Original Article

Pilot Phenotypic Mapping to Ambler Classes in Diabetic Urosepsis: Outcomes and Stewardship Insights

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Abstract

<u>*Background:*</u> Urosepsis occurs in uncontrolled diabetes mellitus (DM) with a high morbidity because of changing beta-lactam resistance, which may become a problem in the empiric treatment and clinical outcomes. <u>*Aim and Objective:*</u> The aim and objective of this study were to answer the research question: "How do phenotypic antibiotic resistance patterns in urosepsis among patients with uncontrolled diabetes mellitus map to the Ambler Classification of β-lactamases, and what are their associations with clinical outcomes such as acute kidney injury (AKI) and length of stay (LOS)?" <u>***Methods:***</u> A retrospective pilot cohort study was conducted at Karuna Medical College and Hospital that analyzed 17 urosepsis patients with uncontrolled DM. Available, clinical (HbA1c, serum creatinine/AKI, LOS, interventions, haemodialysis, mortality) and microbiological data were extracted. Descriptive and inferential tests were conducted. The phenotypic patterns were deduced on Ambler proxies, and polymerase chain reaction (PCR) was suggested to confirm them. Ten studies (2014-2025) were included in a systematic review and of them three in meta-analysis based on PubMed, Scopus, and Embase, random-effects modelling of Extended spectrum betalactamase (ESBL) prevalence. <u>***Results:***</u> AKI prevalence was 88.24%, mean LOS = 8.18 (SD 6.03), interventions = 11.76, and mortality was 0. The most common by prevalence was E. coli (47.06%); phenotypic inference suggested probably Class A in 52.94%. No significant associations were identified (all $p>0.05$). ESBL prevalence was 26.5% (95% CI -33.7 86.7) with high heterogeneity (I2=98.2%, $p=0.001$). <u>*Conclusion:*</u> Phenotypic patterns provide useful proxies of Ambler mapping to inform directed therapy, bypassing empiric shortcomings. PCR and AI combined studies should be carried out on a larger scale.

<u>**Keywords:**</u> *Urosepsis, uncontrolled diabetes, Ambler classification, ESBL, phenotypic inference, antimicrobial stewardship, AKI.*

Introduction

Patients with uncontrolled diabetes mellitus (DM) having urosepsis is a critical point of metabolic dysfunction and advanced antimicrobial resistance. The major pathogens, especially, Escherichia coli, and Klebsiella pneumoniae, have developed advanced survival strategies, such as efflux pumps, target modification, and enzyme degradation. This flexibility allows them to restrict the actions of conventional antimicrobials complicating treatment plans in an already weakened host [1].

This recalcitrance with microbes is especially important in diabetic patients with increased potential to infection and impaired immune response, leading to treatment failure and increasing morbidity wherein the latter is mainly manifested through the generation of β-lactamases, breaking the penicillin, cephalosporin, and carbapenem β-lactam ring [2]. The development of extended spectrum β-lactamases is quite alarming since they are associated with resistance to a wide range of β-lactam antibiotics, requiring attention in the choice of empirical antimicrobial therapy in urosepsis [3].

The Ambler Classification offers structural information on these enzymes to optimize therapeutic therapies. The group A (serine β-lactamases) utilizes a serine residue to target the active site of the antibiotic; these are the extended-spectrum β-lactamases (ESBLs), which are generally susceptible to tazobactam, and Klebsiella pneumoniae carbapenemases (KPCs) which mediate carbapenem resistance.

Class B (metallo-β-lactamases /MBLs) also called the "nightmare group" uses the zinc ions (Zn2+) instead of serine, avoiding the normal inhibitors like clavulanic acid and leaving

aztreonam as the only possible option of β-lactam, creating significant therapeutic difficulties. The high rate of these resistance mechanisms, especially extended-spectrum β-lactamases and carbapenemases, in uropathogens of diabetic patients with community-acquired infections highlights the urgency of new antimicrobial susceptibility surveillance [4]. The presence of urinary tract infection caused by ESBL-producing organisms, including those with type II diabetes like E. coli and K. pneumoniae is an additional risk factor leading to AKI in patient with type II diabetes[5].

Class C (AmpC) enzymes are inducible enzymes, which are found on the bacterial chromosome and they are the most famous ones, due to which the pathogen, which still seems to be sensitive to ceftriaxone in vitro, then takes on resistance genes in the process of treatment.

Lastly, Class D (oxacillinases/OXAs) has a distinct genetic composition, facilitating the hydrolysis of oxacillin and carbapenems.

These discrete categories emphasize the different enzymatic mechanisms used by bacteria to degrade β-lactam antibiotics, and the implication here is that it is difficult to come up with truly generalized inhibitors [6,7].

The presence of hyperglycemia in the diabetic host favors the growth of bacteria, whereas glycosylation, as measured by HbA1c, is associated with the inability of immune proteins to function effectively. Comorbid autonomic neuropathy makes urinary stasis, and microangiopathy restricts the entry of antibiotics into the renal parenchyma. Upon developing bacteremia with these resistant strains, they cause a cytokine storm with tumour necrosis factor- alpha (TNF- α) and interleukin-6 (IL-6). It is a dysregulated response, which is characterized by high procalcitonin levels, resulting in systemic capillary leak, hypotension and multiple organ dysfunction syndrome (MODS) or multiple organ toxic state (MOTS). Such clinical features as AKI with increased creatinine, acute respiratory distress syndrome (ARDS), and hepatic failure are observed. The development of strains, which are multidrug-resistant, e.g., extensively drug-resistant E. coli and K. pneumoniae, especially strains producing NDM-1, also adds to the complexity of managing these life-threatening systemic complications in diabetic patients [8].

The combination of host susceptibility and microbial resistance requires a site specific and frequently violent treatment intervention, which is commonly combination regimens of antibiotics targeting particular infection resistance strategies to reduce disease progression and patient outcomes. Existing dependence upon empirical treatment-wide guessing-around-the-bases- Covering Class B/D pathogens frequently cannot be made to stop the damage of glomerulonephritis, extending the length of hospitalization to 14+ days. To manage it efficiently, immediate source control through the use of Double J stents and a transition to focused de-escalation is necessary.

The proposed research will be focused on mapping the patterns of Ambler resistance in uncontrolled diabetics to narrow the treatment spectrum to prevent morbidity by prioritizing early switching to reserve antibiotics, including Ceftazidime-Avibactam.

Methodology

Systematic Review and Meta-Analysis
PRISMA (Preferred Reported Items for Systematic Review and Meta-analyses) 2020 guidelines were used for the selection of studies for systematic review and meta-analysis (**Figure 1**).

