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## Intravenous Administration of Doxycycline, Azithromycin, or their Combination for Managing Severe Scrub Typhus

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### Abstract

To evaluate the efficacy and safety of intravenous doxycycline, azithromycin and their combination in the treatment of severe scrub typhus. A review of published literature and clinical trials, including the Interest trial and other multi centric studies, was undertaken. Data were assessed for endpoints such as 28-day mortality, fever clearance time, incidence of organopathy, pharmacokinetic profiles, side effects and transition to oral therapy. Combination therapy showed a statistically significant reduction in organopathy compared to monotherapy, though mortality and fever clearance times were similar. Doxycycline and azithromycin exhibited favorable pharmacokinetic profiles for intravenous administration and successful transition to oral therapy. Both agents demonstrated acceptable safety profiles, with side effects such as gastrointestinal disturbances and skin reactions being the most common. Intravenous doxycycline and azithromycin, particularly in combination, offer enhanced clinical benefits in managing severe scrub typhus. Further large-scale trials are needed to optimize treatment protocols and address long-term concerns, such as antimicrobial resistance.

## INTRODUCTION

The intravenous administration of doxycycline, azithromycin, or their combination represents a critical intervention for managing severe scrub typhus, a potentially fatal infectious disease caused by the bacterium, primarily transmitted through infected mite bites<sup>[1-5]</sup>. Scrub typhus poses a significant health risk, particularly in endemic regions of South Asia and the tropics, where it accounts for a substantial portion of infections with an estimated mortality rate of up to 70% in untreated cases. The urgency for effective treatment has driven research towards evaluating various antibiotic regimens to improve patient outcomes. Doxycycline and azithromycin are two antibiotics that have garnered attention in clinical settings for their efficacy against scrub typhus. Doxycycline, a broad-spectrum antibiotic, functions by inhibiting bacterial protein synthesis, while azithromycin, a macrolide, disrupts the same process through a different mechanism. Recent studies, including the multicentric Intravenous Treatment for Scrub Typhus (INTREST) trial, have highlighted that combination therapy significantly enhances therapeutic efficacy compared to monotherapy, resulting in lower rates of mortality and complications among severely affected patients. Despite their effectiveness, the use of these antibiotics is not without controversies, particularly regarding potential side effects and interactions. Both medications can lead to adverse reactions, necessitating careful patient monitoring during treatment. Furthermore, the evolving landscape of antimicrobial resistance raises concerns about the long-term viability of these treatment strategies, prompting ongoing research into alternative therapeutic approaches and preventive measures. In summary, the intravenous administration of doxycycline and azithromycin, whether used separately or in combination, is crucial for the effective management of severe scrub typhus. Continued investigation into their clinical application will inform best practices and treatment guidelines, aiming to reduce morbidity and mortality associated with this serious disease. Scrub typhus is a life-threatening infection caused by the bacteria, primarily transmitted to humans through bites from infected mites. This disease poses a significant public health threat, particularly in India, other South Asian countries and tropical regions, where it results in an estimated 10% mortality rate among the approximately 1 million infected individuals annually<sup>[6,7]</sup>. The clinical presentation of scrub typhus typically includes fever, which may be accompanied by headache, cough, shortness of breath, and neurological symptoms such as confusion and disorientation. Severe cases may develop complications that affect multiple organ systems, leading to dangerously low blood pressure.

The death rates for severe scrub typhus can reach up to 70% without treatment, while treatment can reduce mortality to 24%. Most cases of scrub typhus occur in endemic areas, with significant agricultural exposure reported among infected individuals, particularly those working in rice fields and plantations. The disease is characterized by various symptoms, including fever, rash, eschar and lymphadenopathy, with some patients experiencing severe complications like disseminated intravascular coagulation and circulatory collapse, especially when diagnosis is delayed<sup>[8,9]</sup>. Effective management of scrub typhus has traditionally involved the use of antibiotics such as doxycycline, tetracycline, or chloramphenicol., however, the efficacy of repellents and chemoprophylaxis remains limited. Given the high fatality rates associated with severe scrub typhus, the exploration of alternative treatment methods, including intravenous administration of doxycycline and azithromycin, has become a focus of research to improve patient outcomes.

