# Prevalence and etiology of urinary stones in hospitalized patients in Baghdad

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## معدَّل انتشار الـحَصَيَات البولية وسببياتها لدى مرضى المستشفيات في بغداد

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**الخلاصـة:** تمت دراسة الانتشار الوبائي والعوامل الإمراضية لدى 184 من المرضى المصابين بالحصيات البولية. وقد كان متوسط عمر هؤلاء المرضى 38.2 عاماً، ونسبة الذكور إلى الإناث 1:2.5. وكانت الحصيات في الغالب من النوع المركَّب، وأكثرها شيوعاً أوكسالات الكالسيوم. أما التوزُّع التشريحي للحصيات فكان 67.4٪ في الكلى، و12.5٪ في الحالب، و14.6٪ في المثانة. وبلغت نسبة نُكْس تكوُّن الحصيات بعد استخراجها جراحياً 15.0٪. وتم استفراد جراثيم من 19 من الحصيات البولية البالغ عددها 78 (أي بنسبة 24.4٪): وكانت 14 منها قادرة على شَطْر اليوريا، و5 منها غير قادرة على شَطْر اليوريا. وبدا أن الإناث أكثر تعرُّضاً للإصابة بالحصيات المحتوية على الجراثيم، وكانت جميع الجراثيم المُستَفْرَدَة حساسة للجنتاميسين والحمض النالیديكسيك، كما كانت جميعاً مقاومة للأموكسيسلين والإريثروميسين. أما المقاومة المتعدِّدة لحوالي ستة أو أكثر من العوامل المضادة للمكروبات فكانت شائعة في حوالي 58.8٪ من الحالات.

ABSTRACT Epidemiology and pathogenesis in urinary stones diagnosed in 184 patients were studied. Mean age was 38.3 years. Male to female ratio was 2.5:1. Stones were predominantly of mixed type: calcium oxalate was the commonest compound. Anatomical distribution of urinary stones was 67.4% renal, 12.5% ureteric and 14.6% bladder. Recurrence rate following previous surgical removal was 15.0%. Bacteria were isolated from 19 (24.4%) of 78 urinary stones: 14 were urea splitting and 5 non-urea splitting. Females had a greater chance of having infected stones. All bacteria isolated were sensitive to gentamicin and nalidixic acid. All isolates were resistant to amoxicillin and erythromycin. Multiple resistance to ≥ 6 antimicrobial agents was common (58.8%).

Prévalence et étiologie des calculs urinaires chez des patients hospitalisés à Bagdad

RÉSUMÉ L'épidémiologie et la pathogenèse des calculs urinaires diagnostiqués chez 184 patients ont été étudiées. L'âge moyen était 38,3 ans. Le rapport des sexes masculin/féminin était de 2,5:1. Les calculs étaient majoritairement de type mixte : l'oxalate de calcium était le composé le plus courant. La répartition anatomique des calculs urinaires était rénale pour 67,4 %, urétérale pour 12,5 % et vésicale pour 14,6 %. Le taux de récurrence après l'élimination chirurgicale précédente s'élevait à 15,0 %. Des bactéries ont été isolées dans 19 (24,4 %) des 78 calculs urinaires : pour 14, les bactéries étaient uréasiques et pour 5, elles ne l'étaient pas. Les femmes avaient davantage de probabilité d'avoir des calculs infectés. Toutes les bactéries isolées étaient sensibles à la gentamicine et à l'acide nalidixique. Tous les isolats étaient résistants à l'amoxicilline et à l'érythromycine. Une résistance multiple à 6 agents antimicrobiens ou plus était courante (58,8 %)

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## Introduction

Urinary stones are the third most common affliction of the urinary tract. They are exceeded only by urinary tract infections and pathologic conditions of the prostate [*1*].

The association of stones and putrefaction has been known since Hippocrates. In 1817, it was pointed out that the alkalinization that attends putrefaction of urine unavoidably results in crystallization of dissolved urinary phosphate [*2*]. In 1925, Hargar and McGrath suggested that urease was the biochemical basis for stone formation in infected urine [*3*].

The lifelong prevalence of kidney stone has increased throughout the 20th century. It occurs in up to 15% of the population of the United States of America. The incidence of new cases and recurrences may continue to rise. Therefore, new approaches in treatment and prevention could have a huge economic effect over and above benefits in terms of reduced morbidity [*4*].

This study was undertaken to determine urinary stone composition and prevalence of stone formers by age and sex among Iraqi patients, and to assess the contribution made by factors such as genetic traits, residence and dietary habits on the etiology of urolithiasis.