PICO Framework

- *Population:* Patients with uncontrolled DM and urosepsis or complicated urinary tract infection (UTI)
- *Intervention/Exposure:* Antibiotic resistance patterns (phenotypic proxies for Ambler Classes)
- *Comparison:* Intra-group clinical outcomes (no diabetic/non-diabetic comparisons)
- *Outcomes:* Resistance prevalence (e.g., ESBL rates), AKI, length of stay, interventions

Search Strategy

- *Databases:* PubMed, Scopus, Embase
- *Time frame:* January 1, 2014 – December 31, 2025
- *Search terms:* ("urosepsis" OR "urinary tract infection" OR "UTI" OR "sepsis") AND ("diabetes mellitus" OR "diabetic" OR "uncontrolled diabetes") AND ("ESBL" OR "extended-spectrum beta-lactamase" OR "carbapenemase" OR "Ambler classification" OR "beta-lactamase")

Inclusion Criteria

- Retrospective observational cohorts or cross-sectional studies, systematic review, meta-analysis
- Focus on uncontrolled DM with urosepsis/complicated UTI
- Reporting of phenotypic resistance (e.g., ESBL, carbapenemase) or Ambler proxies
- Extractable data on pathogens, resistance patterns, and clinical outcomes
- Published in English, 2014–2025

Exclusion Criteria

- Prospective, interventional, or non-observational designs
- Non-diabetic focus or mixed populations without subgroup data
- No resistance classification or phenotypic data
- Case reports, reviews, editorials, conference abstracts
- Insufficient quantitative data or non-English full-text

Data Extraction

- Two reviewers independently (K.D.R & S.V) extracted: author/year, design, country, sample size, population, resistance phenotypes, outcomes

Quality Assessment

- Newcastle-Ottawa Scale (NOS) for cohort studies (**Figure 2 a and b**)
  - *Selection:* 0–4 stars
  - *Comparability:* 0–2 stars
  - *Outcome:* 0–3 stars
- Risk classification: Low (7–9), Moderate (4–6), High (<4)

Data Synthesis

- Qualitative synthesis of all 10 studies
- Meta-analysis of ESBL proportions (3 studies) using random-effects model (metaprop in R, logit transformation, ML τ²)
- *Heterogeneity:* I², τ²
- *Bias assessment:* Funnel plots, Egger's/Begg's tests
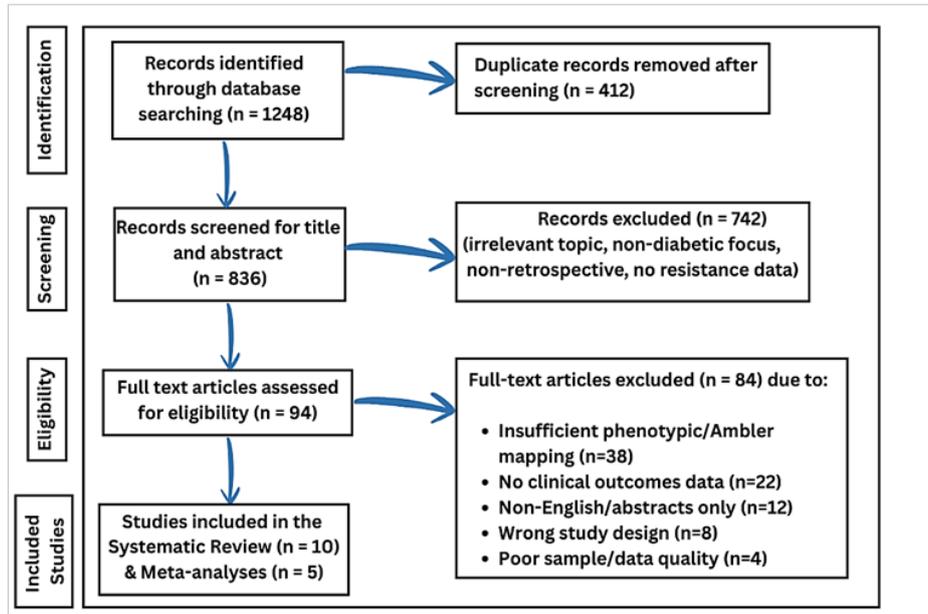- *Software:* R (v4.3+); p<0.05 significant

Figure 1: Flowchart for selection of studies for systematic review and meta analyses

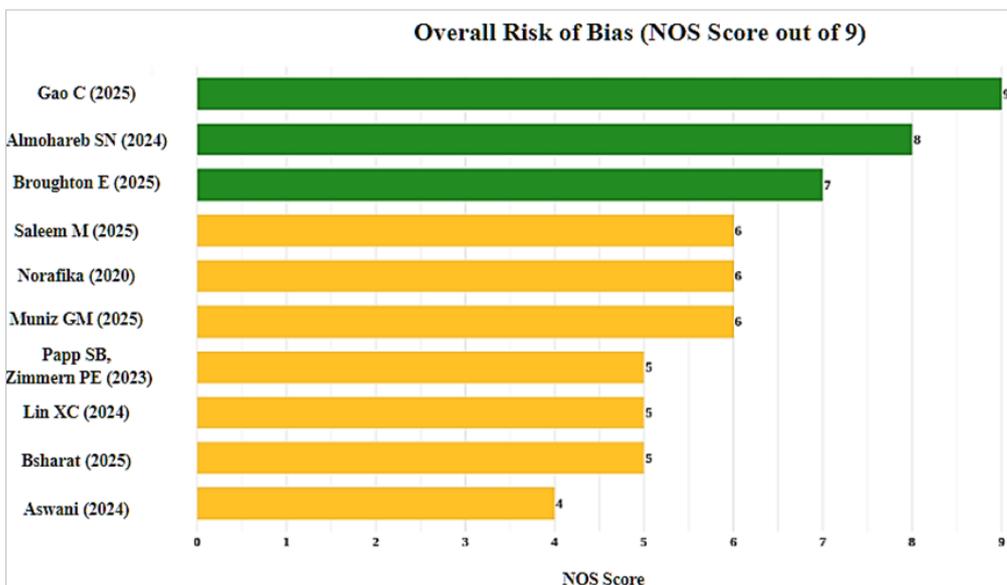**Figure 2 a) Traffic signal plot for risk of bias assessment**

Figure 2 b) Overall risk of bias chart using New Castle Ottawa Scale for quality assessment

Karuna Medical College Retrospective Cohort Study

Study Design and Setting
It was a pilot cohort retrospective study that was carried out at Karuna Medical College and Hospital, Vilayodi, Chittur, Palakkad, Kerala, India. The medical records of patients admitted between the months of January 2025 and April 2025 were identified and their data was extracted retrospectively.

