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Doxycycline: A Versatile Antibiotic for Diverse Conditions

Doxycycline is recognized for its versatility as an antibiotic, boasting broad-spectrum effectiveness against a diverse range of bacterial infections. It belongs to the tetracycline class, and what sets it apart is its capability to address both common and intricate bacterial diseases.[1] The mechanism of action involves inhibiting bacterial protein synthesis through reversible binding to the 30S ribosomal subunit. Notably, doxycycline distinguishes itself with enhanced oral absorption and an extended serum half-life compared to other tetracycline antibiotics.[2]

With its broad-spectrum bacteriostatic properties,[3] doxycycline serves as a flexible antibiotic, demonstrating efficacy against gram-positive, gram-negative, and "atypical" bacterial strains, as well as certain protozoa like those causing malaria.[2]

Approved by the Food and Drug Administration (FDA), doxycycline finds applications in various therapeutic contexts.[2] These include the prevention and treatment of conditions ranging from acute undifferentiated febrile illnesses (e.g., malaria, dengue, rickettsial infections, and leptospirosis)[4–7] to respiratory infections caused by organisms like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Additionally, it proves effective against gynecologic infections such as pelvic inflammatory disease and gastrointestinal infections, encompassing issues like diarrhea and *Helicobacter pylori* infections.[2] Beyond its bacteriostatic effects, doxycycline exhibits antiviral activity against viruses like vesicular stomatitis virus, dengue virus, etc.[8,9]

This special edition offers comprehensive insights into doxycycline, covering its history, pharmacokinetics, and the diverse range of indications where its efficacy has been established. Clinical evidence underscores the effectiveness of doxycycline across the discussed indications.

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REVIEW ARTICLE

Doxycycline: An Overview of Its History and Current Use

Mangesh Tiwaskar*

Abstract

Since their original discovery in 1948, tetracycline antibiotics have had a major impact on the healthcare and molecular biology. Their efficacy against a variety of infectious diseases and discovery of the tetracycline repressor system has yielded an invaluable tool for the inducible control of gene expression. Originally characterized as selective inhibitors of the bacterial 30S ribosomal subunit, tetracyclines appear also to have alternate molecular targets in human tissues, which extends beyond a direct antimicrobial effect. The brief history of development is discussed in the article for our understanding of the molecule.

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Introduction

For over 4 decades, doxycycline has served as a prominent antibiotic within the tetracycline family, finding extensive application in clinical practice.[1]

Introduced in 1967, doxycycline, a semi-synthetic derivative of oxytetracycline (a tetracycline produced by *Streptomyces* species), emerged from the laboratories of Pfizer. Doxycycline has enhanced oral absorption and an extended serum half-life, setting it apart from other tetracycline antibiotics.[1]

With its broad-spectrum bacteriostatic properties,[2] doxycycline serves as a versatile antibiotic, exhibiting effectiveness against an extensive array of gram-positive, gram-negative, and "atypical" bacteria, as well as certain protozoa such as malaria. Moreover, it proves invaluable for prophylaxis and treatment against various significant potential biological warfare agents. Consequently, doxycycline finds extensive global usage, particularly in the management of sexually transmitted infections, respiratory tract infections, malaria prophylaxis, and the therapy of selective rickettsial infections transmitted by arthropods.[1]

Doxycycline has gained approval from the Food and Drug Administration (FDA) for a range of therapeutic applications, including the prevention and treatment of various conditions. These encompass rickettsial infections, sexually transmitted infections, respiratory tract infections, bacterial infections, Lyme disease, ophthalmic infections, anthrax, acute intestinal amebiasis, traveler's diarrhea, and severe acne. Additionally, doxycycline has garnered attention in cancer research, as certain studies suggest its potential in inhibiting cell proliferation, suppressing invasion, inducing apoptosis, and impeding the gap phase, which is a crucial stage in which cancerous cells grow and prepare for deoxyribonucleic acid (DNA) synthesis.[2]

The Discovery of Tetracycline: the Roadmap to the Origin of Doxycycline

Renowned for his extensive research on soil fungi, Duggar gained global recognition for his groundbreaking work. He meticulously collected soil samples from diverse locations, with a particular focus on areas rich in actinomycetes soil bacteria or "ultra-molds." These samples underwent rigorous testing by Duggar's team, employing broth dilution assays to assess their antibiotic activity against a panel of bacteria. However, it was a sample sent by William Albrecht and obtained from the University of Missouri that proved extraordinary. The colony derived from this sample exhibited a distinctive yellow coloration and inhibited the growth of all bacterial strains tested. Moreover, it exhibited notably expansive zones of growth inhibition in agar. Further investigations revealed that crude extracts obtained from this colony possessed potent antibacterial properties, effectively combating lethal diseases such as scrub typhus and rickettsias, including the insidious Rocky Mountain spotted fever, for which no cure existed at the time.[3]

Duggar coined the name aureomycin for the compound (chlortetracycline hydrochloride) due to its yellow color and its extraction from a golden-colored Streptomyces strain. This groundbreaking antibiotic showcased a wide spectrum of activity and remarkable potency against deadly pathogens, earning it the distinction of being one of the earliest "broad-spectrum" antibiotics in medical history.[3]

By December 1, 1948, the FDA granted approval for the clinical use of the drug, marking an immediate triumph in the medical field. This breakthrough antibiotic, known as aureomycin, proved highly effective against several infectious diseases, thus saving innumerable lives.[3]

In 1952, the Pfizer–Woodward team made a significant breakthrough by elucidating the initial chemical structures of aureomycin and terramycin. They identified a common dihydroxy chlorobenzylamine (DCBA) naphthacene core with similar functional groups and minor structural disparities, giving rise to a new class of antibiotics called tetracyclines. Further, through the process of catalytic hydrogenation of aureomycin, they produced a compound with enhanced potency, improved solubility profile, and favorable pharmacological activity.

In 1954, this compound received FDA approval for clinical usage, becoming the first tetracycline derived from a modified natural product.[3]

Second-generation Semisynthetic Tetracyclines

Under the guidance of Robert Blackwood, Pfizer chemists employed a disjunctive strategy in their research. By modifying the C-ring of oxytetracycline, they achieved enhanced chemical stability. Through halogenation and C6-dehydration, they successfully synthesized the antibiotic methacycline. This compound served as a starting material for Charlie Stephens, who further developed an analog known as doxycycline. Doxycycline exhibited remarkable activity, stability, and pharmacological efficacy, leading to its FDA approval in 1967.[3]

Pfizer introduced this groundbreaking antibiotic to the market as vibramycin, marking their first once-a-day broad-spectrum antibiotic.[2,4]

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Doxycycline in Malaria: The History of Its Use

In 1992, Pfizer Inc. submitted a new drug application to the FDA, including an indication for malaria prophylaxis in the product insert.[2]

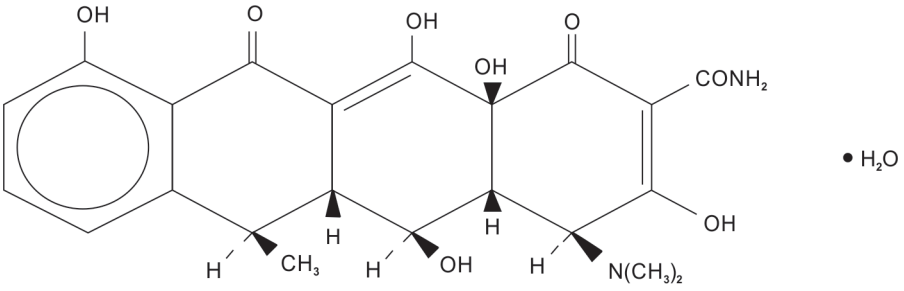
The official inclusion of this indication took place in 1994. Prior to the FDA's approval, the United States Army conducted multiple field and human challenge clinical trials in the late 1980s, showcasing the effectiveness of doxycycline as a preventive measure against malaria. This evidence solidified doxycycline's reputation as a reliable prophylactic option.[2]

Additionally, the simultaneous protection offered by doxycycline against both anthrax and malaria makes it an appealing choice for military operations where these threats are potential risks.[2]

An Overview of Doxycycline

Molecule Description

Doxycycline ($C_{22}H_{24}N_2O_8$),[5] a broad-spectrum antibacterial agent, is a synthetic derivative of oxytetracycline. For oral administration, doxycycline is available in capsule form in varying strengths: 150, 100, 75, and 50 mg. Each capsule contains doxycycline monohydrate (alpha-6-deoxy-5-oxytetracycline) equivalent to the respective dosage strength. Doxycycline monohydrate is a light-yellow crystalline powder.[6]



$C_{22}H_{24}N_2O_8 \bullet H_2O$ M.W. = 462.45

Doxycycline exhibits excellent lipid solubility and demonstrates low affinity for calcium binding. Moreover, it maintains exceptional stability in typical human serum without degrading into an epianhydro form.[6]

Mechanism of Action

Doxycycline acts by inhibiting bacterial protein synthesis through its reversible binding to the 30S ribosomal subunit. This binding effectively prevents the association of aminoacyl-transfer ribonucleic acid (tRNA) with the bacterial ribosome. Furthermore, doxycycline exhibits additional inhibitory effects on protein synthesis in mitochondria by binding to the 70S ribosomes. As a result, it functions as a bacteriostatic drug, halting bacterial growth. To enter the cell, doxycycline utilizes hydrophilic pores present in the outer cell membrane and a pH-dependent active transport system located in the inner cytoplasmic membrane. It also disrupts apicoplast ribosomal subunits in *Plasmodium falciparum*, a malaria-causing parasite. This disruption leads to impaired synthesis of fatty acids and heme, specifically in the late stages of the malarial cell cycle.[1]

Furthermore, doxycycline exhibits a range of additional effects, including the ability to prevent angiogenesis and apoptosis, enhance gingival fibroblast attachment, and promote wound healing. It is recognized for its inhibitory effects on specific matrix metalloproteases (MMPs), which are enzymes produced by inflammatory cells involved in proteolysis. This property has led to the exploration of doxycycline's potential in various anti-inflammatory and antineoplastic applications. In the context of periodontitis, subantimicrobial doses of doxycycline inhibit collagen degradation and counteract the actions of destructive MMPs in the gingivae, contributing to the preservation of tissue integrity.[1]

Pharmacokinetics and Pharmacodynamics

Tetracyclines are efficiently absorbed and exhibit varying degrees of binding to plasma proteins. After being concentrated by the liver in the bile, these compounds are excreted in high concentrations through the urine and feces in their biologically active form.[7] Here are the pharmacokinetic and pharmacodynamic characteristics specific to doxycycline.[1]

Absorption after oral administration: Almost completely absorbed in the stomach and proximal small bowel.

Effect of food and dairy products: Food and dairy products do not significantly affect the absorption of doxycycline, unlike tetracycline and minocycline; serum levels only experience a slight decrease of around 20%.

Serum half-life: Prolonged; 18–22 hours; not altered by impaired renal function.

Peak serum levels: Typically reached within 2–3 hours; intravenous administration yields even faster results, with peak levels achieved within 30 minutes.

Penetration into tissues and body fluids:1

- More lipid soluble compared to tetracycline.
- High levels are detected in several tissues and fluids (lymphatic fluid, peritoneal fluid, colonic tissue, prostate tissue, and breast milk).
- Penetrates cerebrospinal fluid (mean levels of 0.37–1.3 µg/mL or 14–26% of serum concentration).

