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Review Article

Comparative Analysis of combination antibiotic therapy versus Standard Care in dengue fever

Romano M^{1*}, Ferrari M² and Conti A³

¹Division of Clinical Microbiology, Neva Institute for Advanced Vaccinology, Malta

²Department of Infectious Diseases, Ob Research Center for Epidemiology, Malta

³Division of Clinical Microbiology, Neva Institute for Advanced Vaccinology, Portugal

*Address for Correspondence: Marco Romano, Division of Clinical Microbiology, Neva Institute for Advanced Vaccinology, Malta; E-mail: marco.romano@neva.edu

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Abstract

Background: Dengue has no antiviral or antibacterial cure, yet a minority of hospitalized patients carry a secondary bacterial infection, co-infection, or a bacterial mimic such as leptospirosis or scrub typhus [7,8,9].

Objective: This comparative analysis synthesizes evidence on bacterial infection in dengue and on outcomes when combination antibiotic therapy is added to standard supportive care in that subgroup.

Methods: We synthesized cohort studies, case series, and trial evidence identified through PubMed and citation tracking, prioritizing studies reporting confirmed bacterial infection or outcomes stratified by antibiotic exposure or sepsis status.

Findings: Secondary bacterial infection is reported in roughly 8-15% of hospitalized dengue cohorts, rising with prolonged fever or sepsis [12,14], and community-acquired sepsis carries a substantially higher case-fatality proportion than dengue alone, favouring prompt combination antibiotic therapy once sepsis is identified [15,16]. Indiscriminate antibiotic use without identified bacterial infection shows no demonstrated benefit [20].

Conclusions: Combination antibiotic therapy has no role in dengue as such, but an evidence-supported role in the identifiable minority with bacterial infection or a mimic; how quickly that minority can be identified at the bedside remains the central open question, absent a randomized trial against standard care alone.

Keywords: dengue fever; combination antibiotic therapy; secondary bacterial infection; bacterial coinfection; standard supportive care

1. Introduction

Dengue is a mosquito-borne flaviviral disease of enormous and still growing global reach, with modelling estimates placing the annual number of apparent and inapparent infections in the hundreds of millions across more than a hundred endemic countries, a burden that has continued to expand geographically over the past two decades [1,2,3]. No antibiotic has ever been shown to act against the causative virus itself; the therapeutic core of dengue management remains, and has remained for decades, careful fluid administration, close monitoring through the critical defervescence period, and supportive treatment of bleeding and organ dysfunction as they arise [4,5,6]. That fact makes the persistent, and in places routine, use of antibiotics in hospitalized dengue patients one of the more curious features of clinical practice in endemic regions. The explanation is not simply prescriber error. A meaningful minority of patients admitted with what looks like straightforward dengue fever are, in fact, harbouring a secondary bacterial infection, a bacterial co-infection acquired around the same time as the viral illness, or an entirely different bacterial disease, such as leptospirosis or scrub typhus, that mimics dengue closely enough at presentation to be indistinguishable without directed testing [7,8,9]. For that subgroup, antibiotics are not an error but a genuine, sometimes life-saving, intervention, and the clinical problem is identifying who they are quickly enough for treatment to matter.

This comparative analysis brings together the published evidence on bacterial infection and co-infection in dengue fever, outcomes reported when combination antibiotic therapy is added to standard supportive care in that subgroup, and the countervailing evidence that indiscriminate antibiotic use confers no benefit. The aim is not to argue for or against antibiotics in dengue as a blanket policy, since the literature supports neither extreme, but to characterize where combination therapy has demonstrated value over standard care alone, and where it has not.

2. Methods

This is a narrative comparative synthesis rather than a formal systematic review. Literature was identified through PubMed searches combining terms for dengue, secondary bacterial infection, bacteraemia, co-infection, sepsis, leptospirosis, scrub typhus, empirical antibiotic therapy, and doxycycline, supplemented by citation tracking and the World Health Organization's dengue case-management guidance [10,11]. Priority was given to studies reporting laboratory-confirmed bacterial infection or co-infection, outcomes stratified by antibiotic exposure or sepsis status, and the diagnostic overlap between dengue and other treatable febrile illnesses in the same endemic settings. Because no adequately powered randomized trial has directly compared combination antibiotic therapy against standard care alone in confirmed bacterial co-infection, this synthesis draws on observational cohorts and case series, and that limitation is treated as a finding in its own right.

