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ORIGINAL RESEARCH

DRUG UTILIZATION PATTERN IN HOSPITALISED PATIENTS WITH ACUTE UNDIFFERENTIATED FEBRILE ILLNESS AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Acute undifferentiated febrile illness (AUFI) is among the most common indications for hospital admission in tropical and subtropical regions. The overlapping clinical presentations of its diverse aetiologies encompassing rickettsial, leptospiral, viral, and bacterial infections frequently necessitate empirical antibiotic therapy pending a definitive diagnosis. Drug utilization studies provide a systematic framework for evaluating prescribing behaviour, identifying deviations from rational pharmacotherapy, and benchmarking adherence to antimicrobial stewardship principles. This was an observational analytical study conducted in 658 patients admitted with AUFI to a tertiary care teaching hospital. Patients were stratified by duration of hospital stay: Group A (≤ 7 days; n = 389) and Group B (> 7 days; n = 269). Categorical variables were compared using the chi-square test and continuous variables using the independent-samples t-test. A p-value of ≤ 0.05 was considered statistically significant. All 658 patients received antibiotic therapy. Intravenous antibiotic use, oral switch, and therapy modification were significantly more frequent in Group B ($p < 0.001$). Ceftriaxone was the predominant intravenous antibiotic (45.3%), used in all Group B patients. Doxycycline (76.1%) and azithromycin (29.3%) were more commonly administered in Group A, while piperacillin–tazobactam (19.7%) and cefixime as step-down therapy (21.9%) predominated in Group B. Supportive medication use, polypharmacy (mean 6.9 ± 0.97 drugs/patient), and mean antibiotic duration (8.0 ± 1.28 days) were all significantly higher in Group B. Overall, 97.7% of patients were discharged improved; all referrals (2.3%) occurred exclusively in Group B. Antibiotic prescribing in AUFI is predominantly empirical and escalates dynamically with disease severity and duration of hospitalisation. Rational prescribing, enhanced microbiological diagnostics, and structured antimicrobial stewardship programmes are essential to optimise clinical outcomes and curtail the emergence of antimicrobial resistance in this patient population.

Keywords: Acute undifferentiated febrile illness; Drug utilization study; Antibiotic prescribing pattern; Antimicrobial stewardship; Polypharmacy; Empirical therapy

INTRODUCTION

Acute febrile illness is one of the most frequent causes of emergency presentation and hospital admission in tropical and subtropical regions, accounting for a disproportionate share of the infectious disease burden in these settings.[1,2] A substantial proportion of febrile patients present without clinically or microbiologically definable localising features at the time of admission, a presentation collectively designated as acute undifferentiated febrile illness (AUFI). AUFI is formally defined as fever of ≤ 14 days' duration in the absence of an identifiable focus of infection following an initial clinical assessment and baseline laboratory evaluation.[1] The aetiology of AUFI in tropical regions is heterogeneous and may include rickettsioses, leptospirosis, scrub typhus, dengue, enteric fever, malaria, and less commonly, bacteraemia with substantial regional variation in the relative frequency of each.

The clinical management of AUFI is complicated by the overlapping symptomatology of its diverse infectious aetiologies and the limited availability of point-of-care diagnostic tests capable of providing reliable and rapid differentiation.[2,3] In this context, empirical antibiotic therapy guided principally by clinical judgement and the local epidemiological profile of febrile illnesses is frequently initiated at the time of admission, with subsequent modification based on clinical trajectory and, where available, laboratory findings.[4] While this practice is often clinically necessary, indiscriminate or poorly targeted antibiotic use carries well-recognised consequences: it contributes to the selection pressure driving the global emergence of antimicrobial resistance, incurs avoidable treatment costs, and exposes patients to the risks of adverse drug reactions and, in prolonged cases, of healthcare-associated infections.[5]

Drug utilization studies (DUS) are a cornerstone of pharmacoepidemiological research, providing systematic, evidence-based evaluation of drug prescribing patterns in real-world clinical settings.[6] When applied to infectious disease contexts such as AUFI, DUS offer valuable insights into antibiotic selection practices, adherence to stewardship principles, the dynamics of therapy modification and escalation, and the extent of polypharmacy.[7] Such data are indispensable for identifying prescribing inefficiencies, informing clinical governance, and designing targeted interventions to promote rational and evidence-based antimicrobial use.