Dosage and Administration

- Initial dose: Doxycycline is typically initiated with a starting dose of 200 mg/day.[1]
- Maintenance dose: After the initial dose, a maintenance dose of 100 mg/day is commonly prescribed. In severe infections, 100 mg twice daily is given.
- Routes of administration: Doxycycline can be administered orally or intravenously, depending on the specific requirements of the patient and the nature of the infection.
- Oral administration: When taking the oral dose of doxycycline, it is important to consume sufficient fluids. Following administration, the patient should remain upright for 30 minutes to ensure proper absorption.
- Maximum recommended dose: 300 mg/day.
- Pediatric dosing: In children, the use of doxycycline is determined by weighing the benefits against the risks. The dose is typically adjusted based on the child's weight, with a recommended dose of 2.2 mg/kg daily or 2.2 mg/kg twice daily.
- Loading dose: In patients with serious infections, optimal dose-dependent killing may be achieved by prescribing a higher loading dose of doxycycline (e.g., loading dose of 200 mg twice daily for 72 hours).
- Indication-specific variations: Dosing and duration of doxycycline treatment depend on the indication and individual patient circumstances.

Table 1: Antimicrobial activity of doxycycline

Gram-negative bacteria	*Acinetobacter* species *Bartonella bacilliformis* *Brucella* species *Klebsiella granulomatis* *Campylobacter fetus* *Enterobacter aerogenes* *Escherichia coli* *Francisella tularensis* *Haemophilus ducreyi* *Haemophilus influenzae* *Klebsiella* species *Neisseria gonorrhea* *Shigella species* *Vibrio cholerae* *Yersinia pestis*
Gram-positive bacteria	*Bacillus anthracis* *Listeria monocytogenes* *Streptococcus pneumoniae*
Anaerobes	*Clostridium* species *Fusobacterium fusiforme* *Propionibacterium acnes*
Parasites	*Balantidum coli* *Plasmodium falciparum* *Entamoeba* species
Other bacteria	*Actinomyces* species *Borrelia recurrentis* *Chlamydophila psittaci* Rickettsiae *Chlamydia trachomatis* *Mycoplasma pneumoniae* *Treponema pallidum* *Treponema pertenue* *Ureaplasma urealyticum*

Microbiology

Table 1 shows the list of microorganisms against which doxycycline shows antimicrobial action.[7,8]

Indications

Doxycycline is indicated in the following conditions or diseases:[9]

- Rickettsial infections.
- Sexually transmitted infections.
- Respiratory tract infections.
- Specific bacterial infections (e.g., cholera caused by *Vibrio cholerae*).
- Ophthalmic infections.
- Anthrax (including post-exposure anthrax).
- In patients with contraindications to penicillin (e.g., as an alternate treatment for syphilis caused by *Treponema pallidum*).
- Acute intestinal amebiasis and severe acne (as adjunctive treatment).
- Prophylaxis of malaria.

Contraindications

Doxycycline should not be used in individuals who have demonstrated hypersensitivity or allergic reactions to any tetracycline antibiotics.[9]

Use in Special Population

Teratogenic effects. Pregnancy category D: Adequate and well-controlled studies on the use of doxycycline in pregnant women are lacking.

Nursing mothers: Tetracyclines are excreted in the human milk of nursing mothers.

Pediatric use: Doxycycline should not be used in pediatric patients up to the age of 8 years due to the effect of the tetracycline class on tooth development and growth.

Adverse Drug Reactions

Patients receiving tetracyclines have reported the following adverse reactions:[9]

- Gastrointestinal [e.g., diarrhea, nausea, vomiting, glossitis, anorexia, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region].
- Skin (e.g., maculopapular and erythematous rashes).
- Renal (e.g., rise in blood urea nitrogen).
- Hypersensitivity reactions (e.g., urticaria, angioneurotic edema, and anaphylaxis).
- Blood (e.g., hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia).
- Intracranial hypertension (e.g., benign intracranial hypertension in adults).
- Thyroid gland changes (e.g., brown–black microscopic discoloration of thyroid glands).

Overdosage

If an overdose of doxycycline occurs, it is advised to discontinue the medication and provide symptomatic treatment while implementing supportive measures.[9] It is important to note that dialysis does not affect the serum half-life of doxycycline, so it would not provide any significant benefits in managing cases of doxycycline overdosage.

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REVIEW ARTICLE

Antiviral Activity of Doxycycline

Hemant Thacker*

Abstract

Doxycycline is a tetracycline class of antibiotic with a potent antibacterial, anti inflammatory activity against a wide variety of bacteria. Doxycycline displays good activity against gram-positive and gram-negative aerobic and anaerobic pathogens. The oral absorption of doxycycline is rapid and virtually complete. Interestingly doxycycline also demonstrated *in vitro* antiviral activity against respiratory virus. This article is an attempts to focus on the antiviral activity of doxycycline.

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Doxycycline not only exhibits a potent bacteriostatic effect but also demonstrates a broader capability to inhibit viral replication. The initial evidence supporting the antiviral potential of doxycycline emerged from studies revealing a substantial decrease in retrovirus titers within cultured cells upon doxycycline treatment. Subsequent investigations confirmed its effectiveness in inhibiting dengue virus (DENV) infection as well.[1]

Antiviral Effect of Doxycycline: Evidence

Antiviral Activity against Vesicular Stomatitis Virus

Cultured H1299 cells were utilized in an *in vitro* study to examine the antiviral properties of doxycycline against vesicular stomatitis virus (VSV) infection.[1]

- In p53-Tet H1299 cells, the VSV titer showed a significant decrease when doxycycline was present (Dox+) at a concentration of 1 µg/mL compared to its absence (Dox–).
- Vesicular stomatitis virus (VSV) titers were significantly reduced in cells treated with doxycycline (+Dox) compared to mock-treated cells (–Dox).
- Doxycycline exhibited an inhibitory effect on VSV replication without causing significant cytotoxicity.
- At concentrations of 1.0–2.0 µg/mL, doxycycline significantly suppressed VSV replication and VSV-associated cytopathic effect in a dose-dependent manner.

Doxycycline as an Inhibitor of Dengue Virus Replication

An investigation was undertaken to assess the *in vitro* efficacy of doxycycline against the replication of the DENV.[2]

- At both normal human temperature (37°C) and high fever temperature (40°C), doxycycline demonstrated inhibition of the DENV serine protease with an half-maximal inhibitory concentration (IC_{50}) value of 52.3 ± 6.2 and 26.7 ± 5.3 µM, respectively.
- Application of doxycycline at concentrations lower than its 50% cytotoxic concentration (100 µM) resulted in a substantial reduction in the virus titer. The inhibition exhibited a concentration-dependent pattern, with an estimated 50% effective concentration of around 50 µM.
- Doxycycline demonstrated significant inhibition of viral entry and replication for all four dengue serotypes, with higher activity against DENV2 and DENV4 compared to DENV1 and DENV3.

Antiviral Effect of Doxycycline against a Range of Viruses

The 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide assay was utilized in a cell infection model to evaluate the antiviral activity of doxycycline against dengue 2 [American type culture collection (ATCC) VR-1584], influenza A virus [hemagglutinin type 1 and neuraminidase type 1 (H1N1)], influenza B virus, human rhinovirus 17 virus, human adenovirus, and human respiratory syncytial virus.[3] The assessment employed both prophylactic and coculture methods, with ribavirin serving as the positive control. Up to a concentration of 1125 µM, doxycycline did not demonstrate a significant cytotoxic effect.

The antiviral activity against the various viruses is noted below:

Dengue 2 (ATCC VR-1584)

The IC_{50} of doxycycline was 135.5 µM in the prophylactic method and 114.5 µM in the coculture method as against ribavirin (IC_{50} of 27.15 µM in the prophylactic method and 20.94 µM in the coculture method).

Doxycycline showed maximum inhibition of 85 and 87% in the prophylactic and coculture methods, respectively, at 1125 µM. On the other hand, vehicle control (placebo) showed maximum inhibition of 3.3 and 5.2% in the prophylactic and coculture methods, respectively.

Influenza A Virus (H1N1) (ATCC VR-219) in Madin-Darby Canine Kidney (ATCC CCL-34) Cells

The IC_{50} of doxycycline was 262.3 and 184.1 µM, and that of ribavirin was 29.97 and 18.71 µM in the prophylactic and coculture methods, respectively.

Doxycycline showed maximum inhibition of 75 and 80% in the prophylactic and coculture methods, respectively, at 1125 µM; the vehicle control (placebo) showed maximum inhibition of 6.8 and 6.9% in the prophylactic and coculture methods, respectively.

Influenza B Virus (ATCC VR-1735) in Madin-Darby Canine Kidney (ATCC CCL-34) Cells

The IC_{50} of doxycycline was 330.9 and 286.4 µM, and that of ribavirin was 14.79 and 12.87 µM in the prophylactic and coculture methods, respectively.

Doxycycline showed maximum inhibition of 71 and 68% at 1125 µM, and the vehicle control (placebo) showed maximum inhibition of 9.2 and 7.4% in the prophylactic and coculture methods, respectively.

Human Rhinovirus 17 (ATCC VR-1663) in H1HeLa (ATCC CRL-1958) Cells

The IC_{50} of doxycycline was 387.3 and 325.9 µM, and that of ribavirin was 36.97 and 32.37 µM in the prophylactic and coculture methods, respectively.

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Doxycycline showed maximum inhibition of 68 and 72% at 1125 µM, and the vehicle control (placebo) showed maximum inhibition of 9.1 and 9% in the prophylactic and coculture methods, respectively.

Human Adenovirus (ATCC VR-5) in HeLa (ATCC CCL-2) Cells

The IC_{50} of doxycycline was 146.5 and 106.6 µM, and that of ribavirin was 27.46 and 18.38 µM in the prophylactic and coculture methods, respectively.

Doxycycline showed maximum inhibition of 82.5 and 83.8% in the prophylactic and coculture methods, respectively, at 1125 µM; the vehicle control (placebo) showed maximum inhibition of 9.7 and 10.2% in the prophylactic and coculture methods, respectively.

Human Respiratory Syncytial Virus (ATCC VR-1540) in HEp-2 (ATCC CCL-23) Cell Line

The IC_{50} of doxycycline was 225.5 and 165.2 µM, and that of ribavirin was 13.37 and 6.64 µM in the prophylactic and coculture methods, respectively.

Doxycycline showed maximum inhibition of 79 and 81% at 1125 µM, and the vehicle control (placebo) showed maximum inhibition of 8.8 and 9.9% in the prophylactic and coculture methods, respectively.

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REVIEW ARTICLE

Acute Undifferentiated Febrile Illness: The Utility of Doxycycline

Amit A Saraf[1*], Ketan Mehta[2]

Abstract

Acute undifferentiated febrile illnesses are associated with specific characterizations like fever of less than two weeks in duration with no organ-specific symptoms at onset. These range from mild and self-limiting disease to progressive, life-threatening illness. Acute undifferentiated febrile illnesses are classified into malaria and non-malarial illnesses on the basis of microscopy or malaria diagnostic tests. Doxycycline demonstrates the potential to inhibit dengue virus replication and exhibits anti-inflammatory activity. The potential of Doxycycline as an empirical choice among antibiotics is summarized in this article.

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Chronic fever refers to fevers that persist for >14–21 days, while acute febrile illness (AFI) is defined as fevers lasting <21 days, according to certain publications.[1]

In India, acute undifferentiated febrile illnesses (AUFIs), also referred to as "short febrile illness" or "acute fever," are common reasons for seeking healthcare. These febrile illness conditions are characterized by fevers lasting <2 weeks and lacking specific clinical features related to a particular organ.[2] Initially, symptoms may include headache, chills, and muscle pain, while in later stages, specific organs may become involved. In tropical regions, severely ill hospitalized patients have been reported to experience a mortality rate of 12%.[3]

The main disease groups that can cause acute AUFIs can be categorized as follows:[3]

- Malaria: This includes malaria caused by various species of Plasmodium, such as *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax* (*P. vivax*), *Plasmodium ovale* (*P. ovale*), *P. malariae* (*Plasmodium malariae*), and *Plasmodium knowlesi*.
- Arboviral infections: These include diseases like dengue, chikungunya, Japanese encephalitis, Zika, and yellow fever.
- Enteric fever: This category comprises fever caused by *Salmonella enterica*, Serovar typhi, and Paratyphi A, B, and C.
- Spirochaete infections: These include diseases like leptospirosis and tick-borne or louse-borne relapsing fever.
- Rickettsial infections: These include scrub typhus, murine typhus, and various types of spotted fevers.