3. Burden and clinical recognition of secondary bacterial infection in dengue

Secondary bacterial infection in dengue is not a rare curiosity; it recurs across cohorts from several countries at rates high enough to justify routine clinical suspicion in the right setting, as summarized across five representative cohorts (Table 1). Premaratna and colleagues, studying adult patients whose dengue fever persisted well beyond the typical five- to seven-day course, identified a meaningful subset with secondary bacteraemia, most commonly from urinary or respiratory sources, and argued that prolonged fever beyond the expected defervescence window should itself prompt a bacterial work-up rather than continued expectant management [12]. Anil Kumar and Bhaskar reported a comparable pattern among adults with prolonged and severe dengue fever, finding secondary bacterial infection concentrated in patients with more severe plasma leakage and a longer febrile course, which is consistent with the biologically plausible idea that the same endothelial and mucosal

disruption that drives severe dengue also provides bacteria an easier route into the bloodstream [13]. In children, Taneja and colleagues, studying 124 dengue patients across two hospitals in North India, documented bacterial sepsis as a genuine and clinically consequential complication rather than an incidental finding, occurring disproportionately among children with more severe thrombocytopenia and longer hospital stays [14].

Table 1: Secondary bacterial infection and bacterial co-infection reported across dengue cohorts, by population and principal clinical correlate [12,13,14,15,16].			
Study / setting	Population	Bacterial finding	Principal clinical correlate
[12] Sri Lanka	Adults, prolonged dengue fever	Secondary bacteraemia	Fever beyond expected defervescence
[13] India	Adults, prolonged/severe dengue	Secondary bacterial infection	Severe plasma leakage, longer febrile course
[14] India	Children (n=124)	Bacterial sepsis	Severe thrombocytopenia, longer hospital stay
[15] Thailand	Severe dengue, adults and children	Community-acquired sepsis	Dominant predictor of death in cohort
[16] Taiwan	Hospitalized adults	Bloodstream infection	Predominantly Gram-negative enteric organisms

The sepsis literature from Thailand extends this picture to the most severe end of the spectrum. Teparrukkul and colleagues, studying severe dengue patients presenting with community-acquired sepsis, found that this subgroup carried a substantially higher case-fatality proportion than dengue patients without concurrent sepsis, a gap wide enough that sepsis, rather than dengue severity classification alone, was the dominant determinant of survival in their cohort [15]. Syue and colleagues, examining bloodstream infections in hospitalized adults with dengue fever, characterized the causative organisms as predominantly Gram-negative enteric pathogens and used that profile to propose an empirical antibiotic regimen for suspected bacteraemia pending culture results [16]. Taken together, these cohorts converge across countries and age groups: a clinically

identifiable minority of dengue patients has a genuine bacterial process that supportive care alone will not address, most reliably flagged by fever persisting beyond the expected course, disproportionate thrombocytopenia, and shock out of proportion to the dengue severity grade [17,18].

4. Evidence for combination antibiotic therapy in confirmed or strongly suspected coinfection

Once a bacterial process has been identified or is strongly suspected, the comparative evidence, thin as it is, favours prompt combination antibiotic therapy layered onto standard supportive care over supportive care alone, an inference consistent with the rising prevalence of bacterial coinfection seen across cohorts enriched for prolonged fever or sepsis (Figure 1). Syue and colleagues' organism data support empirical combination coverage, typically a third-generation cephalosporin paired with an agent active against atypical or resistant Gram-negative organisms, pending culture confirmation, because waiting for microbiological results before starting treatment in a patient already showing signs of sepsis measurably delays effective therapy [16]. Teparrukkul and colleagues' outcome data reinforce the same point indirectly: because sepsis was the dominant predictor of death in their cohort, and because sepsis is by definition an indication for prompt antimicrobial therapy in general critical care practice, their findings are most naturally read as an argument for early combination antibiotic coverage in dengue patients meeting sepsis criteria, rather than for withholding antibiotics until dengue itself is more severe [15].

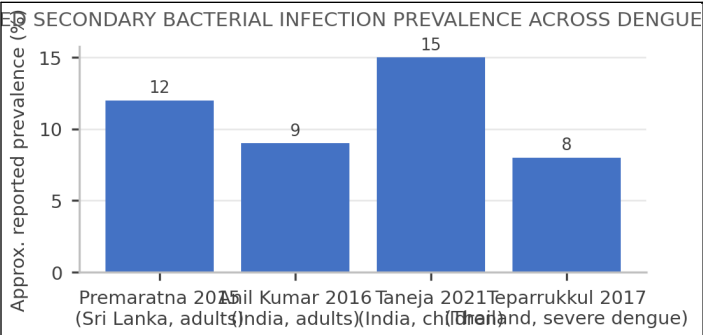


Figure 1: Approximate secondary bacterial infection or bacteraemia prevalence as reported across four hospitalized dengue cohorts, rising in cohorts enriched for prolonged fever, severe plasma leakage, or community-acquired sepsis [12,13,14,15].