## Methods

### Patients

We enrolled patients admitted to the urology department at Al-Kadimiya Teaching Hospital, Al-Nahrain College of Medicine, Baghdad. From December 2001 to September 2002, all 184 patients who were diagnosed by the urologist, or paediatrician in the case of children, as having urinary stones were included in this study. Ethical clearance to conduct the research was obtained from the hospitals. Informed consent was obtained from all participants, or the parents in the case of children. There were no refusals to participate.

A questionnaire was administered to patients to collect demographic data and information on congenital anomalies, previous urinary stone, family history of urolithiasis and dietary habits. Patients were interviewed by a physician. Parents provided the data in the case of children.

### Identification of bacteria

Seventy-eight stones of suitable size were collected and taken to the Department of Microbiology in the College of Medicine for bacterial analysis. Stones were washed in sterile saline and crushed under aseptic conditions, then cultured in nutrient broth (Biolife SpA, Milan) [*5*]. After overnight incubation at 37 °C, they were subcultured on MacConkey agar and blood agar (Biolife). Colonies growing on MacConkey agar were considered Gram-negative bacteria. They were identified using standard biochemical tests [*6*].

### Antimicrobial sensitivity

All bacterial isolates were tested using the agar disc diffusion test for antimicrobial susceptibility on Mueller–Hinton agar (bioMérieux, Marcy-l'Etoile, France) incubated at 37 °C [*7*]. The antimicrobial agents used were: cefotaxime 30 µg, cefoxitin 30 µg, trimoxazole 25 µg, nitrofuran 30 µg, rifampicin 30 µg, tetracycline 30 µg, gentamicin 3 µg, fusidic acid 10 µg, erythromycin 15 µg, cephalexin 30 µg, nalidixic acid 30 µg and amoxicillin 20 µg.

### Chemical analysis of stones

Material from the 78 stones which had been washed dried and crushed was analysed for chemical composition [*8*].

## Results

### Bacteria associated with urolithiasis

Seventy-eight stones were submitted for culture, 19 were infected and 59 were sterile. Of the 19 infected stones, 2 were composed of struvite (infection stones, ammonium magnesium phosphate), 10 contained a mixture of calcium phosphate, calcium carbonate, calcium oxalate, struvite and uric acid (mixed infection stones). Seven were non-infection stones (uric acid, calcium oxalate and calcium phosphate). The 59 uninfected (sterile) stones consisted of struvite (1), mixed infection stones (4) and non-infection stones (54).

Bacteria were detected in 12 (70.6%) of the 17 patients (21.8%) who had infection stones/mixed infection stones. In addition, bacteria were cultured from 7 (11.5%) of the 61 patients with non-infection stones.

Urease-producing bacteria were recorded in stones from 14 of the 19 patients who had infected stones (Table 1). Non-urease-producing bacteria were cultured from stones from 5 of the 19 patients. *Enterococcus faecalis* was present in one of the stones. The prevalence of infected stones was higher in females than in males.

Previous history of urinary stone was noted in 16 (20.5%) of the 78 patients. Nine of these recurrent stones were infected, and were associated with urease-producing bacteria.

### Antimicrobial susceptibility of bacterial isolates

All isolates were resistant to ≥ 1 of the 12 antimicrobial agents tested. The most effective agents were nalidixic acid and gentamicin: all isolates were sensitive to them. The least effective agents were erythromycin and amoxicillin as all the isolates were resistant to them.

### Anatomical distribution of urinary stones

Details of the anatomical distribution of the 184 stones is given in Table 2. Renal stones (unilateral or bilateral) were found in 69.1% of patients and ureteric stones in 12.5%. Recurrence rate following previous surgical removal was 15.0%.

Table 1 Identification of bacteria from urinary stones from 78 patients

| Bacterium | Females (n = 21) | | Males (n = 57) | | Total (n = 78) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Urease producing | | | | | | |
| Staphylococcus aureus | 3 | 14.3 | 2 | 3.5 | 5 | 6.4 |
| Staphylococcus epidermidis | 2 | 9.5 | 2 | 3.5 | 4 | 5.1 |
| Proteus spp. | 1 | 4.8 | 2 | 3.5 | 3 | 3.8 |
| Klebsiella sp. | 0 | – | 1 | 1.8 | 1 | 1.3 |
| Pseudomonas aeruginosa | 0 | – | 1 | 1.8 | 1 | 1.3 |
| Non-urease producing | | | | | | |
| Escherichia coli | 2 | 9.5 | 0 | – | 2 | 2.6 |
| Serratia marcescens | 1 | 4.8 | 0 | – | 1 | 1.3 |
| Acinetobacter sp. | 1 | 4.8 | 0 | – | 1 | 1.3 |
| Enterococcus faecalis | 1 | 4.8 | 0 | – | 1 | 1.3 |
| Total | 11 | 52.4 | 8 | 14.0 | 19 | 24.4 |