Classification of Acute Undifferentiated Febrile Illness

Acute undifferentiated febrile illnesses (AUFIs) are classified into two categories: malarial and nonmalarial illnesses. Nonmalaria illnesses can be viral [includes arboviral infections (dengue, chikungunya, Zika, Japanese encephalitis) and influenza (if respiratory symptoms are not prominent)]; bacterial [bacteremia (enteric fever, infections by others, such as *Escherichia coli*, *Staphylococcus aureus*) and zoonotic infections (spirochetal, such as leptospirosis, relapsing fever and rickettsial infections such as scrub typhus, spotted fever, etc.); and parasitic (hepatic amoebiases such as acute schistosomiasis and acute trypanosomiasis) origin.[2]

Management of Acute Undifferentiated Febrile Illness

The management of acute AUFI is often hindered by several factors. These include a lack of technical knowledge among the management team, the presence of nonspecific symptoms that make timely diagnosis difficult, and a lack of comprehensive guideline recommendations from local governing bodies. Furthermore, inadequate diagnostic facilities add to the challenges faced in managing AUFI.[2]

The nonspecific and overlapping clinical symptoms, coupled with the unavailability of appropriate diagnostic methods, pose a significant challenge for treating physicians. This can make timely treatment difficult, as the underlying cause of the febrile illness may not be immediately apparent.[4]

In cases where patients are clinically stable and do not exhibit any red-flag features, management can be carried out within the community. However, for suspected bacterial AUFI cases with distinctive clinical features, it is advisable to initiate early presumptive antibacterial therapy if confirmatory diagnostic testing is pending or unavailable.[3]

Malaria

Malaria is an illness with the potential to be life-threatening, and it is caused by parasites (*P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*) that are transmitted through the bites of female Anopheles mosquitoes that are infected.[5]

Burden of Malaria

- It is estimated that there were 241 million malaria cases in 2020, increasing from 227 million in 2019, across 85 malaria endemic countries.[6]
- The World Health Organization (WHO) Southeast Asia region had approximately 5 million estimated cases of malaria in 2020.[6]
- India contributed 1.7% of global malaria cases and 1.2% of global malaria deaths in 2020.[6]
- Within the WHO Southeast Asia Region, India accounted for 83% of estimated cases and about 82% of all malaria deaths.[6]
- The WHO reported in the World Malaria Report (WMR) 2020 that India has significantly reduced its malaria burden.[7]
- India reported a decline of 17.6% in malaria cases in 2019 compared to 2018, making it the only high-endemic country to show such a decrease.[7]

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- India has also witnessed the largest drop in malaria cases region-wide, from around 20 million to approximately 6 million between 2000 and 2019.[7]
- During this period, there was a 71.8% decrease in malaria cases and a 73.9% decrease in malaria-related deaths in India.[7]

Characteristics of Malaria

The incubation period of *P. falciparum* is 9–14 days, and that of *P. vivax* is 10–14 days.

The clinical presentation of malaria includes an acute onset of high-grade intermittent fever, accompanied by fever paroxysms, shaking chills, and periodic sweats occurring every 48 or 72 hours, depending on the specific parasite species causing the infection. In severe cases of malaria, patients may experience complications such as cerebral malaria, severe anemia, metabolic acidosis, acute renal failure, acute respiratory distress syndrome (ARDS), and shock.[4]

Doxycycline in Malaria

Doxycycline is Food and Drug Administration-approved for the prophylaxis of *P. falciparum* malaria in short-term travelers (<4 months) visiting regions where chloroquine and/or pyrimethamine-sulfadoxine-resistant strains are present.[8]

Doxycycline is an effective treatment option for malaria when combined with other medications. It can be used in non-pregnant adults and children aged 8 years and above. For uncomplicated, chloroquine-resistant *P. falciparum* malaria, it is administered alongside quinine sulfate. In cases of uncomplicated chloroquine-resistant *P. vivax*, both quinine sulfate and primaquine are used in conjunction with doxycycline. For severe malaria, doxycycline is combined with parenteral quinidine for treatment.[8]

Clinical Evidence

Uncomplicated Plasmodium falciparum Malaria Treatment with Quinine–Doxycycline Combination Therapy: A study was conducted to evaluate the effectiveness and tolerability of quinine–doxycycline combination therapy in treating uncomplicated *falciparum* malaria.[9]

The study included 100 adult males who presented with high-grade fever and tested positive for *P. falciparum* parasites in their peripheral blood films. The participants had not received any antimalarial treatment in the preceding 7 days.

The treatment protocol consisted of oral administration of quinine sulfate (10 mg of salt/kg body weight every 8 hours for 3–7 days), along with oral doxycycline (100 mg twice daily for 7 days).

Early treatment failure, defined as a parasite count on day 2 that was ≥75% of the count on day 0, was the primary endpoint of the study.

The results were as follows:

- The malarial parasite index decreased from an average of 6.34 [standard deviation (SD) ± 2.83) before treatment to zero by day 7 of treatment.
- The average parasite clearance time was 3 days (range 1–7 days).
- No early or late treatment failures were observed.
- Throughout the 28-day observation period, there were no cases of malaria recurrence, and all patients were discharged in good health.

In conclusion, the combination of quinine and doxycycline was found to be effective in treating uncomplicated *P. falciparum* malaria.

Management of Plasmodium falciparum and Plasmodium vivax Malaria with Chloroquine + Doxycycline vs Chloroquine Alone and Doxycycline Alone: A 28-day hospital-based study was conducted to compare the efficacy of chloroquine/doxycycline combination therapy with chloroquine or doxycycline alone for the treatment of *P. falciparum* and *P. vivax* malaria.[10]

The study included patients with uncomplicated *falciparum* malaria (n = 89) and *vivax* malaria (n = 63), who were randomly assigned to receive standard dose chloroquine (n = 30, n = 23), doxycycline alone (100 mg, every 12 hours for 7 days; n = 20, n = 16), or a combination of chloroquine and doxycycline (CD; = 39, n = 24).

The primary endpoints of the study were to determine parasite sensitivity (S) or resistance (RI/RII/RIII).

The study results were as follows:

- The cure rate in *falciparum* and *vivax* malaria: The cure rate of the CD was significantly higher than that of chloroquine alone (*falciparum* malaria: $p < 0.0001$, *vivax* malaria: $p = 0.016$). However, there was no significant difference in cure rates between CD and doxycycline alone.
- Resistance in *falciparum* malaria: In the chloroquine arm, all three grades of resistance (RI, RII, and RIII) were observed. In the doxycycline alone arm, resistance was seen in the RII/RIII category. The CD arm showed resistance only in the RIII category.
- Resistance in vivax malaria: In the chloroquine arm, resistance was observed in the RI/relapse and RII/RIII categories. In the doxycycline alone arm, resistance was seen in the RI/relapse and RIII categories. The CD arm exhibited resistance only in the RI/relapse category.

In conclusion, the combination of chloroquine and doxycycline was effective in treating multidrug-resistant *falciparum* malaria. Additionally, it demonstrated high efficacy in initially clearing chloroquine-resistant *vivax* malaria.

Dengue

The increasing threat of dengue transmission to humans is driven by climate change, urbanization, rising temperatures, vector suitability, and population vulnerability. Dengue has evolved into a yearly epidemic in various regions of Southeast Asia, with its severity escalating due to changing environmental conditions.[11]

Burden of Dengue

The global incidence of dengue has experienced a significant surge in recent decades, as reported cases to the WHO escalated from 505,430 in 2000 to 5.2 million in 2019. However, due to the majority of cases being asymptomatic or mild and self-managed, the actual numbers of dengue cases are likely under-reported. One estimation from modeling suggests an annual occurrence of 390 million dengue virus infections, with 96 million displaying clinical symptoms.[12]

In India alone, the burden of dengue infections is estimated to be 34 million.[13] Data from the Virus Research and Diagnostic Laboratories Network indicate that dengue accounts for one-fourth of AFI cases in the country.[14] Recent statistics reveal that between January and October 2022, a total of 110,473 dengue cases were documented in India.[11]

Characteristics of Dengue

The incubation period for this condition ranges from 3 to 14 days, and it is characterized by the acute onset of high-grade continuous fever, typically occurring around 4–7 days after exposure.[4]

Clinical features include retroorbital pain, headache, arthralgia, myalgia, and rashes for dengue fever; thrombocytopenia, mucosal and gastrointestinal bleeding, and increased hematocrit for dengue hemorrhagic fever (DHF); weak pulse and hypotension for dengue shock syndrome; myocarditis, encephalitis, hepatitis, ARDS, renal failure, and hemophagocytosis for expanded dengue syndrome.[4]

Doxycycline in Dengue

Several studies show that doxycycline has an inhibitory effect against dengue virus. It has been shown that[15]:

- Doxycycline inhibits dengue virus by disrupting viral envelope changes required for entry, inhibiting plaque formation.
- It has the highest inhibitory effect against dengue NS2B-NS3pro compared to other tetracycline derivatives and mefenamic acid.
- Doxycycline, with negatively charged moieties and hydrophobic groups, noncompetitively inhibits dengue NS2B-NS3pro with Ki values of 55.6 µM.
- It interferes with dengue virus protease, impairs virus binding to host cells, and reduces viral replication in infected cells.

Doxycycline's low side effects and positive impact on cytokine levels in dengue-infected patients make it a potential treatment candidate.[15]

Clinical Evidence

Doxycycline Reduces Dengue Mortality by Lowering Proinflammatory Cytokine Levels: In a study examining the impact of doxycycline treatment on cytokine levels and mortality in dengue patients at high risk of complication, a group of 231 DHF patients was randomized to standard supportive care or supportive care with oral doxycycline twice daily for 7 days.[16] Serum tumor necrosis factor (TNF) and interleukin 6 (IL-6) levels were analyzed on days 0, 3, 5, and 7.

The results observed were as follows:

- The mortality rate was 46% lower in the doxycycline group compared with the untreated group (11.2 vs 20.9%, $p = 0.05$).
- There was a significant decrease in levels of TNF and IL-6 with doxycycline treatment on days 3, 5, and 7 (Fig. 1).
- At all time points, patients who died had significantly higher levels of TNF and IL-6 levels compared to those who survived ($p < 0.01$). This was noted in both groups.

It can be inferred that doxycycline may offer a clinical advantage to dengue patients who have a higher risk of complications. This beneficial outcome is likely achieved by reducing the levels of proinflammatory cytokines in the body.

Reduced Mortality Rates with Doxycycline in Patients with Dengue Hemorrhagic Fever: A clinical trial evaluated the effectiveness of adding oral doxycycline to standard supportive care for patients with symptoms of DHF.[17] The trial included 228 patients who received either standard care or supportive care along with oral doxycycline twice daily for a week.

Following were the results observed:

- Doxycycline treatment led to a significant 50% reduction in mortality compared to the control group (Fig. 2).
- Patients treated with doxycycline had shorter hospital stays, with an average duration of 7.2 days compared to 8.2 days for the control group ($p < 0.01$).
- The decrease in mortality among doxycycline-treated patients was linked to lower levels of proinflammatory cytokines.