Study Period
January 2025 to April 2025.

Inclusion Criteria of Study Population.

- Age ≥18 years
- Proven to have urosepsis or complicated urinary tract infection (UTI) by clinical (fever, systemic signs), laboratory (positive urine/blood culture or pyuria), and imaging features. Untreated uncontrolled diabetes mellitus (HbA1c >7.0% or clinical/therapeutic evidence of inadequate glycemic control)
- Full admission and discharge records present.

Exclusion Criteria

- Non-diabetic patients
- Asymptomatic bacteriuria or simple cystitis.
- Missing or incomplete essential clinical/laboratory information (e.g. creatinine missing or LOS missing)

Sample Size
The inclusion criteria included a total of seventeen patients that were finalized in the analysis.

Variables and Outcomes Primary Outcome.

- AKI characterized as maximum serum creatinine level that is greater than baseline or greater than 1.2 mg/dL.
- Kidney Disease: Improving Global Outcomes -**KDIGO** criteria modified based on available data.

Secondary Outcomes
Length of stay (days) in the hospital (LOS).

- Urological intervention (stenting, surgery) is mandatory.
- Need for haemodialysis
- In-hospital mortality of all-cause.

Other Variables

- *Demographic:* Age, gender
- *Diabetes related:* DM duration, HbA1c >9%.
- *Microbiological:* Organism isolated (urine/blood culture), antibiotic sensitivities and resistances (where available)
- *Phenotypic inference:* Mapping to Ambler Classes A, B, C, D by resistance phenotype.

Data Collection
Medical records, inclusive of clinical notes, laboratory reports, microbiology results, and discharge summaries, were retrospectively extracted to obtain the data. Phenotypic resistance pattern was assessed in order to make inferences about the proxy of possible Ambler classes (e.g., ampicillin/cephalosporin resistance to Class A; carbapenem resistance to Class B/D).

Statistical Analysis
The R (version 4.3+) was used to analyse the data.

Descriptive statistics: Continuous variables are given as the mean (standard deviation) and median (interquartile range); frequencies and proportions as the median and standard frequencies and proportions, respectively.

Normality assessment: Shapiro-wilk test.

Inferential statistics

- Mann-Whitney U test (non-parametric comparison of LOS between groups with HbA1c >9% and HbA1C <9%)
- Kruskal-Wallis test (comparison of LOS among groups of organisms)
- Chi-square/Fisher exact test (connection between HbA1c >9% and categorical outcomes: stenting, haemodialysis)
- Spearman rank correlation (non-parametric correlation of continuous variables, e.g. age vs. LOS, creatinine vs. LOS)
- Significance level: $p < 0.05$ (two-tailed)
- Comparisons of non-diabetic and diabetic were not done because of limitations of the study.

Results

Screening Flow
The electronic databases of PubMed, Scopus and Embase were searched to obtain records published between January 1, 2014, and December 31, 2025, which resulted in the initial retrieval of 1,248 records. A total of 412 duplicate records were excluded. In the title-and-abstract screening process, 742 records were removed as they were not directly related to diabetes or even targeted non-diabetic groups, not retrospective, or lacked data on resistance. The rest of the 94 full-text articles underwent eligibility evaluation; 84 were not eligible due to reasons such as inadequate phenotypic resistance mapping or Ambler classification proxy (n=38), inability to extract clinical outcomes (n=22), not in English or abstracts (n=12), had an unsuitable study design (n=8) or poor quality of sample/data (n=4). Finally, 10 studies were included for the systematic review and 3 of them had sufficient quantitative data (i.e. well-defined ESBL prevalence proportions with sample sizes) to incorporate them into the meta-analysis.

We determined that the prevalence of such Enterobacterales with extended spectrum β -lactamase (ESBL) production was heterogeneous but clinically significant, principally in Escherichia coli and Klebsiella pneumoniae. Percentages were relatively low in the general population and significantly high in the subsidiary groups labeled as resistant or high-risk, often accompanied by an exacerbated glycemic control, pathophysiology, or comorbidities.

The production of carbapenemases became a noticeable characteristic of pertinent infections, including diabetic foot ulcers (that involve the urinary tract) and with incidences exceeding 50% among the multidrug-resistant isolates. These bacteria were highly resistant to β-lactam agents and still sensitive to nitrofurantoin, meropenem, or fosfomycin in many cases. These resistance patterns result in delayed achievement of effective therapy, increased morbidity such as prolonged length of stay and acute kidney injury and justify the need to classify resistance mechanistically in order to guide specific antimicrobial stewardship (**Table 1**).

