

53. Venugopal AA, Johnson S. Current state of Clostridium difficile treatment options. Clinical infectious diseases. 2012 Aug 1;55(suppl_2):S71-6. https://doi.org/10.1093/cid/cis355

54. Porter ME, Larsson S, Lee TH. Standardizing patient outcomes measurement. N Engl J Med. 2016 Feb 11;374(6):504-6.

55. Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, Beecham J, Park R, Silverberg S. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. Journal of Clinical Oncology. 1985 Sep;3(9):1240-5. DOI:10.1200/JCO.1985.3.9.1240

56. Cowles RA, Mulholland MW. Solitary hepatic cysts. Journal of the American College of Surgeons. 2000 Sep 1;191(3):311-21. DOI: 10.1016/S1072-7515(00)00345-8

57. Steinmetz LM, Scharfe C, Deutschbauer AM, Mokranjac D, Herman ZS, Jones T, Chu AM, Giaever G, Prokisch H, Oefner PJ, Davis RW. Systematic screen for human disease genes in yeast. Nature genetics. 2002 Aug;31(4):400-4.

58. Kadota JI, Sakito O, Kohno S, Sawa H, Mukae H, Oda H, Khiawakami K, Fukushima K, Hiratani K, Hara K. A mechanism of erythromycin treatment in patients with diffuse panbronchiolitis. American Review of Respiratory Disease. 1993 Jan;147(1):153-9. https://doi.org/10.1164/ajrccm/147.1.153

59. SUNAZUKA T, TAKIZAWA H, DESAKI M, SUZUKI K, OBATA R, OTOGURO K, OMURA S. Effects of erythromycin and its derivatives on interleukin-8 release by human bronchial epithelial cell line BEAS-2B cells. The Journal of Antibiotics. 1999 Jan 25;52(1):71-4. https://doi.org/10.7164/antibiotics.52.71

60. Ariyoshi M, Vassylyev DG, Iwasaki H, Nakamura H, Shinagawa H, Morikawa K. Atomic structure of the RuvC resolvase: a Holliday junction-specific endonuclease from E. coli. Cell. 1994 Sep 23;78(6):1063-72.

61. Uchida S, Oohori T, Tanaka T, Suzuki M, Shirai H. Synthesis of copolymers of poly (amino acid)–urethane in N, N-dimethylformamide. Polymer. 2000 Jan 1;41(2):473-80. https://doi.org/10.1016/S0032-3861(99)00191-3

62. Takahashi T, Kusaka SI, Doi T, Sunazuka T, Omura S. A combinatorial synthesis of a macrosphelide library utilizing a palladium-catalyzed carbonylation on a polymer support. Angewandte Chemie-International Edition. 2003 Nov 3;42(42):5230-4. https://doi.org/10.1002/anie.200352229

63. Sivapalasingam S, Steigbigel NH. Macrolides, clindamycin, and ketolides. InMandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 2015 Jan 1 (pp. 358-376). WB Saunders.

64. Katiyar A, Cardie C. Investigating LSTMs for joint extraction of opinion entities and relations. InProceedings of the 54th Annual Meeting of the Association for Computational Linguistics (Volume 1: Long Papers) 2016 Aug (pp. 919-929).

65. Iwanaga J, Saga T, Tabira Y, Nakamura M, Kitashima S, Watanabe K, Kusukawa J, Yamaki KI. The clinical anatomy of accessory mental nerves and foramina. Clinical anatomy. 2015 Oct;28(7):848-56. https://doi.org/10.1002/ca.22597

66. Hodge CJ, Duerden MD, Layland EK, Lacanienta A, Goates MC, Niu XM. The association between family leisure and family quality of life: A meta-analysis of data from parents and adolescents. Journal of Family Theory & Review. 2017 Sep;9(3):328-46. https://doi.org/10.1111/jftr.12202

67. Kitahara K, Kawai S. Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Current opinion in rheumatology. 2007 May 1;19(3):238-45. DOI: 10.1097/BOR.0b013e328099af80

68. https://BioRender.com

69. Gomez-Lechon MJ, Lahoz A, Gombau L, Castell JV, Donato MT. In vitro evaluation of potential hepatotoxicity induced by drugs. Current pharmaceutical design. 2010 Jun 1;16(17):1963-77. https://doi.org/10.2174/138161210791208910

70. Iwanowski P, Bhatia A, Gupta M, Patel A, Chavan R, Yeole R, Friedland D. Safety, tolerability, and pharmacokinetics of oral nafithromycin (WCK 4873) after single or multiple doses and effects of food on single-dose bioavailability in healthy adult subjects. Antimicrobial agents and chemotherapy.

2019 Dec;63(12):10-128. https://doi.org/10.1128/aac.01253-19

71. Garin N, Genné D, Carballo S, Chuard C, Eich G, Hugli O, Lamy O, Nendaz M, Petignat PA, Perneger T, Rutschmann O. β-Lactam monotherapy vs β-lactam–macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA internal medicine. 2014 Dec 1;174(12):1894-901. doi:10.1001/jamainternmed.2014.4887

72. Lodise TP, Van Le H, LaPensee K. Hospital admission patterns in adult patients with community-acquired pneumonia who received ceftriaxone and a macrolide by disease severity across United States hospitals. Antibiotics. 2020 Sep 4;9(9):577. https://doi.org/10.3390/antibiotics9090577

73. Lodise TP, Van Le H, LaPensee K. Hospital admission patterns in adult patients with community-acquired pneumonia who received ceftriaxone and a macrolide by disease severity across United States hospitals. Antibiotics. 2020 Sep 4;9(9):577. https://doi.org/10.3390/antibiotics9090577

74. Flamm RK, Rhomberg PR, Sader HS. In vitro activity of the novel lactone ketolide nafithromycin (WCK 4873) against contemporary clinical bacteria from a global surveillance program. Antimicrobial agents and chemotherapy. 2017 Dec;61(12):10-128. https://doi.org/10.1128/aac.01230-17

75. Trivedi J, Shaikh J, Chavan N, Thorve D, Chaudhary B, Karade A, Gupta S, Patel A, Bhagwat S. Pretreatment of nafithromycin attenuates inflammatory response in murine lipopolysaccharide induced acute lung injury. Cytokine. 2020 May 1;129:155049. https://doi.org/10.1016/j.cyto.2020.155049