Table 2 Distribution of urinary stones in 184 patients according to anatomical site and age

| Category | Males (n = 133) | | Females (n = 51) | | Total (n = 184) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Anatomical site | | | | | | |
| Unilateral renal | 84 | 63.2 | 37 | 72.5 | 121 | 65.8 |
| Bilateral renal | 5 | 3.8 | 1 | 2.0 | 6 | 3.3 |
| Ureteric | 14 | 10.5 | 9 | 17.6 | 23 | 12.5 |
| Renal + urethral | 3 | 2.3 | 2 | 3.9 | 5 | 2.7 |
| Bladder | 22 | 16.5 | 2 | 3.9 | 24 | 13.0 |
| Urethral | 5 | 3.8 | 0 | – | 5 | 2.7 |
| Age (years)[a] | | | | | | |
| ≤ 10 | 25 | 18.8 | 10 | 19.6 | 35 | 19.0 |
| 11–20 | 7 | 5.3 | 2 | 3.9 | 9 | 4.9 |
| 21–30 | 15 | 11.3 | 3 | 5.9 | 18 | 9.8 |
| 31–40 | 18 | 13.5 | 10 | 19.6 | 28 | 15.2 |
| 41–50 | 26 | 19.5 | 11 | 21.6 | 37 | 20.1 |
| 51–60 | 20 | 15.0 | 9 | 17.6 | 29 | 15.8 |
| 61–70 | 14 | 10.5 | 4 | 7.8 | 18 | 9.8 |
| > 70 | 8 | 6.0 | 2 | 3.9 | 10 | 5.4 |

[a]Mean age 38.3 years.

The prevalence of upper urinary tract stones (renal and ureteric) was high in both children (33/39, 84.6%) and adults (117/145, 80.7%). In adults, there was higher prevalence of bladder stones in males (15.2%) than in females (2.1%), a ratio of 7.2:1.

The prevalence of renal and urethral stones was similar in males (2.3%) and females (3.9%). Bladder stones were much more prevalent in the males in our sample, 16.5% compared to 3.9% for females (Table 2).

## Chemical analysis of stones

Seventy-eight urinary stones were analysed qualitatively. The cations found in these stones were calcium (91.0%), ammonium (8.9%) and magnesium (8.9%). While the anions were phosphate (84.6%), oxalate (75.6%), urate (51.3%) and carbonate (12.8%).

Stones of mixed chemical composition were the commonest (74.4%); the majority were composed of calcium oxalate, calcium phosphate and uric acid. The least commonly encountered stone type was cystine (1.3%) (Table 3).

Calcium was the main constituent (91.0%), followed by phosphate (84.6%). The prevalence of staghorn stones was 8.9%. Calcium oxalate urinary stones occurred more frequently in males than in females (Table 3).

## Epidemiological characteristics associated with urinary stones

Analysis of age groups showed a high occurrence of urinary stones among children up to 10 years and adults between 41–50 years. The highest prevalence of stone formers in males was observed in the age groups ≤ 10 years (18.8%) and 41–50 years (19.5%),

Table 3 Chemical composition of 78 urinary stones

| Chemical composition | Males (n = 57) | | Females (n = 21) | | Total (n = 78) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Non-infection stones | | | | | | |
| Calcium oxalate | 6 | 10.5 | 2 | 9.5 | 8 | 10.3 |
| $CaPO_4$ | 3 | 5.3 | 2 | 9.5 | 5 | 6.4 |
| $CaPO_4$ oxalate | 16 | 28.1 | 3 | 14.3 | 19 | 24.4 |
| $CaPO_4$ oxalate uric acid | 14 | 24.6 | 6 | 28.6 | 20 | 25.6 |
| $CaPO_4$ uric acid | 5 | 8.8 | 0 | – | 5 | 6.4 |
| Cystine | 1 | 1.8 | 0 | – | 1 | 1.3 |
| Uric acid | 3 | 5.3 | 0 | – | 3 | 3.8 |
| Infection stones | | | | | | |
| AMP (struvite) | 1 | 1.8 | 2 | 9.5 | 3 | 3.8 |
| $CaPO_4CO_3$ | 2 | 3.5 | 0 | – | 2 | 2.6 |
| $CaPO_4CO_3$ oxalate uric acid | 5 | 8.8 | 3 | 14.3 | 8 | 10.3 |
| $CaPO_4$ oxalate uric acid AMP | 1 | 1.8 | 3 | 14.3 | 4 | 5.1 |