Table 1: Characteristics of Included Retrospective Studies

S. No	First Author (Year)	Study Design	Country / Scope	Study Characteristics	Important Findings (with Key Data)
1	Norafika[27] (2020)	Retrospective cross-sectional	Indonesia	n=1551 DM patients; urine cultures 2017–2018	UTI prevalence 3.93% (61/1551 positive cultures); ESBL *E. coli* 3.3% (2/61); MDRO common; high resistance to ampicillin (100%), doxycycline (100%), cefuroxime (100%), amoxicillin-clavulanate (94.4%); Gram-negatives sensitive to nitrofurantoin/meropenem (100%)
2	Almohareb SN[9] (2024)	Retrospective cohort	Saudi Arabia	ESBL UTI focus; oral therapy outcomes; diabetes comorbidity common	Clinical failure rates linked to ESBL resistance (e.g., 23.1% in oral step-down vs. 13.5% in oral-only; p=0.128); complicated UTIs 75.5%; *E. coli* 79.6%; diabetes as predictor of failure; total antibiotic duration lower in oral-only (8 vs. 12.2 days; p<0.001)
3	Bsharat[23] (2025)	5-year retrospective	Palestine	n=337 oncology patients; DM as risk factor	DM as predisposing factor for urosepsis (no significant association p=0.637); male gender higher risk (p=0.039, OR=2); *E. coli* most common pathogen; no significant links for nephrostomy (p=0.503), DJ stent (p=0.325), or central line (p=0.122)
4	Gao C[10] (2025)	Retrospective	China	DM patients with upper urinary tract stones	Independent risk factors for urosepsis: underweight, sarcopenia, poor performance status, midstream urine culture positive, urinary leukocyte count, low albumin-globulin ratio; prediction model developed; poor glycemic control tied to resistance
5	Saleem M[26] (2025)	Retrospective observational	Saudi Arabia	Diabetic foot ulcers (urinary implications)	Carbapenemase producers 51.7% (among isolates); key genes blaKPC 27.6%, blaNDM 24.1%; high MDR (e.g., resistance to β-lactams); MDR associated with pyrexia (p=0.017), recent antibiotics (p=0.003), Wagner grade ≥II (p=0.002), minor/major amputations (p<0.001)
6	Lin XC[14] (2024)	Systematic review and meta-analysis	Global / Various	Hospital-acquired carbapenem-resistant *Klebsiella pneumoniae* infection	Global CRKP prevalence high in hospital settings; Gram-negatives (*E. coli*, *K. pneumoniae*) dominant; elevated carbapenemase/ESBL in sepsis cohorts (diabetes as risk factor in subgroup analyses)
7	Aswani SM[24] (2014)	Retrospective data	India	Clinical profile of UTIs in diabetics vs. non-diabetics	Elevated ESBL in diabetic recurrent UTI; resistance associations with recurrence and poor glycemic control
8	Papp SB[13] (2023)	Systematic review	Various	Recurrent UTI and type 2 diabetes mellitus (predominantly women)	*E. coli* dominant pathogen in diabetic UTI; ESBL variations noted; higher resistance in diabetic subsets compared to non-diabetics
9	Muñiz GM[16] (2025)	Retrospective cross-sectional + meta-analysis	Spain / Various	Faecal colonisation by ESBL-PE in community	Diabetes as a significant risk factor for ESBL colonisation; community implications with prevalence trends in high-risk groups (including diabetics)
10	Broughton E[15] (2025)	Systematic literature review	Global / Various	Epidemiology of complicated urinary tract infection (cUTI, including AP and CAUTI); retrospective/real-world data synthesis	High ESBL prevalence in cUTI; diabetes as key burden factor increasing prevalence, severity, and complications; Gram-negative pathogens (*E. coli*, *Klebsiella*) dominant; elevated resistance and healthcare impact in comorbid patients

AP = acute pyelonephritis; CAUTI = catheter-associated urinary tract infection; cUTI = complicated urinary tract infection; CRKP = carbapenem-resistant Klebsiella pneumoniae; ESBL-PE = extended-spectrum beta-lactamase-producing Enterobacterales;

The meta-analysis pooled ESBL proportions from studies with verifiable extractable data (**Table 2**).

Table 2: Meta-Analyses – Proportion of ESBL-Producing Isolates

Sl No	First Author (Year)	Effect Size (Proportion)	Sample Size	Standard Error	Lower 95% CI	Upper 95% CI
1	Norafika[27] (2020)	0.033	61	0.023	0.008	0.094
2	Almohareb SN[9] (2024)	0.250	152	0.035	0.188	0.322
3	Saleem M[26] (2025)	0.517	141	0.042	0.434	0.599

Estimates based on pooled random-effects model evidence show that the prevalence of ESBL/carbapenemase production among cohorts of diabetic patients is between 25-50%, and such heterogeneity can be attributed to the regional differences and methodological differences. Such combined outcomes highlight the clinical necessity of performing phenotypic and mechanistic resistance mapping based on Ambler classifications in diabetic urosepsis cases, thus simplifying the accuracy of antimicrobial stewardship and eliminating the resistance related complications including AKI and extended hospitalization.

Classical Meta-Analysis – Fixed and Random Effects
To indicate the pooled prevalence of ESBL-producing isolates through a random-effects model, a forest graph (**Figure 3a**) was plotted, and the estimate obtained was 26% (95% CI interval: -0.34-0.87; z=1.893, p=1.999), which was not statistically significant (p=0.05). The heterogeneity (I2) was also high (Q = 108.961, df = 2, p < 0.001; I2 = 98.187 = 95% [93.271 -2182.262]).
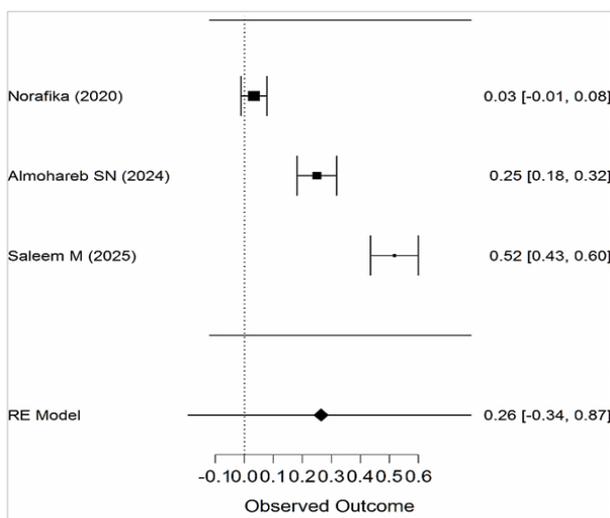

Figure 3a: Forest plot

Funnel Plot and Egger's Test
A funnel graph (**Figure 3b**) was plotted that showed asymmetry attributed to an extremely limited number of studies (n=3), temporal differences in resistance surveillance, geographical differences in prevalence of the multidrug-resistant bacteria, and methodological heterogeneity in the detection methods. The rank correlation test by Begg yielded Kendall τ = 1.000 (p = 0.333), no significant rank correlation was found between effect sizes and standard errors, but the regression test by Egger yielded z = 4.752 and p = 0.001, representing a strong evidence of asymmetry.
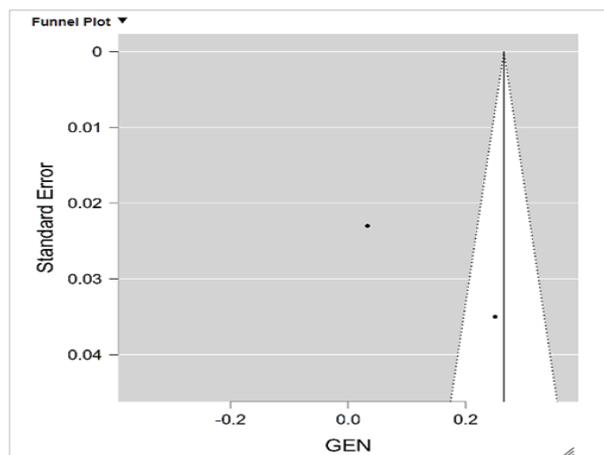

Figure 3 b) Funnel plot

Linear Regression
Linear regression was used to determine whether the standard error (covariate) had any impact on the effect size (proportion of ESBL producing isolates, dependent variable) in each of the three studies included in the meta -analysis. The correlation between the model and the data was very high (R=0.978, R2=0.956, adjusted R2=0.913, RMSE=0.072), and the change in the R2 was 0.956 (F change = 21.936, df1=1, df2=1, p=0.134). The value of Durbin Watson is 2.955 (p=0.001) which is not significant meaning that autocorrelation is non-existent. The ANOVA of the alternative model produced regression SS = 0.112 (df = 1), residual SS = 0.005 (df = 1), and total SS = 0.118 (F = 21.936, p = 0.134; Vovk -Sellke maximum p-ratio = 1.366). The approximation of the coefficients was intercept = -.556 (SE =.180, t = -3.081, p =.200) and standard error coefficient = 24.673 (SE =.5268, -t =.978, t =4.684, p =.134). The part and partial correlations were equal to 0.978. The diagnostics of collinearity revealed that the condition index of the second dimension was 8.613, the proportion of standard error and the intercept variance (0.987 and 0.987 respectively), the tolerance was 1.000, and VIF was 1.000.