Existing literature on AUFI has largely focused on its aetiological spectrum and clinical profile;[8,9,10] comprehensive, longitudinal assessment of drug utilization patterns particularly in relation to the duration of hospitalisation remains limited in the Indian context. The present study therefore aimed to fill this evidence gap by characterising antibiotic and supportive drug utilization, therapy modification practices, polypharmacy, and clinical outcomes in a cohort of hospitalised AUFI patients, stratified by duration of hospital stay. A novel feature of this study lies in its integrated, comparative framework that simultaneously examines multiple dimensions of drug use antibiotic escalation, oral switch therapy, supportive care, and polypharmacy across patient subgroups defined by the severity-related proxy of hospitalisation duration.

The primary aim of this study was to characterise the drug utilization pattern in hospitalised patients with AUFI at a tertiary care teaching hospital. The specific objectives were: (i) to analyse antibiotic and supportive drug use; (ii) to compare prescribing patterns according to duration of hospital stay; and (iii) to evaluate therapy modification, polypharmacy, and clinical outcomes across patient subgroups.

MATERIALS AND METHODS

Study Design, Setting, and Ethical Approval: This was an observational analytical study conducted in the Department of Microbiology at Krishna Hospital and Krishna Institute of Medical Sciences (KVV), Karad, Maharashtra, India. The study was carried out as one year study. Ethical clearance was granted by the Institutional Ethics Committee prior to commencement of data collection (IEC Reference: KIMSDU/IEC/09/18).

Sample Size: The minimum required sample size was calculated using the formula $n = Z^2pq/d^2$, assuming a 95% confidence level ($Z = 1.96$), 50% expected prevalence of drug use ($p = 0.5$), and an absolute precision of 5% ($d = 0.05$), yielding a minimum sample of 384 patients. After allowance for incomplete records, a minimum of 422 was deemed adequate. The final study enrolled 658 patients, ensuring adequate statistical power for all planned analyses.

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they: (i) were admitted to Krishna Hospital during the study period with a diagnosis of AUFI, defined as fever of ≤ 14 days' duration with no identifiable focus of infection after initial clinical assessment and baseline investigations; (ii) remained hospitalised for at least 24 hours; and (iii) had complete medical records inclusive of demographic data, clinical presentation, drug treatment (antibiotics and supportive medications), duration of hospital stay, and final outcome.

Patients were excluded if: (i) a definitive infectious aetiology (dengue, malaria, enteric fever, or tuberculosis) was established at the time of admission and thus did not fulfil the criteria for AUFI; (ii) fever had been present for more than

14 days (chronic or prolonged fever); (iii) fever was attributable to non-infectious causes such as autoimmune disease, malignancy, or drug-induced fever, incomplete data were excluded.

Patient Stratification

All enrolled patients were stratified into two groups based on duration of hospital stay: Group A (≤ 7 days; shorter hospitalisation) and Group B (> 7 days; prolonged hospitalisation). This stratification was used as a clinical proxy for disease severity and treatment complexity.

Data Collection

Data were extracted from indoor case records using a predesigned, standardised data collection proforma. Variables recorded included patient demographics, primary presenting complaints, acuity and duration of fever, antibiotic prescriptions (drug name, route, dose, and duration), supportive medications, therapy modifications (including antibiotic escalation or oral switch), number of drugs prescribed, duration of hospital stay, and clinical outcome at discharge.

Statistical Analysis

Data were entered and analysed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarised as frequencies and percentages; continuous variables were expressed as mean ± standard deviation (SD). Comparisons between Group A and Group B for categorical variables were performed using the Pearson chi-square test, and for continuous variables using the independent-samples t-test. A two-tailed p-value of ≤ 0.05 was considered statistically significant throughout.