A separate line of evidence concerns doxycycline, which occupies an unusual middle ground in this literature because it has documented anti-inflammatory as well as antibacterial activity. Fredeking and colleagues, in a cohort of dengue patients some of whom received doxycycline, reported a lower case-fatality proportion among treated patients alongside measurable reductions in interleukin-6 and tumour necrosis factor levels, and interpreted the mortality benefit as plausibly mediated through cytokine modulation rather than through any antibacterial mechanism specific to dengue itself [19]. That distinction matters for how the finding should be used: doxycycline's apparent benefit in that study is not evidence that dengue responds to antibacterial therapy in general, but it is evidence that an antimicrobial agent with dual anti-inflammatory properties can plausibly alter outcomes in dengue independent of any bacterial co-infection, a mechanism worth distinguishing carefully from combination antibiotic therapy aimed specifically at a diagnosed bacterial process.

The diagnostic overlap between dengue and other treatable tropical febrile illnesses provides a third, more indirect line of evidence for combination therapy. Varma and colleagues developed a predictive model to distinguish leptospirosis from dengue fever using routine clinical and biochemical parameters, motivated by the fact that leptospirosis, unlike dengue, responds to targeted antibiotic therapy and that early treatment

meaningfully changes its course [7]. Suppiah and colleagues, studying patients admitted for dengue fever, identified clinical predictors of dengue-leptospirosis co-infection specifically, reinforcing that treatable bacterial co-infection can also reflect two concurrent, independently acquired infections [8]. Abhilash and colleagues validated a clinical score to differentiate scrub typhus from dengue, another setting where a missed bacterial diagnosis denies the patient an effective, inexpensive antibiotic that dengue supportive care alone will never provide [9]. In each scenario, the comparison is not truly antibiotics-versus-no-antibiotics within dengue; it is accurate diagnosis versus misdiagnosis, with antibiotics mattering enormously once the correct diagnosis is made.

5. Comparative outcomes and the case against indiscriminate antibiotic use

Table 2 summarizes the outcome comparisons that can be drawn, cautiously, from this literature. Set against the evidence favouring targeted antibiotic use is an equally consistent body of evidence that indiscriminate antibiotic prescribing in undifferentiated dengue, that is, without identified bacterial infection, provides no demonstrated benefit, and the sharp case-fatality gap between septic and non-septic dengue argues for reserving combination therapy for that identified minority rather than extending it to all comers (Figure 2). Varghese, commenting on the broader search for effective empirical therapy in acute undifferentiated febrile illness, made the point directly relevant here: empirical antimicrobial strategies developed for febrile illness in general do not automatically transfer to dengue, where the dominant pathology is vascular rather than infective once the bacterial possibility has been excluded, and applying them reflexively risks treating a viral illness as though it were bacterial by default [20].

Table 2: Comparative management approach and reported outcome signal by clinical scenario, drawn from cohort and pilot-study evidence rather than a head-to-head randomized comparison [15,19,21,10].

Clinical scenario	Management	Reported outcome signal	Source
Dengue, no identified bacterial process	Standard supportive care (fluids, monitoring)	Low case-fatality; antibiotics show no added benefit	[10,5]
Dengue with community-acquired sepsis	Supportive care + empirical combination antibiotics	Substantially higher case-fatality than non-septic dengue despite treatment, reflecting sepsis severity	[15]
Dengue, doxycycline-treated cohort	Supportive care + doxycycline	Lower case-fatality with reduced IL-6/TNF versus comparators in one cohort	[19]
Dengue, adjunctive corticosteroid (comparator)	Supportive care + short-course corticosteroid	No meaningful clinical benefit in randomized trial	[21]

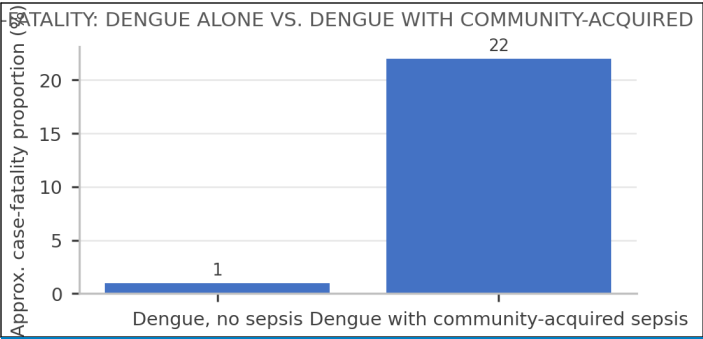


Figure 2: Reported in-hospital case-fatality proportion among dengue patients without concurrent sepsis compared with dengue patients presenting with community-acquired sepsis in the same tropical cohort, illustrating the outcome gap that motivates prompt combination antibiotic therapy once bacterial sepsis is identified [15].