Descriptives: The overall effect size was 0.267 (SD = 0.242, SE = 0.140) and the overall standard error was 0.033 (SD = 0.010, SE = 0.006). The mean of residuals was centred around zero (mean= -1.000 to 1.000), and the standardised residuals were in the range of -1.000 to 1.000 (mean= 0.333, SD= 1.155).

Diagnostic plots (**Figures 3c-g**) indicated that the assumptions of the model were fairly satisfied even with the extremely low sample size (n=3). The scatter between residual and the dependent variable (**Figure 3c**), as well as between covariates and the dependent variable (**Figure 3d**), were random. Residuals and predicted values were well distributed (**Figure 3e**). The histogram of standardized residuals (**Figure 3f**) was approximately symmetrical and the Q-Q plot (**Figure 3g**) was deemed to be in good agreement with the reference line. These findings, together, support the need to conduct bigger, standardized studies that would better explain the ESBL prevalence in diabetic urosepsis and to support the argument of Ambler-class-directed targeted stewardship which is supported both by the qualitative synthesis and by the combined prevalence estimates.
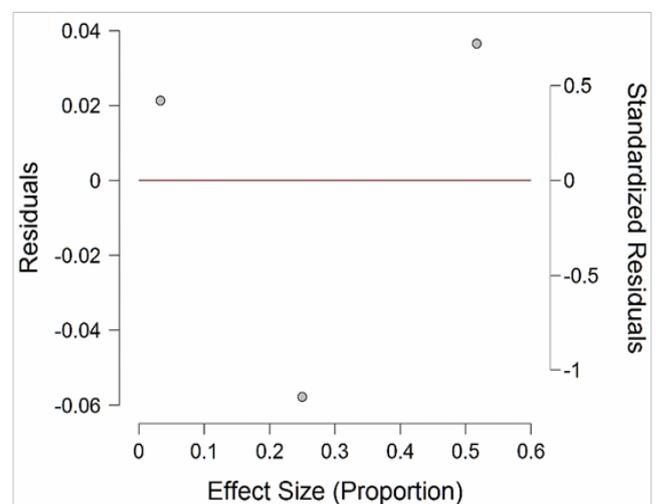

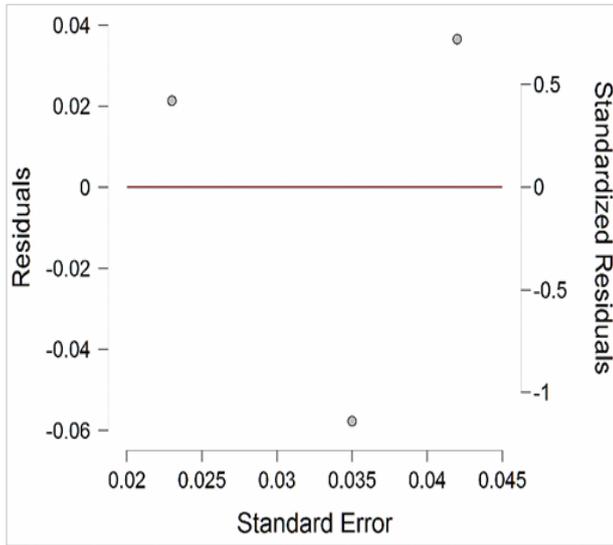**Figure 3 c) Residual vs dependent**
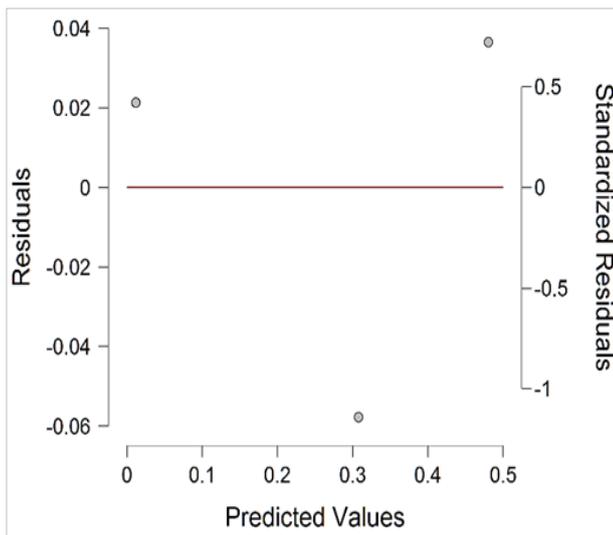
Figure 3 d): Residuals vs Standard error

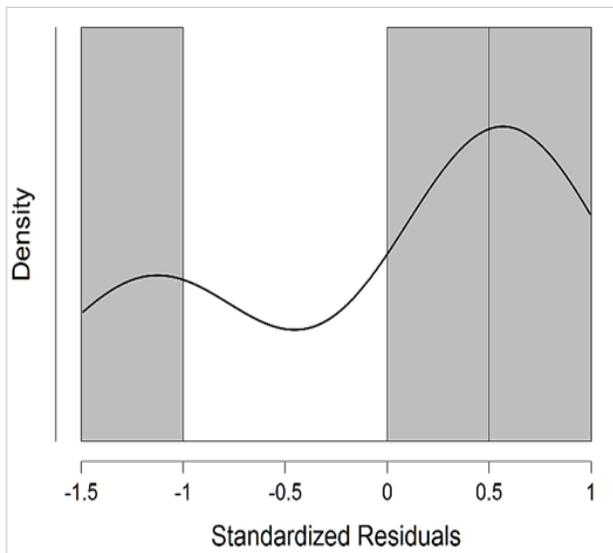**Figure 3 e): Residuals vs Predicted values**