RESULTS

Baseline Characteristics

A total of 658 patients were enrolled in the final analysis (Table 1), of whom 389 (59.1%) were in Group A and 269 (40.9%) in Group B. The cohort comprised 382 males (58.1%) and 276 females (41.9%), with no significant sex difference between the two groups ($p = 0.43$). The overall mean age was 36.8 ± 14.2 years; patients in Group B were significantly older than those in Group A (40.1 ± 14.5 vs. 34.5 ± 13.8 years; $p < 0.001$). Patients aged > 60 years were more frequent in Group B, whereas those aged < 20 years predominated in Group A ($p < 0.001$). The mean duration of antibiotic therapy was 5.9 ± 1.87 days overall, with a significant difference between groups (Group A: 4.4 ± 0.93 days vs. Group B: 8.0 ± 1.28 days; $p < 0.001$). The mean number of drugs per patient was 5.3 ± 1.54 overall (Group A: 4.2 ± 1.25; Group B: 6.9 ± 0.97; $p < 0.001$).

Antibiotic Utilization Pattern

All 658 patients (100%) received at least one antibiotic during their admission, confirming the universal empirical antibiotic prescribing practice for AUFI in this setting (Table 2). Intravenous antibiotic use was significantly higher in Group B than in Group A (100% vs. 7.5%; $p < 0.001$), consistent with the greater severity and clinical complexity of patients with prolonged hospitalisation. Ceftriaxone, a third-generation cephalosporin, was the most frequently prescribed intravenous antibiotic (45.3% of all patients), and was administered to all Group B patients (100% vs. 7.5%; $p < 0.001$), reflecting the preference for broad-spectrum parenteral therapy in more severe or unresolved cases.

Oral switch therapy the transition from intravenous to oral antibiotic administration was documented in 160 patients (24.3%), with a significantly higher proportion in Group B (52.0% vs. 5.1%; $p < 0.001$), consistent with step-down antimicrobial stewardship practices. Change in antibiotic therapy during the admission episode encompassing both escalation and de-escalation was significantly more frequent in Group B (58.4% vs. 5.1%; $p < 0.001$), reflecting the iterative nature of empirical decision-making in prolonged AUFI.

Table 1. Baseline Demographic Characteristics, Antibiotic Duration, Drug Count, and Clinical Outcomes by Group

Variable	Overall (n = 658)	Group A ≤ 7 days (n = 389)	Group B > 7 days (n = 269)	p-value
Sex				
Male	382 (58.1%)	221 (56.8%)	161 (59.9%)	0.43
Female	276 (41.9%)	168 (43.2%)	108 (40.1%)	
Age (years)				
Mean ± SD	36.8 ± 14.2	34.5 ± 13.8	40.1 ± 14.5	< 0.001
Age Group				
< 20 years	92 (14.0%)	70 (18.0%)	22 (8.2%)	< 0.001
20–40 years	278 (42.3%)	181 (46.5%)	97 (36.1%)	
41–60 years	201 (30.5%)	104 (26.7%)	97 (36.1%)	
> 60 years	87 (13.2%)	34 (8.7%)	53 (19.7%)	
Mean antibiotic duration (days)	5.9 ± 1.87	4.4 ± 0.93	8.0 ± 1.28	< 0.001
Mean drugs per patient	5.3 ± 1.54	4.2 ± 1.25	6.9 ± 0.97	< 0.001
Clinical Outcome				
Improved / Discharged	643 (97.7%)	389 (100%)	254 (94.4%)	< 0.001
Referred	15 (2.3%)	0 (0%)	15 (5.6%)	

Note: SD, standard deviation. Chi-square test for categorical variables; independent-samples t-test for continuous variables. p ≤ 0.05 considered significant.