Doxycycline offers a notable clinical advantage to patients with DHF by reducing proinflammatory cytokine levels.

Experience with Doxycycline in Dengue Cases in a Tertiary Care Hospital: A study examined the impact of doxycycline on the progression and ultimate outcome of dengue fever.[18] It involved 24 confirmed dengue patients who were monitored over time. Through simple random sampling, the participants were divided into two groups of twelve patients each. The treatment group received doxycycline, while the control group received a placebo for 5 days.

The results recorded were as follows:

- The treatment group did not experience any major bleeding, whereas 25% of the control group did.
- The treatment group had lower plasma leakage (25%) compared to the control group (58.3%).
- Hemodynamic compromise was less prevalent in the treatment group (8.30%) compared to the control group (16.7%).
- In the treatment group, 41.70% of patients did not have thrombocytopenia, whereas only 16.70% in the control group did not. Additionally, only 8.30% of patients in the treatment group had a platelet count <10,000/cm^3, compared to 16.70% in the control group.

Doxycycline treatment demonstrates a notable decrease in complications related to dengue fever, particularly in terms of the involvement of different organs.

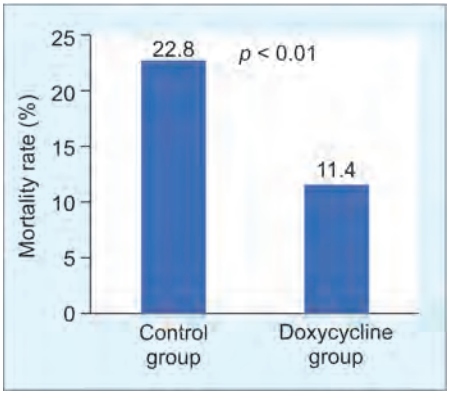


Fig. 2: Significant reduction in mortality with doxycycline treatment

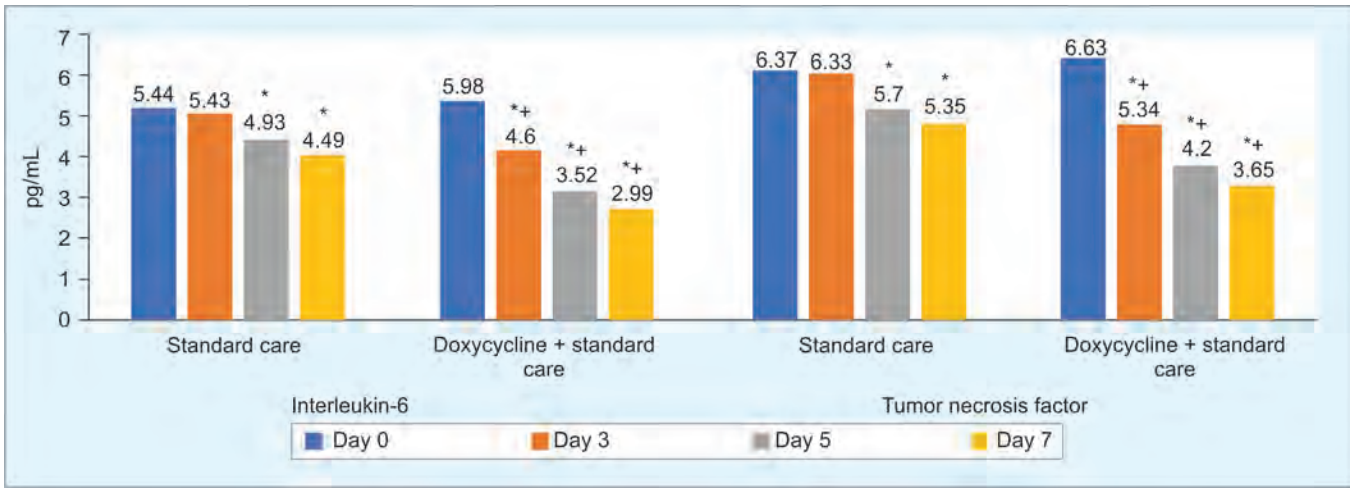


Fig. 1: Reduction in IL-6 and TNF levels with doxycycline treatment; *$p < 0.05$ vs day 0 value within the same group; +$p < 0.01$, control v doxycycline group on the same day

Rickettsial Infections: Scrub Typhus

Rickettsial infections, such as spotted fever group, typhus group, and scrub typhus, are vector-borne diseases that are either reemerging or emerging. Humans act as accidental dead-end hosts. These infections are zoonotic and primarily present in arthropods (ticks, mites, chiggers, fleas, or lice) that serve as natural hosts and can vertically transmit the infection to their offspring.[19]

The treatment for these infections is affordable and highly effective during the early stage. However, diagnosing the disease at this stage is challenging due to low suspicion, nonspecific signs and symptoms, and the unavailability of low-cost, rapid diagnostic tests.[20]

Even if suspected by a healthcare professional, the therapy is empirical because serological tests typically become positive around a week after the onset of fever, and early diagnostic tests like polymerase chain reaction are not widely accessible.[20]

These infections have a significant public health impact in India, with varying effects in areas with different levels of suspicion.[20]

Burden of Scrub Typhus in India

Scrub typhus poses a significant public health threat in India, but its overall burden and distribution remain uncertain.[21] A systematic review of 140 studies identified 18,781 confirmed cases out of 123,067 participants. In certain regions of India, scrub typhus comprises 35–50% of AUFIs requiring hospitalization. One-third of hospitalized scrub typhus cases often involve multi-organ dysfunction, including pulmonary, hepatic, cardiac, neurological, or renal complications, resulting in high fatality rates. Studies conducted in India indicate that the case fatality rate (CFR) of scrub typhus ranges from 1.3 to 33.5%, depending on the extent of organ involvement and complications.

Characteristics of Scrub Typhus

The incubation period for this condition ranges from 1 to 3 weeks.[4]

Clinical features include fever, headache, and myalgia, as well as breathing difficulty, delirium, vomiting, cough, and jaundice. Complications may involve overwhelming pneumonia with ARDS-like presentation, hepatitis, aseptic meningitis, myocarditis, and disseminated intravascular coagulation.

Doxycycline in Rickettsial Infections

Doxycycline stands as the optimal treatment for all rickettsial diseases and is proven to be highly effective. Guidelines from the American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend doxycycline for suspected rickettsial diseases across all age groups. Extensive studies have demonstrated that alternative antibiotics exhibit lower efficacy rates, highlighting the superiority of doxycycline in treating these conditions.[22]

Clinical Evidence

Early Administration of Doxycycline and Reduced Risk of Complications of Scrub Typhus: A retrospective study was conducted, analyzing a group of patients (n = 106) aged ≥18 years and diagnosed with scrub typhus.[23] The study tracked their outcomes over time. Among these patients, only 10 had been administered anti-scrub antibiotics (doxycycline or azithromycin) before admission. The following observations were made:

- The death rate was 6.6% among patients who had not received prior anti-scrub treatment.
- These patients who had not received anti-scrub antibiotics:
- Presented at a later stage with an average illness duration of 9.2 days
- More severe forms of complications were experienced at the time of presentation (Table 1).
- Patients who had received prior anti-scrub treatment had fewer complications, which were milder in nature.

Therefore, the inclusion of doxycycline in the initial empirical antimicrobial therapy for febrile patients during tick season is advisable for the treatment of scrub typhus.

Doxycycline vs Azithromycin for Treatment of Scrub Typhus: In a multicenter, open, randomized controlled trial, adult patients with acute fever (>15 days) and no clear infection focus were included.[24] The study enrolled a total of 296 patients, out of which 57 patients (19.3%) were diagnosed with scrub typhus.

These patients were randomized to doxycycline treatment for 7 days or azithromycin treatment for 3 days. The researchers then compared the cure rate, fever clearance time, and occurrence of adverse drug events between the two groups of patients.

The results were as follows:

- In patients with confirmed scrub typhus, there was one case of treatment failure in the azithromycin group.
- The median time for fever clearance was 48 hours (range: 16–120 hours) in the doxycycline group and 60 hours (range: 12–128 hours) in the azithromycin group, but the difference was not statistically significant (p = 0.13).
- However, within 48 hours of starting treatment, a significantly higher proportion of patients in the doxycycline group (16 patients, 59.3%) became afebrile compared to the azithromycin group (nine patients, 30%) (p = 0.03).

The findings suggest that doxycycline could be considered an economical and efficacious alternative to azithromycin for the treatment of scrub typhus.

Comparison of Doxycycline and Azithromycin in the Management of Pediatric Scrub Typhus: A study was conducted to compare the effectiveness of doxycycline and azithromycin in treating scrub typhus in pediatric patients.[25] The study included 510 children aged ≤12 years with a fever lasting at least 7 days

Table 1: Outcome and complications in patients receiving prior doxycycline vs no treatment

	Total	*Received doxycycline*	*No treatment or no doxycycline*
	Complications		
Liver dysfunction	67	3 (2.8%)	64 (60.4%)
Renal dysfunction	48	4 (3.7%)	44 (41.5%)
Meningitis	23	0 (0%)	23 (21.69%)
ARDS/ALI	32	0 (0%)	32 (30.1)
Shock	14	0 (0%)	14 (13.2%)
Mortality	7	0 (0%)	7 (6.6%)
Total	106	10 (9.4%)	96 (90.6%)

ARDS, acute respiratory distress syndrome; ALI, acute lung injury

and positive immunoglobulin M enzyme-linked immunosorbent assay for scrub typhus. Among them, 267 (52.3%) were administered azithromycin at a dose of 10 mg/kg/day orally once a day, while 243 (47.6%) cases received doxycycline. Doxycycline was prescribed at a dose of 2.2 mg/kg twice daily (patients weighing <40 kg) or 100 mg twice daily (patients weighing >40 kg) for 7 days.

The results were noted as follows:

- Fever clearance time was shorter in the doxycycline group (42 ± 24 hours) compared to the azithromycin group (48 ± 23 hours) ($p = 0.001$) (Fig. 3).
- The doxycycline group had significantly less persistence of fever for >48 hours after starting antibiotic treatment ($p = 0.001$).
- It can be concluded that doxycycline appears to be superior to azithromycin in defervescing fever in pediatric scrub typhus.

Superior Efficacy of Doxycycline Over Azithromycin in Pediatric Patients with Scrub Typhus: A retrospective study analyzing the records of pediatric patients with scrub typhus compared the clinical response to doxycycline and azithromycin antibiotic therapy. The study included 138 patients.[26] The primary outcome measure was the clinical failure rate (CFR) for both doxycycline and azithromycin therapy. The secondary outcome measures were fever control time (FCT) and the proportion of patients showing a rapid response to fever within 48 hours of starting antibiotic therapy.

Following were the results noted after treatment:

- Doxycycline had a significantly lower CFR of 1.3% compared to azithromycin's CFR of 9.6% ($p = 0.04$).
- The median FCT was 12 hours for doxycycline and 24 hours for azithromycin, showing a significant difference ($p < 0.001$).
- Rapid fever control within 48 hours was observed in 92.1% of patients treated with doxycycline and 74.1% of patients treated with azithromycin, demonstrating a significant difference ($p < 0.001$) (Fig. 4).
- Fever persisted beyond 48 hours in 7.9% of patients treated with doxycycline and in 25.8% of patients treated with azithromycin, indicating a significant difference ($p = 0.004$).

In scrub typhus endemic areas, it is preferable to use doxycycline as the first-line antibiotic for undifferentiated fever.