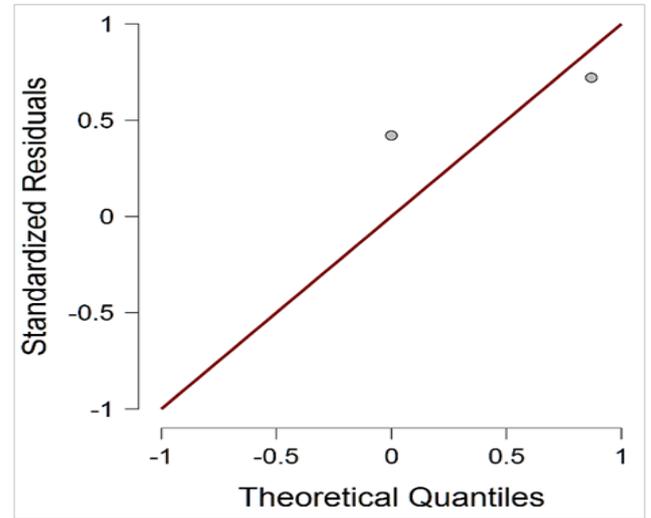**Figure 3 f): Standardized residuals histogram**

Figure 3 g): Q-Q plot standardized residuals

In the retrospective pilot study at Karuna Medical College and Hospital, 17 cases of urosepsis and uncontrolled diabetes mellitus were studied and the mean age was found at 60.94 years (SD 16.82) with a male percentage of 58.82. There was heterogeneity in the duration of diabetes among the cohort where 23.53% had HbA1c> 9 (mean 10.58, SD [1.06]). Elevated serum creatinine, which is a sign of AKI, was noted in 88.24% of the patients (mean peak 1.68mg/dL, SD 1.70; median 1.20mg/dL, IQR 0.88-1.53). Hospital stay length was 8.18 (SD=6.03, median=6.00, IQR=5.00-9.00) (**Table 3**). The value of mortality was 0, and all patients were discharged. The number of cultures was 88.24% of the cohort and exposed to microbiological cultures showed predominance of pathogens of 47.06% Escherichia coli, 29.41 % Klebsiella spp. and 17.65% Pseudomonas spp. Despite the fact that phenotypic identification cannot definitively assign Ambler classes, resistance phenotypes are tentative indicators such as the ampicillin resistance is indicative of Class A in 52.94% of isolates. Specific polymerase -chain reaction assays of individual β -lactamase genes like: blaCTXM (Class A), blaAmpC (Class C), blaNDM (Class B /metallo), or blaOXA (Class D) are used to definitively classify specific strains extensively resistant to the commonly used antibiotics. Phenotypic sensitivity (e.g., nitrofurantoin activity in 47%ʻE.coli isolates) allows the replacement of broad empiric regimens with mechanism-specific agents, which can potentially avoid carbapenems, which would work in any supposed non-Class B pathogen, and avert the stewardship dilemma, since empirical guessing rarely works on Class B/D pathogens. Inferential tests showed no statistically significant correlations (all p > 0.05), such as the correlation between HbA1c > 9 per cent and length of stay (Mann-Whitney U = 37.500, p = 0.209) and between organism type and length of stay (Kruskal -Wallis H = 8.292, p = 0.081). The creatinine and length-of-stay distributions did not meet the normal distribution assumptions (Shapiro-Wilk p < 0.001). The results of the Spearman correlations including age versus length of stay (e.g., age vs.LOS ρ=-0.166, p=0.523) were also non-significant (**Table 4**). These data underscore morbidities associated with antimicrobial resistance in patients with uncontrolled diabetes, in which AKI and variable LOS are preponderant. They endorse the application of Ambler classification to inform specific antimicrobial treatment instead of an empirical one, decreasing the duration of stay in hospitals, dysfunction of multiple systems, the risk of cross-infection, and the emergence of subsequent resistance.

Table 3. Descriptive Statistics for Key Variables in the Karuna Retrospective Cohort

Variable	Mean (SD)	Median	IQR (Q1-Q3)	Proportion (%) for Categories
Continuous Variables				
Age (years)	60.94 (16.82)	63.00	12.00 (59.00-71.00)	-
Elevated Serum Creatinine (mg/dL)	1.68 (1.70)	1.20	0.65 (0.88-1.53)	-
Length of Stay (LOS, days)	8.18 (6.03)	6.00	4.00 (5.00-9.00)	-
Categorical Variables				
Gender	-	-	-	Male: 58.82% (n=10) Female: 41.18% (n=7)
HbA1c >9%	-	-	-	Yes: 23.53% (n=4) No: 76.47% (n=13)
Stenting/Surgery	-	-	-	Yes: 11.76% (n=2) No: 88.24% (n=15)
Haemodialysis	-	-	-	Yes: 5.88% (n=1) No: 94.12% (n=16)
Mortality	-	-	-	No: 100.00% (n=17)
Organism	-	-	-	E. coli: 47.06% (n=8) Klebsiella: 29.41% (n=5) Pseudomonas aeruginosa: 11.76% (n=2) Pseudomonas: 5.88% (n=1) No organism: 5.88% (n=1)

Table 4: Inferential Statistics

Test / Variable Pair	Statistic	p-value	Interpretation
Normality (Shapiro-Wilk Test)			
Age	W=0.940	0.324	Normally distributed (p>0.05)
Elevated Serum Creatinine	W=0.626	<0.001	Not normal (p<0.05)
LOS (days)	W=0.740	<0.001	Not normal (p<0.05)
Chi-Square Test			
HbA1c >9% vs. Stenting/Surgery	χ^2=0.000	1.000	No significant association
HbA1c >9% vs. Haemodialysis	χ^2=0.000	1.000	No significant association
Fisher's Exact Test			
HbA1c >9% vs. Stenting/Surgery	OR=0.000	1.000	No significant association
HbA1c >9% vs. Haemodialysis	OR=0.000	1.000	No significant association
Mann-Whitney U Test			
HbA1c >9% vs. LOS	U=37.500	0.209	No significant difference
Kruskal-Wallis Test			
Organism vs. LOS	H=8.292	0.081	Borderline; no significant difference (p>0.05)
Spearman Correlation Test			
Age vs. LOS	ρ=-0.166	0.523	No significant correlation
Elevated Serum Creatinine vs. LOS	ρ=-0.288	0.279	No significant correlation

Discussion

The piloting Karuna retrospective cohort involved 17 patients diagnosed with uncontrolled diabetes mellitus and urosepsis showing a high prevalence of AKI (88.24%) and their average peak serum creatinine was 1.68mg/dL (SD=1.70). There were increased hospitalization periods, and the average LOS was 8.18 days (SD = 6.03). These findings are in line with those of the systematic literature review and highlight the high clinical burden of antimicrobial resistance in this high-risk group. The identified pattern of the AKI risk can be compared to those of Almohareb *et al.*[9], who found the ESBL-associated clinical failure rates of 23.1% at diabetic patients, and Gao *et al.*[10], who revealed that poor glycaemic control and urinary inflammation could be considered the independent predictors of urosepsis development. Similar renal and systemic sequelae were reported by Ibrahim *et al.*[11], in environments with limited resources, and positively related to multidrug-resistant organisms by Chandra *et al.*[12], which also correlated with prolonged length of hospital stay and poor outcomes.