Table 2. Drug Utilization Pattern in AUFI Patients by Duration of Hospital Stay

Drug / Prescribing Indicator	Overall n (%)	Group A ≤ 7 days n (%)	Group B > 7 days n (%)	p-value
Antibiotic Use				
Any antibiotic	658 (100%)	389 (100%)	269 (100%)	
Intravenous antibiotic	298 (45.3%)	29 (7.5%)	269 (100%)	< 0.001
Oral switch	160 (24.3%)	20 (5.1%)	140 (52.0%)	< 0.001
Change in therapy	177 (26.9%)	20 (5.1%)	157 (58.4%)	< 0.001
Antibiotic Agents				
Ceftriaxone	298 (45.3%)	29 (7.5%)	269 (100%)	< 0.001
Doxycycline	312 (47.4%)	296 (76.1%)	16 (5.9%)	< 0.001
Azithromycin	119 (18.1%)	114 (29.3%)	5 (1.9%)	< 0.001
Piperacillin–Tazobactam	53 (8.1%)	0 (0%)	53 (19.7%)	< 0.001
Cefixime	79 (12.0%)	20 (5.1%)	59 (21.9%)	< 0.001
Supportive Medications				
Paracetamol	658 (100%)	389 (100%)	269 (100%)	
Pantoprazole	494 (75.1%)	225 (57.8%)	269 (100%)	< 0.001
Ondansetron	231 (35.1%)	0 (0%)	231 (85.9%)	< 0.001
IV fluids (NS / RL)	395 (60.0%)	126 (32.4%)	269 (100%)	< 0.001
Multivitamins	145 (22.0%)	40 (10.3%)	105 (39.0%)	< 0.001
Potassium supplementation	53 (8.1%)	0 (0%)	53 (19.7%)	< 0.001

Pattern of Antibiotic Prescription by Severity Group

A marked shift in the antibiotic prescribing pattern was observed with increasing duration of hospitalisation. Doxycycline was the most commonly prescribed antibiotic in Group A (76.1%), with azithromycin also substantially more prevalent in

this group (29.3% vs. 1.9%; p < 0.001), reflecting empirical coverage of atypical and rickettsial pathogens in patients with milder or shorter-duration illness. In contrast, piperacillin–tazobactam a broad-spectrum beta-lactam/beta-lactamase inhibitor combination was used exclusively in Group B (19.7% vs. 0%; p < 0.001), indicating escalation to broader-spectrum parenteral therapy in patients with non-resolving or more severe febrile illness. Cefixime, an oral third-generation cephalosporin, was more frequent in Group B (21.9% vs. 5.1%; p < 0.001), reflecting its role as step-down oral therapy following initial intravenous treatment.

Supportive Drug Utilization

Paracetamol was administered to all 658 patients (100%) in both groups as the standard first-line antipyretic. All other supportive medications were significantly more frequently used in Group B (Table 2): pantoprazole (100% vs. 57.8%; p < 0.001), intravenous fluids normal saline and/or Ringer's lactate (100% vs. 32.4%; p < 0.001), ondansetron (85.9% vs. 0%; p < 0.001), multivitamin preparations (39.0% vs. 10.3%; p < 0.001), and potassium supplementation (19.7% vs. 0%; p < 0.001). The universally greater supportive medication burden in Group B reflects the greater haemodynamic compromise, gastrointestinal symptoms, fluid and electrolyte disturbances, and nutritional deficits characteristic of patients with prolonged febrile illness.

Duration of Antibiotic Therapy and Polypharmacy

The mean duration of antibiotic therapy was significantly longer in Group B compared with Group A (8.0 ± 1.28 vs. 4.4 ± 0.93 days; p < 0.001), consistent with the clinical expectation of prolonged antibiotic courses in patients whose illness did not resolve within the first week. The mean number of drugs per patient was also significantly higher in Group B (6.9 ± 0.97 vs. 4.2 ± 1.25; p < 0.001), indicating a substantially greater polypharmacy burden in patients with more complex or protracted febrile illness.

Clinical Outcomes

The overall clinical outcome was favourable, with 643 patients (97.7%) improving and being discharged from hospital. All 389 patients in Group A were discharged following clinical resolution (100% discharge rate). In Group B, 254 patients (94.4%) were discharged, while 15 (5.6%) required referral to a higher-level facility all referrals (2.3% of the total cohort) being confined to Group B (p < 0.001). This pattern indicates that prolonged hospitalisation was associated with a subset of patients with more refractory or severe disease who could not be adequately managed within the study institution.

