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Article

Oxidative Stress and Inflammatory Markers in Multidrug-Resistant versus Non-Resistant Urinary Tract Infections

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Abstract: Multidrug-resistant (MDR) urinary tract infections (UTI) present a major therapeutic problem. Oxidative stress and inflammation could be involved in host response. Objectives to compare the oxidative and inflammatory markers in patients with MDR UTI and without MDR UTI compared to healthy controls. This is a cross-sectional comparative study. 90 adult patients were recruited into 3 groups (MDR UTI, non-MDR UTI, and healthy control), 30 patients per group. From the 60 patients with infection, one urine isolate was collected. Malondialdehyde (MDA) levels were measured using TBARS spectrophotometric method, total antioxidant capacity (TAC) using colorimetric kit and C reactive protein (CRP) and interleukin-6 (IL-6) using routine hospital methods. All were measured in serum. Results of 60 isolates, 50% were MDR. Most common isolate was Escherichia coli (55%). Patients with MDR had higher MDA (4.6±1.1nmol/ml), CRP (52.8±22.6mg/l) and IL-6 (38.4±15.2pg/ml), and lower TAC levels (0.88±0.21mmol/l) compared to patients with non-MDR and controls ($p < 0.001$). MDA was positively correlated with IL-6 ($r = 0.58$) and CRP levels ($r = 0.49$). TAC was negatively correlated with IL-6 (r=-0.52) and MDA (r=-0.61) levels ($p < 0.001$). MDR group had the highest percentage of patients with diabetes (33%). No adjustment was performed. MDR UTI were associated with increased oxidative stress, decreased antioxidant capacity and increased systemic inflammation.

Keywords: Urinary Tract Infections, Multidrug Resistance, Oxidative Stress, MDA, Total Antioxidant Capacity, CRP, IL-6

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1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, with an estimated 150 million cases each year [1]. Roughly half of all women experience at least one UTI in their lifetime, and many have recurrences [2]. Most are caused by a small group of Gram-negative bacteria, mainly *Escherichia coli* and *Klebsiella pneumoniae*, which are also leading causes of drug-resistant infection [1,3].

Antimicrobial resistance (AMR) makes these infections harder to treat. A global analysis estimated that bacterial AMR was directly responsible for about 1.27 million deaths in 2019 and was associated with nearly 5 million [3]. Resistance has been linked to worse outcomes, including longer hospital stay, higher cost and, for some organisms, higher mortality [4,5]. To make studies comparable, an international expert group defined an MDR isolate as one non-susceptible to at least one agent in three or more antimicrobial categories [6]. Studies on drug resistance include most studies from Iraq [7-9] and often do not assess what affect an infection with drug resistant bacteria can cause. The body will

respond to bacterial attack by neutrophils and macrophages with release of reactive oxygen species (ROS). These help kill the pathogen but can cause damage to host tissue [10, 11]. ROS will attack membrane lipids causing production of malondialdehyde (MDA); this is widely used as a marker of lipid peroxidation [12]. Antioxidants will be used up meaning total antioxidant capacity (TAC) will decrease. Immune cells also release cytokines such as interleukin-6 (IL-6) which will cause the liver to produce C-reactive protein (CRP) [13]. Oxidative stress contributes to the increase in inflammatory markers [11]. Previous studies have shown increased lipid peroxidation and low antioxidants in UTI [14, 15], however to our knowledge there are few studies investigating differences in these markers comparing MDR and non-MDR infections. Due to longer duration of infection with resistant organisms or patients having more severe illness to start with, there may be increased oxidative and inflammatory markers. Comorbidities such as diabetes can also result in increased oxidative stress [16]. The aim of this study was to investigate differences in MDA, TAC, CRP and IL-6 in the MDR, non-MDR and healthy control group. We also wanted to see how these markers are related.

2. Materials and Methods

Design of the study

A comparative cross-sectional study was carried out at Tikrit Teaching Hospital from 12 May to 10 December 2025, after ethical approval. Consent was obtained from all participants. Only urinary tract infections were included.

Participants

- Group 1: culture-confirmed non-MDR UTI (n = 30).
- Group 2: culture-confirmed MDR UTI (n = 30).
- Group 3: healthy controls without UTI, matched for age and sex (n = 30).