Leptospirosis

Leptospirosis is predominantly found in tropical regions, with 73% of cases occurring in areas such as Southeast Asia, East sub-Saharan Africa, the Caribbean, and Oceania. The disease is prevalent among rural farming communities as well as impoverished urban and semi-urban populations, with a higher incidence observed in young adult males.[27]

Burden of Leptospirosis

Leptospirosis, caused by genetically diverse species of *Leptospira*, a spirochaete bacterium, is characterized by the presence of 38 known pathogenic species, with ongoing discoveries of new species. The disease carries significant morbidity and mortality rates in humans, estimated at 1 million cases and 60,000 deaths, respectively.[28]

Characteristics of Leptospirosis

The incubation period for leptospirosis ranges from 2 to 26 days, with symptoms typically appearing around 6–10 days after exposure.[4] Anicteric leptospirosis is characterized by a sudden onset of fever, chills, headache, myalgia, abdominal pain, conjunctival suffusion, and a transient skin rash. Icteric leptospirosis, on the other hand, presents with jaundice, proteinuria, hematuria, oliguria, and/or anuria. Additionally, it may involve complications such as pulmonary hemorrhages, ARDS, and myocarditis.

Doxycycline in Leptospirosis

Doxycycline, a broad-spectrum antibiotic effective against all strains of *Leptospira*, is commonly recommended for the treatment of leptospirosis. Studies have indicated that doxycycline treatment has outcomes comparable to penicillin G and cefotaxime in terms of mortality, time to fever resolution, and hospital stay. Therefore, it can be considered as an alternative option for the management of leptospirosis in place of penicillin G and cefotaxime.[30]

Clinical Evidence

Reducing the Incidence of Leptospirosis among Paddy Field Farmers Using Prophylactic Doxycycline: A study was conducted to evaluate the effectiveness of prophylactic doxycycline in reducing the occurrence of leptospirosis.[31] The study enrolled consenting paddy field farmers ($n = 1371$) residing and working in the study area. The test group received weekly prophylactic doxycycline capsules (200 mg once daily) for 5 weeks, along with Information Education Communication (IEC) activities. The control group did not receive any intervention.

Following were the observations:

- The incidence of leptospirosis was found to be zero in the test group and 7.29% in the control group ($p = 0.0167$).
- These findings suggest that chemoprophylaxis using doxycycline, combined with IEC activities, can effectively contribute to the control of leptospirosis incidence.

Effect of Doxycycline in Leptospirosis Parameters: Results of a Meta-analysis: The role of antibiotics in treating leptospirosis was evaluated through a systematic review and meta-analysis. A total of 10 clinical trials were included in the analysis.[32]

One study specifically investigated the effects of doxycycline on various parameters associated with leptospirosis. The patients with leptospirosis were divided into two groups: a doxycycline group ($n = 14$; 100 mg twice daily for 7 days) and a placebo group ($n = 15$). Patients were followed up for 2–3 weeks.

The study found that doxycycline significantly reduced the duration of illness (5.6 vs 7.7 days), fever (3.7 vs 5.4 days), fever days (7.2 vs 9.3 days), and other symptoms such as malaise, myalgia, conjunctival suffusion, and gastrointestinal symptoms.

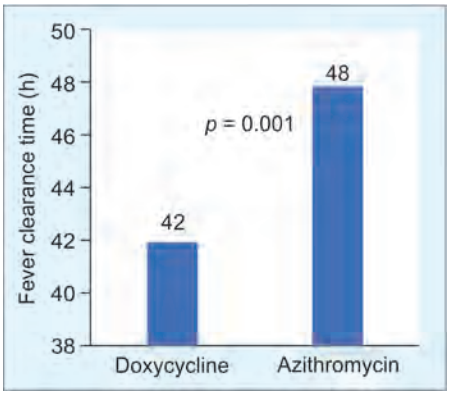


Fig. 3: Fever clearance time with doxycycline vs azithromycin

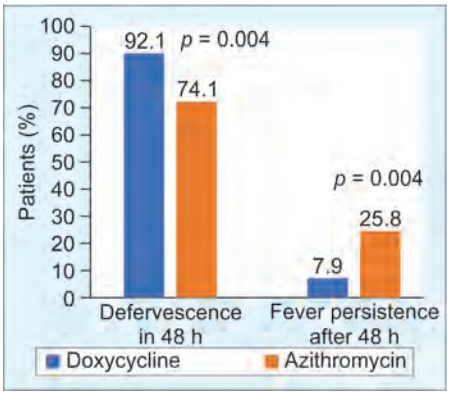


Fig. 4: Positive effect of doxycycline with respect to defervescence in 48 hours and fever persistence after 48 hours

Based on these findings, doxycycline can be considered an effective treatment option for managing leptospirosis.

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REVIEW ARTICLE

Doxycycline in Respiratory Infections

Agam Vora[1*], Pradyut Waghray[2]

Abstract

Respiratory infections acute or chronic are extremely frequent in both adults and children, representing an increased economic burden on healthcare systems, morbidity and mortality. Respiratory infections may result in severe illnesses capable of inducing acute respiratory failure that could progress to acute respiratory distress syndrome. In this article clinical evidence with doxycycline in managing the respiratory infections and slowing the progression of disease are summarized briefly.

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Introduction

Respiratory tract infections (RTIs) are a primary cause for individuals seeking medical advice from general practitioners.[1]

Lower respiratory tract infections (LRTIs), including influenza, stand out as the prevailing cause of death due to infectious diseases.[2] This observation is particularly noteworthy in developing countries, where the World Health Organization (WHO) has identified LRTIs as the leading cause of mortality.[3]

Community-acquired pneumonia (CAP) continues to pose a significant global health concern, with notable morbidity and mortality rates.[4] The primary bacterial culprit behind CAP is *Streptococcus pneumoniae*, accounting for 80% of cases across all age groups. Following closely in frequency is *Haemophilus influenza* (*H. influenzae*), which represents the second most prevalent bacterial pathogen-causing pneumonia. Gram-negative bacteria, such as *H. influenzae*, *Moraxella catarrhalis*, and *Klebsiella pneumoniae*, are responsible for pneumonia cases in individuals with compromised immune systems, newborns, infants, and elderly individuals with chronic illnesses.[3] Atypical bacterial microorganisms contribute to an estimated 7–20% of cases of CAP.[5] Among the atypical pathogens, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* account for 15–40%, 2–15%, and 5–10% of atypical CAP cases, respectively.[6]

Hospital-acquired infections, particularly ventilator-associated pneumonia, are frequently attributed to Klebsiella pneumoniae strains. These strains commonly exhibit multidrug-resistant (MDR) characteristics when isolated from hospital-acquired infections.[7]

Acinetobacter baumannii, a Gram-negative coccobacillus, has gained significant recognition as a prominent nosocomial pathogen. It is characterized as a nonfermentative, aerobic, and opportunistic bacterium. Acinetobacter species exhibit a diverse range of β-lactamases that enable hydrolysis and confer resistance to penicillins, cephalosporins, and carbapenems.[8]

The Role of Doxycycline in Respiratory Tract Infections

Doxycycline exhibits a significant level of effectiveness against numerous prevalent respiratory pathogens. This includes *Streptococcus pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, anaerobic bacteria such as *Bacteroides*, as well as anaerobic/microaerophilic *Streptococci*. Additionally, it demonstrates efficacy against atypical agents such as *Legionella*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.[9]

Research shows that the average tissue-to-serum ratio of doxycycline for the lungs is 2:1.[10]

According to the revised guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), doxycycline monotherapy is now considered a viable choice for treating outpatients without underlying health conditions or significant risk factors for resistant pathogens. Additionally, for adult outpatients with comorbidities and hospitalized patients with CAP, who cannot take macrolides or fluoroquinolones due to contraindications, the guidelines recommend combining doxycycline with a beta-lactam antibiotic.[11]

Clinical Evidence

Efficacy of doxycycline for mild-to-moderate community-acquired pneumonia in adults: results of a systematic review and meta-analysisA systematic review and meta-analysis compared doxycycline to roxithromycin, spiramycin, erythromycin, ofloxacin, fleroxacin, and levofloxacin in six randomized controlled trials.[12] The study involved 834 clinically evaluable patients, with the primary outcome being the clinical cure rate.

Following were the findings:

- There was no significant difference in the clinical cure rate between the doxycycline and comparator groups [87.2 vs 82.6%; odds ratio (OR) 1.29; 95% confidence interval (CI): 0.73–2.28; $I^2 = 30\%$].
- Subgroup analysis of two studies with a low risk of bias revealed significantly higher clinical cure rates in the doxycycline group compared to the comparator groups. The doxycycline group had a cure rate of 87.1% while the comparator groups had a rate of 77.8% (OR 1.92; 95% CI: 1.15–3.21; $p = 0.01$; $I^2 = 0\%$).

Least resistance of A. baumannii and K. pneumoniae isolates from the lower respiratory tract of patients in the intensive care unit

A study examined the bacterial profile and antibiotic susceptibility pattern of lower respiratory tract isolates from ventilated patients in the intensive care unit (ICU).[13] Transtracheal or bronchial aspirates from 207 patients were cultured, identified, and subjected to standard methods for antibiotic sensitivity testing.

Following were the results:

- The most common gram-negative bacilli isolated from the lower respiratory tract were *Pseudomonas aeruginosa* (35%), *Acinetobacter baumannii* (23.6%), and *Klebsiella pneumoniae* (13.6%).
- These bacteria exhibited high resistance (80–100%) to ciprofloxacin, ceftazidime, co-trimoxazole, and the combination of amoxicillin/clavulanic acid.
- On the other hand, the lowest resistance rates were observed for doxycycline (Fig. 1) and meropenem.

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Doxycycline exhibited the lowest resistance among *Acinetobacter baumannii* and *Klebsiella pneumoniae* isolates obtained from ICU patients with ventilator-associated pneumonia (VAP).

Comparison of doxycycline and levofloxacin in the treatment of community-acquired pneumonia

To evaluate the comparative efficacy of doxycycline and levofloxacin for the treatment of CAP in general medical wards, a prospective double-blinded trial was conducted.[14] The study enrolled nonpregnant adults who required hospitalization due to clinical and radiological evidence of pneumonia. The participants were randomized to two groups: intravenous levofloxacin 500 mg daily ($n = 30$) or oral doxycycline 100 mg twice daily ($n = 35$).

Following were the results observed:

- The efficacy rates of doxycycline and levofloxacin were found to be similar in the study.
- Patients in the doxycycline group had a significantly lower average length of stay in the hospital (4.0 ± 1.82 days vs 5.7 ± 2.05 days, $p < 0.0012$; Fig. 2).
- Doxycycline was found to be more cost-effective than levofloxacin.

It can be inferred that doxycycline serves as a viable and cost-effective alternative to levofloxacin in the empirical treatment of CAP.

Doxycycline in Coronavirus Disease 2019

The emergence of the novel coronavirus infection in 2019, known as coronavirus disease 2019 (COVID-19), led to an unparalleled global public health crisis and threatened millions of people globally.[15] In severe cases, it can lead to acute respiratory distress syndrome (ARDS) accompanied by conditions such as hypercytokinemia, severe acute respiratory syndrome, lymphopenia, disseminated intravascular coagulation, renal failure, and increased mortality rates.[16]

While the combination of hydroxychloroquine and azithromycin has been utilized in the past, it has raised significant safety concerns, including the following.[15]

- Drug–drug interactions.
- Cardiotoxicity, which includes the risk of fatal arrhythmia, especially among elderly patients with underlying cardiopulmonary chronic illness.

Why Doxycycline?