DISCUSSION

This study provides a comprehensive characterisation of drug utilization in 658 hospitalised AUFI patients, stratified by duration of hospital stay. Several clinically important patterns emerged. The significantly older age profile of Group B patients, the greater disease severity reflected by higher referral rates, and the substantially greater antibiotic and supportive medication burden in this group collectively indicate that prolonged hospitalisation in AUFI is associated with a more complex and resource-intensive clinical course an observation with direct implications for clinical governance and resource planning.

The predominance of younger adults in the shorter-stay group is consistent with the well-established epidemiology of AUFI, which predominantly affects working-age adults in tropical and subtropical India.[2,8,9,10] The overrepresentation of elderly patients in Group B is explicable by age-related immunosenescence, diminished physiological reserve, and the higher prevalence of comorbid conditions factors that collectively predispose to more severe or prolonged febrile illness, delayed treatment response, and increased mortality risk.[11,12,13,14] These findings are consistent with studies by Norman et al. and High et al., who documented the distinctly altered presentation and increased severity of infectious illnesses in elderly patients.[12,14]

The universal administration of antibiotics across all 658 patients reflects the near-inevitable resort to empirical antibiotic therapy in AUFI, where the absence of rapid diagnostics at admission prevents pathogen-directed prescribing.[2,3] The marked increase in intravenous antibiotic use, oral switch, and therapy modification in Group B (p < 0.001 for all) mirrors

patterns reported by Subramanyam et al. and Norman et al., wherein empirical parenteral therapy is preferentially initiated in patients with greater clinical severity or non-resolving febrile illness.[1,14] The higher rate of oral switch therapy in Group B (52.0%) is consistent with established antimicrobial stewardship principles specifically, the practice of early transition from intravenous to oral antibiotics following clinical stabilisation a strategy endorsed by NICE guidelines and associated with reduced hospital length of stay, cost savings, and a lower risk of device-related complications.[18,19]

The high frequency of therapy change in Group B (58.4%) reflects the inherently dynamic nature of empirical antibiotic decision-making in AUFI.[2,3,15,20] When the initial antibiotic regimen fails to produce the expected clinical response, modification encompassing either de-escalation upon pathogen identification or escalation to broader-spectrum agents in the absence of a diagnosis is clinically necessary. This aligns with the 4 Moments of Antibiotic Decision Making framework described by Tamma et al., which emphasises the need for formal reassessment of antibiotic appropriateness at defined clinical timepoints throughout the admission.[38]

The prescription pattern shift from doxycycline and azithromycin in Group A to ceftriaxone and piperacillin–tazobactam in Group B reflects a clinically coherent transition from coverage of atypical and rickettsial pathogens the dominant aetiologies of milder, shorter-duration tropical fever in India[8,10] to broader-spectrum parenteral therapy appropriate for undifferentiated severe or bacteraemic illness.[17,21] Ceftriaxone was the predominant intravenous antibiotic, consistent with findings from national antimicrobial consumption surveillance and drug utilization studies in Indian tertiary care settings.[8,17,21] The use of piperacillin–tazobactam exclusively in Group B signals antibiotic escalation in patients with suspected or evolving Gram-negative sepsis or non-response to third-generation cephalosporins a pattern consistent with the WHO AWaRe classification, in which piperacillin–tazobactam is categorised in the 'Watch' group, warranting selective and monitored use.[17]

The significantly higher use of pantoprazole in Group B (100% vs. 57.8%) likely reflects dual indications: prophylaxis against stress-related mucosal injury in more severely ill patients and gastroprotection from concurrent antibiotic or non-steroidal anti-inflammatory drug (NSAID) use.[23,24] The exclusive use of ondansetron in Group B (85.9% vs. 0%) is attributable to the higher prevalence of nausea and vomiting in patients with more severe or prolonged febrile illness, as well as antibiotic-associated gastrointestinal intolerance.[23] The universal requirement for intravenous fluids in Group B (100%) reflects the haemodynamic vulnerability encompassing dehydration, poor oral intake, and the risk of circulatory compromise of patients with prolonged febrile illness, consistent with the Surviving Sepsis Campaign recommendations for goal-directed fluid resuscitation in severe febrile illness and sepsis.[4,22]