**Doxycycline:** Doxycycline is a broad-spectrum antibiotic belonging to the tetracycline class, primarily utilized in the treatment of various bacterial infections. It is effective against infections caused by specific types of bacteria and is indicated for conditions such as anthrax, plague and tularemia, which may be associated with bioterrorism threats. Additionally, doxycycline is employed in malaria prevention and serves as a therapeutic agent for acne and rosacea, a skin condition characterized by facial redness and pimples.

**Mechanism of Action:** Doxycycline operates by inhibiting bacterial protein synthesis, specifically by binding to the 30S ribosomal subunit of bacteria, which disrupts their ability to create proteins necessary for their growth and reproduction. This bacteriostatic action prevents the proliferation of bacteria, effectively controlling infections<sup>[10]</sup>. Moreover, it also demonstrates anti-inflammatory properties by hindering calcium-dependent micro tubular assembly, which may contribute to its efficacy in treating inflammatory conditions such as rosacea.

**Pharmacokinetics:** Approximately 40% of doxycycline is excreted by the kidneys through glomerular filtration within 72 hours in individuals with normal renal function. The metabolism of doxycycline is minimal, and a small fraction is expelled in the bile. Its pharmacokinetic profile enables effective dosing regimens for both intravenous and oral administration, making it a versatile option in clinical settings.

**Side Effects:** While generally well-tolerated, doxycycline can lead to a range of side effects. These

may include gastrointestinal disturbances, skin reactions and, in rare cases, more serious effects such as vision changes or severe allergic reactions. Patients are advised to report any unusual symptoms to their healthcare provider, particularly during prolonged treatment courses.

**Azithromycin:** Azithromycin is a macrolide antibacterial drug that is widely used for the treatment of various bacterial infections, including respiratory and skin infections. The mechanism of action of azithromycin involves binding to the 23S ribosomal RNA of the bacterial 50S ribosomal subunit, which inhibits protein synthesis by obstructing transpeptidation and translocation processes within the bacterial cell.

**Pharmacokinetics:** The pharmacokinetic properties of azithromycin include a bioavailability of approximately 37% following oral administration and its absorption is not significantly affected by food. The drug exhibits a correlation between its antibacterial activity and the pharmacokinetic/pharmacodynamic parameter known as the area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for specific pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*<sup>[11,12]</sup>. However, clinical trials have not yet clearly defined the principal pharmacokinetic/pharmacodynamic parameter that is most closely associated with clinical and microbiological cure outcomes when using azithromycin.

**Clinical Use and Efficacy:** Azithromycin has been evaluated in combination therapies for conditions like scrub typhus. In studies assessing the efficacy of azithromycin alone or in conjunction with doxycycline, the outcomes were measured based on recovery rates, onset of action, improvement in symptoms and overall efficacy rates. The total efficacy rate can be calculated using the formula: Total efficacy rate=(Number of recovery cases+number of onset of action cases)/total number of cases×100%. Research indicates that the combination of azithromycin and doxycycline may offer synergistic effects in treating infections such as non-gonococcal urethritis (NGU), potentially influencing inflammatory responses marked by cytokine like Interleukin-6 (IL-6).

**Safety and Side Effects:** While azithromycin is generally well-tolerated, it is important for healthcare providers to monitor patients for potential drug interactions and side effects, particularly in those receiving multiple medications. Azithromycin may influence cardiac electro physiology and has been associated with certain treatment-related adverse

effects, necessitating careful monitoring of patient outcomes during therapy.

**Combination Therapy:** Combination therapy using intravenous doxycycline and azithromycin has emerged as a preferred treatment strategy for severe scrub typhus, a life-threatening infection caused by the bacteria, which is transmitted through bites from infected mites. This dual approach has shown greater therapeutic efficacy compared to monotherapies involving either drug alone.

**Efficacy of Combination Therapy:** A multicentric study conducted in 2023 by Varghese *et al.* provided robust evidence supporting the effectiveness of the combination therapy. The trial, which was a well-conducted, prospective, multicenter, randomized comparative study, involved a large number of patients and aimed to assess the efficacy of doxycycline combined with azithromycin against monotherapy with either antibiotic. The primary endpoints included 28-day mortality, persistent fever at day 5 and the incidence of organopathy at day 7<sup>[13,14]</sup>. While the results indicated that monotherapy did not show inferiority to the combination therapy regarding 28-day mortality and fever clearance time, a notable difference was observed in the incidence of organopathy, which was significantly lower in the combination group.