Antiviral Activity

Doxycycline not only demonstrates anti-inflammatory effects but also exhibits *in vitro* antiviral activity against various ribonucleic acid (RNA) viruses. Its use has been linked to clinical improvement, and in some cases, it has even shown the ability to reverse cytokine storm associated with infections caused by RNA viruses, such as dengue fever.[15]

Matrix Metalloproteinases Inhibitor

- Doxycycline, a highly lipophilic antimicrobial, has the ability to chelate zinc compounds present on matrix metalloproteinases (MMPs) found in mammalian cells.
- Notably, doxycycline acts as a potent MMP inhibitor, even at subantimicrobial doses (25 mg). Given that lung immune injury and acute respiratory distress syndrome (ARDS) are prominent in severe cases of COVID-19, inhibiting MMPs could potentially aid in the repair of damaged lung tissue and facilitate the recovery process.

Anti-inflammatory

- Increased levels of interleukin (IL)—6 in the bloodstream have been frequently observed in severe cases of COVID-19 and among individuals who do not survive, indicating that mortality may be linked to hyperinflammation caused by viral activity and cytokine storm.
- Studies have shown that doxycycline can effectively lower levels of pro-inflammatory cytokines (e.g., IL-6 and tumor necrosis factor-α), in patients diagnosed with dengue hemorrhagic fever.

Inhibition of Papain-like Protease

- The papain-like protease found in severe acute respiratory syndrome-related coronavirus (SARS-CoV) plays a significant role in activating transforming growth factor beta 1 (TGF-β1) through early growth response protein 1 (EGR1), leading to the upregulation of pro-fibrotic responses in the lungs, both *in vitro* and *in vivo*.
- In recent computational studies, doxycycline has been identified as one of the drugs that have the potential to inhibit the papain-like protease of SARS-CoV-2, offering a potential avenue for therapeutic intervention.

Doxycycline offers a multifaceted approach to the treatment of respiratory infections. It not only possesses antibacterial activity against respiratory pathogens[9] but also exhibits antiviral and anti-inflammatory properties, capable of dampening cytokine storms. This makes doxycycline an attractive option for managing COVID-19 and potentially mitigating lung complications associated with the disease.[16]

Conclusion

Doxycycline is an effective treatment option for mild-to-moderate community-acquired pneumonia with an efficacy comparable to that of macrolides or fluoroquinolones.

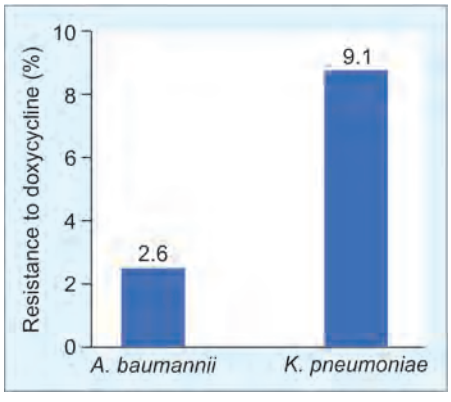


Fig. 1: Least resistance of *Klebsiella pneumoniae* and *Acinetobacter baumannii* toward doxycycline

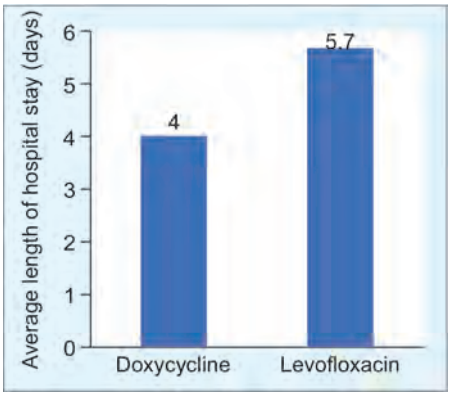


Fig. 2: Shorter length of hospital stay with doxycycline vs levofloxacin

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REVIEW ARTICLE

Doxycycline in Gynecological infections

Milind Gaitonde*

Abstract

In gynecology practice pelvic inflammatory disease is among the most common infections in non pregnant women of reproductive age, and remains an important public health problem. It is associated with major long-term sequelae including infertility, ectopic pregnancy, and chronic pelvic pain. Surgical procedures in gynecologic also carry a high risk of infection. The article summarize the possible application and utility of doxycycline for gynecological infections.

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Gynecologic infections have the potential to manifest externally on the vulva or internally in the vagina, cervix, uterus, and fallopian tubes. While the presenting symptoms can offer valuable insights for identifying these infections, accurate diagnosis can be achieved through physical examination along with laboratory tests.[1]

Numerous infections in the female reproductive system can be transmitted through sexual contact, while others commonly arise from an overgrowth of naturally occurring bacteria or yeast in the vagina. Gynecologic infections can have detrimental effects on quality of life, by causing discomfort, pain, and disruptions in normal sexual function and reproductive ability.[1]

Patients visiting obstetrics and gynecology clinics often present common complaints such as abnormal vaginal discharge, itching, burning sensation, irritation, and discomfort.[2]

Trichomonal vaginitis stands out as the most prevalent sexually transmitted disease, followed by gonococcal infections as the second most common bacterial infection transmitted through sexual contact, leading to significant morbidity worldwide annually. Among women of reproductive age, bacterial vaginosis (BV) is the primary culprit for abnormal vaginal discharge.[2]

Vaginal infections pose a considerable risk of morbidity in women. When left untreated, they can progress to pelvic inflammatory disease (PID), which can have long-lasting consequences including ectopic pregnancy, reproductive dysfunction, tubal infertility, as well as adverse pregnancy outcomes (preterm labor and low birth weight).[2]

Doxycycline in Gynecological Infections

Doxycycline is a part of the empirical treatment of PID.[3]

In the inpatient setting, empiric treatment for PID can be administered using the following options:[3]

- Intravenous (IV) cefotetan 2 mg every 12 hours along with oral doxycycline of 100 mg every 12 hours.
- Intravenous (IV) cefoxitin 2 gm every 6 hours, combined with oral doxycycline of 100 mg every 12 hours.
- Intravenous (IV) clindamycin 900 mg every 8 hours, along with IV gentamicin 3–5 mg/kg body weight, once daily.

For outpatient therapy, the Centers for Disease Control and Prevention (CDC) recommends the following as first-line treatment:[3]

- Oral doxycycline 100 mg twice daily for 14 days along with one dose of intramuscular (IM) ceftriaxone 500 mg or one dose of IM cefoxitin 2 gm with oral probenecid 1 gm or another parenteral third-generation cephalosporin.

Clinical Evidence

Treating Pelvic Inflammatory Disease with Doxycycline and Metronidazole or Penicillin and Metronidazole

A randomized study evaluating the clinical response of penicillin plus metronidazole and doxycycline plus metronidazole included 33 patients diagnosed with PID confirmed through laparoscopy and endometrial biopsy.[4]

Following were the results observed.

Treatment failure rates (overall):

- Chlamydial PID: 5/11 (45%) women.
- Gonococcal PID: 0/6 (0%) women.
- Chlamydial and gonococcal PID: 4/4 (100%) women with both chlamydial and gonococcal infections.
- Non-chlamydial and non-gonococcal PID: 3/12 (25%) women.

Failure rate between treatment groups: Significantly high failure rate with the combination of penicillin and metronidazole than that of doxycycline and metronidazole ($p = 0.038$; Fig. 1).

Doxycycline plus metronidazole emerges as an effective treatment option for PID, demonstrating a significantly lower clinical failure rate.

Doxycycline in Preventing Infections after Gynecologic Procedures

The risk of infection related to hysterosalpingography (HSG) chromotubation is influenced by the patient's history of PID. To mitigate this risk, it is recommended to administer antimicrobial prophylaxis to patients undergoing HSG or chromotubation if they have a history of PID or if abnormalities are observed in their fallopian tubes during the procedure. The presence of tubal dilation is recognized as a risk factor for PID following HSG.[5]

- Hysterosalpingography (HSG) can be done without antibiotic prophylaxis in patients without prior pelvic infection, but if dilated fallopian tubes are found, a 5-day course of doxycycline 100 mg BID is recommended to reduce the risk of post-HSG PID.[5,6]

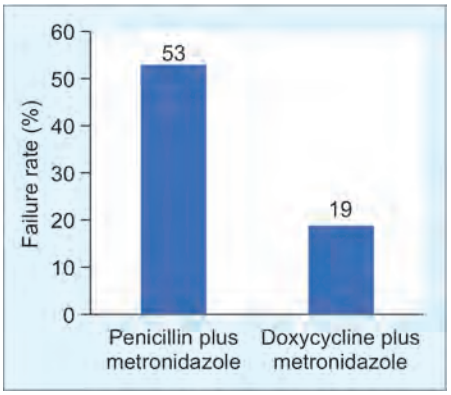


Fig. 1: Treatment failure rate in the two treatment groups

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- For patients with a history of pelvic infection, doxycycline can be given prior to the procedure and continued if dilated fallopian tubes are identified.[5,6]

A retrospective review of 278 HSG procedures showed the following:[6]

- Patients with tubal dilation had an 11% risk of post-HSG PID, while the general population had a 1.4% risk.
- Patients with normal fallopian tube anatomy did not experience any post-HSG PID.
- Post-HSG PID was not reported among patients with tubal dilation who received doxycycline prophylaxis.

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REVIEW ARTICLE

Doxycycline in Dermatology

Sheetal Poojary*

Abstract

Doxycycline is a wide-spectrum antibiotic and has shown to have useful anti-inflammatory properties also that make it suitable for the treatment of a number of noninfectious conditions. Tetracyclines are prescribed commonly in dermatology, where they are usually used at doses lower than those effective against infections. The efficacy and safety profile of tetracycline are proven. And doxycycline's ability to inhibit the molecular pathways. Hence doxycycline can be used to treat hair follicle diseases, granulomatous diseases, and vascular proliferation, among other conditions. in this article we tried to summarize the applications of doxycycline in dermatology.

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Introduction

Tetracyclines are commonly prescribed antibiotics in dermatology, often administered at lower doses than those required to treat infections, making them suitable for dermatological purposes.[1] In particular, doxycycline, a type of tetracycline antibiotic, is extensively utilized in dermatology due to its antibiotic and anti-inflammatory properties, along with its excellent safety profile.[2] Numerous studies have provided evidence of doxycycline's effectiveness in treating various dermatological diseases, which are listed in Table 1.[3–11]

Apart from these, doxycycline is also useful in treating certain uncommon infections, such as inhalational anthrax[8] and atypical mycobacterial infections.[12]

Table 1: Indications of doxycycline in dermatology

Indication	*Mechanism of action*
Melkersson-Rosenthal syndrome[3]	Inhibits the synthesis of protein kinase C[3]
Pityriasis lichenoides chronica, pityriasis lichenoides et varioliformis acuta[4]	Anti-inflammatory effect[4,5]
Lyme disease[6]	Anti-inflammatory effect; reduces TNF-alpha, IL-6, and IL-8 production[7]
Syphilis in penicillin-sensitive patients[8]	Antibacterial activity[9]
Lymphogranuloma venereum[10]	Antibacterial; binds to 30S ribosomal subunits of susceptible bacteria and inhibits protein synthesis[11]

IL: interleukin; TNF: tumor necrosis factor

Doxycycline in Acne Vulgaris

The rationale for using doxycycline, compared to minocycline, in treating acne vulgaris includes the following:[13]

- Less frequent daily dosing.
- Lower prevalence of less sensitive *Propionibacterium acnes*.
- Greater lipophilicity than tetracycline.
- Favorable long-term track records of overall efficacy and safety.