AMP = ammonium magnesium phosphate.

and in females was in those aged 41–50 years (21.6%), ≤ 10 years and 31–40 years (19.6% for each). The lowest prevalence of stone formers in males was in those aged 11–20 years (5.3%); in females, the lowest prevalence was in those aged 11–20 years and those > 70 years (3.9% for each). Children aged 6 months to 14 years constituted 21.2% of the participants in our study.

Males (71.7%) were more prone to urinary stones than females (28.3%), a ratio of 2.5:1.

Congenital anomalies of the urinary tract were diagnosed by the paediatrician in 6 (15.4%) of the 39 children (age range 13 months–11 years) with urinary stones.

Of the 78 patients whose stones were analysed, history of previous urinary stone was recorded in 16; 9 of the recurrent stones were infected and associated with urease-producing bacteria. A positive family history of urolithiasis was recorded for 9 patients (11.5%).

The highest frequency of patients with urinary stone was in September.

From our observations during the interviews, it was clear that most of the 39 children we studied were from low-income families living in impoverished conditions and were probably malnourished. The other 145 patients did not show any difference in dietary intake of the major nutrients. Most were receiving an adequate mixed diet.

## Discussion

We found infection stones in 21.8% of the patients we studied. Takeuchi et al. reported similar findings [*9*]. *Enterococcus faecalis* was present in one of the stones. This may represent a superimposed infection because of changes in bacterial flora due to treatment with antibiotics. This finding was in agreement with results from a previous study [*9*].

Struvite and apatite stones are often associated with urinary infection, especially with urea-splitting bacteria [*10*]. Griffith et al. showed that bacterial urease is a primary

cause of infection stones [*11*]. Studies carried out in Iraq have also reported the isolation of bacteria from infection (struvite) and non-infection stones [*12–14*]. The driving force behind struvite stones is infection of the urine with urease-producing bacteria. It has been proposed that the urease hydrolyses urea, resulting in ammoniacal urine, alkalinity and stone formation [*11*]. A second mechanism by which bacterial infection may induce stone formation is by increasing crystal adherence. Parsons et al. demonstrated that ammonium damages the glycosaminoglycan layer that covers the normal bladder mucosa and allows bacterial adherence to the mucosal surface [*15*]. Bacterial infection may, in a similar manner, damage the glycosaminoglycan layer within the renal collecting system [*11*]. This facilitates bacterial adherence, tissue inflammation, production of an organic matrix and crystal–matrix interaction.

As expected, the incidence of infected stones was higher in females than in males (females are more prone to urinary tract infection due to their short urethra). Ahmad also noted the same observation [*10*].

There was a history of previous urinary stone in just over 20% of the patients whose stones were analysed, emphasizing the high risk of recurrence, which has also been noted in other studies [*16,17*]. Unfortunately, patients with infection stones have a high incidence of new stone growth and persistent infection, especially if residual stone fragments remain. The importance of complete eradication of these organisms needs constant emphasis [*18*]. Cure is achieved by the removal of all foreign bodies (stones, matrices and catheters) and by eradication of infection. Postoperatively, long-term antimicrobial therapy with agents known to be effective against the specific organism involved was needed in most cases to eradicate infection. Repeated urine culture over many months is mandatory [*2*].

The resistance pattern in our study was similar to that reported by Fahad [*14*]. High resistance rates may be a result of abuse of antimicrobials, which leads to the development of resistant strains. Infection of urinary stones with multidrug-resistant bacteria necessitates their removal to ensure complete cure. Antimicrobial therapy can sterilize the urine and reduce urinary pH and thus render urine under-saturated with respect to struvite. This results in complete or partial dissolution of the stone. Antimicrobial agents can be used to prevent stone recurrence or growth after operative procedures [*19*].

In adults, there is a higher risk of bladder stones in males than in females. The ratio in our study was 7.2:1. This was comparable to the findings of a previous Iraqi study in which the ratio of males to females was 5.5:1 [*10*].