Multivitamin supplementation in Group B (39.0%) and potassium supplementation (19.7%) reflect both the nutritional deficits imposed by prolonged anorexia and fever-related catabolism, and the electrolyte disturbances particularly hypokalaemia arising from vomiting, reduced oral intake, and the caloric demands of sustained febrile illness.[25,26,27,28]

The significantly greater polypharmacy burden in Group B (mean 6.9 ± 0.97 drugs/patient vs. 4.2 ± 1.25 in Group A) is consistent with published drug utilization studies in prolonged hospitalisation settings.[29,30,31] While a higher drug count in this context reflects the greater clinical complexity and symptom burden of patients with longer hospital stay, polypharmacy is not clinically neutral: it increases the probability of adverse drug reactions, pharmacokinetic drug–drug interactions, prescribing errors, and adherence difficulties, and is independently associated with increased healthcare costs.[32,33,34] These concerns underscore the importance of prospective medication review and prescribing rationalisation in patients with AUFI who are approaching or have exceeded seven days of hospitalisation.

The overall favourable clinical outcome with 97.7% of patients discharged improved is consistent with reports from comparable AUFI cohorts where most cases are self-limiting or respond well to empirical therapy.[1,2,3,9] The confinement of all referrals to Group B (5.6% of Group B patients), and their complete absence from Group A, confirms that prolonged hospitalisation in this study identifies a clinically distinct subset with greater severity, poorer response to initial management, and a higher likelihood of requiring advanced or specialised care.[3,11,35,36] Prolonged hospital stay in AUFI may reflect delayed diagnosis, emergence of complications (including secondary infections or organ dysfunction),

or the natural history of less common aetiologies considerations that emphasise the value of early targeted diagnostic algorithms and structured reassessment protocols.[4,37,38]

Taken together, the findings of this study provide a detailed, evidence-based characterisation of drug utilization in AUFI that supports several actionable recommendations: (i) the implementation of structured antimicrobial stewardship programmes with defined antibiotic review at 48–72 hours of admission; (ii) investment in improved point-of-care diagnostics including rapid serological tests for rickettsial diseases, dengue non-structural protein-1 antigen, and blood culture facilities to reduce the duration and breadth of empirical therapy; and (iii) the development and dissemination of locally adapted clinical algorithms for AUFI management, calibrated to regional epidemiological patterns.[5,6,7,17,18]

CONCLUSION

Drug utilization in hospitalised AUFI patients is characterised by universal empirical antibiotic prescribing, with a clear and progressive escalation in antibiotic spectrum, supportive medication use, and overall drug burden associated with greater duration of hospitalisation. Doxycycline and azithromycin are the mainstay of empirical therapy in milder, shorter-duration illness, while ceftriaxone and piperacillin–tazobactam predominate in patients with prolonged or severe disease. Although clinical outcomes were favourable for the large majority of patients, the high rates of therapy modification, polypharmacy, and referral in the prolonged hospitalisation group highlight persistent challenges in the rational management of AUFI. These findings underscore the urgent need for strengthened antimicrobial stewardship programmes, improved point-of-care diagnostics, and adherence to evidence-based prescribing guidelines to optimise patient outcomes, reduce avoidable antibiotic exposure, and mitigate the contribution of empirical prescribing to the global burden of antimicrobial resistance.

Limitations

The single-centre design restricts the generalisability of findings to other geographic regions and institutional settings. The lack of microbiological confirmation for the majority of AUFI cases precluded pathogen-directed analysis of antibiotic appropriateness. The stratification by duration of hospital stay, while an informative clinical proxy, does not comprehensively capture disease severity, and formal severity scoring was not applied.

DECLARATIONS

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