Doxycycline targets various receptors and mediators involved in the inflammatory processes associated with acne vulgaris. One study revealed increased activity of protease-activated receptor 2 (PAR2) on keratinocytes in acne vulgaris, leading to the stimulation of several factors such as human β-defensin-2, LL-37, matrix metalloproteinase (MMP)—2, MMP-3, MMP-9, and MMP-13. Doxycycline effectively inhibits PAR2 and multiple MMPs, while also downregulating the nuclear factor kappa B (NF-κB) pathway. The downregulation of NF-κB is particularly significant since it is highly activated in acne vulgaris, resulting in elevated secretion of tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL1β), both of which further contribute to NF-κB signaling. These anti-inflammatory effects of doxycycline make it a favorable choice for managing inflammatory acne vulgaris.[2]

Clinical Evidence

Effects of Sub-antimicrobial Dose Doxycycline in the Treatment of Moderate Acne

A double-blind, randomized trial was carried out across multiple centers to investigate the impact of sub-antimicrobial dose doxycycline hyclate treatment on patients with moderate acne.[14] The trial aimed to determine whether this treatment improved clinical outcomes, influenced skin flora, caused overgrowth or colonization of opportunistic pathogens on the skin or led to increased antibiotic resistance in the surface skin microflora.

A group of 51 adult patients with moderate acne participated in a randomized study where they were assigned to receive either sub-antimicrobial dose of doxycycline (20 mg tablet) or a placebo. The treatment was administered twice daily for a duration of 6 months.

Following were the results observed:

- After 6 months, the group receiving sub-antimicrobial dose of doxycycline showed significant improvements compared to the placebo group in the following aspects:
  - There was a significantly greater reduction in the number of comedones ($p < 0.01$).
  - The combined number of inflammatory and noninflammatory lesions showed a significantly greater reduction ($p < 0.01$).
  - The total number of inflammatory lesions showed a significantly greater reduction ($p < 0.05$).
- According to the clinician's global assessment, the sub-antimicrobial dose doxycycline group demonstrated a significantly greater improvement ($p = 0.03$) compared to the placebo group.

Thus, in patients with moderate facial acne, the use of sub-antimicrobial dose doxycycline treatment twice daily resulted in a significant reduction in the number of both inflammatory and noninflammatory lesions.

Doxycycline Resistance in Acne

Acne affects nearly 1 billion people worldwide, and oral tetracyclines like doxycycline and minocycline are commonly prescribed and effective treatments. However, there is a risk of increase in resistance to these antibiotics due to their widespread use.[15]

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Studies have reported a significant increase in the number of *Cutibacterium acnes* (*C. acnes*) strains that are resistant to doxycycline globally, with over 50% of isolates in the United States showing resistance. Furthermore, resistance to doxycycline has been linked to inadequate improvement in acne symptoms. Beyond treatment failure, the implications of *C. acnes* resistance include potential disruptions to the skin and gut microbiota, the promotion of opportunistic pathogens both locally and systemically, and the dissemination of drug-resistant strains to healthcare providers and the general population.[16]

A Note of Caution for the Use of Doxycycline during Pregnancy and Lactation

The administration of tetracycline-class drugs during the phases of tooth development (specifically from the fetal development stage during the last half of pregnancy until the age of 8) can result in permanent tooth discoloration characterized by yellow–gray–brown hues. It is important to note this potential side effect. Furthermore, tetracyclines, including doxycycline, are excreted in human milk. However, the extent to which breastfed infants absorb these drugs is uncertain. To be on the safer side, it is advisable to avoid the use of doxycycline while nursing, if possible.[17]

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REVIEW ARTICLE

Doxycycline in Gastrointestinal Infections

Mukta Bapat*

Abstract

The goals of pharmacotherapy in cases of gastroenteritis are to reduce morbidity and to prevent complications. Intestinal infections can be caused by viruses or bacteria. The summary of clinical evidence thereby guides us towards the medical management treatable with doxycycline.

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Doxycycline has received the Food and Drug Administration (FDA) approval for the management of acute intestinal amebiasis and traveler's diarrhea (TD).[1] Additionally, it is indicated for the treatment of cholera caused by *Vibrio cholerae*.[2] Furthermore, doxycycline-containing regimens have exhibited efficacy in combating *Helicobacter pylori* (*H. pylori*).[3]

Doxycycline is known to decrease the occurrence and intensity of TD, and studies have demonstrated its ability to offer protection against this condition in 60–85% of individuals, depending on the resistance of enterotoxin-producing *Escherichia coli*.

In a study that compared diarrhea rates between British and Australian medical teams deployed to Iraq during the 1990–1991 Gulf War, it was observed that Australians who used doxycycline for malaria prophylaxis and followed a strict regimen of plate and handwashing had a significantly lower incidence of diarrhea compared to the British group (36 vs 69%, respectively). Moreover, when diarrhea did occur, it was less severe and resolved more quickly ($p < 0.001$).[1]

In individuals diagnosed with cholera, antibiotics are used in conjunction with appropriate fluid and electrolyte replacement. They can aid in reducing *Vibrio* excretion and the volume of diarrhea. Doxycycline (or tetracycline) has traditionally been the preferred treatment option; however, resistance to this class of antibiotics has been observed. Doxycycline can effectively treat infections caused by non-cholera *Vibrio* species and *Aeromonas* species, which typically affect the skin or gastrointestinal tract but can occasionally lead to septic illnesses.[4]

Clinical Evidence

Impact of Doxycycline Malaria Prophylaxis on the Risk of Travelers' Diarrhea among International Travelers

A prospective cohort of travelers was examined in a study to assess the occurrence of TD and identify the factors contributing to its risk, particularly in relation to malaria prophylaxis.

- The study included a total of 3,227 trips, with 62.1% of the participants being male. The median age of the participants was 39 years, with an interquartile range (IQR) of 27–59 years. The median duration of travel was 19 days, with an IQR of 12–49 days. Among the participants, 17.4% experienced TD. In terms of destinations, 32% traveled to Africa, 40% to Asia, and 27% to the Caribbean and Latin America.
- About 20% of the participants took doxycycline as malaria chemoprophylaxis.
- About 50% of the participants took other antimalarials.
- About 30% of the participants did not take any malaria prophylaxis.
- Taking doxycycline was associated with a decreased risk ratio (RR) of TD [RR 0.62 (0.47–0.82), $p < 0.01$].
- Military travel showed a noteworthy decrease in the RR of TD [RR 0.57 (0.47–0.70), $p < 0.01$]. Conversely, an elevated risk of TD was observed in individuals identifying as female [RR 1.28 (1.09–1.50), $p < 0.01$], those staying in hotel accommodations [RR 1.30 (1.10–1.53), $p < 0.01$), those traveling to tropical South America [RR 1.34 (1.09–1.640), $p < 0.01$], and those with longer durations of travel [RR 1.00 (1.00–1.01), $p < 0.01$].[5]

The utilization of doxycycline as a preventive measure against malaria has been linked to a reduced risk of TD. This association suggests that doxycycline may enhance susceptibility to bacterial enteropathogens, aligning with prior findings. Consequently, choosing doxycycline for antimalarial chemoprophylaxis could offer travelers added advantages in preventing infections.

Doxycycline in the Eradication Therapy of *Helicobacter pylori*: A Systematic Review and Meta-analysis

A comparison was made between the success rates of *H. pylori* treatment regimens including and excluding doxycycline. Extensive searches were conducted in English medical literature databases, including MEDLINE, PubMed, EMBASE, Scopus, and CENTRAL.[3] The searches encompassed the period up to August 31, 2015, specifically focusing on treatment regimens involving doxycycline for the eradication of *H. pylori*.

In a fixed model analysis, the odds ratio (OR) indicated a higher likelihood of eradication success with treatment regimens containing doxycycline: OR 1.292, 95% confidence interval (CI) 1.048–1.594, $p = 0.016$. There was no significant heterogeneity in the studies included in the meta-analysis: Q =15.130, degrees of freedom (df) (Q) = 8, $I^2 = 47.126$, $p > 0.10$.

When treatment regimens containing doxycycline were specifically compared to treatment regimens containing tetracycline, no significant disparity was observed in the eradication success rate: OR 0.95, 95% CI 0.68–1.32, $p = 0.77$. However, when treatment regimens with doxycycline were compared to those without tetracycline, the OR favoring doxycycline was even more pronounced: OR 1.59, 95% CI 1.21–2.09, $p < 0.001$.

The efficacy of doxycycline in eradicating *H. pylori* has been established. As a result, it is recommended to consider triple, quadruple, or even high-dose dual therapy regimens that include doxycycline for the treatment of *H. pylori* infection.

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REVIEW ARTICLE

Guideline Recommendations and Miscellaneous Applications of Doxycycline

Pradyut Waghray[1], Mangesh Tiwaskar[2*]

Abstract

Doxycycline is a broad-spectrum bacteriostatic agent synthetically derived from a naturally occurring tetracycline produced by Streptomyces species bacteria. While doxycycline can be used to treat variety of conditions, its use for treatment and prophylaxis is the focus of this article. The different approved indication and the guideline recommendations are discussed briefly in the article.

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Expert Opinion Recommendations for Acute Undifferentiated Febrile Illness Management in India

Diagnosis and Management of Acute Undifferentiated Febrile Illness in India

An algorithm for managing acute undifferentiated febrile illness (AUFI) has been devised, taking into account the pathogen epidemiology, prevailing clinical practices, and heterogeneity across India.[1]

The initial step involves evaluating the patient's fever history, followed by assessing whether there are any indications of systemic inflammatory response syndrome (SIRS) or sepsis. This step is crucial because certain diseases, such as malaria, dengue, and acute respiratory distress syndrome, have similar pathophysiological characteristics, including elevated body temperatures. Subsequently, the clinical features are analyzed to aid in identifying and localizing the specific syndrome associated with the undifferentiated febrile illness. If the fever has persisted for <3 days and rapid diagnostic tests (RDTs) yield negative results, the recommended course of action is to prescribe antipyretics, specifically paracetamol, as a standalone treatment.

The detailed steps are as follows:

Step 1

- The first step involves gathering epidemiological information, including factors such as comorbidities, immune suppression, geriatric status, pregnancy, as well as local disease prevalence, seasonal patterns (such as malaria, leptospirosis, scrub typhus), and exposure to animals and vectors.

Step 2

- The next step involves assessing clinical symptoms (excluding localized infections) and prioritizing patients based on disease severity.
- Factors such as the time of disease onset and specific organ involvement characteristics are considered during this evaluation. If a patient shows signs such as altered mental status, systolic blood pressure below 90, respiratory rate above 24, or indications of SIRS or sepsis, prompt evaluation for sepsis and immediate treatment should be initiated.
- Additionally, it is important to rule out (1) fevers associated with rashes, and if present, determine the type of rash and provide appropriate management, and (2) localized infections affecting the respiratory, urinary, central nervous system, skin, and gastrointestinal tract.

Step 3

- Initial diagnostic tests include complete blood count (CBC) and RDT for malaria antigens (histidine-rich protein 2, *Plasmodium* lactate dehydrogenase, *Plasmodium* aldolase), along with influenza testing if necessary. If malaria test results are positive, appropriate malaria management protocols should be followed.
- For nonmalarial AUFIs, a comprehensive evaluation is conducted. This includes CBC, urinalysis, biochemical tests, and imaging if required, as well as specific tests for identifying pathogens such as dengue, leptospirosis, enteric fever, and scrub typhus.
- In febrile patients, host biomarkers, like C-reactive protein, procalcitonin, etc., can be checked as additional measures to differentiate between bacterial and nonbacterial infections.