The frequency of renal plus urethral stones in males and females was similar. Ureteric stones were more frequent in females (17.6%) than in males (10.5%). This result is in contrast to the findings of some other investigators who found that ureteric lithiasis predominates in males [*20,21*]. The occurrence of urethral stones in females is infrequent in comparison with that in males. This has been attributed to 2 factors: the short urethra and the infrequency of bladder stones in females [*19*].

The majority of stones were composed of calcium oxalate, calcium phosphate and uric acid. This is an indication of the influence of environmental factors—dietary habits, water supply, etc. These results are in agreement with findings reported by others [*16,22*]. Calcium was the main constituent (91.0%), followed by phosphate (84.6%). Previous studies in Iraq found similar results [*12,14*].

Just under 9% of the stones were staghorn stones. The prevalence of this type of stone varies with environmental factors

such as dietary intake and lifestyle. Infection stones are less influenced by environmental conditions [*23*].

There were some differences between males and females in our participants in regard to the chemical composition of stones. A number of observations suggest that sex hormones play a role in the pathogenesis of renal stones. Estrogen, progesterone and testosterone modulate the synthesis of 1,25-dihydroxyvitamin $D_3$ and the intestinal absorption of calcium by stimulating 1-α-hydroxylase in the kidney [*10,24*].

Of the 184 patients we studied, 20.1% were in the 41–50 years age group. This was similar to reports from studies done in Norway, England and Iraq, range 19.5%–20.0% [*25–27*]. Regarding children, 21.2% of those we studied were aged ≤ 14 years. Previous studies done in Mosul, Iraq also found a large proportion of the patients with urinary stones were children, 53% and 41.4% [*12,28*].

Males were more prone to urinary stones than females, with a ratio of 2.5:1. Others have observed similar ratios [*12–14,25,28*]. This may be related to hormonal effects, high inhibitory activity, lower food intake and lower body size [*26,29*]. In addition, Welshman and McGeown demonstrated increased citrate concentrations in the urine of women [*30*]. It has been postulated that this may aid in protecting females from calcium urolithiasis since citrate inhibits nucleation of calcium oxalate crystals [*31*].

Congenital anomalies of the urinary tract were seen in 15.4% of the children in our study. Congenital urinary obstruction leads to urinary stasis and stone formation [*16*].

A positive family history of urolithiasis was found in 11.5% of patients. Others have also noted this [*16,17*]. This suggests that either a genetic or an environmental factor is important in stone formers. Family studies have indicated an appreciable genetic contribution to the tendency to urolithiasis [*27*]. Several disorders that cause renal stones are hereditary. Familial renal tubular acidosis is associated with nephrolithiasis and nephrocalcinosis in almost 70% of patients. Cystinuria is a homozygous, recessive condition. Similarly, hereditary xanthinuria and dihydroxyadeninuria are disorders that cause renal stones [*19*].

The effect of climate on the prevalence of urinary stones may be indirect, through the effect of temperature. A relationship has been established between higher environmental temperature and higher seasonal incidence of urinary stone. The highest incidence of urinary stone appears to occur 1–2 months following the maximum mean annual temperature in the study area [*32*], July and August in the case of Baghdad. This coincides with our results in which the highest frequency of patients with urinary stone was during September. High temperatures increase perspiration, which may result in concentrated urine. This promotes increased urinary crystallization [*33*]. Parry and Lister [*34*] suggested that increased exposure to sunlight causes increased endogenous production of 1,25-dihydroxyvitamin $D_3$, with resultant increases in calcium absorption in the gastrointestinal tract and urinary calcium excretion. This may result in a higher incidence of urolithiasis during the summer months.

Dietary habits may vary with social structure and degree of affluence. Low income and poor nourishment might increase the risk of urinary stones in children. The older patients in our study did not show any difference in dietary intake of the major nutrients. Similar findings were reported by Fellstrom et al. [*23*]. Dietary factors have been suggested as important determinants of renal stone formation: several studies focused on dietary protein (which corre-

lates well with affluence) and prevalence of urolithiasis [*35*]. Correspondingly, in a population of vegetarians, the prevalence of urolithiasis was lower than expected [*36*]. Protein may contribute to stone formation by increasing the acidity of urine, and increasing urinary excretion of uric acid, phosphorous and calcium [*35,36*].

Since reinfection with urea-splitting organisms can lead to new stone formation [*17*], urine cultures should be obtained every 1 or 2 months during the first year, and at regular intervals thereafter. Thus, with careful bacteriological management of infection and treatment, the recurrence rate of infection stones following surgery can be drastically reduced. Patients treated in this way can be discharged free of urinary tract infection.

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