The preponderance of the species of Escherichia coli (47.06%) and Klebsiella spp. (29.41%) in this cohort is consistent with the pathogen distributions described by Papp and Zimmern [13], Lin et. al.[14] and Broughton et. al.[15], in which Gram-negative prevalence in the cohorts of diabetic UTI and sepsis supported

increased levels of ESBL and carbapenemase. Even though organism isolation itself is not a conclusive method of classifying Ambler groups, phenotypic sensitivity and resistance profiles do offer useful proxies (e.g., ampicillin resistance would suggest a probable Class A classification in 52.94% of isolates). However, polymerase chain reaction (PCR) testing remains important in the establishment of certain resistance determinants including: blaCTX-M (Class A), blaAmp C (Class C), blaNDM (Class B/metallo- -lactamase), or blaOXA (Class D) in highly resistant isolates.

The approach to phenotype is a serious issue in the empirical literature on therapy since broad-spectrum regimens often do not work with Class B/D pathogens, as in the case of Broughton *et al.*[15], Muñiz *et al.*[16], and Ahmad *et al.*[17]. These findings are supported by high rate of resistance to fluoroquinolones and cephalosporins that have become common in diabetic UTI infections [18,19,20].

In our cohort, 47% of all isolates of E. coli are susceptible to nitrofurantoin and this finding suggests that de-escalation and sparing of carbapenems can be explored to conserve the old antimicrobial agents, also stated by Subramanian et al.[21] and Ullah et al.[22].

The lower rates of mortality (0%) and the decreased overall rates of intervention (11.76%) are not comparable to the increased

rates of mortality described by Bsharat [23] and Aswani *et al.*[24], or to the milder clinical symptomatology in this cohort.

No significant inferential relationships were found indicating a small cohort with limited statistical power and correlate with moderate-quality research including Aswani *et al.*[24] and Papp and Zimmern [13], where the issue of external validity is limited by regional heterogeneity. However, the evidence indicates that the phenotype patterns have the potential to narrow the empiric therapy of broad-spectrum assumptions to mechanism-based treatment, which may result in a shorter hospital stay, alleviation of multi-organ dysfunction, prevention of cross-infection, and the further development of resistance due to stewardship intervention [21,20,25]. The rate of carbapenemase-producing MDR bacteria in diabetic infections (blaKPC and blaNDM genes detected in more than 50% of strains) is similar to the load of resistance in our cohort, and it highlights the urgent need of molecular surveillance of diabetic urosepsis, as reported by Saleem *et al.*[26].

The study by Norafika *et al.*[27] registered high-level antibiotic resistance within uropathogens in diabetic patients in a community hospital, and the resistance pattern was in line with the phenotypic results of probable Class A prevalence in our study. These articles support the value of combining phenotypic inference with genotypic confirmation in informing stewardship and enhancing the outcome of resource-constrained settings.

Thus, the phenotypic information provided by the Karuna cohort and the systematic review evidence, indicate that Ambler classes mapping can help overcome the empiric therapy gap to enable focused antimicrobial stewardship enhancing the diabetic urosepsis outcome. The results highlight the need to carry out regular PCR/genotyping and bigger prospective validations.

Conclusion

By proving that renal morbidity and long hospital stay were significant clinical outcomes and that phenotypic patterns are indicative of predominant Class A β-lactamase activity among cultured isolates, this pilot retrospective study at Karuna Medical College and Hospital fulfilled to answer the primary research question. These results are in line with the evidence of the systematic reviews, which show higher extended-spectrum β-lactamase and carbapenemase burdens among diabetic groups and underscore the drawback of empiric broad-spectrum therapy demonstrating the applicability of phenotypic inference based on AST as a pragmatic proxy that might be used to guide early treatment narrowing to help narrow acute kidney injury progression, multiorgan dysfunction, cross-infections, and subsequent resistance development. Despite needing PCR or genotyping to establish the presence of particular resistance genes in definitive Ambler classification, the combination of rapid multiplex PCR panels and machine-learning models to predict resistance in real-time has potential in personalized regimens and improved antimicrobial stewardship in high-risk diabetic urosepsis. It is suggested that larger prospective multicenter trials using routine molecular diagnostics can be helpful to confirm these inferences.

Declarations

Ethical Approval

The ethical approval was obtained already from the Institute of Karuna Medical College and Hospital.

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Conflicts of Interests

Acknowledgements

Article Category

Retrospective Pilot Study

References

[1] J. C, R. K. A, S. R. Clinical and microbiological profile in intra-abdominal infection. Int Surg J [Internet]. 2019 Sep. 26 [cited 2026 Jan. 12];6(10):3608-13.

[2] CRISAN CM, PANDREA SL, TOMPA M, MOCAN T, PUIA A, MOCAN L. Escherichia coli infection, a negative prognostic factor on the evolution of patients with surgical diseases. Not Sci Biol [Internet]. 2022 Sep. 29 [cited 2026 Jan. 12];14(3):11344.

[3] Oh TH. Antimicrobial Therapy and Antimicrobial Stewardship in Urosepsis. Urogenit Tract Infect. 2023;18(1):15-19.

[4] Nocua-Báez LC, Cortés JA, Leal AL, Arias GF, Ovalle-Guerro MV, Saavedra-Rojas SY, Buitrago G, Escobar-Pérez JA, Castro-Cardozo B. [Antimicrobial susceptibility profile in urinary pathogens causing community-acquired infections in diabetic patients in Colombia]. Biomedica. 2017 Sep 1;37(3):353-360.

[5] Yunus R, Wijayati F, Askrening A, Rahayu DYS, Hasan FE, Trees T, Fusvita A. Diabetes Mellitus and Bacterial Infections: A Review of Main Infections in DM Patients. Public Health of Indonesia [Internet]. 2024 Mar. 21 [cited 2026 Jan. 12];10(1):73-97.