Guideline Recommendations for Empirical Doxycycline Therapy

Recommendations by Indian Guidelines

- The Indian Council of Medical Research (ICMR) recommends empirical treatment with doxycycline for patients presenting with undifferentiated fever when RDTs for malaria and dengue are negative.
- Doxycycline is an effective antimicrobial choice for treating rickettsial infections and is considered second-line therapy for falciparum malaria.
- In areas with high endemicity, short-term chemoprophylaxis with doxycycline is recommended (100 mg daily for adults and 1.5 mg/kg for children over 8 years old).
- In tuberculosis-endemic regions of India, initiating doxycycline for suspected cases of scrub typhus is a reasonable choice.
- Doxycycline is also the preferred medication for patients with comorbidities and critical illness due to community-acquired pneumonia (CAP).
- A clinically appropriate strategy recommended by the Association of Physicians of India involves empirical treatment with doxycycline to reduce morbidity and mortality in patients with nonmalarial AUFI.

Recommendations by International Regulatory Bodies

- The World Health Organization recommends the use of doxycycline for treating nonspecific fevers.
- Guidelines from the National Institute for Health and Care Excellence guideline

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recommend doxycycline as the preferred oral antibiotic for initial treatment in adult coronavirus disease of 2019 (COVID-19) patients with suspected or confirmed pneumonia. This choice is based on its broader spectrum coverage, particularly against *Mycoplasma pneumoniae* and *Staphylococcus aureus*, the highly probable secondary causative factors associated with commonly associated with bacterial pneumonia during the COVID-19 pandemic.

- Guidance from the Massachusetts General Hospital supports the use of empirical antibiotic treatment for COVID-19 to reduce the risk of superinfections. The recommended empirical regimen includes oral administration of 100 mg doxycycline twice a day for 5 days, along with 1 gm of intravenous (IV) ceftriaxone daily.

Antimicrobial Use in Common Syndromes: ICMR Guidelines, 2022

Acute Fever

Key Principles of Empiric Therapy in Acute Fever Management

Antibiotics are not necessary for most patients with acute febrile illness when a clear clinical diagnosis is absent.[2]

- Initiate antibiotic therapy promptly for presumed bacterial infections, but be prepared to adjust dosage and duration, switch to a different drug, or discontinue treatment if results do not support the continued need for antibiotics.
- Reassess the patient's condition and test results within 48 hours to inform further management decisions.
- Empirical treatment with doxycycline can be considered for patients with undifferentiated fever when RDTs for malaria and dengue are negative.

Chemoprophylaxis in Acute Fever

Chemoprophylaxis is recommended for individuals at risk of malaria, such as travelers, migrant laborers, and military personnel in highly endemic areas. Pregnant women and other vulnerable populations should be encouraged to use personal protection measures like insecticide-treated bednets.

For short-term chemoprophylaxis (<6 weeks):

- Doxycycline: Adults should take 100 mg daily, while children over 8 years old should take 1.5 mg/kg. Start the medication 2 days before travel and continue for 4 weeks after leaving the malarious area. (note: doxycycline is contraindicated in pregnant women and children under 8 years old).

For long-term chemoprophylaxis (>6 weeks):

- Mefloquine: Administer a weekly dose of 5 mg/kg body weight (up to 250 mg) starting 2 weeks before travel, during the stay in the malarious area, and continue for 4 weeks after leaving the area.

Antimicrobial Choice for Disease Conditions (Acute Fever)

- Rickettsial infections: The preferred and first-choice treatment for rickettsial infections is doxycycline, to be administered for a duration of 7 days.
- Leptospirosis: Doxycycline or penicillin G is the preferred and first-choice treatment for leptospirosis, to be given for a duration of 7 days.
- *Falciparum*malaria: In most parts of India, except the northeastern states, doxycycline should be added as a second agent to a regimen of oral artesunate and pyrimethamine on the first day for patients capable of taking oral medications. Only in the Northeastern states doxycycline should be added to oral artemether-lumefantrine. If a patient is unable to take medications orally, IV artesunate should be administered first, followed by switching to oral therapy, and doxycycline can be added as a second agent.

Respiratory Infections

Doxycycline is the preferred choice for adult patients with bacterial sinusitis who have a penicillin allergy.

Skin and Soft Tissue Infections

For the treatment of necrotizing fasciitis, the preferred regimen consists of ciprofloxacin in combination with doxycycline, administered for a duration of 14 days.

Indian Medical Association: Management of Acute Fever in Primary Care

Treatment of Acute Fever in Primary Care

Both pharmacological and nonpharmacological approaches play a role in managing acute fever and alleviating associated discomfort and constitutional symptoms. Nonpharmacological methods, such as tepid sponging, can help reduce temperature in patients with acute fever. Early initiation of presumptive antibiotic therapy is crucial for suspected bacterial AUFIs that exhibit characteristic clinical features. Empirical therapies are necessary when confirmatory diagnostic testing is pending or unavailable.[3]

In severe cases of nonmalarial nonarboviral AUFI, a combination of third-generation cephalosporin and doxycycline can be used as empirical therapy to manage conditions like rickettsioses, leptospirosis, and enteric fever. Doxycycline can also be utilized alongside artesunate and ceftriaxone to address concomitant bacterial sepsis commonly observed in such patients. Considering the limited resources available for fever management and certain compelling indications, the empirical use of broad-spectrum antibiotics like doxycycline can be considered in the management of acute febrile illness.

Below are the recommendations pertaining to doxycycline:

Malaria

For chemoprophylaxis (<6 weeks), adults should take 100 mg of doxycycline daily, while children over 8 years old should take 1.5 mg/kg body weight. The medication should begin two days before travel and be continued for four weeks after leaving the malarious area.

It's important to note that doxycycline should not be taken by pregnant or lactating women, as well as children under 8 years old.

Leptospirosis

- For adults, doxycycline can be taken twice a day at a dosage of 100 mg for a duration of 7 days.
- In the case of chemoprophylaxis during the peak transmission season, a single weekly dose of 200 mg of doxycycline is recommended.

Scrub Typhus

The first-line medication in adults is doxycycline 100 mg twice daily for 7 days.

In the case of children and pregnant women, alternative options such as azithromycin, rifampicin, or chloramphenicol should be considered.

Acute Fever in Respiratory Tract Infections

Bacterial Sinusitis

In adults with a penicillin allergy, the use of doxycycline or respiratory quinolones is recommended.

Community-acquired Pneumonia

For outpatients who have comorbidities or have received antimicrobial treatment within the past 3 months:

- The preferred drugs are coamoxiclav in combination with a macrolide or doxycycline (100 mg taken twice daily for adults).
- As an alternative, cefuroxime or cefpodoxime in combination with a macrolide or doxycycline (100 mg taken twice daily for adults) can be considered.

For non-ICU inpatients with CAP:

- The preferred antibiotic regimen includes ceftriaxone with macrolide/doxycycline (100 mg twice daily for adults).
- Alternatively, cefotaxime/amoxiclav with macrolide/doxycycline (100 mg twice daily for adults).

Skin and Soft Tissue Infections

In patients with necrotizing fasciitis, a combination of ciprofloxacin (IV 750 mg q12h) and doxycycline (IV 200 mg stat f/b 100 mg one in the morning and one in the evening) for 14 days is recommended.

Recommendations on the Use of Doxycycline in Specific Dermatological Conditions

Table 1 shows the recommended dosage of doxycycline in specific dermatological conditions.

Doxycycline Recommendations in Gynecologic Infections

Pelvic Inflammatory Disease

In the inpatient setting, empiric treatment for pelvic inflammatory disease (PID) can be administered using the following options[7]:

- Intravenous (IV) cefotetan 2 mg every 12 hours, along with oral doxycycline of 100 mg every 12 hours.
- Intravenous (IV) cefoxitin 2 gm every 6 hours, combined with oral doxycycline of 100 mg every 12 hours.
- Intravenous (IV) clindamycin 900 mg every 8 hours, along with IV gentamicin 3–5 mg/kg body weight, once daily.

For outpatient therapy, the Centers for Disease Control and Prevention recommends the following as first-line treatment[7]:

- Oral doxycycline 100 mg twice daily for 14 days weeks plus one dose of intramuscular (IM) ceftriaxone 500 mg or IM cefoxitin 2 g with one dose of oral probenecid 1 gm or another parenteral third-generation cephalosporin

Posthysterosalpingography Infections

- Hysterosalpingography (HSG) can be done without antibiotic prophylaxis in patients without prior pelvic infection, but if dilated fallopian tubes are found, a 5-day course of doxycycline 100 mg twice a day (BID) is recommended to reduce the risk of post-HSG PID.[8,9]
- For patients with a history of pelvic infection, doxycycline can be given prior to the procedure and continued if dilated fallopian tubes are identified.[8,9]

Miscellaneous Applications of Doxycycline

Research on doxycycline shows that it is applicable in several medical conditions, as listed below:

- *Helicobacter pylori* infections: In cases of clarithromycin resistance, doxycycline can be utilized as an effective alternative in combination with other medications, serving as a second-line treatment option.[10]
- Whipple's disease: After completing the initial treatment with ceftriaxone or penicillin, patients who cannot tolerate cotrimoxazole can undergo maintenance therapy for 1 year using a combination of doxycycline and hydroxychloroquine.[10]
- Cholera: Antibiotics are used in conjunction with appropriate fluid and electrolyte replacement, and they can help reduce the excretion of *Vibrio* bacteria and the volume of diarrhea. Historically, doxycycline (or tetracycline) has been the preferred treatment option, although there have been cases of resistance to this class of antibiotics.[10]
- Infections caused by noncholera *Vibrio* spp. and *Aeromonas* spp.: They typically affect the skin or gastrointestinal tract, but they can also lead to more severe systemic infections. Doxycycline is commonly used as a treatment option for these infections.[10]
- Brucellosis in adults: The recommended first-line treatment for brucellosis often involves a combination of doxycycline and initial streptomycin administered for a duration of 45 days. Alternatively, a 45-day regimen of doxycycline in conjunction with rifampicin is occasionally utilized and has demonstrated superiority over combining doxycycline with fluoroquinolone.[10]
- Melioidosis: Initially treated with IV carbapenems or ceftazidime, followed by at least three months of oral therapy using cotrimoxazole plus doxycycline.[10]
- Chronic bacterial prostatitis (CBP): Doxycycline is an effective antibiotic for eradicating infection and improving symptoms in CBP and is recommended as a second-line treatment by the Prostatitis Expert Reference Group.[11]
- Periodontitis: Compared to other drugs, doxycycline has greater availability in the gingival crevice; it inhibits bone resorption and promotes reattachment. Subantimicrobial dose doxycycline can help prevent periodontal attachment destruction by controlling matrix metalloproteinase (MMP) activation.[12]
- Idiopathic pulmonary fibrosis: Doxycycline exhibits promising potential in treating idiopathic pulmonary fibrosis by virtue of its anti-MMP activities.[13]

Table 1: Doxycycline dosage for specific dermatological conditions

Indication	*Doxycycline dosage*
Lyme disease	• Oral doxycycline: 200 mg for adults; 4.4 mg/kg for children (maximum 200 mg).[4] • Duration in erythema migrans is 10 days; in meningitis or radiculopathy, cranial nerve palsy, and carditis, it is 14–21 days.[4] • In patients with arthritis as manifestation: the duration for initial treatment and for recurrent/refractory arthritis is 28 days, for acrodermatitis chronica atrophicans 21–28 days, and for borrelial lymphocytoma 14 days.[4]
Syphilis in penicillin-sensitive patients	Oral doxycycline 100 mg BID for 2 weeks[5]
Lymphogranuloma venereum	Oral doxycycline 100 mg BID for 21 days[6]
Inhalational anthrax	• Oral doxycycline 100 mg BID for 60 days [adults and children (body weight ≥45 kg)].[5] • Oral doxycycline 2.2 mg/kg (1 mg/lb) body weight BID for 60 days (children with a body weight <45 kg).[5]

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Conflict of Interest

This project is financially supported by Dr Reddy's Laboratories, Hyderabad, Telangana, India.

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