**Clinical Implications:** The findings from this study suggest that the combination of doxycycline and azithromycin not only enhances the therapeutic outcomes but also potentially improves the quality of life for patients suffering from severe scrub typhus. As stated by the lead author of the study, Prof. George M Varghese, this new evidence could lead to a revision of treatment guidelines, ultimately facilitating quicker recovery and saving thousands of lives annually.

#### Intravenous Administration:

**Overview of Intravenous Therapy:** Intravenous (IV) therapy plays a crucial role in the management of severe scrub typhus, a potentially life-threatening infectious disease. The treatment often involves the use of antibiotics such as doxycycline and azithromycin, either as monotherapy or in combination to improve clinical outcomes. This approach is particularly important for patients exhibiting severe symptoms, where rapid administration of effective medication is essential.

**Clinical Trials and Findings:** The Intravenous Treatment for Scrub Typhus (INTREST) clinical trial investigated the efficacy and safety of three different 7-day intravenous antibiotic regimens: Doxycycline,

azithromycin and a combination of both. The results indicated that combination therapy significantly outperformed monotherapy, yielding better primary composite outcomes including reduced mortality at day 28, decreased rates of persistent complications at day 7 and lower incidence of persistent fever at day 5. Notably, patients receiving the combination therapy experienced a lower frequency of respiratory, renal, hepatic and central nervous system complications, highlighting the advantages of a multi-drug approach in this context<sup>[15]</sup>.

**Pharmacokinetic and Administration:** Doxycycline and azithromycin have distinct pharmacokinetic profiles that influence their effectiveness when administered intravenously. Doxycycline has a broad spectrum of activity and can achieve high tissue penetration, allowing for once-daily dosing in many cases. Studies have indicated that the pharmacokinetic of doxycycline differ between IV and subcutaneous (SC) routes, which is important for clinicians when considering treatment plans. Moreover, clinical evaluations have shown no clinically significant difference in clearance rates between oral and IV dosing for pediatric patients, suggesting that both routes can be viable depending on the patient's condition and response to treatment.

**Transitioning to Oral Therapy:** Switching from intravenous to oral therapy is a strategy employed once patients stabilize clinically. This transition can significantly reduce hospitalization duration and related healthcare costs, underscoring the importance of monitoring patient progress closely to determine the appropriate timing for this change.

#### Clinical Studies:

**Overview of Treatment Success:** Recent studies have evaluated treatment success in patients with Gram-negative bloodstream infections (GN-BSI) who were treated with either intravenous therapy or transitioned from intravenous to oral administration. These studies aimed to assess various outcomes, including the time to discharge, clinical failure rates, mortality and treatment-related adverse effects associated with commonly used antibiotics such as doxycycline and azithromycin.

**Pharmacokinetic and Efficacy:** Doxycycline is noted for its favorable pharmacokinetic, including a broad spectrum of activity and high tissue penetration, which often permits once-daily dosing as a monotherapy in many cases. This can be particularly beneficial in managing conditions like scrub typhus, which may present with serious systemic effects.

**Side Effects and Monitoring:** Doxycycline may cause a range of side effects, necessitating careful monitoring of patients during treatment<sup>[16]</sup>. Some common adverse effects include visual disturbances, skin reactions such as rashes and hives, respiratory difficulties and gastrointestinal issues, including watery or bloody stools. Patients are advised to report any unusual problems to their healthcare providers, as serious side effects should be reported to the Food and Drug Administration's (FDA) MedWatch Adverse Event Reporting program.

**Study Contributions and Ethical Considerations:** The studies reviewed included contributions from various healthcare personnel who were instrumental in collecting epidemiological information and patient samples<sup>[17]</sup>. Approval for these studies was obtained from relevant ethics committees, ensuring that informed consent was secured from participating patients. The findings aim to provide insights into effective management strategies for severe scrub typhus, focusing on the efficacy and safety of doxycycline and azithromycin in clinical practice.

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