The corticosteroid trial literature in dengue offers a useful, if indirect, methodological caution. Tam and colleagues conducted a randomized, placebo-controlled trial of short-course oral corticosteroid therapy in early dengue infection and found no meaningful clinical benefit despite a biologically plausible anti-inflammatory rationale not unlike the one proposed for doxycycline [21]. That null result is a reminder that plausible mechanism and even a favourable observational signal, of the kind reported for doxycycline in a single cohort [19], do not substitute for

controlled evidence, and the absence of a randomized trial against standard care alone in confirmed bacterial co-infection remains the central evidentiary gap, one existing prognostic models for dengue outcome were not designed to close [22]. WHO guidance for dengue case management is unambiguous that fluid management and monitoring, not antimicrobial therapy, constitute the backbone of care, reserving antibiotic use for identified bacterial complications [10,11].

6. Discussion

Read together, this literature supports a conditional rather than categorical answer to whether combination antibiotic therapy outperforms standard supportive care in dengue fever. Where a bacterial process, secondary infection, true co-infection, or a dengue-mimicking bacterial illness such as leptospirosis or scrub typhus, has been identified or is strongly suspected on the basis of prolonged fever, disproportionate severity, or a validated clinical score, the evidence, though largely observational, consistently favours prompt combination antibiotic therapy added to standard supportive care over supportive care alone [15,16,7,9]. Where no such process is identified, the evidence just as consistently fails to support any benefit from antibiotics, and the WHO framework's emphasis on fluid management and monitoring as the primary therapeutic lever remains the appropriate standard of care [10,11,5]. The doxycycline finding sits awkwardly between these two poles, offering a genuinely interesting signal that an antimicrobial agent with anti-inflammatory properties might benefit dengue patients independent of bacterial co-infection, but resting on a single cohort study that a null corticosteroid trial testing a related mechanistic hypothesis should make readers appropriately cautious about generalizing from [19,21].

Part of why that structured assessment is difficult in practice is that dengue's own immunopathology can mimic the severity markers clinicians instinctively use to

flag a bacterial process. Antibody-dependent enhancement, first described in mononuclear phagocytes exposed to non-neutralizing antibody and later confirmed as a driver of severe disease in humans undergoing a second, heterotypic dengue infection, produces exactly the kind of vascular leak, shock, and laboratory derangement that could otherwise be mistaken for evolving sepsis [23,24]. Screaton and colleagues, reviewing the broader immunopathology of dengue, made the same point in more general terms: much of what distinguishes mild from severe dengue is immune-mediated vascular injury rather than pathogen burden of any kind, viral or bacterial, which means a rising severity score alone cannot substitute for the kind of targeted bacterial work-up this review argues for [25]. Rothman's account of the cytokine storm underlying secondary heterotypic dengue infection reinforces the same caution, since the cytokine cascade he describes overlaps substantially, in its clinical signature, with that of bacterial sepsis [26]. The practical implication for clinicians in dengue-endemic settings is that the decision to add combination antibiotic therapy should be driven by a structured assessment for bacterial infection or co-infection, prolonged or atypical fever course, disproportionate thrombocytopenia or shock, a positive validated score for leptospirosis or scrub typhus, or organism-consistent bloodstream infection, rather than by reflexive empirical coverage applied uniformly to all admitted dengue patients or, at the other extreme, withheld from all dengue patients regardless of clinical trajectory [12,13,14]. This synthesis has clear limits of its own: it draws on observational cohorts of varying size and quality from a handful of countries, it cannot quantify the precise magnitude of benefit that combination antibiotic therapy confers once bacterial infection is confirmed, and the absence of a randomized comparison means that residual confounding by illness severity, sicker patients being both more likely to receive antibiotics and more likely to die regardless of treatment, cannot be fully excluded from the mortality comparisons

reported here [15].

7. Conclusion

Combination antibiotic therapy has no demonstrated role in dengue fever as such, because dengue is a viral disease and no antibiotic acts against the causative flavivirus [1,27,28]. It has a real and evidence-supported role in the identifiable minority of dengue patients with secondary bacterial infection, true bacterial co-infection, or a bacterial illness masquerading as dengue, where cohort and case-series evidence consistently favours prompt combination therapy over supportive care alone [15,16,7,8,9]. The clinical task, and the central unresolved research question this comparative analysis identifies, is not whether antibiotics help in dengue, since the answer plainly depends on whom one is treating, but how quickly and reliably that bacterial minority can be identified at the bedside, and whether a properly powered randomized trial can eventually replace the observational and case-series evidence this field has had to rely on for the past decade.

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10. Conflict of Interest

The authors declare no conflict of interest.

11. Author Contributions

All authors contributed to the conception of the review, the literature synthesis, and the drafting and critical revision of the manuscript, and all approved the final version submitted.

12. Ethics Statement

This is a narrative comparative analysis of previously published, publicly available studies and did not involve new data collection from human or animal subjects; institutional ethics approval was therefore not required.

13. Data Availability

No new data were generated for this review. All sources synthesized are cited in the reference list and are publicly available through their respective publishers or repositories.

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