The 60 infected patients each contributed one isolate (the first positive culture), so the 60 isolates correspond one-to-one to the 60 patients, 30 with MDR and 30 with non-MDR isolates. Exclusions: antibiotics in the previous 7 days, chronic kidney disease, cancer, immunosuppressive treatment, pregnancy and smoking.

Bacteriology

Urine was cultured on standard media, and isolates were identified by routine biochemical tests. Susceptibility was tested by Kirby–Bauer disk diffusion and interpreted against CLSI breakpoints [17]. An isolate was classed as MDR if not susceptible to at least one agent in three or more antimicrobial categories [4]; Otherwise, it was classed as non-MDR.

Blood sampling and biomarker measurement

About 5 mL of venous blood was drawn before treatment. Serum was separated and stored at [−20 °C / −80 °C] in single-use aliquots. All four markers were measured in serum; MDA was measured as thiobarbituric acid reactive substances (TBARS) using a spectrophotometric method [11]. TAC was measured with a colorimetric kit, CRP was measured with the routine hospital assay and IL-6 was quantified by ELISA.

Statistics

Normality was checked with (Shapiro–Wilk). Results are given as mean ± SD (or median (IQR) for non-normal variables). Three groups were compared by (ANOVA with post hoc test / Kruskal–Wallis with Dunn test), and MDR against non-MDR by (t-test / Mann–Whitney U). Categorical variables were compared with the chi-square or Fisher exact test. Relationships between markers used Spearman correlation. A p-value below 0.05 was significant. Analysis used SPSS version 26.

3. Results

Of the 60 infected patients, 30 had MDR isolates. Every marker differed in the expected direction, with the MDR group furthest from healthy controls.

Table 1. Participant characteristics

Characteristic	Controls (n=30)	Non-MDR (n=30)	MDR (n=30)	p
Age, years	41.2 ± 11.5	43.8 ± 12.1	46.5 ± 13.0	> 0.001
Female, n (%)	19 (63%)	20 (67%)	21 (70%)	> 0.001
Diabetes, n (%)	3 (10%)	5 (17%)	10 (33%)	<0.001

Overall 30/60 (50%) isolates were MDR. The most common isolate was E. coli (33/60; 55%) and 45% were MDR. K. pneumoniae and Pseudomonas aeruginosa showed higher MDR rates (69% and 67). Proteus mirabilis showed an MDR rate of 40%. None of the Enterococcus spp isolates were MDR (Table 2). Percentages for small number of isolates (n ≤ 13) should be interpreted with care.

Table 2. Isolates and MDR rate

Bacteria	Isolates	MDR, n (%)
Escherichia coli	33	15 (45%)
Klebsiella pneumoniae	13	9 (69%)
Pseudomonas aeruginosa	6	4 (67%)
Proteus mirabilis	5	2 (40%)
Enterococcus spp.	3	0 (0%)
Total	60	30 (50%)

All biomarkers were significantly different between the three groups ($p < 0.001$; Table 3). MDA, CRP and IL-6 increased progressively from controls to non-MDR and then MDR patients. TAC decreased. MDR patients displayed the highest levels of oxidative stress and inflammatory markers but lowest antioxidant capacity.

Table 3. Biomarkers, mean ± SD

Marker	Controls	Non-MDR	MDR	p (3 groups)	p (MDR vs non-MDR)
MDA, nmol/mL	2.1 ± 0.5	3.4 ± 0.9	4.6 ± 1.1	<0.001	<0.001
TAC, mmol/L	1.45 ± 0.22	1.12 ± 0.25	0.88 ± 0.21	<0.001	<0.001
CRP, mg/L	3.2 ± 1.8	28.5 ± 14.2	52.8 ± 22.6	<0.001	<0.001
IL-6, pg/mL	4.1 ± 1.9	21.7 ± 9.8	38.4 ± 15.2	<0.001	<0.001

MDA was positively correlated to IL-6 ($r = 0.58$) and CRP ($r = 0.49$) in the 60 infected patients. TAC was negatively correlated to IL-6 ($r=-0.52$) and MDA ($r=-0.61$). Correlation coefficients were significant for all values ($p < 0.001$) (Table 4). The correlation magnitudes were moderate.