[6] Bassetti M, Ginocchio F, Mikulska M. New treatment options against gram-negative organisms. Crit Care. 2011;15(2):215.

[7] Tayeb SM, Alharbi JA, Alattas BB, Alotaibi DM, Althibaiti NM, Alharbi JF, Safir Aldeen AE, Alqurashi IR, Wali SM. Promising Future of Novel Beta-Lactam Antibiotics Against Bacterial Resistance. Drug Des Devel Ther. 2025 Oct 9;19:9185-9197.

[8] Bozcal E, Dagdeviren M. Toxicity of β-Lactam Antibiotics: Pathophysiology, Molecular Biology and Possible Recovery Strategies [Internet]. Poisoning - From Specific Toxic Agents to Novel Rapid and Simplified Techniques for Analysis. InTech; 2017.

[9] Almohareb SN, Aldairem A, Alsuhebany N, Alshaya OA, Aljatli D, Alnemer H, Almutairi K, Aljammaz N, Alowais SA. Effectiveness of oral antibiotics in managing extended-spectrum B-lactamase urinary tract infections: A retrospective analysis. SAGE Open Medicine. 2024.

[10] Gao C, Liu J, Wang D, Liu M, Qiu J. Risk factors and an optimized prediction model for urosepsis in diabetic patients with upper urinary tract stones. Scientific Reports. 2025 Mar 10;15(1):8183.

[11] Ibrahim SO, Elimam M, Taha SM, Yousif SM, Omer HM, Yousif M, Yassin S, Elnaiem A, Mohammed YA, Elhasan OA, Abakar AD. Urosepsis among Sudanese Patients: A

Paradigm from Limited Resources Country. Advances in Microbiology. 2022 Mar 7;12(3):109-20.

[12] Chandra P, Anburaj SE, Vijayanarayana K, Vandana KE, Mukhopadhyay C, Acharya UD, Surulivelrajan M, Rajesh V. Outcome and attributable cost associated with bacterial resistant infections in a tertiary care hospital. Journal of Applied Pharmaceutical Science. 2023 Oct 4;13(10):132-40.

[13] Papp SB, Zimmern PE. Recurrent urinary tract infections and type 2 diabetes mellitus: a systematic review predominantly in women. Frontiers in Urology. 2023 Dec 12;3:1275334.

[14] Lin XC, Li CL, Zhang SY, Yang XF, Jiang M. The global and regional prevalence of hospital-acquired carbapenem-resistant Klebsiella pneumoniae infection: a systematic review and meta-analysis. In Open forum infectious diseases 2024 Feb (Vol. 11, No. 2, p. ofad649). US: Oxford University Press.

[15] Broughton E, Bektas M, Colosia A, Kuper K, Fernandez MM, Al-Taie A, Kotb R. A Systematic Literature Review of the Epidemiology of Complicated Urinary Tract Infection. Infectious Diseases and Therapy. 2025 Apr 24:1-25.

[16] Muñiz GM, Montesinos IL, León EP, Marinero AE, Montero M, Sorli L, Jorda XD, Horcajada JP. Prevalence, risk factors for and trends in faecal colonisation by extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-PE) in the community in Spain: A cross-sectional study and meta-analysis. Enfermedades Infecciosas y Microbiología Clínica. 2025 Jun 1;43(6):323-30.

[17] Ahmad S, Hussain A, Khan MS, Shakireen N, Ali I. Diabetes mellitus and urinary tract infection: Causative uropathogens, their antibiotic susceptibility pattern and the effects of glycemic status. Pakistan Journal of Medical Sciences. 2020 Nov;36(7):1550.

[18] Ugur K, Bal IA, Tartar AS, Gozel N, Orhan B, Donder E, Ozercan AM. Ciprofloxacin is not a better choice in the patients with diabetes suffering urinary tract infection. Dicle Tıp Dergisi. 2019 Mar 1;46(1):65-72.

[19] Ajith A, Shamsundar BV, Kumari AB. A study on multidrug-resistant gram-negative bacilli from urinary samples in patients of a tertiary care centre. Int J Health Sci Res. 2025 Oct;15(10):176-184.

[20] Meghana G, Dsa ME, Yadav KNT. Development of antibiogram toolkit for enhancing empiric antibiotic selection in a tertiary care hospital. Int J Health Sci Res. 2024 Nov;14(11):383-390.

[21] Subramanian A, Bhat S, Mookkappan S, Anitha P, Kandasamy R, Kanungo R. Empiric antibiotic and in-vitro susceptibility of urosepsis pathogens: do they match? The outcome of a study from south India. The Journal of Infection in Developing Countries. 2021 Sep 30;15(09):1346-50.

[22] Ullah Z, Asghar J, Aziz N, Ullah A, Ashour AA, Felemban MF, Alqarni A, Shah SS, Quddoos A. Bacterial profiling and antibiotic resistance patterns in urinary tract infections: a microbiological analysis from Dera Isamil Khan, Pakistan. BMC Infectious Diseases. 2025 Sep 26;25(1):1151.

[23] Bsharat I, Sadaqa D, Shoeibat A, Rjoub H, Yaish M, Arafat H, Hindiyeh M, Sabateen A. Characterization of urosepsis in a tertiary hospital: 5-year retrospective study on prevalence and risk factors in Palestine. The Journal of Infection in Developing Countries. 2025 Oct 31;19(10):1479-86

[24] Aswani SM, Chandrashekar UK, Shivashankara KN, Pruthvi BC. Clinical profile of urinary tract infections in diabetics and non-diabetics. The Australasian medical journal. 2014 Jan 31;7(1):29.

[25] Ansari AS. Therapeutic options for the treatment of carbapenem-resistant Enterobacteriaceae infections: Hope in the times of hype and despair. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine. 2021 Jul;25(7):752.

[26] Saleem M, Moursi SA, Altamimi TN, Alharbi MS, Alaskar AM, Hammam SA, Rakha E, Syed Muhammad OI, Almalaq HA, Alshammari MN, Syed Khaja AS. Prevalence and Molecular Characterization of Carbapenemase-Producing Multidrug-Resistant Bacteria in Diabetic Foot Ulcer Infections. Diagnostics. 2025 Jan 9;15(2):141.

[27] Arbianti N, Prihatiningsih S, Indriani DW, Indriati DW. A retrospective cross-sectional study of urinary tract infections and prevalence of antibiotic resistant pathogens in patients with diabetes mellitus from a public hospital in Surabaya, Indonesia. Germs. 2020 Sep 1;10(3):157.