Table 4. Spearman correlations in infected patients (n=60)

Pair	r	p
MDA vs IL-6	0.58	<0.001
MDA vs CRP	0.49	<0.001
TAC vs IL-6	−0.52	<0.001
MDA vs TAC	−0.61	<0.001

4. Discussion

Adults with MDR urinary tract infections showed a heavier host burden than adults with non-MDR infections. MDA, CRP and IL-6 were higher, TAC was lower, and healthy controls sat at the other end of the scale. The progression between the control group, non-MDR group and MDR groups indicates a gradual change.

The results would be expected to show increased MDA levels along with decreased TAC levels due to an over production of ROS [10,11]. This is because MDA indicates damage to cell membranes whilst TAC indicates the protection still available. As displayed in table 4 there is a negative correlation between these two variables [12]. Our results match previous research. It has been shown that 164 patients with UTI had increased lipid peroxidation and reduced antioxidant enzyme activity [14]. However this was measured in the urine rather than serum. A systematic review on paediatric UTI also showed a decrease in antioxidants and increase in MDA and ROS [15]. In an animal study, serum MDA was higher and antioxidant enzymes lower in camels with UTI, and MDA was the marker that best predicted treatment failure [19]. None of these studies compared resistant with susceptible infections, so our MDR versus non-MDR gradient adds a new comparison, but it needs replication.

IL-6 is an early signal that drives CRP production in the liver, so the two would be expected to rise together [13]. IL-6 was highlighted in two systematic reviews as some of the more promising biomarkers in blood and urine samples of UTI however the quality of evidence was poor [20,21]. In a more recent meta-analysis of children, CRP was found to have limited accuracy but potential as a biomarker in pyelonephritis when compared with cystitis [22]. This suggests that CRP and IL-6 levels in our patient population may be to some extent a reflection of the severity and location of infection. We did not collect data on whether patients had upper or lower tract infections. This positive correlation between MDA and IL-6/CRP suggests that oxidative stress and inflammatory pathways are exacerbating each other [11].

In our isolates we saw a high proportion of MDR (50% overall, 45% in E. coli and 69% in K. pneumoniae). This was less than in a series from Karbala where 71% of E. coli and 90% of K. pneumoniae isolated from women with UTI were MDR [7]. However, other studies from Iraq have demonstrated high resistance rates to cephalosporins and ampicillin with a large burden of MDR seen in E. coli and Klebsiella [8,9]. Differences in location of study (inpatient vs outpatient), sample collection and defining MDR make comparison difficult. Our *E. coli* share (55%) is higher than the 35% reported in adults in Al-Diwaniya [9], where Gram-positive organisms were common.

Patients with resistant bacteria often have more health-care contact, earlier antibiotic exposure and more underlying disease [4,5]. In Table 1 the MDR group had the highest rate of diabetes (33% against 17% and 10%), and diabetes raises oxidative stress and inflammation independently of infection [16]. Because no adjusted analysis was done, part of the MDR–non-MDR gap may be due to diabetes or other differences between groups.

The group means overlap (for example, CRP in MDR 52.8 ± 22.6 versus non-MDR 28.5 ± 14.2 mg/L) and no diagnostic accuracy analysis was performed, so these markers cannot identify resistance or replace culture and susceptibility testing. Their possible value

is to describe how severe a resistant infection is and to provide a baseline for follow-up studies of treatment response.

The design is cross-sectional with a single sampling point, so only association can be shown; resistance itself is not proven to drive oxidative stress. The sample is small (30 per group) and from one centre. Unmeasured factors such as earlier hospital stays, infection duration, upper versus lower tract involvement and kidney function could explain part of the gap. Larger multicentre studies with repeated sampling during treatment, and adjusted analysis, are the next step.

5. Conclusion

This study identified significant associations between multi drug resistant urinary tract infections and changes in oxidative stress and inflammatory markers. MDR patients showed increased levels of MDA, CRP and IL-6 and decreased levels of TAC compared to non-MDR patients and healthy controls. Markers were also shown to correlate with each other. This suggests that MDA, TAC, CRP and IL-6 could be used as adjunct biomarkers of host response in UTI. Further larger prospective studies are required to confirm associations and determine their clinical significance after controlling for diabetes and other risk factors.

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